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Relationship Between Arrhythmia and Sleep Disordered Breathing

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Abstract

The association between obstructive sleep apnea (OSA) and cardiovascular disease is well known. Data from most studies investigating the prevalence of OSA in atrial fibrillation (AF), and of AF in patients with OSA, have supported the relationship between these common diseases. In addition, several studies have shown a detrimental effect of OSA on AF treatment. These reports vary considerably in methodology, and are particularly diverse in their definitions and diagnosis of OSA and patient populations studied. Considering these studies individually while exploring their methodological variations and the range of results achieved can reinforce the necessity of establishing standards for performing this important research. Reviewing these studies should en courage practitioners to reflect on how the methodologies, patients, and outcomes are relevant to their practices.

Introduction

Sleep-related breathing disorders (or sleep-disordered breathing, SDB) comprise one of the 8 categories of sleep disorders, and are characterized by abnormal depth or frequency of breathing during sleep. SDB is highly prevalent and significantly underdiagnosed worldwide. Although prevalence studies suggest SDB affects 15 million adult Americans, an estimated 60% to 80% of adults are undiagnosed.[1,2]

The most commonly studied sleep disorders in relation to cardiovascular conditions include obstructive sleep apnea (OSA), central sleep apnea (CSA), and Cheyne-Stokes respiration (CSR). OSA and CSA are neurally mediated, and OSA is differentiated by intermittent episodes of partial or complete upper airway obstruction resulting from collapse of the upper airway during sleep. Snoring, repeated arousal, and daytime sleepiness are common symptoms. A patient can have "mixed" SDB when sleep studies indicate both mechanisms are present. CSA and CSR occur mainly in patients with heart failure;[3] therefore, this review focuses on OSA.

Obstructive sleep apnea (OSA) has been shown to be significantly related to several cardiovascular conditions including arterial hypertension, coronary artery disease (CAD), and congestive heart failure (CHF), as well as with arrhythmias.[4,5] The association between OSA and atrial fibrillation (AF) is being extensively studied; however, the basic mechanisms are not completely understood. The possibility of numerous interactions between OSA and AF, in addition to the mechanical effects of apnea, is obvious, as several characteristics of OSA are known to initiate AF. Male gender, obesity, hypertension, and CHF are among the risk fac-

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tors shared by the two conditions.[6] In addition, the association between OSA and other cardiovascularconditions may be involved in the pathophysiology of AF.[7]

Several studies have investigated OSA as a risk factor for AF, which are complicated by their mutual sharing of risk factors. Research is further constrained by diverse patient characteristics and methodological inconsistencies among studies, including the variety of methods that are used to diagnose OSA. It is not surprising, therefore, that discrepant results have been reported among studies, with some studies failing to show an association between sleep apnea and AF.[8] Therefore, a causative link between OSA and AF is often proposed but is not yet proven.[1] As the volume of literature increases, practitioners are challenged to remain informed about the association between OSA and AF, and the effects of OSA on AF management. The significance of these associations and how they may impact practice cannot be overemphasized. Important decisions for practitioners include which patients to screen for sleep apnea, what tools to use, and how to counsel and man age patients in a multidisciplinary setting. This review focuses on 1) developing a practical approach to the current knowledge base that can assist cardiologists with informed decision making, and 2) providing motivation to remain current with developments that may influence best practices for cardiology patient care.

Normal Sleep

Sleep is divided into two physiologically distinct phases: rapid eye movement (REM – active sleep), and non-rapid eye movement (NREM – quiet sleep). Dreams occur primarily during REM sleep, with their resultant central nervous system (CNS) activation and phasic events. Mental activity is greatly diminished or absent during NREM sleep, which comprises 85% of total sleep time in adults. Metabolic factors are in control of the respiratory and cardiovascular systems during that time, with input to the latter reduced by more than one-half compared to wakefulness. Blood pressure and heart rate decrease, while cardiac vagal tone is increased. Sleep apnea can disrupt this quiescent state.[4,10]

Obstructive Sleep Apnea: Pathophysiology in Relation to Atrial Fibrillation

Many recent reviews discuss the potential complex pathophysiological relationships between sleep apnea and cardiovascular conditions, including AF.[9-11] Although the exact mechanisms for a causative link have not been defined, there are several mechanisms by which OSA can predispose to the development of AF, including repetitive and prolonged hypoxemia, hypercapnia, sympathetic hyperactivity, inflammation, exaggerated transmural pressure changes with concomitant increased cardiac wall stress, endothelial dysfunction, and chemoreceptor activation.[12-18]

The ineffective inspiratory efforts in OSA generate exaggerated negative intrathoracic pressure that contributes to one of the main cardiovascular characteristics of OSA. The negative intrathoracic pressure during apneic events produces left ventricular transmural pressure changes with increased left ventricular afterload and venous return to the right ventricle, while hypoxic pulmonary vasoconstriction increases pulmonary artery pressure and right ventricular afterload.[4,15,19,20] The interventricular septum shifts to the left, effectively interfering with left ventricular diastolic filling, and stroke volume and cardiac output decrease. The exaggerated negative intrathoracic pressure can produce sudden passive atrial and ventricular mechanical stretch and pulmonary vein expansion.[10] Pulmonary vein arrhythmogenicity, atrial dilatation and, possibly, atrial fibrillation, may result.[19]

