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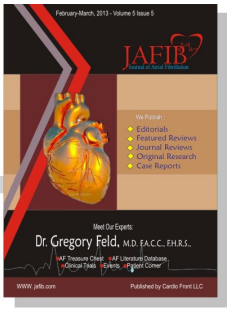

Impact of Obstructive Sleep Apnea on Outcomes of Catheter Ablation of Atrial Fibrillation

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Abstract

Obstructive sleep apnea (OSA) is a growing epidemic in the United States and significantly contributes to the increasing prevalence of atrial fibrillation (AF) in the U.S. population. Although a strong correlation between OSA and AF has been demonstrated, a causal relationship between these two conditions has not been definitively established. Evidence of OSA is an important consideration of AF management and impacts the success rate of catheter ablation. The presence of OSA tends to predict a lower success rate and higher complication rate for catheter ablation of AF. However, recent studies evaluating OSA as an independent risk predictor of AF recurrence following an ablation procedure have yielded conflicting results. A greater understanding of these conditions would allow for a more specific therapy targeting the type of AF associated with OSA. The following review provides a brief summary of obstructive sleep apnea etiology, focuses on the relationship between OSA and AF, and discusses the impact of OSA on the outcomes of catheter ablation of AF.

Introduction

The relationship between obstructive sleep apnea (OSA) and atrial fibrillation (AF) is well established, and reports have shown a strong association between these conditions. OSA has been identified as a potential risk factor for both the development of new-onset AF and the recurrence of AF following cardioversion or catheter ablation.[1] This review will answer a series of frequently asked questions concerning the impact of OSA on AF catheter ablation. The purpose of this report is to provide a review of the interrelationship between OSA and AF, mechanisms that contribute to their association, and the impact of OSA on catheter ablation of AF. First, we describe the etiology and pathology of OSA. Second, we discuss the mechanisms that link OSA with AF. Finally, we conclude by identifying the impact of OSA on the current ablation strategies used to treat AF.

Review of Obstructive Sleep Apnea

What is Sleep Apnea?

Sleep apnea is a prevalent, yet highly underdiagnosed, sleep disordered breathing pattern affecting 6% of adults and 1% - 2% of children.[2,3] It is characterized by abnormal pauses (apnea) in breathing or abnormally low rates of breathing during sleep. Full-night polysomnography or in-home oligosomnography studies are gold standard modalities to evaluate the breathing and po-

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tential consequences of impaired air flow during sleep.[4,5] A recent update of the American Academy of Sleep Medicine Manual (AASM) for the Scoring of Sleep and Associated Events score a respiratory event in adults as apnea if 1) there is a drop in the peak signal excursion by > 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), a positive airway pressure device flow (titration study), or an alternative apnea senor; 2) the duration of the > 90% drop in sensor signal is > 10 seconds.[6] In children under 18 years, the AASM consensus recommends that the event meet respiratory effort criteria and duration criteria for one of the three specific apneas as well: obstructive, central or mixed. However, due to conflicting data, the current AASM scoring rule allows clinicians the option of using pediatric or adult scoring for patients between 13 and 18 years.

What are the Three Types of Sleep Apnea?

Sleep apnea is classified as obstructive, central or mixed in children and adults based on the amount of respiratory effort.[6] Obstructive sleep apnea (OSA) implies an intermittent mechanical obstruction of the upper airway during sleep in the presence of abdominal excursions, which leads to reduced airflow to the lungs with at least 5 respiratory events occurring per hour of sleep and a history of SDB symptoms.[4,5] Alternatively, central sleep apnea (CSA) is characterized by impaired flow without evidence of respiratory effort.[4] Mixed apnea is defined as a respiratory event that has both obstructive and central features; however, the exact number of obstructive breaths allowed under mixed apnea is inconclusive.[4,6] The appropriate diagnostic method for detection of sleep disordered breathing remains controversial. Overnight polysomnography is considered to be the "gold standard" for diagnosis of all sleep apneas.[7,8] However, the Berlin questionnaire is a validated instrument designed to identify individuals with OSA.[9] The AASM consensus recommends that the oronasal thermal sensor serve as the recommended sensor and the nasal pressure transducer serve as an alternative sensor during diagnostic sleep studies in both children and adults.[6] Esophageal manometry or thoracoabdominal respiratory inductance plethysmography belts are recommended to monitor respiratory effort in both children and adults.[6] The task force states that reporting the "respiratory disturbance index (RDI)" to be optional when diagnosing all types of sleep apneas.[6] The RDI is a metric of sum of "AHI" (combined total of apneas and hypopneas per hour of sleep) and "RERA" (respiratory effort-related arousals per hour of sleep) indices.[4,6]

