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Review Article

Integrative hypoxia preconditioning: linking iron–hypoxia-inducible factor pathways and oxygen-based therapies from high-altitude physiology to clinical application: a comprehensive review

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ABSTRACT

Hypoxia, once seen solely as a threat, is now recognized as a potent driver of human adaptation. From Himalayan sojourners to critically ill patients, survival under low oxygen relies on a shared molecular axis the hypoxia-inducible factor (HIF)-iron-erythropoietin (EPO) network. Iron acts as the pivotal regulator, as prolyl hydroxylase enzymes that degrade HIF require ferrous iron, directly linking oxygen sensing to erythropoiesis. At high altitude, hepcidin suppression and erythroferrone induction mobilize iron stores for hemoglobin synthesis, while genetic variants such as EPAS1 and EGLN1 fine-tune erythropoietic response to prevent excessive polycythemia. Controlled hypoxia or hyperbaric oxygen preconditioning at sea level similarly activates HIF and Nrf2-mediated antioxidant defences, improving mitochondrial efficiency and tissue resilience. Clinically, HIF-prolyl hydroxylase inhibitors like roxadustat exploit this pathway to manage renal anemia. Emerging concepts in adaptive oxygen medicine including portable hyperbaric therapy and intermittent hypoxia training translate altitude physiology into therapeutic strategy. Thus, oxygen is redefined not only as a vital substrate but as a modifiable signal coordinating iron metabolism, redox balance, and cellular adaptation, a continuum linking acclimatization, preconditioning, and healing.

Keywords: Adaptive oxygen medicine, Hepcidin, High-altitude adaptation, Hyperbaric oxygen, Hypoxia preconditioning, Oxidative stress

INTRODUCTION

The paradox of hypoxia and human adaptation

Hypoxia, the physiological state of reduced oxygen availability, represents both a universal threat and a fundamental driver of biological evolution. From mountain climbers enduring the thin air of the Himalayas to patients suffering ischemic injury at sea level, oxygen limitation challenges cellular homeostasis but simultaneously provokes powerful adaptive mechanisms.[1,2] The capacity of humans to acclimatize to hypoxia demonstrates an intricate coordination between molecular oxygen sensors, erythropoietic regulators, and systemic cardiorespiratory responses.[3,4] At high altitude, barometric pressure and the partial pressure of inspired oxygen fall dramatically, producing arterial hypoxemia that triggers an orchestrated physiological response involving hyperventilation, tachycardia, hemo-concentration, and vascular remodeling.[5,6] These systemic responses are underpinned by the activity of hypoxia-inducible factors (HIFs), transcriptional regulators that sense oxygen tension through prolyl-hydroxylase domain (PHD) enzymes and modulate genes controlling angiogenesis, erythropoiesis, and mitochondrial metabolism. Iron availability intersects critically with this pathway, as PHD enzymes require ferrous iron as a cofactor; iron deficiency or chelation stabilizes HIFs and mimics hypoxic signaling.[7,8] Over recent decades, clinicians have sought to harness this innate adaptive machinery through preconditioning, a process in which brief, controlled exposures to sublethal hypoxia or

hyperoxia confer tolerance to subsequent severe stress (Figure 1).[8,9] Hyperbaric oxygen preconditioning (HBO-PC) and intermittent hypoxia training exemplify deliberate manipulations of the oxidative environment to induce systemic resilience.[10] Such conditioning invokes hormetic principles where mild oxidative or metabolic stress activates cytoprotective genes, antioxidants, and mitochondrial pathways that subsequently guard against injury.[11] Despite the conceptual overlap, the literatures on molecular iron–HIF signaling, high-altitude physiology, and hyperbaric therapy remain largely siloed. The present review aims to integrate these dimensions into a unified narrative describing how iron metabolism, hypoxia signaling, and oxygen preconditioning converge to sustain oxygen economy and tissue survival. By bridging the mountain and the clinic, the discussion advances a model of "adaptive medicine," in which controlled hypoxic and hyperoxic exposures, supported by molecular insights, are strategically applied to enhance tolerance to oxygen deprivation. The implications of such integration extend beyond environmental physiology.

Hypoxia plays a pathogenic or therapeutic role in a multitude of conditions, including chronic heart failure, anemia, chronic obstructive pulmonary disease, stroke, and cancer.[3,12] Translating lessons from altitude adaptation to clinical care may therefore refine approaches to ischemic preconditioning, optimize oxygen delivery strategies, and inspire novel pharmacologic interventions such as PHD inhibitors (roxadustat, daprodustat) that pharmacologically simulate hypoxic adaptation.[13,1415,16]

Iron metabolism acts as the biochemical fulcrum of these processes. Iron availability dictates the stability of HIF proteins and the activity of numerous oxygen-utilizing enzymes, establishing a feedback network in which iron deficiency, inflammation, and oxygen tension reciprocally influence erythropoiesis and tissue oxygenation.[17,18] During hypoxia, hepcidin suppression and erythroferrone induction mobilize iron stores to meet the augmented demand for hemoglobin synthesis.[19-21] Thus, iron does not merely support oxygen transport; it governs the very sensors that decide when the organism must adapt. High-altitude populations exemplify how evolutionary pressures refine this system. Tibetans display genetic polymorphisms in EPAS1 (HIF-2α) and EGLN1 (PHD2) that blunt erythropoietic responses, preventing the maladaptive polycythemia seen in Andeans.[22,23] These findings confirm that long-term hypoxia tolerance can be achieved through modulating HIF sensitivity rather than maximizing hemoglobin concentrationa principle mirrored in the pharmacologic manipulation of HIF pathways for anemia therapy. Clinically, the concept of preconditioning offers an avenue to emulate such adaptive efficiency within hours or days. HBO-PC, for instance, induces transient oxidative stress that activates HIF-1α and nuclear factor erythroid 2–related factor 2 (Nrf2), enhancing antioxidant capacity and mitochondrial resilience.[8] Intermittent hypoxia exposure, similarly, increases ventilatory sensitivity and augments nitric oxide–mediated vasodilation. Together, these interventions constitute artificial analogues of natural acclimatization. The convergence of molecular regulation and interventional physiology thus outlines a continuum of oxygen adaptation: from evolutionary polymorphisms through environmental acclimatization to deliberate clinical conditioning. Understanding this continuum may enable precision tailoring of oxygen therapy balancing exposure, duration, and redox stimuli to achieve desired protective effects while avoiding oxidative injury. This review, therefore, examines the integrated mechanisms through which humans precondition themselves against hypoxia. The discussion proceeds through four further sections: first, the molecular foundations of the iron–HIF–EPO axis that govern oxygen sensing; second, the systemic adaptations of natural high-altitude acclimatization; third, the evidence and mechanisms of artificial hypoxic and hyperbaric preconditioning; and finally, the translational implications for cardiopulmonary and ischemic disease management. In doing so, it proposes that iron metabolism and HIF signaling represent the central biological script, while preconditioning serves as the clinical performance of that scriptan adaptive dialogue between oxygen and life.