Under resting conditions, parasympathetic influence, expressed by rapid and continuous vagal stimuli (vagal tone) to the sinoatrial node of the heart, allows reduced heart rate.[4] Apnea induces cycles of hypoxia and carbon-dioxide retention, affecting both sympathetic and parasympathetic nervous control of heart rate. This parasympathetic and sympathetic activity may have balancing or disparate effects on heart rate, which may contribute to the varying reports of the heart rate effects of OSA. Intense vagus nerve activity early in the apnea[21-23] is followed by apnea-induced hypoxemia and increased sympathetic activity that peaks with arousal from sleep and breathing resumption.[9,13,24] The heightened cardiac and re-

spiratory activity that occur during OSA-induced sleep arousals may produce surges in blood pressure and transient increases in heart rate.[4,11] This elevated sympathetic nerve activity that is responsible for phasic increases in heart rate and blood pressure has been shown to persist during wakefulness.[4,9,11]

During conditions of sustained hypoxia, an adaptive response is elicited to overcome its effects. However, in OSA, hypoxemia and reoxygenation occur intermittently, which may explain the selective activation of an inflammatory response that has been observed in association with unsustained hypoxemia. Several reports describe the activation of systemic inflammatory pathways in response to the oxidative stress of OSA, ranging from increased levels of inflammatory factors, generation of free radicals, and enhanced leukocyte activation with resulting damage to and dysfunction of vascular endothelial cells.[4,11] These adverse vascular effects can increase blood pressure independently of the sympathetic nervous system.

Despite the effects of confounding comorbidities, hampering efforts to define OSA as a risk factor for AF, this accumulating evidence supports the link between the pathophysiology of OSA and the development of AF. Furthermore, when AF is complicated by OSA, its pathophysiology may contribute to the increased risk of stroke and CHF in these patients.[21] Although these relationships remain to be proven, the probability that OSA may be both a risk factor for AF, and a comorbidity with serious exacerbation potential for existing AF, warrants diligent attention by cardiologists.

OSA Diagnosis and Treatment

OSA Diagnosis

Obstructive apnea is defined as complete cessation of nasal/oral airflow for at least 10 seconds. The definition of obstructive hypopnea has been more open to discussion, with the current definition favored by the American Academy of Sleep Medicine (AASM) being an event of at least 10 seconds duration during which airflow is reduced at least 30% from baseline with oxyhemoglobin desaturation of at least 4%.[25,26] Alternatively, events with at least a 50% reduction in airflow from baseline and a 3% oxygen desaturation or electroencephalographic data supporting a cortical microarousal from sleep can qualify as hypopneas. The apnea-hypopnea index (AHI) is commonly used as a diagnostic threshold for classifying the presence and severity of sleep apnea (Table 1). Although an AHI of 5 was considered diagnostic in some studies, at this level it should be accompanied by sleep-related symptoms including daytime sleepiness, loud snoring, witnessed breathing interruptions, or sleep arousal caused by gasping or choking.[27] An AHI of at least 15 can be diagnostic without investigating or in the absence of sleep related symptoms, due to its association with increased risks of adverse consequences. These criteria are clearly defined in managed care reimbursement policies, which contribute to the importance of using standard definitions. For example, for a positive OSA diagnosis that is eligible to receive Medicare coverage of a positive airway device for OSA treatment in the United States, symptoms must accompany an AHI of 5 to 15.[28] Another commonly used index is the respiratory disturbance index (RDI), which includes respiratory event related arousals (RERAs) as well as hypopneic and apneic events; however, it is sometimes used incorrectly as being synonymous with AHI.[29] It is important to compare diagnostic thresholds used among studies, as these variations make comparisons among studies difficult.
The AASM publishes clinical guidelines for the evaluation, management, and long-term care of OSA in adults, which includes a consensus rec-

Table 1 AASM Classification of Sleep Apnea

Type	AHI	Attention Requirements of Activities Affected by Involuntary Sleepiness
Mild	5-15	Little (e.g., watching TV, reading)
Moderate	15-30	Some (e.g., meetings, presentations)
Severe	>30	More Active (e.g., talking, driving)

ommendation that persons at high risk for OSA, which includes patients with atrial fibrillation, should be screened.[27] A positive sleep history or presence of obesity, retrognathia, or hypertension warrant a more comprehensive sleep history, comorbidity investigation, and physical examination.

The gold standard for diagnosis of OSA is a complete in-laboratory polysomnography (PSG), which measures multiple physiological signals during sleep, with channels for electroencephalography, electro-oculography, electrocardiography, electromyography, nasal airflow, respiratory effort (thoracic and abdominal impedence), pulse oximetry, snoring (tracheal microphone), and leg and sleep position. This is considered type 1 monitoring. However, availability and cost limit the use of this diagnostic method.[30] The disadvantages associated with equipment costs and the expense of laboratory time requiring technician attendance are increased by concerns that delays in diagnosis may have adverse health consequences.[31,32]

