

Review

High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine

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Abstract

Cellular hypoxia is a fundamental mechanism of injury in the critically ill. The study of human responses to hypoxia occurring as a consequence of hypobaria defines the fields of high-altitude medicine and physiology. A new paradigm suggests that the physiological and pathophysiological responses to extreme environmental challenges (for example, hypobaric hypoxia, hyperbaria, microgravity, cold, heat) may be similar to responses seen in critical illness. The present review explores the idea that human responses to the hypoxia of high altitude may be used as a means of exploring elements of the pathophysiology of critical illness.

Introduction

Hypoxaemia is a common consequence of critical illness. Hypoxaemia in critical illness may be caused by hypoventilation, ventilation/perfusion mismatch, right-to-left shunting or limitation of diffusion across the alveolar-capillary membrane. Hypoxaemia may also occur as a result of breathing a low fractional inspired oxygen tension; for example, at high altitude. Tissue hypoxia (reduced cellular or mitochondrial oxygen availability) may arise as a consequence of hypoxaemia or as a result of reduced oxygen delivery due to decreased cardiac output or decreased red-cell concentration (anaemia). Tissue hypoxia may also occur in association with the systemic inflammatory response syndrome. This may be due to decreased tissue oxygen delivery associated with microcirculatory dysfunction, or may occur via alterations in cellular energy pathways and mitochondrial function, resulting in a decreased ability to utilise the available oxygen – a phenomenon termed cellular dysoxia [1].

Conversely, tissue hypoxia may initiate and maintain many aspects of critical illness. Hypoxic epithelial cell activation releases tumour necrosis factor alpha and IL-8, resulting in pathological increases in vascular permeability and in the release of IL-6, the main cytokine of the acute-phase response [2]. Hypoxia-mediated cell death will generate an

inflammatory response, further perpetuating the cascade of critical illness. Furthermore, myocardial tissue hypoxia may impair contractile function, thus reducing the total blood flow and further exacerbating global tissue hypoxia [3].

Responses to continued hypoxaemia and tissue hypoxia may prove detrimental in the long term. For example, in Monge's disease (chronic mountain sickness) occurring in natives or long-life residents living above 2,500 metres, excessive erythrocytosis coupled with hypoxic pulmonary vasoconstriction may result in high pulmonary artery pressures and cor pulmonale, leading to congestive heart failure [4,5]. Time may, however, also allow beneficial adaptive processes that permit an individual to survive severe tissue hypoxia at levels that, encountered more acutely, might prove fatal.

The mechanisms through which hypoxic adaptation occur are poorly understood. Furthermore, exploring these mechanisms in the context of critical illness is difficult. Critically ill patients form a heterogeneous group; preadmission patient characteristics (for example, age, fitness, comorbidities) and precipitating illnesses (for example, trauma, infection, ischaemic event) vary considerably. In addition, many pathological and physiological processes occur concurrently, and separating the cause and effect of just one feature of the disease (tissue hypoxia) can prove extremely difficult. Hypoxic adaptive processes are likely to be common to tissue hypoxia whatever the cause, however, and studying healthy individuals progressively exposed to hypoxia through ascent to high altitude may inform of the nature of the hypoxic adaptive processes occurring in critically ill patients. It might be possible, in other words, to take knowledge 'from mountainside to bedside'. This approach offers the advantages of a relatively homogeneous study population and environmental challenge, in contrast to those observed on critical care units, as well as the availability of 'premorbid'

ACE = angiotensin-converting enzyme; HAPE = high-altitude pulmonary oedema; IL = interleukin.

information and levels of function. Finally, the approach also offers an ethical alternative to hypoxia experimentation in patients; all individuals involved are willing participants in climbing or trekking ventures, as a consequence of which they expose themselves to a hypoxic environment.

