Hypoxia and HIF Signaling in Organ Adaptation and Dysfunction: A Narrative Review

Rifda El Mahroos[1*], Shellya Puti Sudesty[2], Rifka Wangiana Yulia Putri[3], Zulfan Febriawan[1]

[1] Department of Physiology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jawa Timur, Surabaya, Indonesia

[2] Departement of Medical Biology, Molecular Biology, and Physiology, Faculty of Medicine, University of Lampung, Bandar Lampung, 35145, Indonesia

[3] Department of Medicine, Faculty of Medicine, Muhammadiyah University of Surakarta, Central Java, Sukoharjo 57169, Indonesia

Corresponding Author

Rifda El Mahroos

Universitas Pembangunan Nasional Veteran Jawa Timur

Surabaya, East Java, Indonesia 60294

E-mail: rifdaelmahroos.fk@upnjatim.ac.id

ABSTRACT

Hypoxia, defined as a decrease in tissue oxygen level availability, triggers the activation of hypoxia-inducible factor (HIF) and elicits cellular responses including metabolic reprogramming, angiogenesis, and inflammatory modulation. While these initial adaptive mechanisms are essential for cellular survival, prolonged or repeated hypoxic exposure can transform them into maladaptive processes, contributing to tissue dysfunction and disease progression. This narrative review synthesizes current evidence from literature published between 2015 and 2025, retrieved from PubMed, ScienceDirect, and Google Scholar, using keywords related to hypoxia, HIF, cellular adaptation, and organ-specific impacts. Hypoxia manifests in various exposure patterns acute, chronic, and intermittent each activating oxygen sensors and HIF-mediated gene regulation. Although the body initially strives to maintain cellular homeostasis, sustained or recurrent hypoxia overwhelms these adaptive responses, leading to tissue disruption. Organ-specific consequences include cardiac remodeling and heart failure progression, pulmonary vascular remodeling and fibrosis, hepatic stellate cell activation and fibrosis, progression of chronic kidney disease, and impairment of gastrointestinal epithelial barrier integrity. In conclusion, hypoxia is a complex biological stimulus with dualistic effects that are critically dependent on exposure

duration and intensity. Understanding this duality is essential for improving diagnostic and therapeutic strategies for hypoxia-related conditions.

Keyword : HIF pathway; hypoxia, inflammation; organ dysfunction; oxidative stress

Introduction

Oxygen (O_2) is an essential element for multicellular eukaryotic organisms, required primarily for aerobic respiration and optimal adenosine triphosphate (ATP) production within the mitochondria. Under physiological conditions, mitochondria consume approximately 90% of cellular oxygen during oxidative phosphorylation, highlighting the central role of oxygen in energy metabolism [1]. Beyond ATP synthesis, oxygen participates in various fundamental redox reactions, acting as a cofactor or substrate for numerous enzymes, including oxidases and oxygenases involved in biosynthesis, detoxification, and signaling pathways [2,3].

A sustained reduction in oxygen supply to tissues leads to a condition known as hypoxia[4]. The hypoxic state is determined by multiple interacting factors, including local oxygen tension, cellular metabolic demand, tissue perfusion, and intrinsic cellular resistance to low oxygen levels [5]. Hypoxia can be classified into physiological and pathological types. Physiological hypoxia occurs during intense physical exercise, high-altitude exposure, or embryonic development, where transient oxygen fluctuations are part of normal processes [4,6]. In contrast, pathological hypoxia arises from various disease states, including cancer (due to inadequate tumor vascularization), ischemia (from stroke or myocardial infarction), chronic respiratory diseases, and metabolic disorders such as diabetes [6,7].

Importantly, hypoxia is not merely a state of oxygen deficiency; it actively triggers a complex molecular cascade centered on the stabilization and activation of hypoxia-inducible factors (HIFs). HIFs are transcription factors that regulate the expression of hundreds of genes involved in cellular adaptation, including those controlling angiogenesis, glycolysis, erythropoiesis, and cell survival. Under normoxic conditions, HIF-α subunits are hydroxylated and targeted for proteasomal degradation. During hypoxia, hydroxylation is inhibited, allowing HIF-α to translocate to the nucleus, dimerize with HIF-β, and activate target gene expression [8].

