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Forum Review

Clinical Perspective of Obstructive Sleep Apnea–Induced Cardiovascular Complications

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ABSTRACT

Obstructive sleep apnea (OSA) syndrome is a highly prevalent disorder characterized by recurrent upper airway collapse during sleep, and associated with repetitive episodes of transient oxygen desaturation during sleep. It disrupts normal ventilation and sleep architecture, and is typically associated with excessive daytime sleepiness, snoring, and witnessed apneas. Besides being associated with neurocognitive impairment, mood and behavioral effects, and increased risk for work-related and traffic accidents, OSA has also been implicated in the pathogenesis of various cardiovascular diseases, including systemic hypertension, coronary artery disease, congestive heart failure, pulmonary hypertension, stroke, and cardiac arrhythmias. The mechanisms by which OSA affects the cardiovascular system may involve mechanical effects on intrathoracic pressure, increased sympathetic activation, intermittent hypoxia, and endothelial dysfunction. Therapy with continuous positive airway pressure (CPAP) has been demonstrated to improve cardiopulmonary hemodynamics in patients with OSA and may reverse the endothelial cell dysfunction. *Antioxid. Redox Signal.* 9, 701–710.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common medical condition characterized by abnormal collapse of the upper 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. The first description of OSA that recognized that intermittent upper airway obstruction was the major pathogenetic mechanism was in 1965 (34). Complete collapse of the upper airway for at least 10 seconds with persistent effort to breathe is termed obstructive apnea.

Hypopnea, partial collapse of the airway during sleep, is defined as a ≥30% reduction in airflow and a 4% desaturation (67). Sleep-disordered breathing (SDB) is a term which encompasses simple snoring, obstructive hypopneas, and obstructive apneas. 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 of <5/h is normal; an AHI of 5–15 is mild disease, 15–30 is moderate disease, and >30 is severe disease (104). Patients commonly present with loud snoring, witnessed apneas (breathing pauses observed by the bed partner), and excessive daytime sleepiness.

OSA is a common disorder in the United States and other Western countries. Young *et al*. (119) reported, in a study of adults 30–60 years of age, that 24% of the men and 9% of women had an AHI greater than five events per hour of sleep. When the AHI greater than five events per hour of sleep was combined with daytime symptoms of excessive sleepiness [termed as the obstructive sleep apnea hypopnea syndrome (OSAHS)], the prevalence was 4% in males and 2% in females.

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Table 1. Cardiovascular Consequences of OSA

Hypertension[13,29,37,38,39,47]
Coronary heart disease[44,68,69,94]
Congestive heart failure[45,97,101]
Cardiac arrhythmias[100,108]
Sudden death[33]
Pulmonary hypertension[1,5,91,94]
Stroke[3,9,116]

The sleep fragmentation resulting from apnea-related awakenings alters sleep architecture, with reduction in deep sleep (stages 3 and 4) and REM sleep, and an increase in wake and light sleep after sleep onset. This results in excessive daytime sleepiness and cognitive and neuropsychologic impairment, which increases the likelihood of motor vehicle or work-related accidents (61).

Besides the obvious detrimental effect of sleep-disordered breathing on causing daytime sleepiness, impaired daytime cognitive performance, and mood and behavioral effects, OSA has been implicated in the pathogenesis of various cardiovascular diseases including systemic hypertension, congestive heart failure, pulmonary hypertension, cardiac arrhythmias, atherosclerosis, and stroke. In past studies, the association was often confounded by other comorbid conditions, most notably obesity. More recent studies with rigorous methodology, including longitudinal cohort studies and interventional clinical trials, have helped establish an association between OSA and increased risk of these various cardiovascular diseases (Table 1), most notably hypertension.

