Obstructive Sleep Apnea, Cardiovascular Disease, and Pulmonary Hypertension

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With the growing epidemic of obesity in an aging population, obstructive sleep apnea (OSA) is increasingly encountered in clinical practice. Given the acute cardiopulmonary stressors consequent to repetitive upper airway collapse, as well as evidence for cardiovascular homeostatic dysregulation in subjects with sleep apnea, there is ample biologic plausibility that OSA imparts increased cardiovascular risk, independent of comorbid disease. Indeed, observational studies have suggested strong associations with multiple disorders, such as systemic hypertension, heart failure, cardiac arrhythmias, and pulmonary hypertension. Further data in the form of longitudinal cohort studies and randomized controlled trials are accruing to add to the body of evidence. This review examines pathophysiologic mechanisms and explores current concepts regarding the impact of OSA and its treatment on selected clinical disease states.

Keywords: sleep-disordered breathing; positive airway pressure; arrhythmia; stroke

OBSTRUCTIVE SLEEP APNEA: ACUTE PATHOPHYSIOLOGIC MECHANISMS

Acute cardiovascular (CV) stressors resulting from repetitive episodes of upper airway narrowing and/or occlusion characteristic of obstructive sleep apnea (OSA) include hypoxemia, reoxygenation, swings in intrathoracic pressure, and central nervous system (CNS) arousals. Plausibly, these effects are cumulative over time, potentially forming the basis for heightened CV risk in individuals with OSA. There is evidence that CV homeostatic mechanisms in subjects with OSA are disrupted, as demonstrated by daytime abnormalities in sympathetic nervous system function and heart rate variability (1).

There is considerable evidence that hypoxemia, in part by stimulation of peripheral arterial chemoreceptors, drives some important aspects of the pathophysiology in OSA. Stimulation of the chemoreflex increases sympathetic efferent traffic during hypoxic stimulation, as demonstrated by direct peripheral intraneural electrode recordings (2, 3) Those with OSA have been found to have an exaggerated chemoreflex response to hypoxic stimulation, resulting in acute peripheral vasoconstriction and consequent acute increases in arterial blood pressure (BP). Under conditions of uninterrupted ventilation, lung inflation serves to homeostatically maintain autonomic balance on account of stimulation of lung and chest wall stretch receptors mediated by vagal neural circuits. This sympatholysis is incomplete during the apneas and hypopneas characteristic of OSA (4, 5), thus contributing to heightened sympathetic tone.

Each acute oxyhemoglobin desaturation is coupled to an episode of reoxygenation, a process thought to promote oxidative stress through formation of reactive oxygen species (6, 7), a cascade that may be associated with heightened inflammation (8, 9) and mitochondrial dysfunction (10).

Typical inspiratory efforts against an obstructed upper airway during apneas can result in marked reductions in intrathoracic pressure, as measured by esophageal pressure, and have been associated with acute changes in pulmonary arterial pressures and blood flow (11) and increased cardiac afterload. Enhanced venous return that may occur with reduced intrathoracic pressure can result in acute leftward intraventricular septal shift (12) and alterations in transmural cardiac pressures (13), with impedance of left ventricular (LV) filling (14) and increase in myocardial oxygen demand.

Apneas and hypopneas terminate with CNS arousals, forming the basis for sleep fragmentation and neurocognitive sequelae in OSA (15). CNS arousals are also associated with important effects on CV function, resulting in abrupt increases in sympathetic tone, heart rate, and BP (16, 17).

INTERMEDIARY MECHANISMS OF POTENTIAL IMPORTANCE IN CONFERRING CARDIOVASCULAR RISK

Daytime neural circulatory control is disturbed in subjects with OSA, even in the absence of overt CV disease. In part on the basis of increased tonic chemoreflex drive, heightened sympathetic tone is evident during normal waking hours in some patients with OSA, even under conditions of normoxia (1, 18). Abnormalities in variability of both heart rate and BP, both of which have been found to be markers of future cardiovascular disease in population-based studies (19), are present in OSA (18). The presence of endothelial dysfunction in OSA, as evidenced by a blunted small-vessel dilatory response to vasoactive substances, such as acetylcholine in some (but not all [20]) studies, may also be an important marker of CV risk (21–23). There is evidence to support the role of reduced levels of the vasodilator, nitric oxide, in the mediation of vascular disease and BP regulation in OSA (24), whereas levels of serum endothelin, a potent vasoconstrictor, may be higher in patients with OSA compared with control subjects (25).

