Review Article

Sleep Apnea and Cardiovascular Disease

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Introduction:

One third of human life is spent in sleep. Physiology of different systems in the body works under a different mode of central nervous system operation in sleep than in awake. Normal physiologic sleep consists of rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, which alternates within sleep cycles of about 90 minutes in length. Hemodynamic mechanisms change throughout these cycles of sleep due to various metabolic, endocrine, vascular and autonomic changes.

Sleep apnea is characterized by cessation of airflow during sleep. Depending on the mechanism of sleep apnea, it can be divided into two types: obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA is characterized by frequent upper airway collapse during sleep despite respiratory effort. CSA results from loss of respiratory effort leading to partial or complete cessation of breathing. OSA affects 17% to 24% of North American adults.[1]The prevalence of OSA among patients with cardiovascular diseases is 3 to 4 fold higher than healthy persons.[2]Cardiovascular diseases including hypertension, atrial fibrillation, congestive heart failure, stroke and sudden cardiac deaths are associated with OSA. In this review, we will discuss the interaction of sleep apnea with cardiovascular diseases and how to prevent cardiovascular complications among patients with comorbid OSA.

Definition and diagnosis of OSA

OSA is characterized by repetitive interruption of breathing caused by pharyngeal collapse during sleep. An obstructive apnea is defined as pause of breathing for more than 10 seconds with continued respiratory effort. Obstructive hypopneas are defined as reduction of airflow with fall in oxygen saturation. More than 30% reduction of airflow for 10 seconds or more with >3% desaturation from pre-event baseline is considered hypopnea. OSA is diagnosed when the patient has an apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) >5 with the symptoms of excessive sleepiness during the day.[3,4] The area of pharyngeal collapse in OSA is usually posterior to the tongue, uvula or soft palate or some combination of these structures. The diameter of the pharyngeal airway can be small from fat deposition in obesity or due to constriction of airway from arrangement of bone and surrounding soft tissue structures. In children, enlarged tonsils and adenoid are usually the cause of small airway. During wakefulness, the airflow resistance and turbulence can be handled by responsiveness of mechanoreceptors in the larynx causing increased activity of pharyngeal dilator muscles. During sleep, this reflex pharyngeal muscle activity is reduced or lost, leading to pharyngeal narrowing or intermittent collapse.

Diagnosis of OSA should start with screening of patients with high risk for OSA. Loud snoring, observed apneas, fragmented sleep, increased daytime sleepiness, unexplained fatigue and tiredness can be symptoms of OSA. A focused history with physical examination including neck size, oral examination with Mallampati score, BMI, hear rate, rhythm and blood pressure are needed during initial evaluation of sleep apnea. EPWORTH sleepiness scale, STOP BANG questionnaire, the Berlin Questionnaire and overnight oximetry may

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also be used for initial screening. Definitive diagnosis of sleep apnea requires an overnight polysomnography (PSG) or a home sleep study which record multiple physiological variables continuously during sleep. Overnight in-lab PSG channels generally include EEG for sleep staging, EMG for muscle activity, EOG (electro-oculogram) for eye movements, respiration (flow, effort, and oxygen saturation), snoring and a continuous lead of ECG.

Central Sleep Apnea (CSA)

A central apnea is defined as e"90% reduction in breathing amplitude for at least 10 seconds with no respiratory effort. CSA syndrome is present when a patient has e"5 central apnea per hour of sleep with associated symptoms of disrupted sleep (frequent arousals) and/or hypersomnolence during the day. CSA is observed in various disease conditions including congestive heart failure (CHF) and some neurological conditions including stroke. Cheyne-Stokes respiration is a form CSA seen frequently in CHF, characterized by a crescendo decrescendo pattern of breathing with a central apnea or hypopnea at the nadir of respiratory effort. Diagnosis of CSA requires an overnight PSG to determine the frequency and pattern of central apnea.

Pathophysiology of OSA leading to cardiovascular risk

Sleep is characterized by cardiovascular quiescence with decrease in basal metabolic rate, heart rate, blood pressure and sympathetic activity and increase in vagal tone. Heart rate decreases during NREM sleep with a tonic increase in parasympathetic activity which fluctuates during REM sleep. Blood pressure (BP)generally drops by 5-14% during NREM sleep and fluctuates during REM sleep.[5]Cardiac output also decreases progressively during sleep, with the greatest decrease occurring during the last sleep cycle, particularly during last REM sleep (a physiologic phenomenon called "dipping"). OSA causes hemodynamic and autonomic instability by intermittent hypoxia, hypercapnia and heightened adrenergic activation from repeated apneic events. This exaggerated sympathetic drive elicited by apneas during sleep continue during the wakefulness period as well.[6,7] OSA has also been linked to blunting or "non-dipping" of nocturnal blood pressure. A linear correlation has been found between 24 hour BP and AHI independent of BMI in the large cohort of Wisconsin Sleep Cohort Study.[8] Heart rate variability is low and BP variability is high among patients with OSA. Combination of these two factors has been attributed to increase in cardiovascular risk and end organ damages from sleep apnea in several studies. [5,9] (Figure 1)

