

Intermittent Hypoxia and Its Impact on Right Ventricular Remodeling: Pathophysiological Mechanisms and Clinical Implications

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ABSTRACT

Intermittent hypoxia (IH) is a recurrent phenomenon observed in various pathological conditions, most notably in obstructive sleep apnea (OSA), chronic thromboembolic pulmonary hypertension (CTEPH), and high-altitude diseases. This cyclic pattern of oxygen deprivation and reoxygenation induces significant structural and functional alterations in the right ventricle (RV), leading to maladaptive remodeling. The RV is highly susceptible to increased afterload, particularly due to pulmonary vascular changes driven by hypoxia-induced endothelial dysfunction, oxidative stress, and inflammatory cascades. These factors contribute to myocardial fibrosis, increased RV wall stress, and ultimately right ventricular failure.

This review aims to provide a comprehensive analysis of the molecular and cellular mechanisms by which IH influences RV remodeling, focusing on mitochondrial dysfunction, reactive oxygen species (ROS) production, autonomic dysregulation, and hypoxia-inducible factor-1 α (HIF-1 α)-mediated pathways. Furthermore, we discuss the potential role of biomarkers, imaging modalities, and emerging therapeutic strategies to mitigate the adverse effects of IH on the RV. Given the rising clinical burden of conditions associated with IH, understanding these mechanisms is critical for developing targeted interventions to prevent or reverse RV dysfunction.

KEYWORDS: Intermittent hypoxia, right ventricular remodeling, oxidative stress, hypoxia-inducible factor-1 α , pulmonary hypertension, obstructive sleep apnea, myocardial fibrosis.

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INTRODUCTION

The right ventricle (RV) plays a fundamental role in maintaining pulmonary circulation and systemic venous return. Unlike the left ventricle (LV), the RV is anatomically and functionally adapted to a low-pressure, high-compliance environment. However, under conditions of increased afterload, such as pulmonary hypertension (PH) or chronic hypoxic states, the RV undergoes significant structural and functional adaptations. Intermittent hypoxia (IH), characterized by repeated cycles of oxygen deprivation followed by reoxygenation, has been increasingly recognized as a major contributor to RV remodeling. This phenomenon is commonly observed in patients with obstructive sleep apnea (OSA), chronic thromboembolic pulmonary hypertension (CTEPH), and other hypoxia-associated

diseases, leading to progressive RV dysfunction and failure.^{1,2}

IH exerts profound pathophysiological effects on the cardiovascular system, particularly on the pulmonary vasculature and the RV myocardium. The cyclical nature of hypoxia triggers endothelial dysfunction, inflammation, oxidative stress, and sympathetic nervous system overactivation, all of which contribute to maladaptive RV remodeling. Hypoxia-inducible factor-1 α (HIF-1 α) plays a central role in mediating the cellular responses to IH, promoting angiogenesis, metabolic shifts, and fibrosis. Additionally, mitochondrial dysfunction and excessive reactive oxygen species (ROS) production exacerbate myocardial injury, leading to contractile impairment and increased RV wall stress.^{2,3}

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Despite growing evidence linking IH to adverse cardiovascular outcomes, the precise mechanisms underlying IH-induced RV remodeling remain incompletely understood. Furthermore, current therapeutic strategies primarily focus on managing pulmonary hypertension and its hemodynamic consequences, with limited targeted approaches to directly mitigate RV remodeling. The development of novel pharmacological and interventional strategies requires a deeper understanding of the molecular pathways involved in IH-induced myocardial injury.³

This review aims to provide an in-depth exploration of the impact of IH on RV remodeling, emphasizing the underlying molecular mechanisms, potential biomarkers, imaging modalities, and emerging therapeutic strategies. By elucidating these pathophysiological processes, we hope to advance the development of targeted interventions to prevent or reverse RV dysfunction in patients affected by IH-associated conditions.⁴

Epidemiology of Intermittent Hypoxia and Its Impact on Right Ventricular Remodeling

