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CLINICAL REVIEW

# Atrial arrhythmogenesis in obstructive sleep apnea: Therapeutic implications

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SUMMARY

The prevalence of sleep disordered breathing like obstructive sleep apnea (OSA) among patients with atrial fibrillation (AF) is 40–50%. OSA reduces success rate of catheter based and pharmacological antiarrhythmic treatment. Additionally, efficient treatment of OSA by continuous positive airway pressure ventilation (CPAP), the first line therapy of OSA, has been shown to improve catheter ablation success rates in AF-patients. A systematic literature search using several databases was performed to review the pathophysiology of obstructive apneas in OSA potentially leading to the development of a substrate for AF and to explain potential mechanisms involved in the clinically observed atrial antiarrhythmic effect of effective CPAP therapy.



## Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with relevant morbidity and mortality. 1% of the European population suffers from AF and the number of AF patients is expected to double or triple within the next two to three decades [1–5]. The clinical presentation of AF is highly variable, ranging from the complete absence of symptoms to palpitations, heart failure, and hemodynamic collapse. Importantly, AF increases the risk of stroke about five times [6,7]. AF doubles mortality and causes marked morbidity [8]. Symptoms and complications of AF result from the irregular and often rapid ventricular response, loss of atrial contraction as well as from AF-associated hypercoagulability.

A condition, which is associated with a high prevalence of AF is obstructive sleep apnea (OSA) [9–11] and OSA in patients with AF is an independent predictor of stroke [12]. OSA is characterized by obstructive respiratory events due to periodic or complete occlusion of the upper airways resulting in intermittent hypoxia, hypercapnia and intrathoracic pressure swings during the frustrane breathing attempts. Continuous positive airway pressure ventilation (CPAP) is a non-invasive respiratory support and is the first-line treatment for OSA.

In this review, we describe the pathophysiology of obstructive apneas in OSA potentially leading to the development of a substrate for AF and discuss the potential mechanisms underlying the atrial antiarrhythmic effects of CPAP therapy.

## Obstructive sleep apnea

### *Pathophysiology and definitions of sleep apnea*

There are three basic mechanisms for the disruption of respiration during sleep: upper airway obstruction, dysregulation of respiratory control, and hypoventilation. Two main breathing abnormalities are obstructive sleep apnea (OSA) and central sleep apnea (CSA). Disease severity is determined by the number of respiratory events per hour of sleep time (the apnea-hypopnea index [AHI]), and the number and severity of oxygen desaturations.

*Abbreviations:* AERP, atrial effective refractory period; AF, atrial fibrillation; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; CSA, central sleep apnea; NTP, negative thoracic pressure; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation; RAAS, renin angiotensin aldosterone system; RDN, renal denervation.

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Sleep disordered breathing is usually defined as mild when the AHI is 5–15/h, moderate when AHI is 15–30/h and severe when the AHI is > 30/h. OSA is the most common type of sleep disordered breathing in the general population and is characterized by recurrent partial (hypopnea) or complete (apnea) collapses of the upper airway during sleep, which cause decreased or interrupted airflow in spite of continued respiratory effort.

*Prevalence and incidence of atrial fibrillation in sleep apnea*

In young patients with paroxysmal AF with a high AF burden or persistent AF with preserved left ventricular function a high prevalence of sleep disordered breathing can be found (62% vs. 38% in patients without AF) [13]. However, the prevalence of daytime symptoms like excessive daytime sleepiness in OSA patients with cardiac disease like AF or congestive heart failure is rare [14]. Therefore, the prevalence of OSA in AF patients may be even underestimated. Gami et al. [11] showed that the severity of OSA is a strong predictor of incident AF in individuals younger than 65 y. AF patients with severe OSA show a lower response rate to anti-arrhythmic drug therapy than those with milder forms of OSA [15]. Additionally, a prospective analysis by Kanagala et al. [10] demonstrated that patients with OSA have a higher recurrence rate of AF after initial successful cardioversion than patients without OSA. Patients with OSA have a higher risk of AF recurrence after catheter based electrical isolation of the pulmonary veins (pulmonary vein isolation, PVI), than those without OSA [16]. PVI is an important and effective treatment modality of symptomatic AF. During the procedure, radiofrequency energy is applied at the tip of a catheter to form circular ablation lines around the ostium if the pulmonary veins thereby electrically disconnecting them from the left atrium. This reduces triggers for AF generated in the pulmonary veins of patients with paroxysmal and persistent AF [1].