The currently available treatment for OSA is mostly limited to the application of continuous positive airway pressure (CPAP) (26). It is associated with improvement in daytime symptoms (6) and objective measures of sleepiness (46) in patients with mild or severe OSA. However, at present, there are no large randomized controlled trials which have examined the impact of long-term CPAP treatment in patients with OSA on more robust cardiovascular disease (CVD) outcomes. Observational studies have suggested improved CVD outcomes in patients with OSA using CPAP compared with patients on no treatment. Marin and co-workers (64) recently reported on a cohort of patients with varying degrees of sleep-disordered breathing (snoring, mild to severe OSA) and healthy participants who were followed for a mean of 10 years. Patients with severe untreated OSA had a much greater risk of developing fatal [odds ratio (OR) 2.87, 95% CI 1.17–2.51] and nonfatal [OR 3.17, 95% CI 1.12–7.51] CVD than healthy controls after adjustment for potential confounding factors. Furthermore, patients with OSA treated with CPAP did not have an increased rate of events compared with healthy controls. Peker and colleagues prospectively followed 182 middle-aged men referred for a sleep study with no hypertension or CVD at baseline (77). Incident CVD (hypertension, coronary artery disease, stroke, myocardial infarction, arrhythmias) over 7 years occurred in 37% of patients with OSA compared with 6.6% of those without OSA. CVD events were much more frequent in patients who were incompletely treated for their OSA (56% over 7 years) than in those who were well treated (6.7%). Incompletely treated OSA remained a strong independent risk factor for incident CVD after controlling for potential confounders.

HYPERTENSION AND OSA

An association between OSA and hypertension has been observed since the early clinical description of OSA in the 1970s (29, 37, 38, 47). The most compelling evidence that OSA is causally related to hypertension comes from the Wisconsin Sleep Cohort Study (80). In normotensive persons who were followed for 4 years after an initial sleep study, worsening severity of OSA was independently associated with progressively increasing risk for new hypertension. Even persons with very mild abnormalities in the apnea–hypopnea index (0.1–4.9) had 42% greater odds of developing hypertension at follow-up than did those with an apnea–hypopnea index of 0, even after adjusting for age, sex, body habitus, smoking, and alcohol intake.

The Sleep Heart Health Study examined 6,424 patients who were already enrolled in cardiovascular risk trials and would undergo polysomnography at home (86). A linear relationship between the severity of sleep-disordered breathing and prevalence of hypertension was found (75). 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 (94).

Phillipson *et al*. (13, 52) demonstrated similar association between hypertension and OSA in an animal model. 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 (13).

In a recent cross-sectional analyses of the data from the Sleep Heart Health Study, Haas and colleagues (39) showed that SDB and diastolic/systolic hypertension were significantly associated in middle-aged adults (ages 40–59 years), but not in individuals ≥60 years of age. Furthermore, there was no significant association found between SDB and isolated systolic hypertension in either age category.

There is also evidence showing improvements in blood pressure in randomized trials with CPAP (10, 28, 81), with placebo being one of the following: an oral medication that the subjects are told might improve sleep apnea (28), use of sham-CPAP (*i.e.*, CPAP at an ineffective pressure 0.5–1.0 cm H_2O) (81), or CPAP at its lowest setting on conventional machines (i.e., 4.0 cm H_2O) (10). Gotsopoulos *et al*. (36) showed a reduction in wake systolic and diastolic blood pressure and 24-h diastolic blood pressure after 4 weeks of treatment with a mandibular advancement splint. There is, however, an apparent discrepancy between results of association studies and intervention studies. Specifically, association studies show a relationship to hypertension with even mild to moderate sleep apnea (75, 80), but secondary analysis of intervention data (81) shows effects in only the most severe cases. Moreover, studies specifically targeting mild to moderate apnea in randomized trials show no improvements in blood pressure (8).

CORONARY HEART DISEASE AND OSA

The Sleep Heart Health Study also demonstrated a modest increase in the odds ratio of coronary artery disease (CAD) in patients with severe OSA compared with controls (94). Hung *et al*. (44) 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 (4). Patients with OSA have nocturnal ST-segment changes that correlate with oxyhemoglobin desaturation and severity of OSA (40, 53, 79). Whether OSA causes nocturnal ischemia in the absence of coronary artery disease has not been established. 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.

Five-year outcome in patients with ischemic heart disease is negatively influenced in those with OSA compared with those without (69). Milleron *et al*. (68) prospectively monitored 54 patients with both coronary artery disease (≥70% coronary artery stenosis) and OSA (AHI ≥15), 25 of whom were treated with CPAP or upper airway surgery, and 29 who declined treatment for OSA, for a median of 86.5 ± 39 months. The end point (cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization) was reached in only 24% of treated patients compared with 58% of those who declined treatment. A long-term clinic-based observational investigation into the development of CAD in middle-aged OSA patients free of concomitant heart disease at baseline, demonstrated an increased incidence of CAD during a follow-up period of 7 years (78). The main weakness of this study was the lack of polysomnographic data for a fully accurate diagnosis of OSA. The investigators used an overnight oxygen desaturation index (ODI) of >30 events/h, supported by data from oronasal thermistors, as definition of OSA. Efficient treatment of OSA reduced the risk.