Other features of OSA that may indirectly increase the risk for cardiovascular disease include a propensity for glucose intolerance (26), systemic inflammation, as suggested by an increase in serum C-reactive protein levels and up-regulation of leukocyte adhesion factors (27, 28), and abnormalities in coagulation markers (29).

Notwithstanding this and other mechanistic pathways, establishing causality in the relationship between OSA and clinical CV disease has been difficult, in large part because of shared risk factors—in particular, obesity and advancing age, both of which are primary determinants of sleep-disordered breathing, systemic hypertension, heart failure (HF), and pulmonary hypertension (PH), rendering the disentanglement of the independent effects of OSA on clinical disease challenging. Moreover, there is a
relative paucity of high-level, evidence-based data, such as inter-
vention trials of OSA in the setting of CV disease. As
such, much of the above findings are derived from case–control
studies, some of which, it should be noted, have rendered negative
associations between OSA and other biomarkers associated with
CV risk, including serum levels of brain natriuretic peptide (30)
and troponin T (31).

OSA AND SELECTED CARDIOVASCULAR DISEASES

Systemic Hypertension

Disordered breathing events during sleep are associated with well
recognized acute peripheral vasoconstriction and attendant rises
in BP during sleep (1). Further evidence is mounting to support
a probable causative role for OSA in diurnal hypertension as well.
Data on the impact of OSA treatment on BP, particularly with
continuous positive airway pressure (CPAP) therapy, are accu-
mulating, but are not always consistent.

In normal individuals, sleep is associated with a reduced BP
when compared with wakefulness, referred to as the “dipping”
phenomenon, when systolic and diastolic BP may decline as
much as 10–15% (32, 33). Sleep apnea has been found to blunt
the dipping of BP during sleep, a finding that may confer
heightened cardiovascular risk (34).

Observational studies have shown that hypertension and
OSA often coexist and that subjects with OSA tend to have
higher BPs than matched controls (35, 36). Longitudinal studies
have built on these associations, the most notable from the
Wisconsin Sleep Cohort, which provides prospective evidence
implicating OSA as a possible causal factor in hypertension
(35). Specifically, the presence of hypertension 4 years after
initial assessment was found to be dependent upon the severity
of OSA at baseline.

CPAP has been shown to acutely attenuate sympathetic drive
and nocturnal BP in patients with OSA (1, 37, 38). However, the
data regarding effects on daytime BP have been more difficult to
interpret. A number of observational studies, often uncontrolled
and from highly select populations, have suggested improve-
ments in daytime BP control with the use of CPAP. Because of an
apparent true placebo effect realized in measurement of BP,
randomized, placebo-controlled studies, a number of which have
been published and yielded variable results, may be the best
indicator of the antihypertensive effects of CPAP. The largest
trial to date comes from Pepperell and colleagues (39), who found
a small but significant reduction in BP in a normotensive group of
subjects over 4 weeks of CPAP therapy. Data from Becker and
colleagues (40), who conducted a controlled trial testing more
than 60 days of CPAP treatment, showed the most dramatic
reductions in mean BP (9.9 ± 11.4 mm Hg) in a small cohort with
severe OSA (mean apnea–hypopnea index [AHI] > 60/h)
(Figure 1). Notably, there was a high rate of subject dropout
(the data from these subjects were not included in an intention-to-
treat analysis), and the majority of subjects were treated with
various antihypertensive medications. These two studies were
included in a very recent meta-analysis of 12 placebo-controlled,
randomized trials (572 patients), which found a statistically
significant pooled reduction in mean BP of 1.69 mm Hg associated

Figure 1. Changes in mean arterial blood pressure
(MAP) over 20 hours after treatment with (A) therapeu-
tic continuous positive airway pressure (CPAP) and
(B, lower) subtherapeutic CPAP. Reprinted by permis-
sion from Reference 40. nCPAP = nasal CPAP.
Cardiac Arrhythmias and Cardiovascular Mortality

A number of observational studies have shown an association between OSA and various nocturnal arrhythmias. Recent data from the Sleep Heart Health Study, after adjusting for many confounders, showed that, compared with subjects with a respiratory disturbance index less than 5, those with severe OSA (respiratory disturbance index \( \geq 30 \)) had a higher rate of atrial fibrillation, nonsustained ventricular tachycardia, and ectopic ventricular beats (42). Bradycardiac rhythms are commonly encountered in OSA, may correlate with the severity of disordered breathing, can occur with a structurally normal heart, and may be attenuated by effective CPAP therapy (43–45). The Sleep Heart Health Study described above, however, found similar rates of bradycardias and conduction delays between those with severe OSA and those without significant OSA.