What are the Mechanisms of OSA?

Obstructive sleep apnea is defined as at least 5 obstructive respiratory events per hour of sleep in which the upper-airway collapses and reopens.[5,10] Research has indicated six factors that are either responsible for or contribute to the pathogenesis of OSA: 1) upper-airway dilator muscle activity during sleep, 2) upper-airway anatomy, 3) lung volume, 4) ventilator control stability, 5) sleep state stability, and 6) rostral fluid shifts contribute to the pathogenesis of OSA.[10] The dilator muscles, responsible for keeping the upper-airway unobstructed, reduce their activity and relax during sleep causing collapse of the duct.[10-13] Anatomical factors such as increased airway length, lateral wall thickness, tongue volume, skeletal structure, and soft tissue structures determine the level of upper-airway collapsibility and the size of the airway lumen.[10,14] Similarly, lower-end expiratory lung volume increases the tendency of the upper-airway to collapse by the decreased "tug" of the trachea, which stiffens and dilates the upper airway as lung volume increases.[10] Furthermore, if the negative-feedback loop of the respiratory system is unstable during sleep, the ventilator drive will cause a greater fluctuation of muscle activity and promote upper-airway collapse.[10,15] Often, this type of ventilator instability is caused by arousal from sleep.[10,16,17] Additionally, fluid displacement from the legs to the neck reduces upper-airway size and increases airway collapsibility.[10,18,19]

What are the Characteristics of People with OSA?

The AASM consensus suggest features such as increased neck circumference (>17 inches men, >16 inches women), BMI >30 kg/m2, presence of retrognathia, lateral peritonsillar narrowing, macroglossia, tonsillar hypertrophy, elongated/enlarged uvula, high arched/narrow hard palate, nasal abnormalities and/or overjet are associated with the presence of OSA.[5] Several research studies have also indicated obesity, male sex, family history, congestive heart failure, and hypertension as prev-

alent risk factors.[4,5,7,20] Obesity has been indicated in several cross-sectional and population-based studies as the most important of the risk factors, with an increment of 1 SD in BMI associated with a 4-fold increase in OSA prevalence.[7,20-38] The collapsible tube theory and tracheal tug theory postulate that the distribution of body fat, especially in the neck area around the collapsible portion of the upper airway, results in reduction in the functional residual capacity or vital capacity increasing the risk of OSA.[4,39] Men between the ages of 40 to 55 years, pregnant woman, and postmenopausal women are predisposed to this pattern of fat deposition as well.[4,8,20,40-44] Several studies have suggested genetic factors, independent of lifestyle and obesity, have attributed to the predisposition of OSA.[4,45-53] Genetic influence on craniofacial shape and size of bones and soft tissue is involved in the pathogenesis of OSA and may also explain the ethnic differences described in epidemiologic studies.[51,54-56] Additionally, research suggests a correlation between cardiac dysfunction and OSA resulting from arterial oxyhemoglobin desaturation, excessive stimulation of the sympathetic nervous system, and the increases in systemic blood pressure.[20,57-59] Secondary risk factors include pregnancy, age, race, smoking, alcohol consumption, acromegaly, hypothyroidism, polycystic ovary syndrome, and testosterone therapy.[4,5,7]

How is Obstructive Sleep Apnea Treated?

