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CLINICAL REVIEW

Sleep, sleep apnea and atrial fibrillation: Questions and answers

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SUMMARY

Sleep apnea (SA) is a common sleep disorder increasingly recognized as a risk for cardiovascular disease. Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significant morbidity and mortality. An increasing number of investigations in recent years have linked SA to AF. In this review, we aim to provide a critical overview of the existing evidence in a question and answer format by addressing the following: What is the prevalent association between the two conditions (separating nocturnally detected AF episodes from AF as a prevalent condition)? Is SA a risk factor for incident AF? Is SA a risk factor for recurrence of AF following cardioversion/catheter-based ablation? What is the association between SA and AF in patients with heart failure? Are there signature electrocardiographic markers of AF found in patients with SA? Are there electrophysiology-based studies supporting the link between SA and AF? What other sleep characteristics (beyond SA) are found in patients with AF? What is the impact of SA treatment on AF? What is the effect of AF treatment on sleep? Finally, we address unsolved questions and suggest future directions to enhance our understanding of the AF-SA relationship.

Background

Sleep and wakefulness are the yin and yang of our life. Loss of this balance due to pathological sleep conditions can lead to perturbations of physiological systems essential to maintaining health. Sleep is an active state with a dynamic physiological process. Both sleep state and circadian rhythm have important influences on autonomic nervous system (ANS) modulation, playing an important role in cardiac electrophysiology and arrhythmogenesis. While sleep has generally been considered a protective state, there is increasing recognition that disorders such as sleep apnea (SA) can have an unfavorable impact on cardiovascular physiology by disrupting normally balanced ANS activity and causing intermittent hypoxemia and acute hemodynamic changes. Such negative effects can be more pronounced in patients already having impaired cardiovascular function. Under such circumstances, disruption in ANS modulation can acutely increase the risk of clinically significant arrhythmias. In addition, long-term cumulative exposure to SA may increase the risk of developing more permanent arrhythmic conditions such as atrial fibrillation (AF) via structural and electrical remodeling.

Methods

Based on the consensus among three reviewers (YK, RK, GML), targeted areas of review were determined. Thereafter, two reviewers (YK and RK) independently searched MEDLINE, EMBASE and Google Scholar to find studies pertinent to the targeted questions. We restricted our search to manuscripts published in peer-reviewed journals from 1970 to January 2017. The main search terms used included, but were not limited to, “obstructive/central sleep apnea”, “sleep disordered breathing”, “atrial fibrillation,” “cardioversion”, “catheter-based ablation”, “ pulmonary vein isolation”, “continuous positive airway pressure,” “review article”, “risk factor”, “ pathophysiology” and “epidemiology”. Additional studies were identified based on the reference lists of the retrieved studies. A total of 60 articles including 49 articles directly addressing the topic of “SA and AF” and 11 supporting articles were used for this review. Critical

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Abbreviations

ADD	anti arrhythmic drug
AF	atrial fibrillation
AHI	apnea-hypopnea index
ANS	autonomic nervous system
BMI	body mass index
CI	confidence interval
CPAP	continuous positive airway pressure
CSA	central sleep apnea
ECGs	electrocardiographs
HF	heart failure
HR	hazard ratio
MESA	multi-ethnic study of atherosclerosis
MrOS	osteoporotic fractures in men sleep study
OR	odds ratio
ORBIT-AF	outcomes registry for better informed treatment of atrial fibrillation
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
RDI	respiratory disturbance index
SA	sleep apnea
SAPWD	signal-averaged P-wave duration
SHHS	sleep heart health study

assessment for each article was independently performed by two reviewers (GML or AJ). Finally, the eight most important studies were selected based on the consensus among all authors.

Questions and answers

Is prevalence of AF higher in patients with SA vs. no SA?

Despite the prevailing notion about the high prevalence of AF in patients with SA, studies carefully assessing a true prevalent association between SA and AF (beyond the nocturnal AF detected during sleep study) in unselected populations from the community had not been available until recently.

In the multi-ethnic study of atherosclerosis (MESA), the prevalence of AF among those who underwent polysomnography (PSG) (N = 2048; mean age: 68 y; women: 54%; mean body mass index [BMI]: 28.7 kg/m^2) was 4%, 4%, 6% and 7.5% for apnea-hypopnea index (AHI) < 5/h, 5–15/h, 15–30/h and >30/h respectively (linear trend p = 0.04) [1]. However, statistical significance was lost in the fully adjusted model accounting for comorbidities and when AHI events were defined by 'arousal-based' rather than 'desaturation-based' highlighting the importance of careful interpretation of the results in the context of varying definitions of SA. No associations were found with central SA (CSA) index or percent time spent with oxygen saturation below 90%, a frequently used index to assess severity of nocturnal hypoxemia resulting from SA. AF ascertainment in this study was comprehensive, and most AF was diagnosed solely on diagnostic codes and study electrocardiographs (ECGs), rather than by PSG pointing to the paroxysmal nature in most cases of AF. This association needs to be confirmed in other cohort studies. Further studies in non-selected populations are needed to more definitively answer the question of whether people with SA have a higher prevalence of AF than those without SA.

