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ROLE OF OBSTRUCTIVE SLEEP APNEA IN CARDIOVASCULAR DISEASE

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Abstract

Purpose of review—To provide an update on the connection between obstructive sleep apnea (OSA) and cardiovascular disease.

Recent findings—Large prospective studies have established that OSA is associated with an increased incidence of hypertension and, in men, of coronary disease, stroke, and heart failure. Advances in understanding the pathophysiologic basis for these associations include identification of a role for OSA in inducing abnormalities in hepatic lipid-metabolizing enzymes, endothelial dysfunction, and upregulation of pro-inflammatory and pro-thrombotic mediators. A large body of data implicates OSA as playing a significant role in the occurrence and resistance to treatment of atrial fibrillation. Clinical trials have shown small to modest improvements in blood pressure associated with continuous positive airway pressure (CPAP) use, with smaller or uncontrolled studies suggesting that CPAP may improve cardiovascular outcomes or intermediate markers.

Summary—OSA and cardiovascular disease commonly co-aggregate. Multiple studies indicate that OSA contributes to or exacerbates cardiovascular disease, and thus may be a novel target for cardiovascular risk reduction. While the evidence supports screening and treatment of OSA in patients at risk for cardiovascular disease, it also underscores a need for well powered clinical trials to examine the role of CPAP and other therapies in these populations.

Keywords

Obstructive sleep apnea; atrial fibrillation; cardiovascular outcomes; continuous positive airway pressure; coronary heart disease

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder that affects at least 5% of the adult population [1, 2] and is associated with increased risk of hypertension [3, 4], coronary heart disease [5], atrial and ventricular arrhythmias [6], and mortality [7]. The physiologic

Conflicts of interest

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links between obstructive airway events and cardiac pathology are multi-factorial and are expertly summarized in a consensus document from the American College of Cardiology and American Heart Association [8] as well as in several recent reviews [9, 10]. Research on the relationship between OSA and cardiovascular disease has been as multi-faceted as the underlying pathophysiology that connects the two disorders. In addition, a number of studies have reported on the cardiovascular impact of treatment of OSA, a promising step forward. This review will focus on recent findings in four key areas: cardiac risk factors, coronary heart disease (CHD) and stroke, heart failure/cardiomyopathy, and arrhythmia.

CARDIAC RISK FACTORS

A number of the cardiovascular consequences of OSA may be mediated through OSA-related effects on 24-hour blood pressure levels. OSA has been implicated in elevations of blood pressure to pre-hypertensive and hypertensive ranges, an increased prevalence of a non-dipping blood pressure pattern, and increased risk of resistant hypertension. Nocturnal as well as daytime elevations in blood pressure largely have been attributed to sympathetic nervous system activation secondary to apnea-related arousals and/or hypoxemia [11]. Recent research has additionally implicated alterations in fluid balance, specifically identifying a role of the renin-angiotensin-aldosterone system in OSA-related hypertension. In a study of more than 100 individuals with resistant hypertension, overnight indices of OSA indicated more severe OSA in the ~ 30% of the cohort with hyperaldosteronism compared to remaining sample with normal aldosterone status [12]. Primary aldosteronism was reported to be more than 2-fold more common among subjects with both hypertension and OSA (~ 25%) as compared to subjects with hypertension alone (< 10%) [13]. In a pilot study of 12 individuals with moderate-severe OSA, the apnea hypopnea index (AHI) significantly declined, although it remained in the abnormal range, following 8 weeks of spironolactone therapy [14*]. Spironolactone therapy also was associated with a significant decrease in weight (~ 4 lbs), but not in neck circumference, an area where excessive fluid accumulation could contribute to pharyngeal collapsibility. Taken together, these studies suggest that hyperaldosteronism and OSA occur together commonly and that those with resistant hypertension, if being evaluated for one or the other, may benefit from evaluation for both conditions. The intervention study, although small and open-labeled, raises the possibility that hyperaldosteronism could contribute to OSA severity by promoting fluid retention. Further research addressing the role of aldosterone antagonists or fluid management in OSA may help 'personalize' approaches to hypertension management. A physiologic mechanism of how fluid retention can contribute to OSA has been elucidated [15**] and will be reviewed further in the Heart Failure/Cardiomyopathy section.