## Arrhythmogenic mechanisms in obstructive sleep apnea

The above mentioned studies suggest that OSA predisposes patients to develop AF, but it is not clear whether the relationship is completely independent of hypertension, diabetes mellitus, or other confounding factors. Here, we discuss potential underlying pathophysiologic mechanisms that support the plausibility of this interplay.

Obstructive apneas caused by the collapse of the upper airway during sleep result in intrathoracic pressure swings resulting in myocardial stretch of the heart chambers and changes in transmural pressure gradients, particularly affecting the thin-walled atria (Fig. 1) [17]. Additionally, obstructive respiratory events induce intermittent apnea-associated hypoxemia and hypercapnia as well as sympathetic activation and subsequent intraapneic and postapneic hemodynamic fluctuations [18]. Interestingly, in OSA, paroxysms of AF were found to be nocturnal and, at least partly, temporally related to respiratory obstructive events [19,20]. This temporal link between sleep disordered breathing and the occurrence of AF suggests that the trigger for AF may be mainly caused by acute changes during apneas and not by chronic remodeling processes in the atria alone [21]. However, acute factors directly associated with obstructive respiratory events like intrathoracic pressure changes, changes in blood gases and sympatho-vagal imbalance may contribute to the creation of the atrial arrhythmogenic substrate in OSA-patients (Fig. 2).

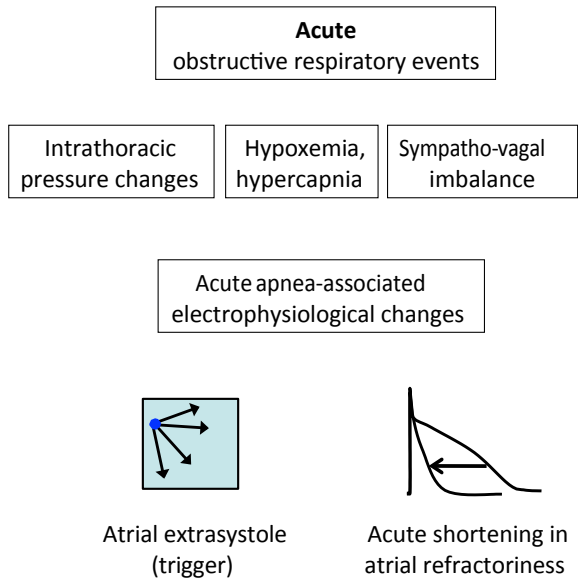


**Fig. 2.** Atrial arrhythmogenic mechanisms during acute obstructive respiratory events.

*Acute effects of obstructive respiratory events on atrial arrhythmogenesis*

*Intrathoracic pressure changes*

Obstructed inspirations generate wide fluctuations in intrathoracic pressure, resulting in changes in cardiac transmural pressure, which in turn lead to atrial stretch. Negative tracheal pressures as low as −80 to −100 mbar were observed in OSA patients [17,19].

