Obstructive Sleep Apnea and Cardiovascular Disease

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KEYWORDS

• Obstructive sleep apnea • Hypertension • Atrial fibrillation
• Premature ventricular contractions • Ventricular tachycardia • Nondipper
• Polysomnography

KEY POINTS

- Obstructive sleep apnea (OSA) is due to repetitive interruptions of ventilation each lasting for more than 10 seconds during sleep as a result of upper airway obstruction and resulting in increased respiratory effort.
- Normally, there is a 10% to 20% decrease in sleep blood pressure (BP) compared with wake BP (dip) on 24-hour ambulatory BP monitoring; however, individuals with OSA typically have an absent dip or paradoxic increase (reverse dip) in sleep period BP.
- The definitive diagnosis of OSA is made by polysomnography, a sleep study that may be performed in a sleep laboratory or at home.
- Clinical trials demonstrate modest reduction of BP with continuous positive airway pressure (CPAP).
- Treatment of OSA with CPAP is necessary for proper management of atrial fibrillation and maintenance sinus rhythm.

INTRODUCTION AND BACKGROUND

Obstructive sleep apnea (OSA) presents as repetitive interruptions of ventilation each lasting for more than 10 seconds during sleep as a result of upper airway obstruction and resulting in increased respiratory effort.[1] This is in contradistinction to central sleep apnea in which there is a loss of ventilatory drive, with a greater than 10-second pause in ventilation, but with no associated increase in respiratory effort. In this article, we explore the relationship between OSA and cardiovascular disease. Observational studies have associated OSA with hypertension often resistant to medication, coronary heart disease, cardiac arrhythmia (particularly atrial fibrillation), and heart failure.

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PREVALENCE OF OBSTRUCTIVE SLEEP APNEA

OSA is a common worldwide problem. Population-based studies suggest the prevalence of OSA to be 3% to 7% for adult men and 2% to 5% for adult women in the general population, although higher in different population subsets, such as overweight or obese people and older individuals.[2] In a meta-analysis of 17 studies, Benjafield and colleagues[3] estimated that 936 million adult men and women aged 30 to 69 years worldwide have mild to severe OSA, with the highest prevalence exceeding 50% in some locations. Men are 3 times more likely than women to have OSA, and the prevalence increases with age, particularly in those older than 60 years. Patients with OSA are often obese and have an increased prevalence of other cardiovascular risk factors, such as hypertension and type 2 diabetes mellitus. Approximately 50% of patients with OSA have high blood pressure (BP), and up to 30% of hypertensive individuals may have OSA. Although OSA is associated with obesity, significant sleep-disordered breathing is more likely to be the sole cause of elevated BP in relatively lean versus obese individuals. Even minimal degree of sleep-disordered breathing can increase BP and may contribute to hypertension in 5% of hypertensive individuals.[4,5] The association between OSA and hypertension appears to be particularly prominent in patients with resistant hypertension. In one study, OSA was found in 71% of individuals with resistant hypertension, compared with 38% of individuals with controlled systemic hypertension.[6]

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE WITH OBSTRUCTIVE SLEEP APNEA

It is not clear if OSA causes cardiovascular disease or is only associated with cardiac disease, because the 2 conditions share independent risk factors, such as age and obesity. Intermittent hypoxia from OSA causes changes in oxygen concentration, carbon dioxide concentration, and blood pH, resulting in an increase in catecholamine production. Catecholamine production may be further enhanced in response to chronic sleep deprivation. Furthermore, carotid chemoreceptors are stimulated producing a vasomotor center reflex, which with increased catecholamines results in an increase in total peripheral resistance. The cyclic ventilatory pattern of sleep apnea also causes tachycardia and increased venous return, leading to an increase in cardiac output. The combination of increased total peripheral resistance and cardiac output promotes hypertension. The increase in catecholamines and heart rate contributes to tachyarrhythmias and heart failure. In addition to sympathetic excitation, intermittent hypoxia promotes inflammation, oxidative stress, and metabolic dysregulation, all of which promote atherosclerosis, myocardial ischemia, cerebrovascular ischemia, left ventricular hypertrophy, and heart failure.[7]

