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Review Article

Insights into obstructive sleep apnea research

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ABSTRACT

Moderate to severe obstructive sleep apnea (OSA) occurs in 10–17% of middle aged men and 3–9% of middle-aged women with a higher prevalence among obese subjects. This condition is an independent risk factor for many cardiovascular diseases. Intermittent hypoxia is a major pathophysiologic character of OSA; it can lead to oxidative stress and inflammation, which in their turn cause endothelial dysfunction, a hallmark of atherosclerosis. Many animal models have been designed to mimic OSA in human patients to allow more in-depth investigation of biological and cellular mechanisms of this condition. This review discusses the cardiovascular outcomes of OSA and some of the animal models that are being used to investigate it.

1. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by momentary cessations in breathing (apnea) or significant reductions in breathing amplitude (hypopnea) caused by an obstructed or collapsed upper airway; both conditions can cause significant arterial hypoxemia and hypercapnia. The apnea/hypopnea index (AHI) describes the total number of apnea/hypopnea episodes per hour of sleep, which is usually <5 in normal individuals. AHI scores of 5–15, 15–30, and >30 categorize patients with sleep apnea as mild, moderate, and severe, respectively [1]. An obstructed airway increases resistance to airway flow that results in a greater breathing effort and swings in intrathoracic pressure, resulting in disruption of sleep, arousal, and reopening of the airway [2].

It is estimated that there are currently approximately 14% of men and 5% of women in the USA who have an AHI $\geqslant$ 5, plus symptoms of daytime sleepiness, with 13% of men and 6% of women also having moderate to severe OSA (AHI $\geqslant$ 15) [3]. Based on the average of prevalence estimates from many clinical studies, it is estimated that nearly one of every five adults has at least mild OSA and that one of every 15 has at least moderate OSA; moderate OSA occurs predominantly at body mass index (BMI) values of 25–28 [4–6]. Despite numerous advancements in medicine, the majority of those affected with OSA remain undiagnosed [7]. OSA is suspected in people who are obese, hypertensive, hypersomnolent and habitual snorers [8]. Polysomnography is the main method for assessing patients with suspected sleep apnea [9]. Sleep stages are recorded along with oxyhemoglobin saturation, breathing, and airflow. In addition, limb and eye movements and the electrocardiogram are also monitored [10].

OSA creates a huge economic burden when compared to other chronic diseases. In 2000, OSA-related automobile collisions alone attributed to 1400 fatalities and a total cost of 15.9 billion dollars in the USA. Treatment with continuous positive airway pressure (CPAP) resulted in saving 7.9 billion dollars and 1000 lives [11]. It is well established that the outcomes of OSA can lead to serious vascular diseases. Data from different studies implicate OSA in the development of hypertension and, to some extent, cardiac ischemia, congestive heart failure, arrhythmias, cerebrovascular disease, and stroke [12].

Many intermediary mechanisms, such as sympathetic activation, endothelial dysfunction, vascular oxidative stress, inflammation, increased coagulation, and metabolic dysregulation, link OSA to vascular disease [13].

2. OSA and cardiovascular disease

Evidence that relates OSA directly to vascular disease comes from small longitudinal studies of incident cardiovascular disease and studies assessing the outcomes of CPAP intervention. Nevertheless, many studies can only indirectly implicate OSA in the

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etiology of cardiovascular disease, mainly because of the cost of establishing the diagnosis of OSA in large population samples, which means that most large-scale epidemiologic studies do not monitor OSA. Another important reason is that patients with OSA also have coexisting morbidities such as hypertension or obesity, making the independent risk of OSA on vascular disease more difficult to assess.

2.1. Hypertension

About 50% of OSA patients have hypertension and, importantly, another 30% of hypertensive patients have undiagnosed OSA [14,15]. Cross-sectional studies show that there is a great association between OSA and hypertension. In a study of 2677 adults who were referred to a sleep clinic, the odds of hypertension increased by 1% for every increase in AHI unit with the prevalence levels for hypertension being 22.8% in control, 36.5% in mild, 46% in moderate, and 53.6% is severe OSA patients (after adjusting for age, BMI, and gender) [16]. In a more recent study, OSA (AHI: >15 events per hour) was the most common condition associated with resistant hypertension (64.0%), followed by primary aldosteronism (5.6%), renal artery stenosis (2.4%), renal parenchymal disease (1.6%), oral contraceptives (1.6%), and thyroid disorders (0.8%) in 125 patients with resistant hypertension [17].

The Wisconsin Sleep Cohort (WSCS) reports that patients with AHI of 15 or higher have a threefold increased risk of developing hypertension during this four-year study [18]. However, the Sleep Heart Health Study (SHHS) showed that associations were weak and not statistically significant (SHHS subjects with an AHI $\geqslant$30 events/h had an adjusted 1.5-fold increased risk of developing hypertension compared to subjects without OSA at baseline) [19].

