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Associations of Obstructive Sleep Apnea With Atrial Fibrillation and Continuous Positive Airway Pressure Treatment
A Review

Dominik Linz, MD, PhD; R. Doug McEvoy, MD; Martin R. Cowie, MD; Virend K. Somers, MD, PhD; Stanley Nattel, MD; Patrick Lévy, MD, PhD; Jonathan M. Kalman, MBBS, PhD; Prashanthan Sanders, MBBS, PhD

IMPORTANCE Obstructive sleep apnea (OSA) is the most common clinically significant breathing abnormality during sleep. It is highly prevalent among patients with atrial fibrillation (AF), and it promotes arrhythmogenesis and impairs treatment efficacy.

OBSERVATIONS The prevalence of OSA ranges from 3% to 49% in population-based studies and from 21% to 74% in patients with AF. Diagnosis and treatment of OSA in patients with AF requires a close interdisciplinary collaboration between electrophysiologists, cardiologists, and sleep specialists. Because the prevalence of OSA is high in patients with AF and most do not report daytime sleepiness, sleep-study evaluation may be reasonable for patients being considered for rhythm control strategy. Acute, transient apnea-associated atrial electrophysiological changes and increased occurrence of AF triggers associated with short episodes of intermittent deoxygenation and reoxygenation, intrathoracic pressure changes during obstructed breathing efforts, and sympathovagal activation combine to create a stimulus for AF triggers and a complex and dynamic substrate for AF during sleep. Repeated episodes of long-term OSA are eventually associated with structural remodeling and changes in electrical conduction in the atrium. Observational data suggest OSA reduces the efficacy of catheter-based and pharmacological antiarrhythmic therapy. Nonrandomized studies have shown that treatment of OSA by continuous positive airway pressure can help to maintain a sinus rhythm after electrical cardioversion and catheter ablation in patients with AF. However, it remains unclear which sleep apnea metric should be used to determine severity and guide such treatment in patients with AF.

CONCLUSIONS AND RELEVANCE Data from nonrandomized studies of patients with AF suggest that treatment of OSA by continuous positive airway pressure may help to maintain sinus rhythm after electrical cardioversion and improve catheter ablation success rates. Randomized clinical trials are needed to confirm the association between OSA and AF the benefits of treatment of OSA and the need for and cost-effectiveness of routine OSA screening and treatment.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Prashanthan Sanders, MBBS, PhD, Centre for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, Adelaide, 5000, Australia (prash.sanders@adelaide.edu.au).

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, affecting 33.5 million people globally.[1] Across the developed world, AF increasingly contributes to a rising tide of hospitalization, morbidity, and mortality.[2,3] The prevalence of sleep apnea, particularly obstructive sleep apnea (OSA), is 21% to 74% in patients with AF.[4-14]

Obstructive sleep apnea is an independent predictor of stroke in patients with AF[15] and reduces the efficacy of catheter-based[16-21] and pharmacological[22] antiarrhythmic therapy. Several studies suggest that treatment of OSA by continuous positive airway pressure (CPAP) may lower the rate of AF recurrence after electrical cardioversion (**Table 1**[4-8,20-22,41]),[5] and it improves catheter ablation success rates in patients with AF.[23-28] With accumulating evidence, international professional societies recommend the examination of patients for clinical symptoms and signs of OSA, as well as CPAP treatment to maintain sinus rhythm.[3,29]

This review provides an update on the current understanding of the pathophysiology of OSA and the associated development of a unique dynamic arrhythmogenic substrate in OSA for AF. We highlight diagnostic and therapeutic considerations in patients with AF who also have OSA, as well as experimental data pointing to possible mechanisms for AF and the antiarrhythmic effects of OSA treatment in patients with AF and comorbid OSA. Finally, we emphasize the need for randomized clinical trials to more definitively establish the role of OSA and its treatment in predisposing to incident and recurrent AF.

