Surviving physiological stress: can insights into human adaptation to austere environments be applied to the critical care unit?

Helen McKenna[1,2] and *Daniel Martin[1,3,4]

1. University College London 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
2. Critical Care Unit, The London Clinic, 20 Devonshire Place, London, W1G 6BW, UK
3. Intensive Care Unit, Royal Free Hospital, Pond Street, London, NW3 2QG, UK
4. University College London Division of Surgery and Interventional Science, Royal Free Hospital, Pond Street, London, NW3 2QG, UK

*Corresponding author:

Dr Daniel Martin

First Floor, 170 Tottenham Court Road, London, W1T 7HA, UK

+44 (0)20 7794 0500 (ext 24518)

daniel.martin@ucl.ac.uk

HIGHLIGHTS

- Critical illness is a state of extreme physiological stress.
- Physiological stress is also encountered in austere environments.
- Cellular and molecular responses determine adaptation to austere environments.
- Lessons learnt from survival of extreme environmental conditions may benefit critically ill patients.

ABSTRACT

The harshest environment that many people will ever face is the critical care unit, where pathology can stress homeostatic mechanisms beyond their limits, leading to multiple organ failure and death. Our understanding of the biology that underlies this catastrophic process remains limited. There is significant variation in survival between individuals with apparently similar severity of organ dysfunction and it is difficult to predict which patients will weather the storm. Survival may be influenced by as yet undiscovered innate adaptive mechanisms that determine an individual's ability to tolerate physiological stress. Identifying favourable phenotypes, and the molecular machinery underlying them, could yield new therapeutic targets to improve outcome in life-threatening illness. Unfortunately, the complexity of critical illness makes it difficult to elucidate subtle adaptive mechanisms that could favour survival during stress. However, comparisons can be drawn between the stress of critical illness and that imposed by austere environments. The Earth is comprised of a wide range of different physical environments, each of which challenges homeostasis. Whilst technological advances have played a

significant role in our capacity to survive in austere environments, biological adaptation and evolutionary change have been crucial. Studying human responses to environmental stressors such as heat, cold, hypoxia and microgravity has taught us a great deal about innate human adaptation, from the system to the cellular level, and the field continues to expand. Translating this to the pathophysiological stress of critical illness could offer alternative approaches to the current practice of intensive care medicine.

Keywords

Critical care; critical illness; body temperature regulation; space medicine; diving; altitude; physiologic adaptation.

BACKGROUND

The human body possesses complex mechanisms to ensure that multiple systems, from micro to macro, oscillate around their natural set point, and this is referred to as homeostasis. Deviation from the set point represents physiological stress, and can lead to cell damage and death. Survival during physiological stress rests on the ability to adapt, and adaptation may occur at the system, organ, tissue and cellular level [1]. Critical illness occurs when the body fails to compensate for severe pathophysiological stress, brought about by illness or injury. Much remains unknown about the precise mechanisms that lead to multiple organ failure and death, and more understanding is required to reduce mortality and morbidity from critical illness.

ADAPTATION AT THE SYSTEM VERSUS THE CELL LEVEL?

We are often able to observe the response to a stressor at the system level. Such phenotypic responses tend to counter the disturbance, in an attempt to shield the cells from potential harm. Although invaluable in surviving a temporary perturbation, such global responses may fail to buffer an excessive or indefinite onslaught. They incur an energetic cost or physiological strain, which ultimately limits their effectiveness as a survival strategy. For example, a rise in core temperature may be counteracted by an increase in sweat rate (in order to protect the cells from heat stress), but this response will ultimately result in dehydration and cardiovascular collapse. The greater the disturbance to homeostasis, the greater the potential devastation wreaked by the response to correct it. This conflict is a fundamental dilemma in critical care medicine, where we attempt to support homeostasis at the system level, by targeting 'normal' values for measures such as global oxygenation or haemodynamics. Although this can yield improvements in outcomes during the acute phase of illness [2], once critical illness is established, such strategies may no longer convey benefit [3]. There is uncertainty regarding the range of physiological values that should be targeted in these patients without causing more harm than good [4]. The significant variability in outcomes for patients with apparently similar disease burden and treatment implies that survivors of physiological stress possess superior adaptive mechanisms, conferred by genetic variation or previous exposure to stress. Identifying survivor phenotypes, and the molecular pathways underlying their expression may yield targets for therapeutic intervention during critical illness. Distinguishing such phenotypes in critically ill patients is challenging. They

may be subtle and easily obscured by the multitude of variables influencing outcome in these patients, including age and co-morbidity, the character and duration of critical illness, and the effects of medical interventions. Limited inferences can be drawn from using animal models of critical illness to distinguish such phenotypes, as the responses can be very different to those seen in humans [5]. An alternative translational approach is to study healthy humans in extreme environments as an experimental model of physiological stress [6].

