Nox2-Dependent Oxidative Stress and Antioxidant Modulation in Right Ventricular Hypertrophy Induced by Chronic Intermittent Hypobaric Hypoxia

Estrés oxidativo dependiente de Nox2 y modulación antioxidante en la hipertrofia ventricular derecha inducida por hipoxia hipobárica intermitente crónica

Eduardo Pena[1]

[1]High Altitude Medicine Research Center (CEIMA), Arturo Prat University, Iquique 1100000, Chile;

Fecha Recepción: 21 de julio de 2026
Fecha Revisión: 19 de agosto de 2026
Fecha Aceptación: 04 de septiembre de 2026
DOI: https://doi.org/10.22370/syc.2.1.2026.5929.

Abstract

Chronic intermittent hypobaric hypoxia (CIHH) is an increasingly prevalent occupational exposure characterized by repetitive cycles of days at high altitude followed by days of rest at sea level that promote pulmonary vascular remodeling, high-altitude pulmonary hypertension, and progressive right ventricular hypertrophy (RVH). Although RVH initially serves as a compensatory response to elevated pulmonary vascular resistance, prolonged exposure to CIHH may result in maladaptive remodeling, fibrosis, metabolic dysfunction, and eventual right ventricular failure. Among the molecular mechanisms involved, oxidative stress has emerged as a central driver of cardiopulmonary injury. Recent evidence identifies NADPH oxidase-2 (Nox2) as a major enzymatic source of reactive oxygen species (ROS) during CIHH. Beyond direct ROS generation, Nox2 functions as a redox signaling hub linking mitochondrial dysfunction, endothelial injury, inflammation, and hypoxia-responsive transcriptional pathways. Excessive Nox2 activation promotes lipid peroxidation, endothelial nitric oxide synthase (eNOS) uncoupling, contribution to hypoxia-inducible factor-1α (HIF-1α) stabilization, and activation of stress-sensitive kinases such as p38 mitogen-activated protein kinase (MAPK). Furthermore, Nox2-derived ROS interact with mitochondrial ROS through mechanisms of oxidase crosstalk, amplifying oxidative injury and sustaining pathological remodeling within both the pulmonary vasculature and the right ventricle. Despite strong mechanistic support for antioxidant therapy, clinical outcomes have remained inconsistent, likely due to limited bioavailability, pharmacokinetic constraints, and the inability of conventional antioxidants to inhibit upstream ROS-generating pathways. In this context, astaxanthin has emerged as a promising next-generation antioxidant owing to its high membrane affinity, modulation of Nox2 expression, preservation of mitochondrial integrity, and activation of endogenous antioxidant defenses through Nrf2-dependent signaling. This narrative review synthesizes current evidence regarding the role of Nox2-mediated oxidative stress in CIHH-induced RVH and discusses emerging redox-targeted therapeutic strategies aimed at mitigating hypoxia-associated non-compensatory cardiovascular remodeling.

Palabras clave: Hypobaric Hypoxia; Cardiac Hypertrophy; Oxidative Stress; Pulmonary Hypertension; Antioxidants; Reactive Oxygen Species.

1. INTRODUCTION

Exposure to chronic intermittent hypobaric hypoxia (CIHH) involved cycles of exposure to high altitude (>2,500 m). This exposure pattern is particularly common among workers involved in high-altitude mining operations, military personnel, transportation crews, and individuals who work at this elevation for prolonged periods, often maintaining this schedule for several years. This exposure pattern, commonly known as the "Chilean miner model", represents one of the most prevalent forms of occupational high-altitude exposure worldwide[1,2].

CIHH creates a complex biological environment that promotes a broad range of physiological adaptations as well as pathological responses. Exposure to CIHH has been associated with the development of altitude-related disorders, including acute mountain sickness (AMS) and high-altitude pulmonary hypertension (HAPH). The latter is characterized by pulmonary arterial remodeling associated with oxidative stress and inflammatory processes, resulting in increased pulmonary vascular resistance and a mean pulmonary artery pressure (mPAP) >30 mmHg, which subsequently contributes to the development of right ventricular hypertrophy (RVH). Although RVH is generally considered a compensatory and reversible adaptation, in severe cases these alterations may progress to right heart failure[3,4], representing a clinically significant concern.

