Sleep-Disordered Breathing and Cardiovascular Disease
Robert Wolk, MD, PhD; Tomas Kara, MD; Virend K. Somers, MD, PhD

Sleep apnea is defined as repetitive episodes of decreased or total cessation of respiratory airflow during sleep, leading to a fall in oxygen saturation of ≥4% and sleep fragmentation. Sleep apnea can be central or obstructive. Central sleep apnea (CSA) is characterized by apneas secondary to diminution or cessation of thoraco-abdominal respiratory movements (due to dysfunction of central respiratory control mechanisms). Obstructive sleep apnea (OSA) is caused by upper airway collapse during inspiration and is accompanied by strenuous breathing efforts. When defined as >5 episodes of apnea or hypopnea per hour of sleep, OSA is relatively common, affecting 24% and 9% of middle-aged men and women, respectively. CSA is primarily seen in patients with congestive heart failure (CHF), although it occasionally may occur in healthy normal subjects, in people at high altitudes, and in association with central neural lesions. Sleep apnea constitutes a major public health problem because of its high prevalence and its emerging association with cardiovascular morbidity.

Central Sleep Apnea
CSA is especially relevant to CHF. The prevalence of CSA in CHF patients is dependent on various factors, such as heart failure etiology, gender, age, ejection fraction, and hemodynamic status, and has been estimated at 40% to 60%. Cheyne-Stokes respiration occurs during CSA and is a distinct pattern of periodic breathing with alternating crescendo-decrescendo sequences of hyperperventilation and apnea (ie, complete breathing cessation).

CSA may have an important influence on prognosis, in that its presence is associated with increased mortality in CHF patients. This effect appears to be independent of other known risk factors, such as left ventricular ejection fraction or peak oxygen consumption. Although the association of CSA with CHF has been recognized for decades, it is unclear whether CSA directly affects CHF pathophysiology and can therefore be causally linked to prognosis, or whether it is rather an index of the severity of CHF. Evidence implicating CSA in CHF progression includes the fact that CSA in CHF is associated, first, with increased sympathetic nerve activity, higher urinary and plasma norepinephrine concentrations, and perhaps elevated endothelin. Elevated catecholamine and endothelin levels are associated with poorer prognosis in CHF. Second, CSA may also be highly prevalent in patients with asymptomatic left ventricular dysfunction, where it is associated with impaired cardiac autonomic control and increased cardiac arrhythmias, suggesting that CSA may precede the development of overt heart failure. Third, prevention of CSA by continuous positive airway pressure (CPAP) may contribute to improved outcome in CHF. On the other hand, CHF patients with CSA are characterized by lower exercise capacity and ejection fraction, increased left ventricular volumes, elevated pulmonary capillary wedge pressure, and a higher prevalence of cardiac arrhythmias. Therefore, CSA may indeed also be an index of more severe CHF. The most likely scenario is that CHF predisposes to CSA and, in turn, CSA contributes to CHF progression.

Treatment
Hemodynamic improvement after pharmacological therapy of CHF is often associated with a significant decrease in CSA. However, persistent CSA despite optimal pharmacological therapy (especially if accompanied by severe oxygen desaturation and refractory CHF) should be treated more aggressively. CPAP therapy has been found to improve ejection fraction in CHF patients with CSA and has been associated with a tendency to enhanced transplant-free survival (Figure 1). Other therapies, such as theophyl-
Obstructive Sleep Apnea
OSA has been associated with several cardiovascular diseases, most notably hypertension, ischemic heart disease, heart failure, stroke, cardiac arrhythmias, and pulmonary hypertension. With the exception of hypertension, evidence implicating OSA in these disease conditions is presently circumstantial, and cause-effect relationships remain to be proven.

Hypertension
The evidence supporting the causal association between OSA and hypertension is compelling. The Wisconsin Sleep Cohort Study prospectively demonstrated a dose-response association between sleep-disordered breathing at baseline and the presence of hypertension 4 years later. This association was independent of other known risk factors, such as baseline hypertension, body mass and habitus, age, gender, and alcohol and cigarette use.

The mechanisms underlying the hypertensive effects of OSA are multifactorial. Nocturnal chemoreflex activation by hypoxia and hypercapnia, with consequent sympathetic activation and increased blood pressure (Figure 2), might carry over into excessive sympathetic activity and higher blood pressure even during daytime normoxia. Chemoreceptor resetting and tonic chemoreceptor activation may also contribute to daytime increases in sympathetic activity and blood pressure. Patients with OSA also have endothelial dysfunction, increased endothelin, and lower nitric oxide levels, all of which would potentiate vasoconstriction.

Ischemic Heart Disease
The clinical importance of OSA in ischemic heart disease is twofold. First, epidemiological evidence supports the concept of OSA being etiologically linked to the development of atherosclerosis. There is a high prevalence of OSA in patients with coronary artery disease, and several case-control or prospective studies suggest OSA as an independent predictor of coronary artery disease. Although the exact mechanisms of any atherogenic effects of OSA have not been established, one intriguing possibility is the involvement of inflammatory processes. C-reactive protein (CRP), a biomarker of systemic inflammation and of an increased risk for coronary events, may also play a direct role in atherogenesis. CRP is elevated in OSA, a finding that supports the role of inflammation as a mechanism of OSA-related atherogenesis. Consistent with this hypothesis, elevated plasma levels and cell expression of several adhesion...
molecules, as well as evidence of increased oxidative stress, have also been noted in OSA.