Mounting data strengthen the association between OSA and atrial fibrillation, two disorders that often coexist (46). Continuous cardiac monitoring with an atrial defibrillator showed that the onset of nearly 75% of episodes of persistent atrial fibrillation in patients with OSA occurred in the overnight hours (8 P.M.–8 A.M.) (47). Retrospective analysis shows that, within 12 months of successful therapeutic electrical cardioversion for atrial fibrillation, untreated subjects with OSA were found to have an arrhythmia recurrence rate double that of patients treated with CPAP (48).

Recent review of 17 years of polysomnographic data from a population-based cohort suggests that nocturnal hypoxemia associated with OSA influences the incidence of atrial fibrillation (49). Because none of these observational data can convincingly implicate OSA as an independent cause of new onset atrial fibrillation, additional longitudinal cohort studies and outcome-based interventional trials are needed to characterize the relationship between OSA and atrial arrhythmias.

Ventricular arrhythmias have been reported in patients with OSA (42, 50), although a causative role for sleep apnea in serious arrhythmias or sudden death has not been definitively proven. Recent data provided by review of polysomnographic measures in 112 patients with sudden death suggest a markedly higher rate of lethal cardiac events between the hours of midnight and 6 A.M. in those with OSA compared with those without, along with a direct correlation between AHI and risk of death during the night (51). Although the study suggests that OSA may influence time of sudden cardiac death, it does not clearly demonstrate that OSA heightens the risk of sudden death from cardiac causes.

In the longest-term prospective cohort study yet published (10 yr), Marin and colleagues (52) demonstrated a higher risk of both fatal and nonfatal cardiovascular events in men with severe OSA who were noncompliant with CPAP therapy compared with snorers, treated patients with OSA, and healthy men (Figure 2). Although biased by potential and difficult-to-measure influences related to treatment noncompliance and imbalances in some confounding variables at baseline (such as prevalence of hypertension and glucose intolerance), this study is among the most persuasive to argue that OSA has detrimental effects on long-term CV outcomes.

Cerebrovascular Disease and Stroke

Several studies have investigated the association between stroke and sleep-disordered breathing (53–55). A large prospective study showed self-reported snoring to be an independent risk factor for stroke in women (56). Until recently, associations with OSA have been reported primarily in cross-sectional and case-control studies, so it is unclear if OSA is a direct contributor to stroke incidence, as comorbidities and risk factors are commonly seen in both diseases. However, reports from two observational cohorts have helped strengthen this association. Using data from the Wisconsin Sleep Cohort, Arzt and colleagues (57) showed moderate to severe sleep-disordered breathing to be a risk factor for prevalent stroke and, with serial polysomnographic data, demonstrated that the preexisting sleep disorder may be a risk factor for incident stroke. Yaggi and colleagues (58) reported longitudinal data (mean follow-up, 3.4 yr) on mortality from stroke and other causes in more than 1,000 patients with preexisting OSA, showing an increasing risk of events with OSA severity. Although not powered to detect potential differences related to treatment of OSA, and in contrast to findings in the Marin cohort (52), there did not appear to be treatment effects in more than half of patients who were either treated with CPAP, lost weight, or underwent upper airway surgery.

It is feasible that stroke, particularly as represented in case-control studies, may itself predispose to sleep-disordered breathing. This may relate to disruption of central respiratory control mechanisms, leading to central sleep apnea or brainstem-mediated upper airway reflexes that may cause obstructive apneas or hypopneas. Indeed, in a report of 161 inpatients with acute stroke
or transient ischemic attack who underwent studies at baseline and after 3 months, over 70% had an AHI greater than 10 (59). Nearly one-third of apneas were central in origin during the acute phase. At 3 months, however, the central apneas were significantly reduced, whereas the obstructive events remained stable. This could suggest that OSA preceded, and perhaps contributed to, stroke, whereas central apneas resulted from the acute neurologic event.