A second accepted and less costly method of diagnosing OSA is home testing with portable monitors (PM), which comprise types 2 through 4 monitoring, with type designation based on the number of channels.[30] Type 2 has the same number of channels as type 1; however, because the study is not attended by a technician it is not equivalent monitoring. Evaluation with PM is appropriate if patients have a high pretest likelihood of moderate to severe OSA, and should be accompanied by a comprehensive sleep evaluation. It is not indicated for patients with CHF and other major comorbidities.[27] The recent decision by the U.S. Center for Medicare Services to cover costs for OSA therapy following diagnosis using PM is expected to have an effect on the use of this methodology; however, more accurate and cost-effective data are needed.[28] Due to its high rate of false negative results, if PM is technically inadequate or does not establish a diagnosis in patients with a high pretest probability, laboratory PSG studies should be performed. Constraints to widespread application and costliness of SDB diagnosis were addressed in the National Sleep Disorders Research Plan, which prioritized research to develop novel noninvasive screening and diagnostic techniques.[33]

Table 2 STOP-Bang Screening Tool for OSA

Snoring	Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	1. Yes	No
Tired	Do you often feel tired, fatigued, or sleepy during the daytime?	2. Yes	No
Observed	Has anyone observed you stop breathing during your sleep?	3. Yes	No
Pressure	Do you have or are you being treated for high blood pressure?	4. Yes	No
BMI	BMI >35 kg/m2?	5. Yes	No
Age	Age >50 years?	6. Yes	No
Neck	Neck circumference >40 cm?	7. Yes	No
Gender	Male?	8. Yes	No

Other methods are used to screen for OSA, and can supplement objective testing, particularly PM. However, they have a variety of poorly documented specificities and sensitivities. Clinical prediction rules can be useful but cumbersome, and screening tools have primarily been validated in patients referred to sleep centers and in preoperative patients, which can be subject to verification and other biases.[34] In addition, not all patients with OSA are symptomatic.[35] Therefore, if positive results from a symptom-based screening tool are a prerequisite for doing objective testing, asymptomatic patients will not be diagnosed.

A commonly used screening method is the 10-item Berlin questionnaire, which has 1) 5 questions on snoring and apnea behavior, 2) 4 on daytime sleepiness, and 3) 1 on hypertension and/or obesity. Scores are positive for categories 1) and 2) if the total score is 2 or more points, and for category 3) if hypertension is present or BMI is >30 kg/m^2. Two or more positive categories result in a high risk designation; otherwise, a low risk is

assigned. In a recent systematic review, 8 sleep apnea screening questionnaires were evaluated in 10 eligible studies.[36] The more recently developed STOP-Bang questionnaire had the highest sensitivity, and the Berlin questionnaire the highest specificity for predicting moderate or severe OSA. The STOP and STOP-Bang questionnaires had the highest methodologic validity, reasonable accuracy, and ease of use (Table 2).[37,38]

OSA Treatment

Nasal continuous positive airway pressure (CPAP) has been accepted as the most effective treatment for OSA for almost 30 years.[39,40] Other treatments, such as oral appliances (OA) that open or dilate the airway, have shown some effectiveness; however, OA are not effective in persons with severe OSA.[41] Lifestyle modifications and adjustments including weight loss when applicable and positional sleep changes, can have an effect.[42] Bilevel PAP is another option that requires more comparative research to confirm if it has any advantages over CPAP; however, current evidence suggests equivalency in adherence and effectiveness with CPAP.[43]

Although CPAP is known to eliminate respiratory disturbances, improve Stage 3 and 4 sleep, and decrease EEG arousals compared with placebo, less is known about its ability to impact cardiovascular risk.[43] Its effectiveness in treating various levels of OSA severity also requires further investigation. Unfortunately, CPAP treatment is fraught with side effects that adversely affect compliance. The device-patient interface can cause claustrophobia as well as physical irritation and even abrasion. There are also several airway and pressure related side effects, and the equipment can be cumbersome and noisy, among other disadvantages. Heated humidification and a systematic educational program may improve use and compliance.

CPAP guidelines recommend determining the pressure to use during an attended sleep study; however, a split-night diagnostic-titration study can be adequate.[40] Benefits of and adherence to CPAP treatment can usually be determined within the first few weeks; therefore, early follow-up is important to allow addressing any use issues. The definition of compliance in relation to duration of use per night is controversial, as there are few data relating duration of use and resolution of OSA signs and symptoms. A study of duration of nighttime CPAP use and functional status outcomes revealed a linear dose-response relationship within each of 3 outcomes; however, effect on AHI was not part of the study.[44]

Arrhythmia Prevalence in Obstructive Sleep Apnea

Many studies have shown increased arrhythmia prevalence and incidence, including atrial fibrillation, in patients with OSA compared to patients without sleep apnea (Table 3). In reviewing these studies it is important to consider patient characteristics and OSA diagnostic methodology and criteria. Regardless of methods and patient samples, the majority of studies show increased AF in patients with OSA, which should be a concern for both primary care physicians and cardiology specialists.