Second, there is evidence that, in patients with or without a history of coronary artery disease, OSA may trigger acute nocturnal cardiac ischemia with ST-segment depression that is often resistant to traditional therapy. Several OSA-related mechanisms, such as oxygen desaturation, high sympathetic activity, increased cardiac oxygen demand (due to tachycardia and increased systemic vascular resistance), and a prothrombotic state, may contribute to the onset of these ischemic episodes. Whether the same mechanisms may also lead to coronary plaque rupture and an acute coronary event remains to be established.

**Heart Failure**

OSA has also been reported in association with CHF, with a prevalence up to 11%. Soft tissue edema (which would increase while supine during sleep) and consequent increased airway resistance may lead to increased inspiratory force and collapse of the upper airway, thus increasing the risk of new-onset OSA. Conversely, epidemiological data suggest that, independent of other risk factors, OSA is associated with an increased risk for CHF. OSA could predispose to CHF by virtue of its effects on sympathetic drive, endothelin, endothelial function, hypertension, and ischemic heart disease, which are known to be important risk factors for CHF. Moreover, OSA may potentiate acute ventricular dysfunction by increasing transmural pressures and ventricular wall stress. The coexistence of CHF and OSA may therefore create a vicious cycle of progressing CHF, with OSA causing deterioration of cardiac function, and with subsequent exacerbation of OSA.

**Stroke**

The prevalence of OSA is increased in patients with stroke, but it is debatable as to what extent stroke-induced breathing abnormalities contribute to this association. The factors that may increase the risk of stroke in OSA include blood flow reduction with individual apnea episodes (caused by negative intrathoracic pressures and increased intracranial pressure), a prothrombotic state, atherosclerosis, and hypertension. From a clinical standpoint, it is an important observation that OSA in stroke survivors may be associated with increased mortality and a worsened long-term functional outcome.

**Pulmonary Hypertension**

Some preliminary studies have suggested the presence of mild-to-moderate daytime pulmonary hypertension (and even right ventricular failure) in OSA patients in the absence of lung and heart disease. In some studies, pulmonary hypertensive OSA subjects tended to have a greater body mass and lower daytime arterial oxygen saturation compared with those without pulmonary hypertension, so that some contribution of the obesity-hypoventilation syndrome to elevated pulmonary pressures in OSA cannot be excluded.

**Cardiac Arrhythmias**

The most frequent arrhythmias reported in association with OSA are sinus arrest, sinoatrial block, or atrioventricular block, all of which may lead to ventricular asystole. The mechanism of these bradyarrhythmias is usually a reflex increase in vagal tone triggered by a combination of apnea and hypoxemia (diving reflex). Therefore, before pacemaker therapy is recommended in patients with nocturnal bradyarrhythmias, the diagnosis of OSA should first be considered and, if present, CPAP therapy should be tried. Because OSA patients sometimes fall asleep during the day, even daytime bradyarrhythmias could be attributed to sleep apnea.

Several reports also suggest that OSA may be associated with both supraventricular and ventricular tachyarrhythmias, although the latter are more likely to occur in the setting of other cardiac comorbidities, such as ischemic heart disease or heart failure.

**Treatment**

Behavioral and lifestyle modifications, such as weight loss, avoidance of sedatives and alcohol, and avoidance of sleeping on the back, will often attenuate OSA severity.

The treatment of choice in OSA is CPAP. Although it is generally accepted that patients with moderate to severe OSA and daytime somnolence should be treated with CPAP, less clear is whether or not to treat mild OSA in the absence of daytime somnolence. In the short-term, effective CPAP treatment (ie, treatment associated with a significant reduction in apnea severity) may reduce systemic (Figure 3) and pulmonary pressures, prevent nocturnal ST-segment depression, improve left ventricular ejection

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**Figure 3.** Changes in blood pressure with effective (closed bars) and subtherapeutic (open bars) CPAP in patients with OSA (*P*<0.05). MAP indicates mean arterial pressure. Reprinted with permission from reference 9.
fraction and functional class, and decrease cardiac arrhythmias in patients with CHF. Treatment for OSA has also been shown to reduce the risk for motor vehicle accidents, probably by lessening daytime somnolence. However, no clear data showing long term benefit with regard to cardiovascular end points with CPAP therapy are presently available.

**Conclusions and Recommendations**

There is strong evidence for an association between sleep apnea and cardiovascular diseases, particularly OSA and hypertension. For other cardiovascular diseases, the evidence, although suggestive, remains circumstantial.

Although the comprehensive diagnosis and treatment of OSA and CSA is determined by overnight polysomnography, a history of witnessed apneas during sleep, daytime somnolence, and evidence of oxygen desaturation on overnight oximetry should heighten the index of suspicion for significant sleep apnea.

OSA should be considered in patients with refractory hypertension, particularly in obese subjects without the expected nocturnal decline in blood pressure, and in patients with nocturnal cardiac ischemia, nocturnal arrhythmias, and stroke. Both OSA and CSA should be considered in CHF patients who are poorly responsive to conventional treatment.

**References**


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