

**EXPERT
REVIEWS**

Obstructive sleep apnea and atrial fibrillation: understanding the connection

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There is a high incidence of atrial fibrillation (AF) in patients with obstructive sleep apnea (OSA). Whether this represents a causative relationship or is merely an association remains to be determined. This review describes the current understanding of pathophysiologic links supporting a causative relationship between OSA and AF. The management of AF with antiarrhythmics, cardioversion and ablation success depends on compliance with OSA treatment. OSA worsens every risk factor resulting in a higher stroke risk in AF patients. Strategies for early screening and compliance with OSA treatment are the need of the hour.

KEYWORDS: atrial fibrillation • management • obstructive sleep apnea • pathophysiology • stroke

Atrial fibrillation (AF) is the most common arrhythmia, and is responsible for one-third of all the arrhythmia-related hospitalizations [1]. AF is estimated to affect between 5 and 15 million people by 2050 [2]. It is estimated that one in four will develop AF over the age of 40 years [3]. AF has been associated with a 1.5–1.9 mortality risk, which stems primarily from increased cardiovascular morbidity and mortality including stroke [4]. The colossal economic burden for AF patients was estimated to be 6.65 billion in 2005 [5].

Obstructive sleep apnea (OSA) affects up to 25% of middle-aged adults [6]. OSA is characterized by repetitive occlusions of the upper airways during sleep. Symptoms include fatigue, daytime sleepiness and snoring. Many patients with OSA may be asymptomatic [7]. The gold standard for diagnosis is overnight polysomnography, where the number of hypopnea and apnea events/hour are noted [7]. The presence of sleep-disordered breathing is defined as five or more episodes of apnea or hypopnea per hour of sleep (apnea–hypopnea index or AHI) in individuals who have excessive daytime sleepiness. Mild, moderate and severe OSA are defined as AHI events >5, 5–10 and >15 events/h, respectively [8]. The most validated treatment for OSA is continuous positive airway pressure

(CPAP). Other options include oral devices and surgery. Strict adherence to the treatment devices leads to considerable improvement in symptoms [9].

OSA is a looming healthcare problem with a high prevalence and tremendous healthcare costs. OSA affects over 15 million people [10], with approximately 20% adults diagnosed with mild OSA and 7% adults with moderate-to-severe OSA [11,12]. An estimated 65–165 billion dollars is used in treatment of moderate-to-severe OSA, which is higher than stroke, heart failure and asthma [13].

The incidence of AF is observed to be three-fold higher in the OSA population compared with the general population [10]. Given the high association of OSA with AF and their associated morbidity and mortality as well as rising healthcare costs, understanding of the relationship between these two disorders is critical. We will review the epidemiological association between OSA and AF, pathophysiologic relationship between these two diseases, the role of OSA in cardiovascular disease and finally the impact of OSA management on AF. For this review, we conducted a non-systematic review of PubMed with the following search terms: ‘obstructive sleep apnea’, ‘atrial fibrillation’, ‘stroke’, ‘cardioversion’, ‘antiarrhythmics’ and ‘ablation’. We also reviewed

