2020-10-01

Human adaptation to hypoxia in critical illness

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10.1152/japplphysiol.00818.2019
Journal of Applied Physiology
American Physiological Society

Invited Mini-Review for Journal of Applied Physiology

Title: Human adaptation to hypoxia in critical illness

Key words:

Critical illness, intensive care, hypoxia, mitochondria, energy metabolism, oxidative stress

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Running head: Hypoxia and critical illness

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Abstract

The syndrome of critical illness is a complex physiological stressor that can be triggered by diverse pathologies. It is widely believed that organ dysfunction and death result from bioenergetic failure caused by inadequate cellular oxygen supply. Teleologically, life has evolved to survive in the face of stressors by undergoing a suite of adaptive changes. Adaptation not only comprises alterations in systemic physiology but also involves molecular reprogramming within cells. The concept of cellular adaptation in critically ill patients is a matter of contention, in part because medical interventions mask underlying physiology, creating the artificial construct of "chronic critical illness", without which death would be imminent. Thus far, the intensive care armamentarium has not targeted cellular metabolism to preserve a temporary equilibrium, but instead attempts to normalize global oxygen and substrate delivery. Here, we review adaptations to hypoxia that have been demonstrated in cellular models and in human conditions associated with hypoxia, including the hypobaric hypoxia of high altitude, the intrauterine low oxygen environment and adult myocardial hibernation. Common features include upregulation of glycolytic ATP production; enhancement of respiratory efficiency; downregulation of mitochondrial density and suppression of energy-consuming processes. We argue that these innate cellular adaptations to hypoxia represent potential avenues for intervention that have thus far remained untapped by intensive care medicine.

Introduction

Critical illness is defined loosely as a pathophysiological state in which artificial organ support is required to maintain systemic homeostasis. A key feature of critical illness is organ dysfunction, which may progress to involve multiple organs (multiple organ failure). The acute risk of death is very high, despite organ support on the intensive care unit (ICU), and increases with the severity of organ failure (52). Critical illness can be triggered by diverse insults, such as severe infection, inflammation and trauma, which, via activation of the hypothalamic-pituitary-adrenal axis, elicit a wide-ranging array of downstream effects on cardiovascular, renal, pulmonary, gastrointestinal, neuroendocrine, immune and coagulation systems (49, 91). The mechanisms underlying cellular dysfunction in critical illness are not well understood, but it has long been assumed that disturbances to convective oxygen (O_2) transport and microcirculatory blood flow result in a critical reduction in cellular O_2 availability and are thus responsible for bioenergetic collapse. Cells require O_2 to synthesize most of their usable energy currency, adenosine triphosphate (ATP), from nutritional energy sources. In most organisms, the vast majority of O_2 consumed by cells (up to 98% in humans) occurs in support of the production of ATP through mitochondrial oxidative phosphorylation. Below a critical threshold, a diminished cellular O_2 availability will limit the bioenergetic capacity of the cell and thus its ability to power processes essential for the organism and its own cell function and integrity (11). To this end, the majority of supportive therapies on the ICU target the restoration or augmentation of O_2 delivery, including: supplementation of inspired O_2 concentration; mechanical ventilation; red cell transfusion; and optimization of cardiac output and mean arterial pressure through administration goal-directed fluid therapy and the administration of of inotropes and vasopressors. However, recent randomized controlled trials have not demonstrated survival benefit from early goal-directed therapy (53, 64) and augmentation of systemic O_2 delivery (88) in critically ill patients (60); in some cases, this therapeutic approach

has even been associated with harm (32, 48). There is evidence that cellular hypoxia exists in critical illness, even after restoration of arterial partial pressure of O_2 (PaO_2) and O_2 hemoglobin saturation (SpO_2) (68). This is likely to be a consequence of disturbances to microcirculatory blood flow, which have been described in critical illness (18). Moreover, therapeutic use of vasopressor support, whilst augmenting upstream arterial pressure, may itself adversely affect microcirculatory flow regulation (2). The persistence of microcirculatory impairment despite corrected systemic hemodynamics is associated with increased mortality (73). Current ICU strategies do not take into consideration the multitude of well-defined adaptive responses to cellular hypoxia (75). Development of life-support strategies in critical illness will require greater understanding of the processes that govern bioenergetic function and cell survival in humans during hypoxia. In this mini-review, we outline aspects of cellular adaptation to hypoxia, gained from cell models of hypoxia, as well as from studies of humans under hypoxic conditions, and consider how they may be relevant to the treatment of critically ill patients.

