

Atrial fibrillation and sleep-disordered breathing

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Abstract: Atrial fibrillation (AF) is a common supraventricular arrhythmia that increases in prevalence with increasing age and in the presence of comorbidities such as heart failure (HF). AF increases the risk of a number of serious complications, including stroke and HF. As a result, the rate of hospitalization is high, making AF a costly disease. Treatment strategies for AF are broadly based around rate and rhythm control, either pharmacological or mechanical. There appear to be a number of links between sleep-disordered breathing (SDB) and AF, although further studies are needed to fully understand the physiological mechanisms that link these conditions. Patients with AF and SDB share a number of risk factors and comorbidities, including age, male sex, hypertension, congestive HF and coronary artery disease (CAD), and the prevalence of SDB in AF is higher than in the general population. Prevalence rates of obstructive sleep apnea (OSA) in patients with AF have been reported to range from 21% to just over 80%. The prevalence of central sleep apnea (CSA) in patients with AF is less well defined, but appears to be particularly high in patients who also have HF and a reduced left ventricular ejection fraction (LVEF). The frequency of apneas can be reduced by effective treatment of AF, while co-existing OSA reduces the effectiveness of treatments for AF and there is an increased risk of arrhythmia recurrence in the presence of SDB. Treating OSA with continuous positive airway pressure (CPAP) therapy has shown the potential to decrease the incidence of AF, improve the effectiveness of AF interventions, and decrease the risk of arrhythmia recurrence, although data from large randomized, controlled clinical trials are lacking. Based on available data, inclusion of SDB recognition and management strategies as part of AF management appears to have the potential to reduce the impact of this arrhythmia at both the individual and societal levels, and has been recognized as important in recent guidelines.

Keywords: Sleep-disordered breathing (SDB); obstructive sleep apnea (OSA); central sleep apnea (CSA); atrial fibrillation (AF); ablation

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Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia, occurring in 1–2% of the general population (1). An estimated 4.5 million people in the European Union and 2.3 million in North America have paroxysmal or persistent AF (2,3). AF is the most common arrhythmia in clinical practice, accounting for approximately one-third

of hospitalizations for cardiac rhythm disturbances (1). It is a disease of older patients, with a prevalence of <0.5% in subjects aged 40–50 years compared with 5–15% at 80 years of age (2,4–8). The prevalence of AF also increases in the presence of congestive heart failure (HF) or valvular heart disease (9), and is more common in men than in women (1). Isolated AF, without associated cardiopulmonary disease, accounts for 12–30% of AF (10).

As is the case for a number of other cardiac conditions, the prevalence of AF is expected to increase dramatically (2.5-fold) by 2050 as the population ages (1-3). European projections, based on data from the Rotterdam Study (a Dutch community-based prospective cohort study), estimate a similar increase in AF prevalence, with more than double the current number of cases expected in adults aged ≥ 55 years by the end of 2060 (11). AF is a costly illness. A systematic review of recent literature estimated the direct costs of AF at \$US2,000 to \$US14,200 per patient-year in the USA and €450 to €3,000 per patient-year in Europe (12). This is comparable to costs associated with other chronic conditions such as diabetes. Hospitalizations were the main contributors to the high direct cost of AF, making up 50–70% of the total (12).

Atrial fibrillation (AF)

Definition and classification

AF is characterized by uncoordinated atrial activation, resulting in deterioration of atrial mechanical function. In the presence of intact atrioventricular conduction, this is associated with an irregular, often rapid, ventricular response. It may be asymptomatic and patients can be unaware that they have AF until it is discovered during a physical examination. Many others experience symptoms, which include palpitations, hypotension, weakness, lightheadedness, confusion, shortness of breath and/or chest pain (1).

An AF episode is defined as AF that is documented by ECG monitoring and has duration of ≥ 30 seconds or, if < 30 seconds, is present continuously throughout the ECG tracing. Recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days (usually within 48 hours) is classified as paroxysmal AF. Persistent AF is continuous AF that is sustained beyond 7 days or requires termination by cardioversion, while continuous AF of > 12 months duration where a decision is made to adopt a rhythm control strategy is known as longstanding persistent AF (1,10). AF can also be classified as permanent when the decision is taken to stop attempts to restore and/or maintain sinus rhythm (13).

Complications

AF increases the risk of developing a number of serious complications, including stroke and HF. The chaotic heart rhythm associated with AF may cause blood to pool in the

atria and form clots, which can then dislodge and travel to the brain and block blood flow, causing an ischemic stroke. The risk of stroke in patients with AF depends on patient age (increasing as age increases) and the presence of comorbidities (such as hypertension, diabetes, HF and previous stroke). As a result, patients with paroxysmal, persistent or permanent AF usually receive antithrombotic prophylaxis. AF can also contribute to the development or worsening of HF (13).