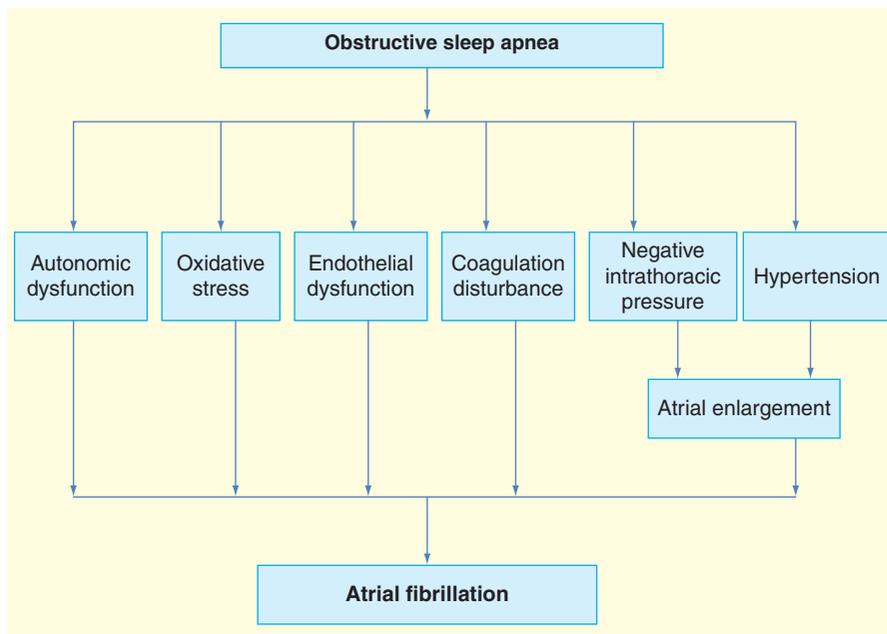


Figure 1. Pathophysiological links between obstructive sleep apnea and atrial fibrillation.

the bibliographies of retrieved articles to examine the published evidence for AF and OSA.

Association of AF & OSA

The earliest studies that suggested a link between OSA and AF were observational population level studies. Guillemainault *et al.* noticed a threefold higher incidence of AF in their OSA patients (prevalence 3% compared with the general population where the incidence is 0.4–1%) [14]. Similarly, the Sleep Health Study showed that there was 4.9% incidence of AF in OSA patients, albeit they did not differentiate between obstructive and central sleep apnea. Gami *et al.* published the first study that established OSA as an independent predictor for AF [2].

Given the presence of AF in up to 50% of OSA patients in some studies, the question is whether OSA is a risk factor for AF. Multiple comorbidities including obesity, diabetes, hypertension, cardiovascular disease and metabolic syndrome are seen in both diseases. This confounds the association versus causality of AF and OSA. At this time, we have considerable evidence linking OSA with AF, OSA severity with increase in AF prevalence and OSA treatment status affecting AF management [15,16]. Also, OSA has been associated with increased incidence of AF in certain subgroups such as patients undergoing coronary artery bypass surgery and patients with congestive heart failure (CHF) [17]. There are several intricate mechanisms, which could link these two diseases (FIGURE 1), and another area of increasing attention is the summation of risk factors conferred by AF and OSA.

Pathophysiologic links between OSA & AF

Autonomic dysfunction in OSA

Chemoreceptor-induced sympathetic activation and diminished baroreflex sensitivity have been described in OSA [2].

Sympathetic activation in OSA patients results from the hypoxia that follows the upper airway obstruction [7]. Repetitive desaturation and reoxygenation activate the carotid chemoreceptors and result in increased basal sympathetic tone. In addition, intermittent hypoxia is to activate atrial catecholaminergic channels. Patients with OSA have elevated levels of plasma and urinary catecholamines consistent with sympathetic activation [18]. Heightened sympathetic activation is critical for the pathogenesis of AF and can contribute to difficult rate control in AF [19].

The effect of OSA on parasympathetic nervous system is a less established link between OSA and AF. While some studies suggest decreased parasympathetic activation [20], other studies report enhanced vagal activation. Several theories for vagal activation have been proposed: negative tracheal pressure, oxygen conservation/diving reflex in response to

the apnea-induced hypoxemia and rapid eye movement [2,10,19]. Bradycardia from vagal activation reduces cardiac conduction period and can predispose to focal electric activation of the pulmonary vein ostia leading to AF [19].

An elegant animal study showed that rapid pacing in dogs with induced apnea lead to AF induction. On ablation of ganglionated plexi adjacent to the pulmonary veins, no further induction of AF was noted in these dogs. This study demonstrated the role of vagosympathetic innervation with sleep apnea on AF, and the critical role of the plexi around the pulmonary veins, a known nidus for AF [21]. Heart rate accelerations and decelerations are used to analyze heart rate variability and heart rate asymmetry architecture. Not surprisingly, patients with severe OSA are noted to have longer runs of acceleration and deceleration [22].

Similar to these observations, the pulmonary vein ostia in humans are densely populated with adrenergic and vagal innervation. These ostia are therefore thought to be the nidus for AF initiation [7,10]. Therefore, the cornerstone of AF management is pulmonary vein ablation.

Reviewing the sympathetic activation and the parasympathetic disturbances noted in OSA and their correlation to AF induction, there is an indisputable link between OSA, AF and dysautonomia (FIGURE 2).