The adaptive response to cellular hypoxia

All multicellular organisms have the capacity to sense and respond to a decline in cellular O_2 availability (39). Whilst plants and animals employ different molecular mechanisms to do so (47), the conservation of this ability across kingdoms of life highlights its universal importance for survival. In 2019, the Nobel Prize for Physiology or Medicine was awarded for the discovery of how animal cells adapt to variations in O_2 supply, by undergoing coordinated shifts in gene expression. The combined work of three groups, respectively led by Gregg Semenza, Peter Ratcliffe and William Kaelin Jr, identified the hypoxia inducible factor (HIF) pathway as a mechanism by which, under hypoxic conditions, an O_2-sensitive transcription factor (HIF) alters gene expression to generate a phenotype with enhanced tolerance to hypoxia

(75). HIF-activation is now understood to regulate the expression of thousands of genes, either directly or indirectly (74). The binding of HIF to a given gene locus is strongly associated with increased expression of that target (74, 84), however HIF-activation can also result in the downregulation of gene expression via an indirect route, by increasing the expression of transcriptional repressors (74). Downstream targets of HIF include proteins responsible for increasing systemic O_2 transport via elevation of hemoglobin concentration (erythropoietin) (30) as well as proteins which promote local microcirculatory blood flow through angiogenesis (vascular endothelial growth factor) (43) and vasodilatation (nitric oxide synthase) (62). However, cellular models have demonstrated a crucial part of the HIF response involves metabolic modifications, which alter the utilization of O_2. These include upregulation of glycolytic ATP production; modifications to promote the efficiency of mitochondrial oxidative phosphorylation; and suppression of energy-expending processes.

Metabolic adaptations to hypoxia

A key metabolic modification promoted by HIF is the upregulation of ATP production in an O_2-independent manner via cytosolic glycolysis. HIF mediates a switch away from oxidative phosphorylation and towards glycolysis via the upregulation of glucose transporters and glycolytic enzymes (77), in conjunction with an increase in lactate dehydrogenase and pyruvate dehydrogenase kinase 1 expression, which regenerates the NAD^+ required to permit glycolysis to continue by shunting the end-product of glycolysis, pyruvate, away from the Krebs cycle and towards lactate production (40, 63).

A second, important bioenergetic adaptation to hypoxia mediated by HIF is enhancement of the efficiency of mitochondrial oxidative phosphorylation with respect to O_2 consumption. One mechanism by which it may achieve this is through substrate-switching. Respiration

supported by fatty acid oxidation (FAO) produces fewer ATP molecules per mole of O_2 consumed, compared with carbohydrate oxidation (87). It is estimated that the oxidation of fatty acids, which are highly reduced, requires 11-12% more O_2 to produce the same amount of ATP as the complete oxidation of glucose (80). Cells can alter their metabolic fuel use to optimize efficiency in response to reduced oxygen availability. One of the downstream targets of HIF is another transcription factor, peroxisome proliferator-activated receptor-alpha (PPARα), which regulates the expression of genes involved in FAO as well as inflammatory mediators (55). Acting through the suppression of PPARα, HIF-1α mediates a substrate switch away from FAO, and thereby improves the efficiency of respiration. One possible consequence of a switch towards enhanced glucose oxidation, however, is the higher yield of CO_2 per ATP produced, compared with FAO. The pathophysiological consequences of this for the critically ill patient are unclear, however, in the case of severe pulmonary injury/disease this could conceivably worsen respiratory acidosis if means of lowering CO_2 production or enhancing its elimination are either absent or prove ineffective.

Another means by which HIF optimizes the efficiency of respiration is by increasing the coupling of mitochondrial electron transport (and O_2 consumption) to ATP production. During oxidative phosphorylation, the energy generated by sequential electron transfer from metabolic substrates, through the mitochondrial electron transport chain, to O_2 is used by mitochondrial membrane complexes to pump protons against a concentration gradient into the intermembrane space. The discharge of the gradient (protonmotive force) generated by this process drives the phosphorylation of ATP (51). Not all of the pumped protons flow through the F_1F_O-ATPase; some "leak" back across the inner membrane, through respiratory complexes themselves or through specific uncoupling proteins (UCPs) (10). Cells can modulate the permeability of their mitochondrial inner membrane to protons, through altered expression/activity of UCPs (9).

Minimizing proton leak has been shown to preserve ATP production in mammalian liver cells in which substrate oxidative capacity was reduced by low temperatures (67). There is evidence that HIF promotes the coupling efficiency of oxidative phosphorylation (24); and one of the downstream targets of PPARα is an uncoupling protein (UCP3) (85).