In the landmark Sleep Heart Health Study (SHHS), Mehra et al.[45] compared the prevalence of arrhythmias in 228 subjects with RDI ≥30 (SDB) with that of 338 patients with RDI <5. AF was more common in persons with SDB than in those without (4.8% vs. 0.9%; P=.003), with an adjusted risk of AF in persons with SDB 4-fold that of persons without SDB (OR 4.02; 95% CI, 1.03-15.74). Two subsequent large, community-based studies reported prevalence of AF among persons with OSA, one as a substudy of a longitudinal study of community-dwelling men ≥65 years of age that enrolled 2,911 subjects who agreed to undergo PSG.[46] That study found a significant association between OSA AHI quartiles and AF; however, the relationship between the highest quartile of OSA and AF did not remain following multivariate analysis. The other study comprised data collection from medical records of 3,542 patients referred for diagnostic PSG, with quantification of incident AF after the initial diagnosis of OSA.[47] These younger patients had a mean age of 49 years. In multivariate analysis, OSA was not an independent predictor of AF. Both studies used an approximate AHI of 5 as the threshold for OSA diagnosis. During a mean follow-up of 4.7 years, new onset AF occurred in 4.3% of patients with OSA and 2.1% of patients without

Table 3 | Atrial Fibrillation in Patients With and Without Obstructive Sleep Apnea

	OSA, N	No OSA, N	Patient Characteristics	Atrial Fibrillation Prevalence in OSA% (vs. No OSA, %)
Mehra, 2006[45]	228[1]	338[2]	Community-based sample aged 46-98 years	4.8% (vs. 0.9%)
Mehra, 2009[46]	727[3]	2184	Community-dwelling men aged >=65 years	5.3% (vs. 3.2%)
Gami, 2007[47]	2626[4]	916	Incident AF in a community cohort after diagnostic PSM (mean age 49 years)	4.3% (vs. 2.1%)
Javaheri, 1998[50]	41[5]	40	HF, LVEF <45	22% (vs. 5%)
Mooe, 1996[53]	78[4]	39	Post CABG, incident AF pre-discharge	32% (vs. 18%)

1RDI ≥30, 2RDI <5,3Data presented as AHI quartiles; bottom quartile AHI <5.9, upper 3 quartiles combined here,4AHI ≥5,5AHI ≥15

OSA in the study of the younger patients. AF was diagnosed from EKG data acquired during PSG in the older patients,[46] with a prevalence of 5.3% in patients with OSA and 3.2% in those without.

Erdogan et al. investigated 587 consecutive patients referred for PSG with suspected OSA.[48] Sleep apnea was defined as AHI >10 with accompanying sleep-related symptoms. The 427 patients diagnosed with OSA had a mean AHI of 35, with 38 (8.9%) of these patients having AF as determined from standard 12-channel ECG and ECG recordings obtained from the PSG data. AHI was not different between patients with and without AF. They did not report the prevalence of AF in the 160 patients without OSA; rather, they used a historical controls approach and concluded that the prevalence of AF in their patients with OSA was approximately 4-fold higher than in the general population. BMI and gender were similar between groups, although patients with AF were significantly older (64 vs. 55 years) than those without AF. HTN and CAD were significantly more prevalent in patients with AF.

It is well known that AF can both cause and worsen heart failure, and is an independent risk factor for death in patients with heart failure.[49] In a study of 81 ambulatory men with stable heart failure, 51% had sleep apnea (AHI ≥15), of whom 40% had CSA and 11% OSA.[50] The high prevalence of SDB in HF patients would not have been clinically suspected, as there were no significant differences between patients with and without SDB in demographics, historical data, and physical exam findings. This was attributed to the increased prevalence of CSA compared with OSA, and the authors emphasized that the pathophysiological consequences were the same among the 2 SDB types, with only the prevalence of loud snoring and mean BMI and diastolic blood pressure being significantly lower in CSA patients. An increased prevalence of AF in these patients with SDB compared to that in patients without SDB (22% vs. 5%; P=.23) was accompanied by increased ventricular arrhythmias and lower left ventricular ejection fraction. On the third night in the sleep laboratory, 29 of the 41 patients with sleep apnea were studied with CPAP.[51] Response, defined as an AHI decrease to <15, was achieved in 7 of 8 (87.5%) OSA and 9 of 21 (42.9%) CSA patients. Although demographics of CSA patients who did and did not respond to CPAP were similar, non-responders had a significantly higher baseline AHI (62 vs. 36; P=.01). These results support the lack of improvement in sleep efficiency and wakefulness after sleep onset that was previously described as a unique feature of heart failure patients given CPAP.[52]

Mooe et al. monitored 121 consecutive patients from the time of coronary artery bypass surgery until hospital discharge.[53] They reported incident AF requiring pharmacological intervention or cardioversion in 32% of 78 patients with preoperatively diagnosed sleep-disordered breathing characterized by AHI ≥5, compared with 18% of 39 patients with AHI <=5; however, the difference was not statistically significant (P=.11). In

this study, an oxygen desaturation index (ODI) ≥5, an alternate definition of sleep-disordered breathing in this study, was significantly associated with development of AF (39% vs. 18%; P=.02), and was an independent predictor of postoperative AF (RR 2.8, 95% CI: 1.2, 6.8).

These results highlight the importance of a multidisciplinary approach to sleep apnea and AF. All practitioners should assure that patients with OSA are referred for appropriate cardiology evaluation as warranted.

OSA Prevalence in Patients with Atrial Fibrillation

The multidisciplinary importance of assuring persons with OSA are adequately screened for AF should be accompanied by cardiac specialist attention to appropriately screen their cardiology patients, particularly those with AF, for OSA. The prevalence of OSA in patients with AF has been demonstrated in several studies (Table 4), and the identification of this treatable condition should be a priority.

