

Review Article

Obstructive Sleep Apnea, Hypertension, and Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) accounts for significant morbidity and mortality globally. Obstructive sleep apnea (OSA) is the repeated stoppage of inspiratory airflow due to oropharyngeal obstruction during sleep. This results in lack of oxygen, disturbance to sleep, and adrenergic nervous system stimulation. Consequently, the blood pressure rises, there are tachycardia, vascular dysfunction, widespread inflammation, and resistance to insulin. All these changes are said to contribute to the development of CVD. A large volume of evidence has accumulated in favor of OSA linking it to hypertension, coronary artery disease, cardiac failure, and various cardiac arrhythmias. Increased public awareness of OSA and its early detection, prompt diagnosis, and institution of appropriate treatment, including continuous positive airway pressure, would help in adequate control of this potentially modifiable risk factor in the era of increasing CVD.

Key words: Cardiovascular disease, hypertension, obstructive sleep apnea

Introduction

Globally, cardiovascular disease (CVD) contributes majorly to increased morbidity and mortality. In addition to the research directed toward the development of newer and more effective treatments, there is also serious thought and research toward modifying risk factors for primary and secondary prevention of CVD.

In the ongoing search for such modifiable risk factors, obstructive sleep apnea (OSA) is one main risk factors for several CVDs such as hypertension (HTN), cardiac failure (CF), cardiac arrhythmias, and coronary artery disease.^[1] In a society, where there is an ever-increasing aging population compounded with the obesity epidemic, OSA prevalence has increased by 30% and thereby its increased association with CVD.

OSA is the repeated stoppage of inspiratory airflow due to oropharyngeal obstruction during sleep. It affects 34% of males and 17% of females in the USA.^[2] This upper airway obstruction results in lack of oxygen, disturbance to sleep, and adrenergic nervous system stimulation. Consequently, there is a rise in blood pressure with tachycardia, vascular dysfunction, widespread inflammation, and resistance to insulin. All these changes are

said to contribute to the development of CVD.^[3] A large volume of evidence has accumulated in favor of OSA linking it to drug-resistant HTN, coronary artery disease, congestive CF, and atrial fibrillation [Table 1].

Pathophysiology

Due to OSA, there is recurrent oropharyngeal airflow obstruction and the consequent intermittent hypoxia and hypercapnia leads on to myocardial ischemia (resulting from decreased myocardial oxygen delivery), pulmonary and systemic vasoconstriction with increased afterload (due to stimulation of the adrenergic nervous system) which leads to the onset of pulmonary and systemic HTN and their obvious consequences.

OSA gives rise to increased sympathetic activity which, in turn, causes tachycardia and HTN. There are several mechanisms which induce the increased sympathetic activity such as chemoreflex stimulation by hypoxia and hypercapnia, baroreflexes, pulmonary afferents, impairment in venous return to the heart, cardiac output alterations, and possibly the arousal response itself.^[3]

The cortical arousal due to OSA results in sympathetic and parasympathetic stimulation with the release of increased of

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Table 1: Prevalence estimates of sleep apnea in various cardiovascular conditions^[3]

| Cardiovascular conditions | Prevalence estimates (%) |
|-----------------------------|--------------------------|
| Angina | 30 |
| Coronary artery disease | 30 |
| Type 2 diabetes | 35 |
| All HTN | 35 |
| Atrial fibrillation | 50 |
| Congestive heart failure | 50 |
| Drug-resistant hypertension | 80 |

HTN: Hypertension

catecholamines into the circulation, along with increased vagal activity, leading to cardiac hypertrophy, diastolic and systolic myocardial dysfunction, and ultimately cardiac arrhythmias and CF.^[3]

The negative intrathoracic pressure from repetitive episodes of OSA results in increased transmural gradient causing atrial stretch, left ventricular (LV) wall tension, structural remodeling, and increased oxygen demand, all of which ultimately lead to cardiac arrhythmias and CF.^[3] Endothelial dysfunction may also play a role.^[4]

OSA is a significant risk factor for CVD and is associated with increased cardiovascular morbidity and mortality.^[5,6] Several clinical trials have been conducted to study the effect of continuous positive airway pressure (CPAP) therapy in OSA on cardiovascular effects.^[7,8] One of the largest multicenter randomized clinical trials (RCTs), sleep apnea cardiovascular endpoints study (in 2717 patients with moderate-to-severe OSA) and CVD, observed the effect of CPAP on the incidence of CVD. Despite adequate control of OSA (apnea-hypopnea index [AHI] reduced from 29 to 3.7), there was no significant decrease in CV episodes. Several meta-analyses of RCTs of OSA patients also did not reveal a statistically significant decrease of risk in CV episodes. This could have been attributed to the overall low adherence rate to CPAP of <4 h per night.^[9]

Diagnosis of OSA

To suspect OSA, a contributory history and clinical examination should be forthcoming in the background of certain risk factors. Some of these risk factors are (1) age 40–70 years, (2) family history of OSA, (3) male:female ratio: 3:1, (4) obesity with body mass index (BMI) >35 kg/m², (5) postmenopausal women not on hormone therapy, and (6) retrognathia.