CONGESTIVE HEART FAILURE AND OSA

Sleep-disordered breathing in patients with congestive heart failure (CHF) can be primarily obstructive due to upper airway collapse, primarily central (Cheyne–Stokes respirations, central sleep apnea), or a combination of both. There is a high prevalence of both obstructive and central sleep apnea in patients with CHF (101). Available evidence suggests that at least 10% of patients with heart failure have clinically significant OSA (45). In the Sleep Heart Health Study, OSA was found to be an independent risk factor for CHF. In the group with an AHI >11, the odds ratio of having CHF was 2.38, higher than that for all other cardiovascular diseases. Some data show that nocturnal upper-airway edema in patients with CHF may predispose to or worsen OSA by narrowing the airway lumen (97).

The most likely pathogenic mechanism linking CHF and OSA is hypertension and its effects on left ventricular (LV) function. The cumulative effects of frequent arousals from sleep, hypoxemia, and increased afterload (secondary to surges in sympathetic activity, blood pressure, and wall stress) may adversely affect ventricular function. The generation of significant negative intrathoracic pressures during apneas causes increased effective afterload on the ventricle. OSA has been associated with both systolic and diastolic dysfunction. Hedner *et al*. (42) reported that LV hypertrophy was more common in normotensive patients with OSA than in controls. Several small studies have suggested a rather high prevalence of OSA in patients with diastolic heart failure (17, 31). In a recent study in patients with nonischemic dilated cardiomyopathy, Usui and coworkers (114) demonstrated increased prevalence of LV hypertrophy in those with than in those without OSA (47.6% vs. 15.4%, $p = 0.016$). Interventricular septal thickness ($p < 0.001$) and relative wall thickness ($p = 0.011$) were significantly greater in those with OSA, indicating that the LV is relatively less eccentric than in patients without OSA.

Several studies have shown that treatment of OSA may improve ejection fraction (49, 54, 62). Salutory effects of CPAP in patients with CHF and central apnea or Cheyne–Stokes respirations has also been demonstrated, with improvement in LV function and symptoms (74), or a tendency toward improved transplantation-free survival (102). CPAP treatment in patients with stable, chronic CHF reduces LV afterload and increases stroke volume (12), reduces cardiac sympathetic tone (51), and reduces atrial natriuretic peptide (73, 112). Mansfield *et al*. (63) studied 40 patients with CHF and OSA (19 patients in the CPAP group and 21 control participants) and found that CPAP therapy improved left ventricular ejection fraction and quality of life, and decreased overnight urinary norepinephrine excretion.

CARDIAC ARRHYTHMIAS AND OSA

Cardiac arrhythmias are frequently seen in patients with OSA. Recurrent intermittent hypoxia and sympathetic nervous system activity surges provide the milieu for cardiac arrhythmia development. Bradyarrhythmias are most likely explained by the vagal response that occurs in response to apneic events (105, 121). The increase in vagal tone causes slowing of atrioventricular conduction and bradycardia. Mechanisms of arrhythmogenesis involve abnormal automaticity, triggered automaticity, and reentry mechanisms. Abnormal automaticity involves spontaneous cardiac impulse formation and may occur in sleep-disordered breathing due to hypoxemia and respiratory acidosis accompanying apneic events (120). Reentry mechanisms may occur through the vagal stimulation, which may lead to bradycardia-dependent increased dispersion of atrial repolarization predisposing to intraatrial entry.

Exaggerated sinus arrhythmia is the most common finding in patients with OSA (108). The prevalence of nocturnal sinus bradycardia and supraventricular arrhythmias in OSA patients correlates with minimum nocturnal arterial oxygen saturation and urine catecholamine levels (2). In contrast to most prior studies evaluating OSA patients for cardiac arrhythmias over short periods of time, Simantirakis *et al*. (100) used a subcutaneously implanted loop recorder and monitored the heart rhythms of 21 patients with moderate to severe OSA (with no known cardiac or sinus node dysfunction) for 2 months prior to the initiation of CPAP therapy, and for 12 months thereafter.

