SLEEP APNEA AND CARDIOVASCULAR DISEASE RISK: MECHANISMS, EVIDENCE, AND CLINICAL IMPLICATIONS

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Abstract

Sleep apnea, particularly obstructive sleep apnea (OSA), is a prevalent sleep-related breathing disorder associated with significant morbidity and mortality. Increasing evidence demonstrates a strong relationship between sleep apnea and cardiovascular diseases (CVD), including hypertension, coronary artery disease, heart failure, arrhythmias, and stroke. This review synthesizes current literature on the epidemiology, pathophysiological mechanisms, and clinical outcomes linking sleep apnea with cardiovascular risk. Key mechanisms include intermittent hypoxia, oxidative stress, sympathetic nervous system activation, endothelial dysfunction, and systemic inflammation. Furthermore, this paper evaluates the impact of treatment modalities such as continuous positive airway pressure (CPAP) therapy on cardiovascular outcomes. Understanding these associations is essential for early diagnosis and targeted interventions to reduce cardiovascular burden.

Keywords: *Sleep apnea; obstructive sleep apnea; cardiovascular disease; hypoxia; hypertension; CPAP*

1. Introduction

Sleep apnea is a disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, leading to disrupted ventilation and intermittent hypoxia. Among its types, obstructive sleep apnea (OSA) is the most common and clinically significant form. Epidemiological studies have identified sleep apnea as an independent risk factor for cardiovascular disease (CVD), contributing to increased morbidity and mortality worldwide. Cardiovascular diseases remain the leading cause of death globally, and understanding modifiable risk factors such as sleep disorders is increasingly important. It is estimated that OSA affects more than one billion individuals globally, with a large proportion remaining undiagnosed. The condition is more prevalent in men, older adults, and those with obesity, though it is increasingly recognized in women and younger populations as well. The bidirectional relationship between sleep apnea and cardiovascular disease has become an area of intense scientific inquiry, with evidence suggesting that OSA not only predisposes individuals to CVD but may also be exacerbated by existing cardiovascular conditions such as heart failure.

2. Epidemiology of Sleep Apnea and Cardiovascular Disease

OSA affects millions globally and is particularly prevalent among individuals with obesity, diabetes, and hypertension. Studies show that sleep apnea is highly prevalent among patients already diagnosed with cardiovascular disease. The apnea-hypopnea index (AHI), which measures the number of breathing interruptions per hour of sleep, is the primary diagnostic metric. An AHI of 5–14 events per hour is considered mild, 15–29 moderate, and 30 or more severe. Population-based studies estimate that moderate-to-severe OSA affects approximately 17% of men and 9% of women aged 50–70 years. Among patients with established heart failure, the prevalence of OSA can exceed 50%, highlighting the critical overlap between these two conditions.

Longitudinal studies demonstrate that untreated OSA increases the risk of:

Hypertension

Stroke

Myocardial infarction

Heart failure

3. Pathophysiological Mechanisms

3.1 Intermittent Hypoxia

A hallmark of sleep apnea is repeated oxygen desaturation during sleep. These hypoxic episodes trigger oxidative stress and inflammation, contributing to vascular damage. During each apneic event, arterial oxygen saturation can drop to 80% or below, followed by a surge in oxygen upon resumption of breathing. This cyclical pattern of hypoxia and reoxygenation generates reactive oxygen species (ROS) that damage endothelial cells, promote lipid peroxidation, and activate transcription factors such as hypoxia-inducible factor-1 alpha (HIF-1α) and nuclear factor kappa B (NF-κB). Over time, these repeated insults accelerate the progression of atherosclerosis and impair vascular repair mechanisms.

3.2 Sympathetic Nervous System Activation

Sleep apnea activates the sympathetic nervous system, resulting in increased heart rate, elevated blood pressure, and chronic cardiovascular strain. This activation is driven primarily by chemoreceptor stimulation in response to hypoxia and hypercapnia. During apneic episodes, elevated catecholamine levels persist even during waking hours, leading to sustained sympathetic overdrive. This contributes to nondipping blood pressure patterns—a failure of blood pressure to decline during sleep—which is an independent risk factor for cardiovascular events. Chronic sympathetic activation also promotes myocardial hypertrophy and accelerates the progression of heart failure.

