

Co-morbidities associated with obstructive sleep apnea

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ABSTRACT

There are many co-morbid conditions that are associated with obstructive sleep apnea (OSA). Though a causative relationship between OSA and some of the co-morbidities is well established or strongly associated, many risk factors of OSA (age, male gender and obesity) are also known risk factors especially for cardiovascular diseases. Other important co-morbid conditions associated with OSA are neurocognitive dysfunction and, erectile dysfunction. Recently there are reports that ocular manifestations are associated with OSA. It is expected that more co-morbidities will be reported in OSA as the research in this area progresses.

Key words: Co-morbidities in OSA, Hypertension, Cardiac arrhythmias, Stroke, Erectile dysfunction

INTRODUCTION

OSA is the repetitive interruption of ventilation during sleep as a result of collapse of the pharyngeal airway. The most important co-morbidities associated with OSA are cardiovascular and cerebrovascular diseases, and neurocognitive dysfunction. The main cardiovascular morbidities reported in OSA are systemic hypertension, pulmonary hypertension, cardiac arrhythmias, cardiovascular mortality, heart failure and stroke. Motor vehicle accidents are also important consequences in OSA(1).

OSA and cardiovascular diseases :

OSA has been shown to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebral vascular disease, congestive heart failure and arrhythmias (1, 2). However, a causal relationship remains controversial. Many risk factor of OSA (age, male gender and obesity) are also known risk factors for cardiovascular disease. OSA is also associated with conditions (diabetic mellitus and hypertension) that are known to increase the risk for cardiovascular disease. Therefore, it is difficult to prove whether OSA independently causes cardiovascular disease or not in these conditions.

a) Systemic hypertension :

In normal individuals, sleep is associated with a reduced blood pressure

compared to wakefulness and this is known as “Dipping” phenomenon. In normal individuals, systolic and diastolic blood pressure may decline as much as 10-15%. Sleep apnea has been found to blunt the dipping of blood pressure during sleep. Disordered breathing during sleep has also been found to be associated with acute peripheral vasoconstriction and rise in blood pressure during sleep (3). Several studies have shown that OSA increases the relative risk of hypertension independent of other confounding factors. Sleep Heart Health Study (SHHS) in a cross sectional analysis of > 6000 patients has shown a linear relationship between systolic and diastolic blood pressure and OSA severity (4). A Canadian population based study involving 2677 adults aged 20-85 years, had shown that each apneic event per hour increased the odds of hypertension by 1% and each 10% reduction in nocturnal O₂ saturation increased the likelihood of hypertension developing by 13% (5). As the above studies were cross sectional in nature linking sleep-disordered breathing to chronically elevated blood pressure, a prospective, population-based study was conducted to know the association between objectively measured sleep-disordered breathing and hypertension (6). This Wisconsin sleep cohort study in 709 participants had demonstrated a dose-response association between sleep disordered breathing at baseline and the presence of hypertension four years later. This was independent of known compounding factors. Peppard et al found a dose-response association between sleep-disordered breathing at base line

and the presence of hypertension four years later that was independent of known confounding factors (6). This study suggested that sleep disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population (6). In another prospective study of 2470 participants of SHHS aged > 40 years without baseline hypertension and not on antihypertensive medication, it has been shown that there is a significant relationship between the risk of developing hypertension and OSA. However, this association was lost after adjustment for BMI. A moderate influence of an AHI > 30 on hypertension could not be excluded in this study (7). Continuous positive airway pressure (CPAP) has been shown to acutely attenuate sympathetic drive and nocturnal BP in OSA (8). Observational studies from uncontrolled and highly selected populations have suggested improvement in BP control with CPAP (9). A meta-analysis of 12 placebo-controlled randomized trials (n = 572) found a statistically pooled reduction in mean BP of 1.69 mm Hg with CPAP treatment (10). Most of these trials were limited to normotensive individuals. The seventh report of the Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII) has listed sleep apnea as a significant cause of secondary hypertension (11).