Is prevalence of SA higher in patients with AF vs. no AF?

Prevalence of SA varies depending on the characteristics of the sample studied (body habitus, age, sex and comorbidities such as hypertension) and the diagnostic criteria (e.g., AHI) used for SA. Therefore cross-examining the prevalence across various studies is often inappropriate. Taking this into consideration, a number of clinic-based studies have generally shown a higher prevalence of SA in patients with AF compared to those without [2,3].

Contemporary prevalence of SA in the community, accounting for body mass index (BMI) distributions, is estimated to be 10–17% and 3–9% for men and women, respectively [4]. In contrast, prevalence of SA in AF is more difficult to estimate as no studies have systematically screened for SA in patients with AF at a large population level. Prior studies have relied on either medical records or survey data, thus making information about SA available only for those who have undergone a sleep study for various clinical indications. Therefore, the estimated prevalence of SA in AF patients from these studies is most likely underestimated, representing those who are more symptomatic. Acknowledging such an issue, the prevalence of SA still appears to be disproportionately high in patients with AF. Gami et al. showed that obstructive SA (OSA) is more prevalent in patients with AF undergoing cardioversion than in comparable patients with multiple other cardiovascular diseases seen in cardiology clinic (49% vs. 32%; adjusted odds ratio (OR): 2.19 [95% confidence interval (CI): 1.40 to 3.42]) [2]. Of note, OSA diagnosis in this prospective study was based on the Berlin questionnaire, although a subgroup of patients underwent sleep study to support the validity of the questionnaire.

In contrast, Stevenson et al. had all eligible subjects undergo sleep study as part of a prospectively designed study protocol [3]. Herein they included 90 middle aged patients with AF but without structural heart disease and 45 age, sex-matched controls with other electrophysiological indications. The prevalence of SA (AHI > 15/h) was higher in AF vs. the control group (62 vs. 38%, p = 0.01). Such a high prevalence of SA was surprising given a relatively normal body habitus (BMI: 26–28 kg/m^2) of participants. In multivariate analysis, the odds of having SA was much greater in AF vs. the control group after accounting for BMI, neck circumference and hypertension (OR: 3.04 [95% CI: 1.24–7.46]).

In a sample of a much larger multi-center cohort undergoing catheter-based AF ablation (N = 3000), the prevalence of documented SA (AHI ≥ 15/h) was 21.3%, although under-reporting likely occurred as OSA was determined by self-reported history [5]. More recent data from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) reported the prevalence of self-reported physician-diagnosed SA or symptomatic SA on continuous positive airway pressure (CPAP) treatment at baseline to be 18.2% [6].

Based on these findings, SA appears to be highly prevalent in patients with AF. However, more rigorous investigations systematically employing sleep studies in all study subjects, with attention to important confounding factors such as body habitus and cardiovascular risks, are needed.

SA prevalence in 'lone AF'?

One strategy to better define the prevalence of SA in AF patients – which could also give insight into the mechanisms intersecting AF and SA – would be to focus on a healthy AF patient population. Porthan et al. compared those with 'lone AF' who, by definition, have a very low cardiovascular risk profile to age-, gender-, and morbidity-matched controls, all of whom underwent a protocol-based sleep study. Among middle-aged, non-obese subjects (BMI: 26–27 kg/m^2), the prevalence of SA (AHI ≥ 15/h) was similar between the 'lone AF' and control group (32% vs. 29%, p = 0.67) [7]. Of

interest, this study showed that larger neck circumference (>40 cm) (even after adjusting for height and SA), but not BMI or waist circumference, was independently associated with lone AF (OR: 5.2 [95% CI: 1.61–16.98]), highlighting the potential implication of anthropometric factors in AF. In examining the relationship between physical activity and lone AF, Calvo et al. using a 2:1 case control design (total N = 172) showed that OSA (AHI > 5/h) was more prevalent in 'lone AF' vs. control (22% vs. 5%, p = 0.01) [8]. Different results between these two studies can be attributed to different AHI cut off (5/h) used in this study and to the fact that only those with high risk features of OSA based on the Berlin questionnaire underwent confirmatory PSG. A paucity of studies makes it difficult to derive a conclusion to this important question.

Is "nocturnal" occurrence of AF higher in patients with vs. without SA?

A novel report by Guilleminault et al., conducted in the 1970s, used 24-h ECG Holter monitoring in 400 obese middle-aged patients with moderate-to-severe SA (AHI ≥ 25/h), and found a 3% prevalence of AF, higher than that of 0.4–1.0% in the general population [9,10]. However, such a difference could have been attributed to the cohort predominantly consisting of patients with obesity, an important shared risk factor for both SA and AF (Fig. 1) [11]. Intriguingly, among eight patients who manifested nocturnal AF during sleep and later underwent tracheostomy, none were found to have AF any longer on the follow up Holter monitoring. This provocative finding of this study provided a basis for many subsequent investigations.