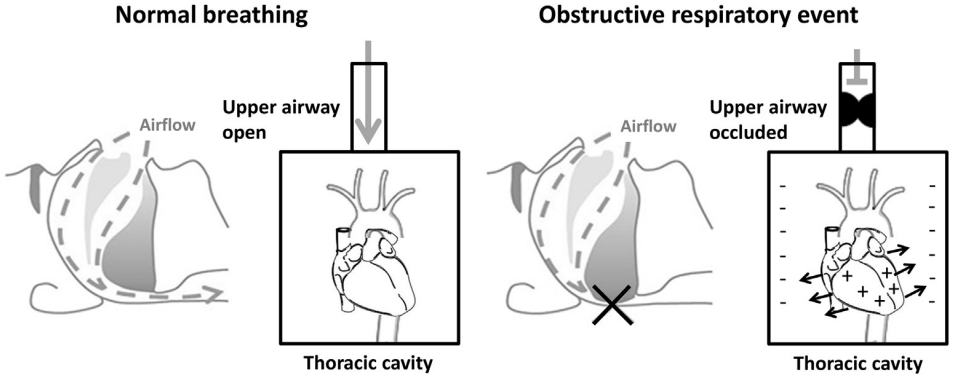


**Fig. 1.** Pathophysiology of obstructive sleep apnea (OSA) and resulting intrathoracic pressure changes.

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Application of negative tracheal pressure at −80 mbar resulted in a negative right atrial pressure of −16 mbar and a negative intrathoracic pressure of −65 mbar in a pig model for OSA [22] suggesting increased atrial transmural pressure gradients resulting in acute atrial distension. Comparable intrathoracic pressure changes and alterations in atrial dimensions were observed during repetitive Mueller maneuvers in humans (attempted inspiration against the obstructed upper airways) [23]. This apnea-associated acute atrial dilation may result in acute arrhythmogenic atrial electrophysiological alterations. In isolated Langendorff-perfused rabbit hearts, atrial dilation has been shown to shorten atrial refractoriness [24], slow conduction and increase the amount of intra-atrial conduction blocks [25]. Additionally, acute atrial stretch in humans undergoing cardiac surgery resulted in conduction slowing along the pulmonary veins, with a greater degree of signal complexity [26]. Shortened atrial refractoriness together with lower conduction velocity and increased heterogeneity increases the excitable gap, potentially underlying AF initiation and maintenance by promoting re-entry [27]. In a pig model for OSA, application of negative tracheal pressure during tracheal occlusion - but not tracheal occlusion without applied negative tracheal pressure– shortened the atrial refractory period and strongly enhanced the inducibility of AF in a reproducible and reversible manner [22] (Fig. 3). These acute electrophysiological changes were mainly mediated by sympatho-vagal imbalance, since they could be influenced by atropine, bilateral vagotomy or beta-receptor blockade [22,28,29]. Besides pronounced shortening in atrial refractoriness, 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 [30,31]. Comparable arrhythmogenic electrophysiological changes were also observed in a rat model for obesity and OSA, which were partly prevented by combined autonomic blockade [32].

*Changes in blood gases*

Hypoxemia, hypercapnia and acidosis are invariably linked with obstructive apneas [17,19]. The magnitude of nocturnal oxygen desaturation is an independent risk factor for incident AF [12]. The electrophysiological effects of isolated hypoxia or hypercapnia were investigated in a sheep model with continuous ventilation under autonomic blockade [33]. Isolated hypercapnia resulted in atrial effective refractory period (AERP)-prolongation. AERP rapidly returned to baseline, but recovery of conduction was delayed about 2 h following correction of hypercapnia. AF vulnerability was reduced during hypercapnia (with increased AERP) but increased significantly with subsequent return to eucapnia (when AERP normalized but conduction time remained disturbed), suggesting that differential recovery of AERP and conduction might be responsible for increased vulnerability to AF [33]. In superfused rabbit atria, hypoxia caused a transient prolongation and an increase in heterogeneity of refractory periods. Additionally, hypoxia caused depressed conduction velocity and a marked increase in inhomogeneity in conduction both leading to increased vulnerability of the atrium for reentrant arrhythmias [34]. In isolated rabbit pulmonary vein preparations, hypoxia followed by reoxygenation induced pulmonary vein burst firings [35]. However, in a pig model for OSA [22] and in a rat model for obesity and OSA [32], changes in blood gases alone were insufficient to promote AF.

*Sympatho-vagal imbalance*

Direct recordings of muscle sympathetic nerve activity showed increased sympathetic activation during apneic episodes in OSA patients [36] or in apnea divers [37]. Severe bradycardia and atrioventricular conduction disturbances together with the arousal reaction characterized by activation of the sympathetic system and postapneic blood pressure rises, are frequently seen in OSA and suggest a simultaneous sympathetic and parasympathetic activation (sympatho-vagal imbalance). Particularly the increasing

