Current Cardiology Reports (2019) 21: 137
https://doi.org/10.1007/s11886-019-1228-3

STROKE (JF MESCHIA, SECTION EDITOR)

Cardiovascular Consequences of Obstructive Sleep Apnea

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Published online: 9 November 2019

Abstract
Purpose of Review To review the clinical evidence for a relationship between obstructive sleep apnea and hypertension, arrhythmias, coronary artery disease, and congestive heart failure.
Recent Findings Current data show that obstructive sleep apnea is a risk for cardiovascular disease. Studies have linked untreated moderate to severe obstructive sleep apnea to hypertension, cardiac arrhythmias, coronary artery disease, and congestive heart failure. However, uncertainty regarding benefits of treatment of obstructive sleep apnea to reduce the risk of cardiovascular disease still exists. The issue of poor compliance has been an on-going limitation of CPAP trials.
Summary Evidence shows obstructive sleep apnea is a risk factor for cardiovascular disease but trials have yet to clarify if cardiovascular disease morbidity and mortality decreases with treatment of the apnea. Future treatment trials are needed to address the question of whether treatment decreases cardiovascular risk in patients with obstructive sleep apnea.

Keywords Sleep apnea · Cardiovascular disease · Hypertension · Obstructive sleep Apnea · Arrhythmia · Congestive heart failure

Introduction

Obstructive sleep apnea (OSA) is the most common breathing disorder of sleep and prevalence is increasing. It is estimated that 2 to 9% of women and 4 to 26% of men have obstructive sleep apnea [1–3]. Obstructive sleep apnea consists of intermittent airway closure resulting in a peak signal excursion drop of ≥ 90% in airflow (apnea) or 30 to 89% (hypopnea) for ≥ 10-s duration with a ≥ 3% arterial oxygen desaturation or associated with an arousal [4]. AHI is calculated by adding all of the apneas and hypopneas during the scored sleep time and dividing by total sleep time in hours. OSA is diagnosed when the apnea-hypopnea index (AHI) is ≥ 5 with associated sleepiness, nonrestorative sleep, fatigue, insomnia, choke/gasp awakenings, witnessed apneic events, and habitual snoring, or the patient has been diagnosed with hypertension, mood disorder, cognitive disorder, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or diabetes mellitus type 2 [5], or if the AHI is ≥ 15 without associated symptoms [5]. OSA severity is categorized into mild (AHI 5–14), moderate (AHI ≥ 15–29), or severe (AHI≥ 30). Several studies have examined the association of severity of OSA and associated cardiovascular disease.

Currently, more than 1 in three American adults have cardiovascular disease with 80 million suffering from hypertension and 15.5 million with coronary heart disease [6]. Cardiovascular disease accounts for 800,000 deaths per year in the USA and is the leading cause of death in males and females [6]. Therefore, understanding associated diseases that play a role in cardiovascular morbidity and mortality is essential. This paper will review the association of obstructive sleep apnea with hypertension, cardiac arrhythmias, stroke, coronary artery disease, and heart failure. Since 1986, positive air pressure (PAP/CPAP) has been used to prevent airway collapse associated with OSA. PAP remains the method of choice for OSA treatment.

This article is part of the Topical Collection on *Stroke*

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Pathophysiology of Sleep-Disordered Breathing and Cardiovascular Disease

Normal sleep architecture consists of non-REM sleep (NREM) and stage R sleep. Throughout the night, the average

adult will spend only 25% of the night in stage R sleep and the remainder in NREM sleep. During NREM sleep, sympathetic activity decreases and parasympathetic activity increases, which provides a state advantageous to the cardiovascular system with lowering of the blood pressure and heart rate [7]. However, sleep-disordered breathing disrupts this state of cardiovascular tranquility. There are four main cardiovascular consequences of hypopneas, apneas, and compensatory hyperpneas: (1) excessive arousals resulting in decreased parasympathetic activity and increase sympathetic activation, (2) intermittent hypoxemia-reoxygenation fluctuations resulting in oxidative stress and inflammation, (3) decreased parasympathetic activity and increase sympathetic activity, (4) large negative intrathoracic pressure swings [7, 8]. The atria are sensitive to the negative intrathoracic pressures that occur when attempting to breathe against a closed airway, resulting in stretching of the atrial receptors causing secretion of atrial natriuretic peptide and subsequently nocturia and activation of ion channels in the atria, possibly facilitating the development of atrial arrhythmias [7]. Intermittent hypoxemia results in oxidative stress and increased inflammatory mediators and cytokines, which contribute to endothelial dysfunction [9].