Mehra et al. assessed the prevalence of nocturnal arrhythmia events based on PSG using the sleep heart health study (SHHS) cohort (Mean age: 68–70 y; Male: approximately 50%; BMI: 30.1 kg/m^2) [12]. PSG-detected nocturnal AF was markedly higher in subjects with SA (respiratory disturbance index (RDI) ≥ 30/h) compared to those without (RDI < 5/h) (4.8% vs. 0.1%) (OR: 4.02 [95% CI, 1.03–15.74]). In addition, this study compared subjects who were considered to have severe SA (RDI ≥ 30/h) to those without. A study from the osteoporotic fractures in men (MrOS) sleep study cohort (Mean age 76 y; Male: 100%; BMI 27.2 kg/m^2) extended the results of the SHHS, showing a dose–response relationship between increasing RDI and nocturnal AF (P values for trend = 0.01; the highest RDI quartile, OR: 2.15 [95% CI: 1.19–3.89]) [13]. Importantly, when respiratory events were classified into obstructive vs. central, the dose response association was found only with central events. In the aforementioned MESA study, while there was a linear association between AHI and the odds of having AF, there was no association between AHI and "nocturnal AF" detected during PSG (not published) [1]. Leung et al., involving clinic patients free of heart failure (HF) and coronary heart disease (Mean age: 55 y; Male: 85%; BMI: 29 kg/m^2), found nocturnal AF to be higher in patients with idiopathic CSA (AHI > 10/h, >50% central apnea), but not in those with OSA (AHI > 10/h, >50% obstructive apnea) as compared to a control group (AHI < 10/h) (27%, 1.7%, and 3.3%, respectively, p < 0.001) [14]. Finally, one study from SHHS showed a temporal association between respiratory events (inclusive of any respiratory disturbances but essentially without CSA events) and the incidence of nocturnal AF events. The odds of paroxysmal AF after a respiratory disturbance were strikingly higher (OR: 17.5 [95% CI: 5.3–58.4]) than that after normal breathing during sleep [15]. While all these studies suggest the prevalent association between SA and nocturnal AF, it appears that central respiratory event carry a stronger association with nocturnal AF events.

Does SA increase the risk of incident AF?

A limited number of studies have examined this question. In a large cohort of sleep clinic patients (Mean age: 49 y; Male: 66%; BMI: 33 kg/m^2), those with OSA (AHI ≥ 5/h) had two-fold higher risk of incident AF than those without OSA after an average follow-up of 4.7 y [16]. In a multivariate analysis, among measures of SA, only the difference between awake oxygen saturation and mean nocturnal oxygen saturation predicted incident AF in the age less than 65 y old group (hazard ratio (HR): 3.29 [95% CI: 1.35–8.04]). AHI was not a significant factor in this study. The degree of oxygen desaturation during sleep, a measure of severity of hypoxemia, may also be associated with the presence of undetected cardiopulmonary disease, and therefore this finding may not be sufficient to derive the conclusion of an OSA-AF incident relationship. In another large sleep clinic-based study, Cadby et al. reported that OSA (AHI ≥ 5/h) was associated with incident AF as measured by AF related hospitalizations in a cohort of 6841 individuals (Mean age:

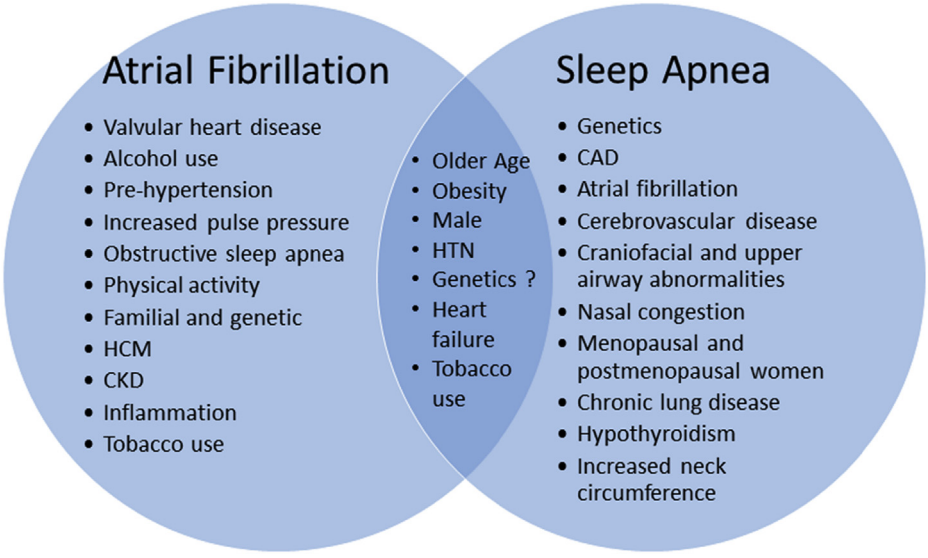

Fig. 1. Shared risk factors between AF and OSA (Venn diagram) [60,61]. HCM, Hypertrophic cardiomyopathy; CKD, Chronic kidney disease; HTN, Hypertension; CAD, Coronary artery disease.