High-altitude physiology and pathophysiology

The troposphere is the lowest portion of the atmosphere and envelopes the earth's entire surface. Within the troposphere, barometric pressure falls as altitude (vertical height above sea level) increases. The concentration of oxygen in air remains constant so, as the barometric pressure decreases, the partial pressure of oxygen decreases proportionately. This condition is referred to as hypobaric hypoxia. For reference, the partial pressure of oxygen at the altitude of Everest Base Camp (5,300 metres altitude) is about one-half of the sea-level value. The summit of Mount Everest is the highest point above sea level on the earth's surface, at 8,850 metres altitude, and has a partial pressure of oxygen about one-third of the sea-level value.

High-altitude physiology may be divided into the study of short-term changes that occur with exposure to hypobaric hypoxia (the acute response to hypoxia) and studies of longer-term acclimatisation and adaptation. Acute exposure to the ambient atmosphere at extreme altitude (for example, above 8,000 metres) is rapidly fatal [6]. Acclimatisation is the set of beneficial processes whereby lowland humans respond to a reduced inspired partial pressure of oxygen. These changes tend to reduce the gradient of oxygen partial pressure from ambient air to tissues (classical oxygen cascade) and are distinct from the pathological changes that lead to altitude illness. Adaptation to high altitude describes changes that have occurred over a number of generations as a result of natural selection in a hypobaric hypoxic environment, and this can be observed in some groups of high-altitude residents.

High-altitude illness may be divided into the acute syndromes that affect lowland or highland residents ascending to altitudes greater than those to which they are accustomed and the chronic conditions that affect individuals resident at high altitude for long periods. The acute adult syndromes of high altitude are acute mountain sickness, high-altitude pulmonary oedema (HAPE) and high-altitude cerebral oedema.

Hypoxia and inflammation as mechanisms of injury

Hypoxia fulfils criteria as a causative agent [7] for the acute high-altitude illnesses. The incidence and severity of acute mountain sickness, HAPE and high-altitude cerebral oedema are related to the speed of ascent and the maximum height gained, suggesting a dose-response type of relationship in susceptible individuals [8]. A number of studies also suggest, however, that inflammation may be contributory in the pathogenesis of altitude illness [8-16]. Several studies have failed to convincingly demonstrate any association between

an acute inflammatory response and the development of acute mountain sickness [12,15,17]. On the other hand, a number of studies have shown that individuals with pre-existing inflammatory conditions (for example, diarrhoeal illness, upper respiratory tract infection) have an increased predisposition to acute high-altitude illnesses (that is, acute high-altitude illnesses occur at lower altitudes or with slower ascents) [8,13,14,18]. This pattern is consistent with Moore and Moore's 'two hit model' of critical illness initiation, whereby a single insult primes the body for a much more severe response to a secondary insult (for example, major trauma followed by hypoxia and hypovolaemia) [19].

The initial pathogenesis in HAPE is thought to be nonuniform hypoxic pulmonary vasoconstriction leading to pulmonary capillary stress failure and a high-permeability type of oedema in the face of a normal left atrial pressure [20]. Although alveolar fluid in early HAPE does not demonstrate inflammatory activation [21], bronchoalveolar lavage fluid from individuals with established HAPE has high levels of inflammatory cells and mediators [9,10,16]. When bronchoalveolar lavage was performed in the field, in patients suffering from HAPE for 24 hours or less, there was a marked increase in total cells, with macrophages being predominant, along with elevated levels of cytokines including IL-6, IL-8 and tumour necrosis factor alpha [10].

In hospitalised patients later in the course of HAPE, the proportion of neutrophils increases and the observation is an inflammatory process similar in magnitude and pattern to acute respiratory distress syndrome in the critical care unit [9]. The development of an inflammatory component may modify the natural history of HAPE; anecdotally, the recovery time for HAPE (and high-altitude cerebral oedema) seems to be related to the duration of illness. This might be explained by postulating that in early HAPE, where mechanical capillary stress failure leads to accumulation of intra-alveolar fluid, relief of hypoxia will reduce pulmonary hypertension and the oedema will rapidly resolve. In more established HAPE, where significant inflammation has developed, resolution requires reversal of the inflammatory state, and takes more time. A similar pattern of injury may occur with critical illness: patients who remain poorly resuscitated on the wards for prolonged periods prior to their admission to critical care commonly have a much more prolonged recovery duration than those who are rapidly resuscitated following an initial insult. The study of the interaction between hypoxia and inflammation as mechanisms of injury occurring in healthy individuals in a hypoxic environment has the potential to increase our understanding of these interactions in the critically ill.