AUSTERE ENVIRONMENT MODEL OF ADAPTATION TO PHYSIOLOGICAL STRESS

Without behavioural and technological intervention, human survival is confined to a narrow range of environmental conditions, based on the environment in which we originated (the East African Rift). Approximately 3.5 million years ago, early humans walked on land and were subject to tropical temperatures, the Earth's gravitational field, barometric pressure associated with relatively low elevations, and Earth's geomagnetic field (the magnetosphere) [7] (Figure 1). Changes in any of these external conditions will challenge homeostasis [8]. Thus when humans explore new and austere environments, both on Earth and beyond its boundaries, they are exposed to physiological stress, to which they must either adapt or succumb. Like their counterparts in the critical care unit, healthy individuals show a significant degree of variation in their ability to tolerate environmental stress [9], and perhaps some survival mechanisms are common to both scenarios. An austere environment experimental model offers an approach to further our

understanding by avoiding the multitude of confounding variables in the critical care unit. Studies at high altitude revealed the existence of physiological acclimatisation to hypoxia within individuals over brief periods of time [10] and genetic adaptation in high altitude populations over hundreds of generations [11]. Harnessing these processes may offer an alternative therapeutic approach to treating the tissue hypoxia commonly seen in critical illness. Studies of environmental stress have drawn attention to adaptation at a cellular and molecular level, in addition to the more easily observable system responses that we currently monitor and target in critical care units. It is apparent that homeostatic pressures are sensed at a cell level and trigger a host of cytoprotective responses that preserve function and survival of the cell, and the organism as a whole [12]. Exploiting cellular adaptation may be a novel strategy for promoting survival during pathophysiological stress, but doing so requires improved understanding of how this process occurs in intact humans, rather than in petri dishes or animal models alone.

Here we review the manner in which different forms of environmental stress threaten survival and how humans adapt to them over time. We propose that, by improving understanding of what determines survival during exposure to external stressors, from heat to hypoxia, studies of humans in austere environments have the potential to transform the practice of critical care medicine.

ADAPTATION TO HEAT STRESS

Excessive heat threatens survival through protein dysfunction and denaturation. Once membrane p2umps fail, ion gradients dissipate and cells lose the ability to produce energy or generate the signals vital for survival, resulting in loss of cell integrity and activation of cell death pathways. This triggers a systemic inflammatory response that culminates in multi-organ failure [13, 14]. To protect against this, the acute systemic response to a rise in core temperature (due to internal or external processes that alter the balance of heat generation and dissipation) diverts blood flow to the peripheries to increase heat loss to the environment. If ambient temperature exceeds 37^{o}C, the only way to lose heat is through sweat production. However, this compensation occurs at the cost of intravascular volume depletion and cardiovascular instability if fluid is not replaced. Above a body temperature of 40-41^{o}C the neurones that coordinate the systemic response are themselves compromised and compensation fails, leading to heat stroke and death [15].

Tolerance to heat stress varies between individuals [16], with the elderly and newborn being particularly vulnerable [17]. Individual tolerance to heat stress can be improved by repeated exposure to sub-lethal temperatures. This is known as heat acclimation, and requires two to six weeks of continuous or intermittent heat exposure to be effective [18]. The process increases exercise capacity of individuals in hotter environments and can double the time to reach a state of physical exhaustion [19]. Acclimated individuals can tolerate higher core temperatures and experience less cardiovascular strain during exercise. Athletes, whose muscles regularly reach temperatures of 44°C during intense exercise [20], are capable of tolerating core temperatures

of 39.5 – 40°C for short periods [21], while untrained individuals demonstrate heat exhaustion at 38°C [19]. Despite having higher sweat rates, intravascular volume and cardiovascular stability is preserved through minimisation of salt loss in sweat and urine [22]. Native populations of hot environments, such as the Bushmen of the Kalahari desert, have enhanced exercise capacity in hot conditions compared to non-natives, and maintain lower core temperatures despite paradoxically lower sweat rates [23]. This implies that they possess alternative thermoregulatory mechanisms, perhaps genetically determined, that counteract the rise in core temperature while circumventing the physiological strain of dehydration.

Part of the heat acclimation process may be occurring at a cellular level. Heat stress activates a set of constitutively expressed transcription factors, which regulate the expression of heat shock proteins (HSP) [20]. HSPs protect the cell from impending heat-induced injury by various mechanisms: scavenging free radicals, eliminating harmful metabolic products and acting as molecular chaperones. For example, HSP72 and HSP90 bind to damaged polypeptides and restore their native structure or assist in their disposal, preventing aggregation within the cell [24]. This defence strategy can also be activated by other forms of stress common in critical illness, from energy depletion to hypoxia [25]. The cellular heat shock response is reduced in the elderly [26], who are notably more susceptible to the effects of physiological stress. As such, it represents a potential target for protecting cellular and organ function without correcting systemic physiological values [27]. One method of activating this response is though exercise training, which, when it generates

198 a sustained increase in body temperature by 1-2ºC, can activate a cellular
199 acclimation responses [24]. This may account for part of the enhanced
200 physiological reserve observed in physically fit individuals (in addition to their
201 superior cardiorespiratory function). Cell adaptation may also be triggered
202 pharmacologically: a molecular activator called BCP-15 increases expression
203 of HSP72 and improves inflammation and metabolic homeostasis in a rat
204 model of type 2 diabetes [28]. In the future, administration of such agents
205 could offer a means of preserving cell integrity and function during critical
206 illness. In situations where future pathophysiological stress can be predicted,
207 such as planned major surgery, programmes of exercise or heat acclimation
208 could be employed to prime the cytoprotective response. There is a need for
209 further clinical research in this area, which has the potential to extend the
210 supportive therapy in critical care beyond modification of systemic responses.
211
212 **ADAPTATION TO COLD STRESS**
213 The physiological stress of cold exposure occurs through progressive slowing
214 of vital chemical reactions; the Arrhenius principle states that metabolic rate
215 will halve for every 10ºC decrease in temperature. Diminished activity of ion
216 channels reduces the rate at which excitable cells can conduct impulses and
217 death may result from central nervous system dysfunction or cardiac
218 arrhythmia. [29] To protect cells against these effects, the body has an acute
219 systemic response to restore the core temperature: minimising heat loss
220 through peripheral vasoconstriction and increasing heat generation by
221 shivering. Below 35ºC, the function of the tissues coordinating the systemic
222 response to cold is impaired, and body will cool to the ambient temperature.