Endothelial dysfunction & coagulation disturbances in OSA

OSA has been strongly linked to endothelial dysfunction, free radical generation and prothrombotic state. The hypoxia, hypercapnia and pressor surges accompanying obstructive apneic events serve as potent stimuli for the release of vasoactive substances. Endothelial dysfunction occurs consistently in patients with OSA [23]. Endothelin, a potent vasoconstrictor, has been noted to

be elevated in untreated OSA patients [24]. Decreased nitric oxide production in OSA patients further increases vessel resistance [25]. Repeated hypoxemia and reperfusion with apneic events leads to increased free radicals in OSA patients [24]. Several coagulation disturbances including high levels of fibrinogen, fibrin degradation products, activated clotting factor VIIA, XIIA, thrombin/antithrombin complexes, platelet activity, D-dimer levels, von Willebrand factor noted in OSA leads to a prothrombotic state [26].

Oxidative stress and endothelial dysfunction have been implicated in AF development. This is thought to occur as a result of ion channel derangement including slow inactivating sodium currents, K channel and L-type calcium channel currents. These channels are implicated in AF initiation and AF perpetuation [26]. Post-coronary artery bypass surgery patients represent a unique population where the link between oxidative stress leading to AF has been well established. Several studies have shown elevated levels of glutathione, reduced levels of vitamin E and ubiquinol post-surgery, which have been implicated in AF development in these patients [26].

It is likely that the oxidative stress in OSA can predispose to AF. OSA treatment with CPAP has been shown to normalize nitric oxide levels, decrease oxidative stress and improve flow-mediated dilatation in the forearm suggesting reversal of endothelial dysfunction [27].

Intrathoracic pressure changes

The obstructive event in OSA patients generates significant negative intra-thoracic pressure up to -65 mmHg. This can be understood by Poiseuille's law: whenever there is a decrease in the radius of a tube, the flow rate of gas can be maintained if there is an increase in the differential pressure [24]. This sets off a vicious cycle, since increasing pressure further reduces the airway leading to complete obstruction.

The generation of high negative intrathoracic pressure can contribute to atrial chamber enlargement and atrial fibrosis, which have been established as risk factors for development of AF [19]. Additionally, these forces can cause remodeling at the pulmonary vein ostia, the nidus for AF [2,19].

Therefore, the atrial enlargement and remodeling of the pulmonary veins noted in OSA are strongly associated with AF development suggesting another strong pathophysiologic link between these two diseases.

OSA & hypertension

Hypertension is a well-established consequence of OSA. The sympathetic activation in OSA predisposes to hypertension,

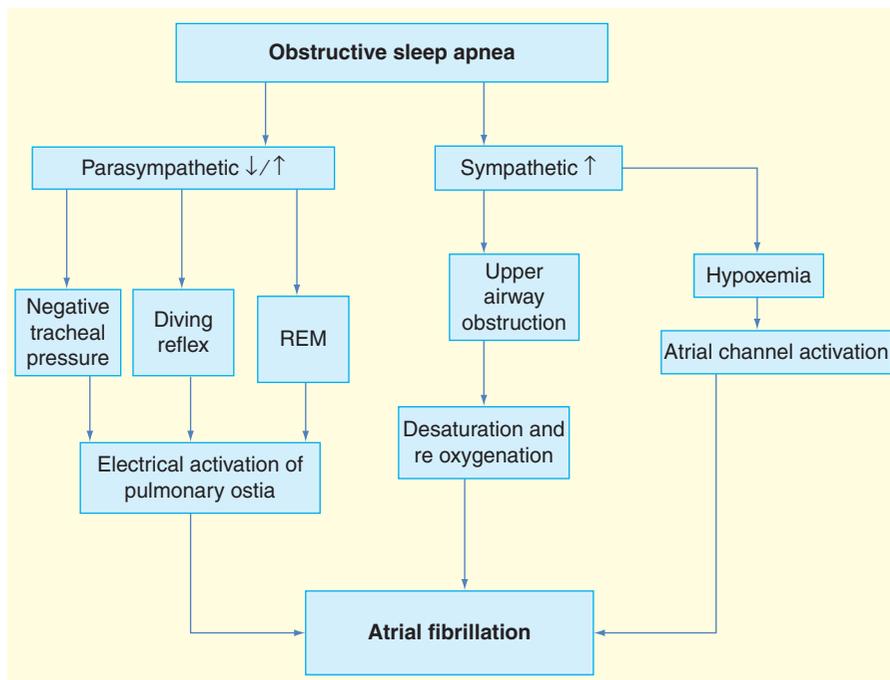


Figure 2. The association of obstructive sleep apnea, atrial fibrillation and dysautonomia.

