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Cardiovascular Effects of Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) is a highly prevalent disorder currently affecting up to 50% of middle-aged men and 23% of middle-aged women with up to 80% of patients with OSA being undiagnosed. This condition has been linked through multiple mechanisms to several cardiovascular diseases, including hypertension (HTN), left ventricular hypertrophy (LVH), thoracic and abdominal aortic dilatation and aneurysm, type 2 diabetes mellitus, coronary heart disease (CHD), congestive heart failure (CHF), atrial fibrillation (AF), and stroke. Our review aims to examine the impact of OSA on cardiovascular disease (CVD) and discuss the relevant associated mechanisms.

Introduction

Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by repetitive partial or complete obstruction of the pharynx during sleep, leading to impaired gas exchange. Snoring is the most frequent symptom, accompanied by periods of pause when air flow is reduced or blocked [1], and choking and gasping sounds when the air flow resumes during sleep. The prevalence of OSA is estimated at 50% in middle-aged men and 23% in middle-aged women [2], with up to 80% of patients with OSA being undiagnosed [3]. The severity of sleep apnea is measured with the apnea/hypopnea index (AHI), which quantifies the number of times per hour an episode of apnea or hypopnea occurs. An AHI ≥ 5 is currently considered as diagnostic of OSA.

This disorder has been associated with multiple conditions such as intermittent hypoxia, oxidative stress, systemic inflammation, catecholamine activation, insulin resistance, and endothelial dysfunction, all of which are important mediators of cardiovascular disease (CVD).

In addition, OSA has been described as a causal factor of hypertension (HTN), and is associated with an increased incidence of stroke, congestive heart failure (CHF), atrial fibrillation (AF) and coronary heart disease (CHD) [4]. Other studies have also linked OSA with type 2 diabetes mellitus, and untreated OSA has been associated with poor glycemic control in such patients [5].

Furthermore, studies have shown a significant, high cardiovascular mortality risk in patients with untreated OSA, independent of age, sex and body mass index (BMI) [6].

Due to the emerging increase in the prevalence of OSA and its strong association with CVD, our review aims to examine the impact of OSA on CVD and discuss the relevant associated mechanisms.

Mechanisms of CVD in Patients with OSA

The adverse effects that OSA inflicts on cardiovascular function are thought to result from several interrelating mechanisms. The Apnea-Hypopnea episodes characteristic of OSA cause pathologic vascular changes, which have been linked with CVD, independent of confounding factors, such as HTN, obesity, diabetes mellitus or hyperlipidemia.

Normally, during sleep, sympathetic activity decreases and parasympathetic activity increases with lowering of blood pressure and heart rate. However, sleep-disordered breathing, such as OSA, disrupts normal sleep. Apneas and hypopneas, along with the consequent compensatory hyperpneas, are associated with decreased parasympathetic activity and increased sympathetic activity [7]. This increase in sympathetic activity promotes repetitive catecholamine surges, which cause a further significant increase in sympathetic tone, leading to an increase in peripheral vascular resistance and endothelial dysfunction. These changes result in episodes of acutely elevated blood pressure levels, release of systemic inflammatory mediators, and worsened insulin resistance [8]. This repeated cycle of events ultimately leads to vasoconstriction and vascular remodeling, which in turn leads to the development of vascular and cardiac dysfunction [9].

Inflammation is another postulated link between OSA and increased cardiovascular morbidity [10]. The repetitive episodes of intermittent hypoxia with subsequent re-oxygenation episodes observed in OSA induce Reactive Oxygen Species (ROS) production [11], resulting in the development of endothelial dysfunction and micro-vascular damage [12]. Moreover, these episodes also promote the up regulation of genes regulated by the transcription factor nuclear factor-κB (NF-κB) pro-inflammatory pathway, leading to elevated levels of tumor necrosis factor-alpha (TNF-α), Interleukin (IL)-6, IL-8, and C-reactive protein (CRP), thus causing HTN and endothelial dysfunction [13,14].

Endothelial dysfunction is now recognized as one of the earliest reversible precursors of atherosclerosis [15,16].

OSA and HTN

OSA is considered to be a causal factor in the pathogenesis of vascular dysfunction and hypertension [17]. Several mechanisms may induce increased blood pressure levels in OSA, including increase autonomic derangements with consequent increases in catecholamine levels and increased sympathetic tone [18], inflammation, oxidative stress and endothelial dysfunction [19].