Pathophysiology

During sleep, respiration is more vulnerable to disruption from upper airway obstruction, dysregulation of respiratory control, and hypoventilation compared with the awake state.[30] The most common clinically significant breathing abnormality during sleep is OSA.[30] This disorder is characterized by repetitive partial collapse of the airway (obstructive hypopnea) or complete collapse of the upper airway (obstructive apnea) during sleep, both of which engender ongoing and typically increasing inspiratory efforts.[30]

Patients with central sleep apnea (CSA) associated with central dysregulation of respiratory control represent just a fraction of the large group of patients with sleep apnea and accompanying cardiovascular diseases.[30] Central sleep apnea is characterized by periodic episodes of hyperventilation and hypoventilation resulting in intermittent changes in carbon dioxide and tidal volume. Dysregulation of respiratory control in CSA is associated with increased sensitivity of peripheral and central chemoreceptors, pulmonary congestion, and prolonged circulation time.[30]

In OSA, episodes of hypopnea typically occur far more frequently than episodes of apnea, and obstructive as well as central respiratory events may both occur during the same night in a single patient. However, individual patients generally show either predominant OSA or predominant CSA. Patients with OSA sometimes convert to CSA once established on CPAP treatment. This likely reflects a central component of unstable ventilatory control underpinning their OSA, which is then unmasked by CPAP. This phenomenon is more prevalent in patients with heart failure and pulmonary edema.[30]

In addition to high-frequency intermittent deoxygenation and reoxygenation, negative intrathoracic pressure swings during inspiration against an occluded upper airway in OSA cause myocardial stretch and changes in transmural pressure gradients, particularly affecting the thin-walled atria.[30,31] Additionally, obstructive respiratory events increase venous return, augmenting right atrial and right ventricular preload,[32,33] while OSA-induced hypoxic pulmonary vasoconstriction increases afterload to the right side of the heart. Consequent right ventricular and right atrial distension, and leftward septal displacement during diastole impairs left ventricular filling and further increases left atrial volume loading.[30,31] The hemodynamic responses to hypopnea or central sleep apnea may be less pronounced compared with those occurring in obstructive apnea because they are usually associated with less severe hypoxemia and intrathoracic pressure changes (**Box**).

Atrial Remodeling in Long-term OSA

Intermittent hypoxia in rats, induced by repetitive interruptions of ventilation during daily intubation, have shown atrial conduction abnormalities associated with connexin dysregulation and increased atrial fibrosis after 4 weeks of simulated sleep apnea.[34] Correspondingly, patients with long-term OSA manifest marked atrial structural changes and conduction abnormalities in the atria without experiencing any changes in atrial refractoriness that form a substrate for AF vulnerability.[35]

Repetitive obstructive respiratory events may cause structural remodeling and myocardial damage through repetitive mechanical atrial distension, atrial wall stretch, and frequent episodes of hemoglobin desaturation and resaturation. Intermittent deoxygenation and reoxygenation of the type that occurs in sleep apnea differs from the sustained hypoxemia occurring at high altitudes and with chronic lung disease. Chronic hypoxemia promotes remodeling by modulating the expression of hypoxia-inducible factor 1 and 2.[36] The cyclical deoxygenation and reoxygenation associated with sleep apnea is comparable with ischemia and reperfusion injury, increasing production of reactive oxygen species, vascular inflammation, and blood pressure.[37] All of these may cause myocardial damage.

Table 1. Epidemiology and Response to Treatment

Condition	Prevalence in General Population	Prevalence in Patients with AF	Prevalence in Patients with OSA
OSA	3%-49%	21%-74%	100%
AF	0.9%	100%	4.8%
Recurrent AF after PVI	NA	23%-27%	31%-35%
Recurrent AF after cardioversion	NA	53%	82%
Response to antiarrhythmic drugs[a]	NA	39%	70%

Abbreviations: AF, atrial fibrillation; NA, not applicable; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation.

[a] Response to antiarrhythmic drugs is defined per study criteria.[22]

Box. Characteristics of Atrial Fibrillation

Attributes of Obstructive Respiratory Events

Intrathoracic pressure changes
- Increase in atrial stretch
- Increase in transmural pressure gradients

Changes in blood gases
- High-frequency desaturation and resaturation
- Oxidative stress

Autonomic nerve system changes
- Vagal activation (diving reflex)
- Sympathetic activation (arousal)
- Sympathovagal activation

Acute Apnea-Associated Arrhythmogenic Changes

Acute atrial dilation

Sympathovagal activation

High-frequency desaturation and reoxygenation

Acute shortening in atrial refractoriness

Atrial extrasystole (trigger)

Intermittent conduction delay

Atrial Remodeling in Long-term OSA

Atrial stretch

Neurohumoral activation and oxidative stress

Progressive structural remodeling

Regional conduction slowing and reentry

Concomitant conditions (hypertension, obesity, metabolic syndrome)

Current Clinical Practice Recommendations

Interrogation for clinical symptoms of OSA and screening for OSA in all patients diagnosed with AF (class IIa, level B^3/class 2A, level B-R^{29}), particularly those considered for a rhythm control strategy.