REM: Rapid eye movement.

which leads to diastolic dysfunction, a common cardiac abnormality in OSA patients [28–30]. Diastolic dysfunction leads to increased left atrial size, which can predispose to AF [31,32].

The relation between OSA on one hand and hypertension and AF on the other hand can contribute to the known association of OSA with stroke. In addition, the presence of AF in a patient with hypertension may raise the suspicion of undiagnosed OSA in this patient (Figure 3).

Adherence to CPAP treatment has been shown to improve hypertension control in OSA patients and reversal of diastolic dysfunction [33]. Details are provided below.

OSA is strongly associated with cardiovascular disease

OSA is a cause of hypertension and can worsen diabetes, coronary artery disease, CHF and stroke [34]. These factors are detailed separately below.

Likewise, these cardiovascular conditions have been proposed to predict for development of AF [1].

Inflammatory response in OSA

Patients with OSA have been noted to have elevated levels of inflammatory markers including C-reactive protein (CRP), ICAM-1, IL-6, TNF- α , serum amyloid A and uric acid [35–37]. Hypoxia induced by OSA activates macrophages and leads to inflammatory mediators like monocyte chemoattractant protein-1 and matrix metalloproteinase 9. Reports suggest that increase in inflammatory markers is proportional to the severity of OSA, especially CRP levels [35,38].

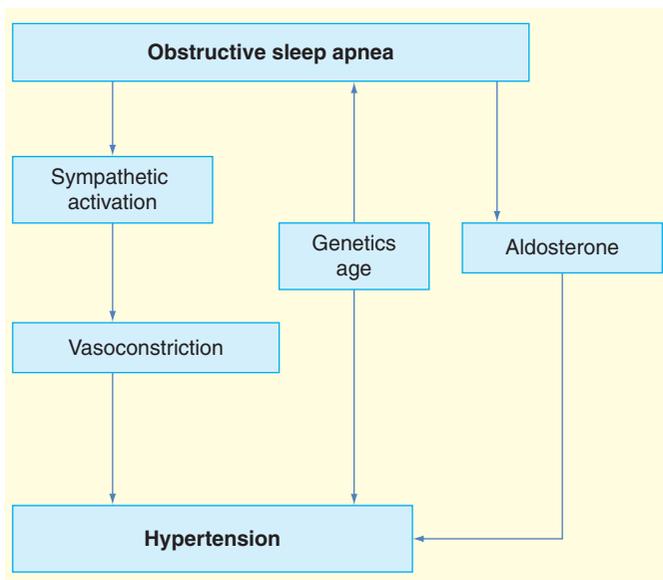


Figure 3. The relationship between obstructive sleep apnea and hypertension.

The role of cytokines in the development of AF has been reported [39]. Notably, CRP and IL-6 elevation have been predicted with development of AF in the future [19]. In patients with established AF, twofold increase in CRP compared with control patients have been noted [40]. Recently, a novel study showed that serum uric acid level was higher in patients with incidence of AF who had OSA [41].

Therefore, OSA increases inflammatory markers, and pro-inflammatory states predispose to AF development. Whether these are two independent mechanisms or not remains to be understood.

Atrial electrical remodeling due to OSA

Interatrial block, which is defined as P-wave duration over 120 ms, can predict for AF development. Thirty-five percent patients with moderate-to-severe OSA were noted to have interatrial block compared with patients with mild or no OSA, which is possibly mediated by the autonomic dysfunction and left atrial enlargement (described below) [10]. Another group similarly showed that P-wave dispersion increases in patients with moderate-to-severe OSA [42].

Impact of OSA on AF management

The earliest effects of OSA on arrhythmias were incidentally observed in patients who underwent tracheostomy [43]. In these patients, there were no reported recurrences of arrhythmias except premature ventricular contractions over 6 months [14].

Treatment options for OSA include surgical interventions and oral appliances. However, CPAP remains the mainstay of treatment for OSA [44]. Adherence to CPAP improves left ventricular systolic function and improves systemic hypertension. Furthermore, there is a clear correlation between CPAP and decrease in nocturnal hypoxia, reduction in inflammation, sympathetic overactivity, hypertension and reductions in

intrathoracic pressure fluctuations [2,19,24]. Similar to tracheostomy findings, CPAP has been shown to reduce the incidence of paroxysmal AF in 1394 Japanese patients ($p < 0.001$) [45].