Like sweating, shivering comes at a physiological cost – in this instance, the increase in energy requirements. However, prolonged or repeated cold exposure results in habituation: with toleration of lower core body temperatures and shivering triggered at lower temperatures (Macari Dauncey and Ingram 1983). Accepting mild core hypothermia to preserve energy is also seen in native residents of cold environments, such as the circumpolar Lapps and Inuit [30–32]. Korean ama divers, who are regularly immersed in 10 ^{o}C water during the winter, undergo a drop in core temperature to 35 ^{o}C and have a significantly higher shivering threshold than non-divers {Park and Hong, 1991, #65005}. Survival at this new set point may be facilitated by increased cellular defences, reminiscent of cellular acclimatisation to heat stress. The molecular pathways involved in the cell response to cold stress are less well described than those for heat. Repeated cold water immersion in winter swimmers results in increased expression of antioxidants [34], which may play a role in this. Specific cold shock proteins have been identified in mammalian cells [35], while cold exposure also increases expression of "heat" shock proteins [36–38], demonstrating that the cell may have a general response to different forms of stress.

It may be possible to utilise the phenomenon of cross-adaptation (whereby repeated exposure to one form of environmental stress also results in adaptation to a different one) to improve clinical outcomes. Subjects exposed to repeated episodes of cold water immersion demonstrate modification of their autonomic response to subsequent exposure to hypoxia [39]. Although prehabilitation prior to unexpected critical illness is not usually feasible, a

significant proportion of patients classified as high risk prior to major elective surgery go on to develop postoperative complications which can spiral into critical illness and multiple organ failure [40]. Heat or cold-acclimatisation programmes, by upregulating cell protective mechanisms, could enhance tolerance prior to a planned episode of stress, such as major surgery, and potentially improve outcomes in these patients. Furthermore, the systemic stress response to surgical trauma, which has been blamed for adverse outcomes following surgery, including: cardiovascular instability, ischaemia, fluid overload, hyperglycaemia, wound infections and thromboembolism [41], has many direct parallels with the acute response to cold exposure. Repeated controlled exposure to cold blunts the acute response, resulting in reduced circulating levels of catecholamines, cortisol and glucose on subsequent exposure to cold [42, 43], and further study is required to discover if such a programme could improve outcomes after surgery.

ADAPTATION TO HYPOXIA

Mitochondria require a continuous supply of oxygen to meet up to 98% of the body's energy demands through the process of oxidative phosphorylation. Tissue hypoxia therefore results in cellular energetic failure, as well as cell damage through oxidative stress, by increasing the generation of reactive oxygen species [44]. As barometric pressure declines on ascent to high altitude (Figure 2), the commensurate decline of oxygen partial pressure (PO_2) reduces the pressure gradient for oxygen diffusion across the alveolar-capillary membrane resulting in hypoxaemia and reduced convective oxygen delivery. The acute response to environmental hypobaric hypoxia restores

oxygen delivery, by increasing cardiac output (mainly via an increased heart rate) and raising the arterial oxygen saturation of haemoglobin through augmented minute ventilation [45]. At the highest point on Earth (8848m), atmospheric pressure and PO_2 are one third of that at sea level [46] and sudden exposure to this degree of atmospheric hypoxia leads to unconsciousness and death within minutes [47]. In contrast, with repeated exposure to sub-lethal levels of hypoxia, humans undergo acclimatisation that make it possible to summit Mount Everest, in some instances even without supplemental oxygen. System level acclimatisation to sustained hypoxaemia consists of increased minute ventilation, heart rate and haemoglobin concentration, which restore arterial oxygen content to sea level values up to altitudes of 7100 m [48]. As with other environments, the extent to which acclimatisation at the system level can support survival is ultimately limited. Increases in cardiac output and minute ventilation are energy inefficient in a situation where oxygen is scarce [49]. Also, an inexorable rise in haemoglobin concentration will limit oxygen delivery through viscosity-related restriction of microcirculatory blood flow [50, 51].

Beneath the surface, however, a myriad of cellular changes occurs in response to hypoxia, preparing cells for an impending oxygen drought. At altitude we have observed skeletal muscle atrophy [52], down-regulation in the production of proteins and autophagy [53]; down-regulation of mitochondrial biogenesis and decreased expression of electron transport chain complexes [54]; decreased cardiac phosphocreatine / ATP ratio; and insulin resistance that correlates to the degree of oxidative stress [55]. All of

these point towards a state of cellular quiescence, which minimises energy utilisation. This phenotype may resemble what we see in critical illness [56, 57], yet it is customary in current practice to push the metabolic pendulum in the opposite direction, pouring oxygen, blood, fluids and inotropic agents into stressed patients. Using the model of high altitude acclimatisation to understand how cellular networks in healthy subjects are modified to tolerate hypoxic stress could drive a shift in this practice, towards support of a hibernation state during critical illness.

