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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*.

4.2. Intrathoracic pressure changes

Ineffective respiratory efforts against an occluded airway result in a precipitous drop in intrathoracic pressure (e.g. −65 mm Hg) with a subsequent increase in afterload and enhancement of venous return which in turn leads to distention of the right ventricle and shifting of the interventricular septum [37]. The combination of increased afterload, interventricular septal shift and impaired left ventricular filling leads to a decrease in stroke volume and a temporary fall in cardiac output [38]. In addition, increased afterload can lead to left ventricular hypertrophy. The Muller maneuver (occluded inspiration), closely simulates the changes in intrathoracic pressure produced during sleep in subjects with OSA [39]. Orban et al. have shown that sudden imposition of severe negative intrathoracic pressure leads to an abrupt decrease in left atrial volume and a decrease in left ventricular systolic performance that reflect the increase in left ventricular afterload [39]. Koshino et al. reported that during the Muller maneuver ventricular longitudinal deformation, as measured by strain and strain rate, was significantly reduced [40]. These changes in left atrial volume and ventricular mechanics may have implications for future development of AF. In a pig model for OSA, negative tracheal pressure (NTP) shortened AERP and enhanced AF inducibility during AERP measurements from 0% at baseline to 90% during NTP [41]. Release of NTP resulted in a prompt restoration of sinus rhythm and AERP returned to normal. NTP induced AERP shortening and AF inducibility were prevented by atropine or vagotomy [41]. By contrast, tracheal occlusion without applied negative tracheal pressure caused comparable changes in blood gases but did not induce ERP shortening or AF inducibility [41]. Obstructive respiratory events also resulted in increased occurrence of spontaneous premature atrial contractions, representing potent triggers for spontaneous AF-episodes in a pig model for OSA and humans [42]. In another experimental model of obesity and acute OSA, forced inspiration-induced acute left atrial distension related to diastolic dysfunction, thereby promoting an arrhythmogenic substrate for AF [43].

4.3. Sympathovagal imbalance

Autonomic changes have been shown to precede the onset of paroxysmal AF [44]. Increased sympathetic tone or decreased parasympathetic tone precede the initiation of paroxysmal AF postoperatively [45], or during sleep [46]. Recurrent nocturnal apneas during sleep in OSA are accompanied by chemoreceptor-induced sympathetic activation and/or decreased parasympathetic tone manifested as impaired vagal input, diminished baroreflex sensitivity and impairment of the parasympathetic components of heart rate variability [47]. Even though decreased parasympathetic activation predominates in severe OSA patients, there is evidence of rare increased parasympathetic activation toward the end of apneas in some. This is supposed to occur as an oxygen conservation reflex (known as the '*diving*' reflex) in response to apnea-induced hypoxia and is mediated through increased vagal tone [8]. Vagal discharge enhances acetylcholine activated K+ current (IKACh), thereby reducing action potential duration and stabilizing reentrant rotors [48]. In experimental models, Ghias et al. induced AF during acute apnea episodes, but inhibited AF inducibility after either autonomic blockade or neural ablation of the right pulmonary artery ganglionic plexus [49].

4.4. Atrial remodeling

Atrial electrical and structural remodeling are critical elements in the pathogenesis of AF [50].

4.5. Electrical remodeling

In a canine model of chronic OSA, upregulation of proteins encoding inward rectifier K+ current (IK1), delayed rectifier K+ current (IKr and IKs), IKACh, transient outward K+ current (Ito) and ultra-rapid delayed rectifier potassium current (IKur), as well as downregulation of protein encoding L-type Ca^{+2} current (ICaL) were found. AF inducibility and duration was increased while AERP was shortened [51].

4.6. Structural remodeling

The repetitive occlusions of the upper airway during sleep generate substantial shifts in intrathoracic pressure that are transmitted from the thorax to the thin-walled atria [37]. These transmural forces are thought to contribute to atrial chamber enlargement, a risk factor for AF [52]. Moreover, it has been suggested that these transmural forces may be important in tissue stretch and remodeling at the pulmonary vein ostia [52], a known focal source of AF [53].