48 y; Male: 77%; BMI: 30.7 kg/m^2) during a median 11.9 y of follow-up (HR: 1.55 [95% CI: 1.21–2.00]) [17]. Unlike the aforementioned study, there was no significant interaction of age and sex for the OSA and AF association in this study.

At a population level, Lin et al. prospectively studied a MESA cohort of 4395 participants free of baseline clinical cardiovascular disease (Mean age: 60 y; Male: 49.3%; BMI: 29.0 kg/m2) and showed that physician-diagnosed OSA based on survey data was associated with incident AF during an average 8.5-year follow-up period (HR: 1.76 [95% CI: 1.03–3.02]) [18]. However, similar to the study by Gami et al. [14], the association between OSA and incident AF was present only in the younger individuals (HR: 3.20 [95% CI: 1.32–7.74]) and in women (HR: 3.97 [95% CI: 1.48–10.65]). A recent study from the MrOS sleep subcohort of 843 ambulatory older men (Mean age: 75 y; Male: 100%; BMI: 27 kg/m^2) showed CSA (central apnea index [CAI] $\geq$ 5/h) and CSA-Cheyne Stokes respiration (CSR), but neither OSA index nor hypoxemia, were associated with incident AF during a mean follow-up of 6.5 y in this older male population [19]. In an age-stratified adjusted analysis, the association was found only in the older age group (median >76 y old). One important limitation of this study is that self-reported AF was included as a measure of outcome. Nonetheless it may be plausible that different subtypes of respiratory events (OSA vs. CSA), via either acute or long-term cumulative fashion, exert varying effects on the pathogenesis of AF and that the effect is modified by age.

Does SA increase the risk of AF recurrence following cardioversion or ablation?

One retrospective prospective study showed that AF recurrence after electrical cardioversion was higher in clinic patients with untreated SA vs. treated SA vs. without SA (82% vs. 53% vs. 42%, respectively ($p = 0.009$)) [5]. A more rigorously designed prospective study that systematically employed PSG as a part of the study protocol (defining OSA as AHI > 15/h) also showed AF recurrence after successful electrical cardioversion was higher in those with OSA vs. without (69% vs. 43% ($p = 0.001$)) [20]. More recently, Linz et al. reported a much higher AF recurrence rate within the first week after successful cardioversion in patients exhibiting obstructive respiratory events during sedation (40%) vs. those without (13%, $p = 0.016$) [21].

There have been a number of observational studies that assessed the impact of OSA on the risk of AF recurrence after catheter-based ablation therapy. A meta-analysis by Ng et al. including six observational studies (~4000 patients) showed that patients with reported OSA based on PSG had 40% greater risk of AF recurrence after catheter ablation than those without OSA (HR: 1.4 [95% CI: 1.16–1.68]) [22].

Does SA make pharmacological rhythm control more challenging?

Monahan et al. reviewed 61 patients on antiarrhythmic drug (AAD) therapy with available sleep study results from their registry. They found that response rate (defined prospectively as successful rhythm control if the patient remained on the same AAD therapy for at least 6 mo after enrollment in the AF registry or demonstrated $\geq$ 75% reduction in symptomatic AF burden [based on the composite score for frequency, duration and severity of symptoms] [25]) to AAD was about twice as high in those with non-severe OSA compared to those with severe OSA (61% vs. 30%; $p = 0.02$) [26]. The study was limited by small sample size and its retrospective design including only those who had available sleep study results. In addition, the study did not properly account for significantly different characteristics noted between the two groups such as proportion of sex, hypertension and coronary artery disease. Although this non-adjustment could be due to limited sample size, these factors can potentially have an important impact on the response to pharmacological therapy. Furthermore, the ambiguous classification of predictor ("severe" vs. non-severe OSA group) and outcome (responder vs. non-responder that is based on mixture of subjective AF burden score and stable use of AAD but without considering rhythm monitoring) raises the question about the generalizability and clinical implication.

What is the association between SA and AF in patients with HF?

Both SA and AF are common in patients with HF but the associations between AF and SA remain unclear in this setting [27]. In a study of 450 stable HF patients, which revealed a high prevalence of either OSA (32% for AHI > 15/h with obstructive events >50%) or CSA (29% for AHI > 15/h with central events >50%), AF was significantly associated with CSA (OR: 3.5 [95% CI: 1.39–8.84]), but not with OSA [28]. The authors did a subsequent study among HF patients on more contemporary therapies and again found that AF was associated with CSA (OR: 7.93 [95% CI: 1.76–35.65]), but not with OSA [29]. In another study of stable HF patients, SA (AHI > 10/h) was associated with prevalent AF [30]. No specific association was reported based on subtype of SA in this study. Similarly, a recent registry-based study by Artz et al. showed that, in addition to BMI, left ventricular ejection fraction, age and male sex, the presence of AF predicted SA (AHI $\geq$ 15/h) without distinguishing subtypes of SA in patients with HF (OR: 1.19 [95% CI: 1.06–1.34]) [31].