Intermittent hypoxia (IH) is a pathophysiological phenomenon observed in a wide spectrum of clinical conditions, most notably in obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), chronic thromboembolic pulmonary hypertension (CTEPH), and high-altitude diseases. The global burden of IH-associated disorders has significantly increased over the past decades, paralleling the rising prevalence of obesity, metabolic syndrome, and chronic lung diseases. Given the direct impact of IH on pulmonary vascular resistance and right ventricular (RV) function, understanding its epidemiology is crucial for assessing its clinical significance and associated cardiovascular risks.⁴

Prevalence of Intermittent Hypoxia in Obstructive Sleep Apnea and Its Cardiovascular Consequences

OSA represents the most extensively studied condition associated with IH. Current epidemiological data suggest that OSA affects approximately 1 billion people worldwide, with prevalence rates varying by age, sex, and geographic region. Population-based studies indicate that moderate-to-severe OSA (defined by an apnea-hypopnea index [AHI] ≥ 15 events per hour) is present in approximately 13% of men and 6% of women aged 30 to 70 years. The incidence of OSA increases substantially in individuals with obesity, type 2 diabetes, and hypertension, making it a major contributor to cardiovascular morbidity.⁴

The recurrent nocturnal hypoxemia observed in OSA leads to chronic intermittent hypoxia, characterized by alternating cycles of arterial oxygen desaturation and reoxygenation. This cyclical pattern is a potent stimulus for oxidative stress, systemic inflammation, and sympathetic nervous system activation, all of which contribute to pulmonary vascular remodeling, increased right ventricular afterload, and

subsequent RV dysfunction. Longitudinal cohort studies have demonstrated that patients with severe OSA have a significantly increased risk of developing pulmonary hypertension (PH), with estimated prevalence rates ranging from 15% to 40%, depending on diagnostic criteria and study population. The presence of PH in OSA patients is associated with more pronounced RV hypertrophy, increased RV wall stress, and a higher likelihood of progression to right heart failure.⁴

Intermittent Hypoxia in Chronic Obstructive Pulmonary Disease and Overlap Syndrome

COPD is another major contributor to IH, particularly in patients with coexisting OSA, a condition referred to as "overlap syndrome." COPD affects over 300 million individuals worldwide and is one of the leading causes of morbidity and mortality. In patients with advanced COPD, the presence of nocturnal oxygen desaturation, secondary to ventilation-perfusion mismatch and respiratory muscle fatigue, leads to chronic IH, which exacerbates pulmonary vascular remodeling and RV strain. Studies have shown that patients with overlap syndrome exhibit a higher prevalence of pulmonary hypertension and more severe RV dysfunction compared to those with isolated OSA or COPD.⁴

Epidemiological investigations have reported that up to 40% of patients with severe COPD develop pulmonary hypertension, with an associated 2- to 3-fold increase in mortality risk. The mechanisms underlying RV remodeling in these patients are multifactorial, involving sustained hypoxic pulmonary vasoconstriction, endothelial dysfunction, and increased oxidative stress. The interplay between IH and hypercapnia further compounds the hemodynamic burden on the RV, leading to progressive right heart failure in a significant subset of patients.⁵

High-Altitude Hypoxia and Its Effects on Right Ventricular Function

Intermittent exposure to high-altitude hypoxia represents another clinically relevant model of IH, particularly in individuals who frequently ascend to altitudes above 2,500 meters. Acute exposure to high-altitude hypoxia triggers adaptive pulmonary vasoconstriction to optimize oxygen delivery; however, chronic exposure or recurrent altitude exposure leads to maladaptive pulmonary vascular remodeling and increased RV afterload. Studies in high-altitude populations, such as those residing in the Andes and the Himalayas, have demonstrated a higher prevalence of pulmonary hypertension, with estimates ranging from 5% to 15% depending on altitude and duration of exposure.⁵

Individuals with chronic mountain sickness (CMS) experience prolonged IH due to inadequate ventilatory acclimatization, resulting in polycythemia, increased pulmonary arterial pressure, and RV hypertrophy. Longitudinal studies have shown that persistent exposure to high-altitude IH accelerates the progression of RV

