

Physiological probability and pathophysiological responses to hypoxia: Mechanisms and clinical implications

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International Journal of Frontiers in Biology and Pharmacy Research, 2026, 09(02), 020-026

Publication history: Received on 06 March 2026; revised on 15 April 2026; accepted on 17 April 2026

Article DOI: <https://doi.org/10.53294/ijfbpr.2026.9.2.0016>

Abstract

Due to a lack of oxygen in the body (hypoxia), a cascade of physiological experiences occurs and leads to the final appearance of hypoxia-related processes aimed at preserving the functions of cells and overall homeostasis. The review will provide an overview of the current information on the acute and chronic adaptive responses to hypoxia, cardiopulmonary, metabolic reprogramming responses, hematological responses, and molecular response in hypoxia-inducible factors (HIFs). Also, it discusses maladaptive sequelae related to the long-term or excessive hypoxic exposure, including oxidative stress and inflammation and organ dysfunction. Clinical significance of this elucidation of these processes is immense to the diseases that involve high-altitude illness, chronic pulmonary disorders, ischemic disorders, and critical care. Knowledge of positive and negative impact of hypoxia could be utilized to inform treatment interventions and oxygen delivery strategies on optimization.

Keywords: Hypoxia; HIFs; Oxidative stress; Oxidative stress; Oxygen

1. Introduction

Oxygen is imperatively essential to aerobic existence, it is the ultimate donor of electrons during oxidative phosphorylation in the mitochondrions and it promotes efficient synthesis of adenosine triphosphate (ATP). The alteration even in the short-term in the oxygen supply can disrupt the homeostasis of the cellular energy and threaten the existence of the tissues[1]. One of the fundamental biological stressor that challenges homeostasis at the molecular, cellular and systemic levels is hypoxia, or the absence of oxygen in comparison with the metabolic requirements. It can either be the result of environmental factors (such as alveolar exposure to the high altitude) or pathology (e.g., respiratory diseases (e.g., chronic obstructive pulmonary disease and acute respiratory distress syndrome), cardiovascular insufficiency, anemia, sepsis, ischemic events)[2].

The pathological implications of hypoxia are not the only physiological implications. Angiogenesis and organogenesis are regulated in the context of controlled hypoxic microenvironment during embryonic development. Equally, transient tissue hypoxia is experienced during vigorous physical exercise and contributes to the adaptive conditioning. But beyond a certain level of compensatory capacity in severity or duration, oxygen deprivation triggers a cascade of maladaptive mechanisms which can culminate in dysfunctional cellular functions, organ failure or death[3].

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The adaptive responses notwithstanding Western pathological processes, chronic or excessive hypoxia is normally characterised by pathological remodelling, oxidative stress, inflammatory acidosis, and organ dysfunction. Persistent pulmonary vasoconstriction may cause pulmonary hypertension; persistent sympathetic stimulation may cause cardiac hypertrophy; and neurodegeneration and cognitive impairment are associated with cerebral hypoxia. Besides, intermittent hypoxia e.g. during an incidence of obstructive sleep apnea has also been of significance to the cause of cardiometabolic disease[6].

The last few decades have been marked by the emergence of the domain of molecular biology, systems physiology, and translational medicine that contributed to the analysis of the hypoxia-related signal profiles and their clinical evaluation. This has not only elucidated central adaptation pathways by having the oxygen sensing pathways discovered, but also provided therapeutic avenues such as pharmacological inhibition (modulation) of HIF-signaling and targeted oxygen delivery [7].

