REVIEW ARTICLE

Cardiovascular consequences of obstructive sleep apnea

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Abstract

The impact of obstructive sleep apnea syndrome on cardiovascular morbidity and mortality is phenomenal. There is a strong evidence base in terms of several longitudinal as well as cross-sectional studies in support of this fact. However, the evidence in favor of its association with hypertension is stronger than with coronary artery disease, arrhythmias and stroke. Prevalence studies on OSAHS have demonstrated an increased odds ratio for hypertension above the background population. Also, prevalence of hypertension is known to increase proportionate to the severity of sleep disordered breathing. Cross-sectional prevalence studies on cardiovascular disease and OSAHS have shown an increased risk of coronary artery disease (CAD) amongst patients with OSAHS. Prevalence of OSA is significantly higher in patients with atrial fibrillation (AF) than in patients without past or current AF. Pulmonary arterial hypertension, congestive heart failure and sudden cardiac death are also commonly associated with OSAHS. Interventional studies clarify the role of effective treatment of this disorder with CPAP. Therapy with CPAP, therefore, should be expected to impact the prognosis of cardiovascular consequences of this syndrome.

Introduction

Although obstructive sleep apnea (OSA) has an anatomical connotation with the upper airway, its impact on the human physiology is all pervasive. The metabolic and cardiovascular implications of OSA are of seminal interest. This short review attempts to summarize the consequences of OSA that manifest in the cardiovascular system. Several conditions like hypertension congestive heart failure, arrhythmias, coronary artery disease, and stroke, would be discussed.

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Pathophysiological basis of cardiovascular consequences of OSA

Normal sleep induces a fall in blood pressure. This is brought about by a fall in cardiac output (resulting from a reduction in stroke volume and heart rate) as well as in peripheral resistance (as a consequence of decreased sympathetic system activity). In patients with OSA, it has been noted that periods of apnea are usually terminated by arousals and tachycardia. The fall in blood pressure that is noticed during sleep in normal subjects is absent in patients with OSA. Reduction in airflow and apnea have been shown to be associated with increase in blood pressure, hypoxia, increased swings in negative intra-pleural pressures and increased sympathetic nervous system activity in such patients[1]. This increase in sympathetic nervous system activity is more prominent in obese patients with occult OSA than

in normal-weight subjects and obese subjects without OSA. Increased sympathetic nervous system activity is evidenced by presence of increased levels of 24 hour urinary nor-epinephrine in apneic patients compared to non-apneic subjects. CPAP treatment lowered daytime plasma nor-epeinephrine levels by 23% compared to no effect on urinary norepinephrine by placebo[2]. Thus, these changes in sympathetic nervous system and blood pressure are not just restricted to the sleep state, but are also spilled over to the daytime wakeful state. Most of the effects of OSA are not apparent when awake, but it leaves some lingering problems. Increased awake sympathetic nervous system activity is one of the hallmarks of OSA. Reduced nocturnal fall in systolic and diastolic blood pressure, and increased diastolic blood pressure during morning and afternoon have been observed in patients with OSA[3]. These changes have been noticed even after common risk factors like increasing age, BMI, cigarette smoking and alcohol use are eliminated. OSA-induced hypertension has also been demonstrated in animal models[4].

The development of atherosclerosis is usually associated with increased levels of oxidative stress, inflammatory mediators and endothelial dysfunction. In patients with OSA, such changes are quite commonly seen. Also, OSA patients demonstrate cyclical intermittent hypoxia, resulting into increased levels of free radicals as well as homocysteine. This, in turn, leads to enhanced inflammatory products and adhesion molecules and reduction in nitric oxide culminating into endothelial dysfunction[5]. Thus, the effects of OSA on the cardiovascular system are not exclusively through hypertension. There are clearly other important effects on inflammatory mediators and immune cell function that are potentially atherogenic. Effects have also been observed on endothelial function that cause functional abnormalities and suggest endothelial damage. Therapy with CPAP has been shown to be associated with reduction in levels of C-reactive protein, interleukin-6, fibrinogen, blood viscosity, and atrial-natriuretic-peptide, circulating endothelial progenitor cells (EPC) and apoptotic microparticles (EMP)[6].