Data from a series of cross-sectional studies strongly support an association between OSA and hypertension; however, the adjusted odds ratios for hypertension seem to vary considerably between studies and do not clearly show causality. Furthermore, not all longitudinal studies in adults support a causal relationship. Additional cohort studies in younger patients who are at risk of hypertension and OSA will provide some useful insights [20].

Studies in rats and mice also show that chronic intermittent hypoxia (IH) increases blood pressure [21,22]. OSA is now included as one of the main causes of hypertension in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [23].

2.2. Type 2 diabetes

The overall prevalence of OSA in type 2 diabetic patients is nearly 71%, based on the average of data from five separate studies [24–28]. These data also suggest that approximately 19 million diabetic patients may have untreated or undiagnosed OSA. However, the prevalence of type 2 diabetes in OSA patients ranges between 15% and 30%, depending on the methods used to diagnose type 2 diabetes and OSA severity [29]. Untreated OSA can lead to poor glycemic control as Aronsohn et al. reported in a study of 60 diabetic patients who underwent full laboratory polysomnography. OSA severity was directly proportional to poorer glycemic control after controlling for age, sex, BMI, level of exercise, and total sleep time. Compared to non-OSA patients (adjusted mean hemoglobin A1c: 5.7%), the adjusted mean hemoglobin A1c was 7.3%, 7.7%, and 9.7% in mild, moderate, and severe OSA patients, respectively [24]. Botros et al. conducted an observational cohort study that examined 1233 patients for sleep-disordered breathing; 544 participants completed a full polysomnogram with no preexisting diabetes. The population was divided based on AHI and the main outcome was incident diabetes, as defined by fasting glucose levels of >126 mg/dL. They found that an increasing severity of OSA was associated with an increased risk of diabetes. After adjusting for sex, BMI, age, and weight change, they reported an independent association between OSA and incident diabetes with a hazard ratio of 1.43 [30]. Overall, there is evidence from many clinical trials that untreated OSA can worsen glycemic control in type 2 diabetic patients [29].

There is still a controversy whether CPAP treatment in OSA improves glucose control. Current data suggest that obesity and the amount of CPAP can influence the metabolic response to CPAP. Large-scale randomized control trials assessing insulin sensitivity and glucose tolerance are required to determine the metabolic effects of CPAP.

2.3. Coronary artery disease

OSA is also related to coronary artery disease (CAD) and stroke, because the prevalence of OSA among hospitalized men with acute myocardial infarction is nearly 70% [31]. IH, sympathetic vasoconstriction, and changes in intrathoracic pressure can all contribute to cardiac ischemia and atherosclerosis. In a prospective cohort study, 408 patients aged 70 years or younger with diagnosed coronary disease were followed up for a median period of 5.1 years. An AHI of $\geqslant$10 and an oxygen desaturation index (ODI) of $\geqslant$5 were used as the diagnostic criteria for sleep-disordered breathing. The primary end point was a composite of death, cerebrovascular events, and myocardial infarction. There was a 70% relative increase and a 10.7% absolute increase in the primary composite end point in patients with disordered breathing as defined by an ODI of $\geqslant$5. Similarly, patients with an AHI of $\geqslant$10 had a 62% relative increase and a 10.1% absolute increase in the composite end point [32] These data were confirmed by Shah et al. who reported that after adjusting for cardiovascular risk factors such as BMI and hypertension, OSA retained a significant association (hazard ratio 2.06) with the composite outcome of myocardial infarction, coronary artery revascularization procedures, and death after 2.9 years of follow-up [33].

A study of 200 patients without a history of CAD shows that the median coronary artery calcification score (Agatston units) was nine in OSA patients and 0 in non-OSA patients. This was measured by electron beam computed tomography on these patients within 3 years of polysomnography [34]. The median calcification score increased with the severity of OSA. A recent study of more than 500 subjects showed that OSA patients are more likely to have a family history of premature death from CAD than non-OSA patients. The results were independent of BMI, gender, and personal history of CAD [35]. A five-year follow-up of 62 patients with CAD reported a higher mortality rate in OSA patients (38%) compared to non-OSA patients (9%) [36]. Drager et al. evaluated the effects of 4 months of CPAP therapy on early markers of atherosclerosis, arterial stiffness, 24-h blood pressure (BP) monitoring, plasma C-reactive protein (CRP), and catecholamines in patients with severe OSA. Their study recruited only relatively young patients without significant comorbidities and who were unmedicated. A four-month CPAP therapy significantly improved validated markers of atherosclerosis, for example, reductions in inflammation markers of inflammation and sympathetic activity, in these patients [37]. In addition, OSA can affect outcomes after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS). Yumino et al. followed ACS patients with OSA for 227 days and reported that the incidence of major cardiac events (cardiac death, reinfarction, and vessel revascularization) was significantly higher in ACS patients with OSA (23.5%) when compared to ACS patients without OSA (5.3%). In addition, binary restenosis was higher in patients with OSA when compared with those without (36.5% vs. 15.4%) [38].

Although the prevalence of OSA in patients with CAD is high, it is suggested that patients with OSA have less severe cardiac injury