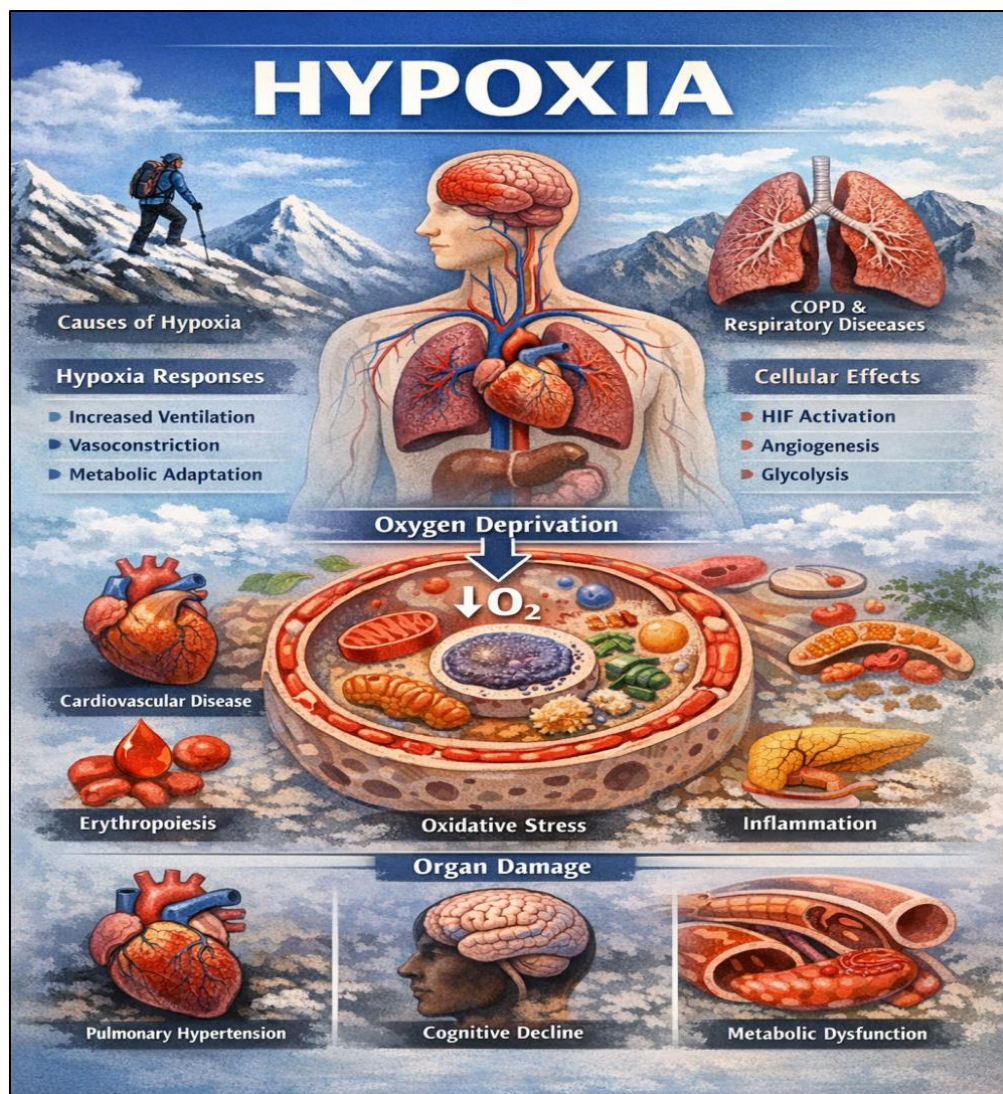


Figure 1 Multilevel Physiological Responses to Acute and Chronic Hypoxia

The purpose of this review is to offer a review of the physiological responses to acute and chronic hypoxia in an integrated, systemic, cellular, and molecular perspective. Moreover, it critically analyses the shift of adaptive to maladaptive pathology[8], which underscores the clinical significance of hypoxia in the interpretation of pulmonary, cardiovascular, neurological, and critical care environment. These mechanisms should be better understood in terms of building evidence-based interventions that are most effective to maximize the use of oxygen and minimize hypoxia-induced damage[9].

2. Acute Physiological Responses to Hypoxia

2.1. Respiratory Adjustments

The acute hypoxia stimulated the most immediate physiological reaction which is the ventilatory drive which is mainly stimulated by the carotid and the aortic body peripheral chemoreceptors. These are oxygen-sensitive receptors that detect the changes in the arterial oxygen tension and thus send the afferent information to respiratory centers of the medulla oblongata. Tidal volume and respiratory rate are then raised as a response; which causes hyperventilation, increasing the uptake of oxygen in the body by the alveoli, and diffusion across the alveolar-capillary membrane. This counter-mechanism reduces concurrently the level of carbon dioxide in the arteries thereby causing a reduction in PaCO₂ [10].

Since the rate at which carbon dioxide is released is higher than its production, the respiratory process of alkalosis can occur, which shifts blood pH towards alkalinity. The subsequent acidbase changes affect the hemoglobinoxygen affinity (Bohr effect) and this may further disrupt oxygen unloading (at tissue levels) and yet the tissue level of oxygen delivery is enhanced. In the short-term, compensatory mechanisms of renal buffering rises to compensate by raising bicarbonate excretion to set the pH at normal levels. All of these respiratory changes are evidence of the defensive response to stabilize oxygen delivery in acute hypoxic exposure and constitute a quick but significantly controlled effort [11].

2.2. Cardiovascular Modulation

The acute hypoxia is another cause provoking the great cardiovascular adaptations which occur primarily due to the stimulation of the sympathetic nervous system. Magnified catecholamine release agitates the heart rate and the myocardial contractility which amplifies the cardiac output in order to boost the delivery of oxygen to the body. Through peripheral vasoconstriction that occurs concurrently, the redistribution of blood is as a result of the prioritization of blood perfusion to the tissues with high metabolic requirements (the brain and heart) as it happens. These hemodynamic treatments are used to maintain arterial pressure and optimize the oxygen delivery process during periods of sudden reduction of ambient or arterial oxygen. [12].