Treatment

Apart from management of thromboembolic risk, there are two main treatment strategies used for the management of AF: rate control and rhythm control (1,13). Rate control focuses on reducing the heart rate closer to normal levels (usually 60–100 beats/min) without any attempt to restore a normal heart rhythm (sinus rhythm). Restoration of sinus rhythm using electrical or pharmacological cardioversion is the goal of rhythm control. If this is not successful then catheter ablation may be attempted. There are a number of approaches to ablation therapy. Maintenance of sinus rhythm is achieved in 85% of patients 1 year after radiofrequency ablation, in 87% 1 year after cryoablation and in 86% at 18 months after high-intensity ultrasound (1). Factors associated with reduced success of ablation therapy include large left atrial size, advanced age, longer duration of AF (permanent *vs.* paroxysmal disease), hypertension, and sleep apnea (14).

AF and sleep-disordered breathing (SDB)

Mechanisms underlying the association between SDB and AF

There are a number of risk factors and comorbidities that are common to both AF and sleep-disordered breathing (SDB), including age, male sex, hypertension, congestive HF and coronary artery disease (CAD) (15). In addition, there are a number of different potential mechanisms by which obstructive sleep apnea (OSA) might contribute to the development of AF. These include intermittent hypoxia, recurrent arousals and increased negative intrathoracic pressure (16–18), all of which result in increased sympathetic nerve activity and oxidative stress, and possible electrical and mechanical remodeling of both atria and the left ventricle (16–18). Electrical abnormalities and cardiac mechanical alterations have been documented in patients with OSA (19,20), supporting the suggestion

that susceptibility to AF is increased in the presence of OSA. Although there are many plausible explanations for the observed association between SDB and AF, more data are needed to allow the physiological mechanisms that link these two conditions to be fully understood (16).

SDB prevalence and impact in patients with AF

SDB has been documented in about three-quarters (74%) of patients with AF and normal systolic left ventricular function (21). Other studies estimate the prevalence of OSA in patients with AF at 21% to just over 80%, a higher rate than in controls without AF (21-25). In addition, the proportion of patients with OSA was greater in those with more severe (high-frequency paroxysmal or persistent) versus less severe (low frequency paroxysmal) AF (26). In a large cohort of AF patients without other significant comorbidities (n=579,521), the occurrence rate of AF was higher in those with versus without SDB [1.3% *vs.* 0.7%; $P<0.001$; adjusted hazard ratio (HR): 1.536, 95% confidence interval (CI), 1.171–2.014 ; $P=0.002$] (27).

In the outcomes registry for better informed treatment of AF (ORBIT-AF), 18.2% of the AF patients enrolled had OSA (28). Patients with versus without OSA were more likely to have severe/disabling AF symptoms (22% *vs.* 16%; $P<0.0001$) and to be receiving rhythm control therapy (35% *vs.* 31%; $P=0.0037$) (28). In addition, on adjusted analysis, the risk of hospitalization was higher in patients with OSA (HR: 1.12, 95% CI, 1.03–1.22 ; $P=0.0078$), although the risk of death was not significantly different in AF patients with or without OSA (HR: 0.94, 95% CI, 0.77–1.15) (28).

Interestingly, even though SDB is quite common in patients with AF, data from two studies showed that most AF patients do not report excessive daytime sleepiness, one of the classic SDB symptoms, and that the Epworth Sleepiness Scale (ESS) score remains low (24,29). This lack of typical symptoms may contribute to the under diagnosis of OSA that has been reported in cardiology outpatient clinics, including in patients with arrhythmias (30).

The prevalence of central sleep apnea (CSA) in patients with AF is not well described and few data are currently available. One study reported that a high proportion of pacemaker recipients with permanent AF had CSA (79%) (31). This high rate of CSA was probably due to a high prevalence of HF and reduced left ventricular ejection fraction (LVEF) in the population studied. Another study documented CSA with Cheyne Stokes respiration [CSA/CSR] in 31% of 150 AF patients with normal left ventricular function (43%

had OSA) (21). In that study, SDB appeared to be more severe in patients with CSA/CSR [based on significantly higher apnea-hypopnea index (AHI)]. In addition, patients with CSA/CSR had higher pulmonary artery pressure and significantly lower carbon dioxide levels than patients with OSA or no SDB (21). In a group of pacemaker recipients with permanent AF, the prevalence of sleep apnea was 74%, and a high proportion of apnea events (79%) were of a central nature (31). In addition, CSA or moderate-to-severe OSA was documented in 29% of patients with drug refractory and symptomatic AF who had been referred for ablation procedures (32).