In addition to effects on atherogenesis and blood vessel function noted previously here, a number of other mechanisms may predispose to stroke in OSA. The strong association with atrial fibrillation may confer a heightened risk of embolic events. Furthermore, OSA has been shown to promote thrombosis, as evidenced by enhanced platelet aggregation (60) and activation (61), elevated fibrinogen levels (62), and diminished fibrinolytic activity (63). Finally, Doppler measurements have suggested that apneic events are associated with reduced cerebral blood flow (64, 65), which can result in cerebral hypoxia (66). Although CPAP treatment has been shown to reverse some of these findings (67, 68), the impact of treatment on the occurrence of stroke and death, as suggested by the study by Yaggi and colleagues (58), may be limited and needs further evaluation.

HEART FAILURE
By their strong associations with aging and obesity, HF and OSA are closely linked, with the prevalence of OSA, approaching 40% in patients with HF referred to a clinical sleep laboratory (69). Further evidence linking OSA to HF comes from the Framingham study, which showed that increasing body mass index (BMI) is directly correlated with incident HF (70), an effect that may be mediated, at least in part, by OSA. Incident atrial fibrillation, an important risk factor for HF, is associated with the degree of oxyhemoglobin desaturation in OSA (49). The cascade of physiological responses to repetitive upper airway closure in OSA may exert deleterious effects on cardiac function, particularly in the already compromised heart. Despite advances in treatment with drugs, lifestyle modifications, and therapeutic devices, mortality from HF continues to rise. Thus, there is increasing interest in the role of OSA treatment on outcomes in HF.

Two controlled, interventional trials of CPAP for OSA in the setting of HF have been cited frequently for their positive impact on various CV variables (71, 72). Using a randomized, parallel comparative design, the control groups in both studies were comprised of subjects optimally medically managed, though not subjected to placebo. Kaneko and colleagues (71) reported an approximately 9% increase in LV ejection fraction (LVEF) and significant reductions in BP after just 1 month of CPAP therapy. Mansfield and colleagues (72), studying a group of subjects with somewhat less severe degrees of both HF and OSA than those reported in the Kaneko paper, applied CPAP therapy for 3 months and showed significant improvements in LVEF and reductions in urinary catecholamines, but no changes in BP.

In an unexpected turn of events, Smith and colleagues (73) very recently published the results of a rigorous, placebo-controlled cross-over study of CPAP in a population with a similar degree of HF as the previous trials, and found no improvement in any parameter of CV function, including LVEF, BP, and exercise tolerance. Although these findings may relate in part to methodologic limitations, such as the lack of a follow-up polysomnogram to confirm treatment efficacy with autotitrating CPAP (74), the currently limited data regarding the impact of OSA treatment on important HF endpoints calls for further interventional trials.

PULMONARY HYPERTENSION
In 1947, Motley and colleagues (75) demonstrated that breathing a gas mixture containing 10% oxygen induced a rise in pulmonary arterial pressure (PAP). This hypoxic pulmonary vasoconstriction is a critical autoregulatory mechanism important in maintaining an appropriate V/Q relationship (76). Over time, hypoxic vasoconstriction may result in pulmonary vascular remodeling, which may or may not be reversible (77), potentially contributing to the development of PH, as demonstrated in populations with advanced lung disorders, such as chronic obstructive pulmonary disease. It may follow then, that repetitive upper airway collapse and oxyhemoglobin desaturations characteristic of OSA could also provide a pathophysiologic basis for chronic elevations in PAP.

Precisely defining the role of OSA in the genesis of PH has been difficult for a number of reasons. First, one limitation has been the various methods by which the diagnosis of PH is made in studies of subjects with OSA, many by way of Doppler echocardiography, with varying right heart/PAP thresholds. Currently, PH is defined as a mean PAP greater than 25 mm Hg at rest or 30 mm Hg with exercise, as measured by right heart catheterization (78). Previous definitions were based upon systolic PAP greater than 40 mm Hg and echocardiographic Doppler measurements, which may be particularly challenging to obtain in obese patients with OSA. Second, as in other disease states mentioned previously here, PH and OSA share common risk factors—namely, obesity and aging, which confound risk factor associations. In fact, a pulmonary artery systolic pressure (PASP) greater than 40 mm Hg is found in 6% of otherwise normal individuals age 50 years or older, and in 5% of individuals with a BMI greater than 30 kg/m² (79). Third, finding appropriate control groups with which to compare endpoints (i.e., matched subjects with PH but no OSA) is challenging. Nevertheless, based upon some literature examining the relationship between OSA and PH, the latest revision of the Clinical Classification of Pulmonary Hypertension identifies sleep-disordered breathing as part of the category of respiratory disorders associated with PH (80). Limited epidemiologic data, coming from numerous case series, comprised primarily of male patients, suggest a prevalence of PH in OSA ranging from 17 to 52% (81–83). The largest published sample to date numbers 220 subjects with OSA, of whom 17% met diagnostic criteria for PH (82). Population-based data are currently lacking.