In a study of Gami et al. patients were diagnosed for OSA using the Berlin questionnaire, which they validated by comparison results with PSG data obtained from 44 patients.[54] Sensitivity and specificity of the questionnaire were 86% and 89%, respectively, and positive predictive value 97%. All patients had established cardiovascular disease, and the 373 patients who did not have AF had a high prevalence of OSA (32%). Patients with AF had an even higher OSA prevalence, affecting approximately half (49%) of 151 patients. On univariate analysis, CAD and CHF were not significantly associated with OSA, and after adjusting for BMI, neck circumference, hypertension, and diabetes, AF and OSA remained significantly associated (OR 2.19; P=.0006), with a higher odds ratio than those for BMI (1.11) and hypertension (1.01). These authors concluded that it is important to identify patients with AF who have OSA. However, they did not advocate universal OSA screening for AF patients; rather, they believe screening may be warranted for patients who are also obese or hypertensive.

Stevenson et al. investigated SDB in patients aged 48 to 63 years with paroxysmal or persistent AF. Diagnosis was made using an at-home overnight polysomnography system that had been previously validated against 12-channel in-hospital polysomnography.[7] An AHI of >15 defined significant SDB. All patients also completed the Berlin sleep apnea questionnaire. Significantly more patients with AF had AHI >15 compared with arrhythmia center referral controls (62% vs. 38%; P=.01). BMI, neck circumference, and AF, but not hypertension, were significantly associated with SDB in univariate analysis. After multivariate analysis, AF remained significantly associated with SDB (OR 3.04, 95% CI: 1.24-7.46; P=.02), as was BMI (OR 1.32; OR 1.02-1.72; P=.03). Using the Berlin questionnaire resulted in 46% of AF and 18% of control patients receiving a "high risk" of SDB classification. However, comparing AHI data obtained from low and high risk patients revealed considerable overlap of AHI distributions between the 2 questionnaire classifications. Patients determined by the Berlin questionnaire as high and low risk for OSA had median AHI values of 21 and 14, respectively suggesting that almost half of low risk patients had an AHI value consistent with significant SDB, which was defined by the authors as AHI >15.

Tang et al. diagnosed OSA using the Berlin questionnaire in 178 consecutive patients with paroxysmal AF who underwent catheter ablation, and reported 58.4% were high risk.[55] Hypertension, neck circumference, and obesity were significantly more prevalent in the high risk group, which also had a significantly greater left atrial diameter; however, age and gender were similar between the two groups.

Matiello et al. assessed sleep apnea with the Berlin questionnaire in 174 AF patients undergoing catheter ablation, and performed PSG in the 51 (29%) patients whose questionnaire score indicated they were at high risk for OSA, of whom 17 were classified as having non-severe (10<AHI<30) and 25 severe (AHI ≥30) OSA.[56] The remaining 132 patients were low risk, with AHI <10 or with low risk Berlin questionnaire scores; therefore, 9 (17.6%) high risk Berlin questionnaire patients were determined by PSG to be low risk. In the cohort of 174 consecutive AF patients undergoing catheter ablation, 24.1% had AF using this diagnosis scheme. Using the Berlin questionnaire as the single diagnostic tool, Chilukuri evaluated

Table 4 Prevalence of Sleep Disordered Breathing in Patients with Atrial Fibrilliation

	SDB*, %	Patient Characteristics
Gami,	49[1]	151 with AF or flutter
2004[54]	32	373 with CVD, no AF
Stevenson,	62[2]	90 with paroxysmal or persistent AF
2008[7]	38	45 tertiary arrhythmia center referral controls matched for age and gender
Altmann,	43[3]	94 with paroxysmal (27%) or persistent (73%) AF hospitalized for cardiac condition
2010[58]		
Tang,	581	178 patients with paroxysmal AF undergoing catheter ablation
2009[55]		
Matiello,	24.1[4]	174 patients undergoing catheter ablation
2010[56]		
Chilukuri,	44[1]	210 patients undergoing catheter ablation:
2009[57]	36	119 with paroxysmal AF
	54	91 with persistent AF
Hoyer,	67	46 AF patients at least 6 months after catheter ablation
2010[15]	87[5]	23 AF patients w/ therapy-resistant paroxysmal AF
	48	23 AF patients w/o recurrence w/in 6 mo matched for age, gender, and ejection fraction
Bitter,	20[6]	75 patients undergoing catheter ablation
2011[64]	9	OSA
		CSA
Patel,	21.3[7]	3,000 patients undergoing catheter ablation
2010[59]	16.1	1,603 with paroxysmal AF
	27.3	1,397 with non-paroxysmal AF

* SDB diagnosed by: [1]Berlin questionnaire, [2]AHI >15 using overnight portable somnography, [3]Trans-nasal airflow measurement, [4]Berlin questionnaire followed by PSM in patients scoring as "high risk;" AHI≥10 = OSA, [5]Overnight PSM with AHI >5 ,[6]AHI ≥15 via cardiorespiratory polygraphy, [7]AHI >15 in patients with positive query for sleep apnea evaluated by PSG

210 consecutive AF patients undergoing catheter ablation for OSA.[57] Almost half (44%) qualified as high risk, and had significantly greater BMI and hypertension prevalence; however, age, gender, and left atrial size were similar between groups.