Over the last decade, evidence from both experimental and clinical studies has demonstrated that CIHH profoundly affects the cardiopulmonary system. As mentioned before sustained pulmonary vasoconstriction and remodeling of pulmonary resistance vessels progressively increase pulmonary vascular resistance, elevating right ventricular afterload and stimulating compensatory hypertrophic growth of the right ventricular myocardium[2]. Although these structural adaptations initially preserve cardiac output, as previously noted, prolonged exposure frequently results in maladaptive remodeling characterized by fibrosis, metabolic dysfunction, reduced contractile reserve, and eventual right ventricular failure (RVF)[5].

Although RVH is a well-recognized consequence of CIHH, the specific molecular mechanisms linking repetitive hypoxia–reoxygenation cycles to maladaptive right ventricular remodeling remain incompletely understood. Among the different enzymatic sources of ROS, including mitochondria, xanthine oxidase, and uncoupled eNOS, NADPH oxidases (Nox) appear particularly relevant because of its sensitivity to hypoxia–reoxygenation stimuli and its established role in cardiovascular remodeling. However, despite the various pathways proposed, oxidative stress is now recognized as a central pathological process linking hypoxic exposure to cardiovascular remodeling. ROS play important physiological signaling functions under normal conditions; conversely, excessive ROS generation (oxidative stress) disrupts redox homeostasis and initiates a cascade of molecular events involving lipid peroxidation, mitochondrial dysfunction, inflammation, endothelial injury, and activation of stress-sensitive transcriptional programs[6]. As mentioned before, increasing evidence indicates that Noxs, particularly the Nox2 isoform, constitute one of the most important enzymatic sources of ROS during hypoxic cardiovascular disease. Nox2-derived oxidants have been implicated in cardiac hypertrophy induced by CIHH[7], suggesting that this enzyme may represent a convergent therapeutic target for cardiac alteration under hypoxia conditions.

Importantly, Nox2 does not act in isolation. Emerging evidence indicates a complex interplay among NADPH oxidases, mitochondria, uncoupled eNOS, and inflammatory signaling pathways, resulting in the sustained amplification of oxidative stress through mechanisms collectively referred to as oxidase crosstalk, which will be discussed in this study. This process appears to be particularly relevant under intermittent hypoxic conditions, where repetitive cycles of hypoxia and reoxygenation promote persistent ROS production, mitochondrial dysfunction, and metabolic reprogramming, thereby contributing to the progression of cardiopulmonary remodeling[8]. Consequently, a deeper investigation into both targeted enzymatic inhibitors and next-generation, highly bioavailable antioxidants is urgently required[9]. Therefore, the aim of this

review is to comprehensively synthesize the molecular networks governing Nox2-mediated oxidative stress in CIHH-induced RVH, contrast the pharmacological profiles of conventional versus next-generation antioxidants, and establish an integrated framework for biomarker-guided, pharmacologically optimized therapies to mitigate hypoxic cardiovascular disease.

1.1. Chronic intermittent hypobaric hypoxia

Chronic intermittent hypobaric hypoxia (CIHH) is a distinctive pattern of high-altitude exposure characterized by repeated cycles of residence and work at high altitude (>2,500 m) alternating with recovery periods at low altitude or sea level. This condition is particularly common among mining workers in the Andes, military personnel, and transportation workers who commute regularly between hypoxic and normoxic environments. Because of its high prevalence in northern Chile, CIHH is frequently referred to as the "Chilean miner model", where workers typically spend several days at altitudes ranging from 3,000 to 5,000 m followed by equivalent rest periods at sea level, maintaining this schedule for many years[1,10,11].

In contrast to permanent high-altitude residence, CIHH exposes individuals to recurrent transitions between hypobaric hypoxia and normoxia, generating unique physiological and pathological responses. These cyclic fluctuations in oxygen availability induce repeated processes of acclimatization and deacclimatization that affect multiple organ systems, particularly the cardiopulmonary circulation. Although certain adaptations may be beneficial for maintaining oxygen delivery, long-term exposure to CIHH has been associated with pulmonary vascular remodeling, oxidative stress, endothelial dysfunction, high-altitude pulmonary hypertension, and right ventricular hypertrophy in both human and experimental studies[11]. One of the earliest and most characteristic responses to alveolar hypoxia is hypoxic pulmonary vasoconstriction (HPV), a physiological mechanism that redistributes blood flow toward better-ventilated lung regions[12]. However, when hypoxic exposure becomes recurrent or prolonged, as occurs during CIHH, sustained vasoconstriction evolves into a pathological process involving endothelial dysfunction and pulmonary vascular remodeling[13].