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dysfunction, predisposing affected individuals to right heart failure if not properly managed.⁵

Intermittent Hypoxia in Chronic Thromboembolic Pulmonary Hypertension and Other Rare Pulmonary Disorders

Chronic thromboembolic pulmonary hypertension (CTEPH) is a relatively rare but significant cause of IH-related RV remodeling. It affects approximately 3 to 4 individuals per million annually and results from unresolved pulmonary thromboemboli leading to persistent pulmonary vascular obstruction and hypoxia. The presence of IH in CTEPH further exacerbates pulmonary vascular resistance, contributing to RV strain and failure.⁶

Additionally, conditions such as sickle cell disease, neuromuscular disorders with nocturnal hypoventilation, and congenital central hypoventilation syndrome (CCHS) have been associated with intermittent hypoxia-induced cardiovascular remodeling. Although these disorders are less prevalent, their impact on RV structure and function highlights the broader implications of IH beyond common cardiopulmonary conditions.⁶

Public Health and Clinical Implications

The growing burden of IH-associated disorders underscores the need for early identification and targeted interventions to mitigate its cardiovascular sequelae. Epidemiological data suggest that untreated IH, particularly in OSA and COPD, significantly increases the risk of cardiovascular morbidity and mortality. The recognition of RV remodeling as a key pathophysiological consequence of IH warrants greater attention to screening strategies, risk stratification, and therapeutic approaches aimed at alleviating hypoxia-induced myocardial injury.⁶

Despite advancements in our understanding of IH and its impact on the RV, gaps remain in the epidemiological characterization of IH-related cardiovascular dysfunction across diverse populations. Future research should focus on refining diagnostic criteria, elucidating genetic and environmental determinants of susceptibility, and developing precision medicine approaches to optimize patient outcomes.⁷

Clinical Manifestations of Intermittent Hypoxia-Induced Right Ventricular Remodeling

Intermittent hypoxia (IH) exerts a profound impact on the cardiovascular system, particularly on the right ventricle (RV), due to its role in regulating pulmonary vascular resistance and maintaining hemodynamic stability under varying oxygenation conditions. The chronic cyclic exposure to hypoxic episodes leads to progressive structural and functional changes in the RV, predisposing individuals to right ventricular dysfunction and, ultimately, right heart failure. The clinical manifestations of IH-induced RV remodeling are highly variable, depending on the severity, duration, and underlying etiology of the hypoxic insult. These

manifestations range from subclinical ventricular dysfunction detected only by advanced imaging modalities to overt heart failure with significant functional impairment.⁷

1. Early-Stage Manifestations: Subclinical Right Ventricular Dysfunction

In the initial phases of RV remodeling due to IH, patients often remain asymptomatic or present with non-specific complaints that may not immediately suggest cardiovascular pathology. The early compensatory responses of the RV to increased afterload include myocardial hypertrophy, enhanced contractility, and neurohormonal activation, which may mask the progression of functional deterioration. However, subtle clinical and subclinical indicators may be present, including:⁸

- **Mild exertional dyspnea:** Patients may report increased shortness of breath during moderate physical activity, reflecting an early rise in pulmonary vascular resistance.⁸
- **Fatigue and reduced exercise tolerance:** Impaired RV diastolic function and diminished cardiac output contribute to systemic hypoperfusion and decreased oxygen delivery to skeletal muscles.⁸
- **Palpitations or mild arrhythmias:** Hypoxia-induced autonomic dysregulation and myocardial fibrosis can predispose patients to supraventricular and ventricular arrhythmias, detected via Holter monitoring or electrocardiographic studies.⁸
- **Mild systemic hypertension or pulmonary hypertension (PH) on echocardiography:** Increased sympathetic drive due to recurrent hypoxia may lead to transient systemic and pulmonary arterial hypertension, promoting RV hypertrophy.