Exposure to hypoxia also reduces energy expenditure, at least in part through the active suppression of protein synthesis, which falls dramatically (35). In particular, HIF may preserve tolerance to hypoxia through a reduction in mitochondrial number. Mitochondrial autophagy relies on the HIF-dependent expression of BNIP3, and this has been argued to minimize cell damage and death from exposure to oxidative stress generated by hypoxic mitochondria (90). Whilst it was once considered controversial, there is significant evidence to support increased mitochondrial reactive oxygen species (ROS) production upon the transition to hypoxia, with the appearance of markers of oxidative stress in skeletal muscle upon sustained exposure to hypoxia (16). Whilst a moderate degree of mitochondrial ROS production is understood to play a vital, signaling role in the cellular response to hypoxia (29, 31), in chronic and severe hypoxia excess ROS production could result in cellular damage.

Evidence for cellular adaptation to hypoxia in humans

Aspects of this adaptive phenotype, shown to be elicited by the HIF pathway in cell models, have also been observed in human conditions associated with hypoxia (76) or disruption of the HIF-signaling pathway (20, 66). For example, during acclimatization to hypobaric hypoxia on ascent to high altitude, lowlander skeletal muscle undergoes a metabolic shift towards glycolysis, in conjunction with the depletion of some Krebs cycle intermediates and enzymes (45). Such lowlander subjects also exhibit a trend towards increased coupling efficiency as well as a decrease in the mitochondrial capacity for respiration supported by FAO and

decreased expression of FAO enzymes (36). Mitochondrial bioenergetic machinery in skeletal muscle is also depleted, with specific decreases in components of the electron transport chain (complexes I and IV) (44) as well as an overall reduction in mitochondrial volume density and downregulation of electron transport capacity (36). This may represent a temporary protective strategy to reduce the generation of mitochondrial ROS (16). In another study, exposure to 28 days of hypobaric hypoxia triggered bioenergetic changes independent of mitochondrial content, including specific inhibition of complex I-supported respiration and FAO, along with an increase in coupling efficiency (37). Inhibition of complex I has previously been shown to reduce oxidative damage during myocardial ischemia (15), and thus its reduced capacity at high altitude is consistent with a protective cell modification to hypoxia.

Generational adaptation in Sherpas may represent the optimal metabolic phenotype in chronic hypoxia

In at least three geographically-distinct regions of the world, human populations have been established at high altitude for sufficient time to allow the selection of physiological traits, underpinned by genetic variants, that support life in conditions of sustained hypobaric hypoxia (5), including a number of metabolic adaptations (58). The phenotypes exhibited by these populations at high altitude may therefore represent optimal human physiology under conditions of sustained hypoxia, and could prove informative when considering the appropriate cellular response to the pathology of chronic critical illness. Populations on the Andean Altiplano, the Tibetan Plateau and in the Ethiopian Highlands, have undergone natural selection on gene loci, including *EPAS1* (encoding HIF-2α) and *EGLN1* (encoding PHD2). In Tibetan populations, high altitude variants in *EPAS1* and *EGLN1* are associated with a relative suppression in erythrocytosis (6) and increased glycolysis (26).

The Himalayan Sherpas, a group descended from Tibetan populations, are thought to have been exposed to extreme environmental hypoxia for 300 generations, and combine an unparalleled functional tolerance to hypoxia with a skeletal muscle phenotype that is distinct from other populations (27). Compared to acclimatized lowlanders, Sherpas display greater glycolytic capacity, lower skeletal muscle capacity for FAO and enhanced coupling efficiency (36), associated with increased incidence of a putatively-adaptive haplotype of *PPARA* (encoding PPARα) (79), and this has been proposed to underpin their superior cellular energetics and performance at high altitude. Whilst downregulation of FAO in lowlanders creates a metabolic bottleneck, resulting in an increased ratio of long-chain to total carnitines (36), this accumulation of lipotoxic intermediates (41) does not occur in Sherpas. Avoidance of this toxicity may be a crucial discriminator between the Sherpa and lowlander hypoxic phenotype. Although the mechanism is unclear, it may involve non-mitochondrial FAO via omega-oxidation (7, 86). Sherpa muscle also appears to be relatively resistant to oxidative damage at altitude, compared to lowlanders (36). This finding, together with their lower maximum oxidative phosphorylation capacity and lower mitochondrial volume density supports the concept that reduced mitochondrial capacity in hypoxic conditions may be protective against ROS production.