Intermittent hypoxia (IH) is the main trigger for the associated cardiovascular and metabolic alterations. IH trigger mitochondrial dysfunction, resulting in increased upregulation of nuclear factor kappa B (NF-κB) demonstrated in neutrophils/monocytes of patients with OSA resulting in production of adhesion molecules, inflammatory cytokines, adipokines. IH leads to preferential activation of NF-κB overactivation of the transcriptional factor hypoxia induction factor-1 (HIF-1α). Vascular wall hypoxia augments the thrombogenic potential of atherosclerotic plaque and thrombus formation on plaques via prothrombotic factor upregulation [10]. VEGF (vascular endothelial growth factor) is critical in nitric oxide vasodilatation and increased vascular permeability. In normoxia, 90% of available O_2 is consumed by mitochondria, leaving sufficient O_2 for hypoxia-induced factor 1 (HIF-1), a transcriptional regulator which promotes induction of adaptive genes that facilitate O_2 supply. In sustained hypoxemia, the mitochondria consume almost all the O_2, and rapid stabilization of HIF-1 occurs, which leads to increased transcription of genes such as EPO.

In chronic intermittent hypoxemia, the extent of hypoxia is not sufficient to allow HIF-1 stabilization; and through mitochondrial stress, it results in the activation of proinflammatory transcription factor NF factor kappa B with the downstream consequences of production of inflammatory genes such as TNF. Activation of systemic inflammatory pathways mediated primarily by the nuclear transcriptional factor kappa B favors the development of atherosclerosis through the synthesis of cytokines and the expression of adhesion molecules, endothelial dysfunction with a decreased availability of nitric oxide, dyslipidemia, insulin resistance, and stimulation of the renin-angiotensin system.

There is circadian alteration of platelet activity in OSA with increased platelet activity during the night [11]. Some indicators of platelet activation such as platelet distribution width (PDW) and platelet-to-lymphocyte ratio (PLR) are potential biomarkers for the concurrent hypertension and OSA. Increased PDW and PLR correlated with AHI in OSA patients and were significantly higher in the severe OSA group [12]. Platelet activation also results in the shedding of platelet-derived procoagulant microparticles (PMPs). The plasma levels of PMPs correlate with the AHI and are significantly higher in patient with severe OSA [13]. In OSA patients treated with PAP, platelet aggregability was improved after 3 months of therapy [14]. Apneas and hypopneas result in increased stress response with elevation of cortisol and decrease leptin further resulting in metabolic syndrome [9] (Fig. 1). Current evidence suggests that CPAP treatment reduces sympathetic activity [15].

Obstructive Sleep Apnea and Hypertension

Hypertension risk development has been shown to correlate with severity of OSA in the Wisconsin Sleep Cohort Study and further studies have shown the association between untreated OSA and new-onset hypertension [16, 17]. Marin and colleagues evaluated 1889 participants with 21,003 person-years follow-up and found 705 developed incident hypertension. In controls, the crude incidence of hypertension per 100 person-years was 2.19 versus 3.34 in persons with OSA ineligible for continuous positive airway pressure (CPAP), 5.84 in patients with OSA who declined CPAP, and 3.06 in patients with OSA on CPAP therapy [17]. Studies examining the effect of CPAP therapy on hypertension have been numerous with mixed results. The inconsistencies of results of lowering systolic and diastolic blood pressure in patients with OSA can be attributed to several factors, including evaluation in patients with only mild OSA versus moderate to severe OSA, compliance of CPAP < 4 h per night and unknown sleep time without the use of CPAP, and unknown primary etiology of hypertension within the patient (e.g., high salt intake, renal disease). Recent meta-analyses have shown decrease in 24-h blood pressure readings in patients with OSA using CPAP therapy [18, 19]. Liu and colleagues examined five randomized control trials with 24-h ambulatory systolic blood pressure and diastolic blood pressure changes of − 4.78 mmHg and − 2.95 mmHg respectively in favor of CPAP treatment [19]. Recent evaluation of patients with hypertension and moderate to severe obstructive sleep apnea was performed to determine if circadian blood pressure variability was a factor to determine blood pressure response to CPAP [20]. They found that a non-dipping pattern, meaning blood pressure elevation persisted through the night, benefited more from CPAP in terms of blood pressure reduction than dippers with −

