Atrial fibrillation in obstructive sleep apnea

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Abstract

Atrial fibrillation (AF) is a common arrhythmia with rising incidence. Obstructive sleep apnea (OSA) is prevalent among patients with AF. This observation has prompted significant research in understanding the relationship between OSA and AF. Multiple studies support a role of OSA in the initiation and progression of AF. This association has been independent of obesity, body mass index and hypertension. Instability of autonomic tone and wide swings in intrathoracic pressure are seen in OSA. These have been mechanistically linked to initiation of AF in OSA patients by lowering atrial effective refractory period, promoting pulmonary vein discharges and atrial dilation. OSA not only promotes initiation of AF but also makes management of AF difficult. Drug therapy and electrical cardioversion for AF are less successful in presence of OSA. There has been a higher rate of early and overall recurrence after catheter ablation of AF in patients with OSA. Treatment of OSA with continuous positive airway pressure has been shown to improve control of AF. However, additional studies are needed to establish a stronger relationship between OSA treatment and success of AF therapies. There should be heightened suspicion of OSA in patients with AF. There is a need for guidelines to screen for OSA as a part of AF management.

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Key words: Atrial fibrillation; Obstructive sleep apnea; Cardioversion; Ablation; Anti-arrhythmic medications

Core tip: Obstructive sleep apnea (OSA) has been linked with the initiation and progression of atrial fibrillation (AF). Patients with OSA have lower success with therapies for AF. Continuous positive airway pressure has been shown to be effective in treatment of OSA and there is some evidence suggesting its role in improving AF control in patients with OSA. In this article, we review and discuss the available data explaining the potential pathophysiological mechanisms linking OSA and AF as well as the therapeutic and prognostic implications of the presence of OSA in AF patients.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its prevalence has increased significantly in past three decades[1-3]. Hypertension, thyroid disease, coronary artery disease, cardiomyopathy and structural heart diseases are conventionally associated with high risk of AF[4-6]. Recently, a high prevalence of obstructive sleep apnea (OSA) has been noted among patients with AF indicating that OSA might be contributing to initiation and progression of AF[7-9].

OSA is a relatively common disorder and the prevalence of sleep apnea has been noted to be as high as 16% among men and 5% among women between 30 and 65 years old. OSA is characterized by repetitive episodes of complete or partial upper airway obstruction followed by arousal from sleep. A diagnosis of OSA is made when it is found that patients have an apnea-hypopnea index (AHI) of >5 events per hour.”

OSA is often associated with cognitive impairment and lower quality of life. It has also been linked with a higher risk of cardiovascular disease including stroke and AF. A recent meta-analysis showed a 2.5-fold increase risk of AF in patients with OSA[10]. This increased risk of AF among patients with OSA is independent of age, gender and body mass index. However, the mechanism behind this association is not well understood.

The pathophysiological link between OSA and AF is not well understood. Findings from animal models and clinical observations suggest a potential role of OSA in the initiation and progression of AF. This is supported by findings that patients with OSA are more likely to develop AF in the long term and that OSA is an independent risk factor of AF in patients with a concomitant atrial structural abnormality[11].

There is also evidence suggesting that OSA impacts the atrial electrophysiology by changing the atrial effective refractory period, promoting atrial discharges and atrial dilation. This might be due to autonomic instability and wide swings in intrathoracic pressure in OSA. OSA patients often have lower systolic and diastolic blood pressure and a lower heart rate variability, suggesting an autonomic imbalance[12]. Intermittent upper airway obstruction in OSA patients is associated with repetitive episodes of apnea and hypopnea which can result in hemodynamic instability and systemic hypoxic and hypercarbic episodes. These can potentially lead to increased sympathetic activity and depressed parasympathetic tone. OSA patients also tend to have reduced inspiratory and expiratory flow rates which can lead to fluid accumulation in the lower and middle third of the thoracic cavity and increased atrial pressure. This can contribute to atrial dilation and atrial discharges[13].

Intrathoracic pressure is also a critical determinant for atrial function. This is due to the following reasons:

1. Intrathoracic pressure affects atrial filling during diastole.
2. Intrathoracic pressure affects atrial emptying during systole.
3. Intrathoracic pressure affects atrial pressure and volume.
4. Intrathoracic pressure affects atrial electrical activity.