Hypoxic adaptation in the fetal heart

The developing fetal heart thrives in the hypoxic intrauterine environment through appropriate substrate selection (70). It relies exclusively on glycolysis, with suppression of oxidative pathways until after birth (4). The metabolic phenotype is achieved by the action of a transcription factor, Hand1, which specifically represses the expression of proteins involved in FAO and the Krebs cycle, by directly binding to and repressing the gene promoters. Hand1 is under direct transcriptional control by HIF1. It is abundant in fetal cardiomyocytes but

undergoes a sharp drop soon after birth (56). The Hand1-triggered substrate switch demonstrates the potential survival benefit from upregulating glycolytic ATP production, and downregulating O_2-dependent pathways when oxygen availability is limited. It also highlights the importance of being able to switch back when oxygen becomes available, as after birth, failure to deactivate Hand1 results in rapid death.

Hypoxic adaptation in adult chronic heart failure

Expression of a fetal gene program can be induced in adult hearts during hypoxia (70). Substrate reprogramming, with a switch away from FAO, is also inducible in adult cardiac muscle in response to cellular hypoxia (80). In animal models of adult heart failure, including pressure overload hypertrophy, PPARα is deactivated and downregulated, resulting in reduced expression of its downstream targets, which include FAO enzymes (3). Clinical benefit from FAO downregulation relies on a compensatory increase in carbohydrate metabolism, and is abolished in the absence of glucose (59, 71). In a mouse model of pressure overload-induced ventricular hypertrophy, upregulation of the glucose transporter (GLUT1) prevented the decline in contractile function (46), and preserved mitochondrial function (65). Mutant adult hearts overexpressing Hand1 show enhanced tolerance to acute ischemic insults and its expression and resulting fetal phenotype can be induced in adult hearts by chronic exposure to hypoxia. Chronic reduction in coronary blood flow reduces resting energy consumption and downregulation of mitochondrial electron transport chain proteins (12). These chronic changes are accompanied by the depletion of contractile elements and contractile function, but also a reduced cellular demand for oxygen and substrate. The downregulation is initially reversible, but when prolonged, can result in inflammation, fibrosis and remodeling (22).

Features of hypoxic adaptation observed in critical illness

Critically ill patients are subject to multiple physiological stressors, in addition to cellular hypoxia, including inflammatory mediators and other biochemical derangements. Due to this heterogeneity, and the masking effects of ICU interventions, combined with the inherent challenges involved in studying cell biology directly in this context, it is not known if cellular adaptation to hypoxia occurs in critically ill patients. Evidence in favor of a hypoxia response includes the demonstration of elevated levels of intramuscular HIF1 in a group of 23 critically ill patients, in which there was also evidence of substrate switching, with decreasing concentrations of FAO enzymes from Day 1 to 7, as well as decreased markers of mitochondrial biogenesis (68). Skeletal muscle bioenergetics, using ATP concentrations as a surrogate marker, have been shown to be lower in some studies of critically ill patients compared with healthy controls (23) or ambulant patients with respiratory disease (68), and a relative reduction in whole-body O_2 consumption has been demonstrated in patients with organ impairment compared with those with uncomplicated infections (42). Meanwhile, the incubation of healthy human cells in serum from septic patients was shown to suppress mitochondrial respiration, suggesting a generalized cellular metabolic response to infection, which may be coordinated systemically (25). Rapid and severe muscle wasting is a well-known feature of critical illness, associated with decreased protein synthesis (69), mirroring the suppression of this energy-expending process in cell models of hypoxia (13) and in healthy humans ascending to high altitude (19). Although these findings have previously been proposed to support the concept of bioenergetic collapse in organ failure, they share many features of the cellular response to hypoxia mediated by the HIF pathway (Figure 1).

Targeting the cellular hypoxia response in critically ill patients

The failure of current strategies in critical illness, which target systemic O_2 transport and hemodynamics, may reflect the failure to take account of cellular survival responses. Similarly,

targeting the delivery of nutritional energy to meet calorie requirements defined in health, whilst neglecting mitochondrial substrate preference, has not improved survival (1, 14). It is possible that both approaches interfere with hypoxia-signaling pathways, or impose a different form of cell stress, and in doing so contribute to a new pathophysiological state in patients who do not succumb to their acute insult: "chronic critical illness" (62).