Prior to CPAP therapy, 47% of the patients had severe, primarily nocturnal, rhythm disturbances. Episodes of bradycardia and sinus pauses were much more common than tachyarrhythmias. The frequency significantly decreased within 8 weeks of CPAP use, and no ectopy was recorded during the last 6 months of follow-up. Conversely, a prospective study found a high prevalence of OSA symptoms in patients with atrial fibrillation according to a validated questionnaire (32). Among patients who underwent cardioversion for atrial fibrillation, the recurrence rate in those with untreated obstructive sleep apnea was nearly double (80%) that seen in those treated with CPAP during 1 year of follow-up (48).

The prevalence of arrhythmias was compared in two samples of participants from the Sleep Heart Health Study (66): 228 subjects with sleep-disordered breathing (respiratory disturbance index ≥30) and 338 subjects without sleep-disordered breathing (respiratory disturbance index <5). The two groups were frequency matched on age, sex, race/ethnicity, and body mass index. Atrial fibrillation, nonsustained ventricular tachycardia, and complex ventricular ectopy (nonsustained ventricular tachycardia or bigeminy, trigeminy, or quadrigeminy) were more common in subjects with sleep-disordered breathing compared to those without: 4.8 versus 0.9% ($p = 0.003$) for atrial fibrillation; 5.3 versus 1.2% ($p = 0.004$) for nonsustained ventricular tachycardia; 25.0 versus 14.5% ($p = 0.002$) for complex ventricular ectopy. Even after adjusting for age, sex, body mass index, and prevalent coronary heart disease, individuals with sleep-disordered breathing had four times the odds of atrial fibrillation (odds ratio [OR] 4.02; 95% CI 1.03–15.74), three times the odds of nonsustained ventricular tachycardia (OR 3.40; 95% CI 1.03–11.20), and almost twice the odds of complex ventricular ectopy (OR 1.74; 95% CI 1.11–2.74).

SUDDEN DEATH AND OSA

The risk of sudden death from cardiac causes in the general population peaks from 6 A.M. to noon and has a nadir from midnight to 6 A.M. (21). In striking contrast, Gami *et al.* (33) found that people with OSA have a peak in sudden death from cardiac causes during the sleeping hours. They also showed that the severity of OSA correlated directly with the risk of nocturnal death from cardiac causes, such that, persons with an AHI >40 had a relative risk of sudden death from cardiac causes during sleeping hours that was 40% greater than those with an AHI between 5–39.

Nakamura *et al*. (70) were able to demonstrate that, even in the absence of overt cardiac disease including arrhythmias, OSAHS causes transient nocturnal myocardial electrical instability as indicated by an increased corrected QT dispersion (QTcD). This may be one of the factors involved in sudden death at night seen in patients with OSA.

PULMONARY HYPERTENSION AND OSA

Several recent studies have revealed a prevalence of diurnal pulmonary hypertension of 20–41% in patients with OSA in whom underlying lung disease has been excluded (1, 5, 91, 94). 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. Patients with OSA and pulmonary hypertension have been shown to have increased pulmonary vascular pressor responses to hypoxemia (90). It is generally accepted that pulmonary artery (PA) pressure rises immediately in response to hypoxemia in patients with OSA, and theoretically, the recurrent increases in PA pressures could result in endothelial damage and eventually vascular remodeling that could cause daytime pulmonary hypertension. However, clear evidence linking OSA to the etiology of pulmonary hypertension remains to be shown. Two studies have shown a reduction in PA pressure in patients treated with CPAP (1, 5), and Sajkov *et al*. (90) were also able to demonstrate a reduction in PA pressure, PA response to hypoxemia, and reduction in pulmonary vascular resistance after treatment with CPAP.

STROKE AND OSA

The relationship between sleep apnea and stroke seems to be bidirectional. Intima-media thickness of the carotid arteries, a marker of generalized atherosclerosis and a risk factor for stroke, is significantly increased in patients with severe OSA compared with those with mild OSA or nonapneic controls, independently of other vascular risk factors (3). Turkington *et al.* (113) found a high incidence of sleep apnea in 120 patients with acute stroke by respiratory monitoring commenced within 24 h of the onset of neurologic symptoms. Similarly, Bassetti and co-workers (9) prospectively studied 152 patients (mean age 56 ± 13 years) with acute ischemic stroke. The apnea–hypopnea index (AHI) was determined 3 ± 2 days after stroke onset and 6 months later (subacute phase). Initial AHI was 18 ± 16 (≥10 in 58%, ≥30 in 17% of patients) and decreased in the subacute phase ($p < 0.001$). Age, diabetes, and nighttime stroke onset were independent predictors of AHI ($r^2 = 0.34$).

