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Review

Obstructive sleep and atrial fibrillation: Pathophysiological mechanisms and therapeutic implications

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ABSTRACT

Atrial fibrillation (AF) is the commonest arrhythmia in clinical practice and is associated with increased cardiovascular morbidity and mortality. Obstructive sleep apnea (OSA), a common breathing disorder, is an independent risk factor for AF. Several pathophysiological mechanisms, including apnea-induced hypoxia, intrathoracic pressure shifts, sympathovagal imbalance, atrial remodeling, oxidative stress, inflammation and neurohumoral activation have been implicated in the occurrence of AF in OSA patients. In addition, OSA has been shown to reduce success rates of antiarrhythmic drugs, electrical cardioversion and catheter ablation in AF. Effective prevention of obstructive respiratory events by continuous positive airway pressure ventilation (CPAP) reduces sympathovagal activation and recurrence of AF. The present review describes the relationship between OSA and AF, presents the pathophysiological mechanisms implicating OSA in AF occurrence, and provides an update of the potential therapeutic interventions for patients with OSA and AF.

1. Introduction

AF is the commonest arrhythmia, occurring in 1–2% of the general population [1]. In the modern era, AF constitutes a major cardiovascular challenge, as it is associated with increased rates of death [2,3], stroke [4] and thromboembolic events, heart failure [5] and hospitalizations. The prevalence of OSA is substantially higher among patients with AF, strongly indicating that OSA may be contributing to the initiation and perpetuation of the arrhythmia [6,7]. The severity of OSA, as measured by nocturnal oxygen desaturations, has been found to correlate to the prevalence of AF [8]. Several pathophysiological mechanisms, including apnea-induced hypoxia, intrathoracic pressure shifts, sympathovagal imbalance, atrial remodeling, oxidative stress, inflammation and neurohumoral activation have been implicated in the occurrence of AF in OSA patients [9]. The relationship between OSA and AF might be even more relevant considering the role of obesity as a common mediating epidemiological and causal link [10]. This review presents the association between OSA and AF, describes the pathophysiological mechanisms implicated in AF occurrence in OSA patients and highlights the emerging therapeutic interventions for patients with OSA and AF.

2. Obstructive sleep apnea: definition and diagnosis

Obstructive sleep apnea is characterized by recurrent episodes of partial or complete upper airway collapse during sleep, that is highlighted by a reduction in - or complete cessation of - airflow despite documented ongoing inspiratory efforts [11]. A hypopneic episode should meet one of the following criteria: i) >50% reduction in airflow or tidal volume for at least 10 s ii) moderate reduction in airflow (<50%) with arterial oxygen desaturation >3%, or iii) moderate reduction in airflow with electroencephalographic evidence of arousal from sleep [11]. The severity of OSA is measured by the apnea-hypopnea index (AHI), the frequency of apneas and hypopneas per hour of sleep. An AHI ≥5 represents mild OSA, while AHI ≥15 represents moderate to severe OSA [12]. The gold standard method for the diagnosis of OSA is a polysomnographic study that records sleep and breathing in a sleep laboratory overnight [11].

3. Obstructive sleep apnea as a risk factor for atrial fibrillation

Several studies have confirmed the increased incident of AF in OSA patients (Table 1) [6,8,13–26]. The Sleep Heart Study demonstrated that the risk of AF is 4 times bigger in patients with sleep disordered breathing (obstructive and central sleep apnea) compared to patients with no sleep-disordered breathing [14]. Gami et al. showed that for patients with OSA under age 65, the hazard ratio of developing any type of AF over a course of approximately 5 years was 3.29 [15]. In a recent study, Cadby et al. concluded that AHI > 5/h, log (AHI + 1), and log

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(time with oxygen saturation <90% + 1) are independent predictors of incident AF [24]. Conversely, patients with AF appear to be more likely to have OSA compared to the general population [6,27–28]. Approximately half of patients with AF were reported to have OSA after adjusting for body mass index, neck circumference, hypertension (HT), and diabetes mellitus [6]. A high prevalence of sleep disordered breathing has also been demonstrated in a relatively young AF population (mean age 55 years) with normal left ventricular function and no structural heart disease. This result was present in patients with paroxysmal as well as those with persistent AF [27].

4. Pathophysiological mechanisms implicating obstructive sleep apnea in atrial fibrillation occurrence

4.1. Changes in blood gases

OSA induces repeated episodes of hypoxia that trigger chemoreflex and enhance sympathetic nerve activity, leading to tachycardia and blood pressure elevation, especially at the end of the apnoeic episodes [29]. Tachycardia and HT increase myocardial oxygen demand while myocardial oxygen supply is at its lowest level due to hypoxia. This results in repeated myocardial and subsequently atrial ischemia during sleep, thereby promoting AF. Atrial myocardial perfusion abnormalities and coronary flow reserve impairment have been reported in lone AF [30]. In isolated rabbit pulmonary vein preparations, hypoxia followed by reoxygenation has been shown to induce pulmonary vein burst firings [31].