The effects of intrathoracic pressure on atrial function are complex and depend on the magnitude and duration of pressure changes. Atrial function is also affected by other factors such as atrial size, atrial stretch, atrial remodel, atrial conduction, atrial automaticity and atrial electrical coupling. These factors can be influenced by intrathoracic pressure.

In summary, OSA has been linked with the initiation and progression of AF. OSA patients have lower success with therapies for AF. Continuous positive airway pressure has been shown to be effective in treatment of OSA and there is some evidence suggesting its role in improving AF control in patients with OSA. In this article, we review and discuss the available data explaining the potential pathophysiological mechanisms linking OSA and AF as well as the therapeutic and prognostic implications of the presence of OSA in AF patients.
years of age\[8\]. Five percent of adults have undiagnosed sleep apnea\[7\]. OSA is even more common among patients with cardiovascular disorders and is associated with multiple autonomic and metabolic derangements. Sleep apnea has been implicated in pathogenesis of multiple cardiovascular disorders including arrhythmias, hypertension, heart failure and stroke\[4-9\]. Its modifiable nature and high prevalence makes it a potential therapeutic target. In this article, we review and discuss the available data explaining the potential pathophysiological mechanisms linking OSA and AF, as well as the therapeutic and prognostic implications of the presence of OSA in AF patients.

OSA is characterized by episodes of nocturnal hypoxemia secondary to diminished and/or interrupted airflow during sleep. Apneic episodes are defined by complete cessation of airflow for ≥ 10 s, while hypopnea episodes are characterized by either ≥ 30% reduction in airflow and ≥ 4% reduction in blood oxygen saturation from baseline for at least 10 s or 50% reduction in air flow and ≥ 3% reduction in oxygen saturation from baseline for at least 10 s or arousal from sleep. It can be categorized as central (absence of inspiratory effort), obstructive (intermittent airway obstruction with preserved/increased respiratory efforts) or mixed sleep apnea (combination of central and OSA). Several easy to use questionnaires have been developed to screen patients for sleep apnea including the Epworth Sleepiness scale\[10\], the Berlin Questionnaire\[11\], the STOP and STOP-BANG Questionnaires\[12\]. Overnight polysomnography is the gold standard test to diagnose and stratify sleep apnea based on the apnea/hypopnea index (AHI)\[13-14\]. OSA is defined as five or more episodes of apnea and hypopnea per hour of sleep (AHI ≥ 5) and can be classified as mild (AHI 5-15), moderate (AHI 16-30), or severe (AHI > 30)\[15\].

**EPIDEMIOLOGY**

Obesity, OSA and AF have a multifaceted relationship. Obesity increases risk of OSA and is also an independent risk factor for development of AF. The risk of AF increases by 4% for every one-unit increase in body mass index (BMI)\[16-18\]. This association is stronger for patients aged < 65 years\[19\]. Sleep apnea (both central and OSA) is more common in patients with congestive heart failure (CHF), and CHF itself is associated with high risk of AF\[20-23\]. Hence, several confounders must be taken into consideration while analyzing the multidimensional relationship between AF and OSA.

**AF IN SLEEP APNEA PATIENTS**

The first insight into a potential link between OSA and AF came from an observational study which reported four times higher prevalence of AF in patients with sleep apnea vs those without sleep apnea (4.8% vs 0.9%)\[24\]. High frequency paroxysmal AF and persistent AF are both associated with presence of OSA\[27\]. The episodes of AF and nonsustained ventricular tachycardia have been noted to be significantly higher during the night after apneic episodes, an observation that further supports the temporal association between AF and sleep apnea\[28\]. Sleep apnea is also an independent predictor for occurrence of postoperative AF among coronary artery bypass surgery patients. In a study by Mooe et al\[29\], the rate of postoperative AF was significantly higher (32% vs 18%) among patients with OSA (AHI ≥ 5) compared to those without OSA.