THE IRON–HIF–EPO AXIS: MOLECULAR FOUNDATIONS OF THE OXYGEN ECONOMY

At the molecular core of human oxygen adaptation lies a remarkably sensitive network that links oxygen tension to erythropoiesis, iron turnover, and metabolic regulation. This network is orchestrated by the HIFs heterodimeric transcription factors that act as master regulators of oxygen-responsive genes. Under normoxia, PHD enzymes hydroxylate specific proline residues on the HIF-α subunit, marking it for ubiquitination and proteasomal degradation via the von Hippel–Lindau (VHL) complex. When oxygen or ferrous iron becomes limiting, hydroxylation slows, HIF-α stabilizes, and the dimerized HIF complex translocates to the nucleus to activate genes that enhance oxygen delivery and utilizationamong them EPO, VEGF, GLUT1, and enzymes of glycolysis.[24]

Schematic representation of erythropoiesis in the bone marrow. The process begins from the common myeloid progenitor and progresses through burst-forming unit–erythroid (BFU-E), colony-forming unit–erythroid (CFU-E), proerythroblast, erythroblast, and normoblast stages, culminating in the formation of reticulocytes and mature erythrocytes. Erythropoietin (Epo) acts primarily from the CFU-E to erythroblast stage, regulating erythroferrone (ErFe) expression that suppresses hepatic hepcidin to ensure iron availability. Transferrin receptor (TfR1/CD71) mediates iron uptake throughout erythroid maturation (Figure 2).[7]

Iron as the hidden oxygen sensor

Iron availability is inseparable from this oxygen-sensing mechanism because PHDs require Fe^{2+} as a cofactor. When

intracellular iron falls due either to true deficiency or to functional sequestration by hepcidin PHD activity declines, producing a pseudo-hypoxic state that stabilizes HIF even at normal oxygen tensions.[7] This biochemical linkage allows iron metabolism to modulate the entire hypoxic transcriptional program. The iron-regulatory protein (IRP)–iron-responsive element (IRE) system further couples' oxygen demand to iron supply by controlling translation of key proteins such as ferritin, transferrin receptor, and ferroportin.[25] During genuine hypoxia, the body prioritizes iron mobilization to sustain erythropoiesis. The hepatic peptide hepcidin, normally responsible for sequestering iron, is transcriptionally suppressed under HIF-2α control and via the erythroid hormone erythroferrone. This suppression increases ferroportin-mediated iron release from macrophages and enterocytes, augmenting plasma iron flux to support hemoglobin synthesis. The coordination of hepcidin down-regulation, intestinal absorption, and marrow utilization exemplifies a systemic "iron-saving mode" tuned by the hypoxia signal.

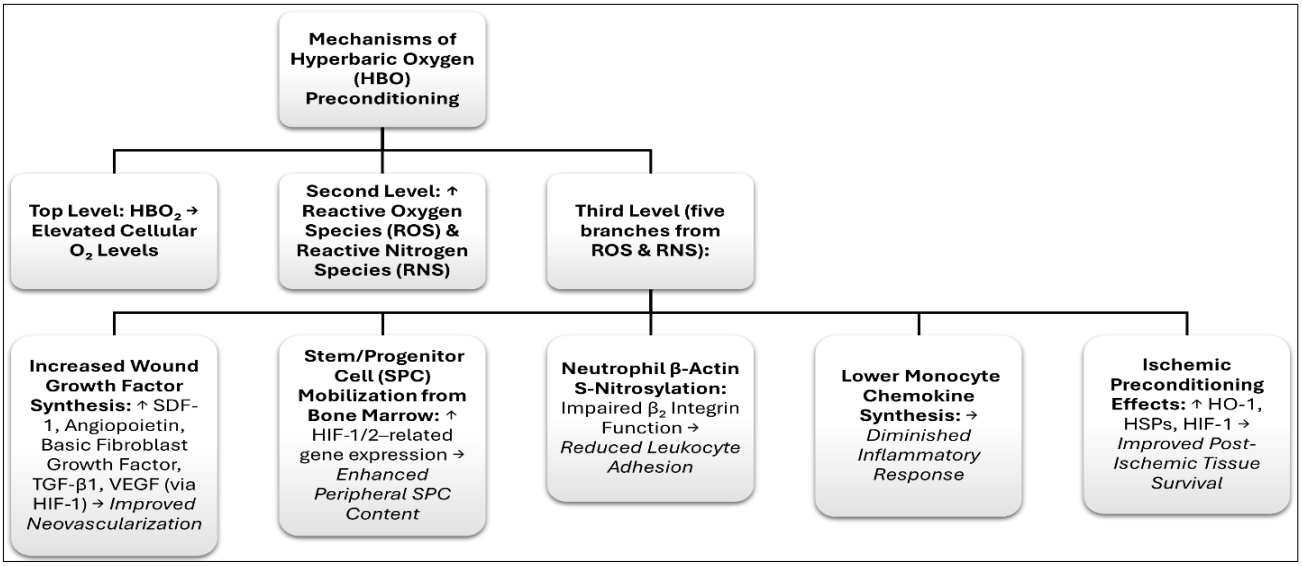

Figure 1: Mechanistic pathways of hyperbaric oxygen (HBO) preconditioning in enhancing cellular adaptation and tissue protection.