Recently, the Outcomes in Sleep Disorders in Older Men (MrOS) cohort identified the potential role of another mechanism for OSA-related hypertension: the effects of reduced slow wave sleep on vascular function [16*]. In this cohort, after adjusting for AHI, hypoxemia, and other co-variates, the incidence of hypertension over nearly 3.5 years was increased significantly by 1.8 fold in the lowest compared to the highest quartile of sleep time spent in slow wave sleep. Slow wave sleep is commonly reduced with OSA and is associated with stable cardiorespiratory function, reduced sympathetic activation, and reduced blood pressure. Reduced slow wave sleep, a marker of poor sleep quality, has been linked to the occurrence of insulin resistance and disturbed hypothalamic-pituitary-adrenal function. Thus, interventions aimed at improving sleep quality may serve as novel targets for improving blood pressure in individuals with OSA as well as with other sleep disorders.

OSA treatment with nocturnal continuous positive airway pressure (CPAP) has been shown to reduce 24-hour ambulatory blood pressure [17–19]. Although the overall impact of CPAP on blood pressure levels is relatively modest, larger improvements have been observed

among patients with more severe OSA and sleepiness, difficult-to-control hypertension, and better CPAP compliance. Recent data from the Spanish Sleep and Breathing Group addressed the role of CPAP therapy in 350 asymptomatic individuals with severe OSA randomized to CPAP vs no CPAP. At 1 year of follow-up, the CPAP group had a significant BP reduction of ~ 2/2 mmHg, but the effect was evident only in those that used CPAP for at least 5–6 hours nightly [20*]. Although the reduction in blood pressure was small, the study raises the possibility that treating asymptomatic OSA patients with CPAP may reduce their long-term cardiovascular risk which, in this cohort, was not negligible given the high prevalence of other hypertension risk factors such as obesity and smoking.

The baseline average blood pressures in the Spanish study (~ 141/85 mmHg) hovered around the lower-limit of the traditional definition of hypertension ($\geq 140/90$ mmHg). Several studies have evaluated the association between OSA and pre-hypertension (blood pressures of 120–139/80–90 mmHg) [21, 22]. Although small ($n = 36$), a randomized study of CPAP for those with severe OSA and pre-hypertension evaluated the effect of OSA treatment in this population [23*]. After 3 months, the CPAP group showed a significant ~ 5/5 mmHg decrease in blood pressure, whereas the control group showed no change in blood pressure. Although the follow-up time was short and there are no data on cardiovascular event rates, these data raise the possibility that CPAP use early in the course of hypertension may be especially beneficial for longer term blood pressure control.

Obesity/inflammation/endothelial dysfunction

The last decade has provided compelling evidence that obesity, as well as OSA, is associated with atherogenic changes to vascular endothelium [24–26]. Such effects may be partially mediated through mechanisms similar to those that have been implicated more generally in atherogenesis. These include upregulation of (1) pro-inflammatory mediators, such as C-reactive protein (CRP), interleukin-1 (IL-6), and tumor necrosis factor (TNF); and (2) molecules that mediate thrombosis, such as plasminogen activator I (PAI-1) and fibrinogen. However, many of these factors are also strongly linked to adiposity, and studies have differed in regards to whether such associations are independent of obesity. In support of an independent influence of OSA are data from a cohort study of generally healthy adolescents that showed a progressive increase in CRP levels with increases in AHI, suggesting that in the absence of significant co-morbidities, even modest levels of OSA may result in elevations in inflammatory markers [27]. Another study identified elevations in soluble IL-6 receptor that varied with OSA severity; this receptor is less strongly linked to obesity than IL-6 and is considered to regulate IL-6 messaging [28]. More recent investigations also reported that (1) independently of obesity, CRP levels were associated with indices of OSA in a cohort with the metabolic syndrome [29*]; and (2) PAI-1 and fibrinogen levels incrementally increased with AHI until reaching a plateau at 15 events/hour [30*].

