

REVIEW

Obstructive Sleep Apnea and Cardiovascular Disease

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Abstract

Obstructive sleep apnea (OSA) is a common medical condition that occurs in approximately 5% to 15% of the population. The pathophysiology of OSA is characterized by repetitive occlusions of the posterior pharynx during sleep that obstruct the airway, followed by oxyhemoglobin desaturation, persistent inspiratory efforts against the occluded airway, and termination by arousal from sleep. Obstructive sleep apnea is associated with daytime sleepiness and fatigue, likely due to fragmented sleep from recurrent arousals. Substantial evidence shows that patients with OSA have an increased incidence of hypertension compared with individuals without OSA and that OSA is a risk factor for the development of hypertension. Recent studies show that OSA may be implicated in stroke and transient ischemic attacks. Obstructive sleep apnea appears to be associated with coronary heart disease, heart failure, and cardiac arrhythmias. Pulmonary hypertension may be associated with OSA, especially in patients with preexisting pulmonary disease. Although the exact cause that links OSA with cardiovascular disease is unknown, there is evidence that OSA is associated with a group of proinflammatory and prothrombotic factors that have been identified to be important in the development of atherosclerosis. Obstructive sleep apnea is associated with increased daytime and nocturnal sympathetic activity. Autonomic abnormalities seen in patients with OSA include increased resting heart rate, decreased R-R interval variability, and increased blood pressure variability. Both atherosclerosis and OSA are associated with endothelial dysfunction, increased C-reactive protein, interleukin 6, fibrinogen, and plasminogen activator inhibitor, and reduced fibrinolytic activity. Obstructive sleep apnea has been associated with enhanced platelet activity and aggregation. Leukocyte adhesion and accumulation on endothelial cells are common in both OSA and atherosclerosis. Clinicians should be aware that OSA may be a risk factor for the development of cardiovascular disease.

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AHI = apnea-hypopnea index; BMI = body mass index; CHF = congestive heart failure; CPAP = continuous positive airway pressure; CRP = C-reactive protein; CSR = Cheyne-Stokes respirations; JNC = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LV = left ventricular; OSA = obstructive sleep apnea; PA = pulmonary artery; VEGF = vascular endothelial growth factor

Obstructive sleep apnea (OSA) is a common medical condition characterized by abnormal collapse of the pharyngeal airway during sleep, causing repetitive arousals from sleep. A key feature of OSA is that patients will make persistent efforts to breathe against the occluded upper airway. These recurrent and strenuous efforts at inspiration contribute substantially to disturbed sleep. In contrast, central sleep apnea, not a focus of this review, is characterized by the absence of any breathing effort and occurs secondary to central inhibition of the drive to breathe.

The most common clinical presentation of OSA is loud snoring, breathing pauses observed by the bedpartner, and excessive daytime sleepiness. Other symptoms include choking or gasping, restless sleep, morning headache, morning sore throat, and excessive fatigue or malaise. Obstructive sleep apnea is associated with a wide variety of health-related consequences,¹ the most common of which is excessive daytime sleepiness, which may be mild or severe enough to interfere with employment or driving an automobile. Several studies have documented an increased risk of automobile crashes in patients with OSA.^{2,3} Quality of life is impaired in patients with OSA but improves with effective treatment.⁴ Additionally, OSA is associated with cognitive abnormalities^{5,6} and affective disorders such as depression.⁷

The chief pathophysiological event is abnormal narrowing and collapse of the upper airway during sleep due to anatomical narrowing of the upper airway and a loss of tone in the pharyngeal muscles, including the genioglossus. Complete collapse of the upper airway for at least 10 seconds with persistent effort to breathe is termed *obstructive apnea*. Often, OSA is associated with snoring, which represents near collapse of the upper airway, high resistance to airflow, and rapid vibration of the soft tissues of the airway. Hypopnea, partial collapse of the airway during sleep, is defined as a 30% or greater reduction in airflow and a 4% desaturation.⁸ The severity of OSA is measured by the apnea-hypopnea index (AHI), obtained by counting the total number of apneas and hypopneas during sleep and dividing that by the hours of sleep. An AHI lower than 5 per hour is normal; an AHI of 5 to 15 is mild disease, 15 to 30 is moderate disease, and greater than 30 is severe disease.⁹ A condition termed *upper airway resistance syndrome* has been described and is characterized by abnormal respiratory-related arousals that do not meet the accepted definition of apneas or hypopneas.¹⁰

Obstructive sleep apnea is common, and the health consequences can be substantial. The Wisconsin Sleep Cohort Study,¹¹ a large population-based study, reported that based on an AHI of 10 or higher OSA affects approximately 15% of men and 5% of women between the ages of 30 and 60 years. Four major studies¹¹⁻¹⁴ of the prevalence of OSA using laboratory polysomnography showed that the estimated prevalence of severe OSA, defined as an AHI greater than 15, is 7% to 14% in men and 2% to 7% in women older than 20 years. If mild disease is considered (AHI, >5 events per hour), the prevalence is 17% to 26% in men and 9% to 28% in women older than 20 years. Obstructive sleep apnea seems to be more common in African Americans than in white people.¹⁵⁻¹⁷

MORTALITY ASSOCIATED WITH OSA

Studies done several years ago found that OSA seemed to be associated with an increase in morbidity and mortality. He et al¹⁸ reported that approximately 40% of patients with severe OSA died during a follow-up period of 8 years. Treatment with continuous positive airway pressure (CPAP) and tracheostomy improved survival, but uvulopalato-pharyngoplasty did not. However, the study was retrospective, had follow-up of only 54% of patients enrolled, and lacked information about cause of death. Other studies, however, suggested similar findings. Partinen et al¹⁹ reported that the age-adjusted odds ratio of mortality due to vascular disease was 4.9 in patients with OSA receiving no treatment compared with those treated with tracheostomy. In a series of 1620 patients with OSA, Lavie et al²⁰ reported that the observed-to-expected mortality ratio was 3.33 in patients younger than 70 years.

Several potential factors might account for an increase in mortality. Patients with OSA have an increased incidence of automobile crashes. Findley et al²¹ showed that patients with OSA have an increased incidence of automobile crashes compared with controls and that the crashes tend to be more severe than those involving patients without OSA. Second, a substantial body of evidence has accumulated that OSA is associated with an increased risk of hypertension and cardiovascular disease (Table 1).