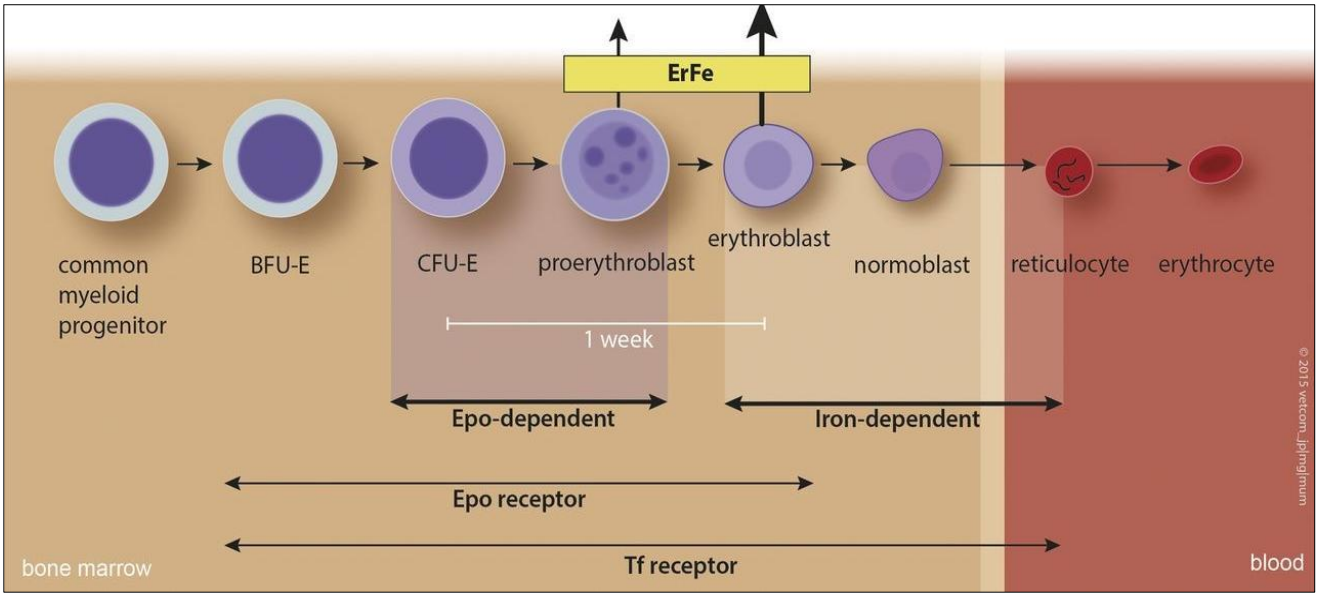

Figure 2: Erythroid lineage differentiation and erythropoietin dependence.

HIF-2α and erythropoietin regulation

Among the HIF isoforms, HIF-2α plays a dominant role in erythropoietin regulation. Expressed in renal interstitial fibroblasts and hepatic perisinusoidal cells, HIF-2α binds to hypoxia-response elements upstream of the EPO gene, increasing transcription and thus stimulating red-cell production.[23] The resulting rise in hemoglobin

concentration expands the oxygen-carrying capacity of blooda cardinal feature of high-altitude acclimatization.[2,26,27] Parallel activation of genes controlling iron uptake ensures substrate availability for heme synthesis, completing a closed feedback loop in which oxygen deficit drives both erythropoiesis and iron mobilization. Recent insights reveal that the relationship between HIF stabilization and erythropoietic response is not linear but context dependent. In Tibetans, genetic variants of EPAS1 (HIF-2α) and EGLN1 (PHD2) attenuate erythropoietin responses, preventing maladaptive polycythemia despite chronic hypoxia. In contrast, Andean highlanders exhibit augmented HIF signaling and elevated hematocrits, predisposing to chronic mountain sickness. These population differences demonstrate how evolutionary modulation of the HIF-EPO pathway calibrates oxygen homeostasis to environmental constraints (Table 1).

Table 1: The iron–HIF–EPO regulatory network in oxygen adaptation.

Component	Site of expression	Function in oxygen regulation	Interaction with iron metabolism	Clinical implication
HIF-1α	Ubiquitous	Activates glycolytic genes, angiogenesis	Hydroxylated by Fe^{2+}-dependent PHD enzymes	Target of ischemic preconditioning
HIF-2α (EPAS1)	Endothelium, kidney, liver	Induces EPO, modulates iron absorption	Upregulates DMT1, ferroportin; suppresses hepcidin	Genetic variants determine altitude tolerance
Prolyl hydroxylase domain enzymes (PHD1–3)	Cytoplasm	Hydroxylate HIF-α → degradation	Require Fe^{2+}, 2-oxoglutarate	Targeted by PHD inhibitors (roxadustat, vadadustat)
Erythropoietin (EPO)	Kidney, liver	Stimulates erythropoiesis	Indirectly increases iron demand	Used therapeutically in anemia
Hepcidin	Liver	Inhibits iron export via ferroportin	Suppressed by HIF and erythroferrone	Modulated by hypoxia and inflammation
Ferritin and ferroportin	Macrophages, hepatocytes	Iron storage and export	Upregulated during hypoxia	Iron redistribution in preconditioning

Iron, oxidative stress, and mitochondrial efficiency

Beyond its role in erythropoiesis, iron serves as a pivot in redox balance. It participates in Fenton chemistry that generates reactive oxygen species (ROS) but also in mitochondrial electron transport where it supports ATP production. During hypoxia, HIF-mediated transcription reprograms metabolism toward glycolysis and attenuates mitochondrial oxygen consumption, thereby limiting ROS generation. At the same time, ferritin synthesis and antioxidant defenses are up-regulated to sequester labile iron and mitigate oxidative injury. This dual regulation reducing oxygen demand while buffering iron-driven radicals underlies the cytoprotective nature of preconditioning. Experimental models confirm that iron chelation or partial inhibition of PHDs can mimic preconditioning by stabilizing HIFs and inducing tolerance to ischemia-reperfusion injury.[28] Conversely, iron overload may blunt HIF activation and exacerbate oxidative stress. These opposing effects highlight the need for precise iron balance when leveraging hypoxic signaling therapeutically.

Mechanistic overview of oxygen and iron-dependent regulation of erythropoiesis. Under hypoxia or iron deficiency, reduced prolyl hydroxylase domain (PHD2) activity stabilizes HIF-2α in renal cells, promoting erythropoietin (Epo) synthesis. Epo stimulates erythroid precursors in bone marrow, inducing secretion of erythroferrone (ErFe), GDF15, and PDGF-BB, which suppress hepatic hepcidin. Hepcidin inhibition enhances iron efflux from macrophages and enterocytes via ferroportin (Fpn), while duodenal HIF-2α upregulates DMT1 and DCYTB to boost iron absorption. Transferrin-bound iron is delivered to developing erythroblasts to support hemoglobin synthesis (Figure 3).[7]

Pharmacological and clinical manipulation of the axis

Understanding the iron–HIF–EPO triad has opened major therapeutic avenues. PHD inhibitors such as roxadustat, vadadustat, and daprodustat transiently stabilize HIFs to stimulate endogenous erythropoietin and improve iron handling in anemia of chronic kidney disease. Unlike exogenous EPO therapy, which can overshoot hematocrit and increase thrombotic risk, PHD inhibition orchestrates a physiologic erythropoietic response coupled with hepcidin suppression and enhanced intestinal absorption. The clinical success of these agents demonstrates the translational power of molecular oxygen sensing discovered through altitude physiology. Moreover, interactions between HIF signaling and nitric-oxide (NO) pathways provide additional therapeutic leverage. Hypoxia-induced up-regulation of endothelial NO synthase improves microvascular perfusion and oxygen diffusion capacity.[29]