3.3 Endothelial Dysfunction

Sleep apnea promotes endothelial injury through oxidative stress, reduced nitric oxide availability, and inflammatory cytokine release. Nitric oxide (NO) is a key vasodilator produced by endothelial cells, and its bioavailability is significantly impaired in OSA patients. Elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are consistently found in OSA patients,

indicative of systemic low-grade inflammation. These inflammatory mediators further compromise endothelial integrity and facilitate the adhesion of monocytes to vessel walls, a critical early step in plaque formation. Flow-mediated dilation (FMD), a clinical marker of endothelial function, is significantly reduced in OSA patients compared to matched controls.

3.4 Inflammation and Metabolic Dysregulation

OSA is associated with elevated inflammatory markers and insulin resistance, increasing cardiovascular risk. Leptin resistance, commonly observed in obese OSA patients, contributes to systemic inflammation and further impairs glucose metabolism. OSA independently predicts the development of type 2 diabetes, and the two conditions share a mutually reinforcing relationship. Adipokine dysregulation—including elevated leptin and reduced adiponectin—observed in OSA further disrupts lipid metabolism and promotes a pro-atherogenic state. These metabolic disturbances compound the direct vascular effects of intermittent hypoxia, creating a multi-pronged pathway to cardiovascular disease.

3.5 Hemodynamic Changes

Apneic episodes cause intrathoracic pressure changes, increasing cardiac workload and contributing to heart remodeling. During obstructive events, vigorous inspiratory efforts against a closed airway generate marked negative intrathoracic pressure swings, which increase left ventricular transmural pressure and afterload. This mechanical stress accelerates left ventricular hypertrophy and diastolic dysfunction. Simultaneously, the reduction in venous return during apneic episodes followed by sudden restoration can cause large swings in right ventricular preload, contributing to pulmonary hypertension over time. These repeated hemodynamic perturbations place cumulative strain on the myocardium that mirrors the effects of chronic pressure overload conditions.

4. Cardiovascular Outcomes

4.1 Hypertension

OSA is strongly linked to resistant and chronic hypertension. It is estimated that OSA is present in more than 80% of patients with treatment-resistant hypertension. The sympathetic surges and nocturnal blood pressure elevation caused by repeated apneic events contribute to sustained daytime hypertension. OSA is recognized by major guidelines as a secondary cause of hypertension that must be addressed for adequate blood pressure control. Even in normotensive individuals, OSA can produce nocturnal hypertension and blunted dipping patterns, which are associated with increased risk of target organ damage.

4.2 Coronary Artery Disease

Sleep apnea contributes to atherosclerosis and myocardial infarction risk. OSA accelerates the development of coronary atherosclerosis through repeated episodes of hypoxia, oxidative stress, and systemic inflammation. Studies have shown that OSA patients have higher rates of coronary artery calcification and more extensive plaque

burden. The risk of acute myocardial infarction is particularly elevated in the early morning hours, coinciding with the REM sleep stage when apneic events tend to cluster. Furthermore, OSA impairs myocardial recovery following ischemic events, worsening outcomes in patients with established coronary artery disease.

4.3 Heart Failure

OSA worsens cardiac function and contributes to heart failure progression. In patients with heart failure with reduced ejection fraction (HFrEF), OSA increases nocturnal sympathetic activity, promotes fluid redistribution from the lower extremities to the thorax during sleep, and worsens pulmonary congestion. This fluid shift can itself worsen upper airway obstruction, creating a vicious cycle. Cardiac resynchronization therapy and optimal diuretic management may partially reduce OSA severity in heart failure patients, underlining the bidirectional nature of this relationship. CPAP treatment in heart failure patients with OSA has been associated with improved left ventricular ejection fraction and exercise tolerance.