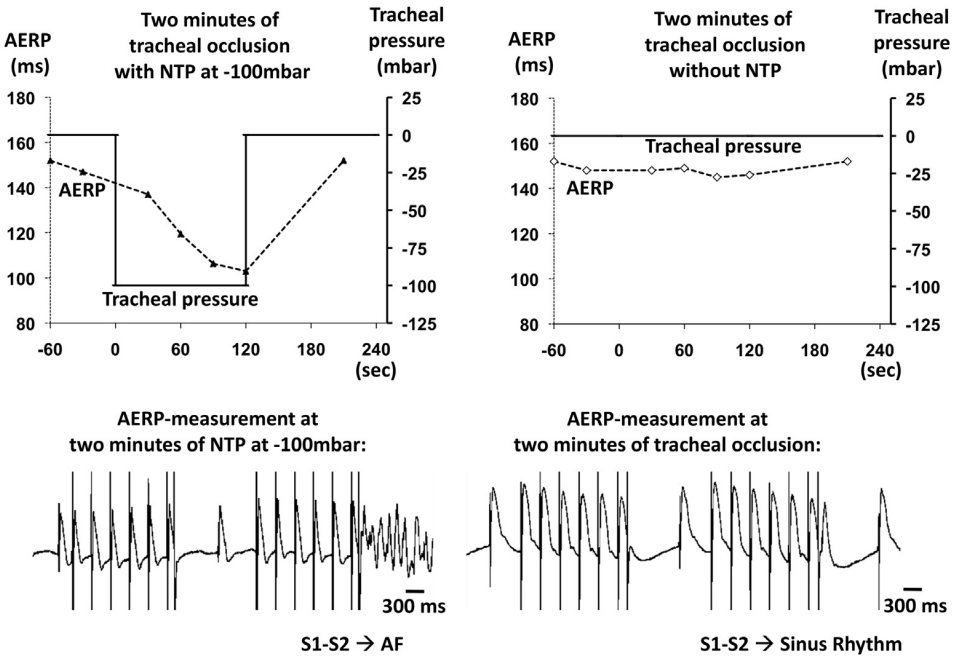


**Fig. 3.** Changes in atrial electrophysiology during 2 min of tracheal occlusion with (left) or without (right) applied negative tracheal pressure (NTP) at −100 mbar. Individual example of changes in atrial effective refractory period (AERP) (first line). Tracheal occlusion with applied NTP at −100 mbar, but not hypoxia alone during tracheal occlusion without applied NTP, resulted in a progressive shortening of AERP and AF was inducible by a premature beat during programmed electrical atrial stimulation to measure the AERP (S1-S2-protocol). (Adapted from Linz et al. [22]).

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inspiratory effort against the collapsed pharynx during obstructive apneas is likely to cause increased sympathetic nerve activity. In healthy humans intrathoracic pressure changes induced by a Mueller maneuver generated an increase of more than 200% in postganglionic sympathetic nerve activity and a 14% increase in mean blood pressure at the end of the apnea [38]. The sympathetic and parasympathetic nervous system has been considered to play a role in the initiation and the maintenance of AF in humans (reviewed in [27,39,40]). In line with this concept, inducibility of AF could be attenuated by the ablation of the ganglionated plexi at the right pulmonary artery or by combined pharmacological neurohumoral blockade in a dog model for central apnea [41]. Forced inspiration-induced acute atrial distension resulted in an arrhythmogenic atrial electrical remodeling in a rat model for obesity and OSA, which was partly prevented by combined pharmacological autonomic blockade by atropine and a beta-blocker. [32]. Another indicator of pronounced autonomic activation during apnea has been provided by a pig model for OSA [22]. Negative tracheal pressure during obstructive apneas leads to pronounced shortening of atrial refractoriness thereby perpetuating AF. These electrophysiological changes were mainly mediated by sympatho-vagal imbalance, since they could be influenced by atropine, bilateral vagotomy or beta-receptor blockade [22,28–31]. Also renal sympathetic denervation (RDN), a strategy to modulate sympathetic nervous system [42], resulted in an attenuation of AERP-shortening induced by negative thoracic pressure [28,30]. In rabbits with simulated OSA, also low-level vago-sympathetic trunk stimulation was capable of suppressing AERP shortening and AF-inducibility [43].