Research indicates that obstructive sleep apnea has severe detrimental effects on physical and mental health; thus, long-term, multidisciplinary management of OSA must be undertaken. Sleep disordered breathing has been linked to hypertension, cardiovascular disease, stroke, diabetes mellitus, depression, motor vehicle crashes, cognitive impairment, diminished quality of life, and increased mortality.[2,60] In its clinical guidelines, the AASM report that medical, behavioral, surgical, and adjunctive therapies are options for treatment of OSA.[5] Additionally, the AASM suggests that the patient and physician decide on the treatment type based on severity of OSA, and the patient's anatomy, risk factors, and preference.[5] The AASM recommends that positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is the choice treatment for all types of OSA and should be offered as an option to all patients.[5] PAP can be administered in three modes: 1) continuous (CPAP), 2) bilevel (BPAP), and 3) autotitrating (APAP).[5] However, CPAP treatment is the gold standard treatment for moderate to severe OSA and optional for mild OSA.[5] In a ground-breaking study, Sullivan et al investigated the effect that CPAP would have on OSA in five patients undergoing a sleep study.[61] In this study, CPAP was applied through the nares and acted as a pneumatic splint that prevented upper airway occlusion.[61] Following a sleep study, the investigators reported that CPAP completely prevented upper airway occlusion in each of the five patients.[61] Additionally, by increasing or decreasing the amount of PAP, the occlusion of the patients' upper airways was turned on or off.[61] Recent studies have shown that the appropriate use of CPAP in OSA patients can improve self-reported sleepiness, improve quality of life, lower blood pressure in hypertensive patients, reverse atrial electrical remodeling by reducing signal-average p-waves, and increase memory function and other frontal lobe functions.[5,62-64] The AASM report that when patients are educated about CPAP therapy and work with a care team to treat their OSA, CPAP therapy is safe with minor and/or reversible side effects and adverse events.[5]

If PAP therapy is not tolerated by the patients, other therapy options can be considered to treat OSA. Historically, surgical therapies that reconstructed or bypassed the upper airway were used to treat OSA. However, due to cost and risk, surgery is considered a secondary treatment for OSA today.[5] Behavioral treatment options include weight loss, positional therapy, and avoidance of alcohol and sedatives before bedtime.[5] Additionally, custom made oral appliances, such as mandibular repositioning appliances and tongue retaining devices, may improve upper airway patency by enlarging the upper airway and/or reducing upper airway collapsibility.[5] Regardless of the treatment option chosen by OSA patients, ongoing, long-term management is recommended by the AASM.[5]

Interrelationship Between Obstructive Sleep Apnea and Atrial Fibrillation

What is the Overlap Between People with AF and OSA?

Several studies have demonstrated the relation-

ship between OSA and AF by investigating the prevalence of OSA in AF patients, and of AF in patients with diagnosed OSA. Gami et al first reported this association in a prospective study assessing the risk of OSA in 463 patients with and without AF.9 In this study, investigators found the presence of OSA in 49% of patients with AF compared to 32% of patients without AF.[9] Subsequently, several studies further examined this relationship reporting that evidence of OSA appeared in 24% - 87% of patients with AF.[9,65-72] The largest of these studies included 3,000 patients undergoing pulmonary vein isolation for AF. In this study, Patel et al screened patients for OSA and CPAP use. The investigators reported 21.3% of patients had a previous diagnosis of OSA by polysomnography prior to ablation.[72] As far as we know, no prospective study exists where randomized patients underwent polysomnography prior to a pulmonary vein isolation procedure. Additionally, research has shown that there is a higher prevalence of OSA in patients with therapy-resistant AF.[70] In a recent study, Hoyer and colleagues compared the prevalence of OSA in 23 patients with recurrent AF after > 2 pulmonary vein isolation procedures with 23 patients who were successfully treated with one PVI procedure.[70] OSA was prevalent in 87% of patients in the therapy-resistant group compared to 48% of patients in the control group. However, the association of AF and OSA is not two directional, the presence of AF is far less common in cohorts of patients with OSA. Research has reported that 5% - 32% of patients with diagnosed OSA have concomitant AF.[73-77] The largest of these studies evaluated the presence of AF in a community cohort of 3,542 adults referred for an initial diagnostic polysomnogram.75 After a 5-year follow-up, AF occurred in 4.3% of patients with OSA and in 2.1% of patients without OSA.[75] These data taken together suggest possible causal relationship between OSA and AF. However, due to varying study design, patient populations, and diagnosis methods of OSA, a large, well-designed study is needed to confirm this relationship.