Sleep study evaluation may be reasonable in patients with AF who do not report daytime sleepiness.[51,52]

Initiation of continuous positive airway pressure treatment to reduce AF recurrences and improve AF treatment results (class IIa, level B^3/class 2A, level B-R^{29})

Diagnostic and Therapeutic Uncertainties and Controversies

Do randomized clinical trials confirm that treatment of OSA prevents incident and recurrent AF?

What level of severity of sleep apnea should be used to determine the need for treatment?

Is AHI the best parameter to determine OSA-severity and guide to decide which patients with AF require treatment?

Does position-dependent OSA with apneas just in the supine position represent a treatment target in patients with AF?

What is the role of CPAP treatment in older patients with AF?

Should other sleep-related abnormalities, such as nocturnal periodic limb movements, be further evaluated and treated in patients with AF?

Abbreviations: AF, atrial fibrillation; AHI, Apnea Hypopnea Index; OSA, obstructive sleep apnea.

Additionally, chronic comorbidities such as obesity and hypertension may contribute critically to progressive structural atrial substrate remodeling (**Figure**; Box).[38]

Acute Apnea-Associated Increase in Atrial Arrhythmogenesis

While atrial structural remodeling is a central contributor to an AF-maintaining substrate in patients with chronic OSA, nocturnal AF paroxysms are often temporally associated with individual respiratory obstructive events,[39-41] which suggests that acute transient arrhythmogenic changes during apnea may further contribute to the development of AF.[30,31] Obstructed inspiration generates large negative intrathoracic pressure fluctuations (up to −60 mm Hg), that leads to acute atrial distension. Acute atrial dilation shortens atrial refractoriness, slows conduction, and increases the occurrence of intra-atrial conduction block in humans.[42] In a pig model of OSA, application of negative tracheal pressure during tracheal occlusion reproducibly and reversibly shortened atrial refractory periods[43] and enhanced AF inducibility,[43-45] but apnea-associated changes in blood gases alone did not create the same outcomes.[43] In rats, obstructive respiratory events mimicked by stopping the ventilator and closing the airway for 40 seconds resulted in substantial negative intrathoracic pressure, acute left atrial dilation, and increased AF inducibility. Prevention of left atrial dilation protected rats from developing AF.[46] In a sheep model with continuous ventilation under autonomic blockade,[47] the transition from hypercapnia back to normal blood-gas levels, rather than longer hypoxic or hypercapnic episodes, was characterized by increased atrial vulnerability because of a differential recovery of atrial refractoriness and atrial conduction properties.[47] Besides these apnea-associated changes in conduction and atrial refractoriness that contribute to the substrate for AF, acute apneas may also increase trigger formation. The pronounced sympathetic activation that occurs toward the end of an obstructive episode is accompanied by vagally mediated bradycardia because of activation of the diving reflex.[48] This sympathovagal activation likely induces acute electrophysiological arrhythmogenic changes and an increased frequency of premature atrial contractions with the potential to initiate AF in a vulnerable substrate (Box).[43,44] Animal models simplify the complex pathophysiology of OSA. Factors such as nocturnal hypoxemic burden and night-to-night variability may be not considered sufficiently and should be evaluated in future translational research projects.

Obstructive Sleep Apnea and a Unique Complex and Dynamic Substrate for Atrial Fibrillation

In long-term OSA, atrial stretch, neurohumoral activation, and chronic concomitant conditions, such as hypertension, metabolic syndrome, and obesity, create a progressive structural atrial substrate remodeling in patients. This progressive atrial structural remodeling, along with transient apnea-associated electrophysiological changes, contributes to the reentry substrate for AF and creates a complex and dynamic arrhythmogenic substrate in the atrium during sleep. Atrial fibrillation risk increases cumulatively with the progressive atrial structural remodeling and apnea-associated