Despite decades of research on hypoxia and HIF signaling, the available evidence remains fragmented across different disciplines and experimental models. A key gap persists in integrating knowledge about distinct hypoxia exposure patterns acute, chronic, and

intermittent with their systemic and multi-organ consequences. This narrative review aims to comprehensively synthesize current understanding of the basic mechanisms of hypoxia, its etiological classification and exposure patterns, the body's adaptive and maladaptive responses, and its clinical implications across major organ systems. By providing an integrated framework, this review seeks to generate new insights that support early diagnosis, targeted prevention, and the development of more effective therapeutic strategies for hypoxia-related diseases.

Material and Methods

This article was compiled using a narrative review method by examining various scientific literature discussing the mechanisms, classifications, and physiological adaptations to hypoxic conditions and their implications on various organ systems. The literature search was conducted through the PubMed, ScienceDirect, and Google Scholar databases, with a publication period spanning the last ten years (between January 2015 and December 2025) to ensure the recency of the information. Keywords used included “hypoxia,” “hypoxic adaptation,” “hypoxia-inducible factor (HIF),” “oxygen transport,” and “pathophysiology of hypoxia.”

Inclusion criteria were: (1) peer-reviewed original research articles or review papers; (2) published in English; (3) addressing molecular mechanisms of hypoxia, HIF signaling pathways, exposure patterns, or organ-level effects; and (4) providing mechanistic or clinically relevant insights. Exclusion criteria included: (1) articles not directly related to systemic or organ-specific hypoxia; (2) case reports, conference abstracts, editorials, and non-peer-reviewed publications; (3) studies lacking sufficient methodological detail; and (4) duplicate records.

Results and Discussion

Types and Classification of Hypoxia

Hypoxic conditions are classified into several subtypes based on: (1) the degree of hypoxia (mild, moderate, or severe) depending on the tissue type, (2) the onset of hypoxia (sudden or gradual), (3) the duration and pattern of hypoxic exposure (acute, chronic, intermittent), and (4) the causative mechanism[1,9,10]. Any tissue experiencing oxygen dyshomeostasis will trigger various cellular responses to compensate for the hypoxic state[1]. Each type of mammalian tissue has different normoxia characteristics and concentration levels of adaptation to hypoxia, but generally tissues experience hypoxia at oxygen pressure

(PO_2) ≤ 1 kPa (≤ 7–10 mmHg or 1% O_2). The oxygen pressure during inspiration is 160 mmHg, the pressure in alveolar blood is 104 mmHg, while in most tissues it is around 40–50 mmHg. Some tissues have lower O_2 levels compared to other body tissues, such as the brain (8 mmHg), thymus (10 mmHg), spleen (16 mmHg), and retina (25 mmHg) (Trayhurn, 2019)[11].

Acute hypoxia is a type of hypoxia whose exposure pattern lasts for a short period of time, less than 24 hours, such as occurs in vascular ischemia. Chronic hypoxia is a type of hypoxia whose exposure pattern lasts for a long period of time, usually lasting more than 48 hours, such as occurs in the mechanisms of chronic kidney disease and cancer. 4,10 Intermittent hypoxia is a type of hypoxia that has a pattern of exposure to hypoxia-reoxygenation cycles that can vary in duration and degree of exposure, thus leading to systemic hypoxia, such as occurs in the mechanism of obstructive sleep apnea (OSA)[12,13]. The definitions used in the literature to describe intermittent and chronic hypoxia are often inconsistent and vary and lack consensus[13].