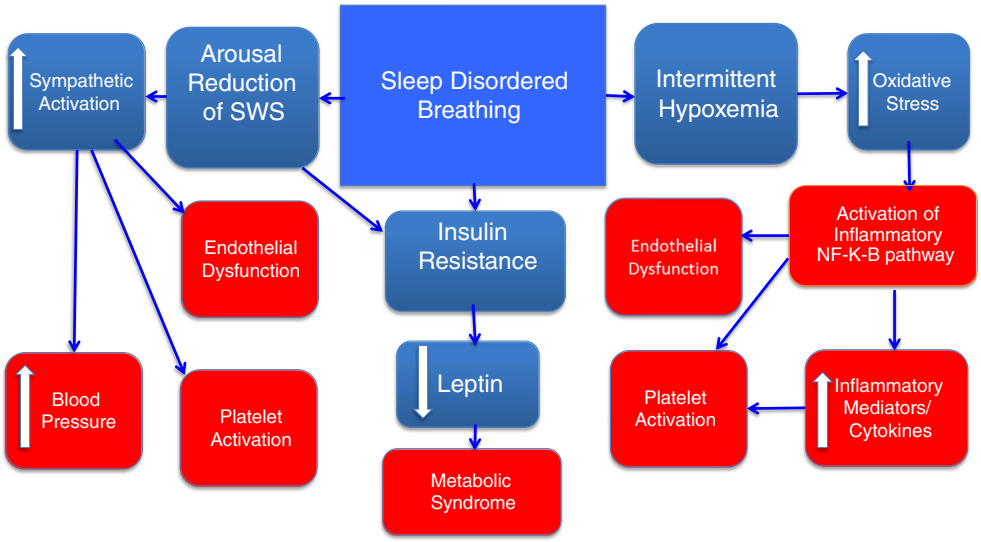

Fig. 1 Mechanisms underlying cardiovascular and metabolic alterations associated with sleep-disordered breathing

2.99 mmHg from the mean 24-h ambulatory monitoring and − 5.35 mmHg for the mean nighttime ambulatory blood pressure monitor [20]. With current data available, we consider OSA a modifiable risk factor in resistant HTN and should be screened for in patients with HTN.

Obstructive Sleep Apnea and Arrhythmias

Obstructive sleep apnea appears to cause cardiac arrhythmias due to intermittent tissue hypoxemia and increased sympathetic output. Since the early 1990s, the association of obstructive sleep apnea and atrial fibrillation has been documented, with Flemons et al. first reporting the association and Javaheri et al. publishing statistically significant association between sleep apnea and atrial fibrillation [21, 22]. Recent studies have examined sleep quality measures in patients with atrial fibrillation and found increased reports of insomnia with frequent awakenings [23].

From the Sleep Heart Health Study, Mehra et al. found individuals with severe obstructive sleep apnea had four times the odds of having atrial fibrillation, three times the odds of non-sustained ventricular tachycardia, and almost twice the odds of complex ventricular ectopy after controlling for potential confounders [24]. Other studies have found similar associations of obstructive sleep apnea and atrial fibrillation [25, 26]. Evaluation of individuals with mild OSA found a similar increase in prevalence of ventricular premature complexes [27]. It was also found that the timing of the arrhythmias tended to cluster after respiratory events, further strengthening the case of the underlying pathophysiology of nocturnal arrhythmias [28].

This association is of importance as targeted therapies for treatment of atrial fibrillation and cardiac arrhythmias need to be individualized to the patient. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) examined if patients with OSA had a greater likelihood of progressing to more persistent forms of atrial fibrillation or had worse outcomes. They followed 10,132 patients over 2 years and found that patients with OSA reported more severe/disabling symptoms (22% vs 16% without OSA) and were more often on rhythm control therapy (35% vs 31% without OSA) [29]. They also found that patients with OSA on CPAP were less likely to progress to more permanent forms of AF compared with patients with OSA not on CPAP therapy [29]. Ng and colleagues evaluated if OSA carried a risk for development of recurrent atrial fibrillation after catheter-based pulmonary vein isolation ablation for treatment of atrial fibrillation. They conducted a meta-analysis of six studies totaling 3995 patients and found patients with OSA had a 25% greater risk of recurrence of AF than those without OSA after catheter ablation [30]. Therefore, identification of obstructive sleep apnea in this patient population is key to optimize appropriate therapy strategies and personalized treatment.

Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without OSA. Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF [31].