These studies suggest that SA, and particularly CSA, is associated with AF in HF, but do not fully address the temporal relationship. Moreover, since SA, specifically CSA, may simply portend severity of HF, the association may have simply been confounded. In contrast, it is noteworthy that a number of studies investigating various aspects of SA in HF, in their description of subjects' characteristics, failed to show any difference in AF prevalence based on the presence of SA alluding to null associations [32–34].

Are there any electrophysiology-based studies supporting the link between SA and AF?

Linz et al. evaluated electrophysiological (EP) properties after simulating OSA by applying negative tracheal pressure up to −100 mbar for a short duration of time in pigs [35,36]. This resulted in shortening of the atrial effective refractory period and increased AF vulnerability. Interestingly, these effects were reduced by renal denervation and abolished by atropine or vagotomy suggesting the importance of autonomic activity as an underlying mechanism. Ghias et al. showed that long apnea duration (up to 2 min) increased neuronal firing from ganglionated plexi adjacent to the pulmonary veins in experimented dogs [37]. AF inducibility also increased, but was mitigated with neural ablation of the ganglia. Iwasaki et al. studied, using a rat model, simulating OSA events 20 consecutive times per day, 5 days a week for 4 weeks [38]. An EP study afterward showed significantly increased AF inducibility. Structural remodeling, including increased left ventricular diameter and mass were also demonstrated. While these animal studies are intriguing, OSA models used in these studies poorly reflect physiological human conditions. And although these studies appear to imply an effect of OSA on short term electrophysiological changes (AF

inducibility), their long term effect is difficult to assess due to the technical difficulties inherent to animal-based experimental models.

Are there electrocardiographic predictors of AF in patients with SA?

P wave indices (e.g., P wave duration, dispersion and terminal force etc.), which describe atrial conduction, are markers for atrial remodeling and have been shown to predict incident AF [39]. In a study using respiratory maneuvers to simulate OSA in both healthy subjects and patients with AF, intrathoracic pressure swings were associated with increased P wave duration and dispersion (the difference between the widest and the narrowest P wave duration recorded from the 12 ECG leads), highlighting SA's instantaneous influence on atrial conduction [40]. In a cross-sectional analysis from the MESA study, SA was associated with an increase in the daytime P wave terminal force in V1 (the duration of the terminal part [negative] of the P wave in lead V1 multiplied by its depth), suggesting potentially more permanent impact of SA on atrial conduction (Fig. 2) [41]. Treatment of SA appears to improve P wave indices. Maeno et al. showed that in patients without AF AHI, age, and hypertension were associated with signal-averaged P-wave duration (SAPWD) [42]. One month of CPAP therapy in patients with moderate-to-severe OSA significantly shortened SAPWD from baseline 138 ± 9 ms to 130 ± 9 ms in contrast to no change in a control group not treated for OSA. Taken together, SA appears to influence left atrial electrical modeling as measured by abnormal P wave indices, and may therefore be a triggering factor in AF. It remains unclear whether P wave indices can predict AF specifically in patients with SA and whether treatment of the SA, while improving P wave indices, can also lower the risk of AF.

Is there any association between sleep duration/poor sleep quality and AF?

Studies have reported, albeit not consistently, that either short or long sleep is associated with adverse health outcomes, such as hypertension, diabetes, cardiovascular disease and total mortality. In the only prospective study to date, Khawaja et al., found that as compared with sleep duration of 7 h, longer sleep duration ≥ 8 h was associated with a modestly increased risk of incident AF (HR: 1.13 [95% CI: 1.00–1.27]) during an mean follow-up of 6.9 y in a large cohort of U.S. male physicians (N = 18,755; Mean age: 67.7 y) in the physicians' health study [43]. Although short sleep duration (≤6 h) was not associated with incident AF in the overall cohort, it did so in the subgroup with self-reported OSA (HR: 2.26 [95% CI: 1.26–4.05]). In a cross-sectional MESA study, no association was found between sleep duration (based on either actigraphy or PSG) and prevalent AF [1]. In addition, this study found that slow wave sleep time, a measure of deep sleep, was associated with lower AF prevalence.

In the aforementioned cross-sectional study by Porthan et al. (see section SA prevalence in 'lone AF'), patients with lone AF reported much more tiredness and sleepiness as compared to controls despite no difference in the prevalence of SA, suggesting that sleep quality or duration might be factors affected by AF [7]. Several sleep deprivation studies have shown subsequent increases in cortisol levels, sympathetic activity, and inflammation, factors that could all mediate AF pathogenesis [44,45]. Long sleep duration could also be associated with AF for varying reasons. One hypothesis implicates an exposure to high parasympathetic and low sympathetic activity that occurs with sleep. Parasympathetic activity, while having heart rate lowering and other beneficial effects on the heart, is paradoxically associated with the induction and maintenance of AF in both human and animal studies [46]. In contrast, long sleep duration may simply represent a marker of ill health [47].

These studies encourage investigators to consider a wide spectrum of sleep characteristics beyond SA while acknowledging the limitations of objective sleep quality assessment and duration.