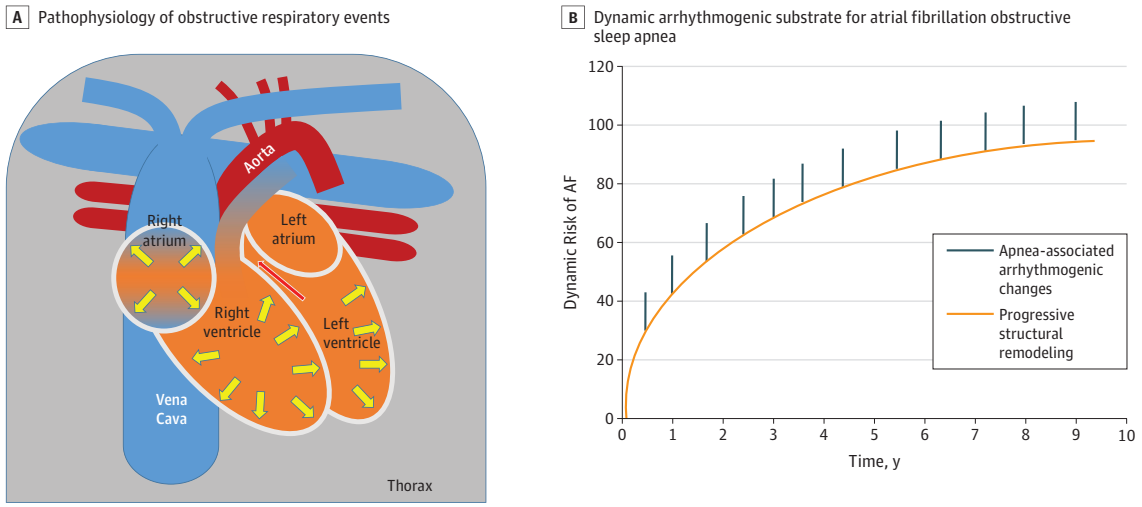
arrhythmogenic changes and the frequency of nocturnal premature atrial contractions transiently increase the risk, creating a unique complex and dynamic substrate for atrial fibrillation (Box).

Assessment and Diagnosis of Sleep Apnea in Patients With AF

Typical clinical symptoms of OSA in patients without cardiovascular disease include snoring, choking arousals from sleep or partner-witnessed breathing pauses, insomnia, nocturia, excessive daytime sleepiness (including drowsy driving), morning headaches, depression, cognitive dysfunction, and erectile dysfunction.[30,31] Questionnaires to assess symptoms of daytime sleepiness, such as the Epworth Sleepiness Scale,[49] are widely used for OSA. However, a cluster analysis in patients with OSA revealed that at least 50% of patients with severe OSA do not report symptoms of unrestful sleep or daytime sleepiness.[50] This proportion is even higher in patients with sleep apnea and cardiovascular diseases such as AF.[9,51,52] While quantification of daytime sleepiness helps to assess the neurobehavioral impact of sleep apnea and the need for treatment, the goal of sleep apnea management in AF is to ameliorate its adverse effects on cardiac structure and function. Several diagnostic sleep-study options are available, including full polysomnography; simpler cardiorespiratory monitoring with a more restricted number of parameters measured (usually oxygen saturation, respiratory effort and airflow) without electroencephalographic assessment of sleep (polygraphy); overnight oxymetry; or special analysis algorithms of ambulatory electrocardiographic testing or implantable device recordings (**Table 2**).[3] Sleep apnea screening can be conducted in a sleep laboratory or at home.

The diagnosis and treatment of sleep apnea in patients with AF requires a close interdisciplinary collaboration between the electrophysiologist or cardiologist and sleep specialists, possibly within an integrated care model. Polygraphy may be a suitable method to ensure patient access to screening for OSA in the standard clinical

Figure. Obstructive Sleep Apnea and a Unique Complex and Dynamic Substrate for Atrial Fibrillation



A, Obstructive apneas during sleep result in intrathoracic pressure swings, changes in blood gas levels, sympathovagal activation, and increases in the size of the right atrium, right ventricle, and left ventricle (yellow arrows). B, In addition to long-term progressive structural remodeling (yellow), transient apnea-associated arrhythmogenic changes (black) repeatedly spike during obstructive respiratory events, contributing to an dynamic increase in atrial fibrillation risk; 100% indicates the clinical threshold for occurrence of atrial fibrillation episodes. AF indicates atrial fibrillation.

