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Exploring the Impact of Chronic Intermittent Hypoxia in Obstructive Sleep Apnea on Cardiovascular Remodeling and Endothelial Dysfunction: Mechanisms and Therapeutic Targets

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1. Abstract

Obstructive sleep apnea (OSA) is a common disorder related to sleep that involves repeated episodes of upper airway collapse during sleep, resulting in chronic intermittent hypoxia (CIH), disrupted sleep, and cycles of reoxygenation. There is growing evidence that CIH is a key pathophysiological factor connecting OSA to cardiovascular diseases (CVD) such as hypertension, atherosclerosis, coronary artery disease, heart failure, and arrhythmias. The cycles of hypoxia and reoxygenation trigger oxidative stress, systemic inflammation, autonomic imbalance, and metabolic disturbances, leading to endothelial dysfunction and structural changes in the cardiovascular system. These pathological changes appear as vascular stiffness, thickening of the intima-media, myocardial fibrosis, ventricular hypertrophy, and reduced vasodilation, which significantly increase cardiovascular morbidity and mortality in OSA patients. This comprehensive review compiles current experimental, clinical, and translational evidence to clarify the molecular, cellular, and physiological mechanisms through which CIH contributes to endothelial dysfunction and cardiovascular remodeling. Key pathways include the production of reactive oxygen species (ROS), activation of hypoxia-inducible factors (HIFs), excessive sympathetic activity, stimulation of the renin–angiotensin–aldosterone system (RAAS), release of inflammatory cytokines, mitochondrial dysfunction, and epigenetic changes including microRNAs like miR-210. We also examine the interaction between endothelial impairment and myocardial remodeling, highlighting how endothelial dysfunction serves as both an initiating and sustaining factor in structural cardiovascular changes. Finally, emerging therapeutic targets are discussed, such as continuous positive airway pressure (CPAP), pharmacological modulation of RAAS, antioxidants, anti-inflammatory agents, mineralocorticoid receptor antagonists, and new molecular therapies targeting HIF signaling and microRNA pathways. By combining mechanistic insights with therapeutic implications, this review underscores future directions for precision medicine approaches aimed at reducing cardiovascular risk in OSA patients. Understanding CIH-induced cardiovascular remodeling and endothelial dysfunction provides a crucial framework for developing targeted interventions that may significantly improve long-term cardiovascular outcomes.

2. Keywords

Obstructive sleep apnea; chronic intermittent hypoxia; endothelial dysfunction; cardiovascular remodeling; inflammation; oxidative stress; sympathetic activation; hypoxia-inducible factors; RAAS; potential therapeutic targets.

3. Introduction

Obstructive sleep apnea (OSA) is a persistent sleep disorder marked by repeated episodes of full or partial blockage of the upper airway during sleep, resulting in intermittent low oxygen levels and awakenings. These cycles of low oxygen and reoxygenation are known as chronic intermittent hypoxia (CIH), which is the main feature of OSA. OSA affects a significant portion of the adult population globally and is closely linked to cardiometabolic disorders and higher mortality rates.

Increasing epidemiological and mechanistic evidence indicates that OSA is an independent risk factor for cardiovascular diseases (CVD), such as hypertension, coronary artery disease, heart failure, and stroke. CIH has systemic effects that lead to endothelial dysfunction, oxidative stress, sympathetic activation, and chronic inflammation, all of which contribute to changes in the structure and function of the heart and blood vessels.

Cardiovascular remodeling involves changes in the structure and function of cardiac and vascular tissues due to chronic stress. In OSA, this remodeling includes left ventricular hypertrophy, enlargement of the atria, thickening of the vascular intima-media, and myocardial fibrosis. These structural alterations often occur before clinical cardiovascular events and serve as early indicators of disease progression.