We will review the impact of OSA treatment status on antiarrhythmic therapy, cardioversion, ablation outcomes and finally consideration of anticoagulation for stroke prevention.

Untreated OSA leads to failure of antiarrhythmic therapy

Monahan *et al.*, studied the impact of OSA severity on the efficacy of antiarrhythmic drugs (AAD). Forty percent of their patients (24 of 61 patients) were diagnosed with severe OSA on overnight polysomnography. Of these patients, non-responders to AADs were more likely to have severe OSA than milder OSA (53 vs 23%). Severe OSA patients were less likely to respond to AAD compared with no severe OSA (39 vs 70%).

Increased recurrence rates of AF in patients with untreated OSA who underwent cardioversion

An observational study showed that AF recurrence after cardioversion is 82% in patients with untreated OSA, 42% in patients with treated OSA and 53% in patients without OSA [46,47]. The relatively high recurrence rate in controls raises the question of whether this group had undiagnosed OSA. Multivariate analysis in this study showed that AF recurrence correlated with severity of OSA.

Untreated OSA requires multiple ablation attempts & is associated with higher rates of failure in AF patients

A recent meta-analysis, which reviewed 402 reports and analyzed approximately 4000 patients, concluded that patients with OSA had over 25% risk of AF recurrence after catheter ablation for pulmonary vein isolation. Interestingly, these results held true for OSA diagnosed by polysomnography and not Berlin questionnaire [7].

Similar results were noted after pulmonary vein isolation. Patients with OSA who were not treated with CPAP had higher rates of acute pulmonary vein reconnection (55%) after pulmonary vein isolation than patients with OSA who were treated with CPAP (33%) [48].

Antar *et al.* studied the effect of CPAP on AF recurrence in patients with severe OSA who underwent pulmonary vein isolation. They reported that 72% of the CPAP users had no recurrence of AF compared with 62% of the CPAP non-users, and concluded that CPAP use was an independent predictor of AF ablation success. The same group reported that CPAP usage resulted in higher AF-free survival off antiarrhythmic drugs or repeat ablation following PVI. Notably AF recurrence in CPAP non-users who underwent ablation were similar to OSA patients who were managed medically without ablation [7].

Our institution recently reviewed records on recurrent AF ablations and noted that 23% patients with OSA required repeat ablations in 1 year. Interestingly, 32% patients with diagnosis of OSA who were not on treatment required more than one attempt at AF ablation [HOUMSSE ET AL., PERS. COMM.].

The current literature suggests that OSA is associated with increased recurrence rate of AF post-cardioversion and ablation. Compliance to OSA treatment is associated with reduced recurrence of AF and reduced need for recurrent ablation. This raises the question whether patients being planned for AF-related cardioversion and ablation would benefit from OSA screening. Berlin questionnaire is the most validated, but has not held ground for cardiovascular disease and OSA. There is a need to devise reasonably priced, easily administered screening tests for this high-risk group.

CPAP therapy reverses atrial remodeling in patients with severe OSA

In this study, 90 severe OSA patients and 10 controls were included in the analysis and their signal averaged P-wave duration, as a marker of atrial remodeling was studied. After CPAP, there was a significant reduction of signal-averaged P-wave duration ($p < 0.001$), while duration did not change after 4–6 weeks in controls [49].

OSA increases risk for stroke & independently worsens risk factors associated with hypercoagulability in AF patients

The CHA₂DS₂VASC (CHF, hypertension, age, diabetes, stroke and vascular disease) score is a well-validated clinical tool to assess the risk of stroke and used to determine anticoagulation strategies in AF management [50]. As described below, we will review literature, which suggests that OSA can independently worsen most of the risk factors, which are part of the CHADS₂VASC scoring system.

OSA predisposes to CHF

The presence of OSA can dramatically increase the likelihood of developing heart failure independent of other risk factors [51]. This has been proposed to result from increased sympathetic activation and vagal withdrawal in conjunction with the stress of intermittent hypoxia on a failing ventricle. Histopathologic evidence shows high sympathetic drive can cause myocyte necrosis and apoptosis, B-receptor downregulation and desensitization and arrhythmogenesis [52]. Sympathetic overdrive also leads to increased renin–angiotensin–aldosterone activation, which leads to volume overload [53].