b) Pulmonary hypertension :

Pulmonary hypertension is defined as a mean pulmonary arterial pressure >25 mm Hg at rest or >30 mm Hg

with exercise as measured by right heart catheterization. It has been demonstrated that hypoxic vasoconstriction over time may result in pulmonary vascular remodeling, contributing to the development of pulmonary hypertension, as seen in patients with chronic lung diseases. It may therefore be possible that repetitive upper airway collapse and oxyhemoglobin desaturation characteristic of OSA could also provide a pathophysiologic basis for elevations in pulmonary arterial pressure (12). Data from case series mainly in male patients have suggested that the prevalence of pulmonary hypertension in OSA varies from 17 to 53%. However, there are no population based data to know the prevalence of pulmonary hypertension in OSA. In a study of patients with OSA with no clinically significant cardiac and pulmonary disease, 41% had pulmonary hypertension. There was no difference in AHI, BMI, smoking history and lung function between patients with pulmonary hypertension and those without pulmonary hypertension (13). A placebo-controlled randomized cross-over trial of CPAP and sham CPAP over 12 weeks has been reported in 23 patients with OSA and CPAP therapy reduced pulmonary arterial systemic pressure in all patients with pulmonary hypertension at baseline (14). The revised "Clinical Classification of Pulmonary Hypertension" has identified sleep-disordered breathing as part of the category of respiratory disorders associated with pulmonary hypertension (15).

c) Cardiac arrhythmias and cardiovascular mortality :

The prevalence of cardiac arrhythmias in two samples of participants from the Sleep Heart Health study showed that compared with subjects with Respiratory Disturbance Index (RDI) < 5, those with severe OSA (RDI > 30) had higher rates of atrial fibrillation, non-sustained ventricular tachycardia, complex ventricular ectopy (bigeminy, trigeminy and quandrigeny). Compared with those without sleep-disordered breathing and 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), three times the odds of nonsustained ventricular tachycardia (OR, 3.40), and almost twice the odds of complex ventricular ectopy (OR, 1.74) (16). Bradyarrhythmias are also reported in OSA and can occur with a structurally normal heart. Effective CPAP therapy has been shown to attenuate bradyarrhythmias (17). People with sudden death from cardiac causes from midnight to 6 a.m. had a significantly higher apnea-hypopnea index than those with sudden death from cardiac causes during other intervals. The relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 for people with obstructive sleep apnea. In contrast, 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. (18). However, a causative role for sleep apnea in serious

arrhythmias or sudden death has not been proven (16, 19). In an observational study to compare incidence of fatal and non-fatal cardiovascular events in simple snorers, patients with untreated obstructive sleep apnoea-hypopnoea, patients treated with CPAP, and healthy men, it has been shown that severe obstructive sleep apnoea-hypopnoea significantly increases the risk of fatal and non-fatal cardiovascular events in men and CPAP treatment reduces this risk (20). In an observational study, it has been reported severe OSA is associated with cardiovascular death in Women as well, and adequate CPAP treatment may reduce this risk (21).

d) OSA and heart failure :

There is a close link between OSA and heart failure by their close association with aging and obesity. The Framingham study had shown that increasing BMI is directly correlated with incident heart failure and may be mediated in part by OSA. Incident atrial fibrillation, an important risk factor for heart failure is also associated with the degree of oxyhemoglobin desaturation in OSA (22-24). Repetitive upper airway closure in OSA can have deleterious effects on cardiac function. In a study of subjects randomly assigned to receive medical therapy either alone or with the addition of continuous positive airway pressure for one month, it has been shown that treatment of coexisting obstructive sleep apnea by continuous positive airway pressure reduces systolic blood pressure and improves left ventricular systolic