Hypertension in OSA

Hypertension and OSA have been observed to co-exist in certain groups of patients. Several cross-sectional studies have shown that there is increased prevalence of hypertension in patients with OSA. Prevalence studies on OSAHS have demonstrated an increased odds ratio for hypertension above the background population[7,8,9,10]. Also, prevalence of hypertension increased proportionate to the severity of disease (AHI score); multiple logistic regressions showed that each additional apneic event per hour of sleep increased the odds of hypertension by about 1% and each 10% decrease in nocturnal oxygen saturation increased the odds by 13%[7,8,9,10]. Thus increase in severity of OSA is associated with increase in prevalence of hypertension. It may be surmised that the two disease conditions may share common risk factors, like obesity. However, cross-sectional studies have demonstrated that the OR for hypertension increased progressively with gradual increase in severity of OSA (AHI score) even after adjustment for age, gender, ethnicity and BMI, waist and neck circumference, and alcohol and cigarette use[10,11]. Sleep related breathing disorder (SRBD) has been found to be an independent risk factor for systemic hypertension[11]. In a longitudinal study to determine incident hypertension in patients of OSA over a four year follow-up, it was seen that the OR for incident hypertension increased progressively with increase in severity of OSA (AHI score)[8]. In a study of resistant hypertension (hypertension continuing despite three or more anti-hypertensive drugs), 96% men and 65% women were found to have OSA[12]. OSA is therefore a risk factor for resistant hypertension[13]. The strong association between hypertension and OSA is further substantiated by interventional studies [14, 15]. In unselected patients with sleep apnea, CPAP has very modest effects on BP. However, one cannot exclude the possibility that certain subgroups of patients may have more robust responses—this may include patients with more severe OSAHS, difficult-to-control hypertension, and patients with better CPAP compliance[16,17]. Effects on blood pressure after treatment of obstructive sleep apnea with a mandibular advancement appliance demonstrated significant reductions in blood pressure that were attained between baseline and the 3-month evaluation ($P < 0{\cdot}001$)[18]. There is, therefore, firm evidence to suggest that there is increased prevalence of hypertension in patients with OSAHS, it increases proportionate to increasing severity of OSAHS, and intervention with CPAP is also helpful in mitigating the problem of hypertension in certain subsets of patients with OSA associated with hypertension.

Pulmonary hypertension in OSA

Numerous cross-sectional studies have observed that OSA is usually associated with mild pulmonary hypertension (PH). It is commonly present when there is co-existing lung disease. Some longitudinal studies conclude that the presence of PH may have prognostic importance in patients with OSA. Interventional studies show that CPAP therapy reduces systolic pulmonary arterial pressure in patients with OSA, more so in patients with OSA[19].

Ischemic heart disease in OSA

Cross-sectional prevalence studies on cardiovascular disease and OSAHS have shown an OR of 1.27 for OSAHS and coronary artery disease (CAD) [20]. Cohort studies have shown the incidence of at least one cardiovascular disease in 36.7% cases of OSA as against 6.6% subjects without OSA (p<0.001)[21]. Cardiovascular events rate was highest amongst untreated severe OSA compared to untreated mild to moderate OSA and snorers and lower in those patients on CPAP[22]. Longitudinal studies in men demonstrated that severe obstructive sleep apnoea-hypopnoea significantly increases the risk of fatal and non-fatal cardiovascular events[22]. Patients with untreated severe disease had a higher incidence of fatal cardiovascular events (1·06 per 100 person-years) and non-fatal cardiovascular events (2·13 per 100 person-years) than did untreated patients with mild-moderate disease (0·55, p=0·02 and 0·89, p<0·0001), simple snorers (0·34, p=0·0006 and 0·58, p<0·0001), patients treated with CPAP (0·35, p=0·0008 and 0·64, p<0·0001), and healthy participants (0·3, p=0·0012 and 0·45, p<0·0001) [22]. Intervention with CPAP treatment reduces this risk [22]. An increased incidence of CAD in OSAHS has been observed in several other studies[21,23,24]. OSA may also exacerbate pre-existing coronary artery disease [25]. Longitudinal and interventional studies show that effective CPAP therapy can reduce late lumen loss and coronary artery re-stenosis after elective percutaneous coronary angioplasty in CAD[26]. in another observational study involving 48 polysomnographycally confirmed cases of OSAHS, a significant association independent of confounders was documented between OSAHS and: (i) blood pressure and hypertension; (ii) previous myocardial infarction, diastolic dysfunction, left ventricular hypertrophy, pulmonary hypertension and arrhythmias; and (iii) carotid artery plaques and intima-media thickness [27].