At this stage, standard clinical evaluation may fail to detect significant RV dysfunction, necessitating the use of advanced imaging modalities such as speckle-tracking echocardiography or cardiac magnetic resonance imaging (CMR) to assess strain patterns and myocardial fibrosis.⁸

2. Progression to Symptomatic Right Ventricular Dysfunction

As IH persists, the RV undergoes progressive maladaptive remodeling, leading to increased chamber dilation, wall stress, and impaired contractility. The clinical presentation at this stage is more overt and is often characterized by signs and symptoms suggestive of right ventricular failure:⁸

- **Worsening dyspnea, particularly at rest or with minimal exertion:** This results from elevated right atrial pressures, increased pulmonary vascular resistance, and compromised RV output.⁹
- **Orthopnea and paroxysmal nocturnal dyspnea:** These symptoms reflect venous congestion due to progressive RV failure and may be particularly pronounced in patients with coexisting left ventricular dysfunction.⁹

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- **Peripheral edema:** IH-induced RV dysfunction frequently leads to systemic venous congestion, resulting in lower extremity pitting edema, ascites, and anasarca in advanced cases.⁹
- **Jugular venous distension (JVD) and hepatojugular reflux:** Elevated right atrial pressures translate into increased central venous pressures, manifesting as prominent JVD and a positive hepatojugular reflux test.⁹
- **Hepatic congestion and hepatomegaly:** Chronic venous congestion secondary to RV dysfunction leads to hepatomegaly, right upper quadrant discomfort, and, in severe cases, cardiac cirrhosis and coagulopathy.⁹
- **Nocturnal hypoxia and worsening oxygen desaturation:** Recurrent desaturation episodes, particularly in conditions such as obstructive sleep apnea (OSA), contribute to increased pulmonary pressures and worsening RV strain.⁹

Cardiopulmonary exercise testing (CPET) in this population often reveals impaired oxygen uptake kinetics, reduced ventilatory efficiency, and an exaggerated ventilatory response to exercise, consistent with right heart failure physiology. Additionally, brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels may be elevated, reflecting increased myocardial wall stress and neurohormonal activation.¹⁰

3. Advanced Right Heart Failure and Systemic Complications

In the final stages of RV failure due to IH, patients exhibit signs of decompensated heart failure with multi-organ involvement. This phase is often associated with:

- **Severe volume overload and refractory edema:** Worsening RV function leads to intractable fluid retention, ascites, and hydrothorax, necessitating frequent diuretic therapy and, in some cases, paracentesis.¹⁰
- **Cardiorenal syndrome:** Congestive hepatopathy and systemic venous congestion contribute to renal dysfunction, with prerenal azotemia progressing to intrinsic kidney injury.¹⁰
- **Gastrointestinal dysfunction:** Chronic venous congestion impairs hepatic and mesenteric circulation, leading to nausea, early satiety, malabsorption, and protein-losing enteropathy.¹⁰
- **Severe hypoxemia and pulmonary hypertension crisis:** Exacerbation of pulmonary vascular disease due to IH can precipitate acute right heart decompensation, necessitating hospitalization and advanced supportive therapies such as non-invasive ventilation or pulmonary vasodilators.¹⁰
- **Arrhythmogenic right ventricular cardiomyopathy-like features:** Chronic hypoxia-driven myocardial fibrosis and electrical remodeling

predispose patients to life-threatening ventricular arrhythmias and sudden cardiac death.¹¹

Patients with advanced IH-induced RV failure often require multimodal management, including positive airway pressure therapy (for OSA-related IH), targeted pulmonary vasodilators (for concomitant PH), and close monitoring for heart transplantation or mechanical circulatory support in refractory cases.¹¹

The clinical spectrum of IH-induced RV remodeling is broad, encompassing a continuum from asymptomatic early dysfunction to overt right heart failure. The variable presentation underscores the importance of early recognition and comprehensive cardiovascular assessment in patients with chronic hypoxic conditions. Advanced imaging techniques, biomarker profiling, and functional assessments such as CPET provide valuable insights into disease progression and therapeutic responsiveness. Given the increasing prevalence of IH-related disorders, a heightened clinical awareness of its impact on RV structure and function is crucial for optimizing patient outcomes and preventing irreversible cardiac deterioration.¹¹