OSA has been shown to be an independent predictor of diastolic dysfunction in several studies [54,55] and the severity of OSA has been correlated with the degree of diastolic dysfunction [54]. Mechanisms contributing to left ventricular dysfunction in the setting of OSA include hypoxia induced pulmonary hypertension, displacement of the interventricular septum leftward during diastole and impaired filling of the left ventricle [56]. Diastolic dysfunction, may lead to an increase in left atrial pressure and size, which are well-demonstrated risk factors for AF.

In addition, there is evidence to suggest that OSA may promote atrial fibrosis. In a murine model, Ramos et al. demonstrated that the presence of OSA was associated with an increase in the expression of angiotensin converting enzyme along with a concomitant decrease in the synthesis of matrix metalloproteinase-2, thereby favouring fibrosis and atrial structural remodeling [57]. In another experimental study, Iwasaki et al. found substantial increases in AF vulnerability, including increased duration and inducibility of AF [58]. Underlying remodeling included atrial conduction slowing, with no changes in atrial refractoriness. Conduction slowing was accompanied by important changes in atrial connexin-43 expression and distribution, along with significant increases in atrial fibrous tissue content [58].

In the clinical setting, the atria of OSA patients are shown to have extensive areas of low voltage or electrical silence and conduction abnormalities as indicated by prolonged P-wave durations, slower atrial conduction velocity and sinus node recovery times [59]. P-wave duration and dispersion are significantly prolonged in patients with OSA compared with controls [59], and correlate positively with the severity of OSA [60]. Similar results were reported by Baranchuk et al., who found a significantly greater incidence of interatrial block (P-wave duration ≥120 ms) in patients with moderate to severe OSA compared with controls, and a positive correlation between the severity of OSA and the maximum P-wave duration [61]. In a recent study, Gaisl et al. reported that intrathoracic pressure swings through simulated OSA increase P-wave duration and P-wave dispersion in healthy subjects and in patients with paroxysmal AF [62]. Atrial electromechanical activation time, as measured by tissue doppler imaging was found to correlate with AHI, reflecting OSA severity, irrespective of other conventional echocardiographic variables [63,64].

Evidence builds a causal role of OSA in HT and its potential role in the pathogenesis of drug-resistant HT [65,66]. HT may facilitate the onset and persistence of AF by stretch-induced changes in the repolarization of atrial myocytes and atrial electrical and structural remodeling [67]. OSA is also a highly prevalent comorbidity of obesity. In obese cohorts, the prevalence of OSA extends up to 90% [68]. Specific clinical conditions including HT, diabetes mellitus, metabolic syndrome, coronary artery disease and OSA link obesity and AF [10]. Moreover, ventricular adaptation, diastolic dysfunction, and epicardial adipose tissue appear to be implicated in atrial electrical and structural remodeling, thereby promoting the arrhythmia in obese subjects [10].

5. Oxidative stress, inflammation and neurohumoral activation

Hypoxia and reoxygenation cycles in OSA cause a change in oxidative balance, leading to the formation of reactive oxygen species capable of reacting with other organic molecules impairing their functions [69]. Thioredoxin, malondialdehyde, superoxide dysmutase, and reduced iron are commonly used biomarkers and show a more consistent relationship between increased oxidative stress and OSA [69]. Noteworthy, reduced polysomnography total sleep time is associated with elevated myeloperoxidase levels and reduced self-reported habitual sleep duration with elevated ox-LDL, suggesting differential up-regulation of oxidative stress in acute versus chronic sleep curtailment [70]. Oxidative stress has been implicated in AF initiation and perpetuation [71]. It is therefore tempting to speculate that OSA related oxidative responses may facilitate atrial remodeling, thereby increasing AF susceptibility.

In addition, long-term OSA was shown to be associated with elevations of circulating markers of inflammation, including C-reactive protein (CRP), intercellular adhesion molecule-1 (ICAM-1), interleukin-8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1) [72–75]. Elevated circulating inflammatory factors, such as CRP or interleukin- 6 (IL-6) have been associated with greater risk of AF, postoperative AF occurrence after coronary artery bypass grafting and AF recurrence after electrical cardioversion or catheter ablation [76].