Physiological and metabolic responses to hypoxia: increased delivery or decreased utilisation

Parallels exist between the pattern of responses seen following acute, in comparison with subacute, hypobaric

hypoxia and those responses that occur during different phases of critical illness.

The physiological response to acute hypobaric hypoxia serves to increase oxygen delivery to the tissues: ventilation, cardiac output and haemoglobin concentrations increase (haemoglobin concentration increases initially by the haemoconcentration and later as a result of increased erythropoiesis). Similarly, the textbook paradigm of acclimatisation to hypobaric hypoxia emphasises the development of mechanisms to increase oxygen flux (increase in ventilation, cardiac output, oxygen carriage, and capillarity) [6].

These observations, however, do not adequately explain the observed differences between individuals in their tolerance of hypobaric hypoxic environments. Neither the baseline cardiorespiratory performance (maximal oxygen consumption) nor changes in the response to chronic hypoxia account for differences between individuals in acclimatisation to prolonged hypoxia [22] or performance at altitude [23]. Maximal oxygen consumption, maximal heart rate and stroke volume are all reduced [24] after acclimatisation despite normalisation of the blood oxygen content to sea-level values (by an increase in haemoglobin concentration) [25]. Furthermore, pure oxygen breathing by acclimatised individuals (which results in an oxygen content greater than that at sea level) does not return maximal oxygen consumption to sea-level values [26]. These surprising findings suggest that oxygen carriage is not a limiting factor for maximal oxygen consumption at altitude. This could be consistent with central nervous system limitation of the maximal exercise capacity, with limitation of oxygen flux within the tissues, or with a downregulation of cellular metabolism.

An alternative model supported by empirical evidence suggests that mechanisms not related to oxygen delivery may play an even greater role: this alternative model proposes that acclimatisation is achieved not solely by increasing the oxygen flux, but also by decreasing utilisation. Acclimatisation may therefore be mediated in part by alterations in oxygen delivery, but also by reductions in cellular oxygen demand, perhaps through hibernation/stunning or preconditioning pathways, or through improvements in efficiency of use of metabolic substrates. Indeed, hypoxia-tolerant systems rarely activate the anaerobic metabolism but tend to favour a reduced energy turnover state and reduce costly cellular activities such as ion-pumping and protein turnover [27]. In this regard, it is interesting to note that other hypoxia-tolerant species tend to adapt to hypoxia by reducing demand (hibernation, reduced metabolic rate) rather than increasing supply [27].

Might these mechanisms be paralleled in critical illness? The available empirical data suggest that this might be so. Early in critical illness (for example, severe sepsis, the immediate perioperative setting or major trauma), when the mitochondrial and metabolic activity is high [28], increasing oxygen delivery

(or maintaining normal oxygen delivery in the face of evidence that the level is reduced) decreases subsequent mortality [29-35]. Conversely, in established critical illness, increasing oxygen delivery is at best of no benefit and may even increase mortality [34-37]. In established critical illness, mitochondrial activity and oxidative phosphorylation are reduced [28]; just as such effects may be beneficial in acclimatisation to hypobaric hypoxia, Singer and colleagues have proposed that such 'reduced metabolic demand' may offer protection against the cellular hypoxia of critical illness [38].

In both critical illness and during exposure to hypoxia at altitude the acute response seems to be to overcome tissue hypoxia by compensating with increased oxygen delivery (consistent with a fight or flight response) whereas the longer term response seems focused on reducing utilisation, perhaps through hibernation/stunning, through 'preconditioning' phenomena [39] or through enhanced efficiency of oxygen utilisation.