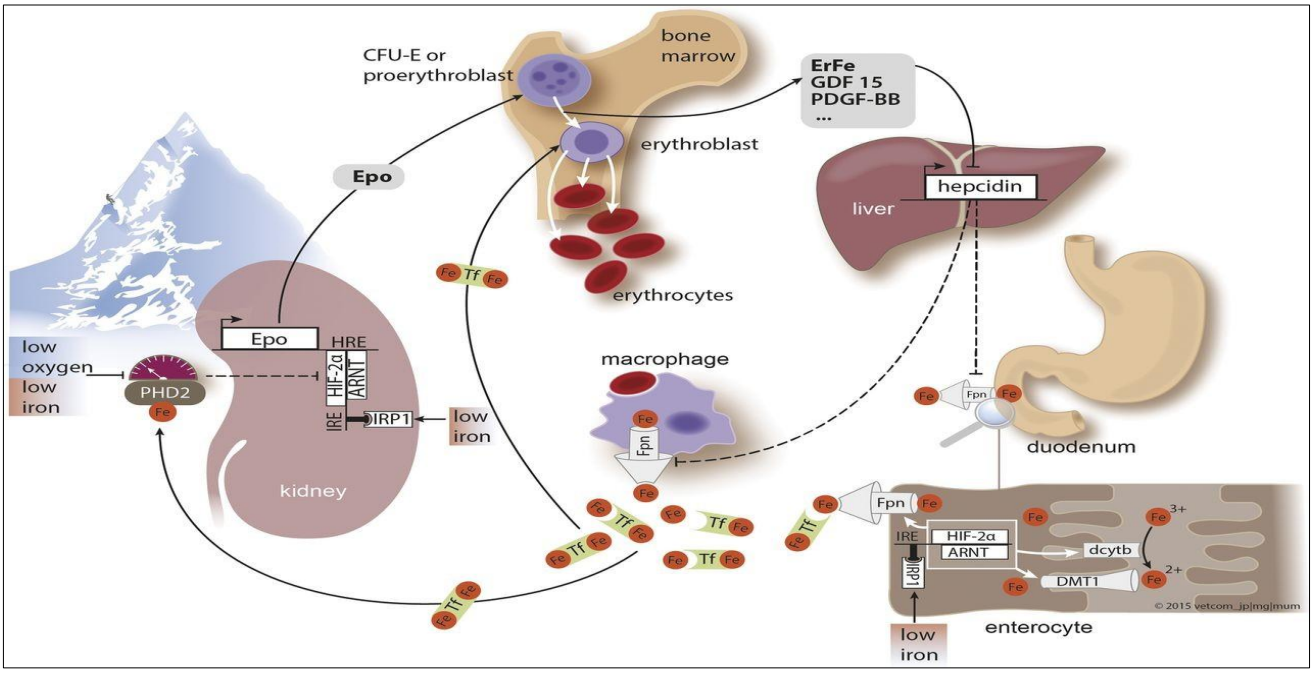

Figure 3: Integrated regulation of iron and erythropoiesis via the hypoxia–HIF–Epo–hepcidin axis.

Iron status influences this axis because iron is a cofactor for NO synthase; deficiency can impair vasodilatory responses. In high-altitude residents and climbers, optimal iron balance therefore contributes not only to erythropoiesis but also to vascular adaptation.

The iron–HIF network as a model of adaptive homeostasis

Collectively, the iron–HIF–EPO axis exemplifies adaptive homeostasis a dynamic equilibrium that maintains oxygen supply within narrow bounds despite environmental or pathologic stress. The system's elegance lies in its bidirectional sensitivity: hypoxia triggers iron mobilization and erythropoiesis, whereas iron deficiency itself mimics hypoxia by stabilizing HIFs. This reciprocity ensures that oxygen and iron, two ancient metabolic partners, regulate each other in continuous feedback.

In the context of preconditioning, this network provides the molecular script upon which external stimuli act. Hyperbaric or intermittent hypoxia exposures engage HIF stabilization and iron redistribution to induce tolerance. The following sections will explore how these molecular processes manifest at the organismal level first through natural acclimatization to high altitude, and later through deliberate conditioning in controlled environments.

NATURAL ADAPTATION TO HYPOXIA AT HIGH ALTITUDE

Life at high altitude represents one of the most profound natural experiments in human physiology. Above 2,500 meters, barometric pressure and inspired oxygen tension decline sharply, reducing the partial pressure of arterial oxygen and challenging every system responsible for oxygen transport and utilization. The ability of humans to tolerate, and even thrive in, such environments reflect multilayered adaptations encompassing ventilation, circulation, hematology, and metabolism.[30] Understanding these adaptations provides the biological blueprint for artificial preconditioning strategies, since the mechanisms that sustain survival in chronic hypoxia are the same ones that confer tolerance to acute hypoxic or ischemic stress.

Ventilatory and cardiovascular adjustments

The earliest and most immediate response to altitude is hyperventilation, driven by hypoxic stimulation of the carotid body chemoreceptors.[5,31] This increases alveolar oxygen tension and enhances arterial oxygen saturation, albeit at the cost of hypocapnia and respiratory alkalosis. Over days to weeks, renal compensation normalizes pH through bicarbonate excretion, allowing sustained ventilatory drive.[32,33]

Simultaneously, cardiac output rises to augment oxygen delivery, with a transient increase in heart rate and stroke volume. At the microvascular level, hypoxia-induced vasodilation mediated by nitric oxide and prostaglandins improves tissue perfusion.[29] These adjustments are tightly coordinated by the HIF pathway. Hypoxia stabilizes HIF-1α in carotid body glomus cells, sensitizing them to low oxygen and reinforcing ventilatory responses. In the vasculature, HIF-1α and HIF-2α drive expression of VEGF and endothelial NO synthase, promoting angiogenesis and microcirculatory expansion. The net effect is an integrated enhancement of oxygen delivery capacity, compensating for reduced inspired oxygen.

Hematologic and erythropoietic responses

Within days of ascent, plasma erythropoietin levels surge, stimulating erythroid progenitor proliferation in the bone marrow. The resultant increase in red-cell mass elevates arterial oxygen content, a hallmark of acclimatization. However, excessive erythrocytosis particularly above 6,000 meters can become maladaptive, increasing blood viscosity and compromising microcirculatory flow. This paradox illustrates the delicate balance between oxygen transport and rheologic efficiency. Differences in erythropoietic response among highland populations underscore the role of genetic adaptation. Andean natives exhibit high hemoglobin concentrations and hematocrits, whereas Tibetans maintain near-sea-level hemoglobin levels despite similar hypoxia exposure. Genome-wide association studies attribute these differences to polymorphisms in EPAS1 (HIF-2α), EGLN1 (PHD2), and PPARA, which modulate HIF activity and downstream erythropoietin signaling. The Tibetan phenotype exemplifies efficient oxygen utilization through enhanced ventilation and perfusion rather than excessive hemoconcentration. In contrast, the Andean pattern emphasizes oxygen transport capacity at the expense of blood fluidity, leading to increased risk of chronic mountain sickness. These population-level insights reveal that natural selection favors not maximal erythropoiesis, but optimal integration of multiple adaptive axes ventilatory, vascular, and hematologic. They also reinforce the centrality of the HIF–EPO–iron system as the evolutionary target of selection in hypoxic environments.[7]