Additionally, the systemic hypertension from sympathetic activation leads to left ventricular hypertrophy over time, which can subsequently remodel and dilate. This has been convincingly demonstrated in dog model studies [54].

Additionally, the prevalence of OSA has been noted in up to 50% in patients with CHF [55–58]. The fluid accumulation in CHF gravitates to the neck resulting in neck distention and pharyngeal edema in the supine position. This can result in upper airway obstruction causing OSA (FIGURE 4) [59].

Interestingly, OSA treatment has been noted to improve ejection fraction, 6-min walk test performance and apnea status, but does not improve survival [60,61]. The lack of effect on mortality is not well understood, but the independent irreversible effects of

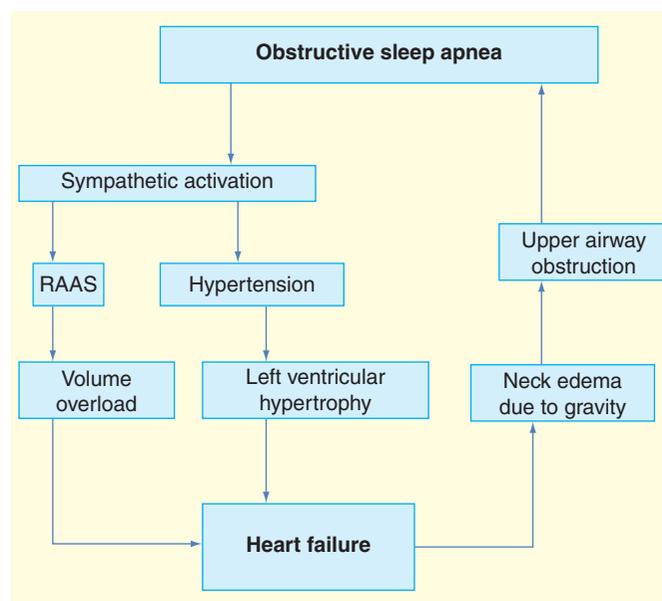


Figure 4. The relationship between obstructive sleep apnea and congestive heart failure.

heart failure outcomes may be implicated. Alternatively, larger studies may be able to signal an improvement in survival.

Hypertension mediates many of the cardiovascular consequences of OSA

As noted above, hypertension is an accepted direct consequence of OSA. Animal models of OSA consistently develop hypertension [62]. The Wisconsin Sleep Study followed patients with OSA and noted development of hypertension within 4 years [63]. The increase in sympathetic activity has been described to cause peripheral vasoconstriction, which leads to systemic hypertension [19].

It has been observed that the association of hypertension and OSA is stronger with increasing age [64]. Genetic factors may also contribute to the association of hypertension and OSA [65,66]. Other factors such as hyperaldosteronism have been implicated to cause hypertension in OSA patients [67]. The importance of OSA in the causation of hypertension has been highlighted by the recognition of OSA as a treatable cause of hypertension by the Seventh Joint National Committee of Hypertension guidelines. Based on the current evidence, patients with resistant hypertension should be screened for OSA and treated with CPAP [68].

There are convincing data to demonstrate that consistent decrease in both systolic and diastolic blood pressure has been noted as early as 1 week of CPAP treatment in OSA patients [69,70]. Therefore, the benefits of OSA treatment on amelioration of hypertension are well established.

OSA is associated with glucose intolerance, insulin resistance & development of diabetes

Up to 40% of OSA patients will develop diabetes [71], and the prevalence of sleep-disordered breathing has been noted in over 50% of the diabetic population [72].

The link between these two diseases has been postulated to result from various interactions. Studies have shown that OSA patients have elevation in leptin, an adipocyte-derived signaling factor and ghrelin, an appetite-stimulating hormone, which have been implicated in metabolic syndrome. Metabolic syndrome predisposes to glucose intolerance [73]. Aside from this link to metabolic syndrome in OSA, the increased sympathetic tone, altered glucocorticoid regulation and hypoxemia-induced glucose intolerance in OSA patients are well described in the development of diabetes [53].