**SLEEP APNEA IN AF PATIENTS**

Obstructive sleep apnea is more prevalent among patients with AF than the general population. Gami et al\[4\] reported significantly higher prevalence (49% vs 32%) and a strong association (adjusted odds ratio of 2.19) between sleep apnea and AF in patients undergoing electrical cardioversion as compared patients without AF. This association was independent of age, sex, body mass index, hypertension and heart failure. High rates of sleep apnea are seen among patients with chronic persistent and permanent AF even after matching for age, sex and other relevant co morbid conditions\[5\]. The association between AF and sleep apnea may be underestimated, as most studies have reported a strong association between AF and sleep apnea despite using higher (AHI > 15) than standard (AHI > 5) threshold to diagnose OSA.

The association between AF and sleep apnea could be attributed to a higher prevalence of traditional risk factors for AF (especially obesity and hypertension) among OSA patients\[6\]. However, the association between AF and sleep apnea is found to be stronger than that of sleep apnea and traditional risk factors for AF\[4\]. OSA is more prevalent even among younger AF patients with normal left ventricular function\[27\]. This association remains statistically significant even after adjustment for covariates including hypertension, body mass index, and neck circumference. These findings highlight OSA as an independent risk factor for AF.

**PATHOPHYSIOLOGY**

The suspected role of OSA in the pathogenesis of AF is based on sound physiological observations (Figure 1). OSA is characterized by repeated episodes of nocturnal hypoxemia. Intermittent hypoxemia causes mitochondrial dysfunction by altering redox state of cytochrome oxidase and results in repetitive oxidative stress\[30-33\]. Hypoxemic episodes induce transcription factors like nuclear factor kappa-B leading to increased production of inflammatory cytokines such as tumor necrosis factor α and interleukin 6. These cytokines, in concert with increased oxidative stress, lead to endothelial dysfunction, insulin resistance, hypercoagulability, and adverse myocar-
Hypoxemic episodes induce sympathetic surges leading to vasoconstriction, hypertension and tachycardia, and ultimately increased myocardial oxygen demand. This increased stress on myocardium results in adverse myocardial remodeling, which is a substrate for cardiac arrhythmias.

Autonomic tone instability seen in OSA also contributes to pathogenesis of AF. Increases in parasympathetic and sympathetic tone are known to trigger AF. During normal sleep afferent inputs from stretch receptors in lung tissue inhibit the paroxysmal parasympathetic discharges that occur during rapid eye movement sleep. These receptors are activated due to lung expansion during normal ventilation. However, in apneic patients this response is attenuated due to pauses in breathing. Uninhibited paroxysmal parasympathetic discharges lead to marked paroxysmal bradycardia. Bradycardia is associated with decrease in atrial effective refractory period (AERP). The reduction in AERP promotes rapid electrical firing from atrial tissue in pulmonary vein ostia, thereby leading to AF. Hypoxemia and hypercapnea associated with apneic episodes promote chronically heightened sympathetic activity. Heightened sympathetic tone induces focal discharges from pulmonary veins, which have high concentration of adrenergic and vagal nerve endings. Hypoxemia may exert an effect on cardiac arrhythmias that is independent and additive of sleep apnea. This hypothesis is supported by increased rates of ventricular ectopy among chronic obstructive pulmonary disease patients who have nocturnal hypoxemia without sleep apnea.

OSA is also associated with sudden and frequent changes in intrathoracic pressures, which are transmitted to thin walled atria and cause atrial stretch. Repetitive stretch may result in atrial enlargement and structural changes in pulmonary vein ostia, predisposing to development of AF.

EFFECT OF OSA ON TREATMENT OF AF

AF patients with OSA respond poorly to both pharmacological and non-pharmacological therapy (cardioversion or ablation) with high rate of recurrence.

Pharmacotherapy
The rate of non-response to pharmacologic treatment increases with the increase in OSA severity. Apneic patients have higher awake and nocturnal sympathetic tone, which may explain the suboptimal response to rate control strategy in AF patients with OSA. Autonomic tone instability contributes to the genesis and propagation of AF in OSA. Acetylcholine-dependent potassium channels are thought to be one of the most relevant components by which vagal tone induces AERP shortening in the atrium. Antiarrhythmic drugs such as amiodarone, which block acetylcholine-dependent activation of $I_{K_{ACh}}$, along with beta-receptors and other potassium channels, could be superior in maintaining sinus rhythm over those antiarrhythmic drugs that do not block $I_{K_{ACh}}$. However, studies showing superiority of amiodarone did not specifically address AF patients with sleep apnea. The clinical efficacy of such pharmacotherapy in patients with OSA needs to be investigated in future clinical trials.