Mechanical effects of OSA:

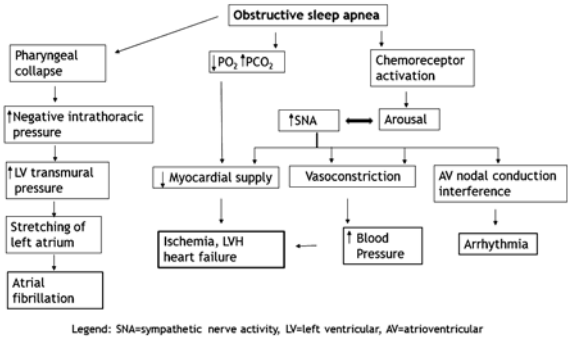

Fig.-1: *Algorithm for pathophysiological effects of OSA. Adapted from Bradley et al., Circulation, 2003.*[34]

During obstructive apneas, negative inspiratory intrathoracic pressure generated against the occluded pharynx increases left ventricular (LV) transmural pressure and thereby increases afterload.[10,11]It also increases venous return, augmenting right ventricular preload, whereas OSA induced hypoxic pulmonary vasoconstriction increases pulmonary afterload. Consequently, RV distension and leftward septal displacement during diastole greatly impairs LV filling. This combination of increased LV afterload and diminished preload reduces stroke volume and cardiac output, which is more pronounced in heart failure patients than in healthy subjects.[11]Increased LV transmural pressure also increases myocardial oxygen demand, while simultaneously reduction in coronary blood flow and hypoxia during an apneic event reduces oxygen delivery. This may lead to chronic myocardial ischemia, cardiac remodeling and heart failure in the long run. OSA was found to be associated with significant atrial remodeling characterized by atrial enlargement, reduction in voltage, site-specific and widespread conduction abnormalities, and longer sinus node recovery.[12] Several studies showed that

OSA predicts new onset atrial fibrillation (AF) or its recurrences following cardioversion to sinus rhythm.[13,14]

Vascular inflammatory effects of OSA:

Intermittent hypoxia in OSA induces oxygen free radicals and activates inflammatory pathways leading to vascular endothelial dysfunction. It also promotes oxidation of lipoproteins, increases expression of adhesion molecules and vascular smooth muscle proliferation. All these effects increase prevalence of hypertension and atherosclerosis in OSA. Platelet activation and adhesions are increased in patients with OSA during sleep, and these have been shown to decrease after one night of CPAP treatment.[15] A randomized trial also demonstrated that treatment of OSA by CPAP reduces carotid intima-media thickness, supporting a cause effect relationship between atherosclerosis and OSA.[16]

Association between OSA and cardiovascular diseases

OSA and hypertension:

OSA has been found to be a significant predictor of cardiovascular diseases among middle aged population followed over seven years period (OR=4.9, CI=1.8-13.6).[17] The prevalence of OSA is higher in population with hypertension (30-83%),[18] heart failure (12-53%),[19] ischemic heart diseases (30-58%)[20] and stroke (43-91%).[21]

Hypertension (HTN) has been extensively studied for its association with OSA. Prevalence of non-dipping (drop of nocturnal mean arterial BP >10%) is very high among patients with moderate to severe sleep apnea, while not being treated with anti-hypertensive.[22]A dose response relationships were found between AHI and hypertension inn Sleep Heart Health Study among 6132 participants. Excluding participants taking anti-hypertensive medications, AHI was linearly associated with blood pressure values in this study.[23]Wisconsin Sleep Cohort Study prospectively studied 709 participants over 8 years and found 2.89 times (95% CI=1.46-5.65) increased risk of developing HTN among participants with AHI of 5 to 15, after adjusting for age, sex, obesity and other comorbid factors.[1]Resistant hypertension increases cardiovascular diseases by 1.5 fold, and patients with OSA have almost five fold higher risk of developing resistant HTN.[24] Multiple multi-centric randomized studies have shown improvement of resistant HTN with CPAP use. [25–27] For obvious reasons, OSA has been included as an identifiable cause of hypertension since 2003 in JNC (Joint National Committee) report for blood pressure management.[28]

OSA and heart failure:

OSA is prevalent (49%-53%) among patients with CHF (LV ejection fraction <45%).[26,29] In a prospective study of 164 patients with CHF, patients with untreated sleep apnea had significantly higher (hazard ratio= 2.89, p=0.029) mortality than the patients with mild or no sleep apnea.[30]Overall, untreated severe OSA significantly increase the risk of fatal (OR = 2.87, 95% CI =1.17-7.75) and non-fatal(OR=3.17, 95% CI =1.12-7.51) cardiovascular events after adjusting for confounding factors.[31]The causal role of OSA in development of CHF has been suggested by many clinical trials that showed improvement of cardiac function after treatment with CPAP. [32–34]Central sleep apnea, resulting in turn from CHF, plays a major role in progressive morbidity and mortality among these patients. CSA is present in 25 to 40% patients with CHF,[34] which results from cyclic hyperventilation and fall in partial pressure of carbon dioxide below the apnea threshold. This leads to tissue hypoxia, repetitive arousals from sleep and activation of the sympathetic nervous system, and independently increases the risk of mortality. CSA worsens the left atrial (LA) function more than OSA by decreasing the LA wall compliance.[35]The CANPAP trial tested the effect of CPAP by randomizing patients of heart failure to CPAP and no-CPAP, and found that CPAP improves central apnea, nocturnal oxygenation, left ventricular ejection fraction and serum norepinephrine level.[36] Adaptive servo ventilation (ASV) was introduced as a novel method of ventilator support designed for Cheyne Stokes Respiration for CHF. Multi centered randomized trials showed promising results with ASV improving left ventricular functions and sleep quality, compared to other modes of positive pressure ventilation.[37]It is to be noted that a recent preliminary result (2015) of a multi-centered randomized trial (SERV-HF) on 1300 patients showed increased mortality among patients with