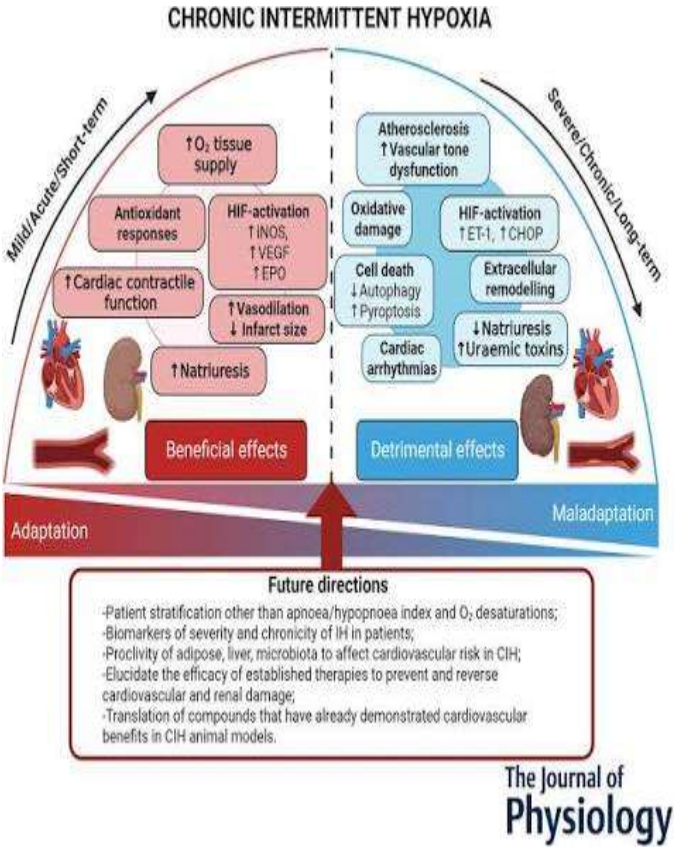
Endothelial dysfunction is considered a crucial initial event in the cardiovascular pathology induced by CIH. The endothelium is vital in controlling vascular tone, inflammation, coagulation, and angiogenesis. CIH reduces the bioavailability of endothelial nitric oxide (NO), increases oxidative stress, and upregulates adhesion molecules and inflammatory cytokines, leading to vascular stiffness and atherosclerosis.

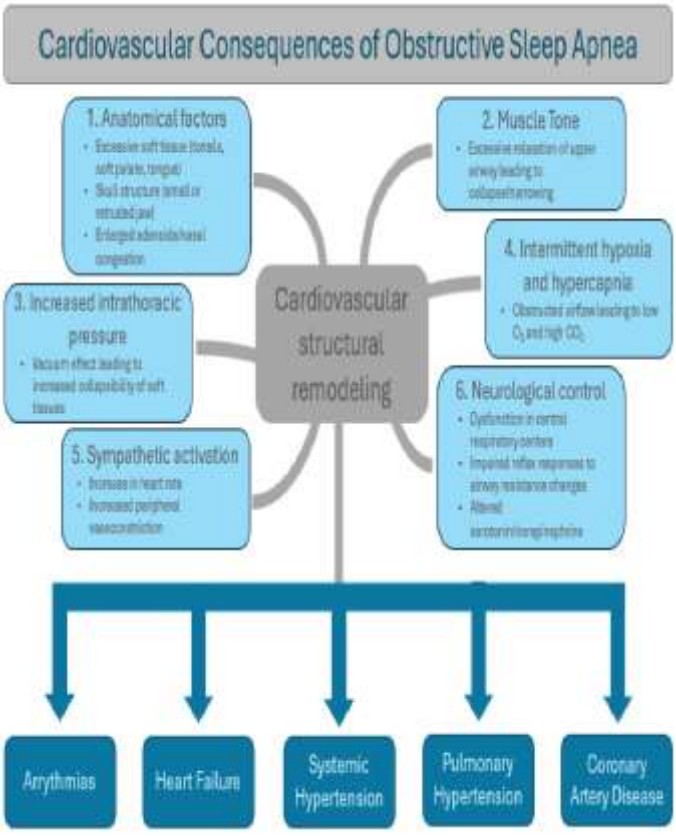
The mechanisms connecting CIH to cardiovascular remodeling are intricate and involve oxidative stress, neurohumoral activation, mitochondrial dysfunction, and epigenetic changes. Furthermore, the interaction between endothelial dysfunction and myocardial remodeling exacerbates cardiovascular damage.