Congestive heart failure (CHF) and OSA

Several cross sectional studies have shown a prevalence of CHF amongst patients of OSA to vary between 30% to 57%. Sleep Heart Health Study has shown an increased OR for CHF in OSAHS [28]. An improvement in left ventricular ejection fraction (LVEF) as well as diastolic dysfunction have been demonstrated in those patients who are treated effectively with CPAP [29,30]. In one study, a fairly high prevalence of sleep-disordered breathing (57.5%) was found in patients of heart failure[31]. With increasing severity of HF a significant worsening of CSA-CSR was observed. Central sleep apnea has often been seen to be unmasked following treatment of patients of OSA & CHF with nCPAP[32].

Arrhythmias and OSA

Cross sectional studies have demonstrated an association of nocturnal arrythmias like atrial fibrillation (AF) (4.8% vs 0.9%), complex ventricular ectopy (25% vs 14.5%), and non-sustained ventricular tachycardia (5.3% vs 1.2%) and patients with sleep disordered breathing (SDB) as against those without SDB[33]. Prevalence of OSA is significantly higher in patients with AF than in patients without past or current AF in general cardiology practice[34]. Sleep-disordered breathing is more frequent in chronic persistent and permanent AF patients than in age-matched community dwelling subjects[35]. Cumulative frequency curves for incidental atrial fibrillation for subjects <65 years with OSA were significantly higher than those for subjects without OSA in cohorts followed up for an average of 4.7 years [36]. In paced patients, there is an excessively high prevalence of undiagnosed OSA (59%) [37]. Undiagnosed OSA is a risk factor for AF. However, cause-and-effect relationship between OSA and AF and the effect of CPAP therapy on the incidence and recurrence of AF remains to be demonstrated. Longitudinal studies have shown that AF may recur in untreated patients of OSA as compared to those who undergo CPAP treatment for 12 months[38]. The diagnosis and treatment of OSA may be an additional preventive strategy for patients with AF.

Stroke and OSA

The relative risk of stroke is higher in patients with OSA[39,40]. CPAP treatment reduces mortality in patients

with ischemic stroke and OSA [41]. OSA is associated with increased risk of stroke, but whether this association is independent remains to be determined. In patients with stroke, OSA may increase the risk of death. Those stroke patients, who present with symptoms suggesting that the OSA preceded the stroke, may benefit from sleep study. The association of stroke and OSA has been addressed in greater detail in a separate section of this document.

Mortality from cardiovascular events in OSA

Several cross sectional studies have demonstrated the increased mortality from cardiovascular events in patients with SDB. Severe SDB (AHI>30) had a 3.8 fold greater risk for all-cause mortality (95% CI 1.6-9.0;p=0.004) and 5.2-fold greater risk for cardiovascular mortality (95% CI 1.4-19.2; p=0.03) than those without SDB [42]. AHI≥30 was associated with a 1.5 fold higher risk for all-cause mortality compared to subjects with an AHI<5 (HR 1.46, 95% CL 1.14-1.86) [43]. The incidence of sudden nocturnal deaths was significantly higher in patients with OSA than in non-OSA patients and general population [44]. There is a worse survival of heart failure patients with untreated obstructive sleep apnea (OSA) than in those with mild to no sleep [45]. interventional studies show that the cumulative event-free survival in those patients with OSA on CPAP therapy was significantly higher than untreated patients [46,47].

Summary

Epidemiological, longitudinal and therapeutic studies have proved convincingly that OSA is associated with increase risk of cardiovascular morbidity and mortality. The strongest evidence supports an independent causal link between OSA and arterial hypertension. OSA may be independently associated with increased risk for IHD, arrhythmias and mortality. It remains to be determined whether OSA is an independent cause of CHF and PH.

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