Recent research also has more directly assessed endothelial function than prior work. Using cultured endothelial cells and brachial artery flow-mediated dilation measured in OSA patients and controls, markers of endothelial function, inflammation, and oxidative stress were less favorable in OSA patients than in non-OSA patients across the spectrum of body mass index; the profiles of the OSA patients improved after 4 weeks of CPAP therapy [31*]. Thus, these lines of research suggest that OSA likely contributes to an upregulation of pro-atherogenic processes over and beyond the effects of obesity alone. Furthermore, treatment of OSA with CPAP may be beneficial to overall vascular function.

Dyslipidemia

A number of elegant animal and human studies have identified that intermittent hypoxemia, characteristic of OSA, induces alterations in hepatic enzymes involved in lipid metabolism (such as transcription factor sterol regulatory element-binding protein-1 [SREBP-1]) and phospholipid biosynthesis (stearoyl-CoA desaturase-1) [32]. Although there has not been strong evidence from clinical trials to support a beneficial effect of CPAP therapy on lipid levels, a recent crossover study of 38 patients with OSA showed that CPAP therapy was associated with reductions in triglycerides and non-HDL cholesterol [33]. The primary outcome in this trial was the area-under-the-curve of triglyceride levels over the course of a 24-hour period; levels were measured 7 times during this interval. If substantiated in larger studies, these findings could provide further justification for OSA treatment to modulate cardiovascular risk.

CORONARY HEART DISEASE AND STROKE

The prevalence of OSA in individuals with coronary heart disease (CHD) is ~30–60% [9], considerably higher than the prevalence in the general population. Among men hospitalized for acute myocardial infarction (MI), the prevalence of OSA has been reported to be nearly 70% [34], further highlighting the co-aggregation of these disorders.

The major prospective findings from the community-based Sleep Heart Health Study (SHHS) provide epidemiologic evidence for a causal role of OSA in the incidence of cardiovascular disease and cardiovascular-related mortality. Over an 8-year follow-up of more than 6000 individuals, the risk of CHD-related death in the male subset of this cohort tracked with all-cause mortality and was 70% greater in those with $AHI \geq 15$ events/hour compared to unaffected individuals [35**]. A similar relationship between AHI and incident coronary heart disease (MI, revascularization, or cardiac mortality) was observed in 40–70 year-old males in the SHHS cohort; compared to those with no OSA, those with severe OSA ($AHI \geq 30$ events/hour) were nearly 70% more likely to develop CHD [36**]. A smaller study ($n \sim 1500$) with shorter follow-up (~ 3 years) likewise showed increased risk of CHD with increasing AHI, even when adjusted for hypertension and BMI [37]. Unlike the SHHS findings, this study showed an increased risk even at AHIs in the ‘mild’ category (5–15 events/hour). Taken together, these studies provide compelling evidence for OSA as a risk factor for incident CHD and for CHD-related mortality. Observational data suggest that CPAP treatment in those with severe OSA reduces the risk of CHD-events [5]. However, the strength of data relating cardiovascular disease and OSA in women is less strong than in men and underscores the need for further study of the influence of gender on this association.

An intriguing study from the SHHS investigators suggests that the association between OSA and CHD may be bi-directional [38]. This analysis found that in the very small fraction of participants that developed incident CHD ($\sim 3\%$), AHI worsened modestly (< 3 events/hour) on follow-up evaluation relative to baseline. The effect was most pronounced in those with OSA at baseline and in those that were neither obese nor overweight.

Stroke

A prospective study of patients referred for an evaluation of sleep disorders reported a nearly 2-fold increase in the composite endpoint of stroke or death in affected individuals [7]. However, applying those results broadly is challenging given (1) the risk of stroke due to OSA is unknown due to the composite nature of the endpoint; and (2) since the cohort came from a referral population, the generalizability of the findings is limited. Subsequent data from the SHHS help clarify the risk related to OSA of incident stroke in the general population [39*]. In this analysis of > 5000 individuals followed nearly 9 years, men with an

AHI in the upper quartile of the distribution (moderate to severe levels) had a nearly 3-fold higher risk of having an incident ischemic stroke relative to those without OSA, even after adjusting for age, body mass index, smoking status, systolic blood pressure, use of antihypertensive medications, diabetes status, and race. The strength of this association supports the need for prospective trials evaluating CPAP for prevention of ischemic stroke in men with OSA. Although the mechanisms implicated in increased stroke risk likely include adverse effects of OSA on cerebral blood pressure regulation and tissue oxygenation, recent data also have highlighted the potential adverse effect of snoring, which causes neck tissue vibration leading to carotid endothelial dysfunction [40]. Thus, the group of individuals at risk for OSA-related stroke may include heavy snorers as well as those with more severe apnea-related hypoxemia.