4.4 Arrhythmias

OSA is associated with atrial fibrillation and ventricular arrhythmias. The hypoxia, autonomic instability, and structural cardiac changes caused by OSA create a substrate for arrhythmogenesis. OSA patients have a two- to four-fold higher risk of developing atrial fibrillation compared to non-OSA individuals. Among patients undergoing electrical cardioversion for atrial fibrillation, untreated OSA significantly increases the rate of arrhythmia recurrence. Ventricular arrhythmias, including premature ventricular contractions and non-sustained ventricular tachycardia, are also more common during sleep in OSA patients, likely driven by the nocturnal surges in sympathetic tone and transient hypoxemia.

4.5 Stroke

OSA increases stroke risk via hypoxia and vascular damage. The risk of ischemic stroke is approximately two to three times higher in individuals with moderate-to-severe OSA. Nocturnal hypoxia leads to cerebral vasoconstriction, impaired cerebral autoregulation, and platelet hyperaggregability, all of which predispose to thromboembolic events. OSA-associated atrial fibrillation further elevates stroke risk by promoting cardioembolism. Additionally, OSA has been identified as both a risk factor for first stroke and a significant contributor to poorer neurological recovery following stroke, reinforcing the importance of OSA screening in cerebrovascular care.

5. Clinical Evidence

Numerous cohort and observational studies confirm the association between OSA and cardiovascular diseases. Reduced oxygen saturation during sleep is a strong predictor of adverse cardiovascular outcomes. The Sleep Heart Health Study, one of the largest community-based investigations, demonstrated that severe OSA was associated with a three-fold increase in incident heart failure in men. The Wisconsin Sleep Cohort Study provided longitudinal evidence linking untreated OSA to all-cause and

cardiovascular mortality. Polysomnography-derived metrics such as the oxygen desaturation index (ODI) and time spent with oxygen saturation below 90% (T90) have emerged as particularly potent biomarkers of cardiovascular risk, often independent of the AHI. Despite this robust observational evidence, large randomized controlled trials such as SAVE and ISAACC have shown more modest cardiovascular benefits of CPAP in secondary prevention settings, suggesting that patient selection and adherence are critical factors.

6. Treatment and Cardiovascular Impact

6.1 Continuous Positive Airway Pressure (CPAP)

CPAP therapy:

Reduces blood pressure

Improves endothelial function

Decreases sympathetic activity

6.2 Lifestyle Modifications

Weight loss

Exercise

Smoking cessation

6.3 Emerging Therapies

Emerging therapies for OSA include oral appliances, upper airway surgery, hypoglossal nerve stimulation, and positional therapy. Oral mandibular advancement devices (MADs) are effective for mild-to-moderate OSA and are better tolerated by some patients than CPAP. Hypoglossal nerve stimulation (HNS), delivered via an implantable device that activates the genioglossus muscle during inspiration, has shown promising results in patients who cannot tolerate CPAP. Surgical options including uvulopalatopharyngoplasty (UPPP) and maxillomandibular advancement may benefit carefully selected patients. Pharmacological approaches targeting upper airway muscle tone and ventilatory control are also under active investigation. Combination therapy strategies that address both anatomical and physiological contributors to OSA may improve outcomes in patients who respond poorly to monotherapy.

7. Clinical Implications

Early screening is essential

Sleep studies recommended in high-risk patients

Multidisciplinary management improves outcomes

8. Future Directions

Future research should focus on:

Long-term randomized trials

Personalized treatment

Identification of high-risk phenotypes

9. Conclusion

Sleep apnea is a major modifiable risk factor for cardiovascular disease. Early diagnosis and effective treatment can significantly reduce cardiovascular morbidity and mortality. Integrating sleep health into cardiovascular care is essential. The multifactorial pathophysiology of OSA—encompassing intermittent hypoxia, sympathetic activation, endothelial dysfunction, and systemic inflammation—underscores the need for a comprehensive management approach. Clinicians caring for patients with hypertension, coronary artery disease, heart failure, atrial fibrillation, or stroke should routinely assess for OSA, as its treatment may augment the benefits of standard cardiovascular therapies. Collaborative efforts between sleep medicine specialists, cardiologists, and primary care providers are essential to close the diagnostic and treatment gap that currently leaves millions of patients with OSA unmanaged and at elevated cardiovascular risk.

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