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REVIEW ARTICLES

Obstructive sleep apnea and cardiovascular effects-a review

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Abstract

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, affecting 5–15% of the population. It is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep that disrupts normal ventilation and sleep architecture, and is typically associated with excessive daytime sleepiness, snoring, and witnessed apneas. Patients with obstructive sleep apnea present risk to the general public safety by causing 8-fold increase in vehicle accidents, and they may themselves also suffer from the physiologic consequences of OSA; these include hypertension, coronary artery disease, stroke, congestive heart failure, pulmonary hypertension, and cardiac arrhythmias. Of these possible cardiovascular consequences, the association between OSA and hypertension has been found to be the most convincing. Although the exact mechanism has not been understood, there is some evidence that OSA is associated with frequent apneas causing mechanical effects on intrathoracic pressure, cardiac function, and intermittent hypoxemia, which may in turn cause endothelial dysfunction and increase in sympathetic drive. Therapy with continuous positive airway pressure has been demonstrated to improve cardiopulmonary hemodynamics in patients with OSA and may reverse the endothelial cell dysfunction. Limited availability of diagnostic measures and unawareness of physicians, many patients with OSA remain undiagnosed. Awareness and timely initiation of an effective treatment may prevent potential deleterious cardiovascular effects of OSA.

Key words

Obstructive Sleep apnea, Hypertension, Atherosclerosis, Continuous positive airway pressure.

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disease, affecting 4% of men and 2% of women.[1] Obstructive sleep apnea (OSA) is a common and frequently under diagnosed condition characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep, decrease in oxygen saturation and daytime somnolence.[2] Significant clinical consequences of OSA cover a wide spectrum including neurocognitive dysfunction[3], cardiovascular disease (CVD),[4,5] metabolic dysfunction,[6,7] respiratory failure, and cor pulmonale.[8] OSA patients frequently have several risk factors for CVD development, such as obesity, hypertension, and diabetes.[4-6] These risk factors are entangled in such a way that it is difficult to isolate the relative contribution of OSA to cardiovascular risk. OSA is independently associated with several CVD, including hypertension, ischemic heart disease, atrial fibrillation, cerebrovascular disease, and heart failure,[4,5,] though the magnitude of OSA effects, as compared to other risk factors for cardiovascular disease, is not well established.

Pathophysiology of CVD: The pathophysiology of possible deleterious cardiovascular effects of OSA is thought to involve two major components: first, the mechanical effect of apneas on intrathoracic pressures and heart function and second intermittent hypoxemia resulting in sympathetic overdrive and endothelial cell dysfunction (figure1).[9] Although there is no definitive evidence to determine whether OSA directly causes cardiovascular disease, the available data do suggest an increased risk of having car

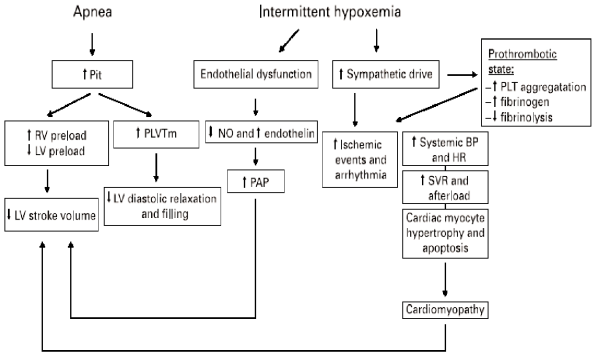

Fig. 1. Possible cardiovascular changes in OSA. Pit = Intrathoracic pressure; RV = right ventricle; LV = left ventricle; PLVTm = left ventricular transmural pressure; NO = nitric oxide; BP = blood pressure; HR = heart rate; SVR = systemic vascular resistance.

diovascular events in sleep apnea patients. However, there is more substantial data to support an association between OSA and hypertension.