Pathophysiology of Intermittent Hypoxia-Induced Right Ventricular Remodeling

Intermittent hypoxia (IH), characterized by recurrent cycles of oxygen desaturation and reoxygenation, induces a complex pathophysiological response in the cardiovascular system, particularly in the right ventricle (RV), which is inherently sensitive to variations in pulmonary vascular resistance. The RV, being a low-pressure, high-compliance chamber, undergoes significant structural and functional adaptations in response to IH-driven changes in pulmonary hemodynamics, myocardial metabolism, and neurohormonal signaling. These maladaptive processes ultimately contribute to RV dysfunction, culminating in right heart failure if left unchecked. The underlying pathophysiological mechanisms of IH-induced RV remodeling encompass pulmonary vascular dysfunction, myocardial remodeling, oxidative stress, metabolic dysregulation, and neurohormonal activation.¹¹

1. Pulmonary Vascular Dysfunction and Right Ventricular Afterload Increase

The primary driver of RV remodeling in IH is the development of hypoxia-induced pulmonary hypertension (PH), which results from multiple converging mechanisms, including:

- **Hypoxia-induced pulmonary vasoconstriction (HPV):** IH leads to repetitive episodes of alveolar hypoxia, triggering HPV via increased intracellular calcium levels in pulmonary arterial smooth muscle cells (PASMCs). This process acutely increases pulmonary vascular resistance (PVR) and, over time, leads to sustained vascular remodeling.¹²
- **Endothelial dysfunction:** Chronic cycles of hypoxia and reoxygenation promote endothelial

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injury, reducing the bioavailability of vasodilators such as nitric oxide (NO) while increasing vasoconstrictors like endothelin-1 (ET-1). This imbalance contributes to a persistent hypertensive pulmonary environment, placing sustained pressure overload on the RV.¹²

- **Pulmonary vascular remodeling:** IH promotes proliferation of PASMCs and fibroblasts, leading to medial hypertrophy, adventitial fibrosis, and perivascular inflammation in the pulmonary arteries. These structural changes increase vascular stiffness and impair vasodilatory responsiveness, further exacerbating RV afterload.¹³
- **Inflammatory and thrombogenic milieu:** IH enhances systemic and local inflammation through upregulation of cytokines (e.g., IL-6, TNF- α) and oxidative stress pathways, fostering a prothrombotic state that predisposes to microvascular occlusion and increased pulmonary vascular impedance.¹³

As these processes progress, the RV is subjected to chronic pressure overload, necessitating structural and functional adaptations to maintain cardiac output.¹³

2. Right Ventricular Myocardial Remodeling

The RV initially compensates for increased afterload through adaptive hypertrophy, but prolonged exposure to IH-induced stressors precipitates pathological remodeling, characterized by:

- **RV hypertrophy (RVH):** Sustained pressure overload triggers myocyte hypertrophy via upregulation of mechanotransductive pathways, including the mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) signaling cascades. This hypertrophic response is initially beneficial, enhancing contractility and reducing wall stress; however, chronic hypertrophy leads to increased myocardial oxygen demand and vulnerability to ischemic injury.¹⁴
- **Fibrosis and extracellular matrix (ECM) remodeling:** Cyclic hypoxia-reoxygenation episodes promote fibroblast activation and excessive collagen deposition via transforming growth factor-beta (TGF- β) signaling. The resultant interstitial and perivascular fibrosis increases myocardial stiffness, impairs diastolic relaxation, and disrupts electrical conduction, predisposing to arrhythmias.¹⁴
- **Capillary rarefaction and myocardial ischemia:** Despite compensatory hypertrophy, RV microvascular density fails to match increased myocardial mass due to impaired angiogenesis. This results in a supply-demand mismatch, exacerbating ischemic injury and promoting myocyte apoptosis. Chronic ischemia further stimulates reactive oxygen

species (ROS) generation, perpetuating myocardial damage.¹⁴

- **Contractile dysfunction and RV failure:** With progressive fibrosis, ischemia, and oxidative injury, the RV transitions from a compensatory to a decompensatory phase, characterized by reduced contractile reserve, impaired systolic function, and chamber dilation. Eventually, maladaptive remodeling leads to RV failure, with reduced cardiac output and systemic venous congestion.¹⁴