CLINICAL PRESENTATION OF OBSTRUCTIVE SLEEP APNEA WITH CARDIOVASCULAR DISEASE

Early recognition of the symptoms and signs of OSA is important to initiate treatment before the development of significant cardiovascular disease. Clinical features suggestive of OSA include witnessed gasping during sleep, morning headaches, excessive daytime somnolence, loud snoring, and neck circumference greater than 16 inches (40.6 cm).[8] Screening questionnaires for OSA, such as the Berlin Questionnaire, STOP- Bang Questionnaire, or the Epworth Sleepiness Scale may be helpful, but have varying degrees of accuracy. Features of the physical examination suggestive of OSA include large neck circumference, high body mass index, posterior chin

position (retrognathia), reduced distance and increased angles from the chin to the thyroid cartilage, narrow oropharyngeal opening (pharyngeal crowding), macroglossia, chronic nasal or sinus congestion (eg, by trans-illumination), and a deviated nasal septum. Twenty-four–hour ambulatory BP monitoring may be done to assess for changes in the pattern of BP. Normally, there is a 10% to 20% decrease in sleep BP compared with wake BP (dip). Individuals with OSA typically have an absent dip or paradoxic increase (reverse dip) in sleep period BP (Fig. 1). The definitive diagnosis is made by polysomnography, a sleep study that may be performed in a sleep laboratory or at home. These studies quantify the amount of apneic events in which there is complete obstruction of airflow for at least 10 seconds, as well as the number of hypopneic episodes, in which there is partial obstruction of airflow with oxygen desaturation of at least 3% lasting for 10 seconds or more. By measuring these events, an apnea-hypopnea index is calculated by adding all apneas and hypopneas and then dividing by total sleep time. An apnea-hypopnea index of 15 or more events per hour, or 5 or more events per hour in the presence of symptoms or cardiovascular comorbidities, is diagnostic for OSA.[7] An example of an apneic event during polysomnography is illustrated in Fig. 2.[9]

IMPACT OF TREATMENT OF OBSTRUCTIVE SLEEP APNEA ON CARDIOVASCULAR DISEASE

Lifestyle modifications may be considered the initial treatment for mild OSA. Obesity results in fatty deposits around the neck, which contribute to pharyngeal collapse.

Weight loss may decrease critical closing pressures of the airway and be curative for some individuals, but is very difficult to achieve and maintain. Behavioral therapy

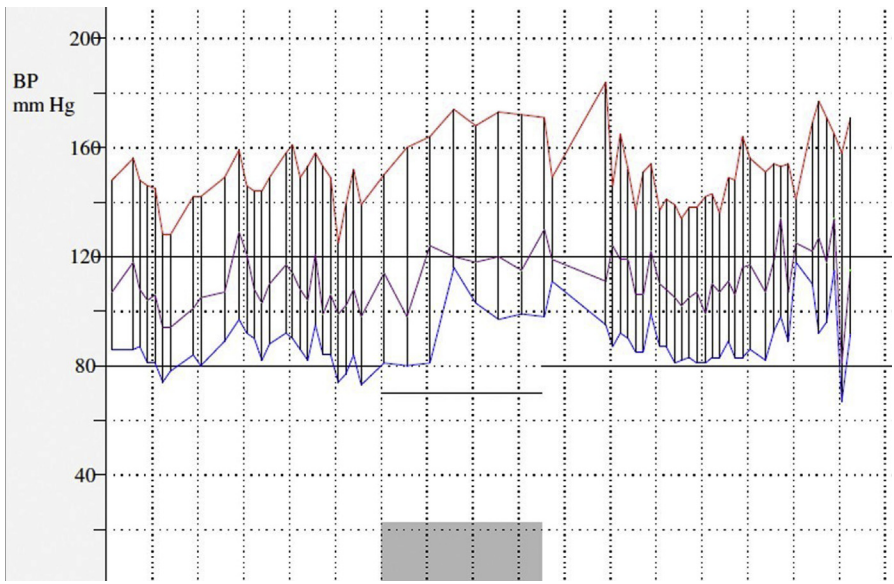

Fig. 1. Plot of BP from 24-hour ambulatory BP monitor with BP in millimeters on the vertical (y-axis) and time on the horizontal (x-axis). The sleep period is represented by a gray rectangle on the x-axis. Each systolic, mean diastolic BP reading is connected by a vertical line. Mean wake period BP is 150/88 ± 12/10 mm Hg. Mean sleep period BP is 166/94 mm Hg ± 9/14 mm Hg. This is a paradoxic BP response or reverse dip.

