SPECIAL ISSUE 3: INVITED ARTICLE

Sleep-disordered Breathing and Cardiac Disorders

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Abstract

Obstructive sleep apnea (OSA) is known to be associated with metabolic syndrome, diabetes, hypertension which predispose to cardiovascular disease. Hypoxia due to OSA can predispose an individual to development of endothelial dysfunction. Additionally, imbalance between sympathetic–parasympathetic activity can initiate arrhythmias and result in sudden cardiac death. If OSA is diagnosed early and appropriately treated, we can prevent morbidity and mortality in patients with cardiac disease who also have OSA.

Keywords: Cardiovascular diseases, Diabetes, Endothelial dysfunction, Hypertension, Metabolic syndrome

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Multiple studies have demonstrated the importance of sleep disturbance in cardiovascular hemodynamics. Patients with obstructive sleep apnea (OSA) are exposed to chronic intermittent hypoxia. This results in overactivity of sympathetic nervous system, renin–angiotensin–aldosterone (RAAS) system. The consequence is oxidative stress and endothelial dysfunction which promotes hypertension, atherosclerosis, arrhythmias and plaque rupture. In OSA patients, sympathetic nerve activity, plasma concentration of angiotensin II (ANG-II) and vasoconstrictor response to ANG-II are elevated. OSA is associated with increased efferent postganglionic muscle sympathetic nerve activity (MSNA). Heart failure with systolic dysfunction HFrEF EF <40%, or with mid-range dysfunction HFmrEF, EF 40–49% or near-normal function, EF >50% HFPEF have all been seen to be present in patients with OSA. OSA affects hemodynamics with its effect on intrathoracic pressures as depicted in Figure 1.

Why are Patients with OSA more Susceptible to Cardiovascular Risk?[1]

Intermittent but recurrent hypoxia may be cardioprotective as it can cause "preconditioning" of heart. However acute recurrent hypoxia can be proarrhythmogenic by increasing sympathetic nerve activity.

- *Sympathetic overactivity* caused by recurrent hypopnea and apnea during sleep persists even during daytime wakefulness.
- *Altered cardiovascular variability* is detrimental to cardiovascular health. OSA patients have diminished heart rate variability and increased BP variability at rest and when awake. The Framingham Heart Study has associated lower heart rate variability to the development of future hypertension. Labile BP has been implicated in increased risk of end-organ damage in patients with hypertension.
- *Vasoactive substances*: Recurrent hypoxia causes release of vasoactive substances like endothelin, that promote vasoconstriction persisting for hours. Also, endothelin has been associated with development of pulmonary and systemic hypertension.
- *Inflammation*: Hypoxia is known to trigger systemic inflammation and release cytokines. Repeated hypoxia and sleep deprivation in OSA patients is known to be associated with increased levels of plasma cytokines, adhesion molecules, which can cause vasoconstriction or precipitate thrombosis.

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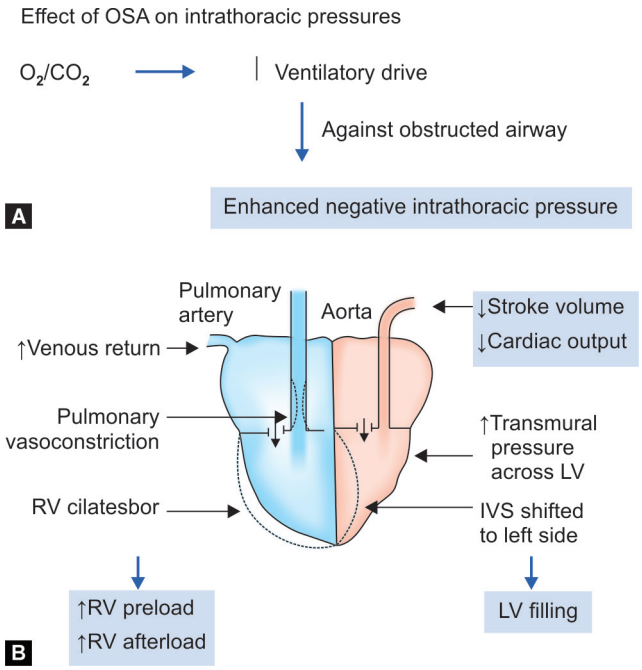

Figs 1A and B: Effects of OSA on hemodynamics

- *Endothelial dysfunction*: It is the end result of Systemic inflammation and associated overactive sympathetic nervous system, labile BP and oxidative stress.
- *Metabolic dysregulation and insulin resistance and hyperleptinemia and leptin resistance*: Leptin resistance causing obesity and consequent metabolic syndrome also have been linked to

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OSA. The predominant cardiovascular response to chronic hyperleptinemia is a vasoconstriction and raised BP.

- *Thrombosis*: OSA also been associated with increased platelet activation, increased fibrinogen.