A key mechanism underlying this transition is the impairment of the nitric oxide (NO) signaling pathway, characterized by reduced endothelial NO bioavailability resulting from decreased eNOS activity, increased oxidative degradation of NO by ROS, and accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS. Consequently, the imbalance between vasodilatory and vasoconstrictor mediators promotes increased pulmonary vascular tone and resistance[14,15,16]. In parallel, excessive ROS generation activates redox-sensitive signaling pathways and inflammatory mediators, including cytokines and adhesion molecules, which stimulate endothelial injury, smooth muscle cell proliferation, extracellular matrix deposition, and muscularization of distal pulmonary arteries[13].

These processes collectively promote pulmonary vascular remodeling, leading to a progressive elevation in pulmonary arterial pressure and, ultimately, the development of HAPH, one of the major cardiopulmonary complications associated with long-term exposure to hypobaric hypoxia. Among the molecular mechanisms involved in this pathological process, accumulating evidence has identified oxidative stress and NADPH oxidase-derived ROS as key mediators linking hypoxic exposure to endothelial dysfunction, inflammation, and pulmonary vascular remodeling[13,14]. Importantly, the detrimental effects of oxidative stress are not restricted to the pulmonary circulation. Similar redox-dependent mechanisms have also been implicated in cardiac remodeling, particularly in the development of right ventricular hypertrophy (RVH), which will be discussed in the following section.

1.2. Oxidative Stress and Nox2 Activation in CIHH

The Nox family constitutes a major source of non-mitochondrial ROS within the cardiovascular system, with Nox2 being heavily localized in both cardiomyocytes and endothelial cells[8].

Nox2 activation requires the assembly of a multicomponent enzymatic complex consisting of membrane-bound Nox2/gp91phox and p22phox together with the cytosolic regulatory proteins p47phox, p67phox, p40phox, and the small GTPase Rac1. Hypoxia–reoxygenation cycles promote the translocation of these cytosolic subunits to the membrane, triggering ROS generation. Under CIHH conditions, the expression of Nox2 and its essential regulatory subunit, p22phox, is markedly up-regulated[7]. This enzymatic activation triggers an overproduction of superoxide anions ($O_2\bullet^-$), which rapidly dismutate to hydrogen peroxide (H_2O_2), triggering intracellular signaling pathways associated with maladaptive hypertrophic growth[7]. A major consequence of this Nox2 activation is the induction of lipid peroxidation, which damages cell membranes and generates reactive aldehydes such as malondialdehyde (MDA). Furthermore, Nox2-derived ROS act as critical secondary messengers that activate the p38 mitogen-activated protein kinase (p38 MAPK) pathway, a key driver of transcription factors responsible for protein synthesis and hypertrophic gene expression in cardiomyocytes. Concurrently, elevated ROS levels influence the stabilization of hypoxia-inducible factor 1-alpha (HIF-1α) even under intermittent conditions, perpetuating a pro-hypertrophic and pro-inflammatory phenotype within the right ventricular myocardium[7]. Consequently, the Nox2–ROS axis represents a highly relevant therapeutic target for preventing the transition from adaptive hypertrophy to heart failure.

1.3. Nox2 Activation Machinery and Oxidase Crosstalk

The pathological consequences of Nox2 activation during CIHH extend beyond simple ROS overproduction and involve the coordinated regulation of a highly specialized enzymatic complex. Nox2, also known as gp91phox, forms a membrane-bound heterodimer with p22phox that remains inactive under basal conditions. Full enzymatic activation requires the translocation and assembly of several cytosolic regulatory subunits, including p47phox, p67phox, p40phox, and the small GTPase Rac1. Exposure to repetitive hypoxia–reoxygenation cycles promotes the phosphorylation of p47phox and the subsequent recruitment of cytosolic components to the membrane, enabling electron transfer from NADPH to molecular oxygen and generating superoxide anions ($O_2\bullet^-$). This tightly regulated activation process allows Nox2 to function as a cellular redox sensor but simultaneously renders the enzyme highly responsive to pathological stimuli associated with hypoxic stress.

Beyond direct ROS production, growing evidence indicates that Nox2 operates as part of an interconnected redox signaling network involving mitochondria, uncoupled eNOS, and inflammatory pathways[7,13]. This phenomenon, commonly referred to as oxidase crosstalk, amplifies oxidative injury and sustains redox imbalance long after the initial hypoxic stimulus has subsided. Under CIHH conditions, Nox2-derived ROS impair mitochondrial electron transport chain function, particularly at complexes I and III, increasing electron leakage and secondary mitochondrial ROS generation. The resulting mitochondrial dysfunction further stimulates Nox2 activity, establishing a self-perpetuating feed-forward mechanism known as ROS-induced ROS release.