Metabolic and cellular adaptations

At the cellular level, hypoxia provokes a shift from oxidative phosphorylation to glycolysis, conserving oxygen by reducing mitochondrial oxygen demand. HIF-mediated upregulation of GLUT1, LDHA, and PFK1 enhances glucose uptake and anaerobic ATP generation. Concurrently, HIF-dependent induction of pyruvate dehydrogenase kinase (PDK1) inhibits pyruvate entry into the Krebs cycle, limiting mitochondrial ROS generation. This metabolic reprogramming represents a survival strategy that maintains energy balance under limited oxygen availability. In skeletal muscle, prolonged altitude exposure induces mitochondrial remodeling, capillary proliferation, and altered oxidative enzyme expression.[34] These adaptations improve oxygen diffusion and utilization efficiency during exercise, contributing to preserved performance despite hypoxemia. The heart and brain likewise undergo vascular and metabolic plasticity, enhancing tolerance to intermittent oxygen fluctuations.[35] At the molecular level, antioxidant systems including superoxide dismutase, catalase, and glutathione peroxidase are upregulated to buffer ROS generated during hypoxic stress. Mitochondrial biogenesis is modulated via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), linking metabolic flexibility to oxygen sensing. Iron availability modulates these processes, as iron-containing enzymes govern both oxidative metabolism and ROS production. Ferritin induction and iron sequestration during hypoxia may serve protective antioxidant roles.

Pulmonary and vascular remodelling

Chronic hypoxia also drives structural changes in the pulmonary circulation. Hypoxic pulmonary vasoconstriction, an adaptive mechanism to match ventilation and perfusion, becomes generalized and maladaptive at high altitude, leading to pulmonary hypertension in susceptible individuals. HIF-dependent expression of endothelin-1 and vascular remodeling genes contributes to this process. Paradoxically, long-term residents such as Tibetans exhibit blunted hypoxic pulmonary vasoconstriction, reflecting genetic or epigenetic desensitization. Endothelial nitric oxide production, facilitated by HIF-2α and iron-dependent enzymes, counterbalances vasoconstriction and maintains pulmonary vascular homeostasis. Reduced bioavailability of iron, however, can impair nitric oxide synthesis, predisposing to pulmonary hypertension.[36] These interactions again highlight how iron metabolism integrates with vascular adaptation.

Chronic mountain sickness and the limits of adaptation

When these adaptive mechanisms overshoot or fail, chronic mountain sickness (CMS) emerges a syndrome characterized by excessive erythrocytosis, hypoxemia, and pulmonary hypertension.[37] CMS reflects an imbalance in the HIF–EPO axis, wherein erythropoietin overproduction and hepcidin suppression drive unrestrained red-cell proliferation. Iron availability becomes both a cause and a consequence: low hepcidin facilitates iron release, fueling further erythropoiesis. Studies in Andean populations reveal elevated plasma erythroferrone and reduced soluble EPO receptor concentrations, amplifying the erythropoietic drive.[20] These observations confirm that the same adaptive pathways that sustain life under hypoxia can, when dysregulated, become pathogenic. The fine-tuned equilibrium between oxygen sensing, iron regulation, and erythropoiesis thus defines the boundary between adaptation and disease.

Lessons for preconditioning

The physiology of high-altitude adaptation offers a natural template for artificial preconditioning. The controlled activation of HIF pathways, enhancement of antioxidant defences, and optimization of iron flux seen in acclimatized individuals can be replicated through intermittent hypoxia or hyperbaric oxygen exposure.[10] Moreover, the genetic and phenotypic diversity observed across highland populations provides valuable insight into how individual variability influences response to conditioning stimuli. Understanding these natural adaptations informs the rational design of preconditioning protocols aimed at maximizing protective benefits while avoiding maladaptive hematologic responses. In summary,

high-altitude physiology demonstrates how the human organism harmonizes molecular and systemic processes to survive oxygen scarcity. Through a hierarchy of ventilatory, vascular, hematologic, and metabolic adjustments all orchestrated by the iron–HIF–EPO network humans achieve a dynamic equilibrium between oxygen supply and demand. This equilibrium, sculpted by evolution and experience, now serves as a model for therapeutic conditioning in clinical settings.

ARTIFICIAL PRECONDITIONING: HYPERBARIC AND HYPOXIC EXPOSURE AS THERAPEUTIC MIMICS OF NATURAL ADAPTATION

The biological sophistication of natural high-altitude acclimatization has inspired researchers and clinicians to replicate its benefits under controlled conditions an approach broadly termed preconditioning. This concept, originating in cardiovascular research, refers to brief, non-lethal exposures to hypoxia or oxidative stress that induce long-lasting tolerance to subsequent, more severe oxygen deprivation. In recent decades, two principal modalities have emerged: hypoxic preconditioning (HPC), which uses intermittent exposure to low oxygen levels, and hyperbaric oxygen preconditioning (HBO-PC), which employs transient hyperoxia at elevated pressures. Despite their apparent opposition, both act through overlapping molecular pathways dominated by redox signaling, HIF stabilization, and mitochondrial adaptation.[10]

Hypoxic preconditioning: harnessing intermittent oxygen deprivation

Hypoxic preconditioning capitalizes on the paradox that short bouts of oxygen shortage can protect tissues from subsequent hypoxic injury. Initially described in the myocardium and brain, HPC has since been extended to the respiratory and hematologic systems.[29] Exposure to intermittent hypoxia for example, cycles of 10–14% inspired oxygen for minutes to hours over days stimulates ventilatory plasticity, enhances antioxidant enzyme expression, and increases tolerance to ischemia. The protective effects are mediated by moderate ROS generation that activates HIF-1α and nuclear factor erythroid 2–related factor 2 (Nrf2), leading to transcription of cytoprotective genes such as SOD2, HSP70, and HO-1.