Papers dating back more than three decades have documented increases in PAP associated with sleep-related hypoxemia. Coccagna and colleagues (84) continuously measured PAP during sleep in 10 patients with sleep-disordered breathing and found sleep stage–dependent increases in PAP, with more marked changes occurring during rapid eye movement sleep. Most early clinical studies suggested that abnormalities in underlying lung function sufficient to induce daytime hypoxemia were required for the development of PH and right heart failure (85, 86). Further supporting this notion was the finding that the severity of sleep-disordered breathing, as measured by the AHI, and PAP elevations often failed to correlate. It should also be noted that not all studies adequately excluded increases in left atrial pressure, suggested by elevated pulmonary capillary wedge pressures, as a contributor to the development of daytime increases in PAP (87–89).

In an attempt to control for some of these confounding variables, Sajkov and colleagues (90) studied 27 patients with OSA in whom clinically significant cardiac and pulmonary disease had been excluded. A total of 11 (41%) were found to have PH, with a mean PAP of 26 mm Hg. No difference was noted between patients with PH and those without PH in AHI, BMI, smoking history, or lung function. However, those with
PH were found to be more hypoxemic during daytime wakefulness than patients without PH, a finding that could either contribute to or result from PH.

Treatment in the form of tracheostomy or supplemental oxygen has been shown to reduce PAP in patients with chronic obstructive pulmonary disease and nocturnal hypoxemia (91). In 1978, the Stanford group reported an approximate 50% reduction in PAP in six selected patients with OSA who underwent tracheostomy, some of whom may have had comorbid disease (92).

There are very limited data on the effects of CPAP treatment of OSA on PAP. Alchanatis and colleagues (93) studied a group of 29 patients with OSA (with no evidence of pulmonary or cardiac disease) with Doppler echocardiography before and after 6-month CPAP treatment. Comparisons were made with 12 healthy subjects. A total of 20% of the patients with OSA had PH that was clinically mild (mean PAP, 25.6 mm Hg). Greater age and increased BMI distinguished these from the patients with OSA without PH; 6 months of CPAP treatment was associated with reductions in mean PAP in both patients with OSA with PH (25.6 ± 4.0 to 19.5 ± 1.5 mm Hg) and those without PH (14.9 ± 2.2 to 11.5 ± 2.0 mm Hg).

Sajkov and colleagues (94) treated 20 patients with OSA (without coexistent pulmonary or cardiac disease) with 4 months of CPAP therapy. Only 5 patients met criteria for PH, with a mean PAP for the whole group of 16.8 mm Hg. To assess the reversibility of PH in these patients, PAP was measured by echocardiography at three levels of inspired oxygen (50, 21, and 11%). After 4 months of CPAP therapy, PAP (for all patients) decreased to a mean of 13.9 mm Hg. CPAP may also affect vasoactivity, as the pulmonary artery pressor response to hypoxia was attenuated.

Finally, in the first placebo-controlled trial of treatment of OSA in PH, Arias and colleagues (95) recently reported the results of a randomized cross-over trial of CPAP and sham CPAP over 12 weeks in 23 patients with OSA. A total of 10 patients with PH (defined as PASP > 30 mm Hg by Doppler echocardiography) were more obese, had more ventilatory limitation (reduced FVC), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 patients without PH. CPAP therapy reduced PASP in all patients with OSA, though more so in those with PH at baseline (mean reductions, 8.5 vs. 2.6 mm Hg) (Figure 3). Although the baseline differences in obesity and lung function between groups preclude the attribution of PH to OSA alone, these data are the first to show, in a placebo-controlled fashion, the positive impact of CPAP therapy on PH in a small group of patients with OSA. Further research is needed to assess the durability of CPAP therapy on PAP and right heart function and how CPAP therapy fits into the treatment paradigm amid an ever-increasing arsenal of pharmacologic treatments for PH.

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