*Longterm OSA and atrial structural remodeling*

In patients, longterm OSA has been shown to be associated with significant atrial remodeling characterized by atrial enlargement, local conduction disturbances and longer sinus node recovery [44], atrial electromechanical delay and left atrial dysfunction [45]. Additionally, in a rat model, chronically repeated episodes of apnea caused atrial conduction abnormalities related to connexin dysregulation and increased atrial fibrosis formation [46].

Several mechanisms have been considered to cause OSA-related myocardial damage including systemic inflammation, neurohumoral activation, chronic atrial dilation by repetitive changes in intrathoracic pressure and multiple comorbidities like obesity and hypertension (Fig. 4):

*Inflammation and neurohumoral activation*

Longterm OSA has been shown to be associated with increased activation of autonomic nervous system and elevations of circulating markers of inflammation [47,48]. C-reactive protein is associated with vascular inflammation and its serum concentration correlates with AF stability, predicting postoperative AF and failure of PVI [9].

The carotid body is a cluster of chemoreceptors located near the bifurcation of the carotid artery. It responds to decreases in oxygen partial pressure and relays the information to the central nervous system via the afferent fibers of the glossopharyngeal nerve. At an oxygen partial pressure below 60 mmHg the activity of the carotid body increases rapidly. Activation of carotid bodies by intermittent hypoxia has been shown to be associated with a reduction in baroreflex sensitivity in cats [49]. Additionally, repeated episodes of hypoxia induce augmented activities of the carotid chemosensory activity and ventilatory hypoxic responses [49]. Altered sensitivity of the chemo-reflex has also been reported in patients with sleep apnea, which significantly contributes to the increase of sympathetic activity mediated by the chemo-reflex [50]. The mechanism of augmented carotid chemo–afferent activity is multifactorial and could be attributed to local oxidative stress, local activation of the renin-angiotensin system and inflammation induced by intermittent hypoxia [51,52]. Denervation of the carotid body could normalize the elevated blood pressure induced by intermittent hypoxia in animals [53,54].

In OSA, neurohumoral activation, namely the circulating renin angiotensin aldosterone system (RAAS), together with increased oxidative stress may underlie atrial structural and electrical remodeling [55,56]. The RAAS has been shown to play a relevant role for the development of a structural atrial remodeling under different pathophysiological conditions [27]. In a pig model for OSA, RAAS activation was mainly driven by increased sympathetic activation, as it was almost completely attenuated by renal sympathetic denervation [18,30].

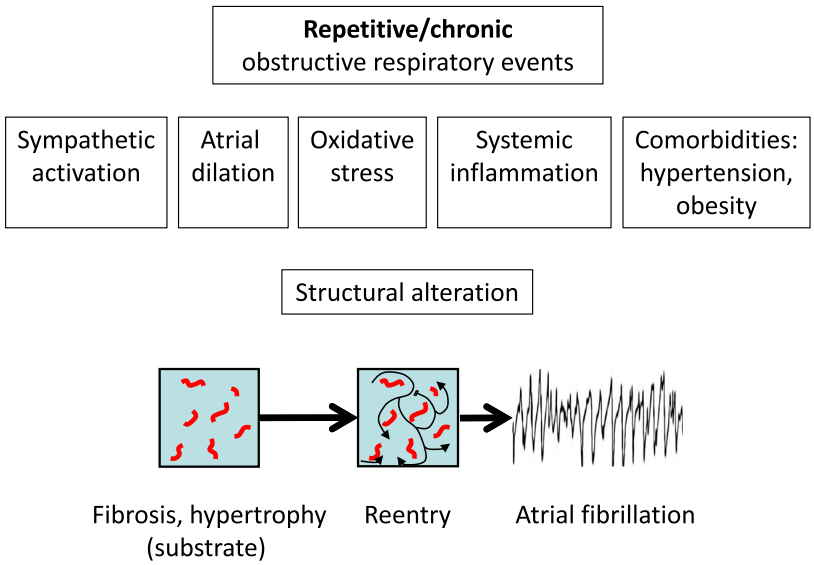


**Fig. 4.** Atrial arrhythmogenic mechanisms during chronic/repetitive obstructive respiratory events.

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*Effect of hypertension and obesity on structural remodeling*