In this regard, the Sleep Heart Health Study, in a cross-sectional analysis of >6000 patients, showed that over 50% of individuals with OSA have hypertension and revealed a linear relationship between systolic and diastolic BP and OSA severity [20].

OSA and Left Ventricular Hypertrophy (LVH)

Another condition associated with OSA is LVH. Earlier studies have linked the severity of OSA-induced hypoxemia with a gradual deterioration of left ventricular filling. These findings may explain the presence of LVH in patients with coexisting OSA in the absence of previous history of HTN [21,22].

OSA and Aortic Dilatation

OSA has been linked with thoracic aortic dilatation and or aneurysms [23]. This effect of OSA on aortic disease may be related, at least in part, to its association with HTN. As we mentioned earlier, the increased sympathetic activity observed in OSA leads to HTN, which plays an important role in the development of aortic dilatation/aneurysms/aortic dissection [24].

On the other hand, the repetitive apneic episodes lead to repeated inspiratory efforts against an occluded airway, which generate an increase in the negative intrathoracic pressure and promote a marked increase in transmural pressure of the aortic wall, which may result in aortic dilatation [25]. However, up to date, it remains unclear if the association between OSA and aortic dilatation is causal or if it is actually secondary to the OSA-induced hypertension.

OSA and Insulin Resistance

The hypoxemia induced by OSA has been also linked to glucose intolerance, independently of obesity [26], age, gender, ethnicity, smoking status, body mass index, waist circumference, and sleep duration [27]. Other studies have shown that serum insulin levels and insulin resistance tend to be significantly higher in obese patients with OSA, as compared to obese patients without OSA [28].

OSA and Ischemic Heart Disease

Studies have shown that the prevalence of CHD in patients with OSA is 3-5 times higher compared to individuals with no previous history of OSA [29]. However, due to overlapping risk factors between OSA and CHD, the association between CHD and particularly mild OSA remains controversial.

The association of OSA with CHD is mostly evident in cases with moderate and severe OSA. In addition, severe OSA increases dramatically the risk for both fatal and nonfatal cardiovascular events [30], leading to a 68% higher risk of CHD in the male population between 40-70 years of age [31].

OSA and CHF

The association between OSA and CHF has been described as bidirectional, as many risk factors for heart failure and OSA overlap. In this regard, coexisting OSA is very frequent among patients with CHF [32].

OSA is associated with worse outcome in CHF. Independently of confounding factors, there is an increased mortality in patients with concomitant OSA and left ventricular ejection fraction ≤ 45%, as compared to those without OSA [33]. In addition, studies have described OSA as a predictor of incident CHF in men [31].

Moreover, in patients with CHF and coexisting OSA, treatment with Continuous Positive Airway Pressure (CPAP) has been shown to significantly improve cardiac function and quality of life [32].

OSA and AF

There is a strong association between tachyarrhythmias, especially AF, and OSA [34]. These conditions are highly prevalent in patients with moderate to severe OSA. Furthermore, OSA has been identified as an independent risk factor for both bradyarrhythmias and tachyarrhytmias [35].

Several factors have been implicated in the development of cardiac arrhythmias in patients with OSA, including nocturnal hypoxia, hypercapnia, negative intrathoracic pressure, elevated sympathetic tone, acute atrial stretch, inflammation, and left ventricular diastolic dysfunction. All these disturbances may lead to functional and structural changes that predispose to cardiac arrhythmias [35].

In addition, CPAP therapy has been shown to significantly reduce the risk of recurrence of AF after AF ablation in OSA patients [36].

OSA and Stoke

OSA is considered an independent risk factor for incident stroke [37,38]. The association of OSA and stroke is due to several factors, such as nocturnal HTN, insulin resistance, CHD, and arrhythmias [39].

OSA is extremely common in stroke patients, with up to 72% of such patients having an AHI of at least 5 [40]. In addition, other studies have shown that patients with moderate OSA have a 2-3 times higher risk for stroke, as compared to the general population [37]. Moreover, OSA patients have a worse prognosis after a stroke, as compared to those with no prior history of OSA [41]. In fact, there is some evidence that early CPAP therapy in patients with moderate to severe OSA may favorably affect long-term survival after ischemic stroke [42,43].

Conclusions

From the above review of the clinical data, it becomes apparent that OSA is strongly associated with CVD via multiple noxious mechanisms. CPAP is the leading therapy for sleep apnea and its application, especially early in the course of the disease, may lead to favorable outcomes.

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