In a recent observational cohort study (116), 1,022 consecutive patients underwent polysomnography, and subsequent events (strokes and death) were verified. 697 (68%) patients had obstructive sleep apnea (defined by an AHI >5). In an unadjusted analysis, OSA was associated with stroke or death from any cause (hazard ratio 2.24; 95% CI 1.30–3.86; $p = 0.004$). After adjustment for age, sex, race, smoking status, alcohol-consumption, body mass index, and presence or absence of diabetes mellitus, atrial fibrillation, hypertension, and hyperlipidemia, OSA retained a statistically significant association with stroke or death (hazard ratio 1.97; 95% CI 1.12–3.48; $p = 0.01$). In a trend analysis, increased severity of sleep apnea at baseline was associated with an increased risk of the development of the composite end-point ($p = 0.005$).

METABOLIC ABNORMALITIES IN OSA

The relationship between sleep apnea and metabolic abnormalities such as insulin resistance and impaired glucose homeostasis are being increasingly evaluated. Data from

Sleep Heart Health Study showed increased odds for fasting glucose intolerance with either SDB or sleep-related hypoxemia (85). Coughlin *et al*. (23) reported a nine times higher prevalence of metabolic syndrome (hypertension, insulin resistance, impaired glucose tolerance, and hypertriglyceridemia) in individuals with OSA than those without. Hypoxia may be a prominent factor underlying this association, as concluded by Punjabi *et al.* (84) after a systematic review of studies evaluating the relationship between SDB, glucose intolerance, and insulin resistance. However, these authors concluded that studies done thus far show conflicting results with regard to whether CPAP therapy improves metabolic parameters.

POSSIBLE MECHANISMS OF CARDIOVASCULAR DISEASE IN OSA

The mechanisms by which OSA may play a pathogenic role in cardiovascular disorders are yet to be fully elucidated. Likely mechanisms are described below, and are summarized in Table 2.

Hemodynamic alterations and increased daytime sympathetic activity

Hemodynamics are significantly different during normal sleep and sleep complicated by periodic obstructed breathing. During normal sleep, there is a 10–15% decrease in heart rate and blood pressure, likely mediated by increased vagal activity and decreased vascular sympathetic traffic (106). In contrast, OSA elicits acute hemodynamic changes mediated in large part by sympathetic activation (76, 92, 96, 107, 109). Also, during obstructive apneas, repetitive, progressively vigorous efforts at inspiration against the occluded upper airway result in progressively acute decreases in intrathoracic pressure, sometimes as low as –80 cm H_2O (43, 98). The negative intrathoracic pressure results in an increased transmyocardial pressure gradient, which effectively acts to increase cardiac afterload. Decreased intrathoracic pressure also leads to increased venous return, leftward shift of the interventricular septum, reduced LV compliance, and decreased LV end-diastolic volume (99). The combination of increased afterload and decreased end-diastolic volume results in decreased stroke volume and cardiac output (14, 115).

Activity of the sympathetic nervous system is abnormal in patients with OSA (Fig. 1). Patients with OSA were found to have elevated 24-h urinary catecholamine levels, which decreased to normal when treated with tracheostomy (30). Sympathetic nervous system activity is elevated during apneic events and peaks at apnea termination in association with the arousal. Patients with untreated OSA have higher sympathetic nervous system activity compared with controls, even when awake and normoxic. They have faster heart rates, blunted heart rate variability, and increased blood pressure variability during normoxic daytime wakefulness (71, 72).