What is the Impact of OSA and AF on each Other?

There is increasing evidence that demonstrates that mechanisms of OSA evoke AF through electrical and structural remodeling of the left atrium resulting from arterial oxyhemoglobin desaturation, excessive stimulation of the sympathetic nervous system, and increases in systemic blood pressure.[20,78–80] Intermittent hypoxemia, hypercapnia, and chemoreceptor excitation resulting from collapse of the upper-airway activate a significant sympathetic response and enhanced vagal tone.[79,81] Sympathetic vasoconstriction during apneic episodes elevates blood pressure resulting in left ventricular overload and atrial stretching, a known risk factor of AF.[80,81] Consequently, investigators have reported that once left atrial pressure rises above 10 cm H20, the rate and organization of AF waves from the superior pulmonary veins increases.[82] Orban et al investigated the effect of the Mueller maneuver, which simulates OSA, on left-sided cardiac morphologic characteristics and function in healthy patients.[83] Following the maneuver and 10-minute recovery period, patients exhibited a distinctly decreased left atrial volume, ejection fraction, stroke volume, and cardiac index.[83] In addition to structural remodeling, Demetri et al found evidence of significant electrical remodeling in 40 patients with OSA undergoing an initial PVI procedure for paroxysmal AF.[78] Compared to 40 control patients without OSA undergoing PVI, patients with OSA had prolonged conduction times along the coronary sinus, more wide spread complex electrograms in both atria, longer P-wave duration, longer sinus node recovery time, lower atrial voltage, and slower atrial conduction velocity.[78] In another study, Maeno et al reported that OSA is associated with increased P-wave duration, a known precursor of AF, in 250 subjects.[84] Although OSA and AF share multiple risk factors and comorbidities, the strong association found between OSA and AF suggests a unique interaction between the pathophysiology of these two conditions.

Treatment of AF, OSA, or Both

Does OSA Impact the Outcome of AF Ablation?

The impact of OSA on the outcomes of AF ablation is an area of intense research. The presence of OSA has been identified as a predictor of lower efficacy of radiofrequency catheter ablation and cryoballoon ablation in several studies.[85-90] Jongnarangsin et al first recognized OSA as a predic-

tor of AF recurrence following radiofrequency catheter ablation of CFAEs in 324 patients with paroxysmal and persistent AF.[85] After a 7-month follow-up, 63% of patients without OSA and 41% of patients with OSA were free from AF without antiarrhythmic drug therapy.[85] Multivariate analysis of this data indicated OSA was the strongest independent predictor of recurrent AF after catheter ablation.[85] A recent meta-analysis presents the findings from 6 studies on the role of OSA on AF recurrence after pulmonary vein isolation. The results demonstrated that OSA patients have a 25% greater risk of AF recurrence following catheter ablation compared to controls (RR 1.25, 95% CI 1.08 to 1.45, p = 0.003).[86] However, a subgroup analysis of diagnostic tools for OSA did not show an association between OSA and AF recurrence when using the Berlin Questionnaire for diagnosis.[86]

More recently, Bitter and colleagues reported independent predictors of AF recurrence in 82 patients undergoing PVI with the cryoballoon technique.[87] Twenty-two patients presented with sleep-disordered breathing (SDB) of which 15 patients had moderate to severe OSA and 7 had central sleep apnea. After a median of 12 months, sinus rhythm could not be maintained in 45.5% of patients with moderate to severe sleep disordered breathing and 24.5% of patients with mild or no sleep disordered breathing.[87] Although the results of this study indicate OSA as a predictor of cryoballoon ablation failure, additional research is needed to validate this correlation.