Hypertension and OSA: OSA is now recognized as an independent risk factor for hypertension[10] and about 40% of patients with OSA are documented to be hypertensive while awake, according to standard criteria.[11] How OSA causes a sustained elevation in blood pressure is not well understood. It is possible that sympathetic over-activity plays at least some role in the elevated blood pressure found in OSA patients.[12] Other potential mechanisms include hyperleptinemia, insulin resistance, elevated angiotensin II and aldosterone levels, endothelial cell dysfunction and impaired baroreflex function.[13] The Sleep Heart Health Study, which enrolled more than 6,000 individuals, showed a definite independent association between OSA and hypertension, and the prevalence of hypertension was increased with the severity of OSA.[4] Similarly, the Wisconsin Cohort Study of 1,069 patients and a prospective follow-up of 893 patients revealed the apnea-hypopnea index (AHI) as being an independent predictor of daytime hypertension. [14,15] OSA has been found to be more common in patients with treatment-refractory hypertension,[16] conversely, controlling hypertension by conventional therapeutic means has been found to be more difficult in patients with OSA than in hypertensive individuals without OSA.[17] Continuous positive airway pressure (CPAP) treatment leads to a fall in blood pressure as measured by both an intra-arterial device [18] and by ambulatory blood pressure measurements, [19] with a greater effect noted in patients with severe OSA.[20] The fact that a 50% reduction in the AHI did not result in a decrease in blood pressure emphasizes the importance of highly effective treatment and the need for a close follow-up to establish the effectiveness of CPAP therapy. Mild OSA does not appear to be associated with a substantial decline in blood pressure with CPAP therapy, but is apparently independently associated with elevated blood pressure in this population.[21] These data suggest that untreated OSA plays an independent role in the pathogenesis of hypertension, and emphasizes the importance of detecting and treating OSA for optimal management of hypertension. Physicians should be aware of OSA as a reversible and treatable cause of hypertension.

Atherosclerotic Effect of OSA on the Cardiovascular System: OSA is suspected to be an independent risk factor for atherosclerotic artery disease. Different studies have proposed possible mechanisms for the atherosclerotic effect of OSA. These include repetitive surges in blood pressure due to sympathetic over-activity, oxidative stress [22,23], endothelial cell dysfunction,[24] resulting in increased plasma levels of endothelin-1,[25] decreased nitric oxide production, [26] and elevated inflammatory response[27] as evidenced by increased C-reactive protein and interleukin-6. [28] On the other hand, elevated plasma levels of various adhesion molecules and increased expression of adhesion molecules on leukocytes and their adherence to endothelial cells have been reported and are thought to have a role in endothelial cell dysfunction, formation of atherosclerosis, and clot formation.[29] Studies on OSA treated with CPAP have demonstrated improved insulin resistance, [30] a reversal of the inflammatory response as evidenced by a decrease in serum endothelin-1,[25] an increase in serum nitric oxide levels,[26] and a decrease in C-reactive protein and interleukin-6 [31], thus further supporting a relationship between OSA and the metabolic syndrome. Although these studies suggest a relationship between OSA and atherosclerosis formation, there is presently no definite evidence to prove this. At the present time, we can only state that there is a complex relationship between OSA, atherosclerosis and the metabolic syndrome.

Acute Coronary Syndromes: A few studies have demonstrated a possible correlation between OSA and myocardial infarction[32,33], and patients with coronary artery disease (CAD) and ongoing untreated OSA were found to have higher mortality rates than patients treated with CPAP.[34] CPAP treatment has also been shown to abolish nocturnal angina.[35] ST segment depression in association with OSA was noted with or without clinically significant CAD[36]. Moreover, several studies have reported a high incidence of OSA in patients with CAD.[5,37] The Sleep Heart Health Study found an association with increased multivariate adjusted relative odds of self-reported CAD.[4] Although these findings do not establish a definite relationship between OSA and CAD, they do suggest that sleep apnea may be associated with or may even predispose to CAD. Possible mechanisms include an indirect effect of hypertension, the formation of atherosclerosis, oxygen desaturation, sympathetic nervous system overactivity, increased coagulopathy, and increased inflammatory response.