HYPERTENSION AND OSA

An association between OSA and hypertension has been observed since the early clinical description of OSA in the 1970s.²²⁻²⁵ Several studies have suggested that the prevalence of hypertension is higher than expected in patients with OSA and that OSA occurs frequently in patients with hypertension.^{23,24,26} The importance of this observation is that an association between hypertension and OSA would provide a mechanistic link for the increase in cardiovascular mortality seen with OSA. However, the association of OSA as an independent risk factor for hypertension has always been controversial because of multiple confounding variables for hypertension that are usually also characteristic of patients with OSA, such as age, sex, body mass index (BMI), alcohol use, and smoking.²⁷ In many studies of the association between hypertension and OSA, these variables have not been controlled adequately. Because of the difficulty in accounting for multiple confounding factors, the association between OSA and hypertension has remained controversial with conflicting findings in multiple studies.²⁸

TABLE 1. CARDIOVASCULAR CONDITIONS ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA	
Hyper tensio n	
Cardi ac arrhyt hmias	
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Sinu	

s brady cardi a	
Atrio ventri cular block	
Tach ydysr hyth mia	
Supr avent ricula r tachy cardi a	
Atria l fibrilla tion	
Vent ricula r tachy cardi a	
Left ventri cular systol ic dysfu nction	
Left ventri cular diasto lic	

dysfunction
Congestive heart failure
Stroke
Coronary heart disease
Pulmonary hypertension

Large recently published population-based prospective studies provide strong evidence that OSA is indeed an independent risk factor for hypertension, although the effect is small to moderate.²⁹⁻³² The Wisconsin Sleep Cohort Study analyzed the development of hypertension as a function of the severity of OSA.³⁰ Initially, 1189 subjects were enrolled, and the presence of OSA was determined by polysomnography. Of the original group, 709 subjects were followed up for 4 years, and 184 were followed up for 8 years. The unadjusted odds ratio for developing hypertension was 4.5 in the group with an AHI greater than 15 compared with the group without sleep apnea. When adjusted for age, sex, body habitus, smoking, and alcohol intake, the odds ratio for the development of hypertension was 2.9, providing strong evidence that OSA is an independent risk factor for hypertension.

The Sleep Heart Health Study examined 6424 patients who were already enrolled in cardiovascular risk trials and would undergo polysomnography at home.³³ A linear relationship between the severity of sleep-disordered breathing and prevalence of hypertension was found.²⁹ The odds ratio for the most severe group compared with the normal group was 1.37; thus, the overall effect was small to moderate. An independent association with all cardiovascular disease was also observed in that study.³⁴

To avoid the confounding variables encountered in observational or case-control studies, an animal model of OSA was created by Phillipson et al.^{35,36} Experimentally induced OSA in dogs resulted in a 15% increase in both nocturnal and daytime blood pressure within 5 weeks, and blood pressure returned to baseline after cessation of the experiment. A similar number of noise-induced arousals resulted in a small increase in nocturnal blood pressure but not in daytime blood pressure.³⁶

Although the general consensus is that CPAP treatment reduces nocturnal blood pressure in patients with OSA, the effect on daytime blood pressure is less clear. Recently, 3 major studies³⁷⁻³⁹ assessed

the effect of CPAP on daytime blood pressure in patients with OSA. These studies found small to moderate decreases in blood pressure with CPAP. The most consistent finding was a significant decrease in diastolic blood pressure after 24 hours of CPAP. Additionally, the effect seemed greatest in patients with more severe OSA compared with those with mild OSA.

The increasing evidence of OSA as a contributory factor to hypertension was recognized in 2 sequential sets of guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). The sixth set of guidelines (JNC VI)⁴⁰ recommended that OSA be excluded as a possible contributory factor in patients with resistant hypertension, particularly in the setting of coexisting obesity. The most recent set of guidelines (JNC VII) identified OSA as first on the list of identifiable causes of hypertension.⁴¹

The mechanisms linking OSA with hypertension are complex and not elucidated fully. Obstructive sleep apnea results in recurrent episodes of airway collapse, vigorous inspiratory effort, negative swings in intrathoracic pressure, hypoxemia, hypercapnia, and arousal from sleep at termination of the apnea. The following pathophysiological consequences of recurrent apneas have been shown and are likely related to the development of hypertension in patients with OSA. Both increased nocturnal and daytime sympathetic nervous system activity have been shown in untreated patients with OSA. Increased sympathetic activity leads to increased heart rate, cardiac output, peripheral vascular resistance, and increased tubular sodium reabsorption in the kidney, which may lead to elevated blood pressure. Patients with OSA, compared with those without OSA, have faster heart rates, decreased heart rate variability, and increased blood pressure variability. These changes in cardiovascular autonomic variability are associated with increased cardiovascular risk. Additionally, OSA is associated with an increase in C-reactive protein (CRP), impaired vascular endothelial function, elevated leptin levels, and a possible predisposition to weight gain. These pathophysiological abnormalities are discussed subsequently.

STROKE AND OSA

A higher than expected incidence of OSA in patients who have had a stroke has been observed. In a case-control study, Partinen and Palomaki⁴² found that the relative risk of stroke in snorers compared with nonsnorers was 10.3. Palomaki et al⁴³ observed an odds ratio of 8.0 for stroke in individuals with a history of OSA after adjustment for hypertension, obesity, alcohol consumption, and coronary heart disease. Spriggs et al⁴⁴ reported that a history of snoring was associated with a relative risk of 3.2 for stroke. Neau et al⁴⁵ found that habitual snoring was associated with a relative risk of 3.37 for stroke. Obstructive sleep apnea was shown to occur more frequently in patients admitted to the hospital with stroke than in controls.^{43,46,47} Mohsenin and Valor⁴⁸ showed that, in patients recovering from hemispheric stroke, 80% had OSA compared with age-matched controls. Additionally, OSA is associated with a less favorable clinical outcome 1 year after stroke compared with stroke without OSA.⁴⁹ In the Sleep Heart Health Study, OSA was associated with a small but significant increase in the prevalence of stroke.³⁴ Other studies have shown a higher than expected incidence of OSA in patients with stroke.^{50,51} Further intriguing observations include a diurnal pattern to the time of onset of stroke, with stroke occurring more frequently in the early morning hours. The early morning hours are associated with rapid eye movement sleep, during which time apneas are most likely to be the longest and associated with the most significant oxyhemoglobin desaturation. In the largest series, 31% of strokes were present on awakening from sleep.⁵²