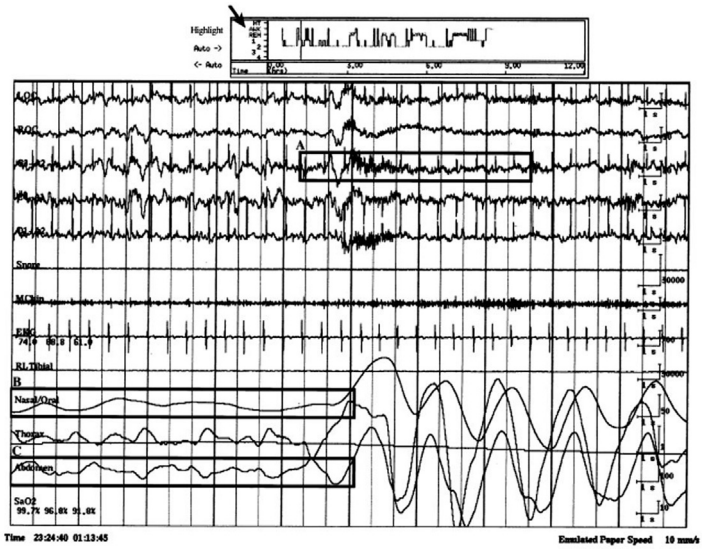

Fig. 2. The upper box (*arrow*) summarizes the total sleep pattern from midnight (0.00 hour) to 9:00 AM (AWK = awake, REM = rapid-eye movement, and sleep stages 1–4). The frequent spikes indicate a disruptive sleep pattern. The vertical line between 0.00 hour and 3:00 AM is detailed in the figure (1:13 AM). It is represented in the first 5 lines by electroencephalogram (EEG) tracings, followed by the nasal/oral airflow tracing, the thorax and abdomen motion tracings, and the oxygen saturation measurements in the lower left corner of the illustration. The nasal/oral airflow tracing shows significant absence of airflow in the boxed region labeled B. There is also paradoxic motion of the abdomen as compared with the motion of the thorax (illustrated in box C). These findings indicate obstructive airflow. Oxygen saturation decreases from 99.7% to 91.8%. Immediately after this period is a sudden increase in airway movement on the nasal/oral tracing with concomitant arousal signals on the EEG tracings (illustrated in the box labeled A). The abdominal and thoracic movement tracings are now synchronized. Over the course of this polysomnography, 68 of these apneic episodes were recorded.

includes avoidance of alcohol before going to sleep, avoidance of sedative use, avoidance of sleep deprivation, and sleeping in a lateral position, thus avoiding the supine position, in which upper airway obstruction occurs most commonly. Mandibular advancement devices hold the mandible slightly down and forward relative to the natural, relaxed position and this results the tongue being farther away from the back of the airway. This may relieve apnea or improve breathing for some individuals. One meta-analysis of 51 studies of patients with hypertension and OSA reported that compared with patients on placebo or not receiving therapy, mandibular advancement devices were associated with a small, but significant reduction in both systolic BP and diastolic BP to levels similar to what is seen with continuous positive airway pressure (CPAP).[10] CPAP remains the first-line treatment for OSA. Randomized trials and meta-analyses have found that effective treatment of OSA using CPAP reduces BP, regardless of whether the patients are hypertensive at baseline. However, the reduction in systemic BP due to positive airway pressure therapy is usually small. In a 2014 meta-analysis that included 30 randomized trials and more than 1900 patients, CPAP therapy was associated with a mean net lowering in systolic BP of 2.6 mm Hg.[11] The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines indicate in adults with hypertension and OSA, that the effectiveness of

CPAP to reduce BP is not well established.[12] The BP lowering effect of CPAP may be less than that observed with antihypertensive medication. In a randomized crossover trial of 23 patients with both untreated hypertension and untreated OSA, antihypertensive medication (valsartan 160 mg per day) lowered mean 24-hour BP significantly more than CPAP therapy (−9.0 vs −2.1 mm Hg).[13] In another small randomized clinical trial, spironolactone reduced the severity of OSA and reduced BP in individuals with resistant hypertension and with moderate-to-severe OSA. Thirty patients were enrolled in a prospective, randomized, open trial, with 15 in the treatment group, receiving 20 to 40 mg daily of spironolactone in addition to their usual antihypertensive therapy and 15 receiving usual therapy. After 12 weeks of follow-up, apnea-hypopnea index, hypopnea index, oxygen desaturation index, clinical BP, ambulatory BP, and plasma aldosterone level were reduced significantly in the spironolactone-treated group compared with the control group.[14] This study suggested a potential role for spironolactone not only as a treatment for hypertension, but also as a treatment for OSA. Observational data suggest that treatment of OSA with positive airway pressure may reduce the incidence of cardiovascular events, including events related to coronary artery disease; however, this has not yet been confirmed by randomized clinical trials.[15] In one multicenter randomized trial of 725 patients with moderate-to-severe OSA, but no history of cardiovascular events, randomly assigned to receive CPAP therapy or no active intervention, there was no significant difference in the rate of systemic hypertension or cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina/arrhythmia, or cardiovascular death) after a median follow-up of 4 years.[16] Surgical approaches to OSA include uvulo-palato-pharyngoplasty (UPPP) and genio-glossal/mandibular advancement in adults, and tonsillectomy/adenoidectomy in children. UPPP is often ineffective, with up to 50% recurrence rate of OSA in 2 years. This procedure should be used only as a last resort except in patients with severe, specific craniofacial abnormalities.[17] Bariatric surgery in obese patients with OSA may result in improvement in more than 75% of patients and a remission rate of 40% after 2 years.[18]