Arrhythmias: Both bradyarrhythmias and tachyarrhythmias have been described in patients with OSA. However, bradyarrhythmias are more commonly observed, the most common being sinus bradycardia, sinus arrest, and complete heart block .[38] The risk of arrhythmia appeared to be related to the severity of OSA.[39] The likely explanation of bradyarrhythmia in OSA is chemoreceptor-mediated increase in vagal tone secondary to apneas and hypoxemia .[40] The observation that bradyarrhythmias occur only at night in association with apneic episodes in otherwise

asymptomatic patients supports this theory. Gillis et. al.[41] found QT prolongation at the onset of apnea, with subsequent shortening during the apnea and post-apnea hyperpneic phase. Reversion of OSA with CPAP or tracheostomy has been shown to abolish arrhythmia in most patients.[39,42] Atrial overdrive pacing during sleep has been shown to reduce the number of episodes of OSA or central sleep apnea (CSA) without reducing the total sleep time.[43] Arrhythmias, especially tachyarrhythmias, may have a role in the pathogenesis of stroke by thrombus formation and embolism.

Left Ventricle and OSA: 50% of patients with heart failure have OSA or CSA. [44] Left ventricular hypertrophy, systolic and diastolic dysfunctions have been demonstrated in OSA patients; these findings resolved with CPAP treatment .[45-47] The severity of the dysfunction correlated with the severity of OSA. Minimum oxygen saturation of less than 70% was an independent predictor for diastolic dysfunction, irrespective of age and hypertension.[47] In the Sleep Heart Health Study, the presence of OSA conferred a 2.38 relative increase in the likelihood of having heart failure independent of other known risk factors[4] OSA is common in heart failure, with approximately 11% of heart failure patients being affected. However, CSA is more common than OSA in patients with heart failure.[48] Possible mechanisms of OSA induced left ventricular dysfunction include impaired myocardial contraction secondary to hypoxemia, intermittent changes in intrathoracic pressures during apneic episodes, sympathetic overactivity, daytime hypertension, and loss of vagal heart rate regulation. Negative intrathoracic pressure decreases left ventricular relaxation. These effects may cause myocyte necrosis and apoptosis, leading to cardiomyopathy and cardiac remodeling.

Right Ventricle, Pulmonary Hypertension and OSA: The reported prevalence of pulmonary arterial hypertension in OSA varies from 20 to 41% in different studies. [49-51] A possible mechanism is thought to be secondary to hypoxemia-induced endothelial cell dysfunction and pulmonary artery remodeling.[52] This may be related to hypoxia upregulation vascular endothelial growth factor, which is a mediator in angiogenesis, resulting in vascular remodeling.[53,54] Most experts feel that OSA may modestly increase pulmonary arterial pressures, and evaluation for OSA should be part of the initial work-up in patients with pulmonary hypertension.[55] Therapy with CPAP has been shown to decrease pulmonary pressures in OSA patients with either high or normal pulmonary pressures. [55,56] It is likely that right ventricular dysfunction is due to PAH associated with OSA, and treatment with CPAP reverses right ventricular dysfunction.[57]

Conclusion

There is a complex relationship between OSA and cardiovascular disease, and an understanding of the various mechanisms between these two conditions continues to evolve. Studies show a convincing link between hypertension and OSA. The data regarding ischemic heart disease and other cardiovascular pathology are not as convincing; however, OSA appears to be a risk factor for cardiovascular diseases. Treatment of OSA reverses or corrects the adverse cardiovascular effects of OSA, although the exact mechanisms have not been clearly elucidated. More animal and clinical studies are needed to understand the mechanisms underlying the deleterious cardiovascular effects of OSA. Physicians caring for patients with cardiovascular disease should be aware of the possible coexistence of OSA and should also recognize that most patients with OSA are either not diagnosed or have inadequate therapy for their disease. Initiating effective therapy for OSA may help treat underlying cardiovascular pathology, eliminate unnecessary work-up and decrease health care expenses.

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