Several compelling reasons exist for an association between OSA and stroke, including abnormal cerebral hemodynamics associated with OSA. Cerebral blood flow has been shown to fluctuate in response to apneas. A significant increase in intracranial pressure and a decrease in cerebral

perfusion during obstructive apneas have been shown in several studies.⁵³⁻⁵⁵ In one study, intracranial pressure increased during sleep in association with obstructive apneas and hypopneas; the increase in intracranial pressure was linearly related to the duration of apneic events.⁵³ Obstructive apneas and hypopneas elicit a 50% reduction in cerebral blood flow compared with central apneas.⁵⁴ In a study using transcranial Doppler ultrasonography, middle cerebral artery blood flow was reduced 15% to 20% during obstructive apneas.⁵⁶ Furthermore, after apnea termination, cerebral blood flow increased 15%, followed by a 23% reduction compared with baseline.⁵⁷ In patients with OSA, there is evidence that suggests cerebral autoregulation of blood flow is abnormal⁵⁷ and that there is diminished cerebral vasodilator response to hypercapnia that reverses with CPAP treatment.⁵⁸ Nevertheless, despite data suggesting that OSA is associated with the occurrence of stroke and may be associated with a less favorable outcome and evidence to suggest abnormal cerebral blood flow and hemodynamics, definitive evidence implicating OSA in the etiology of stroke is lacking.

CORONARY HEART DISEASE AND OSA

Current evidence indicates that OSA occurs commonly in patients with coronary artery disease, is associated with nocturnal angina and nocturnal ST-T segment depression, and adversely affects outcome. Additionally, OSA is an independent risk factor for ischemic heart disease. Hung et al⁵⁹ reported that in patients with myocardial infarction OSA was as strong a risk factor as obesity, smoking, and hypertension. In one study, clinically important OSA was evident in 50% of patients with coronary artery disease.⁶⁰ The Sleep Heart Health Study showed a modest increase in the odds ratio of coronary artery disease in patients with severe OSA compared with controls.³⁴ Severe sleep apnea is present in patients with ischemic heart disease who have nocturnal angina.⁶¹ Patients with OSA have nocturnal ST-segment changes that correlate with oxyhemoglobin desaturation and severity of OSA.⁶²⁻⁶⁴ The mechanism of ST-segment ischemic changes is likely related to increased myocardial oxygen demand during the postapneic surge in blood pressure and heart rate at the time when the oxyhemoglobin saturation is at its lowest point. Whether OSA causes nocturnal ischemia in the absence of coronary artery disease has not been established. In one study, treatment with CPAP reduced the duration of ST-segment elevation,⁶³ but no randomized or controlled studies have been done examining the effects of CPAP on treating nocturnal ischemia in patients with coronary artery disease. Five-year outcome in patients with ischemic heart disease is negatively influenced in those with OSA compared with those without.⁶⁵

CONGESTIVE HEART FAILURE

Obstructive sleep apnea has been associated with idiopathic cardiomyopathy and congestive heart failure (CHF).^{66,67} Although OSA has been noted frequently in patients with CHF, whether the prevalence differs from that expected in a closely matched population without heart failure is unclear. Sleep-disordered breathing in patients with CHF can be primarily obstructive due to upper airway collapse, primarily central (Cheyne-Stokes respirations [CSR], central sleep apnea), or a combination of both. Cheyne-Stokes respirations occur in patients with CHF because of increased carbon dioxide chemosensitivity and hyperventilation.⁶⁸⁻⁷⁰ Both CHF and CSR may contribute to upper airway collapse and OSA if reduced respiratory drive during the hypoventilation phase results in reduced drive to the pharyngeal muscles that normally maintain patency of the airway. If the pharyngeal muscle drive decreased below some critical pressure, the upper airway would collapse. Additionally, elevation of central venous pressure could cause edema of the upper airway, predisposing it to collapse.⁷¹ This may be because of edema-induced dysmotility in the pharyngeal vasculature and/or edematous narrowing of the airway lumen. A decreased luminal diameter would result in marked increases in airway resistance with consequently greater inspiratory pressures, thus predisposing to airway

collapse. Any such effect of elevated venous pressures resulting in upper airway edema would be especially marked when patients with heart failure are sleeping supine.

The most likely pathogenic mechanism linking CHF and OSA is hypertension and its effects on left ventricular (LV) function. During a lengthy period, the cumulative effects of frequent arousals from sleep, hypoxemia, and increased afterload may adversely affect ventricular function. In the Sleep Heart Health Study, OSA was found to be an independent risk factor for CHF. In the group with an AHI greater than 11, the odds ratio of having CHF was 2.38, higher than that for all other cardiovascular disease. In other series of patients with CHF, OSA was found in 11% and 37%.^{72,73} However, studies that have documented a high prevalence of OSA in patients with heart failure⁷³ may be substantially overestimating the prevalence of OSA by studying only those with heart failure who were referred for sleep studies. The more impressive symptoms associated with OSA are likely to bias any such sample toward an excess of patients with OSA among those referred for sleep studies, and therefore they cannot be used reliably as a reasonable indicator of the prevalence of OSA in the heart failure population at large.

Nevertheless, the surges in sympathetic activity, blood pressure, and wall stress, together with the severe metabolic and hypoxic consequences of OSA, would reasonably be expected to contribute to a deterioration of function in the diseased heart. Indeed, several studies have shown that treatment of OSA may improve ejection fraction.^{66,74-76}

Obstructive sleep apnea has been associated with both systolic dysfunction and diastolic dysfunction. Hedner et al⁷⁷ reported that LV hypertrophy was more common in normotensive patients with OSA than in controls. Diastolic dysfunction might be caused not only by long-standing hypertension but also by increased afterload and transmural wall stress associated with the direct effect of recurrent apneas during a lengthy period. The generation of significant negative intrathoracic pressures during apneas causes increased effective afterload on the ventricle. The effect of long-standing adrenergic stimulus from apneas also may contribute to myocardial hypertrophy and diastolic dysfunction. Indeed, several small studies have suggested a rather high prevalence of OSA in patients with diastolic heart failure.^{78,79}

Several studies have shown that CPAP can have salutary effects in patients with CHF and CSR. In patients with CHF, central sleep apnea and CSR are common, and treatment with CPAP is associated with an improvement in LV function and symptoms.⁸⁰ Continuous positive airway pressure treatment of patients with stable, chronic CHF reduces LV afterload and increases stroke volume,⁸¹ reduces cardiac sympathetic tone,⁸² and decreases CSR, increases LVEF and inspiratory muscle strength, and reduces atrial natriuretic peptide.⁸³⁻⁸⁵ Supplemental oxygen also reduces CSR.⁸⁶⁻⁸⁹ In a randomized study of CPAP or no treatment in patients with CSR, there was a tendency toward improved transplantation-free survival in patients with heart failure and central sleep apnea who were receiving CPAP treatment.⁹⁰ Nevertheless, central sleep apnea in patients with heart failure is not readily amenable to effective treatment, although newer therapeutic strategies may allow more effective treatment of OSA in CHF. Many patients with heart failure will not easily tolerate CPAP treatment.