Effective treatment of sleep-disordered breathing have been shown to decrease leptin levels in OSA patients [73]. The effects on glucose control have been controversial. Analysis of subgroups show that CPAP has maximal benefit in patients with BMI less than 30, obviating the confounding effects of obesity. Additionally, CPAP treatment improves hemoglobin A1c rather than day-to-day glucose control [74], suggesting a long-term improvement in insulin responsiveness, and this effect has been best noted in patients with severe OSA [75].

OSA increases the risk of stroke

Yaggi *et al.* showed an association between OSA and stroke, which was independent of hypertension, age, AF, diabetes and hyperlipidemia [76] (hazard ratio: 1.97). Patients with stroke are three- to fourtimes more likely to have OSA than the normal population. A recent review studied the stroke risk in AF patients not on anticoagulation. They noted that OSA predicted stroke with a higher relative risk than the CHADS2 variables [77].

Martinez-Garcia *et al.* reported that CPAP non-users had up to fivefold greater incidence of new vascular events compared with CPAP users in stroke patients with OSA [78]. Wessendorf *et al.* reported improved blood pressure control and sense of wellbeing in stroke patients with OSA using CPAP [78]. Ryan *et al.* randomized stroke patients with OSA (AHI ≥ 15) to a CPAP (n = 22) group or control (n = 22) group and reported improvement in functional and motor outcomes, but not neurocognitive outcomes [78].

OSA is strongly associated with peripheral vascular disease

An interesting study showed up to 85% patients with peripheral arterial disease had undiagnosed OSA. Having reviewed the multiple factors in OSA, which predispose to atherosclerosis, this correlation is not surprising [79]. We did not find literature to suggest reversal of peripheral vascular disease with CPAP. This could be an interesting area for future research.

Therefore, we notice a strong correlation of OSA with risk factors for AF. An insightful paper by Wilcox *et al.* suggested that OSA identifies patients with a cluster of risk factors (hypertension, obesity, glucose dysregulation) and could further independently increase cardiovascular risk [80]. Therefore, they proposed that Syndrome X should include OSA and be

referred to as Syndrome Z. Akin to their observations, we speculate whether OSA status should be accorded a risk factor in a revised scoring system to determine anticoagulation. Further studies are needed to determine this.

Although the above literature increases the appeal of CPAP therapy on improving outcomes, it also raises the omniscient question about compliance. Patients using CPAP are generally more compliant to therapy, and this may independently reduce AF recurrence risk.

Expert commentary

Given the high prevalence of AF in OSA patients, and the high prevalence of these diseases, it is important to recognize this association. There are several pathophysiologic links, of which hypertension and increased sympathetic activation are most consistently recognized as triggers for AF in OSA patients. Additionally, OSA is a risk factor for several cardiovascular diseases, which can independently increase the risk of AF. Diagnosis of OSA and treatment status affects the management outcomes for AF. Higher rates of recurrence of AF are noted in patients with untreated OSA status. Of concern, OSA independently increases the risk for developing each of the risk factors for stroke in AF patients.

Five-year view

Considering the strong association of OSA with AF and the multiple interactions with overlapping risk factors, there are several areas for further research. There is a need for developing a screening modality for OSA in patients who present to the cardiovascular clinic. Developing in-patient screening tests would be another high yield idea for early recognition of OSA. Additionally, it may be important to risk-stratify patients who are planned for AF cardioversion and ablation strategies. The latter are expensive and high-risk strategies. Untreated OSA can lead to multiple procedures with increasing risk every time. Another area of interest is need for follow-up to verify CPAP settings. Large-scale studies to determine the direct and indirect effect of OSA on stroke risk, and whether this should be included as a factor during anticoagulation management decision will be another critical area for research. There is a huge unmet need for multidisciplinary collaboration to ensure patient compliance. Close collaboration between pulmonologists and cardiologists is required to improve cardiovascular outcomes.

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Key issues

- Atrial fibrillation (AF) and obstructive sleep apnea (OSA) are highly prevalent with enormous healthcare costs.
- The incidence of AF is threefold higher in the OSA population than the general population.
- Although causality is unclear, the sympathetic activation, hypertension, inflammatory states and changes in intrathoracic pressure associated with sleep apnea have been strongly related to development of AF.
- OSA independently increases the risk of congestive heart failure, hypertension and diabetes, which are associated with higher stroke risk in AF patients.
- The OSA treatment status is a major determinant in recurrence of AF on antiarrhythmic drugs, after cardioversion and ablation.

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