TABLE 2. PATHOGENIC MECHANISMS OF CARDIOVASCULAR DISEASE IN OSA

Hemodynamic alterations and increased daytime sympathetic activity[76,92,96,107,109]
Endothelial dysfunction and increases in inflammatory mediators[19,24,56,82,93]
Increases in prothrombotic factors[11,18,87]
Hypoxia/reoxygenation and oxidative stress[57,111]

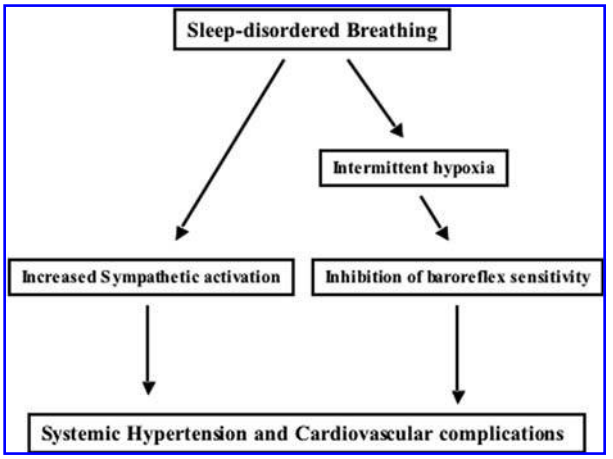

FIG. 1. Hemodynamic alterations in sleep-disordered breathing.

It is also possible that impairments in the sympathetic and baroreflex functions may result in an uncontrolled condition with abnormally elevated arterial pressure in patients with OSA. Baroreceptor reflex, which detects systemic hypertension and elicits decreases in sympathetic activity and arterial pressure, has been shown to be decreased in OSA patients (15, 88). Recently, Lai *et al.* (55) were able to demonstrate facilitation of cardiovascular sympathetic outflow and inhibition of baroreflex sensitivity in conscious rats, using an animal model of chronic intermittent hypoxia (IH)-induced hypertension (Fig. 1).

Endothelial dysfunction and increases in inflammatory mediators

Under normal physiologic conditions, the endothelium regulates vascular tone and interactions between the vessel wall and circulating substances and blood cells. It maintains homeostasis by keeping the balance between vasoconstrictors and vasodilators. On disruption of this balance, the endothelium is activated and acquires a proatherogenic and proinflammatory phenotype (60), characterized by overexpression of adhesion molecules. Atherosclerosis, the culprit behind cardiovascular and cerebrovascular events, is currently viewed as dynamic and progressive disease arising from the subclinical condition of endothelial dysfunction (24) (Fig. 2).

There is evidence for endothelial dysfunction in patients with OSA. Endothelin-1 is a potent long-acting vasoconstricting substance synthesized in the vascular endothelium and is important in regulating vascular tone. It has been found to be elevated in OSA, and decreases with CPAP therapy (82). OSA patients have blunted vasodilation in response to cholinergic stimulation with acetylcholine (16, 50). An important mechanism of atherosclerosis is inflammation resulting in

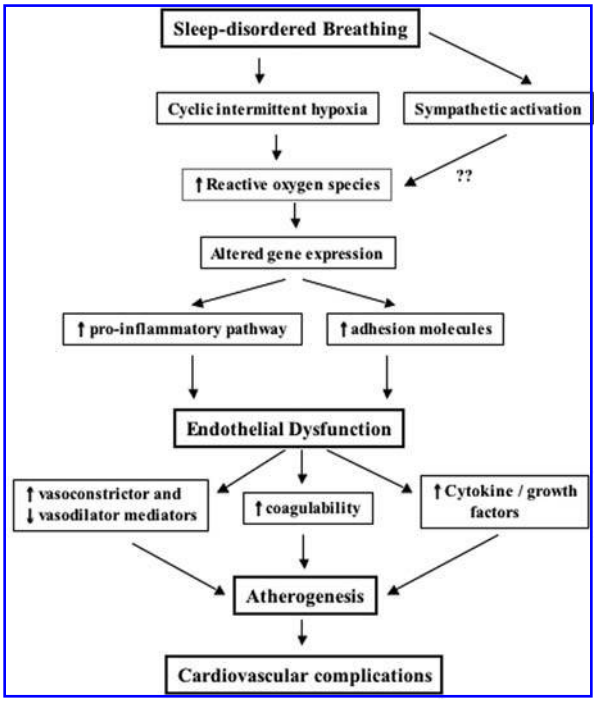

FIG. 2. Proposed link between sleep-disordered breathing and atherogenesis. Sleep-disordered breathing leads to production of reactive oxygen species (ROS) via cyclic intermittent hypoxia/reoxygenation and, perhaps, sympathetic activation. Generation of ROS leads to altered gene expression, with upregulation of pro-inflammatory cytokines and various adhesion molecules, which together elicit endothelial dysfunction. Endothelial dysfunction leads to an imbalance between vasoconstrictor and vasodilator mediators (favoring vasoconstriction), increased coagulability, and increased production of various cytokines and growth factors. These lead to increased atherogenesis, an initial step to various cardiovascular diseases.