CARDIAC ARRHYTHMIAS

An increased incidence of both bradyarrhythmias and tachyarrhythmias has been associated with OSA and is likely related to the severity of OSA and degree of hypoxemia associated with apneic events.^{91,92} Severe bradycardia and atrioventricular block are seen frequently in association with OSA. These arrhythmias are most likely explained by the vagal response that occurs in response to apneic events.^{93,94} The increase in vagal tone causes slowing of atrioventricular conduction and bradycardia.

Bradycardias are probably associated with the severity of OSA and are usually reversible with CPAP therapy.^{95,96}

Ventricular tachycardia and supraventricular tachycardia are reported in association with OSA and may improve with CPAP therapy.⁹⁷ In patients with heart failure, tachydysrhythmias, including atrial fibrillation, are more common in those with OSA than in those without OSA.⁷² Additionally, atrial fibrillation is more likely to occur after coronary artery surgery in patients with OSA than in those without OSA.⁹⁸ In patients who undergo cardioversion for atrial fibrillation, the recurrence rate in patients with OSA who are not receiving effective treatment is 2-fold higher (80%) than in patients with OSA who are receiving effective CPAP therapy.⁹⁹ Whether recurrence occurs after cardioversion in patients with known OSA appears to be determined primarily by whether they are receiving effective treatment and does not appear to be explained by differences in BMI, cardiac function, atrial size, or antiarrhythmic therapy or by the presence or absence of hypertension or diabetes.

PULMONARY HYPERTENSION

Although it is generally accepted that pulmonary artery (PA) pressure rises immediately in response to hypoxemia in patients with OSA, there is no general consensus that OSA alone can cause daytime pulmonary hypertension because most early studies did not adequately control for the presence of underlying cardiac or pulmonary disease. Diurnal pulmonary hypertension in patients with OSA has been found to correlate more with a lower daytime PaO₂ and higher PaCO₂ than with severity of OSA.¹⁰⁰ However, several recent studies showed a prevalence of diurnal pulmonary hypertension of 20% to 41% in patients with OSA in whom underlying lung disease had been excluded.^{34,101-103} In these studies, severity of OSA did not always correlate with severity of pulmonary hypertension, but factors such as BMI and low daytime PaO₂ were more closely associated with mild degrees of pulmonary hypertension. Theoretically, the recurrent increase in PA pressures associated with apneas could result in endothelial damage and eventually vascular remodeling that could cause daytime pulmonary hypertension. Patients with OSA and pulmonary hypertension have been shown to have increased pulmonary vascular pressor responses to hypoxemia.¹⁰⁴ Two studies showed a reduction in PA pressure in patients treated with CPAP.^{103,105} One study showed a decrease in PA pressure, PA response to hypoxemia, and reduction in pulmonary vascular resistance after treatment with CPAP¹⁰⁵; in this study the greatest treatment response was in patients with baseline pulmonary hypertension. In summary, daytime pulmonary hypertension occurs frequently in patients with OSA, improves with CPAP, and is more closely associated with BMI and daytime PaO₂ than with severity of OSA. However, clear evidence linking OSA to the etiology of pulmonary hypertension remains to be shown.

POSSIBLE MECHANISMS OF CARDIOVASCULAR DISEASE IN OSA

Mechanisms that might explain a relationship between OSA and cardiovascular disease have been investigated extensively ([Table 2](#)). Hemodynamics are significantly different during normal sleep and sleep complicated by periodic obstructed breathing. During normal sleep, the decrease in heart rate and blood pressure is approximately 10% to 15%, which is likely mediated by an overall increased vagal activity and decreased vascular sympathetic traffic.¹⁰⁶ Cardiac output declines about 10% in normal non-rapid eye movement sleep, associated with a reduction in heart rate and stroke volume. In contrast, OSA elicits acute hemodynamic changes mediated in large part by sympathetic activation.^{74,107-110} Occlusion of the upper airway is associated with a decrease in the tone of genioglossus and other pharyngeal muscles during sleep. Normally, during inspiration, pressure in the posterior pharynx becomes relatively negative compared with the atmosphere, and airway patency is maintained by pharyngeal dilator muscle tone. With an obstructive apnea, the pressure generated by these dilator muscles decreases below the pharyngeal air pressure (critical pressure), causing the

airway to collapse during inspiration. Occlusion of the upper airway results in a decrease in alveolar oxygen tension, followed by a reduction in arterial oxyhemoglobin saturation. Also, during obstructive apneas, repetitive, progressively vigorous efforts at inspiration against the occluded airway result in progressively acute decreases in intrathoracic pressure. At the end of the apnea, a cortical arousal often occurs, associated with an increase in genioglossus tone, opening of the occluded airway, resumption of breathing, and increase in the oxyhemoglobin saturation. Intrathoracic pressure during an apnea can be as low as $-80 \text{ cm H}_2\text{O}$.^{111,112} The negative intrathoracic pressure results in an increased transmural pressure gradient, which effectively acts to increase cardiac afterload. Decreased intrathoracic pressure also leads to increased venous return, leftward shift of the intraventricular septum, reduced LV compliance, and decreased LV end-diastolic volume.¹¹³ The combination of increased afterload and decreased end-diastolic volume results in decreased stroke volume and cardiac output.^{114,115}

The physiologic changes in heart rate, blood pressure, sympathetic activity, and cardiac output that occur in healthy controls do not occur in patients with OSA. Systemic blood pressure increases gradually during the apnea and increases further after termination of the apnea in association with arousal and acceleration of heart rate. Cardiac output and heart rate decrease during the apnea but suddenly increase at apnea termination. Because oxyhemoglobin saturation decreases during the apnea and recovers slowly after apnea termination, myocardial oxygen demand increases at the precise time that the oxyhemoglobin saturation is the lowest and hence available oxygen is the lowest. During hypoxemia and apnea, catecholamine levels increase, causing an increase in systemic vascular resistance and in systemic and PA blood pressure.^{107,112}

TABLE 2. POTENTIAL MECHANISMS OF VASCULAR DISEASE ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA	
Increased daytime sympathetic activity	
Increased resting heart rates	
Decreased R-R	

inter val vari ability	
Incr ease d bloo d pres sure vari ability	
End othel ial dysf uncti on	
Incr ease d endo theli n-1 activi ty	
Blun ted vaso dilati on to choli nergi c stim ulati on	
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Interleukin 6	
Oxidative stress by oxygen free radicals	
Increases in prothrombotic factors	
Fibrinogen	
Platelet activation and aggregation	
Plasminogen activator inhibitor	