Table 2. Screening and Diagnosis of Sleep Apnea

Diagnostic Sleep-Study Options	Details	Sensitivity	Specificity	Comparison
Level I: complete polysomnography	Occurs in a laboratory with a technician present	NA	NA	Gold standard
Level II: complete polysomnography	Occurs outside of the laboratory with no technician present	NA	NA	Gold standard
Level III: portable polygraphy	Procedure records airflow, respiratory effort, and oxygen saturation, but not sleep stages	79% and 97%[a]	60% and 90%[a30,38]	Polysomnography
Level IV: overnight oximetry	Procedure records oxygen saturation with or without airflow	93%	75%[30,38]	Polygraphy
Questionnaire	eg, Epworth Sleepiness Scale[52]	32%[b] or 54%[c]	54%[b] or 65%[c30,38]	Polysomnography

[a] Specificity for this measure is across 2 different Apnea Hypopnea Index cutoffs.

[b] In patients with atrial fibrillation.

[c] In the general population.

examination of patients with AF who are being considered for rhythm control strategies, although specific validation studies in populations with AF are needed. Questionnaires, like the Epworth Sleepiness Scale, can help to quantify subjective daytime sleepiness, but the absence of subjective sleepiness is not a reliable means of ruling out OSA in patients with AF.[9,51,52] Whether structured interrogation for other OSA-specific symptoms may help to identify moderate to severe OSA without requiring sleep study in every patient with AF is an important area for future research. Frequent episodes of sedative-induced obstructive respiratory events during interventions, such as electrical cardioversion or catheter ablation, may also suggest OSA in patients with AF.[44]

In accordance with current recommendations,[49] the severity of sleep apnea in patients with AF has been determined in most clinical studies with the Apnea Hypopnea Index (AHI). The AHI was initially used in pulmonology and sleep medicine to quantify respiratory disturbances. It is defined as the number of apneas and hypopneas per hour of sleep (polysomnography) or per hour of recording time (polygraphy), which may only be a crude estimate of sleep apnea severity. In this index, apneas are defined by a drop greater than 90% from the peak signal excursion of the pre-event baseline of the thermistor signal for longer than 10 seconds without a requirement for oxygen desaturation. Hypopneas are assessed based on a peak of the thermistor signal excursion drop greater than 30% for at least 10 seconds accompanied by oxygen desaturation of 3% to 4% or more from pre-event baseline or by an arousal from sleep.[49]

The AHI does not specifically encapsulate the absolute degree and duration of oxygen desaturation, and cannot differentiate between patients with short episodes of apnea or hypopnea and slight oxygen desaturation from those with the same or similar number but much longer and more marked oxygen desaturation. Additionally, the fact that hypopneas are not scored uniformly and that the definition of an apnea does not require a concomitant desaturation can result in a significant divergence between the AHI and the oxygen desaturation index defined as the number of desaturations per hour of sleep (polysomnography) or per hour of recording time (polygraphy). Thus, the AHI may not be the best sleep apnea metric to predict the progression of cardiac remodeling and cardiovascular events triggered by hypoxia. In a cohort study of 3542 adults, all of whom were free of history of AF, Gami et al[53] reported that, in patients younger than 65 years, obesity and the magnitude of nocturnal oxygen desaturation were independent predictors of new-onset AF, not the AHI. Interestingly, a similar link was found for patients with heart failure, where previous studies had suggested that the nocturnal hypoxemic burden was a much stronger independent predictor of all-cause mortality than the AHI was.[54-56]

Prevalence of Sleep Apnea in Patients With AF

The threshold AHI score used for the diagnosis of sleep apnea in the various studies investigating the prevalence and incidence of AF ranges between 5 and 15 episodes of apnea or hypopnea per hour. A revision of American Academy of Sleep Medicine scoring rules in 2012[49] led to a less strict definition of hypopnea, more people being diagnosed with sleep apnea, and larger numbers considered to have severe sleep apnea. These and other limiting factors make a direct comparison of the different studies difficult. Partly because of the increasing sensitivity of sleep-study recording techniques and scoring criteria, the prevalence of sleep apnea has ranged widely (between 3% and 49%) in different population-based samples.[4-8] Notwithstanding these methodological limitations, the estimated prevalence of sleep apnea in patients with AF has been found to be much higher (21% to 74%) than in control participants without AF (Table 1).[4-8,41]