Understanding these mechanisms is crucial for identifying new therapeutic targets beyond standard treatments like CPAP therapy. Therefore, this review aims to thoroughly examine how CIH in OSA leads to cardiovascular remodeling and endothelial dysfunction, focusing on molecular pathways and emerging therapeutic strategies.

Figure 1

Title: Pathophysiological Cascade Linking Chronic Intermittent Hypoxia to Cardiovascular Remodeling
(Conceptual diagram showing CIH → ROS → inflammation → endothelial dysfunction → vascular remodeling → cardiac remodeling)





4. Review of Literature

4.1 Epidemiology of OSA and Cardiovascular Risk

Obstructive sleep apnea (OSA) affects close to one billion people worldwide and frequently goes undiagnosed. It has a strong link to hypertension, ischemic heart disease, and heart failure. The recurrent episodes of apnea cause fluctuations in blood pressure and cardiac output, which elevate myocardial oxygen demand and increase the risk of ischemic damage.

Meta-analyses of imaging studies have shown that individuals with OSA display atrial enlargement, ventricular hypertrophy, and subclinical myocardial injury, underscoring the connection between the severity of OSA and structural changes in the heart.

4.2 Chronic Intermittent Hypoxia as a Central Pathogenic Mechanism

CIH involves repeated episodes of low oxygen levels followed by reoxygenation while sleeping. These episodes lead to oxidative stress and activate the sympathetic nervous system, which causes inflammation in blood vessels and damage to the endothelium. Research indicates that CIH contributes to high blood pressure, increased arterial stiffness, and reduced endothelium-dependent relaxation, highlighting its significant impact on vascular dysfunction. Additionally, CIH heightens the sensitivity of the carotid body, which boosts sympathetic nerve activity and plays a role in systemic hypertension and cardiovascular disease.

4.3 Endothelial Dysfunction in OSA

Endothelial dysfunction is an early indicator of cardiovascular harm in individuals with OSA. Research has indicated that patients with

moderate-to-severe OSA experience decreased flow-mediated dilation (FMD) and compromised vasodilation mediated by nitric oxide. Mechanistically, the production of ROS is stimulated by intermittent hypoxia, which diminishes nitric oxide and lowers vasodilatory capacity. Furthermore, inflammatory pathways that activate NF-κB result in the heightened expression of adhesion molecules like VCAM-1 and ICAM-1, which exacerbates endothelial damage.

4.4 Molecular Mechanisms: Oxidative Stress and Inflammation

Cycles of hypoxia followed by reoxygenation replicate the effects of ischemia-reperfusion injury, leading to an overproduction of reactive oxygen species and the peroxidation of lipids. These mechanisms encourage the remodeling of coronary arteries and the development of unstable atherosclerotic plaques. Additionally, CIH triggers the release of proinflammatory cytokines such as TNF-α and IL-6, which play a role in causing vascular inflammation and activating the endothelium.

4.5 Autonomic Nervous System and RAAS Activation

CIH exposure is characterized by heightened sympathetic activity. Chemoreceptors are stimulated by repeated hypoxic events, leading to elevated catecholamine levels, which cause persistent high blood pressure and greater cardiac strain. The activation of the RAAS also contributes to vascular changes and endothelial impairment. Recent research indicates that during CIH, the activation of mineralocorticoid receptors (MR) leads to dysfunction in the coronary microvasculature, and using MR antagonists can enhance vascular health without necessarily affecting blood pressure.