Hypertension and OSA

Fifty percent of OSA patients are likely to have hypertension. Thirty percent of hypertensive patients have been diagnosed to have concomitant OSA.[1] Guidelines have mentioned that OSA is an independent risk factor for the development of essential hypertension. Higher levels of sympathetic drive causes increase in heart rate and cardiac output, increases peripheral vascular resistance, increases sodium reabsorption in the tubules of the kidney, and thereby increases blood pressure.[2] OSA should always be considered in every person diagnosed with resistant hypertension.[3] Alternatively, many obese individuals with OSA have resistant hypertension. Uncontrolled hypertension causes LV hypertrophy, systolic and diastolic heart failure, affects renal function and results in peripheral vascular disease.

Diuretics, aldosterone antagonists, RAAS inhibitors (either ACE inhibitors or angiotensin receptor antagonists) are drugs used in treating hypertension. 2–3 drugs may be needed to control BP. CPAP intervention trials suggest that CPAP used as an adjunct to these drugs to lower blood pressure in hypertensive patients with OSA. The maximum benefit is seen in patients with severe sleep apnea and in patients already receiving optimum antihypertensive treatment.[4] A meta-analysis has shown a mean reduction in systolic blood pressure of 2.46 mm Hg and a mean reduction in diastolic blood pressure of 1.83 mm Hg.[5] This reduction is rather small and hence long-term benefits of CPAP use in reducing BP are ambiguous. BP reduction secondary to treatment with aldosterone antagonists alone has been shown to decrease AHI without use of CPAP.[5] Surgical anatomical corrections to benefit OSA and thereby control hypertension remains controversial. The most common procedure is the revised uvulopalatopharyngoplasty, for which a small study showed improvement in nighttime but not daytime blood pressure.[6]

Arrhythmias and OSA

Nocturnal arrhythmias have been demonstrated to occur in around 50% of OSA patients. Common arrhythmias during sleep are frequent premature supraventricular or ventricular contractions,[1] nonsustained ventricular tachycardia and bradyarrhythmias like sinus arrest or rarely high-grade atrioventricular conduction blocks. Those with severe SDB (sleep disordered breathing) have a 2- to 4-fold-higher risk of complex arrhythmias while asleep or occasionally during daytime. Isolated atrial and ventricular ectopics were more frequent in patients with moderate/severe obstructive sleep apnea as compared to control. During an obstructive apnea, inspiratory effort against a collapsed upper airway generates negative intrathoracic force of −60 mm Hg, thereby stimulating cardiac mechanoreceptors and increasing cardiac transmural pressure. This predisposes patients to develop arrhythmias.[16,17]

Prolonged and recurrent apnea and associated hypoxia in OSA, can elicit the diving reflex, which results in cardiac vagal over-activity and precipitate bradyarrhythmias like sinus bradycardia, SA blocks, AV blocks and cardiac asystole.

Atrial fibrillation is common in OSA. Hypoxia, sympathetic nervous system activation, BP changes, transmural pressure changes, and systemic inflammation which occurs in OSA, may be mechanisms that predispose to the development of atrial fibrillation[1] and can cause through electrical and structural remodeling with long-term effects.[7] All patients with lone atrial fibrillation (no discernible etiology of AF) need to be evaluated for OSA. OSA has been shown to contribute to increased AF burden. Epidemiologic studies have identified a strong association of OSA and AF, with an increased risk for AF that is 2–4 times that of those without OSA. Ventricular arrhythmias, primarily premature ventricular contractions, have been reported in up to 66% of patients with sleep apnea, which is much higher than the rates reported in those without sleep apnea.

OSA and Sudden Cardiac Death (SCD): The Hanging Sword

Acute myocardial infarction is not necessarily only cause of SCD; unheralded abnormal heart rhythms are major culprits. In a study performed by Gami et al.[18,19] in a population of 10,701 adults referred for sleep studies, the presence and severity of OSA predicted probability of SCD. SCD is more likely to occur during usual sleep hours in individuals with OSA. The increased risk was predicted by higher AHI and lower nocturnal oxygen desaturation. The severity of nocturnal hypoxemia, which is an important pathophysiological feature of OSA, strongly predicted SCD independent of other risk factors.

Heart Failure

Sleep-disordered breathing (SDB) occurs in more than one-third of patients with HF. The most common types are central sleep apnea (CSA), (similar to Cheyne–Stokes respiration, CSR) obstructive sleep apnea (OSA), or commonly, a mixed pattern of the two.[13] Sleep of HF patients may be disturbed by acute LV failure, arrhythmias, diuretics or drug-induced diuresis, or nocturnal angina.