endothelial dysfunction, and several of the mediators implicated in the pathogenesis of atherosclerosis are abnormal in patients with OSA. C-reactive protein (CRP), a marker of systemic inflammation and considered a factor in the pathogenesis of atherosclerosis, is elevated in patients with OSA (95). Both CRP and interleukin-6 levels (also increased in OSA patients) decrease with CPAP therapy (118). Abnormal leukocyte adhesion and aggregation to endothelial cells have been shown to have a role in the atherogenic process. OSA is associated with increased expression of adhesion molecules CD15 and CD11c on monocytes. Additionally, monocytes from OSA patients show increased adherence to human endothelial cells in culture, increased production of intracellular reactive oxygen species in some subpopulations of granulocytes and monocytes, and upregulation of adhesion molecule CD15. Treatment with CPAP reversed these changes (27). Other mediators postulated to be important in the development of atherosclerosis, such as, intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin, have also been shown to be elevated in OSA patients, but decreased after CPAP therapy (19).

Endothelial dysfunction also represents a state where nitric oxide (NO) bioavailability is compromised, resulting in vasoconstriction (24). In addition to its strong vasodilatory properties, NO mediates many of the protective functions of the endothelium. It limits leukocyte recruitment and expression of leukocyte adhesion molecules. Vascular smooth muscle cell proliferation and platelet aggregation and adhesion are also inhibited. Diminished NO bioavailability, measured by nitrite/nitrate concentrations, is detected in patients with OSA (56, 93), and treatment with nocturnal CPAP restores NO levels (24).

Increases in prothrombotic factors

Patients with OSA have also been noted to have abnormalities in coagulation that may play an important role in the adverse cardiovascular effects of sleep apnea. Total serum fibrinogen and whole blood viscosity levels are elevated in OSA (18). Patients with OSA have increased platelet activation and platelet aggregation that returns to normal with CPAP treatment (11). Fibrinolytic activity is reduced in patients with OSA, and plasminogen activator inhibitor, an inhibitor of tissue-type plasminogen activator, is elevated (87).

Hypoxia/reoxygenation and oxidative stress

OSA is characterized by repeated episodes of hypoxia (which can last for 10 sec to as long as 2 min) followed by reoxygenation/normoxia (2–3 min). These events are similar to ischemia-reperfusion events, and may induce oxidative stress of vascular endothelium (57). Suzuki *et al*. recently reviewed the current evidence for oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases (111). During the hypoxic phase, cells adapt to the low oxygen environment; however, the reoxygenation phase causes a sudden increase of oxygen in the cells. The reoxygenation phase is thought to result in production of reactive oxygen species (ROS) (Fig. 2) and promotion of oxidative stress (25, 57, 83). Several enzymatic systems responsible for increased ROS formation, including enzymes of the mitochondrial respiration chain, xanthine oxidase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase from leukocytes and endothelial cells, are affected by hypoxia/reoxygenation (57). These ROS, which include superoxide anion radical ($\bullet O_2$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\bullet OH$), can oxidize various biological molecules including lipids, proteins, and DNA, and alter biological functions. ROS can also serve as signal transduction mediators to elicit oxygen-sensing mechanisms as well as cell growth events, which play critical roles in cardiovascular diseases (110). These oxidant species can activate redox-sensitive signaling pathways that initiate adaptive responses to hypoxia (such as hypoxia inducible factor 1α) (57) and inflammatory pathways (65). Consequently, endothelial cells, leukocytes, and platelets undergo activation (59), and these activated cells contribute further to reperfusion injury by further release of ROS and increased expression of adhesion molecules on leukocytes, platelets, and endothelial cells. Intermittent hypoxia–reoxygenation (IHR) favors the activation of a proinflammatory response as mediated through the