An additional consequence of excessive Nox2 activation is the oxidation of tetrahydrobiopterin (BH_4), an essential cofactor for eNOS. Oxidation of BH_4 promotes eNOS uncoupling, shifting the enzyme from nitric oxide production toward superoxide generation[13]. This transition simultaneously reduces nitric oxide bioavailability and increases oxidative stress, thereby contributing to endothelial dysfunction, pulmonary vasoconstriction, and vascular remodeling. Because endothelial dysfunction is a critical precursor to high-altitude pulmonary hypertension, the interaction between Nox2 and uncoupled eNOS may represent an important mechanistic bridge linking pulmonary vascular pathology with progressive right ventricular overload[7].

Nox2-derived ROS also regulate several redox-sensitive transcriptional pathways implicated in myocardial hypertrophy. Oxidative inhibition of prolyl hydroxylase domain enzymes promotes the stabilization of hypoxia-inducible factor-1

alpha (HIF-1α), leading to increased transcription of genes involved in glycolytic metabolism, angiogenesis, inflammation, and cellular growth. Simultaneously, ROS activate stress-associated kinases including p38 MAPK, ERK1/2, and JNK, which modulate the expression of fetal cardiac genes and hypertrophic proteins. Persistent activation of these pathways favors the transition from compensatory hypertrophy to maladaptive remodeling characterized by fibrosis, impaired contractility, and metabolic dysfunction[17].

Collectively, these observations suggest that Nox2 should not be viewed merely as an isolated ROS-generating enzyme but rather as a central signaling hub integrating mitochondrial dysfunction, endothelial injury, inflammatory activation, and hypoxia-responsive transcriptional programs. This integrated model provides a mechanistic explanation for how repetitive hypoxia–reoxygenation cycles induce progressive cardiopulmonary remodeling during CIHH and further supports the rationale for developing selective Nox2-targeted therapeutic strategies.

1.4. Antioxidant Strategies: Experimental and Clinical Evidence

Given the prominent role of oxidative stress in RVH, numerous preclinical and clinical trials have evaluated the therapeutic potential of antioxidant supplementation. Mechanistically, neutralizing free radicals before they interact with cellular components should prevent downstream MAPK activation and structural remodeling. However, large-scale clinical and meta-analyses have produced mixed results. Although the biological rationale for antioxidant therapy is well established, clinical outcomes consistently show favorable trends toward cardiovascular protection without reaching definitive statistical significance across diverse populations. This inconsistency is largely attributable to substantial methodological heterogeneity among studies, including differences in high altitude exposure, duration, and frequency of intermittent hypoxia cycles, and antioxidant regimens. Furthermore, non-targeted antioxidant approaches may fail to achieve sufficient intramyocardial concentration to effectively counteract the rapid and localized bursts of ROS generated by activated Nox2 complexes during hypoxia period. Consequently, despite strong mechanistic support, the clinical translation of antioxidant therapies has remained inconsistent. In summary, meta-analytic evidence suggests a protective trend of traditional antioxidant interventions on cardiac structures and function, although these effects often fail to achieve robust statistical significance[18]. This discrepancy stems from a profound "mechanism–efficacy gap," where promising in vitro or animal-model results are diluted in human trials due to unoptimized dosing, high inter-individual heterogeneity in altitude exposure, and a failure to consider how hypobaric environments alter drug absorption, distribution, and overall pharmacokinetics[19,20].

To resolve this mechanism–efficacy gap, greater attention should be given to the pharmacokinetic and pharmacodynamic (PK/PD) properties of antioxidant compounds, including their bioavailability, tissue distribution, and ability to reach relevant redox-sensitive targets. Differences in these characteristics may partially explain why favorable preclinical findings have not consistently translated into clinical benefit[19]. For instance, vitamin C is a hydrophilic antioxidant characterized by dose-dependent absorption and rapid renal elimination, potentially limiting sustained tissue exposure. In contrast, vitamin E (α-tocopherol) is a lipophilic antioxidant whose distribution depends on specialized transport proteins and lipoprotein-mediated trafficking, factors that may influence tissue delivery and therapeutic efficacy[21,22].

Importantly, these pharmacological considerations may be further compounded under hypobaric hypoxic conditions. High-altitude exposure acts as a systemic modifier of xenobiotic metabolism by altering gastrointestinal blood flow, modulating hepatic cytochrome P450 activity, and affecting renal clearance. Such physiological adaptations can substantially influence drug absorption, distribution, metabolism, and elimination, thereby altering antioxidant exposure at the target tissue level. Consequently, antioxidant compounds that demonstrate robust free-radical scavenging activity in vitro may fail to achieve sufficient bioavailability or tissue concentrations to attenuate RVH in clinical settings.