Hypoxia is divided into hypoxic hypoxia, anemic hypoxia, ischemic hypoxia, and histotoxic hypoxia based on its causative mechanism. (1) Hypoxic hypoxia is hypoxia caused by low partial pressure of oxygen, resulting in inadequate hemoglobin (Hb) saturation in arterial blood. This condition can be caused by failure of respiratory gas exchange due to airway obstruction or fluid in the lungs. Hypoxic hypoxia can also occur at certain altitudes, causing hypobaric high-altitude hypoxia. (2) Anemic hypoxia is hypoxia that occurs because there is too little functional hemoglobin in the blood, reducing O_2 transport to tissue cells. This condition can be caused by a decrease in erythrocytes due to bleeding, anemia, and failure of Hb to carry the normal complement of O_2, such as in carbon monoxide poisoning. (3) Ischemic hypoxia or circulatory hypoxia is hypoxia that occurs because the blood flowing to the tissue contains too little oxygen. This hypoxia can be caused by blockage of blood vessels in certain areas, reducing blood flow. Circulatory hypoxia generally occurs due to congestive heart failure or circulatory shock. The partial pressure of O_2 and the arterial O_2 content are usually normal, but too little oxygenated blood reaches the cells in this type of hypoxia. (4) Histotoxic hypoxia is hypoxia caused by the inability of the tissue to optimally utilize the available oxygen, even though the amount of O_2 in the tissue is sufficient. Usually, this condition is caused by the action of several toxic agents, such as in cyanide poisoning [9,14].

The Body's Response to Hypoxia

The body's first response to hypoxia is the activation of chemosensors, which detect

and initiate a non-transcriptional adaptive response. Activated chemosensors stimulate the respiratory center in the medulla oblongata, immediately increasing the depth and rate of breathing. An acute decrease in arterial PO_2 also triggers a response through mitochondrial signaling, such as (reactive oxygen species) ROS and ATP levels, to rapidly alter ion channel activity in the carotid body[8].

In addition, transcriptional detection of systemic hypoxia is also mediated by hypoxia-inducible factor (HIF)[8]. Hypoxia-inducible factor, which has two subunits: HIF-α and HIF-β, is a heterodimeric transcription factor[1,7]. Hypoxia-inducible factor-1α (HIF-1α) is the most potent member of the HIF family, acting as a transcriptional activator and a key regulator of gene expression involved in the response to hypoxia in all mammalian cells, while HIF-2α and HIF-3α play a more limited role and are present only in certain cell types, such as endothelial cells, neurons, interstitial cells, cardiomyocytes, hepatocytes, adipocytes, and renal glomeruli[1,4,15]. as well as HIF-β, whose gene expression is thought to be constitutive[1]. Activation of gene expression by HIF is an adaptive cellular response to regulate O2 supply, aiming to arrest the cell cycle, reduce the rate of oxidative phosphorylation, shift metabolism to anaerobic glycolysis, and stimulate new blood vessel formation. Changes in cellular cytoskeletal morphology also occur during hypoxia, such as protein aggregation and changes in polarization, leading to increased membrane permeability. Oxygen dyshomeostasis can further lead to cytotoxicity caused by increased ROS production[1].

The primary adaptive response of many HIF-activated genes is a metabolic switch from oxidative phosphorylation to anaerobic glycolysis and a reduction in mitochondrial electron transport chain (ETC) activity. Hypoxia-inducible factor-1α (HIF-1α) directly reprograms the metabolic state in cells. Hypoxia-inducible factor-1α (HIF-1α) and HIF-2α maximize ETC efficiency and modulate the expression of cytochrome β oxidase (COX) isoforms. Deficiencies in these mechanisms negatively affect ATP production and lead to increased ROS production in hypoxic tissues[1].

Hypoxia-inducible factor also plays an active role in activating nuclear factor-κB (NF-κB), which plays a role in regulating a large number of genes involved in various immune and inflammatory response processes[1]. Hypoxia and inflammation are described as "two sides of the same coin." Inflammation can cause hypoxia, and vice versa. Inflammatory conditions can also activate HIF signaling. Chronic inflammation can support more severe ROS accumulation[7]. Any imbalance between ROS production and the scavenger system in the body will induce oxidative stress mechanisms that induce tissue damage. This condition will trigger the pathogenesis of various diseases, such as cancer, neurological diseases,

kidney disease, cardiovascular disease, infertility, and others[16].