Direct current cardioversion
Kanagala et al. followed 118 patients after direct current cardioversion (for AF/atrial flutter) and found that the presence of polysomnography-established OSA was associated with significantly higher rates of recurrent AF. Increased risk among patients with OSA was independent of age, sex, body mass index, hypertension, diabetes, echocardiographic parameters or antiarrhythmic therapy. Patients with OSA who were treated appropriately with continuous positive airway pressure (CPAP) had 82% lower rate of recurrence than patients who did not receive treatment.
AF ablation

The presence of OSA is associated with a high rate of recurrent AF after ablation. In a retrospective study, Jongsangsim et al. reported presence of OSA as a strong predictor of AF recurrence after radiofrequency catheter ablation. This risk was independent of atrial size and body mass index. Chilukuri et al. reported high rates of recurrence after catheter ablation among patients who were classified as high risk for OSA on Berlin questionnaire. Tang et al. classified 178 patients into high risk and low risk for OSA depending on Berlin questionnaire and prospectively followed them for 11 mo after pulmonary vein isolation. They reported no statistically significant difference in the rate of AF recurrence among patients with different risk profiles for OSA at the end of the follow up period. These patients were classified in different risk categories for OSA based on Berlin questionnaire, but no confirmatory test was performed to establish diagnosis of OSA. Thus, misclassification bias cannot be excluded. Mattiello et al. overcame this limitation; they prospectively followed 174 patients after circumferential pulmonary vein isolation and classified them as low or high risk for OSA on Berlin questionnaire. High-risk patients underwent a sleep study to diagnose OSA and classify its severity. OSA was an independent predictor for AF recurrence after ablation, and risk of recurrence increased with increasing severity of OSA. Naruse et al. prospectively studied 153 patients who underwent pulmonary vein isolation for drug refractory AF. The standard overnight polysomnographic evaluation was performed one week after ablation, and the total duration and the number of central or OSA or hypopnea episodes were examined. Of 153 patients, 116 patients were identified as having OSA. Eighty-two patients with OSA underwent CPAP therapy as 34 patients with OSA refused CPAP therapy. Data regarding the use of CPAP and recurrences of AF were obtained in all patients. During a mean follow-up period of 18.8 ± 10.3 mo, 51 (33%) patients experienced AF recurrences after ablation. A Cox regression analysis revealed that the left atrial volume (HR = 1.11; 95%CI: 1.01-1.23; P < 0.05), concomitant OSA (HR = 2.61; 95%CI: 1.12-6.09; P < 0.05), and usage of CPAP therapy (HR = 0.41; 95%CI: 0.22-0.76; P < 0.01) were associated with AF recurrences during the follow-up period.

Available evidence supports the role of effective OSA therapy in reducing the risk of AF recurrence. The exact mechanism by which CPAP use improves success of AF therapies in OSA is not clear. The use of the CPAP may reduce the structural and electrical remodeling of the atria due to OSA, resulting in a lower AF recurrence rate. Serum markers of oxidative stress and free radical production predict AF recurrences after AF ablation. CPAP therapy has been known to decrease oxidative stress in OSA. An improvement in the oxidative stress by using CPAP could help attenuate the risk of recurrent AF.

However, currently available data is not robust, and supporting studies have small sample size and several limitations. CPAP therapy is known to be associated with a reduction in preload. Its use in patients with systolic heart failure and AF may compromise diastolic ventricle filling, which is already compromised due to loss of organized atrial contraction. Hence careful patient selection is warranted. Further data from prospective randomized control trials is needed before advocating widespread use of CPAP in patients with systolic heart failure and AF.

CONCLUSION

Several observational studies have indicated a high prevalence of OSA among patients with AF. Concomitant OSA is associated with poor response to treatment for AF. Limited data indicate that treatment of OSA results in a lower rate of AF recurrence. Patients with AF may be screened for OSA with a simple tool such as Berlin questionnaire, and high-risk patients should be considered for formal sleep study. The educational, behavioral and therapeutic interventions for sleep apnea should be offered to AF patients with OSA.

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