AF in patients with SDB

The prevalence of nocturnal AF in patients with OSA has been estimated at 3–5%, somewhat higher than the prevalence rate for controls or the general population (0.4–1%) (33-35). The HR for AF in patients with versus without OSA has been estimated at 2.2 (36). The Sleep Heart Health study compared the prevalence of cardiac arrhythmias in subjects with or without SDB and reported AF prevalence rates of 4.8% and 0.9%, respectively ($P=0.003$) (35). Data from this study also showed that an arrhythmic event was nearly 18 times more likely to occur after a hypopneic or apneic episode than after normal breathing (35). Both OSA and decreased nocturnal oxygen saturation were independent predictors of incident AF in subjects aged <65 years in a large retrospective study of adults with no prior history of AF (36).

The independent contribution of OSA to the development of AF was highlighted by data showing that the prevalence of AF was higher in patients with CAD and OSA *vs.* CAD without OSA (32% *vs.* 18%, respectively) (37), in HF patients with versus without OSA (22% *vs.* 5%, respectively) (38), and in those with both hypertrophic cardiomyopathy and OSA compared with cardiomyopathy alone (31% *vs.* 6%, respectively) (39).

The severity of OSA has been shown to influence the prevalence of AF. Patients with an AHI of ≥ 10 /h had an AF prevalence rate of 58% compared with 42% in those with an AHI of ≤ 10 /h ($P<0.0001$), and the prevalence of AF was even higher (70%) in patients with severe OSA (AHI ≥ 40 /h) (40). In a population of young patients (mean age: 38.9 ± 13.1 years) without significant comorbidities, after adjustment for age and sex, the presence of SDB with an indication for continuous positive airway pressure (CPAP) treatment was a significant risk factor for new-

onset AF (HR: 4.507, 95% CI, 1.691–12.010; $P=0.003$); For patients with SDB for whom CPAP was not indicated, the HR value was 1.457 (95% CI, 1.099–1.932; $P=0.009$), indicating again that AF risk increases as the severity of SDB increased (27). Data from a US population-based case-control study showed that patients with OSA who experienced a stroke had a significantly higher rate of AF than those who didn't have a stroke (50% *vs.* 10.8%, $P<0.01$) (41). The observed relationship between AF and stroke in OSA patients remained significant after controlling for multiple confounding factors (age, body mass index, CAD, hypertension, diabetes, hyperlipidemia and smoking status; adjusted OR: 5.34, 95% CI, 1.79–17.29) (41). OSA was also identified as an independent predictor of stroke in patients with AF in a retrospective cohort study (42). The rate of ischemic stroke in AF patients with OSA (25.4%) was higher than that in patients with AF but no OSA (8.2%; $P=0.006$). The increased stroke risk remained after adjustment for age, male gender and CAD (OR: 3.65, 95% CI, 1.252–10.623), and the rate of stroke increased as the AHI increased ($P=0.0045$) (42).

OSA: a risk factor for recurrent AF

There is a growing body of evidence consistently demonstrating that patients with OSA are much less likely to maintain sinus rhythm after treatment of AF with radiofrequency catheter ablation (23,32,43-49). For example, the risk of AF recurrence after ablation in a recent study was significantly higher in patients with versus without OSA (65.2% *vs.* 45.6%; $P=0.001$) (49). In addition, untreated OSA has been shown to double the risk of AF recurrence after electrical cardioversion (37). The negative effects of OSA on AF recurrence are not limited to electrical interventions. Patients who do not respond to antiarrhythmic drug therapy were significantly more likely to have severe OSA rather than mild OSA (52% *vs.* 23%; $P=0.05$), and those with severe OSA were much less likely to respond to antiarrhythmics than patients with mild OSA (39% *vs.* 70%; $P=0.02$) (50).

Effect of treating OSA on AF

Treatment of OSA with CPAP was associated with a significant reduction in the occurrence of paroxysmal AF in a Japanese study (33). In addition, using CPAP to treat OSA has been shown to improve the success of cardioversion strategies. Although the number of patients treated with

CPAP was small ($n=12$), a cohort study by Kanagala and colleagues showed that 12-month AF recurrence rates were higher in untreated OSA patients (82%) than in those receiving CPAP (42%; $P=0.013$) (51). Patients with OSA and AF also appear to be much less likely to progress to permanent forms of the arrhythmia when treated with CPAP compared with no treatment (HR: 0.66, 95% CI, 0.46, 0.94; $P=0.021$) (28).