Plasma angiotensin II and aldosterone have also been found to be elevated in OSA [77]. In an experimental model for OSA, renin angiotensin aldosterone system (RAAS) activation was mainly driven by increased sympathetic activation, and it was completely attenuated by renal sympathetic denervation (RDN) [78,79]. Activation of the systemic and local atrial RAAS with accompanying atrial oxidative stress may result in atrial tissue fibrosis, potentially creating an arrhythmogenic substrate for AF [80–83].

The potential pathophysiological mechanisms for AF occurrence in OSA patients are summarized in Fig. 1.

6. Therapeutic implications

6.1. Continuous positive airway pressure

The gold standard for OSA therapy is CPAP [84]. The positive pressure keeps the pharyngeal area from collapsing and thus helps alleviate the airway obstruction [84]. Muscle sympathetic nerve activity is greatly elevated in patients with OSA during normoxic daytime wakefulness. Continual CPAP treatment seems to be an effective long-term treatment for elevated muscle sympathetic nerve activity likely due to its effects on restoring brainstem structure and function [85,86]. Baroreflex sensitivity, an established index of cardiac sympathovagal balance, is depressed in patients with OSA and CPAP therapy has been shown to increase baroreflex sensitivity [87]. There is also evidence that CPAP therapy in OSA reduces 24 h urinary catecholamine excretion as well as plasma norepinephrine levels, consistent with a reduction in sympathetic nerve activity [87,88]. Moreover, CPAP therapy has been associated with improved renal hemodynamics and down-regulation of renal RAAS activity, suggesting a potential therapeutic benefit for kidney function [89,90]. In contrast to sympathetic activity and RAAS, however, CPAP does not seem to alter inflammatory markers or oxidative stress in OSA [91].

In hypertensive patients with OSA, CPAP has been shown to improve blood pressure [92]. CPAP seems to be more effective in treating resistant than nonresistant HT. A possible explanation is that sympathetic overactivity and altered vascular reactivity in OSA could be more severe in resistant than in nonresistant HT [93]. Both systolic and diastolic abnormalities in patients with OSA can be reversed as early as after 3 months of CPAP therapy, with progressive improvement in cardiovascular remodeling over 1 year [94].

Recent studies have also shown that CPAP reverses atrial remodeling in OSA. 6 months of CPAP therapy significantly improves interatrial, left intraatrial and right intraatrial electromechanical delays, as well as P-wave dispersion in OSA [95]. 12 weeks into CPAP therapy has been