4.6 Epigenetic and Mitochondrial Mechanisms

Recent studies emphasize the involvement of microRNAs in endothelial dysfunction caused by CIH. Notably, miR-210 is markedly elevated in OSA, leading to mitochondrial dysfunction in endothelial cells, which hinders oxygen use and disrupts vascular balance. This elevation results in heightened oxidative stress and inflammation in the vascular endothelium. Furthermore, changes in the expression of other microRNAs, like miR-126 and miR-155, are associated with impairments in endothelial repair processes. Together, these molecular alterations worsen vascular dysfunction under chronic intermittent hypoxia conditions.

4.7 Structural Cardiovascular Remodeling

Research using animal models reveals that chronic intermittent hypoxia (CIH) leads to thickening of the intima-media, accumulation of collagen, and myocardial fibrosis, which are indicative of early cardiovascular remodeling. Notably, these modifications can be partially reversed when normal oxygen levels are restored, highlighting the clinical advantages of treating obstructive sleep apnea (OSA) effectively. These structural changes result in compromised vascular function and an increased cardiac workload, potentially leading to hypertension and heart failure. The fibrotic changes in myocardial tissue further worsen diastolic dysfunction and decrease cardiac compliance. Therefore, addressing intermittent hypoxia by effectively managing obstructive sleep apnea may help reduce these negative cardiovascular impacts.

Table 1

Title: Summary of Major Mechanisms Linking CIH to Cardiovascular Remodeling

Mechanism	Pathophysiological Effect	Cardiovascular Outcome
Oxidative stress	ROS overproduction, NO depletion	Endothelial dysfunction
Inflammation	NF-κB activation, cytokine release	Atherosclerosis
Sympathetic activation	Catecholamine surge	Hypertension
RAAS activation	Aldosterone excess	Vascular fibrosis
Mitochondrial dysfunction	Energy imbalance	Vascular stiffness
Epigenetic changes	miR-210 upregulation	Endothelial impairment

5. Materials and Methods

5.1 Study Design

This research article employs a thorough narrative review method to integrate mechanistic, experimental, and clinical evidence regarding the effects of chronic intermittent hypoxia (CIH) in obstructive sleep apnea (OSA) on cardiovascular remodeling and endothelial dysfunction. CIH, a defining feature of OSA, initiates a series of pathophysiological processes that lead to changes in cardiovascular structure. These processes, which include oxidative stress, inflammation, and activation of the sympathetic nervous system, collectively damage endothelial function. Gaining insight into these mechanisms is essential for creating targeted therapeutic approaches to reduce cardiovascular risk in individuals with OSA.

5.2 Literature Search Strategy

A comprehensive search of the literature was performed using key biomedical databases such as PubMed, Scopus, Web of Science, and Google Scholar. The search utilized the following terms:

“chronic intermittent hypoxia”

“obstructive sleep apnea”

“cardiovascular remodeling”

“endothelial dysfunction”

“oxidative stress”

“RAAS activation”

“therapeutic targets OSA cardiovascular”

The focus was on studies published from 2000 to 2025, encompassing experimental animal research, clinical trials, meta-analyses, and translational studies.

5.3 Inclusion Criteria

1. Peer-reviewed papers exploring CIH in OSA
2. Research evaluating endothelial function or cardiovascular remodeling
3. Clinical, experimental, or mechanistic studies
4. English-language articles

5.4 Exclusion Criteria

1. Research excluding intermittent hypoxia
2. Case studies lacking detailed mechanistic information
3. Sources not subjected to peer review

5.5 Data Extraction and Synthesis

Data pertinent to molecular pathways, physiological effects, and therapeutic interventions were gathered and organized into thematic categories: Pathophysiological mechanisms, Cardiovascular remodeling, Endothelial dysfunction, and Therapeutic strategies. A narrative synthesis was conducted to combine the findings and pinpoint new research gaps.