OSA is considered an etiological factor in the development of hypertension and in the evolution of drug resistant hypertension [57,58]. In a sheep model, chronically elevated blood pressure was associated with significant atrial electrical and structural remodeling characterized by local conduction disturbances, shortening of atrial wavelength, and increased occurrence of AF, atrial myocyte hypertrophy and myolysis, increased atrial collagen and apoptosis [59]. In another sheep model with induced "one-kidney, one-clip" hypertension, increased blood pressure was associated with early and progressive changes in atrial remodeling [60]. In spontaneously hypertensive rats hypertension was associated with the development of a substrate for atrial tachyarrhythmia involving left atrial fibrosis without changes in the atrial effective refractory period [61].

Obesity and the metabolic syndrome, both prevalent in OSA patients, may be associated with the development of AF by systemic changes related to these conditions [62]. There is a 3–8% higher risk of new AF-onset with each unit increase in body mass index, and this association is independent of other cardiovascular risk factors like lipid levels, blood pressure or diabetes [62]. Pericardial fat is associated with occurrence of AF, persistence of AF, left atrial enlargement, and bad outcomes of PVI [63]. Additionally, obesity results in progressive atrial structural and electrical remodeling. In sheep, following a high-calorie diet, obesity was associated with atrial electro-structural remodeling, increased atrial size and changes in conduction, histology, and expression of profibrotic mediators. These changes were associated with spontaneous and more persistent AF episodes [64]. Whether OSA can result in arrhythmogenic structural changes in the atrium completely independent of concomitant risk factors like for example hypertension and obesity is unclear.

## Treatment of obstructive sleep apnea

The gold standard therapy for OSA is continuous positive airway pressure ventilation (CPAP), which splints the upper airway and maintains upper airway patency, thus alleviating obstructive respiratory events [65].

*Modulation of neurohumoral activation by CPAP in OSA*

In hypertensive patients, nocturnal CPAP decreases sympathetic traffic in OSA, interestingly not just during night but also during daytime [66]. In patients with heart failure and OSA, short-term CPAP improved myocardial sympathetic nerve function, but overall did not affect energetics suggesting improved cardiac efficiency [67]. Different studies provided evidence that continuous positive airway pressure (CPAP) therapy in OSA reduces 24 h urinary catecholamine excretion as well as plasma norepinephrine levels, consistent with a reduction in sympathetic nerve activity [68,69]. Baroreflex sensitivity, an established index of cardiac sympathovagal balance, is depressed in patients with OSA and four weeks of CPAP therapy increased baroreflex sensitivity by 24% [69]. CPAP therapy has been shown to decrease both inflammation and oxidative stress levels in airways of OSA-patients. Also, this treatment helps to decrease systemic oxidative stress levels in serum [70]. Additionally, CPAP therapy was associated with improved renal hemodynamics and down-regulation of activity of the renin-angiotensin system [71].

*CPAP and cardiac remodeling*

In patients with moderate-to-severe obstructive sleep apnea, three months of CPAP therapy lowers blood pressure and partially reverses metabolic abnormalities [72]. By contrast, nocturnal supplemental oxygen did not result in a significant reduction in blood pressure [72,73]. Inhibition of increased central sympathetic vasoconstrictor outflow may be one mechanism by which nocturnal CPAP reduces awake blood pressure and heart rate in heart failure patients with moderate to severe OSA. Efficient treatment of OSA was associated with improved left ventricular diastolic function and left atrial passive emptying, but not left atrial structural variables in OSA patients [74,75]. Both systolic and diastolic abnormalities in patients with OSA can be reversed as early as after three months of CPAP therapy, with progressive improvement in cardiovascular remodeling over one year [76]. Additionally, CPAP therapy provided more homogenous conduction through atria in patients with OSA [77].