ELECTROPHYSIOLOGICAL EFFECTS OF OBSTRUCTIVE SLEEP APNEA

Atrial Fibrillation and Obstructive Sleep Apnea

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population with a prevalence of 1% to 2%.[19,20] The prevalence increases with age to more than 30% of individuals older than 80 years.[21,22] AF carries significant morbidity, mortality, and health care costs. OSA is exceedingly prevalent in patients with AF.[23] Adults with OSA have almost 2 to 4 times increased risk of developing AF.[24] Similarly, adults with AF have a high prevalence of OSA reported in some trials up to 39%.[25–27] As noted previously with respect to hypertension, OSA may not be the cause of AF in all of these individuals. Their coexistence may in part be due to common risk factors, including advanced age, obesity, diabetes, hypertension, and structural heart disease. The relationship between AF and OSA is multifactorial; however, there may a direct causal relationship that is mutually perpetuating. A significant independent association between the 2 disorders exists.[28] This includes sympathetic and parasympathetic system regulation and cardiac electrical and structural remodeling, particularly of the atria, as shown in **Fig. 3**.[29–31]

During an apneic episode, when there is collapse of the pharyngeal airway leading to interruption of ventilation, vagal efferent output is enhanced, which leads to transient bradycardia as well as a shortened atrial effective refractory period. Episodic hypoxemia during sleep apnea in animal models results in surges of the sympathetic

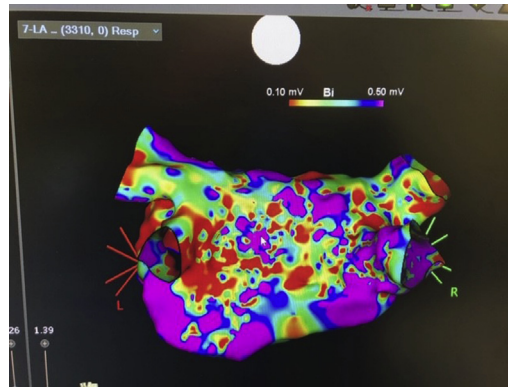

Fig. 3. The posterior wall of the left atrium in a patient with OSA presenting for an AF ablation. There are patchy areas of low voltage as shown by the shades of red and yellow compared with the purple areas of normal voltage.

nervous system, thus reducing the induction threshold for AF.[32] However, the pathophysiology is beyond just neurohormonal activation. Sympathetic ganglion blockade provides only incomplete protection against AF associated with apnea.[33–35] There is also electrical and structural remodeling of atrial tissue due to stretch mediated shortening of atrial refractoriness with resultant susceptibility to excitatory stimuli. Furthermore, collagen deposition and changes in gap junction function have been described in individuals with OSA.[36,37] Repetitive apneic episodes resulting in exaggerated changes in intrathoracic pressure lead to left atrial dilatation and fibrosis.[38,39] Electrophysiology studies of these atria in patients with OSA show areas of slow conduction, reduced atrial electrogram amplitude, and complex fractionated atrial electrograms, correlating with the electrical remodeling, as shown in **Fig. 3**. Atrial electrical remodeling, structural remodeling, and neuro-hormonal activation during apneic episodes provide the milieu for the induction of AF.[36,37] Treatment of AF is more difficult in patients with OSA. In the ORBIT-AF trial, patients with OSA had significantly worse symptoms and were more likely to be on rhythm control therapy.[40] Individuals with OSA had more episodes of recurrent AF, even after catheter ablation.[41–44] Treatment of OSA is indispensable for proper management of AF and maintenance of sinus rhythm. The cohort of patients treated with CPAP in the ORBIT-AF trial were less likely to progress to persistent AF compared with those not treated with CPAP.[11] In addition, other trials have shown less AF after catheter ablation in those patients with OSA treated with CPAP compared with a 57% risk of recurrence of AF in those not treated with CPAP.[43]

Current guidelines recommend treating OSA with CPAP for rhythm control of AF, particularly after catheter ablation. It is especially important in diagnosing and treating suspected OSA in any patient who presents with symptomatic AF and is a candidate for ablation.[45] Suspected OSA should be evaluated in those individuals with drug-refractory AF and those with recurrent AF after cardioversion or catheter ablation.