The Impact of Hypoxia on Various Organs

The impact of hypoxia on various organs depends largely on the duration and intensity of exposure. Mild or intermittent hypoxia can trigger adaptive responses that provide cellular protection, while severe or chronic hypoxia tends to cause organ dysfunction through increased oxidative stress and inflammation.4 These distinct response patterns demonstrate that hypoxia is not simply a simple oxygen deficiency but a complex biological stimulus that mediates metabolic and molecular changes, the effects of which are highly dependent on the duration and intensity of the hypoxia.

In the cardiovascular system, intermittent hypoxia has a protective effect when it occurs in a controlled intensity pattern. This type of exposure reduces oxidative stress, stimulates cellular adaptive pathways, and supports cardiac tissue regeneration[17]. However, when hypoxia persists chronically, heart cells experience mitochondrial dysfunction, increased ROS, and ventricular cell remodelling, contributing to the development of heart failure[4]. In the lungs, hypoxia is closely linked to fibrosis and pulmonary hypertension. Hypoxic conditions activate fibrogenic pathways, primarily through the involvement of HIF and nuclear factor of activated t-cells (NFAT) pathways, and increase fibroblast proliferation, which promotes the progression of pulmonary fibrosis[18]. Chronic hypoxia also triggers epithelial inflammation and pulmonary vascular remodeling[19].

The effects of hypoxia on the liver also exhibit a dualistic pattern. Chronic hypoxic exposure induces hepatic stellate cell activation, progression of liver fibrosis, and increased extracellular matrix deposition.19 The pathogenesis and exacerbation of non-alcoholic fatty liver disease (NAFLD) are mediated by chronic intermittent hypoxia (CIH)[4]. Conversely, shorter exposures or targeted modulation of hypoxic pathways can stimulate protective programs and improve tissue health. These differences in effects emphasize the importance of understanding the temporal dynamics of hypoxia as a basis for therapeutic interventions[19]. In the kidney, chronic hypoxia contributes significantly to the progression of chronic kidney disease because the renal medulla has a low oxygen tolerance. A hypoxic environment accelerates capillary loss, promotes tubulointerstitial fibrosis, and increases interstitial inflammation. In intermittent hypoxia in the kidney, HIF activity increases significantly approximately 2–8 hours after hypoxia induction, providing a protective effect. However, this protective effect declines thereafter. During reoxygenation/reperfusion, the protective effect increases again as it plays a role in correcting the hypoxic state. This process facilitates the release of erythropoietin (EPO), promotes cell regeneration, reduces apoptosis, and

ultimately improves kidney function. Relatively insufficient HIF release in the kidney when hypoxia persists for more than 24 hours, disrupting glomerular endothelial cell microcirculation, eliminating microvilli, and decreasing vascular endothelial growth factor (VEGF) levels. HIF-1α activity was barely detectable in glomeruli when hypoxia persisted for 3 days leading to the development of injury [20].

Hypoxia also plays a crucial role in gastrointestinal barrier modulation. In chronic intestinal inflammation, increased inflammation and epithelial dysfunction due to hypoxia exacerbate mucosal damage.4 However, short-term HIF activation has been shown to improve mucosal barrier integrity and increase the expression of epithelial-protective genes. This suggests that hypoxia has protective potential under certain exposure ranges and patterns[19].

Conclusion

Hypoxia is a decrease in oxygen in tissues that triggers HIF activation and various cellular responses, such as metabolic changes, increased angiogenesis, and inflammatory modulation. This response is dualistic, as under certain conditions it can support cellular adaptation, but if prolonged or repeated, it will become maladaptive and cause oxidative stress, chronic inflammation, and damage to organs such as the heart, lungs, liver, kidneys, gastrointestinal tract, and others. Overall, hypoxia is a complex biological stimulus with significant damaging potential, so understanding its mechanisms is crucial to support more appropriate management of hypoxia-related conditions.