3. Oxidative Stress and Mitochondrial Dysfunction

IH-induced cyclic desaturation-reoxygenation events generate a profound oxidative stress response, with mitochondria playing a central role in this process. Key mechanisms include:

- **Mitochondrial ROS production:** Hypoxia-induced mitochondrial dysfunction leads to excessive production of ROS, primarily through complex I and III of the electron transport chain. Reoxygenation further exacerbates oxidative stress, inducing lipid peroxidation, DNA damage, and protein oxidation.¹⁴
- **Endoplasmic reticulum (ER) stress and apoptosis:** Persistent oxidative stress activates ER stress pathways, leading to unfolded protein response (UPR) activation and apoptotic signaling through CHOP and caspase cascades, contributing to myocyte loss and contractile dysfunction.¹⁵
- **NADPH oxidase (NOX) activation:** Hypoxia-reoxygenation cycles upregulate NOX enzymes, particularly NOX2 and NOX4, in cardiac and vascular cells, amplifying ROS production and perpetuating inflammatory and fibrotic pathways.¹⁵

The interplay between oxidative stress, mitochondrial dysfunction, and impaired energy metabolism contributes to progressive myocardial injury, exacerbating RV remodeling.¹⁵

4. Metabolic Dysregulation and Right Ventricular Energetic Failure

IH disrupts normal myocardial metabolic homeostasis, shifting RV energy production from oxidative phosphorylation to glycolysis, a process similar to the Warburg effect in cancer. This metabolic shift results in:¹⁵

- **Impaired fatty acid oxidation (FAO):** Hypoxia suppresses key regulators of FAO, such as peroxisome proliferator-activated receptor-alpha (PPAR- α) and carnitine palmitoyltransferase-1 (CPT-1), reducing ATP generation from lipid metabolism.¹⁵
- **Increased glycolysis and lactate accumulation:** Upregulation of hypoxia-inducible factor-1 α (HIF-1 α) promotes glycolytic enzyme expression, increasing glucose utilization but reducing overall ATP yield, leading to energy inefficiency.¹⁵

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- **Altered substrate utilization and cardiac inefficiency:** The RV becomes reliant on inefficient glucose metabolism, which fails to meet the high-energy demands of hypertrophied myocardium, ultimately impairing contractile function and accelerating failure.¹⁶

5. Neurohormonal Activation and Systemic Implications

IH-induced RV remodeling is further modulated by systemic neurohormonal responses, including:

- **Sympathetic overactivation:** Chronic hypoxia drives excessive sympathetic output, leading to tachycardia, increased myocardial oxygen demand, and progressive RV dysfunction.¹⁶
- **Renin-angiotensin-aldosterone system (RAAS) activation:** IH stimulates RAAS activity, promoting vasoconstriction, sodium retention, and myocardial fibrosis.¹⁶
- **Imbalance in natriuretic peptides:** BNP and NT-proBNP are elevated in response to RV wall stress, serving as biomarkers of progressive dysfunction but also reflecting maladaptive neurohormonal responses.¹⁷

These systemic neurohormonal alterations contribute to progressive RV decompensation, systemic hypertension, and multiorgan dysfunction.¹⁷

The pathophysiology of IH-induced RV remodeling is multifactorial, involving complex interactions between pulmonary vascular dysfunction, myocardial hypertrophy, fibrosis, oxidative stress, metabolic dysregulation, and neurohormonal activation. While compensatory mechanisms initially support RV adaptation, chronic exposure to IH ultimately drives pathological remodeling, leading to progressive RV dysfunction and failure. Understanding these mechanistic pathways is crucial for developing targeted interventions aimed at mitigating IH-related RV pathology and improving cardiovascular outcomes in affected patients.