Predictive clinical history include “choking”/gasping episodes during sleep, morning headaches, excessive daytime sleepiness, loud snoring, and a neck circumference of >40 cm.

There are several questionnaires for screening for OSA. Epworth Sleepiness Scale, Berlin questionnaire, and STOP-BANG questionnaire are the ones which are often used.

Physical examination to look for a short neck with a large circumference (>40 cm), a high BMI (>35 kg/m²), retrognathia,

and a narrow, “crowded” oropharyngeal opening with a large tongue all of which may suggest the presence of OSA.

OSA is confirmed by performing an overnight sleep study (polysomnography) in a sleep laboratory (Type I study) or at home, which can detect and quantify the AHI. Apnea occurs when a complete cessation of airflow for >10 s is recorded. Hypopnea is a partial obstruction to airflow lasting for >10 s and desaturation of >3%. The AHI is calculated by adding all the apneas and hypopneas and dividing by the total sleep time. An AHI of 5 or <5 is normal, 5–15 is mild, 15–30 is moderate, and >30 is diagnostic of severe OSA.^[10]

OSA and HTN

In OSA patients, when compared with controls, there is a higher frequency of HTN. Around 50% of OSA patients have coexisting HTN.^[11–13] Furthermore, in patients with resistant HTN, there is a higher frequency of OSA. In resistant HTN patients, 71% had OSA whereas only 38% of patients had OSA in well-controlled systemic HTN.^[14] OSA is a well-recognized secondary cause of HTN.^[15]

Several mechanisms have been put forward to explain the effects of OSA on the evolution and worsening of HTN. Recurrent episodes of hypoxemia and hypercapnia cause reflex stimulation of the adrenergic nervous system with associated increase in adrenaline/noradrenaline levels resulting in increases of blood pressure. Furthermore, hypoxic vasoconstriction occurs as a result of release of various chemical mediators.^[16]

The use of CPAP in patients with OSA has contributed immensely to the control of HTN. Marin *et al.* studied 1889 patients of OSA without HTN and demonstrated the 5 times higher possibility of developing HTN in OSA patients who were not treated with CPAP.^[17] Pedrosa *et al.* also reported significant reductions in systolic and diastolic BP. The Joint National Committee concluded from the results of all these studies that OSA is a preventable liability for the development of HTN.^[18]

OSA and Coronary Heart Disease

Severe OSA is an underlying risk factor and is associated with an increased incidence of CAD. In the Sleep Heart Health Study of over 6000 patients, there was an independent association of OSA and the CAD incidence.^[19] Other studies by Shah *et al.* of 1436 patients also showed a significant association between OSA and CAD.^[20] Worse outcomes with higher incidence of cardiac deaths and reinfarction were also seen in another study by Yumino *et al.*^[21]

Various mechanisms have been proposed for atherosclerosis in OSA. Repeated hypoxic events can induce oxidative stress, systemic inflammation, and endothelial dysfunction and the consequent decreased nitric oxide production causing lack of vascular relaxation.^[22] Other studies have provided evidence of OSA increasing platelet aggregation and decreasing the breakdown of fibrin which may lead to acute coronary syndromes.^[23]

The application of CPAP in OSA to reduce the incidence of CAD and acute coronary syndrome has been extensively researched. McEvoy *et al.* studied 2687 patients with OSA (being treated with CPAP) and CAD, and there was no statistically significant benefit in endpoints.^[9] The RICCADSA (randomized intervention with CPAP in CAD and OSA) trial of 244 patients established that the routine use of CPAP in patients with CAD with non-sleepy OSA did not significantly reduce long-term adverse cardiovascular outcomes. However, CPAP therapy in OSA does control HTN and CV episodes if used for at least 4 h per night.^[7]

OSA and CF

There is a higher prevalence of CF in OSA patients, particularly in those with decreased ejection fraction. About 30% of those patients with CF and low ejection fraction and around 35% of those with preserved ejection fraction were found to have OSA. Furthermore, in patients with existing CF and untreated OSA, the mortality rates were significantly higher.^[16]