Fluid retention in heart failure can cause airway obstruction. OSA with an AHI >15 was detected in 26% with heart failure with reduced ejection fraction (HfrEF). OSA also has been detected in 50% of heart failure patients with preserved systolic function (HfpEF). Nocturnal oxygen desaturation affects ventricular relaxation during diastole, and therefore predisposes to HFpEF. In patients with heart failure, the coexistence of OSA may be associated with higher sympathetic nerve activity; consequently, the nocturnal and daytime BP may be higher in these patients. OSA could lead to the progression of heart failure through various pathophysiological mechanisms: (1) by increasing sympathetic activity to the heart, kidney, and resistance vessels during wakefulness and sleep; (2) by increasing left ventricular afterload both acutely/intermittently and chronically; (3) by inducing hypoxia, increasing pulmonary artery pressure and secondary increases in right ventricular afterload; and (4) by increasing the risk of myocardial ischemia and infarction.[8] Treatment with CPAP may benefit patients with OSA and all phenotypes of heart failure viz HfrEF/ HfmrEF/HfpEF.[10] Central sleep apnea, which may manifest as Cheyne–Stokes respiration, is found in 25–40% of patients who have heart failure with reduced ejection fraction. The prevalence of central sleep apnea increases in parallel with increasing severity of heart failure.[1] In the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study, patients with heart failure and central sleep apnea were randomly assigned to receive continuous positive airway pressure (CPAP) or no CPAP. The trial was stopped prematurely and did not show a beneficial effect of CPAP on morbidity or mortality. CPAP in HF related CSA has been shown to reduce the frequency of

episodes of apnea and hypopnea, and improve LVEF and 6-minute walk test distance, but did not improve prognosis or the rate of HF related hospitalizations.[13] The Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation (ASV) in Patients with Heart Failure (SERVE-HF) trial investigated the effects of adding adaptive servo-ventilation to guideline-based medical treatment on survival and cardiovascular outcomes in patients who HFrEF and predominantly central sleep apnea. The trial showed that adding adaptive servo-ventilation to guideline-based medical treatment did not improve the outcome but rather increased the risk of cardiovascular death by 34%, which was sustained throughout the trial, and there was no beneficial effect on quality of life or symptoms of heart failure. These results were seen despite effective control of central sleep apnea during adaptive servo-ventilation therapy. However, HFrEF patients with sleep disordered Breathing demonstrated substantial reverse cardiac remodeling during the CAT-HF trial. LVEF increased and LV volumes decreased significantly irrespective of whether patients were treated with ASV + optimal medical treatment (OMT) or OMT alone. However, compared with OMT alone, both HFrEF and HFpEF patients receiving ASV + OMT therapy had greater reductions in LA volumes, suggesting that ASV therapy may impact diastolic function and hence further investigation is indicated.[9,11,12]

Myocardial Ischemia and Infarction

Severe intermittent hypoxemia, acidosis, fluctuating BP, and sympathetic overactivity, in addition to changes in intrathoracic and cardiac transmural pressures, can trigger coronary ischemia in OSA. Association of endothelial dysfunction and systemic inflammation, with increased risk of vascular thrombosis, may promote structural coronary artery damage and acute coronary syndrome. There is also higher incidence of nocturnal silent coronary ischemia and arrhythmias.

The main influencing mechanisms of OSA, as a risk factor of CAD, are as follows:

- Hypoxia in OSA patients, caused by repeated apnea can activate the cytokine release and sympathetic nervous activity, resulting in vascular smooth muscle remodeling and hypertrophy; simultaneous increase in oxygen consumption of heart aggravates myocardial ischemia.
- The platelet activity and aggregation capacity in OSA patients is increased, leading to the occurrence of coronary thrombosis and acute coronary syndrome.
- The activity and content of tissue plasminogen activator inhibitor in OSA patients are increased, which inhibits the fibrinolytic system in the body and leads to a hypercoagulable state, and subsequent thrombosis.
- Repeated apnea, hypopnea-induced hypoxia induces oxidative stress, causing vascular endothelial dysfunction and increased cytokine production.
- Comorbid factors like obesity, lipid metabolism disorders, hypertension are commonly seen in patients with OSA. In order to reduce the incidence rate and improve the prognosis of CAD in OSA patients, treatment for OSA is indicated. A study has suggested that in patients with combined OSA and coronary artery disease, treatment of OSA was associated with a decrease in fresh cardiovascular events.[14]

Pulmonary Arterial Hypertension

Pulmonary artery pressure can increase during sleep in patients with OSA. Hypoxia can acutely increase in pulmonary arterial pressure. The pulmonary hypertension seen in patients with OSA is generally mild and is due to elevated pulmonary vascular resistance with normal cardiac output and capillary wedge pressure at rest. The most recent clinical classification of pulmonary hypertension identifies SDB in the category of respiratory disorders associated with pulmonary hypertension. In patients with OSA, pulmonary artery pressures fall after treatment with CPAP. The development of pulmonary hypertension is a poor prognostic sign in patients with OSA and increases mortality and worsens quality of life. Pulmonary hypertension in the setting of OSA can also result due to left heart failure with either preserved (HFpEF) or reduced ejection fraction (HFrEF). Longstanding increased left heart filling pressures eventually lead to pulmonary venous hypertension. The combination of hypoxic pulmonary vasoconstriction and pulmonary venous hypertension, will result in vascular cell proliferation and abnormal vascular remodeling, finally leading to pulmonary hypertension. The mechanisms of PH in OSA are multifactorial. Abnormal production of ROS, reduced NO production, increased angiogenic factors and vasoactive agents, result in partially reversible vasoconstriction.[15]

The prevalence and consequences of both OSA and CSA are likely to increase. Heightened interaction between specialists in cardiovascular, pulmonary and sleep medicine is indicated for future improved and integrated patient care.

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