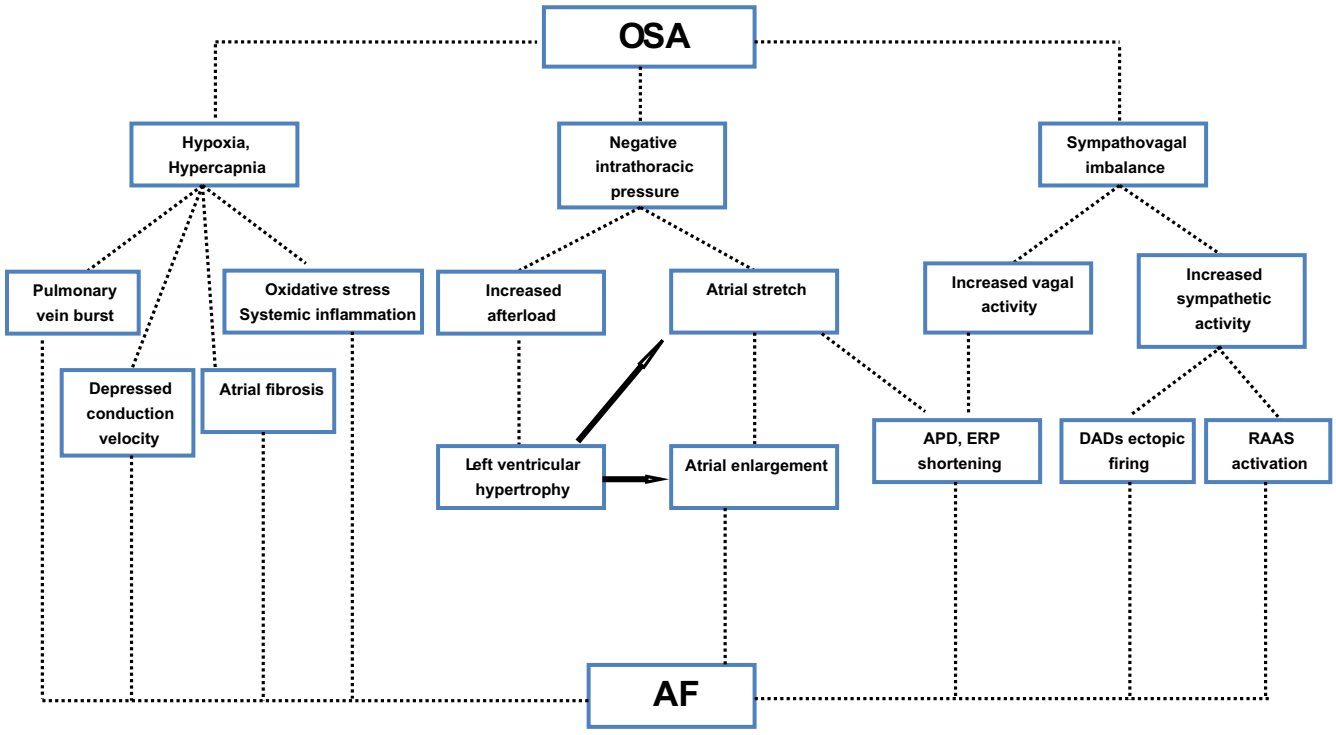

Fig. 1. Pathophysiological mechanisms implicated in atrial fibrillation in obstructive sleep apnea patients.

shown to reverse left atrial volumetric and deformation abnormalities in OSA patients, with progressive improvement in left atrial structural remodeling over 24 weeks, as assessed by conventional and two-dimensional speckle-tracking echocardiography [96]. Neilan et al. reported that in patients with sleep apnea, CPAP therapy is associated with lower blood pressure, atrial size, and ventricular mass [97].

Moreover, CPAP has been shown to decrease the risk of transition from paroxysmal to persistent AF among OSA patients, implying a dynamic interaction between OSA and AF substrate, capable of attenuation by treatment [98]. Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without OSA and appropriate treatment with CPAP is associated with lower recurrence of AF [99,100]. A recent meta-analysis reported that OSA patients treated with CPAP have a 42% decreased risk of AF (pooled risk ratio, 0.58; 95% confidence interval, 0.47 to 0.70; $p < 0.001$) [101]. An inverse relationship between CPAP therapy and AF recurrence was also observed, while benefits of CPAP were stronger for younger, obese, and male patients [101]. However, so far no effects of CPAP on P-wave duration and P-wave dispersion in minimally symptomatic OSA patients have been described [102]. The impact of OSA treatment has been extended to the ablation context and results remain consistent with non-ablation studies [103–110]. In a meta-analysis, Li et al. concluded that patients with OSA have a 31% greater risk of AF recurrence after catheter ablation than patients without OSA, and this risk is increased by 57% in patients with OSA not undergoing CPAP therapy [111]. Noteworthy, CPAP users have a risk of AF recurrence similar to that of patients without OSA [111]. Interestingly, compared to non-OSA patients, OSA-patients not treated with CPAP have an enhanced prevalence of non-pulmonary vein antrum triggers and posterior wall firing, possibly a reflection of atrial electrical and structural remodeling [106]. Another important finding is that CPAP therapy in AF patients with OSA undergoing pulmonary vein isolation has been associated with a higher AF-free survival rate [108].

6.2. Autonomic nervous system modulation

RDN may be a promising new therapy for AF related to hyperactivity of the sympathetic nerves [112]. Several experimental studies have indicated that RDN might be effective in suppressing OSA induced AF. Linz et al. investigated the effects of RDN compared with β-blockade on atrial electrophysiological changes, AF inducibility, and blood pressure during obstructive events and on shortening of AERP induced by high-frequency stimulation of ganglionated plexi in anesthetized pigs and reported that, RDN but not atenolol reduced NTP- induced-AF inducibility and attenuated NTP-induced AERP shortening more than atenolol [113]. In the same model, Linz et al. also reported that RDN inhibits postapneic blood pressure rises and decreases plasma renin activity and aldosterone concentrations [79]. The occurrence and duration of spontaneous AF were reduced comparable with a combined pharmacological blockade of angiotensin receptor and β-adrenoceptor [79]. In the clinical setting, Witkowski et al. reported that RDN lowered blood pressure in patients with refractory HT and OSA, which was accompanied by improvement of sleep apnea severity [114].