In a large cohort study ($n=3,000$), patients with OSA had more pulmonary vein isolation (PVI) procedure failures than those without this SDB ($P=0.024$). Furthermore, not using CPAP was a strong predictor of procedural failure (HR: 8.81; $P<0.001$) (23). Over 42 months of follow-up in another group of AF patients undergoing PVI ($n=720$), the arrhythmia recurrence rate was 30% in patients with SDB, 68% in patients with untreated SDB and 35% in SDB patients treated with CPAP for >4 h/night (52). In this study, the risk of AF recurrence was significantly associated with the presence of SDB (HR: 2.79, 95% CI, 1.97–3.94) and untreated SDB (HR: 1.61, 95% CI, 1.35–19.2; $P<0.0001$) (52). Prospectively-collected data on the effects of CPAP treatment on AF recurrence after catheter ablation confirmed that rates were significantly higher in untreated OSA patients (53%) compared with those receiving CPAP therapy (30%) (47). This study also reported that compliance with CPAP therapy was important for reducing AF recurrence (47). CPAP therapy appears to have the ability to reduce the risk of AF recurrence after catheter ablation to a level similar to that in patients without OSA (53). The incidence of newly-diagnosed AF after radiofrequency ablation is also reduced when OSA is treated with CPAP (54). An overview of studies investigating the effects of CPAP treatment on the recurrence of AF after ablation therapy is provided in *Table 1*. A meta-analysis of studies investigating the risk of recurrent AF concluded that use of CPAP in patients with OSA significantly reduced the risk of recurrent AF (33.3% *vs.* 57.6% in non-users of CPAP; relative risk: 0.58; 95% CI, 0.50–0.67; $P<0.001$), with a similar effect size across all patient subgroups, including those treated with PVI (55).

A number of hypotheses have been proposed to explain the beneficial effects of CPAP treatment on AF in patients with OSA. One is that CPAP therapy prevents large negative swings in intrathoracic pressure and associated arterial oxygen desaturations (56). It has also been suggested that CPAP treatment improves atrial conduction and reverses electrical remodeling (57), ameliorates oxidative stress (58,59), and has the potential to prevent left atrial

Table 1 Summary of studies investigating the effect of CPAP treatment for sleep apnea on recurrence of AF after ablation therapy

Study	Design	Population	Baseline SDB	AF therapy	Results	Conclusions	Limitations
Kanagala <i>et al.</i> 2003 (51)	Prospective, single center; 1-year FU	118 pts analyzed (39 received CPAP)	OSA; mean AHI 45/h (treated group) or 34/h (untreated group)	CV	Recurrence of AF at 12 months: 82% of untreated OSA pts vs. 42% of treated OSA pts (P=0.013) and 53% of controls (P=0.009)	Appropriate treatment with CPAP in OSA pts is associated with less AF recurrence	Small sample; no information on device used; no information on CPAP compliance
Patel <i>et al.</i> 2010 (23)	Retrospective, multicenter; mean 32-month FU	3,000 pts; (315 OSA + CPAP; 325 untreated OSA)	OSA; AHI >15/h	RFCA	Early AF recurrence rate: 33% in CPAP group vs. 55% in untreated pts Free of AF at end of FU: 68% (CPAP) vs. 79% (untreated) (P=0.003)	OSA was an independent predictor for pulmonary vein antrum isolation (PVAI) failure; treatment with CPAP improved PVAI success	Retrospective; no information on device used
Naruse <i>et al.</i> 2013 (47)	Prospective, single center, mean 18.8-month FU	153 pts	OSA; AHI >5/h; 9.6% of pts overall; 12.7% in AF recurrence group; 8.7% in no AF recurrence group (P=0.042)	RFCA	116 (76%) pts had OSA on PSG; 82 (54%) received CPAP therapy; AF recurrence rate: 53% in the no-CPAP group, 22% in the no-OSA group and 30% in the CPAP group (P<0.01)	Untreated OSA pts have higher AF recurrence of AF after ablation; appropriate CPAP treatment in pts with OSA reduces AF recurrence	Small sample; CPAP treatment not randomized
Fein <i>et al.</i> 2013 (53)	Retrospective, single center; 1-year FU	114 pts; (32 CPAP user, 30 CPAP non-user, 30 control, 22 CPAP user treated medically)	OSA; AHI >15/h	PVI	AF-free survival rate: 71.9% in CPAP users vs. 36.7% in CPAP non-users (P=0.01); AF-free survival off anti-arrhythmic drugs or repeat ablation: 65.6% in CPAP users vs. 33.3% in CPAP non-users (P=0.02); AF recurrence rate in CPAP users similar to that in pts without OSA (HR: 0.7; P=0.46); AF recurrence rate in CPAP non-users significantly higher (HR: 2.4, P<0.02) and similar to that in OSA pts managed medically without ablation (HR: 2.1, P=0.68)	CPAP is an important therapy in OSA pts undergoing PVI that improves arrhythmia-free survival; PVI offers limited value to OSA pts not treated with CPAP	Retrospective study; No information on device used