1.5. Astaxanthin as a Novel Antioxidant Strategy

Considering the limitations of conventional therapies, astaxanthin—a marine-derived, lipophilic xanthophyll carotenoid—has garnered significant attention. Structurally, astaxanthin possesses a unique conjugated polyene chain flanked by ionone rings, allowing it to span the entire cellular bilayer. This precise orientation enables it to scavenge ROS both within the hydrophobic core and on the hydrophilic surface of cell membranes, providing superior protection against lipid peroxidation compared to standard antioxidants in patients with coronary artery disease[9].

Experimental animal model under CIHH have demonstrated that astaxanthin administration significantly down-regulates the expression of Nox2 and p22phox, effectively reducing MDA levels in right ventricular tissue[23]. Beyond its direct scavenging capabilities, astaxanthin enhances the endogenous antioxidant network by up-regulating glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities via the Nrf2 signaling pathway. By suppressing upstream oxidative injury and preserving membrane integrity, astaxanthin significantly attenuates right ventricular wall thickening and limits fibrotic remodeling, making it a premier next-generation candidate for hypoxic cardio protection (Figure 1).

Despite growing experimental evidence supporting the role of Nox2 in CIHH-induced RVH, several critical gaps remain. First, most mechanistic data originate from animal models, whereas human studies remain scarce. Second, the relative contribution of Nox2 compared with mitochondrial ROS, Nox4, or uncoupled eNOS remains uncertain. Third, selective Nox2 inhibitors have not yet been evaluated in controlled clinical trials involving CIHH-exposed populations.

1.6. Discussion and Integrated Cardiopulmonary Model

The pleiotropic actions of astaxanthin support a broader and more integrated view of cardiovascular

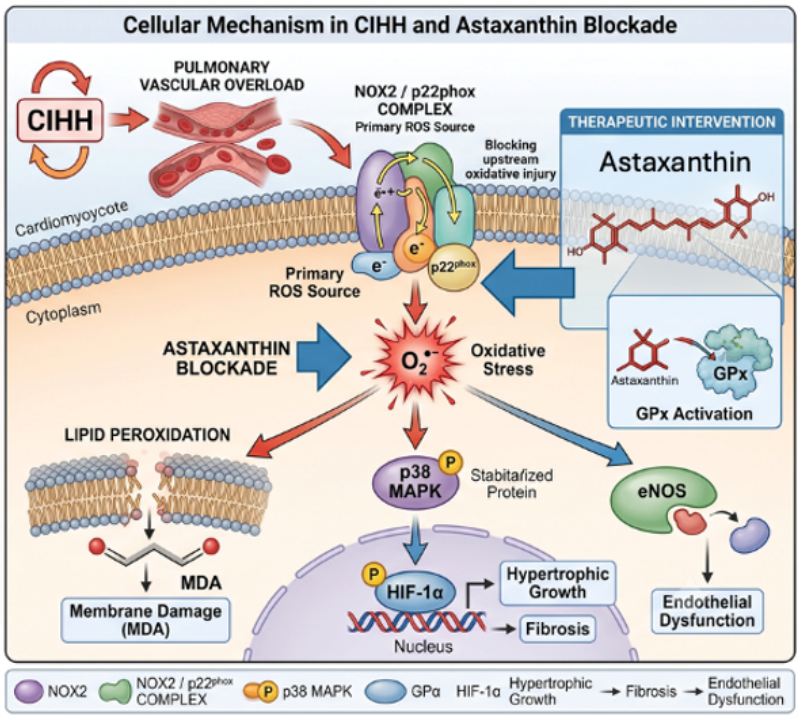

Figure 1. Representation of the pathophysiological cascade and point of selective blockade. The methodological diagram shows the progression of myocardial damage secondary to CIHH exposure. Intermittent hypoxia triggers an increase in oxidative stress through the activation of the NADPH oxidase 2 (Nox2 / p22phox) cellular complex. This acts as a second messenger, stabilizing factors such as HIF-1α and phosphorylating the p38 MAPK pathway to consolidate right ventricular hypertrophy (RVH). The molecular rescue mechanism exerted upstream by Astaxanthin is highlighted, which blocks the pro-oxidant enzyme and stimulates the endogenous activity of glutathione peroxidase (GPx).

adaptation to chronic intermittent hypobaric hypoxia (CIHH). Rather than acting as an isolated source of oxidative stress, Nox2 occupies a central position within a complex cardiopulmonary signaling network that links pulmonary vascular dysfunction with right ventricular remodeling. Sustained Nox2 activation promotes the oxidation of BH_4, resulting in eNOS uncoupling, reduced nitric oxide bioavailability, and endothelial dysfunction. These alterations contribute to persistent pulmonary vasoconstriction and elevated right ventricular afterload, thereby increasing mechanical stress on the myocardium and establishing a self-perpetuating cycle of oxidative injury and ventricular remodeling[24].