*CPAP, PVI and electrical cardioversion of atrial fibrillation*

Although PVI has been established as an effective treatment for AF, some patients experience conduction recurrence across a previously disconnected pulmonary vein. Sauer et al. characterized this group and concluded that acute return of pulmonary vein conduction is more likely after successful PVI in patients who are elderly, hypertensive, with nonparoxysmal AF, a large left atrium, and sleep apnea [78]. Recent meta-analysis determined that OSA patients have a 25% greater AF recurrence rate after PVI [79]. OSA was the strongest predictor of recurrent AF after PVI, associated with a threefold increase in the probability of recurrence [79–83]. In a larger study ($n = 426$) [82], CPAP therapy in patients with OSA and AF undergoing pulmonary vein isolation was associated with a higher AF-free survival rate (71.9% vs. 36.7% in untreated patients) and almost similar to a group of patients without OSA. Interestingly, the effect of CPAP in patients without PVI was comparable to the effect of pulmonary vein isolation in CPAP non-user OSA patients [82]. The proportion of patients who were free of AF without drug treatment or repeated PVI procedures was also significantly higher in CPAP users versus non-users [82].

Compared to non-OSA patients, OSA-patients not treated with CPAP had an enhanced prevalence of non-pulmonary vein antrum triggers and posterior wall firing (31% vs. 19%), possibly a reflection of electrical and structural remodeling of the atria [16]. Not using CPAP in addition to having non-pulmonary vein triggers strongly predicted PVI-failure (hazard ratio, 8.81) [16].

A prospective analysis by Kanagala et al. [10] demonstrated that patients with OSA have a higher recurrence rate of AF after initial successful cardioversion than patients without OSA. Interestingly, patients who showed obstructive respiratory events during sedation for electrical cardioversion had a higher relapse rate of AF during one week after electrical cardioversion compared to patients without obstructive respiratory events during sedation [31].

*Non-CPAP interventions*

The effects of alternative treatment strategies for OSA on AF, like weight loss, cessation of drinking or other non-CPAP interventions have not been investigated.

## Central sleep apnea

Central sleep apnea (CSA) is rarely found in the general population. However it is a common sleep disordered breathing pattern seen in patients with chronic heart failure, with a prevalence of 25–40% [84]. The prevalence of CSA appears to increase as the severity of heart failure increases, and the severity of CSA seems to mirror cardiac dysfunction [85]. Adaptive servo ventilation is currently the most effective treatment option for CSA. The prevalence of CSA in patients with AF is not well described and few data

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are currently available. One study has reported a high proportion of CSA (79%) in a group of pacemaker recipients with permanent AF [86]; this was probably a result of a high rate of heart failure and depressed left ventricular ejection function in this study population. Another study in AF patients with normal left ventricular function showed prevalence rates of 31% for CSA and 43% for OSA [87]. Future studies are needed to clarify mechanisms responsible for AF in CSA and whether adaptive servo ventilation is helpful to prevent AF and to improve symptoms and decrease mortality in heart failure AF-patients.

## Conclusion

OSA creates a complex substrate for AF. In addition to the development of a structural remodeling, acute obstructive respiratory events result in acute arrhythmogenic electrophysiological changes contributing critically to the development of an arrhythmogenic substrate during night. These conditions likely are responsible for increased recurrence rate of AF following cardioversion or PVI. Effective prevention of obstructive respiratory events by CPAP therapy reduces sympatho-vagal activation and recurrence of AF. OSA-associated factors should be considered during the development of future antiarrhythmic pharmacologic and interventional treatment strategies for AF. First available randomized controlled trials suggest that patients with OSA should be given special consideration when they are being evaluated for PVI as OSA-treatment improves ablation results. Future larger clinical randomized controlled trials are needed to further support and confirm these findings and to implement the treatment of OSA as a relevant antiarrhythmic strategy in the heart rhythm guidelines.

**Practice points**

1) In patients with atrial fibrillation the prevalence of sleep apnea (AHI > 15) is 40–50%
2) Sleep apnea limits efficacy of antiarrhythmic treatment strategies.
3) Efficient treatment of sleep apnea reduces AF-recurrence after electrical cardioversion and pulmonary vein isolation.

**Research agenda**

1) Does treatment of sleep apnea improve outcome in AF-patients?
2) Can adaptive servo ventilation improve managment in AF-patients with heart failure?

## Conflict of interest

None.

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* The most important references are denoted by an asterisk.

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