Premature Ventricular Contractions, Nonsustained Ventricular Tachycardia, and Obstructive Sleep Apnea

Most studies focus on the relationship of AF with OSA. However, there is an increasing body of evidence linking OSA with ventricular arrhythmias (VAs), particularly premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia

(NSVT). VAs have been reported in up to two-thirds of patients with OSA.[46–48] VAs are more common during apneic episodes.[49–51] The mechanisms are similar to those causing the induction of AF in adults with OSA. As with AF, neurohormonal changes, such as enhanced parasympathetic activation during, and sympathetic surges create the arrhythmogenic substrate necessary for VAs.[48] Exaggerated intrathoracic pressure changes cause myocardial stretch, leading to the structural changes in the ventricles similar to the atria. Increased systemic inflammation and endothelial dysfunction from repetitive apneic episodes may directly trigger VAs. These mechanisms also lead to hypertension, ventricular hypertrophy, myocardial fibrosis, ventricular dysfunction, and coronary artery disease, all of which may further predispose these patients to arrhythmia.[52] The frequency of PVCs correlates with the degree of sympathetic tone during waking hours. PVC frequency decreases during normal rapid-eye movement (REM) sleep. Thus, sympatho-vagal balance plays a role in the frequency of PVCs in adults with OSA.[53] NSVT may also be seen with OSA; however, not to the same degree as with PVCs. Abe and colleagues[54] showed that PVCs are more frequent in the more severe forms of OSA. NSVT, however, is not consistently more common in patients with OSA. One study by Mehra and colleagues[55] did find NSVT to be more common in individuals with sleep-disordered breathing (SDB). However, PVCs and OSA have a stronger link. Furthermore, Koshino and colleagues[56] found that 51% of individuals with idiopathic PVCs without heart failure were found to have OSA. This strengthens the idea that of all the VAs, PVCs were more clearly associated with OSA. Other VAs do occur. A study of intracardiac defibrillator (ICD) therapy, including shocks and antitachycardia pacing, in patients with SDB found that VAs were more common during apnea/hypopnea than with normal breathing.[57,58] The presence of SDB was an independent predictor of ICD therapy and the severity of OSA correlated with an increased risk of VAs.[59]

Sudden Cardiac Death and Obstructive Sleep Apnea

In 2005, a study by Gami and colleagues[60] looked at the association of OSA and sudden cardiac death (SCD). The investigators reviewed the death certificates of 112 people who died during sleep and found that 46% of those who died between midnight and 6 AM had OSA. In 2013, a longitudinal study of 10,000 patients found that VAs were not the sole cause of death in patients with OSA. Acute myocardial infarction and pulmonary embolism were also included.[61]

SINUS NODE DYSFUNCTION, ATRIOVENTRICULAR BLOCK, AND OBSTRUCTIVE SLEEP APNEA

Sinus node dysfunction and atrioventricular (AV) block have been linked to patients with OSA. The mechanism is similar to that attributed to AF and VAs, involving electrical and structural remodeling of the myocardial tissue. Fibrosis and dilation of the atria provoke areas of low voltage and slow conduction, resulting in sinus node dysfunction and AV block. Simantirakis and colleagues[62] reported a 22% prevalence of bradycardia with significant pauses on implantable loop recorders in patients with OSA. An observational study by Garrigue and colleagues,[63] showed a 59% prevalence of undiagnosed OSA in patients with permanent pacemakers. Becker and colleagues, found AV block and sinus arrest in 30% of patients with OSA.[64]

There is currently no conclusive evidence that connects the prevalence or severity of electrophysiological effects, including AF, VAs, heart block, and SCD with the treatment of OSA. However, there have been observational trials suggesting that CPAP is an effective strategy in limiting the arrhythmogenic complications of OSA. Larger

prospective trials are needed to firmly establish the true role of CPAP in limiting the electrophysiological sequelae of OSA.

CLINICS CARE POINTS

- OSA may be a cause of resistant hypertension.
- OSA is a contributing factor in patients with atrial fibrillation, PVCs and NSVT.
- OSA may be diagnosed with polysomnography.
- OSA may cause a blunted or paradoxical increase in sleep BP.
- Spironolactone may provide benefit for OSA independent of BP lowering effect.
- Treatment of OSA with CPAP may help lower BP, and help maintain sinus rhythm in patients with atrial fibrillation.

DISCLOSURE

The authors have nothing to disclose

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