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6. Results

6.1 Impact of CIH on Endothelial Function

Research consistently indicates that CIH negatively affects endothelial function by diminishing nitric oxide availability, elevating oxidative stress, and triggering inflammatory responses. Clinical investigations have observed a decrease in flow-mediated dilation among OSA patients, which aligns with the severity of the condition. These vascular alterations increase the cardiovascular risk for individuals with obstructive sleep apnea (OSA). On a mechanistic level, intermittent hypoxia leads to endothelial cell dysfunction by enhancing the production of reactive oxygen species (ROS) and activating pro-inflammatory pathways. Treatments focused on restoring nitric oxide levels and minimizing oxidative stress have shown potential in enhancing endothelial function in this group.

6.2 Cardiovascular Remodeling Induced by CIH

Research involving animals and clinical trials indicates several structural changes caused by CIH:

Thickening of the intima-media layer

Collagen buildup and fibrotic changes

Hypertrophy of the left ventricle

Increased vascular rigidity

Experimental studies demonstrate that CIH results in aortic remodeling and myocardial fibrosis, which can be reversed when normal oxygen levels are restored.

6.3 Molecular Pathways Activated by CIH

CIH triggers several crucial pathways, such as:

Excessive ROS generation

HIF-1α pathway activation

Inflammation through NF-κB

Activation of the sympathetic nervous system

Increased RAAS activity

Epigenetic changes (miR-210)

Together, these pathways contribute to endothelial damage and changes in cardiovascular structure.

6.4 Role of Sympathetic Overactivation

CIH augments the sensitivity of chemoreflexes, resulting in ongoing sympathetic stimulation, raised blood pressure, and a heightened cardiac workload. This increased sensitivity of the chemoreflexes plays a role in the continuous rise in sympathetic nerve activity, which worsens hypertension. Over time, this ongoing sympathetic stimulation places excessive pressure on the cardiovascular system, leading to negative remodeling and dysfunction. As a result, individuals subjected to CIH face a higher likelihood of developing cardiovascular conditions such as heart failure and arrhythmias.