Activity of the sympathetic nervous system is abnormal in patients with OSA. Fletcher et al¹¹⁶ found that 24-hour urinary catecholamine levels were elevated in patients with untreated OSA but decreased to normal when treated with tracheostomy. Sympathetic nervous system activity is elevated during apneic events and peaks at apnea termination in association with the arousal. Continuous positive airway pressure attenuates the increase in sympathetic nervous system activity seen in OSA ([Figure 1](#)). Patients with untreated OSA have higher sympathetic nervous system activity compared with controls, even when awake and normoxic. They also have faster heart rates, blunted heart rate variability, and increased blood pressure variability during normoxic daytime wakefulness.^{74,106,117,118}

Intriguing evidence suggests that OSA results in abnormalities in coagulation that may be important in adverse cardiovascular effects of OSA. Total serum fibrinogen and whole blood viscosity levels are elevated in OSA.¹¹⁹ Patients with OSA also have increased platelet activation and platelet aggregation that return to normal with CPAP treatment.¹²⁰ Fibrinolytic activity is reduced in patients with OSA, and plasminogen activator inhibitor, an inhibitor of tissue-type plasminogen activator, is elevated.¹²¹

An important mechanism of atherosclerosis is inflammation resulting in endothelial dysfunction. Several mediators that have been implicated in the pathogenesis of atherosclerosis are abnormal in patients with OSA and may contribute to vascular disease by damaging the vascular endothelium. Abnormalities in vascular endothelium associated with OSA have been described. For example, endothelin-1, a potent long-acting vasoconstricting substance synthesized in the vascular endothelium, is important in regulating vascular tone, is elevated in OSA, and decreases with CPAP therapy.¹²² There is evidence of endothelial dysfunction in patients with OSA characterized by blunted vasodilation in response to cholinergic stimulation with acetylcholine.^{123,124} In contrast, Kraiczi et al¹²⁵ found an enhanced vasoconstrictor response with angiotensin II but not acetylcholine in patients with OSA, suggesting enhanced vasoconstriction but not endothelial dysfunction.

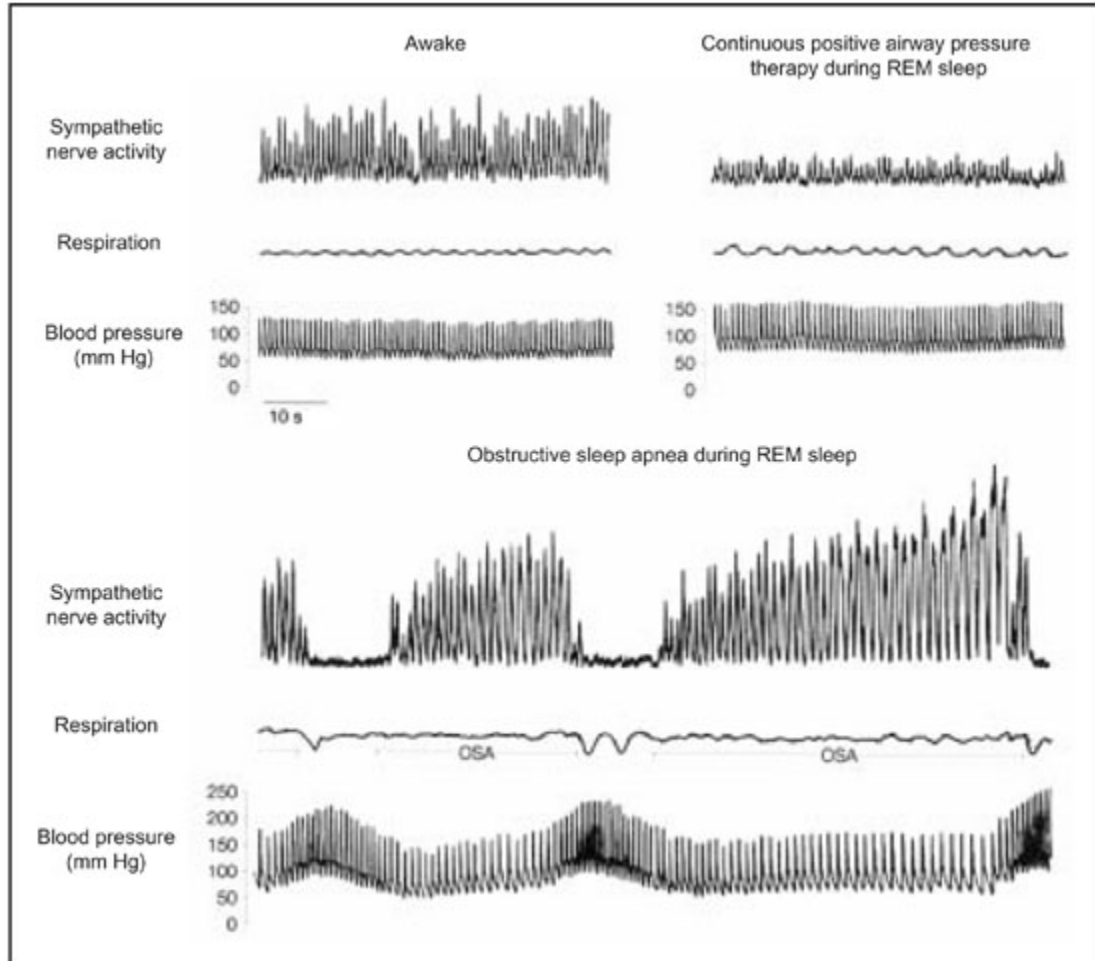


FIGURE 1. Recordings of sympathetic nerve activity, respiration, and intra-arterial blood pressure in an otherwise healthy patient with obstructive sleep apnea (OSA) during wakefulness (top left), during recurrent obstructive apneas (bottom panel), and during treatment with continuous positive airway pressure (CPAP) (top right). Even during wakefulness and normoxia, patients with OSA have high levels of resting sympathetic nerve activity. During obstructive apneas, chemoreflex activation by hypoxemia and hypercapnia causes even further increases in sympathetic activity, with recurrent surges in blood pressure most notable at the end of apneic events. Blood pressure increases up to 250/130 mm Hg even though the patient is normotensive during wakefulness. Treatment with CPAP lowers both sympathetic activation and blood pressure. REM = rapid eye movement. Reprinted from Somers et al,⁷⁴ with permission from the American Society for Clinical Investigation.