Another phenomenon elicited by hypoxia in the pulmonary circulation is called hypoxic pulmonary vasoconstriction (HPV) wherein the small pulmonary arteries contract in the poorly ventilated areas of the lungs. This functioning increases ventilation matching perfusion by redirecting the blood to the more oxygenate alveoli, and thus enables the overall effectiveness of gas exchange. Whereas it is useful in localized hypoxia, extensive or chronic HPV can potentially raise the pressure of the pulmonary artery and strain the left ventricle of the heart. Therefore, acute cardiovascular modulation is initially helpful to the adaptive redistribution of oxygen but could be pathophysiologically important in case of prolonged hypoxic exposure [13].

3. Chronic Adaptations to Hypoxia

3.1. Hematological Adaptations

Hypoxia in chronic conditions leads to a long-term elevation in synthesis of renal erythropoietin (EPO) which is largely driven by oxygen-sensitive regulators of transcription that signal the decrease in tissue oxygen tension. High levels of EPO in circulation trigger the proliferation and differentiation of the erythroid precursors, in the bone marrow, and the growth of red blood cells mass and hemoglobin level [14]. The result of this hematological adjustments is an improvement of arterial oxygen-carrying capacity, as well as systemic oxygen delivery to peripheral tissues. In the long run, this could be supplemented with more hematocrit and the red cell deformability to be able to carry oxygen during moments of hypoxia. These compensatory mechanisms can especially be noted in people living in high altitude or in chronically pulmonary disease patients [15].

The hematocrit viscosity of the blood is increased resulting in an increase in the vascular resistance and cardiac workload. This hyperviscosity can undermine a microcirculatory circulation and prevent a successful tissue perfusion with increased oxygen levels [16]. Long-term augmentation of afterloaded might provoke ventricular hypertrophy and the augmentation of the risks of thromboembolic activity. Therefore, there is need to develop hematological adaptation in its initial protective fashion, but at one stage, the adaptive mechanism becomes more resilient than physiological performance causing extensive cardiovascular stress. [17].

3.2. Metabolic Reprogramming

Prolonged hypoxia at the cellular scale results in severe metabolic reorganization that is geared towards the preservation of energy production in the face of low oxygen concentration. In order to maintain the ATP production, the cells become more addicted to anaerobic glycolysis and decreased reliance on mitochondrial oxidative phosphorylation. Hypoxia-inducible factors, i.e., HIF-1 α and HIF-2 α that mediate the transcription of glucose transporters (GLUT1), glycolytic enzymes (hexokinase and lactate dehydrogenase), and factors involved in mitochondrial-remodeling mediate this transition of metabolism in many cases [18].

Hypoxia effects in human tissues include augmenting the glycolysis process, although it modifies the environment of the mitochondria, improving structural and functional aspects and minimizing the generation of reactive oxygen species and maximizing functionality. To utilize less oxygen, the cell can decrease the mitochondrial mass or alter the expression of enzymes. Even though such metabolic plasticity facilitates short- and medium-term adaptation, its result is the general increase in lactate levels and improper maintenance of intracellular pH. These long-term changes in biochemistry can result in tissue remodelling, and in pathology, in impaired metabolism of cells[19].

3.3. Vascular and Tissue Remodeling

Upregulation of the vascular endothelial growth factor (VEGF) and other pro-angiogenic mediators enhance endothelial cell proliferation, migration and capillary formation. The resultant increased density of the capillaries reduces the distance of diffusion needed to deliver oxygen and enhances the perfusion of tissues in the region. Such microvascular adaptations play an important role in maintaining the oxygen levels in the cells during conditions that are permanently hypoxic such as in high altitude or chronic lung disease. [20].

Along with angiogenesis, tissue remodelling induced by hypoxia maximizing oxygen consumption is also present. The chronic exposure of skeletal muscle may enhance the ratio of capillary to the fiber and relocate the mitochondria in closer association with the capillaries, which enables easier extraction of oxygen. Modulation of the extracellular matrix and vascular smooth muscle are also structural changes that can alter tissue compliance and perfusion dynamics. Although these changes tend to improve adaptive capacity, when overgrown or unregulated, remodelling may be the cause of pathological vascular alterations, such as pulmonary hypertension or fibrotic activities [21].