Animal models demonstrate that HPC reduces infarct size following myocardial or cerebral ischemia and improves mitochondrial efficiency through enhanced expression of PGC-1α and sirtuins. In humans, intermittent hypoxia training has been used to improve exercise capacity, glucose metabolism, and erythropoietic response in athletes and patients with chronic obstructive pulmonary disease.38 Importantly, iron status influences the magnitude of these effects: mild iron limitation amplifies HIF stabilization and erythropoietic responses, whereas iron overload blunts them. Hence, the iron–HIF axis again emerges as the molecular regulator determining the balance between beneficial and detrimental hypoxic adaptation. Beyond the hematologic effects, HPC modulates cardiovascular function through improved nitric oxide bioavailability and endothelial function. By increasing endothelial nitric oxide synthase (eNOS) activity, intermittent hypoxia enhances vasodilation and tissue perfusion.[29] These vascular benefits parallel those observed in high-altitude dwellers and may underlie the improved performance seen in endurance athletes following hypoxia training.[39]

In contrast to HPC, hyperbaric oxygen preconditioning (HBO-PC) employs transient exposure to 100% oxygen at pressures between 2.0 and 3.0 atmospheres absolute. This increases plasma oxygen tension by up to 20-fold, creating a controlled oxidative challenge that paradoxically triggers adaptive antioxidant and cytoprotective pathways. When administered intermittently typically one to two hours daily for several sessions HBO-PC enhances tolerance to ischemia-reperfusion injury in cardiac, neural, and hepatic tissues. The mechanism again involves ROS-mediated signaling leading to stabilization of HIF-1α, activation of Nrf2, and upregulation of antioxidant and anti-apoptotic proteins (Figure 4).[40,41]

HBO preconditioning enhances hypoxia tolerance by improving oxygen utilization, reducing inflammation and apoptosis, inducing HIF-1α and EPO expression, stabilizing mitochondria, and boosting antioxidant defenses (CAT, HSP).[41]

Hyperbaric oxygen preconditioning: conditioning through controlled hyperoxia

Clinically, HBO-PC has demonstrated neuroprotective effects in models of stroke, spinal cord injury, and traumatic brain injury by preserving mitochondrial function and attenuating inflammation. In cardiac surgery, preoperative HBO sessions have been shown to reduce postoperative ischemic biomarkers, suggesting improved ischemic tolerance.[42,43] Importantly, HBO-PC may also influence hematologic parameters: repeated hyperoxic exposures transiently suppress erythropoietin but subsequently lead to rebound stimulation through ROS-dependent HIF activation.[44] This cyclical modulation of oxidative stress mirrors the alternating hypoxia–reoxygenation patterns experienced during acclimatization to fluctuating altitude conditions.

Convergence of hypoxic and hyperoxic preconditioning pathways

Despite their differing oxygen stimuli, both HPC and HBO-PC converge on similar molecular effectors. The transient oxidative or nitrosative stress generated by these stimuli acts as a signal rather than as damage, triggering cascades that culminate in increased antioxidant capacity, enhanced mitochondrial biogenesis, and improved oxygen utilization efficiency.[45,46] Central to both processes is the activation of redox-sensitive transcription factors, including HIF-1α, Nrf2, and nuclear factor kappa B (NF-

κB). Together, these factors coordinate a shift toward cryoprotection, inflammation control, and metabolic efficiency. Iron metabolism integrates tightly with these pathways. During HPC, iron mobilization supports erythropoiesis and oxygen delivery, while during HBO-PC, transient oxidative stress promotes ferritin induction to sequester reactive iron and limit radical damage. Both mechanisms converge on the same goal: preserving cellular redox balance under oxygen flux. The interplay between iron homeostasis, ROS signaling, and transcriptional adaptation thus represents the biochemical foundation common to all preconditioning strategies.

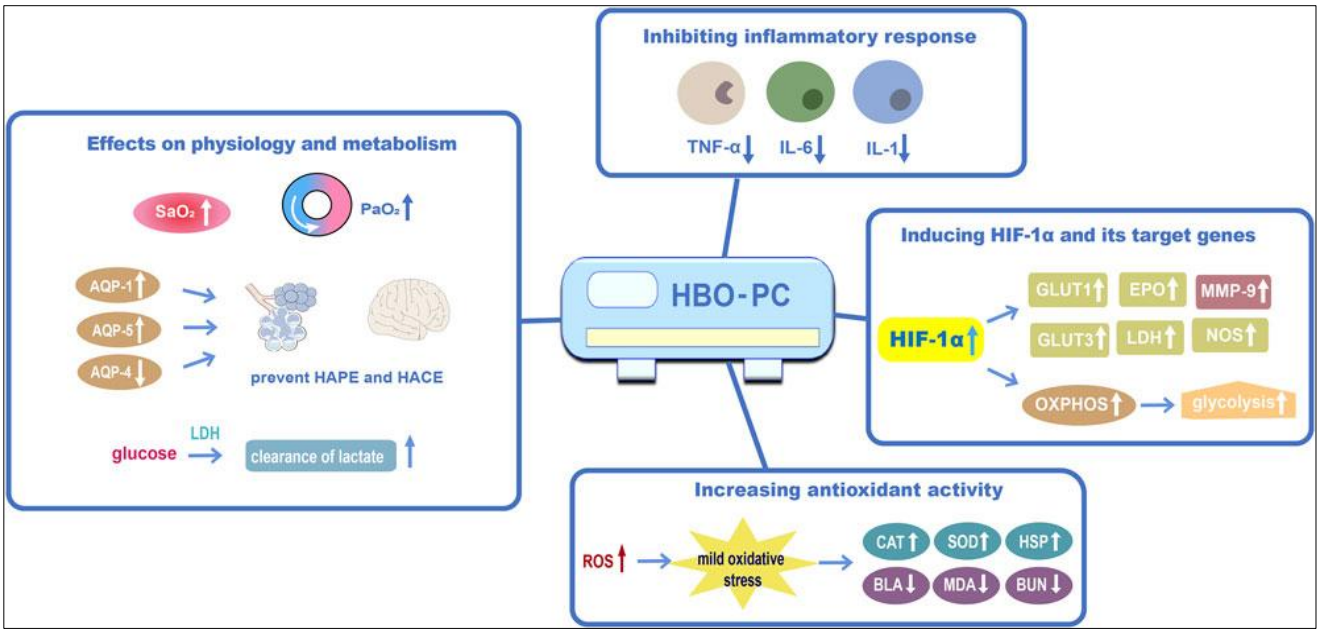

Figure 4: Mechanisms of HBO preconditioning against high-altitude disease.

HBO-PC stands for hyperbaric oxygen preconditioning; HIF-1α, hypoxia-inducible factor-1 alpha; EPO, erythropoietin; GLUT1 and GLUT3, glucose transporter-1 and -3; MMP-9, matrix metalloproteinase-9; NOS, nitric oxide synthase; LDH, lactate dehydrogenase; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; CAT, catalase; SOD, superoxide dismutase; HSP, heat-shock protein; BLA, blood lactate; MDA, malondialdehyde; BUN, blood urea nitrogen; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1, interleukin-1; SaO_2, arterial oxygen saturation; PaO_2, partial pressure of arterial oxygen; AQP-1, AQP-5, and AQP-4, aquaporins 1, 5, and 4; HAPE, high-altitude pulmonary edema; HACE, high-altitude cerebral edema

Portable hyperbaric chambers and field applications

Beyond laboratory and hospital settings, portable hyperbaric chambers provide an operational form of preconditioning and emergency therapy for altitude illness. First described by Taber (1990) and refined through UIAA recommendations, these chambers create an environment equivalent to a rapid descent of 1,000–2,000 meters by increasing ambient pressure. Used as both prophylaxis and treatment, they relieve acute mountain sickness, high-altitude pulmonary edema, and cerebral edema. The physiological mechanism parallels HBO-PC: cyclic pressurization enhances oxygenation, stabilizes HIF signaling, and stimulates antioxidant responses. Recent innovations combine hyperbaric technology with oxygen enrichment devices that deliver controlled FiO_2 at simulated altitudes.[47] These hybrid systems can serve as training platforms to induce mild intermittent oxidative stress before ascent, effectively functioning as portable preconditioning units. They also hold potential for low-resource clinical settings as mobile oxygen therapy systems capable of both delivering and conditioning oxygen exposure.