Recent advances in hypoxia research further indicate that Nox2-derived oxidative stress is closely intertwined with mitochondrial dysfunction and metabolic reprogramming. Excessive ROS production disrupts mitochondrial function, promotes secondary mitochondrial ROS generation, and establishes a feed-forward cycle that amplifies oxidative stress, inflammation, and tissue remodeling within both the pulmonary vasculature and the right ventricular myocardium[25,26].

The limited success of conventional antioxidant therapies may therefore reflect an inability to effectively target this interconnected redox network. Consequently, future therapeutic strategies should prioritize compounds with high bioavailability and subcellular specificity, such as astaxanthin, capable of reaching critical sites of ROS generation, including mitochondrial and plasma membranes. In parallel, future clinical studies should incorporate validated biomarkers of oxidative stress and Nox2 activity—including plasma F_2-isoprostanes, advanced oxidation protein products, and enzyme-specific activity assays—together with rigorous pharmacokinetic and pharmacodynamic monitoring. Such an approach may facilitate the development of personalized redox-based therapies tailored to the magnitude of hypoxic exposure and the individual cardiopulmonary response (Figure 2).

2. CONCLUSION

Accumulating evidence identifies Nox2-derived oxidative stress as a central mediator linking chronic intermittent hypobaric hypoxia to pulmonary vascular remodeling, high-altitude pulmonary hypertension, and right ventricular hypertrophy. Through interactions with HIF-1α signaling, mitochondrial dysfunction, inflammation, and endothelial injury, Nox2 contributes to the transition from adaptive remodeling to maladaptive

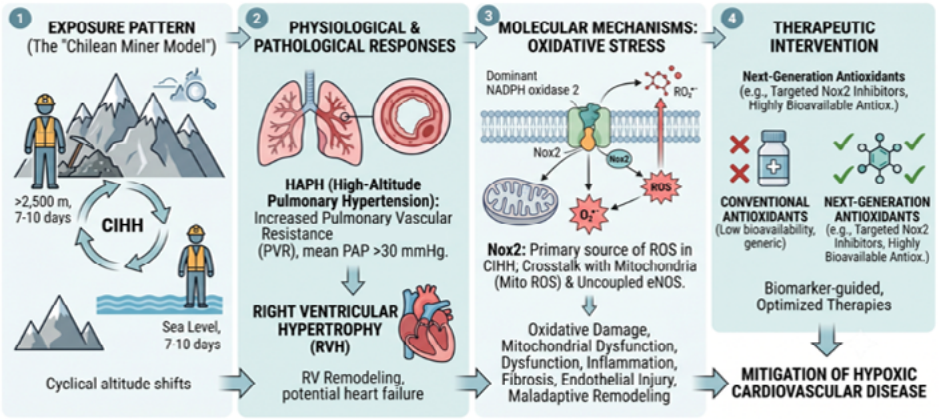

Figure 2. Pathophysiological framework of chronic intermittent hypobaric hypoxia (CIHH) and its role in right ventricular hypertrophy (RVH). The schematic representation illustrates: (1) The Exposure Pattern ("Chilean miner model"), characterized by cyclical shifts between high altitude (>2,500 m for 7–10 days) and sea level (for 7 days); (2) Physiological and Pathological Responses, where CIHH triggers hypoxic pulmonary vasoconstriction (HPV) and pulmonary vascular remodeling, leading to High-Altitude Pulmonary Hypertension (HAPH; mean pulmonary artery pressure [mPAP] >30 mmHg) and subsequent compensatory or maladaptive RVH; (3) Molecular Mechanisms of Oxidative Stress, highlighting NADPH oxidase 2 (Nox2) as the primary source of reactive oxygen species (ROS) and its pathological crosstalk with mitochondrial ROS and uncoupled endothelial nitric oxide synthase (eNOS), which drives mitochondrial dysfunction, inflammation, and fibrosis; and (4) Therapeutic Intervention, contrasting the limitations of conventional antioxidants (low bioavailability) with the potential of biomarker-guided, next-generation antioxidants (e.g., targeted Nox2 inhibitors) to mitigate hypoxic cardiovascular disease.

cardiovascular disease. While conventional antioxidant therapies have demonstrated limited clinical success, next-generation compounds such as astaxanthin and selective Nox2-targeted strategies represent promising therapeutic avenues. Future studies integrating molecular biomarkers, pharmacokinetic optimization, and precision medicine approaches will be essential for translating these findings into clinical practice.