What is the impact of SA treatment on AF?

Although no randomized controlled study exists, there are a number of observational studies that provide insight into this question. In the aforementioned study by Kanagala et al., among patients with OSA and AF who underwent cardioversion, those who received CPAP therapy had a lower recurrence of AF than those who did not (42 vs. 82%, p = 0.013) [48]. Among the number of studies evaluating the impact of SA treatment with CPAP on the risk of AF recurrence after ablation, the study by Patel et al. represents the largest sample size. This retrospective evaluation of a prospectively collected multi-site database showed that patients who complied with CPAP therapy had a lower recurrence rate over an average of 2.5 y of follow up compared to those who did not (HR: 0.17 [0.08–0.36] [5]). In this study, patients not treated with CPAP and who had non-pulmonary vein triggers (during electrophysiology evaluation) were strikingly more likely to fail the procedure (HR: 8.8 [4.04–19.23]). In support of this finding, two recently conducted meta-analyses assessing the overall effect of OSA treatment on AF

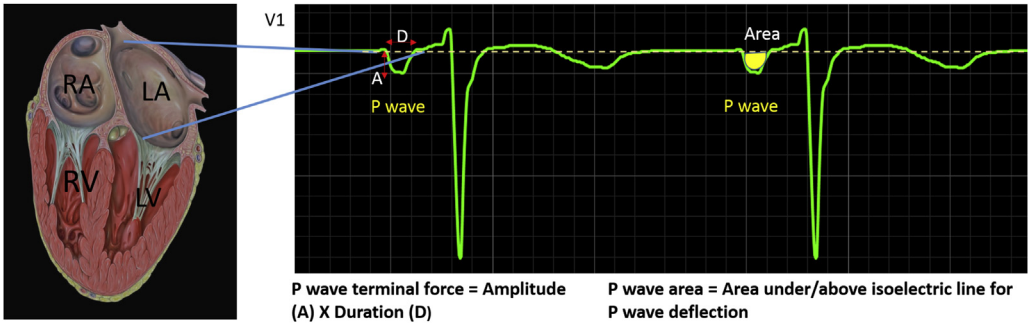

Fig. 2. Depiction of ECG P wave terminal force. Diagram showing P wave terminal force measurements (Left panel) and calculation as well as P wave area (Right panel). Total P wave area is determined by taking the area under the curve from the positive deflection of the p-wave to the isoelectric line and adding it to the area calculated from the area of the P wave below the isoelectric line (dotted line). These are measures for left atrial electrical function and are associated with atrial fibrillation. ECG, electrocardiography; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

recurrence reported about 40% reduction in the risk of AF recurrence [23,24]. Further randomized controlled trials are needed to support these findings, as these studies may have been limited by residual confounding factors and healthy-user bias (i.e., patients with high CPAP compliance may be different from those without use or low CPAP compliance).

What is the effect of AF treatment on sleep?

Sleep quality

In patients with AF, sleep quality seems to improve when sinus rhythm is restored. In a study assessing sleep quality using the Pittsburgh sleep quality index (PSQI), a self-reported measure of sleep quality, patients with AF had poorer sleep quality in comparison to age-matched controls with sinus rhythm (9.4 vs. 5.8, $p = 0.001$). In addition, patients who were successfully cardioverted from AF to sinus rhythm, their sleep quality improved (lower PSQI score: 7.2) after 6 mo of sinus rhythm compared to baseline [49].

Sleep apnea

Small scale studies have shown mixed results with regards to the effect of restoration of sinus rhythm from AF on SA severity. One recent study enrolling 138 consecutive patients with AF or atrial flutter (Mean age: 68 y; Male: 67%; BMI: 29 kg/m^2; Cardiomyopathy prevalence: 40%), all underwent multichannel cardiorespiratory polygraphy at the night before and immediately after electrical cardioversion. The prevalence of SA in this population was 92%, defined as an AHI $\geq$ 5/h. Effective cardioversion to sinus rhythm occurred in 84% of subjects, wherein the AHI decreased from 23 ± 16 (Mean $\pm$ SD) to 16 ± 12 per hour ($p < 0.001$). This effect was predominantly driven by a reduction in central respiratory events [50]. However, this study lacked a control group and as such the minor reduction in AHI shown in this study, albeit statistically significant, could simply reflect commonly observed night to night variability of AHI [51]. In addition such a finding was not replicated in another recent study in which various measures of SA and other commonly derived PSG-based sleep characteristics did not change after cardioversion to sinus rhythm [52].Considering mixed results from existing studies, currently there is no definite evidence that treatment of AF will have any impact on SA [52–55].

What are the remaining questions and challenges?

Is there truly an independent association?