Obstructive Sleep Apnea and Coronary Artery Disease

The role of OSA in the pathogenesis of coronary artery disease is felt to be related to endothelial dysfunction from intermittent hypoxemic and reoxygenation that occurs during apneas, hypopneas, and hyperpneas. This promotes inflammation through cytokines and, specifically, transcription factor NF-κB [32]. In a community-based cohort study of black

and white participants, moderate to severe OSA was modestly associated with endothelial dysfunction determined by EndoPAT (peripheral arterial tone) device and subclinical atherosclerotic coronary artery disease by coronary artery calcium quantified by electron beam computed tomography [33]. However, a study by Rivera-Perez et al. that examined patients undergoing cardiac catheterization due to suspicion of CAD observed moderate to severe OSA correlated with Gensini score ≥ 2 with a large effect size (OR 4.46) when adjusted for confounders [34]. This finding further suggests OSA influences the pathophysiology of CAD but a dose-response severity relationship is questionable [34]. The Sleep and Stent Study was performed across five countries examining major adverse cardiac and cerebrovascular events (MACCEs) in patients undergoing percutaneous coronary intervention. They enrolled 1311 patients and performed a sleep study within 7 days of intervention and found 45.3% of patients had moderate to severe OSA. The study reported that OSA was a predictor of MACCEs with adjusted hazard ratio of 1.57 and the crude incidence of MACCEs was 18.9% in the OSA group over 3 years than 14% in the non-OSA group ($p = 0.001$) [35]. One of the longest studies was conducted by Gunnarsson and colleagues through the Wisconsin Sleep Cohort, which examined individuals over mean 13.5 years for OSA, carotid artery intima-media thickness, and plaque [36]. They found that after adjusting for age, sex, BMI, systolic blood pressure, smoking, use of lipid-lowering, antihypertensive, and diabetes medications, the baseline AHI independently predicted future carotid artery intima-media thickness, plaque presence, and plaque score [36]. This was a pivotal study as it documented the role OSA plays in cardiovascular pathology over a decade later.

With studies showing an association with OSA and the development of coronary artery disease, it would be reasonable to hope that treatment of OSA with positive airway pressure therapy would improve CAD. However, data are conflicting regarding improved outcomes in cardiovascular events. In 2016, two major papers were published examining the effect of positive airway pressure therapy on cardiovascular outcomes. The first was the RICCADSA randomized controlled trial looking at the effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with non-sleepy obstructive sleep apnea [37]. Peker and colleagues randomized patients with OSA (AHI ≥ 15) with newly revascularized CAD to either auto-titration CPAP or no PAP therapy. Their primary endpoint was repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality. They found no statistically significant difference between groups in primary endpoint; however, after performing an adjusted on-treatment analysis, there was a significant cardiovascular risk reduction in patients using CPAP therapy greater than or equal to 4 h versus less than 4 h per night or who did not receive therapy [37]. The issue of poor compliance has been an on-going limitation of CPAP trials. As sleep physicians, we request our patients to use his or her CPAP during their total sleep duration, not for at least 4 h per night. Therefore, the actual percentage of sleep per night an individual is using his or her CPAP and treating the OSA is of importance in an intention-to-treat analysis. This was a key limitation to the CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea (SAVE) trial [38••]. In the CPAP treatment group, the mean adherence to therapy was only 3.3 h per night. McEvoy and colleagues found no significant effect on any individual or composite cardiovascular endpoint [38••]. They did report that CPAP significantly reduced snoring and improved health-related quality of life and mood with decreased daytime sleepiness [38••]. Other limitations of this study include generalizability as the majority of the cohort was of Asian descent, eligibility concerns given the lack of the diagnostic technology to be able to differentiate individuals with central sleep apnea from OSA, and exclusion of patients with severe OSA. Two more recent meta-analyses conducted in 2017 and 2018 have had similar issues with adherence to CPAP therapy, potentially limiting therapeutic benefit. Yu and colleagues reviewed studies with composite outcomes of acute coronary syndrome events, stroke, or vascular death that included PAP treatment. They reviewed 10 trails (9 CPAP and 1 adaptive servo-ventilation). They found that PAP compared with no treatment or sham was not associated with reduced risk of cardiovascular outcomes or death in patients with sleep apnea [39]. However, upon review of baseline study characteristics, median CPAP usage ranged from 1.4 to 6.6 h [39]. The studies reviewed consisted of patients without excessive sleepiness, which may represent an important difference in target population from patients with excessive daytime sleepiness. Khan and colleagues performed a meta-analysis of CPAP therapy in prevention of cardiovascular events. An analysis of 4268 patients revealed a 26% relative risk reduction in major adverse cardiovascular events with CPAP and noted that an increase in CPAP usage time increased the risk reduction in major adverse cardiovascular event and stroke [40•]. Again, CPAP adherence time ≥ 4 h showed higher risk reduction (57%) [40•]. However, no benefit was seen with CPAP in myocardial infarction, all-cause mortality, atrial fibrillation/flutter, or heart failure.