Finalmente, se identificaron facilitadores y limitantes clave para la implementación de la aromaterapia en el entorno de atención obstétrica. La coherencia con prácticas de parto humanizado, el bajo costo y facilidad de administración son facilitadores cruciales. Sin embargo, la dificultad para cegar estudios debido a la variabilidad individual en la tolerancia, la presencia ocasional de efectos leves y la ausencia de protocolos estandarizados se reconocen como limitantes. Estas últimas observaciones no debilitan la evidencia, sino que impulsan la necesidad de avanzar hacia el desarrollo de guías clínicas y protocolos que permitan su incorporación segura, uniforme y estandarizada en los servicios de salud.

References

1. Brito, J., Siques, P., & Pena, E. (2020). Long-term chronic intermittent hypoxia: a particular form of chronic high-altitude pulmonary hypertension. Pulmonary circulation, 10(1 Suppl), 5–12. https://doi.org/10.1177/2045894020934625
2. Richalet, J.P., Lhuissier, F.J., Rathat, C., et al. (2023). Cardiovascular physiology and pathophysiology at high altitude. Nature Reviews Cardiology, 21, 157–176.
3. Pena, E., El Alam, S., Siques, P., & Brito, J. (2022). Oxidative Stress and Diseases Associated with High-Altitude Exposure. Antioxidants (Basel, Switzerland), 11(2), 267. https://doi.org/10.3390/antiox11020267
4. Yang, X., Liu, H., & Wu, X. (2025). High-altitude pulmonary hypertension: a comprehensive review of mechanisms and management. Clinical and experimental medicine, 25(1), 79. https://doi.org/10.1007/s10238-025-01577-3
5. Pullamsetti, S. S., Vanderpool, R. R., de Man, F., de Jesus Perez, V. A., Hemnes, A. R., Mukherjee, M., et al. (2026). Advanced Molecular, Metabolic, and Imaging Approaches to Characterizing Right Ventricular Failure: A Scientific Statement from the American Heart Association. Circulation, 153(19), e1304–e1322.
6. Guo, Z., Tian, Y., Liu, N., Chen, Y., Chen, X., Yuan, G., Chang, A., Chang, X., Wu, J., & Zhou, H. (2024). Mitochondrial Stress as a Central Player in the Pathogenesis of Hypoxia-Related Myocardial Dysfunction: New Insights. International journal of medical sciences, 21(13), 2502–2509. https://doi.org/10.7150/ijms.99359
7. Pena, E., Siques, P., Brito, J., Arribas, S. M., Böger, R., Hannemann, J., León-Velarde, F., González, M. C., López, M. R., & López de Pablo, Á. L. (2020). Nox2 upregulation and p38α MAPK activation in right ventricular hypertrophy of rats exposed to long-term chronic intermittent hypobaric hypoxia. International Journal of Molecular Sciences, 21(22), 8576. https://doi.org/10.3390/ijms21228576
8. Jie, H., Zhang, J., Wu, S., Yu, L., Li, S., Dong, B., & Yan, F. (2025). Interplay between energy metabolism and NADPH oxidase-mediated pathophysiology in cardiovascular diseases. Frontiers in pharmacology, 15, 1503824. https://doi.org/10.3389/fphar.2024.1503824
9. Heidari, M., Chaboksafar, M., Alizadeh, M., Sohrabi, B., & Kheirouri, S. (2023). Effects of Astaxanthin supplementation on selected metabolic parameters, anthropometric indices, Sirtuin1 and TNF-α levels in patients with coronary artery disease: A randomized, double-blind, placebo-controlled clinical trial. Frontiers in nutrition, 10, 1104169. https://doi.org/10.3389/fnut.2023.1104169
10. Calderon-Jofre R, Moraga D and Moraga FA (2022) The Effect of Chronic Intermittent Hypobaric Hypoxia on Sleep Quality and Melatonin Serum

Levels in Chilean Miners. Front. Physiol. 12:809360. doi: 10.3389/fphys.2021.809360