transcription factor nuclear factor-κB (NFκB), a master regulator of inflammatory gene expression (35). Ryan *et al*. (89) used a novel *in vitro* method using HeLa cells to demonstrate selective activation of NFκB ($p < 0.001$ by ANOVA) in HeLa cells exposed to IHR. HIF-1 was not activated, as demonstrated by luciferase reporter assays and DNA binding studies. They also studied 19 male OSA patients prospectively (mean AHI 48.5 episodes per hour; interquartile range [IQR] 28.5–72.9) and 17 matched normal control subjects. Circulating tumor necrosis factor-α levels were higher in OSA patients (2.56 p/ml; IQR 2.01–3.42 pg/ml) than in control subjects (1.25 pg/ml; IQR 0.94–1.87 pg/ml; $p < 0.001$), but normalized with continuous positive airway pressure therapy (1.24 pg/ml; IQR 0.78–2.35 pg/ml; $p = 0.002$).

Barcelo *et al*. (7) reported that lipid peroxidation profile is abnormal in OSA patients. Using LDL particles isolated from 14 patients with severe OSA (mean AHI 59/h) and 13 healthy subjects, they found that thiobarbituric acid-reactive substance (TBARS) formation was higher in OSA patients, which improved with CPAP treatment. In a study of 114 patients, Lavie *et al.* (58) reported that morning levels of TBARS and peroxides were significantly higher in OSA patients, with or without cardiovascular disease, than in controls. CPAP treatment decreased nocturnal levels of TBARS and peroxides. Evidence for occurrence of oxidative stress in OSA patients was also provided by Yamauchi *et al*. (117), who demonstrated that urinary 8-hydroxy-2'-deoxyguanosine excretion was significantly higher in patients with severe OSA ($n = 58$) compared with control subjects ($n = 70$). Levels of hypoxia-sensitive molecules, such as heat shock protein-70 (Hsp-70), tissue factor (TF), monocyte chemotactic protein-1 (MCP-1), and highly-sensitive C-reactive protein (hs-CRP) are significantly higher in patients with OSAHS compared with control subjects (41). Furthermore, the levels increased with severity of OSA and were higher in nonobese OSAHS patients compared to body mass index (BMI) matched controls.

Because oxidative stress results from an altered balance of oxidant producing systems and antioxidant defense mechanisms, increased oxidative stress can also result from lower antioxidant capabilities. Christou and co-workers (20) demonstrated attenuated antioxidant capacity in severe OSA. Lavie and coworkers demonstrated lower activity of paraoxonase-1 (PON1) in patients with OSA, that was more pronounced in those who had cardiovascular comorbidities (58). PON1, a protective enzyme located exclusively on high density lipoproteins, protects low and high density lipoproteins from oxidative modification by acting as an antioxidant.

ROS production in OSA patients could also occur via inflammatory responses (22), as well as increased sympathetic tone and elevated catecholamine-induced ROS production (103) (Fig. 2).

SUMMARY

OSA is a common under-recognized disorder characterized by recurrent upper airway collapse during sleep. These recurrent episodes of upper airway collapse lead to sleep fragmentation, oxyhemoglobin desaturation, and excessive daytime sleepiness. OSA also causes sustained activation of the sympathetic nervous system, endothelial dysfunction, systemic inflammation with increased levels of CRP and interleukin-6, and oxidative stress. Many of these physiological and biochemical abnormalities are implicated in the pathogenesis of CVD. There is also compelling epidemiologic data implicating OSA in the development of various cardiovascular diseases, especially systemic hypertension. Furthermore, therapy with nasal continuous positive airway pressure (nCPAP), which ameliorates oxygen desaturations, decreases cardiovascular morbidity and mortality. A greater understanding of the cellular response to intermittent hypoxia and reoxygenation should provide insight into pathophysiological pathways in OSA.

ABBREVIATIONS

AHI, apnea–hypopnea index; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CVD, cardiovascular disease; IH, intermittent hypoxia; IHR, intermittent hypoxia–reoxygenation; IQR, interquartile range; LV, left ventricular; NFκB, nuclear factor-κB; NO, nitric oxide; OSA, obstructive sleep apnea; OSAHS, obstructive sleep apnea hypopnea syndrome; PA, pulmonary artery; PON1, paraoxonase-1; REM, rapid eye movement; ROS, reactive oxygen species; SDB, sleep-disordered breathing; TBARS, thiobarbituric acid-reactive substance.

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