4. Cellular and Molecular Responses

4.1. Hypoxia-Inducible Factor (HIF) Pathway

The general regulating system in the responses of the cells to the low oxygen tension is Hypoxia-inducible factor (HIF) pathway. Under normal oxygen levels, the hydroxylases of oxygen-dependent prolyl hydroxylases hydroxylate HIF- α subunits that are ubiquitinated and degraded through proteasomes[22]. These enzymes are inactivated when oxygen concentration is reduced leading to stabilisation and cytoplasmic build-up of HIF- α proteins. The stabilized subunits move to the nucleus, dimerize with HIF- β and bind hypoxia-responsible elements (HREs) in target genes. This communication stimulates transcriptional pathways that promote glucose uptake, glycolysis, erythropoiesis, angiogenesis and cell survival [23].

Besides the metabolic regulation, the HIF signaling is also global, and short-term oxygen compensation is not limited to HIF signaling. It regulates iron usage, formation of the mitochondria and autophagy consequently making the functioning of cells in low oxygen levels easier[24]. HIF unique isoforms, especially HIF-1 and HIF-2 have tissue-specific roles and selective gene targets, which play a role in delicate physiological regulation. The pathological conditions associated with the dysregulation of this pathway include the development of cancer, chronic lung disease, and cardiovascular remodeling. Continuous activation of HIF can encourage maladjusted angiogenesis and metabolic reorganization, which is beneficial to the development of diseases. Hence, to ensure the balance between adaptive and maladaptive cellular functions, HIF activity needs to be accurately regulated[25].

4.2. Oxidative Stress and Inflammation

Hypoxia however strange, leads to increased generation of reactive oxygen species (ROS), especially in mitochondria, despite the drop in oxygen tension. The lack of the electron transport chain activity in low oxygen conditions results in the incomplete depletion of oxygen and increased the production of superoxide[26]. At regulated concentrations, ROS are signaling molecules, which strengthen hypoxia-sensitive pathways and regulate cell adaptation. They aid in stabilization of transcription factors, and regulate the expression of redox sensitive genes. This is a short-lived oxidative

signaling that is significant in cellular communication and adaptation to stress. Nonetheless, the fine tuning of the ROS production and antioxidant defences balance is essential in avoiding cell damage[27].

In cases where the production of ROS is excessive or too long, oxidative stress develops and alters the redox homeostasis of the cells. Cumulative oxidative aging impacts on membrane lipids and structural proteins and genomic DNA impairing cell integrity and cellular functionality. Pro-inflammatory transcription factors including NF- κ B are also activated by oxidative stress resulting in cytokine, chemokine, and adhesion molecule up-regulations[28]. Hypoxia, oxidative stress, and inflammation have been shown to interact especially in ischemia reperfusion injury, chronic cardiovascular diseases, and inflammatory lung diseases. The knowledge of these interconnected mechanisms can offer an underlying basis to the application of specific therapeutic interventions to minimize oxidative and inflammatory harm [29].

5. Pathophysiological Consequences of Prolonged or Severe Hypoxia

Even though initial physiological responses to hypoxia are more or less compensatory, prolonged or dramatic de-oxygenation can instigate maladaptive and pathological effects. Prolonged hypoxic pulmonary vasoconstriction might increase pulmonary arterial pressure, which eventually results in pulmonary hypertension and the strain of right ventricles[30]. Persistent sympathetic stimulation and elevated cardiac output are added factors in structural cardiac remodelling, such as hypertrophy and eventual ventricular dysfunction. Cerebral hypoxia can lead to disruption of neuronal metabolism and synaptic activities causing impairment of cognitive functions and neuropsychological functioning. In severe diseases whereby the systemic delivery of oxygen is significantly impaired, a prolonged hypoxia may trigger dysfunction or failure of the multi-organs because of the extensive cellular damage[31].

6. Clinical Implications and Therapeutic Considerations

Hypoxic responses can be clinically managed based on a comprehensive understanding of hypoxic responses. SOT should be intensively adjusted to correct hypoxemia and reduce the chance of oxidative injury caused by hyperoxia[32]. It has been discovered that pharmacological regulating processes on hypoxia-inducible factor can be used in various diseases like anemia, cardiovascular diseases, and even in ischemic diseases. Ventilatory support in patients with critical illness requires optimization in relation to the adequate oxygenation of the patients and the preservation of acid/base balance as well as the prevention of ventilator-associated lung damage. Combining the understanding of the molecular explanations and personalized evaluation of a patient helps increase the specificity of treatment and boost clinical outcomes[33].

7. Conclusion

Hypoxia causes a scale of physiological shifts that are indispensable to adaptation and survival. The acute responses include respiratory and cardiovascular adaptations whereas the chronic exposure causes hematological, metabolic and molecular adaptations. Nevertheless, hypoxia may lead to the onset of pathological effects when prolonged. The progress in knowledge about hypoxia-based signaling pathways can provide possibilities to use it in a specific pattern of the therapeutic intervention with the applicability to a variety of clinical issues.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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