Three studies have examined whether the severity of OSA was predictive of catheter ablation.[88-90] All studies administered the Berlin Questionnaire (BQ) to identify patients with OSA and classify the severity of OSA in each patient. The BQ has been validated as a diagnostic tool for OSA in a number of patient populations.[5] In the first study, Chilukuri et al sought to determine whether OSA assessed by the Berlin Questionnaire (BQ) is useful in predicting the efficacy of catheter ablation.[88] Patients were classified as high risk or low risk for OSA depending on their responses to the questionnaire. At a mean follow-up of 25 +/- 12 months, 85% of low risk patients and 70% of high risk patients had clinical success. A multivariate analysis indicated that the only independent predictor of procedural failure was a classification of high-risk for OSA on the BQ.[88] Matiello and colleagues reported similar results in their study which included classification of OSA based on a sleep study in addition to the BQ.[89] However, Tang et al report no significant difference in recurrence rate in patients with different risk profiles of OSA.[90] It should be noted that the end point of ablation in both Chilukuri and Matiello's studies was complete electrical isolation of pulmonary veins, while the endpoint of ablation in Tang's study was circumferential ablation of the pulmonary veins. Additionally, Naruse et al found that restoration of sinus rhythm by radiofrequency catheter ablation significantly decreased the median AHI calculated from polysomnography in 25 patients with OSA and AF.[91] These findings taken together suggest a possible two way relationship between the severity of OSA and AF recurrence after catheter ablation.

Is Treating OSA Beneficial for Alleviating AF?

Recently, research has explored the effect of treating OSA with continuous positive airway pressure (CPAP) to attenuate the risk of AF recurrence. Kanagala and colleagues initially reported the benefit of CPAP treatment of OSA on the AF recurrence rate following cardioversion.[92] One year after successful cardioversion, 82% of patients with untreated OSA and 42% of patients with treated OSA had AF recurrence.[92] Subsequently, several studies examined the effect of CPAP therapy on catheter ablation efficacy. The largest of these studies reported success rates of pulmonary vein isolation (PVI) in patients with and without OSA as well as in OSA patients receiving or not receiving treatment with continuous positive airway pressure (CPAP).[72] At the end of the follow-up period (32 +/- 14 months), ablation success was achieved in 78% of non-OSA patients compared to 73% of OSA patients.[72] Additionally, 79% of OSA patients treated with CPAP and 68% of OSA patients not treated with CPAP were free for AF. In another study, Naruse et al evaluated the efficacy of appropriate treatment with CPAP on recurrence of AF following a PVI ablation in 153 patients.[93] Nineteen months after ablation, AF recurred in 53% of patients with OSA who did not adhere to CPAP therapy, 30% of patients with OSA who did adhere to CPAP therapy, and in 22% of patients who were not diagnosed with concomitant OSA.[93] Limited research has examined the significance of

CPAP therapy on preventing OSA-associated arrhythmias prior to ablation procedure. Abe et al reported that CPAP therapy significantly reduced the occurrences of paroxysmal AF.[94] However, further research is needed to determine the correlation between CPAP therapy and AF prevention.

Conclusions

AF and OSA are two rapidly growing epidemics in the United States. Over the past 20 years, research has established a strong association between the presence of OSA and AF. As a result of mechanistic investigations of both conditions, hypotheses of bidirectional causality have been proposed. It is well established that OSA causes structural and electrical substrate remodeling in the left atrium. Data from epidemiological studies indicate that patients with AF are significantly more likely to have OSA compared to patients without AF. Additionally, patients with diagnosed OSA have an increased risk of AF compared to patients without OSA, but to a much lesser degree.

Studies also suggest that evidence of OSA predicts a lower efficacy of common AF therapies including cardioversion, cryoballoon ablation, and radiofrequency catheter ablation. Studies investigating the presence of OSA or the severity of OSA as an independent predictor of ablation failure have reported conflicting results. The modality used to diagnosis OSA, whether the BQ questionnaire or polysomnography, is a determinate of this controversy. Despite the present understanding of the interrelationship between OSA and AF, several important questions remain unresolved that require large-scale, long-term randomized trials. Arguable, the most pertinent: Does treating OSA reduce the recurrence of AF following a pulmonary vein isolation procedure?

Disclosures

No disclosures relevant to this article were made by the authors.

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