Obstructive Sleep Apnea and Heart Failure

Patients with sleep-disordered breathing in the form of obstructive and central sleep apnea have a higher prevalence of heart failure than the general population [41]. Therefore, it is an important co-morbidity and possible therapeutic target that is important to identify in patients with heart failure. The Sleep-Disordered Breathing in Heart Failure (SchlaHF) Registry has been used to identify the prevalence and predictors of sleep-disordered breathing by Artz and colleagues. The

prevalence of moderate to severe sleep-disordered breathing was 49% in men and 36% in women with chronic, stable, symptomatic heart failure NYHA functional class ≥ II and left ventricular rejection fraction ≤ 45% [41]. The prevalence increased with increasing age, male sex, BMI, and severity of symptoms and left ventricular dysfunction [41]. However, the question if sleep-disordered breathing increases mortality in patients with heart failure is of the most importance. A recent study by Oldenburg and colleagues evaluated nocturnal hypoxemia in relationship to mortality in patients with stable heart failure. They obtained unattended in-hospital polygraphy data to determine AHI and hypoxemic burden (time with oxygen less than 90%) as well as all-cause mortality. They reviewed 963 individuals and found similar numbers in the frequency of sleep-disordered breathing as Artz and colleagues with 58% of individuals having sleep-disordered breathing [42]. They found that time spent less than 90% saturation was significantly ($p < 0.001$) associated with time to death from any cause and the risk of death increased by 16.1% per hour of time spent less than 90% [42]. Data from the Outcomes of Sleep Disorders in Older Men and the Sleep Heart Health Study support these findings by Oldenburg and colleagues. They determined hypoxic burden by measuring the respiratory event–associated area under the desaturation curve from pre-event baseline [43]. This was performed as the authors felt the AHI did not represent the level of disease burden. Such as, one patient may have an AHI of 20 with oxygen nadir of only 90% and time spent below that < 10 min and another patient may have an AHI of 20 with an oxygen nadir of 68% with time spent below 90% of 189 min. They found that in the Outcomes of Sleep Disorders in Older Men, the hypoxic burden in the highest two quintiles had hazard ratios of 1.81 and 2.73. In the Sleep Heart Health Study, the hypoxic burden in the highest quintile had a hazard ratio of 1.96 [42]. However, the answer to the question of treating sleep-disordered breathing leading to improved heart failure outcomes is not clear. The prevalence of both obstructive and central sleep apneas in heart failure is a complicating picture as studies may not fully account for each type or whether there is a predominant type. Also, further research needs to be done on the pathophysiology of the development of central and/or obstructive sleep apnea in an individual patient with heart failure and what characteristics determine the prevalent sleep-disordered breathing pattern.

Conclusion

Current evidence strongly suggests that OSA is a valid cardiovascular risk factor. Before widespread use of CPAP as a standard of care in 1986, patients with OSA treated conservatively had increased mortality compared with OSA patients who had undergone tracheostomy, with most deaths of cardiovascular cause [44]. CPAP has been shown to decrease hypertension, improve glycemic control, increase left ventricular ejection fraction, restore the cerebral vascular response to hypoxia, decrease markers of platelet activation and hypercoagulation, normalize inflammatory markers, and normalize circulating markers of vascular damage. Despite these encouraging CPAP-related outcomes, the Sleep Apnea cardioVascular Endpoints (SAVE), which was a secondary prevention trial in adults with cardiovascular disease and OSA, demonstrated that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone [38]. There are few admonitions to consider regarding SAVE; first, the mean duration of CPAP adherence was only 3.3 h per night, which is consistent not only with poor CPAP compliance but also with exposure to worsening OSA during REM sleep. Second, since patients who had excessive daytime somnolence (Epworth Sleepiness Scale > 15) and severe hypoxia (oxygen saturation < 80%) were excluded, it is imperative to understand that the SAVE trial findings are not generalizable to all patients with OSA. Remarkably, despite the negative result for the primary endpoint, CPAP still had a significant beneficial effect on quality of life, mood, daytime sleepiness, and work productivity. Further long-term studies are needed on the role of CPAP therapy in preventing the cardiovascular consequences of untreated obstructive sleep apnea.

Compliance with Ethical Standards

Conflict of Interest Brynn K. Dredla and Pablo R. Castillo declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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