11. Figueroa, E. G., González-Candia, A., Candia, A. A., Paz, A. A., Arias, P. V., Rodríguez-Borges, J., Herrera, E. A., & Castillo, R. L. (2026). Lung Vascular Remodeling and Oxidative Damage Induced by Chronic Intermittent Hypoxia. International journal of molecular sciences, 27(8), 3434. https://doi.org/10.3390/ijms27083434
12. von Euler, U. S., & Liljestrand, G. (1946). Observations on the pulmonary arterial blood pressure in the cat. Acta Physiologica Scandinavica, 12(4), 301–320. https://doi.org/10.1111/j.1748-1716.1946.tb00389.x
13. Siques, P., Brito, J., & Pena, E. (2018). Reactive Oxygen Species and Pulmonary Vasculature During Hypobaric Hypoxia. Frontiers in physiology, 9, 865. https://doi.org/10.3389/fphys.2018.00865
14. Lüneburg, N., Siques, P., Brito, J., De La Cruz, J. J., León-Velarde, F., Hannemann, J., Ibanez, C., & Böger, R. H. (2017). Long-Term Intermittent Exposure to High Altitude Elevates Asymmetric Dimethylarginine in First Exposed Young Adults. High altitude medicine & biology, 18(3), 226–233. https://doi.org/10.1089/ham.2016.0123
15. Siques, P., Brito, J., Schwedhelm, E., Pena, E., León-Velarde, F., De La Cruz, J. J., Böger, R. H., & Hannemann, J. (2019). Asymmetric Dimethylarginine at Sea Level Is a Predictive Marker of Hypoxic Pulmonary Arterial Hypertension at High Altitude. Frontiers in physiology, 10, 651. https://doi.org/10.3389/fphys.2019.00651
16. Hannemann, J., Siques, P., Schmidt-Hutten, L., Zummack, J., Brito, J., & Böger, R. (2021). Association of Genes of the NO Pathway with Altitude Disease and Hypoxic Pulmonary Hypertension. Journal of clinical medicine, 10(24), 5761. https://doi.org/10.3390/jcm10245761
17. Wang, X., Liu, R., & Liu, D. (2025). The Role of the MAPK Signaling Pathway in Cardiovascular Disease: Pathophysiological Mechanisms and Clinical Therapy. International journal of molecular sciences, 26(6), 2667. https://doi.org/10.3390/ijms26062667
18. Pena, E., Del Río, A., & Flores, S. (2026). Systematic review and meta-analysis of antioxidant treatment in patients with acute mountain sickness induced by high altitude exposure. Frontiers in Physiology, 17, 1779008. DOI: 10.3389/fphys.2026.1779008.
19. Poyatos, P., Gratacós, M., Samuel, K., Orriols, R., & Tura-Ceide, O. (2023). Oxidative Stress and Antioxidant Therapy in Pulmonary Hypertension. Antioxidants (Basel, Switzerland), 12(5), 1006. https://doi.org/10.3390/antiox12051006
20. Zhao, A., Li, W., & Wang, R. (2023). The Influences and Mechanisms of High-altitude Hypoxia Exposure on Drug Metabolism. Current drug metabolism, 24(3), 152–161. https://doi.org/10.2174/1389200224666221228115526
21. Lykkesfeldt, J., & Tveden-Nyborg, P. (2019). The Pharmacokinetics of Vitamin C. Nutrients, 11(10), 2412. https://doi.org/10.3390/nu11102412
22. Traber M. G. (2007). Vitamin E regulatory mechanisms. Annual review of nutrition, 27, 347–362. https://doi.org/10.1146/annurev.nutr.27.061406.093819
23. Pena, E., El Alam, S., Gonzalez, C., Cortés, I., Aguilera, D., Flores, K., & Arriaza, K. (2024). Astaxanthin Supplementation Effects in Right Ventricle of Rats Exposed to Chronic Intermittent Hypobaric Hypoxia. Antioxidants, 13(10), 1269. https://doi.org/10.3390/antiox13101269
24. Camargo, L. L., Rios, F. J., Montezano, A. C., & Touyz, R. M. (2025). Reactive oxygen species in hypertension. Nature reviews. Cardiology, 22(1), 20–37. https://doi.org/10.1038/s41569-024-01062-6
25. Wang, H., Song, T. Y., Reyes-García, J., & Wang, Y. X. (2024). Hypoxia-Induced Mitochondrial ROS and Function in Pulmonary Arterial Endothelial Cells. Cells, 13(21), 1807. https://doi.org/10.3390/cells13211807
26. Yang H. M. (2025). Mitochondrial Dysfunction in Cardiovascular Diseases. International journal of molecular sciences, 26(5), 1917. https://doi.org/10.3390/ijms26051917