In the study by Altmann et al. of 94 cardiology inpatients with AF, 43% were diagnosed with sleep apnea using a trans-nasal air-flow measurement device.[58] This validated procedure does not acquire information allowing differentiation between OSA and CSA; therefore, their results were presented as SDB. Patients with an AHI ≥15 were counseled about the association between SDB and cardiovascular events, and offered overnight PSG to confirm and, if applicable, differentiate the diagnosis, with subsequent CPAP treatment available as indicated. In this patient cohort, age, gender, BMI, hypertension, DM, smoking status, and left arial size enlargement, several factors that are often associated with SDB, were similar between patients with and patients without SDB. Despite counseling, only 6 of 40 (15%) patients with SDB

accepted to have a PSG study performed. The SDB diagnosis was confirmed; however, only 2 of the 6 accepted CPAP therapy. One reported a reduction in significant daytime sleepiness and continued therapy, while the other discontinued CPAP after 1 month due to absence of daytime symptoms before as well as during treatment. In fact, in this study daytime sleepiness as measured by the Eppworth sleepiness scale was similar in AF patients with and without SDB (P=.14).

In the multi-center study of Patel et al. that included 3,000 consecutive AF patients undergoing ablation, patients were queried for a history of sleep apnea, and OSA was confirmed by PSG.[59] OSA, defined as an AHI >15 with >80% of events obstructive, was diagnosed in 21.3% of patients. Age, gender, BMI, hypertension, and pre- and post-left atrial size were among characteristics that were statistically different between patients with and without OSA. Patients with nonparoxysmal AF were more likely to have OSA (27.3%) than those with paroxysmal AF (16.1%).

Once again, it is clear from the range of prevalence data and variety of patient populations sampled that much additional research is required to enhance understanding of the association between OSA and AF. Adjusting for confounders removed the association between OSA and AF in some studies; while in others shared risk factors for both OSA and AF were not more prevalent in patients with both conditions compared with patients having only one.

Effects of OSA on AF Management

Several studies have shown associations between OSA and AF treatment failure. The study of Kanagala et al. compared 1-year AF recurrence rate in 39 OSA patients with AF/atrial flutter referred for electrical cardioversion with that of 79 controls without OSA.[60] Recurrence was significantly greater in the 27 patients whose OSA was untreated (82%) compared with that of the 79 non-OSA controls (53%; P=.009), and with that of the 12 patients who received CPAP therapy for their OSA (42%; P=.013). The authors proposed that all patients with AF, and particularly those who are obese, should be screened for OSA.

Sauer et al. (2006) found that patients who had acute pulmonary vein reconnection were more likely to have a history of OSA compared with those who did not experience conduction recurrence.[61] OSA was present in 12% of 211 patients with electrical reconnection compared with 5% of patients without (P=.02). Additional lesions were placed to achieve electrical isolation before completing the procedure. OSA remained a significant predictor of PV reconnection after multivariable adjustment (RR 2.2; 95% CI: 1.32, 3.94; P=.01). Other risk factors included a history of hypertension (RR 1.5), left atrial size >4.5 cm (RR 1.7), age (RR 1.05), and persistent AF subtype (RR 1.3). However, acute PV reconnection was not related to long-term AF control during 6 to 37 months (average: 22 months) of follow-up. The method for diagnosing sleep apnea was not mentioned; therefore, it was inferred to have been included in the medical history obtained through patient interview.

Although most studies have shown an association between OSA and unsuccessful AF treatment outcomes, some failed to show a difference in AF recurrence in patients with and without OSA. Of 178 patients with paroxysmal AF who underwent catheter ablation, 58% were assessed as being high risk for OSA using the Berlin questionnaire.[55] In this study, AF recurrence rate after a mean follow-up of 344 days (91-572) was similar in both the high (25.0%) and low (24.3%) risk groups (P=.855). These authors suggested the different results between their study and others may be related to their inclusion of only paroxysmal AF cases. In addition, the difference in OSA diagnostic methods among studies may have resulted in classification differences. OSA was diagnosed at enrollment using the Berlin questionnaire, with 30 patients subsequently undergoing PSG to validate questionnaire results. The sensitivity, specificity, positive predictive value, and negative predictive value of the questionnaire were 100%, 30%, 74%, and 100%, respectively, with a significant difference in AHI between the high and low risk questionnaire groups, respectively (28.5 ± 22.7, 2.2 ± 1.4, P=.001). Finally, they suggested using a 12-week post-procedure blanking period during which potentially transient early recurrences were not included as failures, may have complicated comparing results with studies using a shorter period. For example, using an 8-week blanking period, Jangnarangsin et al. reported 63% of patients without OSA and

41% with OSA were without AF recurrence 7 ± 4 months after a single ablation procedure (P=.02).[62] In multivariate analysis, OSA was the only significant predictor of recurrent AF (OR 3.04, 95% CI 1.11, 8.32; P=.03).

Matielo et al. however, also used a 3-month blanking period, and reported that arrhythmia recurrence at 1-year in 174 consecutive patients was significantly less in low risk for OSA patients (31%) compared with non-severe OSA patients (10<AHI<30; 16%, P=.019) and severe OSA patients (AHI ≥30; 86%, P<.001).[56] Multivariate analysis showed left atrial diameter (HR 1.05, 95% CI: 1.00, 1.09; P=.03) and severe OSA (HR 1.87, 95% CI: 1.11, 3.16; P=.02) as independent predictors of arrhythmia recurrence.

