# Consequences of Obstructive Sleep Apnea

## Cardiovascular Risk of Obstructive Sleep Apnea and Whether Continuous Positive Airway Pressure Reduces that Risk

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**KEYWORDS**

• Obstructive sleep apnea • Sleep-disordered breathing • Cardiovascular disease
• Systemic hypertension • Intermittent hypoxia • Sympathetic activation • Coronary artery disease
• Heart failure

**KEY POINTS**

- Obstructive sleep apnea (OSA) is associated with unique perturbations that include intermittent hypoxia, sympathetic activation, and oxidative stress.
- OSA is a cause of hypertension, and can worsen the outcome of coronary artery disease, atrial fibrillation, and stroke.
- Treatment of OSA can improve the outcomes of all cardiovascular disorders.
- Expedited approaches to identification and treatment of OSA are important interventions in the management of cardiovascular disease.

### INTRODUCTION

Obstructive sleep apnea (OSA) is increasingly recognized as an important modifiable risk factor for cardiovascular disease (CVD). The prevalence of OSA in the United States is estimated at 20% to 30% in adult men and 10% to 15% in adult women.[1,2] This prevalence is likely increasing because of increasing obesity and the aging population. With an incidence approaching 50%, CVD remains a leading cause of morbidity and mortality in Western societies.[3] Identification and treatment of modifiable CVD risk factors such as OSA is a critical part of the public health approach to CVD.

This article discusses the mechanistic link between OSA and CVD and presents an overview of the evidence for the causative relationship between OSA and CVD. It then addresses the relationship between OSA and the major manifestations of CVD, including systemic hypertension, coronary artery disease (CAD), cardiac arrhythmias, stoke,

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pulmonary hypertension, and heart failure (HF). It presents a focused discussion of the role and expected effects of OSA treatment on modifying the outcomes of these. In addition, it addresses practical approaches to OSA as a modifiable risk factor for CVD.

## OVERVIEW OF SLEEP-DISORDERED BREATHING

The term sleep-disordered breathing (SDB) encompasses all respiratory disorders of sleep and includes both OSA and central sleep apnea (CSA). SDB is defined by the presence of 5 or more respiratory events (apneas or hypopneas) per 1 hour of sleep; that is, an apnea-hypopnea index (AHI) of 5 or more events per hour. The SDB is classified as OSA if more than half of the events are classified as obstructive and CSA if more than half of the events are central. Determination of the obstructive or central nature of a respiratory event relies mainly on the presence or absence of respiratory effort signal during the event. Regardless of type, sleep apnea is defined as mild if the AHI is 5 to 14, moderate if the AHI is 15 to 30, and severe if the AHI is more than 30. The presence or absence of reported sleep-related symptoms is sometimes used to further define the disorder as a syndrome. OSA syndrome is defined as an AHI of 5 to 15 events/h in the presence of significant sleep-related symptoms, or an AHI of 15 events/h or more regardless of symptoms. Likewise, CSA syndrome is defined as an AHI of 5 to 15 in the presence of significant sleep-related symptoms or an AHI of 15 or more regardless of symptoms. CSA is often found in patients with already established end-stage CVD, particularly HF and stroke. Note that a significant overlap between CSA and OSA can occur in the same patient. This overlap is most often seen in patients with HF.

## MECHANISM OF CARDIOVASCULAR DISEASE IN OBSTRUCTIVE SLEEP APNEA

Extensive work in the past 3 decades has greatly expanded the understanding of the mechanism of CVD in patients with OSA. Several pathways have been identified as important for the development of CVD in OSA. These pathways may provide targets for therapeutic interventions in the near future.

### *Intermittent Hypoxia*

Patients with OSA can experience recurrent episodes of apnea or hypopnea ranging in frequency from 5 to more than 100 events per hour. Each of these obstructive respiratory events results in an episode of hypoxia followed by reoxygenation (after the termination of the respiratory episode and resumption of recovery breaths). Each episode of hypoxia stimulates the carotid chemoreceptors,[1] resulting in sympathetic nerve activation[2,4] and a secondary surge in blood pressure.[5] The recurrence of these respiratory events and their respective recovery phases produces a characteristic pattern of nocturnal intermittent hypoxia that is unique to OSA/SDB. As a result, patients with OSA spend their sleep periods in a state of intermittent hypoxia and a cycling pattern of recurrent surges of vasoconstriction.

The pattern of intermittent hypoxia is unique to OSA and results in a different profile of biological consequences from other types of hypoxia exposure.[6–9] The sympathetic activation seen in OSA, caused by intermittent hypoxia, during the sleep period persists through the daytime owing to a memory effect (plasticity) in the sympathetic activation.[10] This plasticity was recently shown to be mediated by a reactive oxygen species–dependent pathway unique to the intermittent hypoxia exposure.[6] Thus, the nocturnal intermittent hypoxia pattern of OSA mediates the vascular response to apnea.[2,5,11,12] Intermittent hypoxia is the critical abnormality in OSA leading to the immediate-term and long-term cardiovascular consequences of OSA, including systemic hypertension,[4,13] left ventricular hypertrophy,[14,15] and endothelial dysfunction.[16–18]

### *Sympathetic Activation, a Critical Mediator for Cardiovascular Disease in Obstructive Sleep Apnea*

Hypoxia activates the sympathetic system, which induces vasoconstriction and increases in blood pressure. Sympathetic activation has several deleterious cardiovascular consequences in patients with SDB. Increased sympathetic tone exerts systemic changes that promote the persistence of increased blood pressure[19,20] and augment the response to subsequent sympathetic stimuli.[21] Sympathetic overactivity is the critical link between OSA and systemic hypertension.[22,23] Intermittent hypoxia not only increases basal sympathetic activity but also augments the sympathetic response to subsequent episodes of hypoxia.[24–26] The role of sympathetic activation is well established in the pathogenesis of systemic hypertension. Young patients with early essential hypertension have increased cardiac sympathetic tone compared with age-matched controls.[27] In a population-based study, increased heart rate (a manifestation of sympathetic activation) correlated with future development of systemic hypertension.[28]