Table 1 (continued)

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Study	Design	Population	Baseline SDB	AF therapy	Results	Conclusions	Limitations
Bazan et al. 2013 (54)	Prospective, single center; 1-year FU	56 pts	OSA; AHI >5/h (82%) AHI >30/h (45%)	CTI catheter ablation	AF recurrence: n=21 (38%); freedom from AF prior to ablation and CPAP initiation in pts without previously documented AF at inclusion were associated with a reduction of AF episodes during follow-up (P=0.019 and P=0.025, respectively); CPAP did not prevent AF recurrence when AF was documented prior to ablation (P=0.25)	Treatment with CPAP is associated with a lower incidence of newly-diagnosed AF after CTI ablation	Small size
Neilan et al. 2013 (52)	Prospective, single center, observational; 3.5-year FU	720 pts	SA diagnosed using AASM criteria	PVI	AF recurrence: n=245 (34%); cumulative incidence of AF recurrence: 51% in pts with SA, 30% in pts without SA, 68% in pts with untreated SA, 35% in pts with treated SA; in a multivariable model, the presence of SA (HR: 2.79, 95% CI, 1.97–3.94; P<0.0001) and untreated SA (HR: 1.61, 95% CI, 1.35–1.92, P<0.0001) were highly associated with AF recurrence	CPAP therapy is associated with a lower risk of AF recurrence after PVI	No data about AHI

AASM, American Academy of Sleep Medicine; AF, atrial fibrillation; AHI, apnea-hypopnea index; CI, confidence interval; CPAP, continuous positive airway pressure; CTI, cavo-tricuspid isthmus; CV, cardioversion; FU, follow-up; HR, hazard ratio; OSA, obstructive sleep apnea; PSG, polysomnography; pts, patients; PVI, pulmonary vein isolation; RFCA, radiofrequency catheter ablation; SA, sleep apnea.

structural remodeling (60,61).

Although currently-available data are promising, additional information from adequately-powered, randomized controlled trials specifically addressing the effects of CPAP, or other interventions, on AF outcomes in patients with OSA are needed to allow cardiologists to widely recommend such approaches. Nevertheless, sleep apnea has been mentioned in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, where it was highlighted that “*attention to control of HTN [hypertension] and addressing other AF risk factors such as sleep apnea and obesity remains an integral part of AF management after the ablation procedure*” (62). In addition, the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation lists OSA as a clinical risk factor for AF (13).

Effect of treating AF on SDB

A single overnight treatment with overdrive ventricular pacing was able to reduce the number of central apnea events in patients with permanent AF and HF (31). A reduction in central respiratory events was also documented in a study of 138 patients with AF or atrial flutter after restoration of sinus rhythm with electrical cardioversion; the number of patients with CSA before and immediately after cardioversion was 53 and 23, respectively ($P < 0.001$) (63). In patients with drug-refractory persistent AF, treatment with radiofrequency catheter ablation was associated with a significant reduction in the AHI, and there was a significant correlation between the outcome of the ablation procedure and the percent change in AHI ($P = 0.003$) (64).

Effect of treating CSA on AF

There is currently a lack of data on the effects of treating CSA on AF. This is an area for future research, and could be of particular interest in patients with HF, who have a high incidence of both CSA and AF.

Conclusions

The incidence of AF and the negative consequences of this condition are increasing worldwide, providing considerable challenges to minimize its impact both at the individual and societal levels. Improved disease management strategies to reduce AF-related hospitalizations and decrease the overall cost burden of AF are needed. One such approach appears

to be management of SDB. The prevalence of SDB in patients with arrhythmias is high, and the prevalence of AF in those with SDB is also increased. Furthermore, the presence of SDB appears to predict negative outcomes in patients with AF. Guidelines recognize SDB as a clinical risk factor for AF, and that treatment of SDB is an important part of AF management after ablation procedures. Better management of SDB in patients with AF should allow the effectiveness of antiarrhythmic treatment strategies to be optimized, improving outcomes for patients and decreasing the cost of care.

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Footnote

Conflicts of Interest: All authors are employees of ResMed.

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