Mechanistic overlap with ischemic preconditioning

The preconditioning paradigm extends beyond environmental physiology into cardiology and neurology. Ischemic preconditioning, whereby brief episodes of ischemia protect against subsequent infarction, operates through mechanisms nearly identical to those of hypoxic and hyperbaric conditioning.[8] ROS-mediated activation of HIF-1α and Nrf2, increased expression of heat shock proteins, and improved mitochondrial K^+ channel function are shared hallmarks. These similarities suggest a universal stress-response module, conserved across tissues and stimuli, designed to transform transient oxygen imbalance into durable protection (Table 2).

Optimizing the conditioning dose

A central challenge in both HPC and HBO-PC is the determination of optimal "dose" the balance between beneficial stress and deleterious toxicity. Excessive hypoxia induces inflammation and apoptosis, while excessive hyperoxia generates damaging ROS and lipid peroxidation.[8] The window of hormesis where mild stress elicits protection is narrow and influenced by factors such

as age, sex, comorbidities, and baseline iron status. Controlled trials and meta-analyses suggest that three to five HBO sessions or ten to twelve intermittent hypoxia sessions yield maximal benefit without oxidative injury.

Synergistic conditioning approaches

Emerging research explores combining hypoxic and hyperoxic exposures in intermittent hyperoxia–hypoxia conditioning (IHHC) protocols, which alternate oxygen-rich and oxygen-poor environments to amplify redox signaling and mitochondrial adaptation. These regimens harness both arms of the oxygen spectrum to engage HIF-1α and Nrf2 sequentially, achieving broader cytoprotection. Iron supplementation or modulation during these interventions may further fine-tune responses by adjusting PHD enzyme activity.[7,48] Such integrative conditioning represents the practical manifestation of the theoretical continuum linking altitude physiology, molecular adaptation, and clinical therapy. It demonstrates how controlled manipulation of oxygen tension can intentionally activate evolutionary conserved pathways of resilience. In essence, both hypoxic and hyperbaric preconditioning simulate the stress of altitude exposure while avoiding its prolonged deleterious effects. By exploiting transient oxidative signals to strengthen endogenous defenses, these methods operationalize the body's natural capacity for adaptation. The following and final section will discuss how these insights translate to clinical medicine bridging the world of high-altitude biology and the bedside management of hypoxia-related diseases.

TRANSLATIONAL PERSPECTIVES, CLINICAL APPLICATIONS, AND FUTURE DIRECTIONS

The adaptive strategies that enable survival at high altitude are not merely curiosities of mountain physiology; they embody fundamental biological principles that can be applied to medicine. The same molecular networks that defend the brain, heart, and lungs against hypoxia during ascent can be recruited deliberately to protect organs from ischemic or inflammatory injury at sea level.[3,12] Integrating the iron–HIF–EPO axis with controlled oxygen conditioning now represents one of the most promising frontiers in translational physiology.

From mountain physiology to medicine

Preconditioning has demonstrated efficacy across multiple organ systems. In cardiology, brief hypoxic or hyperbaric exposures before ischemic events limit infarct size and enhance post-ischemic recovery.[8] HIF stabilization up-regulates vascular endothelial growth factor (VEGF) and endothelial nitric-oxide synthase, improving coronary perfusion and collateral growth. In neurology, HBO-PC and intermittent hypoxia pre-exposure reduce neuronal apoptosis and preserve mitochondrial integrity after stroke or spinal-cord ischemia. In nephrology and hepatology, these same interventions attenuate reperfusion-induced oxidative stress through induction of heme-oxygenase-1 and ferritin, proteins directly linked to iron handling.[18] Such protective effects parallel those seen in naturally acclimatized high-altitude residents who exhibit enhanced antioxidant capacity and microvascular density. The translational implication is clear: what evolution achieved through generations of selection can be reproduced, in part, through short-term physiological training or pharmacologic manipulation.

Hypoxia-mimetic pharmacology

A direct extension of these discoveries is the clinical development of HIF-prolyl-hydroxylase (PHD) inhibitors, often called "hypoxia mimetics." Agents such as roxadustat and daprodustat transiently inhibit PHDs, stabilizing HIF-α subunits and activating downstream erythropoietic and iron-mobilizing genes.[15,16] In patients with chronic kidney disease, these drugs correct anemia by stimulating endogenous erythropoietin and reducing hepcidin, thereby enhancing both red-cell production and iron availability.[25] Beyond anemia, controlled HIF activation may improve ischemic tolerance in cardiovascular and neurological disease. Experimental models show that PHD inhibition before reperfusion reduces tissue necrosis and inflammation.[11,49,50] However, long-term or excessive HIF activation carries potential risks including pulmonary hypertension and tumor progression underscoring the need for precise temporal control.[22,23,51] Thus, pharmacologic preconditioning must emulate the intermittent, self-limiting nature of physiologic hypoxia rather than its chronic extremes.[52-55]

Oxygen therapy reconsidered

The insights from high-altitude and preconditioning research are reshaping how clinicians view oxygen therapy itself. Traditional practice equated oxygen with benefit and hypoxia with harm. Yet evidence now shows that excessive oxygen delivery can paradoxically worsen outcomes in stroke, myocardial infarction, and critical illness through oxidative injury and vasoconstriction.[8] Conversely, short, intermittent hypoxic episodes carefully dosed and monitored can strengthen endogenous defenses. This emerging philosophy reframes oxygen not simply as a drug but as a biological signal whose timing and intensity determine therapeutic value.

Hyperbaric oxygen therapy exemplifies this new paradigm. Once confined to decompression sickness and carbon-monoxide poisoning, it is increasingly applied for chronic wounds, radiation injury, and neuro-rehabilitation.[8] When administered intermittently, HBO functions as a preconditioning agent rather than a purely oxygen-delivery tool. The resulting cyclical ROS formation activates adaptive transcription factors, induces angiogenesis, and enhances mitochondrial quality control mechanisms that mirror natural acclimatization (Table 3).[10]

Table 2: Comparison of natural and artificial preconditioning modalities.