Chilukuri et al. investigated clinical success of 210 patients undergoing catheter ablation for AF.[57] Complete success was defined as the absence of AF or other atrial tachycardias while off anti-arrhythmic drug therapy, and improvement as ≥90% reduction in AF burden while not taking anti-arrhythmic drug therapy or while using a previously ineffective therapy. This study also included a blanking period of 3 months, with a mean follow-up of 25 ± 12 months. In this patient cohort, left atrial size was not a significant predictor of clinical success in univariate analysis, and high risk of OSA as determined by the Berlin questionnaire was the only independent predictor of failure after catheter ablation of AF (OR 4.5, CI: 1.21-16.87; P=.02). Another study enrolled 109 patients and explored the association of obesity and OSA with ablation outcome.[63] Overall, clinical success was achieved by 75 patients (68.8%). In univariate analysis, success was more common in lower weight categories (P=.04) and in patients without OSA (77%% vs. 58%; P=.036). In this study, BMI was the only independent predictor of failure on multivariate analysis (OR 1.11, CI: 1.00, 1.21; P=.03).

Hoyer et al. performed PSG in a control group of 23 AF patients without recurrence following ablation and 23 patients who had recurrence after ≥2 pulmonary vein isolation procedures.[15] The groups were not different in age, gender, BMI, LVEF, or prevalence of comorbidities including CAD, DM, and HTN. Using a definition of OSA as AHI >5, the prevalence in the entire cohort was 67%, and was significantly higher (87%) in therapy-resistant patients compared with controls (48%; P=.005). Snoring and results from the Epworth sleepiness scale were similar in both groups.

Bitter et al. followed 75 patients who underwent pulmonary vein isolation using the cryoballoon technique.[64] During a median follow-up of 12 months with a 3-month blanking period, independent predictors for AF recurrence included AHI ≥15 (HR 3.2, 95% CI: 1.14, 8.95; P=.03) but not AHI ≥5. Neither hypertension nor obesity were significantly associated with AF recurrence on multivariate analysis.

In an attempt to resolve the disparate results comprising individual reports, a recent meta-analysis of studies reporting the association between OSA and AF recurrence was performed. The analysis included 6 reports with a total of 3,995 patients that met eligibility criteria.[65] The study found that patients with OSA have a 25% increased risk of AF recurrence after catheter-based pulmonary vein isolation compared with those without OSA (RR: 1.25, 95% CI: 1.08, 1.45; P=.003). OSA diagnosed with PSG was a strong predictor of recurrence (RR: 1.40, 95% CI: 1.16, 1.68; P=.0004); however, risk of AF recurrence was similar between OSA and non-OSA in the subgroup that was diagnosed with the Berlin questionnaire (RR 1.07, 95% CI: 0.91, 1.27; P=.39). The authors concluded that a diagnosis of OSA should be considered when evaluating patients for AF ablation.

Despite the variety of diagnostic methods used and differences among patient populations, the majority of reports suggest that sleep apnea can contribute to AF treatment failure. When differences are not detected, it may be due to small patient numbers and baseline variation among patients. These data must be interpreted cautiously, and additional large studies are necessary. However, available data suggest it is important for clinicians to identify and treat OSA in AF patients. [66]

Management of OSA and Its Effects on AF

There are no conclusive studies on the effects of OSA treatment on AF, and several studies have shown mixed results. The possibility of beneficial effects on OSA status through cardiovascular interventions has also been considered; for example, when reports noted an association between

bradyarrhythmias and OSA, it was suggested that overdrive pacing might have the added benefit of resolving OSA. Several subsequent studies failed to show a clinical benefit; therefore, CPAP remains the gold standard for OSA treatment.[67-69]

In a multicenter study of 3,000 AF patients undergoing ablation, significantly more of the 2,360 patients without OSA achieved success compared with the 640 patients with OSA during a follow-up of 32 ± 14 months (78% vs. 73%; P=.024).[59] Not having OSA provided a significant protection against AF recurrence in multivariate analysis (HR 0.78, 95% CI: 0.64, 0.95; P=.015), while having a non-pulmonary vein (PV) trigger (those not located at the level of the PV antra, HR 8.71), CAD (HR 1.57), and non-paroxysmal AF (HR 1.53) also remained as significant risk factors for recurrence. In that study, almost half (49.2%) of the 640 patients with OSA had been receiving CPAP therapy for at least 3 months before the procedure, with treatment continuing during the entire follow-up interval. The proportions of procedural failures for CPAP-treated and non-treated patients, reported as approximately 20% and 32%, respectively, were similar between subgroups with paroxysmal and nonparoxysmal AF, with a significantly different approximate 79% and 68% success rate for CPAP-treated and non-treated patients in the entire cohort of OSA patients (P=.003).