The importance of adaptations at the distal end of the oxygen cascade is further emphasised by studies of native high altitude populations. Tibetans have occupied high altitude for the longest period of time (at 4500m for up to 20,000 years) and arguably represent the pinnacle of human hypoxic adaptation. As such their cellular phenotype may represent a target to be emulated therapeutically in order to improve outcomes in the critically ill. Contrary to popular belief, Tibetans do not exhibit a raised haemoglobin concentration at high altitude [58], but instead have enhanced function of the peripheral microcirculatory-mitochondrial unit. Their capillary density and microcirculatory blood flow is higher, in conjunction with elevated levels of nitric oxide products (such as nitrate, nitrite and nitroso proteins) in peripheral blood [59, 60]. They may also have more efficient mitochondrial metabolism, demonstrated by greater maximal oxygen consumption normalised to mitochondrial volume, despite lower mitochondrial density [59]. Some light has been shed on underlying molecular mechanisms, with a suggestion that Tibetans undergo a metabolic switch away from the more oxygen-expensive

substrates, preferring carbohydrate over lipid oxidation [61]. They possess enhanced cellular defences against oxidative stress, with reduced lipofuscin accumulation in muscle at high altitude [62]. Superior adaptive mechanisms appear to have a genetic basis, with natural selection demonstrated in many genes involved in the hypoxia inducible factor (HIF) pathway, which is responsible for sensing and coordinating the response to hypoxia in almost every living creature on earth [63]. Hypoxia stabilises the HIF heterodimer, which moves to the nucleus and activates the transcription of genes with hypoxia response elements in their promoter regions, regulating production of proteins such as erythropoetin and vascular endothelial growth factor. HIF also reduces the expression of peroxisome proliferator-activated receptor alpha (PPARα), and this pathway may mediate enhancements in metabolic efficiency, through downstream actions on fatty acid oxidation and mitochondrial coupling [64].

ADAPTATION TO MICROGRAVITY

Microgravity is a form of environmental stress for astronauts on board the international space station (ISS); it results from orbiting the Earth in continuous free-fall. However, prolonged six degree head-down tilt in a supine individual mimics almost all of the cardiovascular and musculoskeletal disturbances of microgravity [65], and many can be observed in bedbound critically ill patients. Unlike thermal and hypoxic stress, the effects of microgravity do not impose a defined limit on human survival, even after 468 days in space [66]. Interestingly, in this case, it is the adaptation itself (to the stressor imposed by the new environment) that results in almost complete

incapacitation of the astronaut on return to Earth. The negative consequences of adaptation to weightlessness could be easily overlooked during the storm of other active insults affecting critically ill patients, but observing this phenomenon in otherwise healthy astronauts highlights the magnitude of the problem. Understanding the mechanisms underlying this "mal-adaptation" could prove to be extremely valuable in future active promotion of recovery and rehabilitation, and studying space travellers may be the best approach for doing so [65].

In a microgravity environment, the hydrostatic pressure difference between the upper and lower extremities (90 mmHg increase from head to foot) normally created by the Earth's gravitational force while in the upright position is abolished and body fluid shifts upwards from the lower extremities. This is misinterpreted by baroreceptors as an increase in overall fluid volume, driving an inappropriate diuresis. Plasma volume and cardiac output progressively decline with time spent in microgravity, with stroke volume decreasing by up to 30% [67]. On Earth, every time we stand, the gravity-induced drop in blood pressure is compensated for by the baroreceptor reflex. In the absence of this trigger during months in space, baroreceptor sensitivity becomes blunted and vagal-cardiac activity decreases [68] {Nyhan et al., 2002, #90805} and this has been associated with endothelial dysfunction {Coupé et al., 2009, #10917}. The same problems compound prolonged critical illness, resulting in orthostatic intolerance, which can significantly impede rehabilitation [69].

Bone and muscle are dynamic structures, continually remodelling in response to changing mechanical loads. Diminishing gravitational force interferes with osteoblast/osteoclast activity and results in bone demineralisation, with the greatest impact on the weight-bearing bones [70]. On the international space station (ISS), bone mineral density has been shown to decline by 1% per month and full recovery from a four-month mission takes years [71]. The mechanism is not fully understood, but we know that weightlessness results in calcium loss {Michel et al., 1976, #2783}, and that the demineralisation can be abated by inhibitors of osteoclast-mediated bone resorption [72]. Astronauts also suffer a substantial loss of muscle mass and power [73]. Postural muscles are particularly sensitive and undergo a dramatic loss in type I (slow twitch) fibres. Studies in rats following a 16 days in space revealed a pathway for the degradation of these proteins. Supplementation of their diet with the antioxidant, cysteine, reduced oxidative stress, protein ubiquitination and muscle loss [74, 75]. Microgravity also leads to atrophy of cardiac muscle, resulting in diastolic dysfunction, orthostatic intolerance, and increased incidence of arrhythmia in long-term space residents [76].

The devastating deconditioning of physically fit astronauts in microgravity mirrors the effects of prolonged passivity in critical illness [77]. Given the multitude of active insults afflicting these patients, it is easy to overlook the insidious development of orthostatic intolerance or the silent but relentless wasting of bone and muscle. It has been shown that 92% of critically ill patients undergo bone hyper-resorption after only one month [78] and muscle wasting can reach rates of up to 2% per day [79]. The molecular mechanisms

underlying these processes may be obscured by pathological processes in critical illness, but studying otherwise healthy human explorers of the most alien environment of all may assist in the search for targets for therapeutic intervention.