Conversely, the prevalence of nocturnal AF in patients with sleep apnea has been estimated at 3% to 5%,[39] which is somewhat higher than the prevalence in control patients or the general population (0.4% to 1%).[40] The Sleep Heart Health study compared the prevalence of cardiac arrhythmias on overnight sleep-study in participants with sleep apnea vs participants without sleep apnea and reported AF prevalence of 4.8% and 0.9%, respectively.[41] Sleep apnea is associated with new-onset AF after coronary artery bypass grafting[13] and is an independent predictor of postoperative AF.[14]

The above prevalence estimates of sleep apnea in patients with AF are based on analyses of cross-sectional studies. Clinical history or diagnostic questionnaires (eg, the Berlin Questionnaire[49] or Epworth Sleepiness Scale[49]) formed the basis of OSA diagnosis in some studies, whereas the diagnosis was not always excluded by sleep-study in control groups without OSA.[12,23,24] Prospective longitudinal population-based studies evaluating the association between untreated OSA and incident AF are not currently available. Additionally, in patients with AF and comorbid OSA, concomitant conditions like hypertension, obesity, and metabolic syndrome are highly prevalent, but the relative contribution of each condition remains unclear.

Subclassification of Respiratory Events in Patients With AF

In some studies, sleep apnea was characterized by distinguishing between predominant OSA or CSA. A study of relatively young patients (with a mean [SD] age of 56 [12] years) with paroxysmal high-burden AF or persistent AF with preserved left-ventricular function found a high prevalence of sleep apnea (62%, compared with 38% in patients without AF).[7] The proportion of patients with sleep apnea was greater in those with more severe (high-frequency paroxysmal or persistent) AF vs less severe (low-frequency paroxysmal) AF.[7] In this study,[7] a further characterization of sleep apnea revealed the presence of mainly OSA. In 2911 participants of the Outcomes of Sleep Disorders in Older Men study, increasing severity of sleep apnea was associated with a progressive increase in the odds of AF and cardiovascular events.[39] Although CSA was very rare in this study, cardiovascular events were most strongly associated with OSA and hypoxia, whereas AF was most strongly associated with CSA.[39] Interestingly, in patients with persistent AF, rhythm control by electrical cardioversion did not have an associate with changes in the absolute AHI scores but did have an association with reduced nocturnal central respiratory events and unmasked OSA.[57] A high proportion of central respiratory events may therefore reflect the pulmonary congestion and prolonged circulation time due to the underlying cardiac disease, in this case AF, rather than representing a causal factor for AF.[30]

Sleep Apnea Reduces the Effectiveness of AF Treatment

The presence of OSA substantially limits the effect of antiarrhythmic treatment strategies in patients with AF. Patients with AF who have severe OSA show a lower response rate to antiarrhythmic drug therapy than those with milder OSA (Table 1).[22] A prospective analysis by Kanagala et al[5] demonstrated that patients with OSA have a higher recurrence rate of AF after initially successful cardioversion than those without OSA do. The risk of AF recurrence after catheter-based pulmonary vein isolation (PVI) is also higher in patients with OSA than in those without diagnosed OSA.[12,16-19] Acute return of pulmonary vein conduction is more likely in patients who are elderly, hypertensive, experiencing nonparoxysmal AF, having a large left atrium, and experiencing sleep apnea.[16] Compared with patients without OSA, patients with OSA who were not treated with CPAP had more nonpulmonary vein antrum triggers and posterior wall firing, which is possibly a reflection of atrial electrical and structural remodeling.[12] Not using CPAP, in addition to having nonpulmonary vein triggers, predicts PVI failure (hazard ratio, 8.81).[12] Meta-analyses of observational studies with a total of approximately 1000 patients show that patients with OSA have a 31% greater AF recurrence rate after PVI (Table 1).[20,21]