In superfused rabbit atria, hypoxia caused a transient prolongation and an increase in heterogeneity of refractory periods. Moreover, hypoxia caused depressed conduction velocity and a marked increase in inhomogeneity in conduction both leading to increased vulnerability for reentrant arrhythmias [32]. Hypoxia-induced vascular endothelial growth factor (VEGF) expression is strongly regulated by hypoxia-inducible factor-1a (HIF-1a), the transcriptional factor for VEGF, which is a critical modulator for sensing and responding to changes in oxygen concentration [33]. MMP-9 expression increases in fibrillating atrial tissue and may contribute to atrial structural remodeling of AF [34]. It is possible that upregulation of HIF-1a/VEGF is involved in the enhancement of MMP-9 expression under hypoxic conditions [33]. In a recent study, Xu et al. reported increased levels of Toll-like receptor 2 (TLR2), HIF-1a and MMP-9 in patients with persistent and permanent AF, and suggested that TLR2 and HIF-1a may promote left atrial structural remodeling [35].

In another experimental model, isolated hypercapnia resulted in atrial effective refractory period (AERP) prolongation. AERP rapidly returned to baseline, but recovery of conduction was delayed following correction of hypercapnia. Even though AF vulnerability was reduced during hypercapnia, it increased significantly with subsequent return to eucapnia [36].

Table 1
Risk for atrial fibrillation in obstructive sleep apnea patients.

Investigator	Methods of diagnosis for OSA	Results
Mooe et al. (1996) ($n = 121$)	PSG	Risk for AF after CABG in OSA patients (OR 2.8 [95% CI 1.2–6.8])
Gami et al. (2004) ($n = 463$)	BQ	The proportion of patients with OSA was significantly higher in the AF group than in the general cardiology group (49% versus 32%; $p = 0.0004$); association between AF and OSA (OR 2.19 [95% CI 1.40–3.42])
Mehra et al.(2006) ($n = 566$)	PSG	Risk for AF in OSA patients (adjusted OR 4.02 [CI 1.03–15.74])
Tanigawa et al.(2006) ($n = 1763$)	Pulse oximeter	Risk for AF for severe OSA (adjusted OR 5.66 [CI 1.75–18.34])
Gami et al. (2007) ($n = 3542$)	PSG	Incident AF in OSA for patients aged <65 (HR 3.29 [CI 1.35–8.04])
Monahan et al. (2009) ($n = 2816$)	PSG	Risk for AF after a respiratory disturbance compared with normal breathing (OR 17.9 [CI 2.2–114.2])
Mehra et al. (2009) ($n = 2911$)	PSG	Increasing OSA quartile associated with CVE ($p = 0.01$) but not AF
Mungan et al. (2013) ($n = 73$)	BQ and ESS	The prevalence of high score in ESS was higher in POAF group compared to control group (52% vs 27%; p: 0.030). There was a higher prevalence of high risk for OSA in BQ in the POAF group (58% vs 34%; p: 0.044).
Valenza et al.(2014) ($n = 1210$)	PSG	Compared with patients with an AHI <5, patients with an AHI >30 were older and had a higher BMI, a higher rate of hypertension and a higher CHADS2 score than those with AHI <5
Van Oosten et al.(2014) ($n = 277$)	BQ	OSA was found to be a strong predictor of POAF (45.5% vs 29.7%, $p = 0.007$).
Zhao et al. (2015) ($n = 171$)	PSG	OSA was an independent predictor of post-CABG AF (OR 4.4 [CI 1.1–18.1])
Uchôa et al.(2015) ($n = 67$)	PSG	AF was more common in patients with than without OSA (22% vs 0%, $P = 0.0068$)
Wong et al.(2015) ($n = 545$)	1)PSG 2) prior diagnosis of OSA documented by two independent sources 3) prior diagnosis of OSA documented by one source with explicit documentation of whether the patient was using CPAP	Risk for AF after CABG in OSA patients (adjusted HR 1.83 [95% CI: 1.30–2.58])
Cadby et al. (2015) ($n = 6841$)	PSG	After multivariable adjustment, independent predictors of incident AF were apnea/hypopnea index (AHI) >5/h (HR 1.55[CI, 1.21–2.00]), log (AHI + 1) (HR 1.15[CI, 1.06–1.26]), and log (time with oxygen saturation <90% + 1) (HR 1.12 [CI, 1.06–1.19])
Akyüz et al. (2015) ($n = 90$)	PSG	AHI was associated with AF (OR = 1.91[CI, 1.26–3.32])

Pts = patients; OSA = obstructive sleep apnea; AF = atrial fibrillation; *PSG = polysomnogram*; *CABG = coronary artery bypass graft*; *BQ = berlin questionnaire*; *AHI = apnea–hypopnea index*; *HR = hazard ratio*; *OR = odds ratio*; *CVE = complex ventricular ectopy*; *ESS = Epworth Sleepiness Scale*; *BMI = body mass index*; *POAF = postoperative atrial fibrillation*; *CHADS2 = congestive heart failure, hypertension, age, diabetes and prior stroke*.

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