CLINICAL CONUNDRUMS AND NEW PARADIGMS

Pathophysiological stress threatens human survival during critical illness and multiple organ failure. Harnessing innate biological responses to stress, which are more complex and elegant than any current manmade intervention, may be the future of critical care medicine. The difficulties we face are: understanding the myriad of responses to disease, determining which are of potential therapeutic value, and how best to support such a multifaceted state effectively. With regard to the latter our traditional approach has been to intervene at the system or organ level, to maintain measures such as global oxygenation or haemodynamics within a 'normal' range, defined by that seen in health. However, meeting such targets in patients with established critical illness has not been consistently associated with improved outcomes and striving to achieve them may be associated with harm, either through bystander effects of the methods used [80] or the tendency towards supra-normalisation of values. Thus we have already started to see a relaxation of target parameters, with permissive anaemia, hypercarbia and hypoxaemia, in some cases improving outcomes [81–84].

It may be that the optimal physiological milieu that fosters health and regeneration in critically ill patients is different from that in the unstressed

422 subjects on which current ‘standard’ targets are based. We may need to
423 reconsider what constitutes ‘normal’ in this cohort and begin to develop and
424 evidence base to define future targets. However, determining which
425 phenotypes are associated with better outcomes, and are thus worth
426 supporting through medical intervention, is hindered by the mass of
427 confounding factors that influence survival in the context of critical illness.
428 Observations of how humans grow and thrive under profound and prolonged
429 environmental stress may guide us. Acclimatisation and genetic adaptation to
430 different environmental extremes often appear to involve a resetting of
431 homeostasis to a new set point, which could thus represent valid alternative
432 approach to emulate in our attempts to promote survival during the sustained
433 stress of critical illness. We are now beginning to recognise the importance of
434 the role of innate intracellular mechanisms, such as the HSP and HIF
435 systems, in sensing and defending against stress. The field of chronobiology,
436 in which the timing of molecular events within the cell are co-ordinated by
437 global rhythms, is now emerging as a significant factor influencing physiology
438 in critical illness [85]. These ancient cytoprotective responses remain
439 untapped by current clinical interventions. Animal models may help to further
440 our understanding in this field, but they are notoriously unrepresentative of the
441 human response in some conditions [5]. Humans exposed to physiological
442 stress in laboratories or in the field could provide a more robust model, in
443 which the translation to critical illness is more direct. The phenomenon of
444 cross-adaptation, in which acclimatisation to one form of stress (such as heat)
445 can improve tolerance to another (such as hypoxia), through activation of a
446 common adaptive pathway, may represent an new strategy for pre-

habilitation, and although difficult to utilise in unpredicted critical illness, it could improve outcomes prior to predictable episodes of stress, such as high risk surgery, the complications of which commonly lead to critical illness and multiple organ failure. Finally, understanding the molecular mechanisms underlying the “mal-adaptation” to sustained exposure to microgravity, the consequences of which are problematic during recovery and rehabilitation, appear to be of increasing importance. Space medicine has not just highlighted the extent of deconditioning produced by weightlessness, independently of disease, but the investment in technology and pharmacology to circumvent this problem during prolonged spaceflight could have a direct application in critical care units [86].

CONCLUSION

New insights into how the human body adapts to physiological stress in austere environments may provide the key to promoting survival during critical illness. The practice of intensive care, traditionally limited to intervention at the system and organ level to achieve phenotypes seen in health, may one day extend to harnessing the innate cytoprotective response.

DECLARATIONS

Nil

LIST OF ABBREVIATIONS

DNA: deoxyribonucleic acid

FI: fractional inspired concentration (of a gas)

HIF: hypoxia-inducible factor

HSP: heat shock protein

ISS: international space station

P_{at}: atmospheric partial pressure (of a gas)

P_B: barometric pressure

PPARα: peroxisome proliferator-activated receptor alpha

ROS: reactive oxygen species

VO_2peak: peak oxygen uptake

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

Neither author has any competing interests.

FUNDING

Nil.

Acknowledgements

HM thanks The London Clinic for its support.

Authors' information

HM is a research fellow based at the Royal Free Intensive Care Unit and University College London Centre for Altitude, Space and Extreme Environment Medicine (CASE). DM is a senior lecturer at University College London, director of CASE and Consultant in Intensive Care and Anaesthesia at the Royal Free Hospital, London.

REFERENCES

[1] Hunter P, Robbins P, Noble D, The IUPS human Physiome Project., Pflugers Arch. 445 (2002) 1-9.

[2] Rivers E, Nguyen B, Havstad S et al., Early goal-directed therapy in the treatment of severe sepsis and septic shock., N Engl J Med. 345 (2001) 1368-1377.

[3] Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D, Elevation of systemic oxygen delivery in the treatment of critically ill patients., N Engl J Med. 330 (1994) 1717-1722.

[4] Marini JJ, Too much for too long-wrong targets, wrong timing?, Crit Care Med. 41 (2013) 664-665.

[5] Seok J, Warren HS, Cuenca AG et al., Genomic responses in mouse models poorly mimic human inflammatory diseases., Proc Natl Acad Sci U S A. 110 (2013) 3507-3512.

[6] Grocott M, Montgomery H, Vercueil A, High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine, Crit Care. 11 (2007) 203.

[7] Maslin MA, Shultz S, Trauth MH, A synthesis of the theories and concepts of early human evolution., Philos Trans R Soc Lond B Biol Sci. 370 (2015) 20140064.

[8] Bevington M, Lunar biological effects and the magnetosphere., Pathophysiology. 22 (2015) 211-222.

[9] Martin DS, Levett DZ, Grocott MP, Montgomery HE, Variation in human performance in the hypoxic mountain environment., Exp Physiol. 95 (2010) 463-470.