Parameter	Natural high-altitude adaptation	Hypoxic preconditioning (HPC)	Hyperbaric oxygen preconditioning (HBO-PC)
Primary stimulus	Chronic hypobaric hypoxia	Intermittent hypoxia (normobaric or hypobaric)	Intermittent hyperoxia (2–3 ATA)
Duration	Weeks to generations	Minutes–hours per session, repeated	1–2 hours per session, repeated
Key molecular pathways	HIF-1α, HIF-2α, EPO, VEGF, erythroferrone	HIF-1α, Nrf2, antioxidant enzymes	HIF-1α, Nrf2, HO-1, HSP70
Physiologic outcomes	Polycythemia, angiogenesis, increased ventilation	Enhanced ischemic tolerance, antioxidant response	Reduced oxidative damage, enhanced mitochondrial function
Iron metabolism changes	Decreased hepcidin, increased ferroportin	Mild functional iron deficiency, enhanced erythropoiesis	Ferritin induction, transient iron sequestration
Clinical utility	Natural acclimatization	Cardioprotection, neuroprotection, athletic training	Preoperative protection, ischemia mitigation
Potential adverse effects	CMS, pulmonary hypertension	Oxidative stress if excessive	Barotrauma, oxidative injury at high doses

Table 3: Translational and therapeutic applications of oxygen preconditioning.

Target condition	Mechanism of protection	Experimental/clinical insights	Status and potential use
Ischemic heart disease	Enhancement of vascular endothelial growth factor (VEGF), nitric oxide signaling, and antioxidant enzyme activity	Demonstrated reduction in myocardial injury and improved post-ischemic recovery following preconditioning exposure	Being explored for perioperative myocardial protection and rehabilitation therapy
Cerebral ischemia/stroke	Stabilization of HIF pathways and activation of neuroprotective genes reducing neuronal apoptosis	Consistent improvement in cerebral perfusion, reduced infarct size, and better neurological outcomes in preclinical models	Investigational; may support future adjunctive stroke management protocols
Chronic kidney disease–related anemia	HIF-mediated stimulation of erythropoietin and suppression of hepcidin enhancing iron utilization	Proven capacity to restore hemoglobin and iron homeostasis through physiologic activation of erythropoiesis	Therapeutic applications through oral HIF stabilizers approved or in advanced trials
High-altitude illness prevention	Pre-activation of antioxidant defenses and optimization of ventilatory response before ascent	Reduction in acute mountain sickness symptoms and improved acclimatization capacity under simulated altitude exposure	Applicable for mountaineers, soldiers, and aviation personnel as a preventive measure
Chronic wound and tissue ischemia	Promotion of angiogenesis, collagen synthesis, and stem-cell recruitment improving oxygen delivery	Marked acceleration in wound closure and tissue regeneration under controlled oxygen conditioning	Widely adopted as an adjunct in reconstructive and vascular medicine
Neurodegeneration/aging	Enhancement of mitochondrial biogenesis, redox homeostasis, and cellular repair signaling	Preliminary findings show improved cognitive performance and metabolic resilience after conditioning	Emerging application requiring further long-term clinical validation

Integrating iron and redox biology into clinical conditioning

Iron metabolism provides a unifying thread connecting molecular and clinical dimensions. Both hypoxic and hyperbaric exposures alter systemic iron flux and ferritin expression. In anaemia or inflammatory states characterized by elevated hepcidin, transient HIF activation or mild iron restriction may restore proper erythropoietic signalling.[7] Conversely, in ischemia-

reperfusion injury, induction of ferritin and heme-oxygenase-1 sequesters labile iron, reducing ROS-driven damage.[18] Future conditioning protocols may incorporate iron modulation as an adjunct for example, combining intermittent hypoxia training with dietary or pharmacologic iron regulation to fine-tune PHD activity and optimize HIF responses. Personalized approaches could adjust iron status, oxygen exposure, and pressure cycles based on genetic variants such as EPAS1 or EGLN1 that influence individual hypoxia sensitivity.[56] This convergence of genetics, nutrition, and environmental control represents a step toward precision preconditioning.

Toward personalized oxygen medicine

Advances in wearable sensors and artificial-intelligence–assisted monitoring now permit real-time measurement of oxygen saturation, heart rate variability, and tissue perfusion during conditioning sessions. Integrating these technologies into portable hyperbaric or hypoxic devices can create smart adaptive systems that automatically adjust FiO_2 or chamber pressure to maintain optimal hormetic zones.[57,58] Such systems could personalize conditioning regimens for athletes, mountaineers, or patients recovering from ischemic injury, ensuring efficacy while minimizing risk. In the military and aerospace sectors, preconditioning protocols are being explored to enhance resilience to hypoxia and oxidative stress during rapid altitude changes or spaceflight. Similarly, in sports medicine, intermittent hypoxia and hyperoxia are combined to augment performance through improved mitochondrial efficiency and erythropoiesis.[59] The same physiological logic applies to geriatric and metabolic medicine, where conditioning may counteract age-related declines in vascular and mitochondrial function.

Ethical and safety considerations

As conditioning strategies enter mainstream practice, ethical oversight is essential. Manipulating oxygen levels particularly through hyperbaric exposure carries inherent risks, including barotrauma, oxidative stress, and hemodynamic fluctuations. Equally, pharmacologic HIF activation requires vigilance for off-target effects such as unwanted angiogenesis or erythrocytosis. Establishing standardized "safe-stress" protocols and monitoring frameworks will be crucial. Furthermore, equitable access should be ensured so that conditioning technologies do not become limited to elite athletes or specialized centers.

Future directions in research

Several frontiers demand focused investigation. First, elucidating the crosstalk between HIF and Nrf2 pathways could reveal new combinatorial targets for antioxidant and metabolic conditioning.[8] Second, exploring the role of the microbiome in modulating systemic iron metabolism and hypoxic responses may open an unexpected dimension of adaptation. Third, longitudinal trials are needed to determine how repeated preconditioning over months or years influences cardiovascular and cognitive aging. Finally, integration of omics technologies genomics, metabolomics, and proteomics will allow identification of biomarkers predictive of individual conditioning responses and safety thresholds.[60]

CONCLUSION

From the cellular choreography of the iron–HIF–EPO axis to the systemic resilience achieved through hyperbaric and hypoxic conditioning, the capacity for adaptation to oxygen stress is an intrinsic feature of human biology. Evolution has refined this machinery for survival at altitude; modern medicine now seeks to harness it for therapy. By viewing oxygen not solely as a metabolic substrate but as a controllable signal, clinicians can transform a once-feared element of pathology into a tool for protection. Ultimately, the integration of molecular insight, environmental physiology, and technological innovation defines a new discipline adaptive oxygen medicine. Here, the lessons of the mountains meet the precision of the clinic: iron balance, redox modulation, and transient stress are orchestrated to sustain health in the face of hypoxia. The journey from hypoxic threat to therapeutic opportunity epitomizes the resilience of life itself a continuum from survival to adaptation, from adaptation to healing.

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