Studies confined to low risk profile, non-obese patients would be extremely valuable in determining whether SA and AF are independently associated. Obesity, hypertension and metabolic syndrome, while commonly associated with OSA, are also considered risk factors for AF, and thus are major confounding factors on the causal pathway between OSA and cardiovascular diseases including AF (Fig. 2). Not only does BMI alone add to these confounding effects, but other measures of body habitus such as neck circumference or waist size warrant statistical adjusting. Recruitment of low profile, "healthy" patients with OSA and AF can be logistically challenging but is not impossible given the high prevalence of AF even in a non-obese population. Such an approach would clearly be superior to statistical adjustment. With regard to CSA, the association with AF could be related to severity of HF rather than CSA itself. It is also important to recognize the limited body of evidence supporting the causal association. There is an unmet need of high quality prospective studies.

Does treatment of SA reduce the risk of incident AF?

No randomized controlled trial has yet to exclusively examine the effect of SA treatment on the incidence or recurrence of AF. Partly driven by the ethical dilemma of withholding treatment of SA, particularly in the presence of symptoms, investigations have relied on observational study designs, exposing them to the risk of healthy-user bias. Thus, uncovering a causal relationship, particularly over a long period of observation for incident AF, remains challenging. However, a randomized controlled trial over a short period with outcomes focused on recurrence of AF, such as following catheter-based therapy, may be more feasible. More simply, the effect of SA treatment on overall AF burden (e.g., as measured by Holter monitoring) may also be an important outcome to assess since reduced AF burden in patients could lead to overall symptom improvement. Existing studies have only evaluated the effect of CPAP on SA, and while being the most commonly used treatment, is limited by low compliance due to discomfort. Alternative treatment options such as mandibular advancement device, positional therapy, or other emerging novel therapies on the incidence of AF are warranted.

Which types of SA? Does it matter?

The association between SA and AF has been inconsistent depending on the subtype of SA (i.e., OSA vs. CSA) and the underlying conditions (such as HF) of included subjects in the study. A more fundamental challenge lies in the fact that many patients with SA frequently exhibit both types of SA in a given night. Many studies have classified the types of SA based on the predominant pattern in a given night. Therefore OSA vs. CSA classification employed in these studies is thus, to some extent, arbitrary. Indeed, the rationale of forcefully classifying SA into a specific type needs to be better defined. Moreover, classification into two different types is based on the assumption that the two are pathophysiologically different in nature. However, the distinction between OSA and CSA is not as intuitive. "Mixed" SA is not uncommon in many patients including those with HF [56,57]. Differentiating the two types using a standard sleep study is not always accurate. In the absence of esophageal manometer, subtle obstructive efforts may not be readily manifested on the respiratory efforts channel, which results in misclassification of OSA as CSA. Finally, assuming differentiation of subtypes of breathing to be important, it becomes necessary to critically appraise the capability of newly entering diagnostic devices in distinguishing subtypes of respiratory events.

Is AHI the best metric to use?

Many investigations have focused on respiratory-based measures derived from a sleep study in studying the association. However, a one night sleep study is subject to misdiagnosis, and thus misclassification, particularly in the case of milder forms of sleep apnea. It is well known that there exists both short and long term variability in severity of SA as measured by AHI [51,58]. Average values from multiple night measurements may be essential, but challenging unless a portable sleep study is utilized. The most commonly used respiratory measure, AHI, while offering a valuable tool to detect SA, has underappreciated limitations as a metric for quantifying the degree of cardiovascular response to SA [59]. In OSA, measures of the degree of sympathetic activity enhancement or the degree of intrathoracic pressure change might be useful. Moreover, cumulative exposure to such responses would be more important than simple "counts" of apnea or hypopnea in understanding the mechanisms linking OSA to various cardiovascular outcomes including genesis and maintenance of AF. On the

Table 1
Summary of major studies.

Studies	Study population	Study design	N	SA (%)	Definition of SA	Major findings	Strengths (S) and limitations (L)
Prevalence of AF in SA							
Mehra et al. (2006) [12]	Community-based cohort	Cross-sectional	400	40	PSG: RDI $\geq$ 30 events/h	Marked higher prevalence of nocturnal AF in subjects with severe SDB vs. without SDB	(S) Binary ethnic community-based study (L) Prevalence of AF based on PSG alone (Nocturnal AF)
Kwon et al. (2015) [1]	Community-based cohort	Cross-sectional	2048	34	PSG: AHI $\geq$ 15 events/h	AF prevalence associated with AHI severity. Attenuation of the association when measures of sleep architecture are considered.	(S) Multiethnic community-based study and prevalence of AF estimated by events, ECG and PSG (L) AF type not verified
Prevalence of SA in AF							
Gami et al. (2004) [2]	Cardiology clinic patients with AF referred for DCCV	Cross-sectional	463 (151 with AF, 312 without AF)	38	Berlin questionnaire	Higher prevalence of OSA in patients with AF vs. matched cardiology clinic patients without AF.	(S) a case-control study with large sample size (L) SA diagnosed by Berlin questionnaire criteria,
Stevenson et al. (2008) [3]	Clinic patients with AF	Cross-sectional	135 (90 with AF, 45 without AF)	54	PSG: AHI $\geq$ 15 events/h	Higher prevalence of OSA in patients with AF vs. matched electrophysiology clinic patients without AF.	(S) Matched electrophysiology clinic patients without AF as the control group. (L) Small sample size of the control group
Patel et al. (2010) [5]	Multi-center cohort of patients undergoing AF ablation	Retrospective cohort	3000 (all with AF)	21	PSG: AHI > 15 events/h	Presence of OSA increased AF ablation failure rate. Treatment of OSA with CPAP improved the success rate.	(S) Multicenter study with large sample size (L) CPAP therapy was not randomized
Porthan et al. (2004) [7]	Clinic patients with lone AF	Cross-sectional	115 (59 with AF, 56 without AF)	31	PSG: AHI $\geq$ 15 events/h with symptoms	Prevalence of OSA similar between 'lone AF' vs matched community control subjects.	(S) participants had very low cardiovascular risk and presented as lone AF (L) a small sample size
Longitudinal evaluations of AF in SA							
Gami et al. (2007) [16]	Sleep clinic patients	Retrospective cohort	3542 without AF	74	PSG: AHI > 5 events/h	Magnitude of nocturnal oxygen desaturation associated with an increased risk of future AF.	(S) PSG-defined SA (L) Sleep clinic-based study not applicable to the general population
Lin et al. (2015) [18]	Community-based cohort	Prospective cohort	4395	4	Self-reported PDSA	PDSA associated with an increased risk of future AF.	(S) Multiethnic community-based study (L) SA was not verified by objective PSG