Exploring these differences by studying humans exposed to the hypoxia of high altitude has the potential to identify mechanisms important in established critical illness and perhaps to alter our therapeutic focus towards increasing the efficiency of oxygen utilisation rather than improving delivery. Consistent with this model there is a suggestion that improved performance at altitude associated with genotype II of the angiotensin-converting enzyme (ACE) polymorphism (see below) may be related to alterations in the efficiency of oxygen utilisation [40].

Genes, hypoxia and adaptation

Just as in the outcome from critical illness, there is wide variation between individuals regarding performance at high altitude and susceptibility to high-altitude illness. This phenotypic variation occurs as a result of genetic variation, and the selection of 'advantageous genetic variants' may underpin fundamental differences in the physiology of long-term highland dwellers when compared with lowland populations. Native Tibetan populations have been resident at high altitude for hundreds of generations, whereas the Han Chinese residents of Tibet have migrated from lowland regions during the past 60 years. When compared with the Han Chinese, native Tibetans have greater maximal oxygen uptakes and vital capacities [41], a reduced alveolar-arterial oxygen gradient [42], a higher arterial oxygen saturation at birth and during the first 4 months of life [43], and an increased uterine artery blood flow [44] leading to a reduction in the incidence of intrauterine growth rate and of low-birth-weight babies [45]. Some of these changes have also been noted in South American Andean natives when compared with lowland residents [46].

Among lowlanders ascending to high altitude, genetic differences have been identified that confer performance benefits at high altitude. Individuals homozygous for the

insertion variant of the human ACE gene, which is associated with reduced ACE levels, seem to perform better at altitude [47,48]. The association of ACE polymorphisms with acute and chronic high-altitude illnesses is more complex. In a Japanese (lowland resident) population there was no difference in the insertion/deletion allele distribution between HAPE-resistant and HAPE-susceptible groups, although pulmonary vascular resistance was higher in those individuals with the D allele when they developed HAPE [49]. This contrasts with studies in Kyrghyz (highland resident) populations suggesting that high-altitude pulmonary hypertension is associated with the ACE gene insertion (I) allele [50,51]. There are also data suggesting that variants of the endothelial nitric oxide synthase gene could be involved in adaptation to altitude. Nitric oxide is synthesised in the lungs and is involved in the regulation of pulmonary blood flow. Exhaled nitric oxide levels are higher in native populations resident at high altitude [52]. In Japanese subjects, polymorphisms of the endothelial nitric oxide synthase gene resulting in decreased nitric oxide synthesis were associated with an increased susceptibility to HAPE [53]. In Caucasians, however, no difference in nitric oxide synthase genotype frequencies was found when comparing HAPE-susceptible and HAPE-resistant individuals [54], and there was also no association between pulmonary artery systolic pressure in acute hypoxia and the nitric oxide synthase genotype [55]. The nitric oxide synthase gene polymorphisms associated with lower nitric oxide activity were found to have an increased frequency in Nepalese sherpas when compared with nonsherpa lowland residents [56]. Interactions with other gene systems will probably be responsible for the contrasting effect of the ACE gene insertion allele and nitric oxide synthase gene alleles observed in different groups.

If the paradigm proposed at the outset of the present review has validity, then it would be expected that genes conferring benefit for high-altitude performance might be related to improved outcomes in critical illness. In keeping with this hypothesis, the ACE gene insertion allele is associated not only with improved performance at high altitude, but with a lower mortality from acute respiratory distress syndrome [57,58], improved outcomes in childhood meningococcal septicaemia [59] and improved cardiorespiratory response to premature birth [60].

Conclusion

Cellular hypoxia is a fundamental element of critical illness. Studying human responses to hypobaric hypoxia may offer important insights into the pathophysiology of critical illness.

Competing interests

The authors declare that they have no competing interests.

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