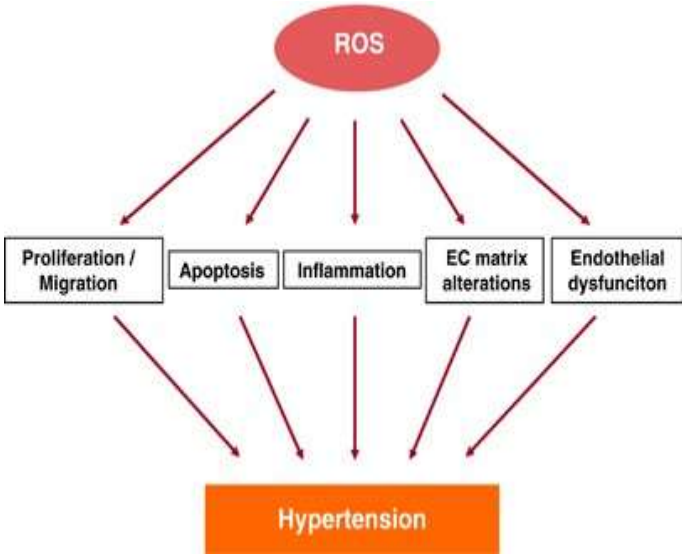
6.5 Therapeutic Target Evidence

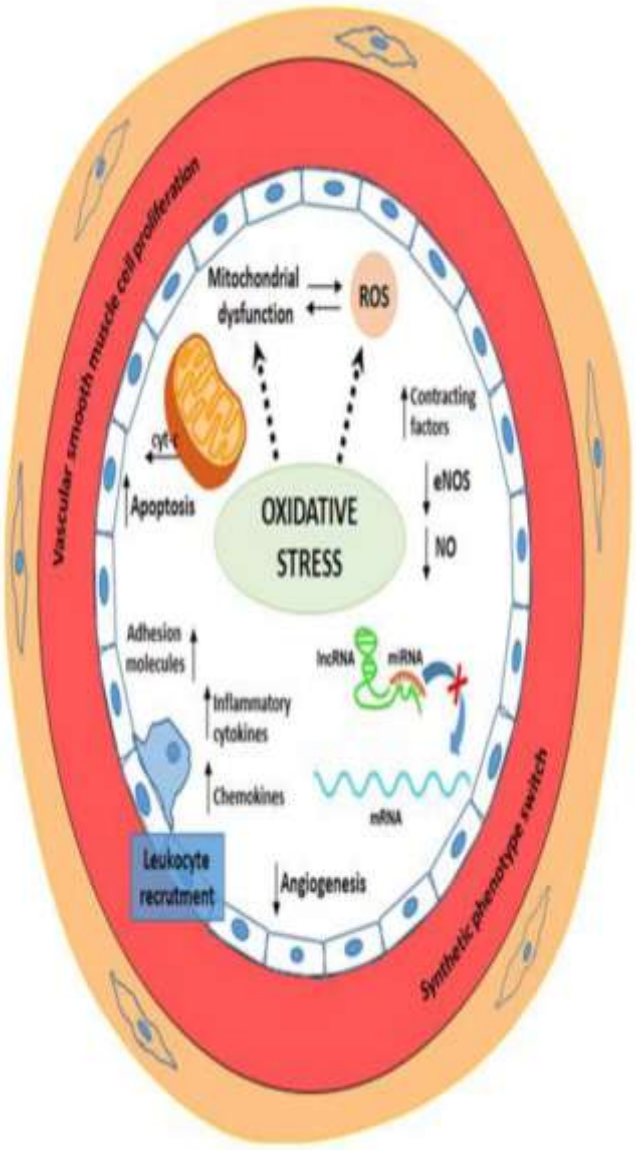
Research on pharmacology reveals that MR antagonists enhance coronary vascular function when exposed to CIH, suggesting that blocking RAAS could be an effective treatment approach. While statins, antioxidants, and anti-inflammatory treatments may help reduce

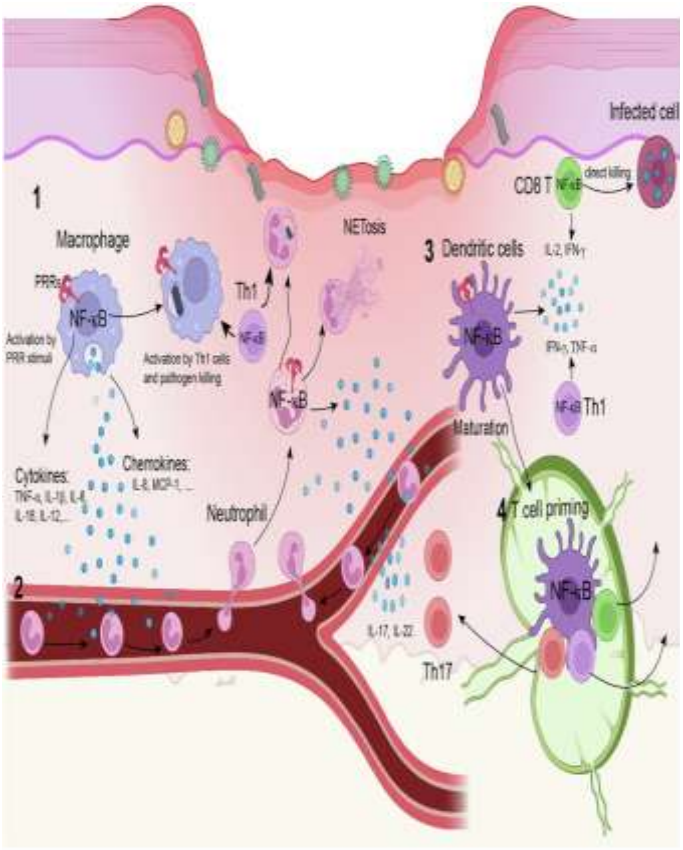
endothelial dysfunction, the clinical evidence is still inconclusive.