534 [10] West JB, Human responses to extreme altitudes, Integrative and
535 Comparative Biology Integr Comp Biol. 46 (2006) 25-34.
536 [11] Simonson TS, McClain DA, Jorde LB, Prchal JT, Genetic determinants
537 of Tibetan high-altitude adaptation., Hum Genet. 131 (2012) 527-533.
538 [12] Landry J, Bernier D, Chrétien P, Nicole LM, Tanguay RM, Marceau N,
539 Synthesis and degradation of heat shock proteins during development
540 and decay of thermotolerance., Cancer Res. 42 (1982) 2457-2461.
541 [13] Yan YE, Zhao YQ, Wang H, Fan M, Pathophysiological factors
542 underlying heatstroke., Med Hypotheses. 67 (2006) 609-617.
543 [14] Adams T, Stacey E, Stacey S, Martin D, Exertional heat stroke., Br J
544 Hosp Med (Lond). 73 (2012) 72-78.
545 [15] Hanna EG, Tait PW, Limitations to Thermoregulation and Acclimatization
546 Challenge Human Adaptation to Global Warming., Int J Environ Res
547 Public Health. 12 (2015) 8034-8074.
548 [16] Selkirk GA, McLellan TM, Influence of aerobic fitness and body fatness
549 on tolerance to uncompensable heat stress., J Appl Physiol (1985). 91
550 (2001) 2055-2063.
551 [17] Robertshaw D. Man in Extreme Environments, Problems of the Newborn
552 and Elderly. In: Cena K, Clark JA, editors. Bioengineering, Thermal
553 Physiology and Comfort. Elsevier; 1981. p. 169-179.
554 [18] Garrett AT, Rehrer NJ, Patterson MJ, Induction and decay of short-term
555 heat acclimation in moderately and highly trained athletes., Sports Med.
556 41 (2011) 757-771.
557 [19] González-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldig T, Nielsen
558 B, Influence of body temperature on the development of fatigue during

559 prolonged exercise in the heat., J Appl Physiol (1985). 86 (1999) 1032-
560 1039.
561 [20] Dehbi M, Baturcam E, Eldali A et al., Hsp-72, a candidate prognostic
562 indicator of heatstroke., Cell Stress Chaperones. 15 (2010) 593-603.
563 [21] Kofler P, Burtscher M, Heinrich D et al., Performance limitation and the
564 role of core temperature when wearing light-weight workwear under
565 moderate thermal conditions., J Therm Biol. 47 (2015) 83-90.
566 [22] Kirby CR, Convertino VA, Plasma aldosterone and sweat sodium
567 concentrations after exercise and heat acclimation., J Appl Physiol
568 (1985). 61 (1986) 967-970.
569 [23] Wyndham CH, Strydom NB, Ward JS et al., Physiological reactions to
570 heat of Bushmen and of unacclimatized and acclimatized Bantu., J Appl
571 Physiol. 19 (1964) 885-888.
572 [24] Gibson OR, Turner G, Tuttle JA, Taylor L, Watt PW, Maxwell NS, Heat
573 acclimation attenuates physiological strain and the HSP72, but not
574 HSP90α, mRNA response to acute normobaric hypoxia., J Appl Physiol
575 (1985). 119 (2015) 889-899.
576 [25] Kregel KC, Heat shock proteins: modifying factors in physiological stress
577 responses and acquired thermotolerance., J Appl Physiol (1985). 92
578 (2002) 2177-2186.
579 [26] Verbeke P, Fonager J, Clark BF, Rattan SI, Heat shock response and
580 ageing: mechanisms and applications., Cell Biol Int. 25 (2001) 845-857.
581 [27] Macario AJ, Conway de Macario E, Molecular chaperones: multiple
582 functions, pathologies, and potential applications., Front Biosci. 12
583 (2007) 2588-2600.

584 [28] Henstridge DC, Whitham M, Febbraio MA, Chaperoning to the metabolic
585 party: The emerging therapeutic role of heat-shock proteins in obesity
586 and type 2 diabetes., Mol Metab. 3 (2014) 781-793.
587 [29] Lim C, Duflou J, Hypothermia fatalities in a temperate climate: Sydney,
588 Australia., Pathology. 40 (2008) 46-51.
589 [30] Young AJ. Homeostatic Responses to Prolonged Cold Exposure: Human
590 Cold Acclimatization. John Wiley & Sons, Inc.; 2010.
591 [31] Andersen KL, Loyning Y, Nelms JD, Wilson O, Fox RH, Bolstad A,
592 Metabolic and thermal response to a moderate cold exposure in nomadic
593 Lapps., J Appl Physiol. 15 (1960) 649-653.
594 [32] Stromme S, Andersen KL, Elsner RW, Metabolic and thermal responses
595 to muscular exertion in the cold., J Appl Physiol. 18 (1963) 756-763.
596 [33] Kreider MB, Iampietro PF, Buskirk ER, Bass DE, Effect of continuous
597 cold exposure on nocturnal body temperature of man., Tech Rep CP.
598 117 (1959) 1-6.
599 [34] Siems WG, Brenke R, Sommerburg O, Grune T, Improved antioxidative
600 protection in winter swimmers., QJM. 92 (1999) 193-198.
601 [35] Fujita J, Cold shock response in mammalian cells., J Mol Microbiol
602 Biotechnol. 1 (1999) 243-255.
603 [36] Lindquist JA, Brandt S, Bernhardt A, Zhu C, Mertens PR, The role of
604 cold shock domain proteins in inflammatory diseases., J Mol Med (Berl).
605 92 (2014) 207-216.
606 [37] Holland DB, Roberts SG, Wood EJ, Cunliffe WJ, Cold shock induces the
607 synthesis of stress proteins in human keratinocytes., J Invest Dermatol.
608 101 (1993) 196-199.