The pathophysiology of OSA and CF has a number of mechanisms. Negative intrathoracic pressure due to obstruction of upper air flow (apnea) and consequent hypoxia and sympathetic hyperstimulation results in increase in the LV transmural pressure which, in turn, decreases LV preload and increased afterload. The net result of these changes is myocardial strain and impairment in contractility, LV hypertrophy leading onto the development and progression of CF.^[3]

The use of CPAP in OSA patients with CF significantly improves the symptoms. In a small study of 24 patients of severe CF with OSA, the application of CPAP produced 9% improvement in cardiac function.^[24] Another study by Mansfield *et al.* also showed 5% improvement in the LV ejection fraction, lower urinary catecholamine levels, and improved quality of life compared to controls.^[25]

OSA and Cardiac Arrhythmias

A strong association exists between OSA and cardiac arrhythmias. Their incidence depends on the stage of OSA and frequency of hypoxic episodes. Several studies have shown the increased prevalence of nocturnal arrhythmias, atrial fibrillation, sinus arrest, ventricular premature contractions, and ventricular tachycardia in patients with OSA. Guilleminault *et al.* studied 400 patients with OSA of whom, 48% had cardiac arrhythmias. Tracheostomy was done in 50 of these patients which completely relieved them of any cardiac arrhythmias.^[26] A four-fold increase in cardiac arrhythmias was seen in severe OSA patients when compared to controls in the subgroup analysis of patients from the Sleep Heart Health Study.^[27] There was a two-fold increase in atrial fibrillation in OSA patients when compared to controls in a meta-analysis of 19,837 patients by Youssef.^[28]

Many different explanations have been offered for the increased incidence of cardiac arrhythmias in OSA. Repeated

episodes of hypoxemia during upper airway obstructive events induce baroreflex and chemoreflex activation resulting in abnormal electric remodeling of the atria and the myocardium. This could explain the high incidence of AF in OSA. Increased sympathetic activity could also trigger cardiac arrhythmias. Reflex cardiac vagal stimulation due to repeated apneic-hypopneic events could explain the basis of the development of bradyarrhythmias in OSA patients.^[3]

The incidence of sudden cardiac death (SCD) in severe or untreated OSA may increase due to fatal cardiac arrhythmias. The rate of SCD decreased with the application of CPAP in such patients when compared with those who discontinued CPAP therapy.^[29]

The effect of CPAP therapy in OSA on the occurrence of cardiac arrhythmias has been studied in 3000 patients of AF and found 11% decrease in AF recurrence.^[30] Ryan *et al.* showed 58% decrease in the occurrence of cardiac arrhythmias in 18 patients of OSA treated with CPAP compared to controls.^[31]

OSA and Pulmonary HTN (PH)

Advanced stages of OSA are associated with a higher prevalence of PH to the tune of approximately 20%. It is usually mild when there is no associated lung disease. Other risk factors for PH in this setting are comorbid lung disease, obesity hypoventilation syndromes, and increasing severity of OSA along with daytime hypoxemia.^[32]

OSA-PH has a lower functional capacity and quality of life.^[33] The increased mortality seen in PH is more due to the nocturnal hypoxia than due to OSA with higher apnea-hypopnea index.^[34]

The regular application of CPAP in patients with OSA-PH reduced PH and resistance in the pulmonary circuit in a period of 3–4 months. Bariatric surgery-induced significant weight loss may also lead to decrease in pH. The effects of other modes of treatment in OSA such as the use of oral devices, oral surgery, tracheostomy, and pharmacotherapy are unknown.^[35]

OSA and Venous Thromboembolism (VTE)

There is a two- to three-fold higher incidence of VTE in OSA. That OSA could contribute independently to the occurrence of VTE which has been revealed in a review of 15 studies.^[36] There is a hypercoagulable state as evidenced by detection of increased markers such as fibrinogen and plasminogen activator inhibitor-1 in OSA patients with VTE. The impact of use of CPAP in OSA on VTE is unknown.^[37]

Conclusion

OSA is a potentially treatable risk factor for CVD. The inflammatory, autonomic, hemodynamic, and metabolic consequences of OSA have contributed to the pathogenesis and worsening of many CVDs such as coronary artery disease, CF, HTN, and various often fatal cardiac arrhythmias. The

appropriate and timely management of OSA decreases the incidence and prevalence of these cardiovascular disorders. Increased public awareness of OSA and its early detection, prompt diagnosis, and institution of appropriate treatment including CPAP lead to prompt control of this potentially modifiable risk factor in the era of increasing CVD.

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