Figure 2

Title: Molecular Mechanisms of CIH-Induced Endothelial Dysfunction
(Include ROS production, NF-κB activation, NO depletion, cytokine release, RAAS activation)







7. Discussion

7.1 Integrative Pathophysiology of CIH-Induced Cardiovascular Remodeling

CIH triggers a complex series of pathological events that include oxidative stress, inflammation, autonomic imbalance, and hormonal activation. These interrelated mechanisms lead to endothelial dysfunction, which serves as an initial step towards structural changes in the cardiovascular system. Endothelial dysfunction interferes with vascular balance, reducing vasodilation and enhancing vascular rigidity. This increased hemodynamic load leads to myocardial hypertrophy and fibrosis, eventually advancing to heart failure.

7.2 Cross-Talk Between Endothelial Dysfunction and Cardiac Remodeling

Endothelial dysfunction and cardiac remodeling are interconnected, forming a pathological feedback loop. When endothelial signaling is impaired, it leads to increased vascular resistance, which raises cardiac afterload and encourages ventricular hypertrophy. On the other hand, myocardial remodeling worsens endothelial damage due to changes in hemodynamics and neurohormonal activation. This reciprocal relationship establishes a vicious cycle that hastens the progression of cardiovascular disease. Therefore, therapeutic approaches that focus on improving endothelial function might help reduce adverse cardiac remodeling. Gaining insight into the molecular mechanisms of this interaction is crucial for creating effective treatments.

7.3 Translational Implications

Animal studies have demonstrated that cardiovascular remodeling caused by CIH can be reversed, underscoring the need for prompt diagnosis and management of OSA. While CPAP therapy is the primary treatment, its effects on cardiovascular health vary, prompting the exploration of additional pharmacological approaches. These supplementary treatments, which focus on reducing oxidative stress, inflammation, and sympathetic activation, have shown potential in early studies but need more clinical trials for confirmation. Lifestyle changes, such as losing weight and using positional therapy, enhance CPAP by tackling the root risk factors. Current research is focused on discovering biomarkers to forecast individual treatment responses and refine personalized care plans.

7.4 Emerging Therapeutic Targets

Possible therapeutic targets encompass:

Agents that counteract ROS through antioxidants

Inhibitors of the RAAS and antagonists of MR

Therapies aimed at reducing inflammation

Therapies based on microRNA, such as modulation of miR-210

Modulators of the HIF pathway

These strategies are designed to disrupt the pathological cascade at various stages, providing a framework for precision medicine.

Table 2

Title: Emerging Therapeutic Targets for CIH-Induced Cardiovascular Remodeling

Target	**Mechanism**	**Potential Benefit**
CPAP therapy	Eliminates CIH	Prevents remodeling
MR antagonists	RAAS blockade	Improves endothelial function
Antioxidants	Reduces ROS	Protects vasculature
Anti-inflammatory drugs	Suppresses cytokines	Limits atherosclerosis
microRNA modulation	Regulates gene expression	Restores endothelial function

8. Conclusion

In obstructive sleep apnea, chronic intermittent hypoxia is crucial in triggering cardiovascular remodeling and endothelial dysfunction through intricate molecular and physiological processes. The oxidative stress, inflammation, autonomic imbalance, and RAAS activation caused by CIH collectively damage endothelial function and lead to structural changes in the cardiovascular system. These alterations result in vascular stiffness, myocardial fibrosis, ventricular hypertrophy, and atherosclerosis, which greatly elevate the risk of cardiovascular morbidity and mortality in OSA patients.

Gaining an understanding of how CIH interacts with cardiovascular remodeling offers important insights into the disease's pathogenesis and potential treatment strategies. Although CPAP therapy is the primary treatment, new pharmacological and molecular strategies that address oxidative stress, inflammation, RAAS activation, and epigenetic pathways show potential for enhancing cardiovascular outcomes.

Future studies should emphasize precision medicine strategies that combine phenotypic and molecular profiling of OSA patients to pinpoint high-risk individuals and customize treatment plans. Long-term clinical trials that assess combination therapies targeting various mechanistic pathways are necessary to effectively reduce CIH-induced cardiovascular damage.