609 [38] Rada A, Merentes E, Rodríguez M, Anselmi G, Strauss M, Human
610 hepatoma cell line (HepG2) cellular response to hypothermic stress with
611 recovery. Induction of Hsp70, Hsp60 and Hsf1 expression., Invest Clin.
612 51 (2010) 479-488.
613 [39] Lunt HC, Barwood MJ, Corbett J, Tipton MJ, Cross-adaptation':
614 habituation to short repeated cold-water immersions affects the response
615 to acute hypoxia in humans., J Physiol. 588 (2010) 3605-3613.
616 [40] Pearse RM, Moreno RP, Bauer P et al., Mortality after surgery in Europe:
617 a 7 day cohort study., Lancet. 380 (2012) 1059-1065.
618 [41] Desborough JP, The stress response to trauma and surgery., Br J
619 Anaesth. 85 (2000) 109-117.
620 [42] Huttunen P, Rintamäki H, Hirvonen J, Effect of regular winter swimming
621 on the activity of the sympathoadrenal system before and after a single
622 cold water immersion., Int J Circumpolar Health. 60 (2001) 400-406.
623 [43] Hermanussen M, Jensen F, Hirsch N et al., Acute and chronic effects of
624 winter swimming on LH, FSH, prolactin, growth hormone, TSH, cortisol,
625 serum glucose and insulin., Arctic Med Res. 54 (1995) 45-51.
626 [44] Misra HP, Fridovich I, The univalent reduction of oxygen by reduced
627 flavins and quinones., J Biol Chem. 247 (1972) 188-192.
628 [45] Martin D, Windsor J, From mountain to bedside: understanding the
629 clinical relevance of human acclimatisation to high-altitude hypoxia.,
630 Postgrad Med J. 84 (2008) 622-627.
631 [46] West JB, Lahiri S, Maret KH, Peters RM, Jr., Pizzo CJ, Barometric
632 pressures at extreme altitudes on Mt. Everest: physiological significance,
633 J Appl Physiol. 54 (1983) 1188-1194.

634 [47] Ernsting J, The effect of brief profound hypoxia upon the arterial and
635 venous oxygen tensions in man., J Physiol. 169 (1963) 292-311.
636 [48] Stroncek DF, Egging MS, Eiber GA, Clay ME, Neutrophil alloantibodies
637 react with cytoplasmic antigens: a possible cause of false-positive
638 indirect immunofluorescence assays for antibodies to neutrophil
639 cytoplasmic antigens., Am J Kidney Dis. 21 (1993) 368-373.
640 [49] Butterfield GE, Gates J, Fleming S, Brooks GA, Sutton JR, Reeves JT,
641 Increased energy intake minimizes weight loss in men at high altitude., J
642 Appl Physiol (1985). 72 (1992) 1741-1748.
643 [50] Martin DS, Ince C, Goedhart P, Levett DZ, Grocott MP, Abnormal blood
644 flow in the sublingual microcirculation at high altitude., Eur J Appl
645 Physiol. 106 (2009) 473-478.
646 [51] Martin DS, Goedhart P, Vercueil A, Ince C, Levett DZ, Grocott MP,
647 Changes in sublingual microcirculatory flow index and vessel density on
648 ascent to altitude., Exp Physiol. 95 (2010) 880-891.
649 [52] Edwards LM, Murray AJ, Tyler DJ et al., The effect of high-altitude on
650 human skeletal muscle energetics: P-MRS results from the Caudwell
651 Xtreme Everest expedition., PLoS One. 5 (2010) e10681.
652 [53] Levett DZ, Vigano A, Capitanio D et al., Changes in muscle proteomics
653 in the course of the Caudwell Research Expedition to Mt. Everest.,
654 Proteomics. 15 (2015) 160-171.
655 [54] Levett DZ, Radford EJ, Menassa DA et al., Acclimatization of skeletal
656 muscle mitochondria to high-altitude hypoxia during an ascent of
657 Everest., FASEB J. 26 (2012) 1431-1441.
658 [55] Siervo M, Riley HL, Fernandez BO et al., Effects of prolonged exposure

659 to hypobaric hypoxia on oxidative stress, inflammation and gluco-insular
660 regulation: the not-so-sweet price for good regulation., PLoS One. 9
661 (2014) e94915.
662 [56] Puthucheary ZA, Rawal J, McPhail M et al., Acute skeletal muscle
663 wasting in critical illness., JAMA. 310 (2013) 1591-1600.
664 [57] Brealey D, Brand M, Hargreaves I et al., Association between
665 mitochondrial dysfunction and severity and outcome of septic shock.,
666 Lancet. 360 (2002) 219-223.
667 [58] Beall CM, Reichsman AB, Hemoglobin levels in a Himalayan high
668 altitude population., Am J Phys Anthropol. 63 (1984) 301-306.
669 [59] Kayser B, Hoppeler H, Claassen H, Cerretelli P, Muscle structure and
670 performance capacity of Himalayan Sherpas., J Appl Physiol (1985). 70
671 (1991) 1938-1942.
672 [60] Erzurum SC, Ghosh S, Janocha AJ et al., Higher blood flow and
673 circulating NO products offset high-altitude hypoxia among Tibetans.,
674 Proc Natl Acad Sci U S A. 104 (2007) 17593-17598.
675 [61] Hoppeler H, Vogt M, Muscle tissue adaptations to hypoxia., J Exp Biol.
676 204 (2001) 3133-3139.
677 [62] Gelfi C, De Palma S, Ripamonti M et al., New aspects of altitude
678 adaptation in Tibetans: a proteomic approach., FASEB J. 18 (2004) 612-
679 614.
680 [63] Moore LG, Human genetic adaptation to high altitude., High Alt Med Biol.
681 2 (2001) 257-279.
682 [64] Narravula S, Colgan SP, Hypoxia-inducible factor 1-mediated inhibition
683 of peroxisome proliferator-activated receptor alpha expression during

hypoxia., J Immunol. 166 (2001) 7543-7548.