CHF (EF<45%) who were treated with ASV for their CSA.[38]Though final in-depth analysis of the study finding is yet to come, excess death appeared to be driven by sudden cardiac deaths.

OSA and Atrial Fibrillation:

Approximately 20-50% of patients with atrial fibrillation (AF) have OSA.OSA is more prevalent in patients with AF than in high-risk patients with multiple other cardiovascular diseases (49% versus 32%, P=0.0004) and the odds of having AF in patients with OSA is about 2.19 (95% CI 1.40 -3.42, P=0.0006).[39]Patients with OSA are likely to be more symptomatic(p=0.001) and be on rhythm control therapy than patients without OSA (p=0.0037).[40]The diagnosis (hazard ratio= 1.55; 95% CI= 1.21-2.00) and severity (HR= 1.15; 95% CI,=1.06-1.26) of OSA have been reported to be independent predictors of hospitalization for incident atrial fibrillation.[41]Risk of recurrence of AF is two-fold among patients with untreated OSA compared to those who has been compliant with their CPAP therapy (p=0.013).[14]CPAP treated patients are also twice as likely to have AF-free survival after catheter ablation compared to those not treated with CPAP (71.9% vs. 36.7%; p = 0.01).[42]

OSA and Stroke:

The prevalence of OSA is high (up to 60%) among patients with stroke.[43–46]Incompletely treated OSA increases the risk of CVD by 11 folds compared to those treated adequately with CPAP. AHI and hypoxemia are strongly correlated with the prevalence of CVD with relative odds of 2.1 to 2.5 for moderate to severe sleep apnea.[47] In Sleep Heart Health Study, a total of 5,422 participants without a history of stroke at baseline and untreated for sleep apnea were followed for a median of 8.7 years. One hundred ninety-three ischemic strokes were observed in this population, and a significant positive association was found with ischemic stroke with a linear increase of AHI (P=0.016).[48]Yaggi et al. followed a cohort of 1022 patients who underwent PSG and were followed for subsequent events of stroke or death. After adjusting for age, sex, dyslipidemia, HTN, DM, atrial fibrillation, OSA retained a statistically significant association with development of stroke and death (HR=1.97, P=0.01).[43]

Sudden death from cardiovascular diseases:

Clinical evidence of sudden cardiac death induced by OSA has been addressed in different studies. Yumino et al., in a prospective cohort study of 89 patients with ACS who underwent polysomnography, found OSA in 57% of patients. After a mean follow up of >7 months, the incidence of cardiac death, re-infarction or new revascularization was higher in patients with OSA compared to those without OSA.[49]People with OSA suffer from sudden death more frequently while sleeping than awake. An observational study on 112 residents of Minnesota who died suddenly from a cardiovascular event showed that 64% of patients with OSA died between midnight to 6 AM compared to 21% people without OSA (P=0.01), 16% of general population (P<0.001), and 25% expected by chance. For people with OSA, relative risk of sudden death from cardiovascular event occurring between midnight to 6 AM was 2.57 (95% CI =1.87-3.52).[50]

Mechanism of sudden cardiac death in OSA was explored in a recent study. Microvolt T wave alternant (MTWA) was used as a tool to measure myocardial vulnerability to assess the potential arrhythmogenicity of sleep apnea on causing sudden deaths. The severity of sleep apnea (AHI) was directly proportional to the presence of MTWA, suggestive of the direct effect of OSA on sudden death.[51]OSA may lead to to higher incidence of sudden cardiac death due to reentrant arrhythmia initiated by ventricular extra-systole that excite myocardial fibers at the height of its vulnerable period, and reentrant beats trigger runs of ventricular tachycardia and ventricular fibrillation.

Conclusion:

Obstructive sleep apnea may increase the risk of cardiovascular morbidity and mortality by various mechanisms. Repetitive nocturnal hypoxemia and arousals lead to increased risk of atherosclerosis and hypercoagulability, cardiac ischemia, cellular degeneration, and apoptosis. It may also promote cardiac remodeling causing diastolic and systolic dysfunctions; which provide fertile environment for reentrant arrhythmias. Since the prevalence of obstructive sleep apnea is fairly high, screening for this condition in vulnerable population with early detection and treatment may help prevent

cardiovascular complication in this group of patients.

Conflict of Interest - None.

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