HEART FAILURE/CARDIOMYOPATHY

The prevalence of OSA in patients with heart failure is ~ 10–35% [41–43] and more than half of those with OSA have diastolic dysfunction, which can improve with CPAP [44]. A small study showed modest, but significant, improvement in left ventricular ejection fraction (LVEF) among those with OSA and heart failure treated with CPAP [45], but was limited to men. The risk of developing new heart failure attributable to OSA was evaluated in a recent study from the SHHS [36**]. In the SHHS cohort, OSA predicted incident heart failure in men, but not in women, in a graded fashion (13% increase per 10 event/hour increase in AHI). In analyses adjusted for multiple possible confounders, men with severe OSA were nearly 60% more likely to develop heart failure compared to those without OSA. Whereas the SHHS study examined the effect of OSA on heart failure, there is also evidence for reverse causality. Recent work from the Toronto group provides evidence that excessive fluid retention, with rostral overnight fluid shifts (from the interstitium of the lower extremities to the neck) can contribute to worsening OSA [15**]. In those with OSA and impaired LVEF ($\leq 45\%$), nocturnal decrease in leg circumference correlated with increased neck circumference and higher AHI. With CPAP, the observed decrease in leg circumference did not change, but the increases in neck circumference and AHI were attenuated. If confirmed in more general samples, this mechanism could inform new strategies directed at managing fluid shifts with posture and sleep.

A large proportion of patients with heart failure have predominantly central-type sleep apnea, a marker of ventilatory instability associated with prolonged circulation time. A clinical trial conducted in patients with heart failure and central sleep apnea did not show a survival benefit associated with CPAP treatment [46]. However, the high prevalence of residual sleep apnea in study participants treated with CPAP suggested a need for more effective interventions in this challenging population. Ongoing trials are examining the use of adaptive servo-ventilation, which modulates pressure support as breathing varies, in this population. Both central and obstructive sleep apnea may co-exist in the same patient, emphasizing a need for further research elucidating patient characteristics associated with specific intervention responses.

Cardiomyopathy

A recent series of articles has highlighted the role of OSA in those with hypertrophic cardiomyopathy (HCM), a disease state that, due to its abnormal myocardial substrate, severe diastolic dysfunction and predilection for arrhythmias, is particularly susceptible to the physiologic effects of OSA. The prevalence of OSA in 100 individuals with echocardiographically-defined HCM was recently estimated to be 70% [47]. An increased prevalence of atrial fibrillation (AF) in HCM patients with OSA compared to those without OSA was also reported (40% vs 11%; $p = 0.005$) [48]. In a second cohort of HCM patients that underwent in-home polysomnography, the prevalence of OSA ($\text{AHI} \geq 15$ events/hour)

was 40%; > 30% of those with OSA had AF compared to just 6% of those without OSA [49]. Together, these studies establish that (1) OSA is common in HCM; and (2) OSA may contribute to the burden of AF in this population. As with CHD, stroke, and heart failure, these findings underscore the need for further evaluation of outcomes in those with OSA and HCM as well as for trials to assess whether CPAP therapy can favorably impact those outcomes.

ARRHYTHMIA

Prior work from the SHHS established that AF and non-sustained ventricular tachycardia (NSVT) are more prevalent in those with OSA than in unaffected individuals [6]. A recent study from the same group extended these findings by demonstrating a strong temporal relationship between OSA-related respiratory events and the occurrence of these arrhythmias [50**]. A paroxysm of AF or an episode of NSVT was 18-times more likely to occur within 90 seconds of an apnea or hypopnea than during normal breathing. When applied to a hypothetical patient with moderate OSA sleeping 8 hours/night, these data suggest that OSA would be responsible for 2 extra arrhythmias per year. Taken in the context of the high and growing prevalence of OSA in the general population, OSA-events may contribute to a considerable number of excess episodes of AF and NSVT.