Treatment of Sleep Apnea in Patients With AF

CPAP treatment

There have been no randomized studies on the effect of CPAP on AF recurrence. Nonrandomized observational studies suggest that CPAP can help to maintain sinus rhythm in patients with AF who have OSA (**Table 3**).[23-28] Among 39 patients with OSA undergoing cardioversion for AF, patients receiving CPAP treatment were less likely to have AF recurrences at 12 months compared with an untreated group (no CPAP, 82%; vs CPAP, 42%; $P = .01$; vs no OSA, 53%; $P = .009$).[5] In patients with OSA and AF undergoing PVI (n = 62), CPAP treatment was associated with a higher AF-free survival rate at 12 months after the procedure (71.9% vs 36.7% without CPAP), and this rate of survival was almost similar to patients without OSA.[23] Interestingly, in this study, AF recurrence in patients with OSA treated with CPAP without PVI was comparable with the AF recurrence after PVI in patients with OSA who did not use CPAP treatment.[23] A recent meta-analysis of several nonrandomized studies by Li et al[21] placed patients with OSA not treated with CPAP at a 57% greater risk of AF compared with patients without OSA. In contrast, patients who had CPAP treatment had recurrence risks similar to patients without OSA. In another meta-analysis of 7 prospective cohort studies with a total of 1087 patients, the use of CPAP was associated with a significant reduction in AF recurrence.[27] This effect remains consistent across patient populations irrespective of whether they underwent PVI.[27] Additionally, in a meta-regression analysis, benefits of CPAP were stronger for younger, obese, and male patients, which should be investigated in future randomized clinical trials (eTable in the Supplement).[28]

In contrast to the encouraging outcomes of CPAP treatment in patients with AF have been the outcomes of randomized clinical trials of CPAP use in cardiovascular patients. In the recent Sleep Apnea Cardiovascular Endpoints (SAVE) trial, CPAP use in patients who had both moderate to severe OSA and documented vascular disease did not result in a difference in cardiovascular outcomes, and new-onset AF was not different in the CPAP-treated patients with OSA compared with those who did not use CPAP.[58] Furthermore, the negative results of the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial[59] suggest that adaptive servo ventilation therapy should not be used in patients with heart failure with reduced ejection fraction, predominantly CSA and Cheynes Stokes respiration (in whom AF occurs in approximately one-quarter).[3] Notably, in both randomized studies, AF was not a predetermined end point, rhythm-monitoring was not sufficient to systematically detect incident AF, and the effects on rhythm control in patients with established AF was not reported.

One possible problem with positive-pressure mask therapies is limited tolerance and adherence. As with CPAP adherence in the broader population of patients with OSA,[60] approximately half of patients with AF and diagnosed OSA were recently found to adhere to CPAP.[12] In most studies, treatment efficacy was assessed by self-reported CPAP use, leading to a suboptimally defined treatment outcome of CPAP on AF recurrence after PVI. Additionally, several points concerning the guidance of sleep apnea treatment remain unclear: what severity of sleep apnea should be used to determine the need for treatment? Does an increased AHI score without elevation in the oxygen desaturation index or very limited nocturnal hypoxemic burden pose any cardiovascular risk? Is AHI the best parameter to determine OSA severity and to decide which patients with AF require treatment? What is the role of CPAP treatment in

Table 3. Study Characteristics and Relative Risk of Atrial Fibrillation Recurrence After Ablation in CPAP-Using Patients vs CPAP Nonusers

Source	Study Design	AF Ablation Strategy	Follow-up, Mo.	Patients with OSA, No. (Male, No. [%])	Relative Risk (95% CI)
Jongnarangsin et al,[24] 2008	Retrospective, observational	PVI or CFAE	7	32 (26 [81])	0.7 (0.40-1.24)
Patel et al,[12] 2010	Retrospective, observational	PVI, posterior LA, or SVC	20	640 (475 [74.2])	0.61 (0.51-0.73)
Fein et al,[23] 2013	Retrospective, observational	PVI	12	62 (46 [74])	0.58 (0.37-0.91)
Naruse et al,[26] 2013	Prospective, case-control	PVI, posterior LA, or SVC	18	116 (102 [87.9])	0.52 (0.37-0.74)
Neilan et al,[19] 2013	Prospective, case-control	PVI, roof, posterior LA, or CFAE	42	142 (115 [81.0])	0.58 (0.5-0.67)

Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrograms; LA, left atrium; OSA, obstructive sleep apnea; PVI, pulmonary vein isolation; SVC, superior vena cava.

older patients with AF? Should other sleep-related abnormalities, such as nocturnal periodic limb movements that increase the arousal index and have been shown to be associated with prevalent AF,[61] incident AF,[62] and AF progression[63] be evaluated and treated in patients with AF? (These questions are presented in the Box.)