C-reactive protein, a marker of systemic inflammation and considered a factor in the pathogenesis of atherosclerosis, is elevated in patients with OSA.¹²⁶ Both CRP and interleukin 6 levels (also increased in OSA) decrease with CPAP therapy.¹²⁷ Plasma homocysteine levels are elevated in patients with ischemic heart disease and OSA but not in patients with OSA only.¹²⁸

Reperfusion-reoxygenation injury has been defined as the injury or damage that occurs when blood flow is restored to a hypoxic or ischemic tissue or muscle. Exposure of myocardial muscle, for example, to ischemia-reperfusion is known to result in muscle dysfunction. Such injury is probably caused by reactive oxygen species, molecules with 1 or more unpaired electrons. Reactive oxygen species can cause oxidative stress and injury to cells or tissues. Similarly, OSA is characterized by episodes of hypoxia followed by reoxygenation. The repeated apnea-related hypoxic events, similar to reperfusion injury, may induce oxidative stress of vascular endothelium.¹²⁹ Free oxygen radicals have been associated with cardiovascular disease by inducing oxidative stress. Patients with OSA have been found to have markedly enhanced neutrophil superoxide generation that decreases with CPAP therapy.¹³⁰

Vascular endothelial growth factor (VEGF), a glycoprotein that stimulates normal and abnormal vessel growth, is essential for angiogenesis. Expression of VEGF is stimulated by hypoxia. Levels of VEGF are elevated in severely hypoxic patients with OSA and are related to severity of desaturation.¹³¹ A recent study showed that in patients with OSA VEGF levels are related to the severity of OSA, are increased during sleep at night compared with controls, and decrease with CPAP therapy.¹³² The relationship of VEGF to cardiovascular disease is unclear, but it may play a protective role in inducing angiogenesis and protecting against cardiovascular disease. Intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin, mediators postulated to be important in the development of atherosclerosis, were elevated in patients with OSA but decreased after CPAP therapy.¹³³

Data show that abnormal leukocyte adhesion and aggregation to endothelial cells have a role in the atherogenic process. Obstructive sleep apnea is associated with increased expression of adhesion molecules CD15 and CD11c on monocytes. Additionally, monocytes from patients with OSA show increased adherence to human endothelial cells in culture, increased production of intracellular reactive oxygen species in some subpopulations of granulocytes and monocytes, and up-regulation of adhesion molecule CD15. When patients with OSA were treated with CPAP, there was down-regulation of CD15 and CD11a monocyte expression, decreased production of reactive oxygen species in monocytes, and decreased monocyte adherence to endothelial cells.¹³⁴

SUMMARY

Obstructive sleep apnea is common in the general population and has been implicated in adverse cardiovascular effects. It is associated with hypertension, and treatment with CPAP reduces both nocturnal and daytime blood pressure, in part by attenuating sympathetic nervous activity. Obstructive sleep apnea appears to be a potential risk factor for ischemic heart disease, has been associated with nocturnal ST-segment depression in patients with coronary heart disease, and may affect outcome adversely in patients with coronary artery disease. Sleep-disordered breathing, both obstructive and central, is seen commonly in patients with CHF and is associated with an increased risk of arrhythmias, including atrial fibrillation, and a poor prognosis. Treatment of OSA with CPAP improves ejection fraction in patients with CHF. Obstructive sleep apnea may be associated with ventricular arrhythmias, pulmonary hypertension, stroke, and transient ischemic attacks, although the evidence is predominantly circumstantial. Several mechanisms could explain the relationship of OSA with the development of atherosclerosis, including abnormalities in various inflammatory and metabolic factors that have been associated with endothelial dysfunction and the development of atherosclerosis. On the basis of the evidence accumulated thus far in the literature, it appears that OSA is an important risk factor for the development of cardiovascular disease. Clearly, more studies are needed to understand the mechanisms that might explain this relationship and to study the effect of treatment with CPAP or

surgery on the progression of cardiovascular disease in patients with OSA. Clinicians caring for patients with cardiovascular and cerebrovascular disease should be aware of these associations and should attempt to identify patients with OSA.



REFERENCES

1. Redline S, Strohl KP. Recognition and consequences of obstructive sleep apnea hypopnea syndrome. *Clin Chest Med*. 1998;19:1-19.
2. Findley LJ, Bonnie RJ. Sleep apnea and auto crashes: what is the doctor to do? [editorial]. *Chest*. 1988;94:225-226.
3. Findley L, Smith C, Hooper J, Dineen M, Suratt PM. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. *Am J Respir Crit Care Med*. 2000;161(3, pt 1):857-859.
4. Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. *J Allergy Clin Immunol*. 1997;99:S750-S756.
5. Engleman HM, Douglas NJ. Cognitive effects and daytime sleepiness. *Sleep*. 1993;16(8, suppl):S79.
6. Engleman HM, Kingshott RN, Martin SE, Douglas N. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep*. 2000;23(suppl 4):S102-S108.
7. Day R, Gerhardstein R, Lumley A, Roth T, Rosenthal L. The behavioral morbidity of obstructive sleep apnea. *Prog Cardiovasc Dis*. 1999;41:341-354.
8. Meoli AL, Casey KR, Clark RW, et al, Clinical Practice Review Committee. Hypopnea in sleep-disordered breathing in adults. *Sleep*. 2001;24:469-470.
9. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research: the report of an American Academy of Sleep Medicine Task Force. *Sleep*. 1999;22:667-689.
10. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. *Chest*. 1993;104:781-787.
11. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230-1235.

12. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med.* 2001;163(3, pt 1):608-613.
13. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men, I: prevalence and severity. *Am J Respir Crit Care Med.* 1998;157:144-148.
14. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med.* 2001;163(3, pt 1):685-689.
15. Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, Fell R. Sleep-disordered breathing in African-American elderly. *Am J Respir Crit Care Med.* 1995;152(6, pt 1):1946-1949.
16. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians [published correction appears in *Am J Respir Crit Care Med.* 1997; 155:1820]. *Am J Respir Crit Care Med.* 1997;155:186-192.
17. Redline S. Epidemiology of sleep-disordered breathing. *Semin Respir Crit Care Med.* 1998;19:113-122.
18. He J, Kryger MH, Zorick FJ. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest.* 1988;94:9-14.
19. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. *Chest.* 1988;94:1200-1204.
20. Lavie P, Herer P, Peled R, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. *Sleep.* 1995;18:149-157.
21. Findley LJ, Levinson MP, Bonnie RJ. Driving performance and automobile accidents in patients with sleep apnea. *Clin Chest Med.* 1992;13:427-435.
22. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med.* 1976;27:465-484.
23. Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnoea in a hypertensive population. *Lancet.* 1984;2:1005-1008.
24. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med.* 1985;103:190-195.
25. Guilleminault C, Simmons FB, Motta J, et al. Obstructive sleep apnea syndrome and tracheostomy: long-term follow-up experience. *Arch Intern Med.* 1981;141:985-988.
26. Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J.* 1984;108:373-376.
27. Stradling J, Davies RJ. Sleep apnea and hypertension—what a mess! *Sleep.* 1997;20:789-793.
28. Silverberg DS, Oksenberg A. Essential hypertension and abnormal upper airway resistance during sleep. *Sleep.* 1997;20:794-806.
29. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study [published correction appears in *JAMA.* 2002;288: 1985]. *JAMA.* 2000;283:1829-1836.

30. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378-1384.
31. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ*. 2000;320:479-482.
32. Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med*. 2000;160:2289-2295.
33. Quan SF, Howard BV, Iber C, et al. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997;20:1077-1085.
34. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163:19-25.
35. Kimoff RJ, Makino H, Horner RL, et al. Canine model of obstructive sleep apnea: model description and preliminary application. *J Appl Physiol*. 1994;76:1810-1817.
36. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension: evidence from a canine model. *J Clin Invest*. 1997;99:106-109.
37. Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure: a placebo trial. *Hypertension*. 2000;35(1, pt 1):144-147.
38. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;163:344-348.
39. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation*. 2003;107:68-73.
40. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [published correction appears in *Arch Intern Med*. 1998;158:573]. *Arch Intern Med*. 1997;157:2413-2446.
41. Chobanian AV, Bakris GL, Black HR, et al, National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.
42. Partinen M, Palomaki H. Snoring and cerebral infarction. *Lancet*. 1985;2:1325-1326.
43. Palomaki H, Partinen M, Juvela S, Kaste M. Snoring as a risk factor for sleep-related brain infarction. *Stroke*. 1989;20:1311-1315.
44. Spriggs DA, French JM, Murdy JM, Curless RH, Bates D, James OF. Snoring increases the risk of stroke and adversely affects prognosis. *Q J Med*. 1992;83:555-562.
45. Neau JP, Meurice JC, Paquereau J, Chavagnat JJ, Ingrand P, Gil R. Habitual snoring as a risk factor for brain infarction. *Acta Neurol Scand*. 1995;92:63-68.
46. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. *Stroke*. 1996;27:401-407.
47. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. *Sleep*. 1999;22:217-223.

48. Mohsenin V, Valor R. Sleep apnea in patients with hemispheric stroke. *Arch Phys Med Rehabil.* 1995;76:71-76.
49. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke.* 1996;27:252-259.
50. Wessendorf TE, Teschler H, Wang YM, Konietzko N, Thilmann AF. Sleep-disordered breathing among patients with first-ever stroke. *J Neurol.* 2000;247:41-47.
51. Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *Am J Respir Crit Care Med.* 2000;161(2, pt 1):375-380.
52. Marler JR, Price TR, Clark GL, et al. Morning increase in onset of ischemic stroke. *Stroke.* 1989;20:473-476.
53. Jennum P, Borgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest.* 1989;95:279-283.
54. Netzer N, Werner P, Jochums I, Lehmann M, Strohl KP. Blood flow of the middle cerebral artery with sleep-disordered breathing: correlation with obstructive hypopneas. *Stroke.* 1998;29:87-93.
55. Loeppky JA, Voyles WF, Eldridge MW, Sikes CW. Sleep apnea and autonomic cerebrovascular dysfunction. *Sleep.* 1987;10:25-34.
56. Fischer AQ, Chaudhary BA, Taormina MA, Akhtar B. Intracranial hemodynamics in sleep apnea. *Chest.* 1992;102:1402-1406.
57. Balfors EM, Franklin KA. Impairment of cerebral perfusion during obstructive sleep apneas. *Am J Respir Crit Care Med.* 1994;150(6, pt 1):1587-1591.
58. Diomedes M, Placidi F, Cupini LM, Bernardi G, Silvestrini M. Cerebral hemodynamic changes in sleep apnea syndrome and effect of continuous positive airway pressure treatment. *Neurology.* 1998;51:1051-1056.
59. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet.* 1990;336:261-264.
60. Andreas S, Schulz R, Werner GS, Kreuzer H. Prevalence of obstructive sleep apnoea in patients with coronary artery disease. *Coron Artery Dis.* 1996;7:541-545.
61. Schafer H, Koehler U, Ploch T, Peter JH. Sleep-related myocardial ischemia and sleep structure in patients with obstructive sleep apnea and coronary heart disease. *Chest.* 1997;111:387-393.
62. Koehler U, Dubler H, Glaremin T, et al. Nocturnal myocardial ischemia and cardiac arrhythmia in patients with sleep apnea with and without coronary heart disease. *Klin Wochenschr.* 1991;69:474-482.
63. Hanly P, Sasson Z, Zuberi N, Lunn K. ST-segment depression during sleep in obstructive sleep apnea. *Am J Cardiol.* 1993;71:1341-1345.
64. Peled N, Abinader EG, Pillar G, Sharif D, Lavie P. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment. *J Am Coll Cardiol.* 1999;34:1744-1749.

65. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med*. 2001;164(10, pt 1):1910-1913.
66. Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet*. 1991;338:1480-1484.
67. Naughton MT. Impact of treatment of sleep apnoea on left ventricular function in congestive heart failure. *Thorax*. 1998;53(suppl 3):S37-S40.
68. Ponikowski P, Chua TP, Piepoli M, et al. Chemoreceptor dependence of very low frequency rhythms in advanced chronic heart failure. *Am J Physiol*. 1997;272(1, pt 2):H438-H447.
69. Sun SY, Wang W, Zucker IH, Schultz HD. Enhanced peripheral chemoreflex function in conscious rabbits with pacing-induced heart failure. *J Appl Physiol*. 1999;86:1264-1272.
70. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis*. 1993;148:330-338.
71. Shepard JW Jr, Pevernagie DA, Stanson AW, Daniels BK, Sheedy PF. Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 1996;153:250-254.
72. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations. *Circulation*. 1998;97:2154-2159.
73. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med*. 1999;160:1101-1106.
74. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897-1904.
75. Laaban JP, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. *Chest*. 2002;122:1133-1138.
76. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003;348:1233-1241.
77. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens*. 1990;8:941-946.
78. Chan J, Sanderson J, Chan W, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. *Chest*. 1997;111:1488-1493.
79. Fung JW, Li TS, Choy DK, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest*. 2002;121:422-429.
80. Naughton MT, Bradley TD. Sleep apnea in congestive heart failure. *Clin Chest Med*. 1998;19:99-113.

81. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. *Am Rev Respir Dis*. 1992;145(2, pt 1):377-382.
82. Kaye DM, Mansfield D, Aggarwal A, Naughton MT, Esler MD. Acute effects of continuous positive airway pressure on cardiac sympathetic tone in congestive heart failure. *Circulation*. 2001;103:2336-2338.
83. Naughton MT, Liu PP, Bernard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. *Am J Respir Crit Care Med*. 1995;151:92-97.
84. Granton JT, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 1996;153:277-282.
85. Tkacova R, Liu PP, Naughton MT, Bradley TD. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 1997;30:739-745.
86. Hanly PJ, Millar TW, Steljes DG, Baert R, Frais MA, Kryger MH. The effect of oxygen on respiration and sleep in patients with congestive heart failure. *Ann Intern Med*. 1989;111:777-782.
87. Franklin KA, Eriksson P, Sahlin C, Lundgren R. Reversal of central sleep apnea with oxygen. *Chest*. 1997;111:163-169.
88. Franklin KA, Sandstrom E, Johansson G, Balfors EM. Hemodynamics, cerebral circulation, and oxygen saturation in Cheyne-Stokes respiration. *J Appl Physiol*. 1997;83:1184-1191.
89. Xie A, Wong B, Phillipson EA, Slutsky AS, Bradley TD. Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. *Am J Respir Crit Care Med*. 1994;150:489-495.
90. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation*. 2000;102:61-66.
91. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983;52:490-494.
92. Shepard JW Jr, Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. *Chest*. 1985;88:335-340.
93. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea: characteristics and mechanism. *J Clin Invest*. 1982;69:1286-1292.
94. Somers VK, Dyken ME, Mark AL, Abboud FM. Parasympathetic hyperresponsiveness and bradyarrhythmias during apnoea in hypertension. *Clin Auton Res*. 1992;2:171-176.
95. Koehler U, Becker HF, Grimm W, Heitmann J, Peter JH, Schafer H. Relations among hypoxemia, sleep stage, and bradyarrhythmia during obstructive sleep apnea. *Am Heart J*. 2000;139(1, pt 1):142-148.

96. Grimm W, Koehler U, Fus E, et al. Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. *Am J Cardiol.* 2000;86:688-692, A9.
97. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. *Chest.* 2000;118:591-595.
98. Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. *Coron Artery Dis.* 1996;7:475-478.
99. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation.* 2003;107:2589-2594.
100. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis.* 1988;138:345-349.
101. Sanner BM, Doberauer C, Konermann M, Sturm A, Zidek W. Pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Arch Intern Med.* 1997;157:2483-2487.
102. Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. *Thorax.* 2000;55:934-939.
103. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB. Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. *Respiration.* 2001;68:566-572.
104. Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, Mcevoy RD. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. *Am J Respir Crit Care Med.* 1999;159(5, pt 1):1518-1526.
105. Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2002;165:152-158.
106. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med.* 1993;328:303-307.
107. Shepard JW Jr. Gas exchange and hemodynamics during sleep. *Med Clin North Am.* 1985;69:1243-1264.
108. Stoohs R, Guilleminault C. Cardiovascular changes associated with obstructive sleep apnea syndrome. *J Appl Physiol.* 1992;72:583-589.
109. Parish JM, Shepard JW Jr. Cardiovascular effects of sleep disorders. *Chest.* 1990;97:1220-1226.
110. Schroeder JS, Motta J, Guilleminault C. Hemodynamic studies in sleep apnea. In: Guilleminault C, Dement WC, eds. *Sleep Apnea Syndromes.* New York, NY: Alan R Liss, Inc; 1978:177-196. Kroc Foundation Series, Vol 11.
111. Hudgel DW. Mechanisms of obstructive sleep apnea. *Chest.* 1992;101:541-549.
112. Shepard JW Jr. Cardiopulmonary consequences of obstructive sleep apnea. *Mayo Clin Proc.* 1990;65:1250-1259.

113. Shiomi T, Guilleminault C, Stoohs R, Schnittger I. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea. *Chest*. 1991;100:894-902.
114. Virolainen J, Ventilla M, Turto H, Kupari M. Influence of negative intrathoracic pressure on right atrial and systemic venous dynamics. *Eur Heart J*. 1995;16:1293-1299.
115. Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT II, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. *N Engl J Med*. 1979;301:453-459.
116. Fletcher EC, Miller J, Schaaf JW, Fletcher JG. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. *Sleep*. 1987;10:35-44.
117. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens*. 1997;15(12, pt 2):1613-1619.
118. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation*. 1998;98:1071-1077.
119. Chin K, Ohi M, Kita H, et al. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 1996;153(6, pt 1):1972-1976.
120. Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure: a preliminary investigation. *Chest*. 1995;108:625-630.
121. Rangemark C, Hedner JA, Carlson JT, Glerup G, Winther K. Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients. *Sleep*. 1995;18:188-194.
122. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. *J Hypertens*. 1999;17:61-66.
123. Carlson JT, Rangemark C, Hedner JA. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. *J Hypertens*. 1996;14:577-584.
124. Kato M, Roberts-Thomson P, Phillips BG, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation*. 2000;102:2607-2610.
125. Kraiczi H, Hedner J, Peker Y, Carlson J. Increased vasoconstrictor sensitivity in obstructive sleep apnea. *J Appl Physiol*. 2000;89:493-498.
126. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation*. 2002;105:2462-2464.
127. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation*. 2003;107:1129-1134.
128. Lavie L, Perelman A, Lavie P. Plasma homocysteine levels in obstructive sleep apnea: association with cardiovascular morbidity. *Chest*. 2001;120:900-908.
129. Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. *Sleep Med Rev*. 2003;7:35-51.
130. Schulz R, Mahmoudi S, Hattar K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy. *Am J Respir Crit Care Med*. 2000;162(2, pt 1):566-570.

131. Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. *Am J Respir Crit Care Med.* 2002;165:67-70.
132. Lavie L, Kraiczi H, Hefetz A, et al. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. *Am J Respir Crit Care Med.* 2002;165:1624-1628.
133. Chin K, Nakamura T, Shimizu K, et al. Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. *Am J Med.* 2000;109:562-567.
134. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med.* 2002;165:934-939.