A recent study included subjects who were referred for sleep testing based on clinical history and symptoms.[70] They were divided into groups based on PSG results as having no sleep apnea (n=44), or mild (n=197), moderate (n=368), or severe (n=785) OSA according to AASM guidelines. Patients with CSA were excluded. Patients with an AHI ≥20 were offered CPAP therapy, with 573 refusing and 316 accepting treatment and undergoing a sleep study for CPAP titration. CPAP therapy significantly reduced the AHI in the 316 patients, from an average of 50.3 ± 22 before to 10.8 ± 12 after CPAP (P<.001). Paroxysmal AF was present in 16 (5.1%) of these patients prior to CPAP therapy, and in 1 patient after (P<.001).
The small study by Matiello et al. of 51 AF patients scoring as high risk for OSA using the Berlin questionnaire included 9 who were treated with CPAP prior to catheter ablation, and 2 who began treatment after the procedure.[56] All had severe OSA (AHI ≥30), and all had recurrences during follow-up, compared with 86% recurrences in the entire severe OSA cohort (n=25). Although the small numbers preclude rejecting CPAP benefit and indicate further studies are necessary, the authors suggested that CPAP treatment may be unable to restore stable rhythm if atrial damage is established. They support that early OSA detection and treatment in AF patients may be beneficial.

In a larger retrospective study exploring incident AF in 2,626 patients with sleep apnea, CPAP therapy was reported in the medical records for 18%, 30%, 39%, and 52% of subjects with increasing severity of OSA based on AHI quartiles.[47] Multivariate regression failed to show an effect of CPAP treatment on the incidence of AF. The authors suggested that the retrospective nature of the study, depending on subjective reporting of CPAP therapy and documentation in the medical record, precluded acquiring relevant treatment information including frequency, duration, and compliance. In addition, they postulated that the greater prevalence of CPAP treatment in patients with the most severe OSA may have confounded the association.

OSA and Clinical Practice Guidelines

The American Society of Anesthesiologists issued guidelines in 2006 for the perioperative management of patients with OSA, that recommend diagnostic screening for all patients preoperatively.[71] In the absence of a sleep study, presence of anatomic anomalies and information possible from standard screening questionnaires should be acquired. Generalization of recommending sleep apnea screening for all surgical patients remains controversial; however, the potential benefits of preoperative screening for cardiology patients, particularly those with AF, should be considered.

The American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) released a scientific statement in 2008 on sleep apnea and cardiovascular disease, in which they define obstacles that must be overcome to allow reaching a consensus regarding best practice.[1] These include: 1) general absence of sleep medicine education in cardiovascular training programs; 2) logistic and economic barriers to both the diagnosis and treatment of sleep apnea; 3) numerous comorbidities that complicate de-

termining an independent role of sleep apnea in cardiovascular disease; 4) predominantly device-based SDB treatment options that are often associated with poor patient compliance; and 5) the lack of data from robust longitudinal intervention studies exploring the benefit of SDB treatment on cardiovascular outcomes. It is not surprising, therefore, that the 2010 European Society of Cardiology guidelines for managing patients with AF and the 2006 NICE AF guidelines do not mention sleep apnea.[72,73] The ACC 2006 AF management guidelines acknowledge an association between AF and sleep apnea, and suggest that sleep apnea should be considered in patients with nocturnal AF.[74] The 2007 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation created by a task force from six organizations in the United States and Europe, makes passing mention of sleep apnea in the section on Antiarrhythmic and Other Drug Therapy Post Ablation, by emphasizing that "attention to control of hypertension and addressing other AF risk factors such as sleep apnea and obesity remain an integral part of AF management after the ablation procedure."[75] Finally, the Canadian guidelines alone recommend screening AF patients for SDB, stating that "screening history and physical evaluation for obstructive sleep apnea should be performed in all patients, and further testing, such as ambulatory oximetry or polysomnography, or appropriate referral to a specialist in sleep medicine should be considered if the history is suggestive of sleep apnea."[76]

Conclusions

The pathophysiology of OSA includes several mechanisms that may be involved in the development and maintenance of AF, and that may contribute to treatment failure. However, considerable additional research is required to clarify and explain relationships. An effort should be made to standardize diagnosis and research methodology and definitions that will facilitate comparing data among studies and, where appropriate, robust randomized controlled trials should be performed.

Many studies show similarities among groups with and without OSA for many OSA risk factors. When screening tools such as the Berlin and STOP-Bang questionnaires, which have questions about hypertension and obesity, are used for diagnosis, it is interesting when patients diagnosed by these instruments do not have significantly greater BMI and hypertension prevalence. More research is needed to define an optimal screening and diagnosis pathway, to assure patients who would benefit from diagnosis and intervention are identified. The Berlin and STOP-Bang questionnaires have been well-studied, and incorporating their use into standard patient management should be easily achieved, while being prepared to implement improvements in screening and diagnosis procedures. The feasibility of using PM diagnosis should be considered. Combined with a screening tool, PM may provide a more available and affordable method to expand diagnostic capabilities. Sleep apnea training is essential to instruct cardiologists on the current status of diagnosis and management of sleep apnea, and motivate them to be diligent in following research reports in this dynamic field. Efforts to overcome the lack of motivation to accept CPAP therapy in AF patients with SDB should be developed and pursued, and informed clinicians can help overcome this reluctance in their patients. However, a significant research effort is required to understand the benefits of treating OSA of varying severities, and to clarify its benefit in preventing AF development and enhancing success of AF treatment.

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