Non-CPAP Interventions

Sleep positional therapy and the use of mandibular advancement devices may be effective in patients with OSA who refuse or are intolerant of CPAP treatment. In CSA, phrenic nerve stimulation is a new treatment approach, with initial results showing that it may reduce central respiratory event frequency by approximately 50%.[64] In preclinical studies, apnea-associated inducibility of AF could be attenuated by ganglionated plexus ablation,[65] renal sympathetic denervation,[45] low-level vagosympathetic trunk stimulation,[66] and low-level baroreceptor stimulation.[67]

Lifestyle Interventions

Patients with sleep apnea and AF should be screened for exacerbating factors, such as obesity[68] and alcohol consumption.[69] Previous clinical studies reported that alcohol consumption prior to bedtime is associated with an increased number and duration of hypopnea and apnea occurrences in people who snore and patients with sleep apnea, and requires higher levels of CPAP to prevent apnea and hypopnea.[70] Additionally, excess weight is strongly associated with OSA and, in more extreme cases, obesity hypoventilation syndrome. Weight loss by behavioral changes or bariatric surgery has beneficial effects on OSA through body mass and AHI score reduction.[71] Thus, interventions like weight loss and drinking cessation may be effective in treating sleep apnea and may thereby potentially reduce cardiovascular complications. In obese patients, risk factor management including weight loss within a goal-directed program improves the long-term success of AF ablation.[72-74] Additionally, weight loss through bariatric surgery reduces incident AF among persons treated for severe obesity.[75] However, most of the studies generating these findings were not specifically performed in patients with AF and OSA. Whether interventions such as weight loss, cessation of alcohol, or other non-CPAP interventions show antiarrhythmic effects in patients with OSA is unknown and needs to be further investigated.

Professional Society Recommendations

The 2016 European Society of Cardiology guidelines on AF[3] recommends that consideration be given to elicited clinical symptoms and signs of OSA and CPAP treatment to reduce AF recurrence and improve AF treatment results (calling this recommendation reasonable to perform). The "2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation"[29] mentions OSA as a relevant modifiable risk factor for AF and recommends screening for signs and symptoms of OSA when evaluating a patient for an AF ablation procedure. It also states that treatment of OSA can be useful for patients with AF, including those who are being evaluated to undergo an AF ablation procedure (judging this recommendation reasonable to perform, with moderate-quality evidence) (Box).

Conclusions

Sleep apnea creates a unique complex and dynamic substrate for AF. As most patients with AF and severe OSA do not report daytime sleepiness, sleep study evaluation may be reasonable in symptomatic patients with AF considered for a rhythm control strategy. The prevalence of sleep apnea is 3% to 49% in population-based samples and 21% to 74% in patients with AF. The presence of OSA reduces the efficacy of catheter-based and pharmacological antiarrhythmic treatment. Observational data suggest that treatment of OSA by CPAP helps to maintain sinus rhythm after electrical cardioversion and to improve catheter ablation success rates in patients with AF. However, before further recommendations can be made, randomized prospective clinical trials are required to confirm the association between OSA and AF, to clarify the benefits of treatment of OSA, to clarify the need and cost-effectiveness of routine OSA screening and treatment, and to firmly establish the role of OSA treatment in AF management guidelines. The optimal metric to determine sleep apnea severity and guide OSA therapy for patients with AF also needs further study.

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Author Affiliations: Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia (Linz, Sanders); Adelaide Institute for Sleep Health, College of Medicine and Public Health, Flinders University (McEvoy); Sleep Health Service, Respiratory and Sleep Services, Southern Adelaide Local Health Network, Adelaide, Australia (McEvoy); Faculty of Medicine, National Heart and Lung Institute, Imperial College London, London, England (Cowie); Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota (Somers); Department of Medicine, Montreal Heart Institute and Université de Montréal, Montréal, Quebec, Canada (Nattel); Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada (Nattel); Institute of Pharmacology, West German Heart and Vascular Center, Faculty of Medicine, University Duisburg-Essen, Essen, Germany (Nattel); HP2 and Sleep Lab, Institut National de la Santé et de la Recherche Médicale, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France (Lévy); University Grenoble Alpes, Grenoble, France (Lévy); Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia (Kalman); Department of Medicine, University of Melbourne, Melbourne, Australia (Kalman).

Author Contributions: Drs Linz and Sanders had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
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