The potential benefit of adjusting the composition of upstream substrate supply e.g. carbohydrate-to-fat ratio in feeding regimens represents one simple avenue for investigation. Rather than trying to reverse the catabolic response to critical illness, the therapeutic benefit of supporting it, for example via exogenous administration of ketone bodies and amino acids should be investigated (17, 54). It may also be possible to target the entire suite of cellular adaptations in a coordinated manner, through activation of the HIF pathway itself (8). Pharmacological stabilization of HIF through administration of prolyl hydroxylase inhibitors has been trialed in stable patients with renal anemia, although there are concerns about the possibility of these agents promoting tumor growth (38). In animal models, activation of HIF1 has shown to reduce inflammation and bone loss in periodontal infection and suppress LPS-stimulated macrophage differentiation (33).

There has been renewed interest in the therapeutic potential of vitamin C administration for patients with sepsis and acute respiratory distress syndrome (ARDS). Putative protective roles for ascorbate of relevance to hypoxia-sensing and redox homeostasis might arise from its function as an antioxidant (61) and/or its role as a co-factor for the prolyl hydroxylases (34) albeit a dispensable one (57). In a recently-reported study of 167 patients with sepsis and ARDS (CITRIS-ALI), however, high-dose vitamin C infusion did not improve organ dysfunction scores or alter markers of inflammation and vascular injury compared with placebo (21).

The complex nature of the HIF-supported response to hypoxia, encompassing both cellular and systemic effects, suggests that some caution should be exerted when targeting HIF activity in a global manner. Indeed, HIF-activation itself might exert detrimental effects depending on the duration and/or tissue specific nature of the underlying hypoxia. For instance, HIF activation is strongly associated with pulmonary vascular responses to both acute and chronic hypoxia including hypoxic pulmonary vasoconstriction (HPV) (78). HPV appears to improve ventilation/perfusion ($\dot{V}A/\dot{Q}$) matching in patients with ARDS and acute lung injury (ALI) (83), but at the cost of increased pulmonary arterial pressure (72). Moreover, HIF-1α activation in type 2 alveolar epithelial cells is associated with increased inflammation and worsened injury in mice following lung contusion (82) and gastric acid aspiration-induced lung injury (81). Ultimately, therapeutic approaches that consider the nature of the underlying pathology and selectively target downstream elements of HIF-activation, possibly in a time/tissue-dependent manner might prove more effective than more global approaches.

An alternative means of targeting the HIF pathway may be to avoid the obscuration of hypoxic signaling, by implementing ventilatory strategies which either target so-called "permissive hypoxaemia" (otherwise known as conservative oxygen therapy) in critically ill patients or at least prevent hyperoxia. Studies comparing a conservative oxygenation intervention with virtually normal oxygenation are currently being undertaken (4, 89), whilst the avoidance of hyperoxia whilst maintaining normal arterial oxygen saturation is also currently under investigation (28). A greater understanding of dose-response relationships in critical illness adaptation is required to translate this approach safely to patients (50).

Conclusion

Thus far, supportive therapy on ICU has neglected to consider the fundamental processes of cellular adaptation to hypoxia, which are known to be vital for the survival of all complex organisms. Cells can implement O_2-independent ATP production, alter metabolic fuel preference and "tune" down mitochondrial proton leak, in a highly regulated manner, to modulate bioenergetic efficiency in response to reduced O_2 availability. They may also downregulate mitochondrial density and activity to limit exposure to mitochondrial-generated ROS; and suppress energy expenditure. Several of these cellular modifications are consistent with changes observed in critically ill patients, supporting the concept that organ dysfunction may, in part, represent an evolutionarily conserved strategy of cellular reprogramming to limit damage during hypoxic stress. Review of hypoxic adaptation in different contexts has demonstrated novel therapeutic avenues to investigate in the critically ill patient. During the precipitating phase of critical illness, preventing hypoxia may circumvent deterioration into critical illness, but once organ dysfunction is underway, it may be more appropriate to support a more efficient cellular use of O_2, until the triggering disease process can be resolved. Currently, the manner in which cellular metabolism and mitochondrial function alter during different phases of critical illness, and how this influences clinical outcomes, is not well understood. Exploring the relationship between cellular hypoxia, bioenergetic capacity, redox signaling and cellular adaptation will be vital in harnessing innate adaptive strategies to improve survival in the sickest patients.

Disclosure

Daniel Martin has received lecture and consultancy fees for Edwards Lifesciences and Siemens Healthineers.

Figure Legend

Figure 1. Infographic showing aspects of the cellular/metabolic response to hypoxia observed in humans ascending to high altitude and critically ill patients.

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