References

1. Mattia M Di, Mauro A, Citeroni MR, Dufrusine B, Peserico A, Russo V, et al. Insight into hypoxia stemness control. Cells. 2021;10(2161):1–45.
2. Choudhry H, Harris AL. Advances in hypoxia-inducible factor biology. Cell Metab [Internet]. 2018;27:281–98. Available from: https://doi.org/10.1016/j.cmet.2017.10.005
3. Keeley TP, Mann GE. Defining physiological normoxia for improved translation of cell physiology to animal models and humans. Physiol Rev. 2019;99:161–234.
4. Chen PS, Chiu WT, Hsu PL, Lin SC, Peng IC, Wang CY, et al. Pathophysiological implications of hypoxia in human diseases. J Biomed Sci. 2020;27(63):1–19.
5. Wang, Li ZL, Zhang YL, Wen Y, Gao YM, Liu BC. Hypoxia and chronic kidney disease. eBioMedicine [Internet]. 2022;77:1–11. Available from:

https://doi.org/10.1016/j.ebiom.2022.103942

6. Mylonis I, Simos G, Paraskeva E. Hypoxia-inducible factors and the regulation of lipid metabolism. Cells. 2019;8(214):1–16.
7. Corrado C, Fontana S. Hypoxia and HIF signaling: one axis with divergent effects. Int J Mol Sci. 2020;21(5611):1–17.
8. Taylor CT, Scholz CC. The effect of HIF on metabolism and immunity. Nat Rev Nephrol. 2022;18(9):573–87.
9. Kawagoe Y, Sameshima H. Hypoxia: animal experiments and clinical implications. J Obstet Gynaecol Res. 2017;43(9):1381–90.
10. Liu Q, Palmgren VAC, Danen EH, Le Dévédec SE. Acute vs. chronic vs. intermittent hypoxia in breast cancer: a review on its application in in vitro research. Mol Biol Rep. 2022;49:10961–73.
11. Millet GP, Burtscher M, Burtscher J. Is hypoxic/altitude training an important topic in the field of hypoxia? J Sci Sport Exerc [Internet]. 2022;4:293–305. Available from: https://doi.org/10.1007/s42978-021-00144-y
12. Zhu J, Kang J, Li X, Wang M, Shang M, Luo Y, et al. Chronic intermittent hypoxia vs chronic continuous hypoxia: Effects on vascular endothelial function and myocardial contractility. Clin Hemorheol Microcirc. 2020;74(4):417–27.
13. Hunyor I, Cook KM. Models of intermittent hypoxia and obstructive sleep apnea: molecular pathways and their contribution to cancer. Am J Physiol Regul Integr Comp Physiol. 2018;315:R669–87.
14. Manninen PH, Unger ZM. Chapter 21 - Hypoxia [Internet]. Complications in Neuroanesthesia. Elsevier Inc.; 2016. 169–180 p. Available from: http://dx.doi.org/10.1016/B978-0-12-804075-1.00021-3
15. Watts D, Gaete D, Rodriguez D, Hoogewijs D, Rauner M, Sormendi S, et al. Hypoxia pathway proteins are masterregulators of erythropoiesis. Int J Mol Sci. 2020;21(8131):1–18.
16. Honda T, Hirakawa Y, Nangaku M. The role of oxidative stress and hypoxia in renal disease. Kidney Res Clin Pract. 2019;38(4):414–26.
17. Kimura W, Nakada Y, Sadek HA. Hypoxia-induced myocardial regeneration. 2017;75390:1676–81.
18. Senavirathna LK, Hu C, Yang X, Cristina M, Sathiaseelan R, Xu D, et al. Hypoxia induces pulmonary fibroblast proliferation through NFAT signaling. 2018;(February 2017):1–16.

19. Strowitzki MJ, Ritter AS, Kimmer G, Schneider M. Hypoxia-adaptive pathways : A pharmacological target in fi brotic disease ? 2019;147(July).
20. Li QY, Liu F, Tang X, Fu H, Mao J. Renoprotective role of hypoxia-inducible factors and the mechanism. Kidney Dis. 2022;8:44–56.