Catheter ablation is an increasingly common modality of therapy for AF. Several studies have examined the effect of OSA on the outcome of these procedures. Compared to a cohort successfully treated with a single procedure, those that remained in AF despite at least 2 ablation procedures had a much higher prevalence of polysomnographically-proven OSA (87% vs 48%; $p = 0.005$) [51]. In another cohort, the rate of clinical success of AF ablation was significantly reduced in those with OSA (defined by the Berlin Questionnaire) compared to unaffected participants, although the effect was attenuated when corrected for obesity [52]. A large multi-center study of consecutive patients undergoing AF ablation procedures ($n = 3000$; 21% with polysomnographically-proven OSA) showed several important results: (1) OSA patients had lower procedural success and more procedure-related complications; (2) those on CPAP had lower AF recurrence rates; and (3) OSA patients more commonly had AF triggers originating from non-pulmonary vein sites [53*]. A recent meta-analysis analyzed these and other trials of catheter ablation for AF and found that OSA is a significant predictor of recurrent AF following the procedure, but that this effect was attenuated considerably when OSA was defined by the Berlin Questionnaire rather than by polysomnogram [54]. In summary, these studies show that OSA decreases the success of AF ablation and may be associated with a different 'AF phenotype' than is present in unaffected individuals. The observation of improved success with CPAP therapy provides justification for trials designed specifically to test the impact of CPAP in this population.

As the volume of AF ablation procedures has increased, a post-ablation syndrome of diastolic dysfunction, secondary pulmonary hypertension, and unexplained dyspnea has been recognized and is thought to be related to extensive atrial scarring from the ablation procedure causing decreased left atrial compliance [55]. OSA is associated with a 6-fold increase in risk of this 'stiff left atrial syndrome' [56*] and may act to decrease pulmonary vascular compliance pre-ablation, thus leaving the pulmonary vasculature more vulnerable to the effects of increased post-capillary pressure following the procedure. CPAP could potentially ameliorate these effects by decreasing preload and thus blunting the increase in pulmonary pressure that contributes to symptoms.

CONCLUSION

The body of evidence linking OSA and cardiovascular disease continues to grow. These disease conditions commonly co-aggregate, with recent data providing further support for OSA operating as a contributor to the pathogenesis of cardiovascular disease. Recent studies have shown an increased incidence of coronary events, heart failure, stroke, and cardiac mortality in those with OSA relative to unaffected individuals, with associations stronger in men than in women. There have been a number of advances in understanding the pathogenesis of these associations; animal and human work has demonstrated that OSA-related stresses contribute to the release of pro-inflammatory reactive oxygen species and pro-thrombotic mediators, alter lipid metabolism, and adversely impact endothelial function. New roles for altered fluid regulation in the pathogenesis of OSA and its impact on blood pressure control also have been reported, including identification of hyperaldosteronism as a potential co-conspirator in OSA-mediated hypertension. OSA likely plays a clinically significant role in the occurrence and resistance to treatment of AF, the most common arrhythmia seen in clinical practice. In aggregate, the data to date justify the conduct of well powered clinical trials to examine the role of OSA treatment in reducing cardiovascular morbidity and mortality.

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KEY POINTS

- Obstructive sleep apnea (OSA) is associated with elevated blood pressure, non-dipping blood pressure, and resistant hypertension. Mechanisms relate to augmented sympathetic nervous system activation, and possibly to increased levels of hormones that influence fluid balance, such as aldosterone. Treatment with CPAP may reduce systolic blood pressure on average by 2 to 5 mmHg.
- OSA increases the risk of developing coronary heart disease, heart failure, stroke, and atrial fibrillation (AF), especially in men. Small or non-controlled studies support the use of CPAP as a means of reducing cardiovascular morbidity.
- There are multiple mechanisms by which OSA may increase risk for cardiovascular disease, including altering blood pressure and inducing pro-atherogenic processes.
- OSA may serve as a direct trigger for inducing paroxysms of AF and may contribute to the recurrence of AF after catheter ablation.
- Attenuation by continuous positive airway pressure (CPAP) of the cardiovascular effects of OSA has been observed in several studies. However, large prospective trials of CPAP therapy to assess its impact on incident and recurrent cardiovascular events in those with OSA are warranted.