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

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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 pumps 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°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°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
a sustained increase in body temperature by 1-2°C, can activate a cellular acclimation responses [24]. This may account for part of the enhanced physiological reserve observed in physically fit individuals (in addition to their superior cardiorespiratory function). Cell adaptation may also be triggered pharmacologically: a molecular activator called BCP-15 increases expression of HSP72 and improves inflammation and metabolic homeostasis in a rat model of type 2 diabetes [28]. In the future, administration of such agents could offer a means of preserving cell integrity and function during critical illness. In situations where future pathophysiological stress can be predicted, such as planned major surgery, programmes of exercise or heat acclimation could be employed to prime the cytoprotective response. There is a need for further clinical research in this area, which has the potential to extend the supportive therapy in critical care beyond modification of systemic responses.

**ADAPTATION TO COLD STRESS**

The physiological stress of cold exposure occurs through progressive slowing of vital chemical reactions; the Arrhenius principle states that metabolic rate will halve for every 10°C decrease in temperature. Diminished activity of ion channels reduces the rate at which excitable cells can conduct impulses and death may result from central nervous system dysfunction or cardiac arrhythmia. [29] To protect cells against these effects, the body has an acute systemic response to restore the core temperature: minimising heat loss through peripheral vasoconstriction and increasing heat generation by shivering. Below 35°C, the function of the tissues coordinating the systemic 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 °C water during the winter, undergo a drop in core temperature to 35 °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 (PO₂) 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
subjects on which current ‘standard’ targets are based. We may need to reconsider what constitutes ‘normal’ in this cohort and begin to develop and evidence base to define future targets. However, determining which phenotypes are associated with better outcomes, and are thus worth supporting through medical intervention, is hindered by the mass of confounding factors that influence survival in the context of critical illness. Observations of how humans grow and thrive under profound and prolonged environmental stress may guide us. Acclimatisation and genetic adaptation to different environmental extremes often appear to involve a resetting of homeostasis to a new set point, which could thus represent valid alternative approach to emulate in our attempts to promote survival during the sustained stress of critical illness. We are now beginning to recognise the importance of the role of innate intracellular mechanisms, such as the HSP and HIF systems, in sensing and defending against stress. The field of chronobiology, in which the timing of molecular events within the cell are co-ordinated by global rhythms, is now emerging as a significant factor influencing physiology in critical illness [85]. These ancient cytoprotective responses remain untapped by current clinical interventions. Animal models may help to further our understanding in this field, but they are notoriously unrepresentative of the human response in some conditions [5]. Humans exposed to physiological stress in laboratories or in the field could provide a more robust model, in which the translation to critical illness is more direct. The phenomenon of cross-adaptation, in which acclimatisation to one form of stress (such as heat) can improve tolerance to another (such as hypoxia), through activation of a 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

$P_a$: atmospheric partial pressure (of a gas)

$P_B$: barometric pressure

PPARα: peroxisome proliferator-activated receptor alpha

ROS: reactive oxygen species

$\text{VO}_2\text{peak}$: peak oxygen uptake

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

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CONSENT FOR PUBLICATION

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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.