9. References

1. MDPI Review on OSA and cardiovascular system.

2. Sleep fragmentation and cardiovascular dysfunction in OSA models.

3. Systematic review of cardiovascular abnormalities in OSA imaging studies.

4. Association of OSA with endothelial dysfunction and cardiac remodeling.

5. miR-210 mediated endothelial dysfunction in OSA.

6. Pulmonary vascular responses to chronic intermittent hypoxia.

7. Oxidative stress and inflammatory endothelial activation in OSA.

8. Cytokine-mediated endothelial activation under intermittent hypoxia.

9. Mineralocorticoid receptor antagonism in intermittent hypoxia-induced vascular dysfunction.

10. Reversibility of intermittent hypoxia-induced cardiovascular remodeling.

11. Prothrombotic and endothelial mechanisms and statin therapy implications in intermittent hypoxia.

12. Lurie, A. (2011). *Inflammation, Oxidative Stress, and Procoagulant and Thrombotic Activity in Adults with Obstructive Sleep Apnea* (Vol. 46, pp. 43–66). S Karger Ag. https://doi.org/10.1159/000325105

13. Qin, W., Yeping, B., Fuchao, Y., Qiang, Z., Guanghao, Z., Yang, L., Songsong, S., Xiaomei, R., & Jiayi, T. (2016). Chronic intermittent hypoxia induces cardiac inflammation and dysfunction in a rat obstructive sleep apnea model. *The Journal of Biomedical Research*, *30*(6), 490. https://doi.org/10.7555/jbr.30.20160110

14. Vijayan, V. K. (2012). Morbidities associated with obstructive sleep apnea. *Expert Review of Respiratory Medicine*, *6*(5), 557–566. https://doi.org/10.1586/ers.12.44

15. Olea, E., Valverde-Pérez, E., Docio, I., Prieto-Lloret, J., Aaronson, P. I., & Rocher, A. (2024). Pulmonary Vascular Responses to Chronic Intermittent Hypoxia in a Guinea Pig Model of Obstructive Sleep Apnea. *International Journal of Molecular Sciences*, *25*(13), 7484. https://doi.org/10.3390/ijms25137484

16. Drager, L. F., Polotsky, V. Y., O'Donnell, C. P., Cravo, S. L., Lorenzi-Filho, G., & Machado, B. H. (2015). Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. *American Journal of Physiology-Heart and Circulatory Physiology*, *309*(7), H1101–H1111. https://doi.org/10.1152/ajpheart.00094.2015

17. Arnaud, C., Dematteis, M., Pepin, J.-L., Baguet, J.-P., & Lévy, P. (2009). Obstructive sleep apnea, immuno-inflammation, and atherosclerosis. *Seminars in Immunopathology*, *31*(1), 113–125. https://doi.org/10.1007/s00281-009-0148-5

18. Lavie, L. (2008). Intermittent hypoxia: the culprit of oxidative stress, vascular inflammation and dyslipidemia in obstructive sleep apnea. *Expert Review of Respiratory Medicine*, *2*(1), 75–84. https://doi.org/10.1586/17476348.2.1.75

19. Ma, L., Zhang, J., & Liu, Y. (2016). Roles and Mechanisms of Obstructive Sleep Apnea-Hypopnea Syndrome and Chronic Intermittent Hypoxia in Atherosclerosis: Evidence and Prospective. *Oxidative Medicine and Cellular Longevity*, *2016*(12), 1–10. https://doi.org/10.1155/2016/8215082

20. Mochol, J., Gawrys, J., Gajecki, D., Szahidewicz-Krupska, E., Martynowicz, H., & Doroszko, A. (2021). Cardiovascular Disorders Triggered by Obstructive Sleep Apnea-A Focus on Endothelium and Blood Components. *International Journal of Molecular Sciences*, *22*(10), 5139. https://doi.org/10.3390/ijms22105139

21. Foster, G. E., Poulin, M. J., & Hanly, P. J. (2007). Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. *Experimental Physiology*, *92*(1), 51–65. https://doi.org/10.1113/expphysiol.2006.035204