Low level vagus nerve stimulation (LLVS) has been shown to prevent AF inducibility by inhibiting major ganglionated plexi [115,116]. In a rabbit model, Gao et al. reported that ERP shortening and AF duration induced by OSA can be suppressed by LLVS at voltages not slowing sinus rate or atrioventricular conduction [117]. Thereby, LLVS may serve as a new therapeutic approach to treat OSA-induced AF.

Low-level baroreceptor stimulation (LL-BRS) has also been shown to suppress NTP-induced AERP shortening and AF inducibility [118]. By contrast, high-level baroreceptor stimulation has been shown to further perpetuate NTP-induced AERP shortening and to increase AF inducibility. These findings support only the use of LL-BRS as a novel therapeutic modality to treat AF in OSA [118].

6.3. Upper airway stimulation

Upper airway stimulation, specifically hypoglossal nerve stimulation, is a new, alternative therapy for patients with OSA who cannot tolerate CPAP, the first-line therapy for symptomatic patients [119]. Based on the available data, particularly the results of the STAR trial, upper airway stimulation therapy has a very favorable risk-benefit profile and is well-positioned as a salvage treatment for patients with moderate-severe OSA [120]. Upper airway stimulation may have a therapeutic role in patients with OSA and AF in the future, but at the moment studies are lacking.

6.4. Weight loss

Growing evidence supports aggressive risk factor modification, especially weight loss, in order to prevent AF and to reduce AF burden and arrhythmia related complications [121–123]. However, so far trials investigating the role of weight reduction in OSA patients with AF are missing.

7. Treatment of obstructive sleep apnea reduces thromboembolic risk in atrial fibrillation

OSA is directly and independently associated with elevated thromboembolic risk in AF. OSA patients have higher CHADS2 and CHA2DS2-VASc scores than patients without sleep disordered breathing [124]. Also, mean CHADS2 and CHA2DS2-VASc scores rise with OSA severity and the differences in the stroke risk are significant even across different age strata, and the trend for point values in CHADS2 and CHA2DS2-VASc scores rises along with OSA severity according to AHI [124]. Yaranov et al. reported that in low-risk AF patients (defined as having CHA2DS2-VASc = 0), the diagnosis of OSA was associated with a risk of stroke increased by 62% [4]. Additionally, the more severe the disease was, as expressed by a higher AHI value, the higher the stroke risk was [4]. The strongest contributors responsible for the elevated thromboembolic risk observed in AF patients with OSA are congestive heart failure, HT, diabetes mellitus, and vascular disease [125]. All those diseases can be consequences of OSA, and they along with the disease itself make the occurrence of stroke or peripheral thromboembolism in AF patients more likely [125]. Therefore, screening AF patients for OSA improves identification of “high risk” patients for thromboembolism [126], while OSA treatment improves thromboembolic risk by attenuating impact of OSA itself and the four diseases mentioned above.

Consequently, AF patients with OSA should be monitored more carefully for stroke risk factors and promptly introduced with anticoagulation therapy if needed. Further studies are needed to decide if OSA carries a risk beyond its most often comorbidities incorporated in the CHADS2 and CHA2DS2-VASc scores and if it should be included in the risk prediction schemes.

8. Conclusion

OSA represents a well-established, but possibly overlooked risk factor for AF. Several pathophysiological mechanisms seem to be implicated in AF occurrence and negatively affect the efficacy of pharmacological and ablative therapy for AF in OSA. CPAP therapy reduces sympathovagal activation and has been shown to decrease the risk of transition from paroxysmal to persistent AF, as well as arrhythmia recurrence. The existing evidence base advocates for screening and treatment of OSA in cases of newly diagnosed AF. Further randomized clinical trials are needed to evaluate the efficacy of autonomic nervous system modulation and risk factors modification in AF occurrence and recurrence in OSA patients, as well as the additive predictive value of OSA indices to AF/stroke risk prediction algorithms. New evidence

may implement the treatment of OSA as a relevant AF antiarrhythmic strategy in the forthcoming guidelines.

Conflict of interest statement

No conflicts of interest to declare.

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