[65] Liu J, Li Y, Verheyden B et al., Orthostatic Intolerance Is Independent of the Degree of Autonomic Cardiovascular Adaptation after 60 Days of Head-Down Bed Rest., Biomed Res Int. 2015 (2015) 896372.

[66] Manzey D, Lorenz B, Poljakov V, Mental performance in extreme environments: results from a performance monitoring study during a 438-day spaceflight., Ergonomics. 41 (1998) 537-559.

[67] Nicogossian A, Hoffler GW, Johnson RL, Gowen RJ, Determination of cardiac size following space missions of different durations: the second manned Skylab mission., Aviat Space Environ Med. 47 (1976) 362-365.

[68] Cooke WH, Ames JE IV, Crossman AA et al., Nine months in space: effects on human autonomic cardiovascular regulation., J Appl Physiol (1985). 89 (2000) 1039-1045.

[69] Thomas DC, Kreizman IJ, Melchiorre P, Ragnarsson KT, Rehabilitation of the patient with chronic critical illness., Crit Care Clin. 18 (2002) 695-715.

[70] Vico L, Collet P, Guignandon A et al., Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts., Lancet. 355 (2000) 1607-1611.

[71] Sibonga JD, Evans HJ, Sung HG et al., Recovery of spaceflight-induced bone loss: bone mineral density after long-duration missions as fitted with an exponential function., Bone. 41 (2007) 973-978.

[72] Lloyd SA, Morony SE, Ferguson VL et al., Osteoprotegerin is an effective countermeasure for spaceflight-induced bone loss in mice., Bone. 81 (2015) 562-572.

[73] Trappe S, Costill D, Gallagher P et al., Exercise in space: human skeletal muscle after 6 months aboard the International Space Station., J Appl Physiol (1985). 106 (2009) 1159-1168.

[74] Ikemoto M, Nikawa T, Takeda S et al., Space shuttle flight (STS-90) enhances degradation of rat myosin heavy chain in association with activation of ubiquitin-proteasome pathway., FASEB J. 15 (2001) 1279-1281.

[75] Ikemoto M, Nikawa T, Kano M et al., Cysteine supplementation prevents unweighting-induced ubiquitination in association with redox regulation in rat skeletal muscle., Biol Chem. 383 (2002) 715-721.

[76] Wang E, Age-dependent atrophy and microgravity travel: what do they have in common, FASEB J. 13 Suppl (1999) S167-74.

[77] Krasnoff J, Painter P, The physiological consequences of bed rest and inactivity., Adv Ren Replace Ther. 6 (1999) 124-132.

[78] Nierman DM, Mechanick JI, Bone hyperresorption is prevalent in chronically critically ill patients., Chest. 114 (1998) 1122-1128.

[79] Plank LD, Connolly AB, Hill GL, Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis., Ann Surg. 228 (1998) 146-158.

[80] Schmittinger CA, Dünser MW, Torgersen C et al., Histologic pathologies of the myocardium in septic shock: a prospective observational study., Shock. 39 (2013) 329-335.

[81] Holst LB, Haase N, Wetterslev J et al., Lower versus higher hemoglobin threshold for transfusion in septic shock., N Engl J Med. 371 (2014) 1381-1391.

[82] Panwar R, Hardie M, Bellomo R et al., Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial., Am J Respir Crit Care Med. 193 (2016) 43-51.

[83] Hickling KG, Henderson SJ, Jackson R, Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome., Intensive Care Med. 16 (1990) 372-377.

[84] Helmerhorst HJ, Schultz MJ, van der Voort PH et al., Effectiveness and Clinical Outcomes of a Two-Step Implementation of Conservative Oxygenation Targets in Critically Ill Patients: A Before and After Trial., Crit Care Med. 44 (2016) 554-563.

[85] Reitz CJ, Martino TA, Disruption of Circadian Rhythms and Sleep on Critical Illness and the Impact on Cardiovascular Events., Curr Pharm Des. 21 (2015) 3505-3511.

[86] Green DA, How the UK Can Lead the Terrestrial Translation of Biomedical Advances Arising from Lunar Exploration Activities, Earth, Moon, and Planets. 107 (2010) 127-146.

FIGURES

Figure 1. The main physiological constraints determining human survival on Earth.

Less than a sixth of the Earth's surface can be permanently inhabited; the rest is either covered by water or lies outside the tolerable zones of pressure and temperature. Away from the Earth's surface, gravity and the protective effect of the magnetosphere are dramatically diminished.

Figure 2. The decline in barometric pressure (P_B) on ascent to altitude. P_B determines the oxygen partial pressure at any given altitude.

The summit of Mt Everest (8848m) is close to the limit of human tolerance to hypoxia and the Armstrong limit line is the altitude at which free water spontaneously vaporises.