function in medically treated patients with heart failure (25). In another randomized study of patients with congestive heart failure and OSA receiving 3 months of CPAP, it has been shown that there is significant improvements in left ventricular ejection fraction (LVEF) and reductions in urinary catecholamines, but no changes in BP (26). However in another rigorous, placebo-controlled cross-over study using auto-titrating CPAP, Authors found no improvement in any parameter of cardio-vascular function, including left ventricular ejection fraction, blood pressure and exercise tolerance (27). Further trials are required to know the exact role of CPAP in patients with heart failure and OSA. High sensitivity troponin T (hs-TnT) levels have been shown to be predictor of coronary artery disease and heart failure (28). In a study of 1645 participants from Atherosclerosis Risk in Community (ARIC) and Sleep Heart Health Study (SHHS), it has been observed that there is an association between severity of OSA and high levels of hs-TnT suggesting that subclinical myocardial injury caused by OSA may play a role in subsequent risk of heart failure (28).

e) OSA and incident stroke :

The incidence of stroke was studied in a geographically diverse, community based sample of male and female participants in SHHS. Based on 8 years of prospective data from the study, it has been observed that modest to severe levels of sleep apnea are associated with an approximately three-fold increased

risk of ischemic stroke in men (29). A prospective study had shown that self-reported snoring was an independent risk factor for stroke in women (30). Data from the Wisconsin Sleep Cohort had demonstrated that moderate to severe sleep-disordered breathing is a risk factor for prevalent stroke and that the preexisting sleep disorder may be a risk factor for incident stroke (31). Longitudinal data with a mean follow-up of 3.4 yr on mortality from stroke and other causes in patients with preexisting OSA, it has been shown that there is an increasing risk of events with OSA severity (32). It is feasible that stroke may itself predispose to sleep-disordered breathing. The strong association with atrial fibrillation may confer a heightened risk of embolic events. OSA has been shown to promote thrombosis and doppler measurements have suggested that apneic events are associated with reduced cerebral blood flow (33).

f) Erectile dysfunction :

A high prevalence of erectile dysfunction in OSA patients has been reported (34). It has been suggested that the nocturnal oxygen saturation observed in OSA may be an important factor contributing for the occurrence of OSA (34). Treatment with nasal CPAP has been found to resolve erectile dysfunction resulting in improvement in quality of life (35).

g) Aortic aneurysm :

Abdominal aortic aneurysm has

been found to be highly prevalent in OSA and it has been reported that there was further expansion of abdominal aortic aneurysm in patients with severe OSA (36).

Ocular manifestations :

Recently reported ocular manifestations in OSA are floppy eyelid syndrome (FES), glaucoma, papilledema, non-arteritic anterior ischemic optic neuropathy and retinal vein occlusion (37). Papillary conjunctivitis and a rubbery, redundant upper eyelid tissue is the characteristic features of FES and frequently manifests unilaterally affecting the eyelid on the side the patient most often sleeps on. Although the specific etiology of this association is not well described, one proposed mechanism suggests. It has been suggested that damage to the optic nerve head caused by apnea-induced ischemic events may be responsible for glaucoma in OSA patients, as it has been reported that glaucoma severity correlates with both the frequency and duration of apnoeic episodes. There is forced inspiration against a closed airway in OSA and this can lead to an increase in venous pressures and impaired venous return with subsequent increase in intracranial pressure resulting in papilledema. Papilledema can also result from hypercapnea which has been reported to occur in OSA. Though the mechanism of nonarteritic ischemic optic neuropathy is not well understood, it is possible that intermittent apnea-induced increases in blood pressure and intracranial pressure

and nocturnal hypoxemia may result in optic nerve edema leading to optic neuropathy. Retinal vein occlusion in patients with OSA may be to the consequences of impaired venous return of the retina and atherosclerotic defects of the feeding arterioles.

Other medical consequences :

Other medical consequences of OSA include excessive daytime sleepiness, loss of alertness, memory deficit, reduced vigilance, impaired executive function, increased risk for automobile and occupational accidents and decreased quality of life (38).

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