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CONCLUSION

Intermittent hypoxia (IH) represents a significant pathophysiological challenge to the cardiovascular system, particularly to the right ventricle (RV), which is uniquely vulnerable to sustained increases in pulmonary vascular resistance and the resulting pressure overload. The chronic and cyclical nature of IH, as seen in conditions such as obstructive sleep apnea, chronic obstructive pulmonary disease, and high-altitude exposure, triggers a cascade of deleterious effects on the pulmonary vasculature and right ventricular myocardium, ultimately driving maladaptive remodeling and functional decline.

The interplay between hypoxia-induced pulmonary vasoconstriction, endothelial dysfunction, inflammatory and oxidative stress responses, and metabolic reprogramming creates a hostile microenvironment within the RV. Initially,

the myocardium adapts through compensatory hypertrophy to counteract the increased afterload; however, as exposure to IH persists, pathological remodeling ensues, characterized by excessive fibrosis, capillary rarefaction, mitochondrial dysfunction, and impaired contractility. These alterations lead to progressive right ventricular dysfunction, culminating in right heart failure if left unchecked.

One of the key mechanistic drivers of IH-induced RV remodeling is the profound pulmonary vascular dysfunction that accompanies chronic hypoxia. The imbalance between vasodilatory and vasoconstrictive mediators, with reduced nitric oxide (NO) bioavailability and increased endothelin-1 (ET-1) signaling, fosters a pro-hypertensive pulmonary environment. Additionally, structural changes in the pulmonary vasculature, including smooth muscle hyperplasia and perivascular fibrosis, further contribute to increased right ventricular afterload. These processes are exacerbated by a systemic inflammatory response and a heightened oxidative stress burden, leading to cellular injury and apoptosis within the RV myocardium.

At the molecular level, IH drives metabolic dysregulation, shifting RV energy production from efficient oxidative phosphorylation to a glycolysis-dominant phenotype. This metabolic shift, largely mediated by hypoxia-inducible factor-1 α (HIF-1 α) and peroxisome proliferator-activated receptor- α (PPAR- α) signaling pathways, ultimately results in energy depletion, increased lactate accumulation, and reduced ATP availability. Furthermore, chronic oxidative stress and mitochondrial dysfunction contribute to an escalating cycle of ischemia-reperfusion injury within the RV, further compromising contractile function.

Beyond the intrinsic myocardial and pulmonary vascular consequences, IH-induced RV remodeling is also modulated by neurohormonal activation, including heightened sympathetic nervous system activity and renin-angiotensin-aldosterone system (RAAS) dysregulation. The resultant increase in systemic vascular resistance, fluid retention, and myocardial fibrosis places additional strain on the failing right ventricle, hastening the progression toward overt right heart failure.

Despite these detrimental effects, the recognition of IH as a potent driver of RV remodeling presents an opportunity for early intervention and therapeutic modulation. Emerging evidence suggests that targeted strategies aimed at mitigating pulmonary hypertension, reducing oxidative stress, improving mitochondrial function, and restoring metabolic homeostasis may hold promise in attenuating IH-induced RV dysfunction. Additionally, interventions aimed at optimizing nocturnal oxygenation, such as continuous positive airway pressure (CPAP) therapy in obstructive sleep apnea, may prove beneficial in reversing some of the maladaptive processes associated with IH.

In conclusion, IH-induced RV remodeling is a multifaceted process driven by complex interactions between pulmonary

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vascular dysfunction, myocardial maladaptation, oxidative and inflammatory injury, metabolic reprogramming, and neurohormonal dysregulation. While compensatory mechanisms initially sustain RV function in response to chronic hypoxic stress, prolonged exposure ultimately leads to decompensatory changes, resulting in progressive RV failure. A deeper understanding of these intricate pathophysiological mechanisms is essential for the development of novel therapeutic strategies aimed at preserving RV function and improving cardiovascular outcomes in patients exposed to chronic IH. Future research should focus on identifying early biomarkers of RV dysfunction in IH, exploring pharmacological and non-pharmacological interventions to mitigate maladaptive remodeling, and elucidating the long-term clinical consequences of IH-related right heart disease.

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