AHI, apnea hypopnea index; AI, apnea index; AF, atrial fibrillation; CPAP, continuous positive airway pressure; DCCV, direct current cardioversion; ECG, electrocardiography; OSA, obstructive sleep apnea; PSG, polysomnography; PDSA, physician-diagnosed sleep apnea; RDI, respiratory disturbance index; SA, sleep apnea.

other hand, the underlying mechanism linking CSA and AF and the causal direction is less well-defined. More fundamental mechanistic studies are needed in this area.

Sleep beyond sleep apnea

Most investigations have ignored potential effects of other sleep characteristics that may have implications beyond SA in the pathogenesis of AF. Non SA studies such as self-reported sleep duration did not adequately control for SA in their analysis due to lack of objective SA evaluation [43]. Conversely, no previous studies focusing on SA in this review except one [1] accounted for sleep duration or other potentially important sleep characteristics in their analyses. The potential consequence of this was highlighted in the aforementioned MESA study in which the association of SA (based on AHI) and AF was lost when accounting for such factors [1].

Detection and outcome measures of AF

The under-diagnosis of AF due to the use of clinic visit ECGs or limited ECG monitoring affects our interpretation of these studies. In this regard, the use of longer term monitoring would surely increase detection of AF.

Conclusions

Despite the increasing number of investigations and a prevailing notion of the close relationship between SA and AF in the representative studies which were summarized in Table 1, our critical dissection of the existing body of evidence in this area still reveals many unanswered questions. While SA appears to play an important role in recurrence of AF following catheter-based ablation therapy, its independent role in the incidence of new onset AF is unclear. The main challenge owes to the many shared risk factors between the two common conditions. Thus, the majority of current evidence for the association of SA with incident or recurrent AF appear to be present and stronger in middle-aged adults and patients with multiple cardiovascular risk factors. In this regard, rigorously designed studies effectively separating out confounding factors, albeit with anticipated challenges, will be highly valuable in resolving this conflict. In addition, the importance of differentiating

SA subtypes in regard to SA's relationship with AF has been recommended but there is an unmet need to better define SA and to search for alternative ways to characterize its severity. Finally, randomized controlled trials testing the effect of SA therapy on the incidence and recurrence of AF after ablation therapy should be the ultimate future direction.

Practice points

1) The prevalence of nocturnal AF is higher in subjects with SA. An association between SA and AF (beyond nocturnal AF) is less well defined.
2) A limited number of prospective studies have shown the association between OSA and incident AF. The association appears stronger in the younger individuals.
3) Both SA and AF are common in patients with HF but the associations between AF and SA remain unclear in this population.
4) Coexisting OSA confers greater risk of AF recurrence after catheter ablation than those without OSA and the treatment of OSA with CPAP reduces the risk of AF recurrence after ablation.
5) Studies examining the association between sleep duration or quality and AF are scarce.

Research agenda

1) Obesity, hypertension and metabolic syndrome, while commonly associated with OSA, are potential risk factors for AF, and thus are major confounding factors on the causal pathway between OSA and AF. Study designs strictly controlling for these factors are needed.
2) Randomized controlled trials to examine the effect of SA treatment on the incidence or recurrence of AF are needed.
3) The association between SA and AF has been inconsistent depending on the subtype of SA (i.e., OSA vs. CSA) in the study.
4) The most commonly used respiratory measure, AHI, while offering a valuable tool to detect SA, has underappreciated limitations as a metric for quantifying the degree of cardiovascular response to SA. Thus, SA-AF studies based on AHI may have inherent limitations.
5) Most investigations have ignored potential effects of other sleep characteristics such as sleep duration that may have implications beyond SA in the pathogenesis of AF. More studies will be needed to clarify the association between other sleep characteristics rather than SA and AF.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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