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Relation of the Severity of Obstructive Sleep Apnea in Response to Anti-Arrhythmic Drugs in Patients with Atrial Fibrillation or Atrial Flutter

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Abstract

Atrial fibrillation (AF) is more common in those with obstructive sleep apnea (OSA) than in unaffected individuals and recurs more frequently in the presence of severe OSA after electrical cardioversion and AF ablation. However, it is unknown whether severity of OSA influences the efficacy of anti-arrhythmic drug (AAD) therapy in patients with OSA and AF. This study examined the impact of OSA severity on treatment of symptomatic AF with AADs. We studied 61 patients (62 ± 15 years; 21 women) treated with AADs for symptomatic AF who had overnight polysomnography. Rhythm control was prospectively defined as successful if a patient remained on the same AAD therapy for a minimum of 6 months with $\geq 75\%$ reduction in symptomatic AF burden. Twenty-four patients (40%) had severe OSA. Thirty patients (49%) were rhythm controlled with AADs. Non-responders to AADs were more likely to have severe OSA than milder disease (52% vs 23%; $p < 0.05$); those with severe OSA were less likely to respond to AADs than participants with non-severe OSA (39% vs 70%; $p = 0.02$). Non-responders had higher apnea-hypopnea indices than responders (34 ± 25 vs 22 ± 18 events/hour; $p = 0.05$), but there were no differences between these groups in minimum oxygen saturation or % time spent in REM sleep. In conclusion, patients with severe OSA are less likely to respond to AAD therapy for AF than those with milder forms of OSA.

Keywords

obstructive sleep apnea; atrial fibrillation; anti-arrhythmic drugs

INTRODUCTION

The presence of OSA has been demonstrated to decrease the efficacy of several therapies for AF. In a study of patients undergoing electrical cardioversion, the risk of AF recurrence was increased in those with OSA compared to unaffected individuals¹, despite the fact that nearly 50% of the OSA group was treated with an anti-arrhythmic drug (AAD) compared to less than 20% of the non-OSA group. In addition, when severe OSA is present, an increased rate of AF recurrence following catheter ablation has been consistently reported^{2–5}. The impact of OSA on the efficacy of AAD therapy for AF has not been robustly explored.

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Given that pharmacologic management of AF is common and is employed both prior and subsequent to electrical cardioversion and catheter ablation, characterizing the impact of OSA on AAD therapy of AF is clinically important. In this study, we tested the hypothesis that treatment of AF-related symptoms with AADs is less successful in patients with severe OSA than in those with milder forms of the disease.

METHODS

The cohort used for this study and the techniques for measuring AF symptom burden have been previously described⁶. Briefly, adults with documented AF or atrial flutter treated with at least 1 conventional AAD were prospectively enrolled in the Vanderbilt AF Registry, a clinical and genetic database. At enrollment and at 3, 6, and 12 months of follow-up, patients completed the modified University of Toronto AF Severity Scale (range 3–30) to gauge symptomatic AF burden⁷. The AADs reported here reflect the agents that patients were on at the time of their enrollment in the AF Registry.

Arterial hypertension was defined by a history of hypertension and/or the presence of antihypertensive therapy. Criteria for *coronary artery disease (CAD)* included a history of myocardial infarction or typical angina, previous coronary bypass surgery or angioplasty, and drug treatment. *Heart failure* was defined by history and/or drug treatment for heart failure. Left atrial and left ventricular measurements from M-mode echocardiograms were made at the time enrollment if a recent echo (< 3 months) was not available in medical record. The echocardiograms were read by an experienced physician blinded to the genotype status of the patient. The echocardiograms were evaluated according to the recommendations of the American Society of Echocardiography.

Response to AAD therapy was defined prospectively as successful rhythm control if the patient remained on the same AAD therapy for a minimum of 6 months after enrollment in the AF Registry or demonstrated ≥75% reduction in symptomatic AF burden (based on the composite score for frequency, duration and severity of symptoms)⁷. Non-response was defined as < 75% reduction in symptomatic AF burden score and a change to another AAD or to non-pharmacologic therapy such as atrio-ventricular node ablation and pacemaker implantation.

Polysomnography data

The Vanderbilt AF registry was screened for participants that underwent a diagnostic overnight polysomnogram (PSG) for clinical reasons at the Vanderbilt Sleep Center⁸. Sleep parameters were abstracted from clinical reports generated by specialists at our institution certified by the American Board of Sleep Medicine. If the study was a split-night examination, data from the diagnostic portion (without application of continuous or bi-level positive airway pressure) were utilized.

Full-night PSGs were carried out using the Polysmith Sleep system (Nihon Kohden America Inc, Foothill Ranch CA). Airflow was monitored by an oral-nasal sensor and respiratory effort was monitored by impedance plethysmography. Electroencephalogram, electro-oculogram, and submental electromyogram were recorded according to American Academy of Sleep Medicine standards. A single lead EKG signal as well as oxyhemoglobin saturation via digital pulse oximetry were continuously recorded throughout the study. Apnea was defined as a ≥90% decrease in the airflow signal from baseline for ≥10 seconds. Hypopneas were defined as ≥50% reduction in airflow from baseline for ≥10 seconds accompanied by a decrease in oxyhemoglobin saturation of ≥4%. Individuals with an apnea-hypopnea index (AHI) (sum of apneas and hypopneas divided by the total sleep time) ≥5 events per hour were considered to have OSA. Severity of OSA was further categorized by AHI as follows:

mild: 5–15 events/hour; moderate: 16–30 events/hour; severe: > 30 events/hour. The minimum oxygen saturation was taken as the nadir of the continuous oximetry reading during the PSG.

Data are reported as mean $\pm$ standard deviation for continuous variables and as percentages for categorical variables. Differences between groups were evaluated by the Wilcoxon rank-sum test for continuous variables and with Pearson's chi-squared test for categorical variables. Analyses were performed with the R software package (version 2.12.0; Vienna, Austria). Comparisons were considered statistically significant if the p value was less than 0.05 for two-tailed tests.

RESULTS

The analysis consisted of 61 individuals that underwent polysomnography and had serial evaluations of AF symptoms. Table 1 displays their demographics, cardiac history, echocardiographic characteristics, and key sleep parameters stratified by response to AADs. Two-thirds were taking either a beta-blocker and/or calcium channel blocker; 50% were taking amiodarone, 25% were taking sotalol, and 25% were taking either flecainide or propafenone. Approximately half of the cohort (49%) had symptomatic response to AADs.

Among the non-sleep related variables, only the type of AF differed between the non-responders and responders, with paroxysmal AF being more common and persistent AF less common in the responders. Both the AHI and frequency of severe OSA were increased in non-responders compared to responders. Individuals that did not respond to AADs had higher AHIs (34 ± 25 vs 22 ± 18 events/hour, $p = 0.05$) and more commonly had severe OSA (52% vs 23%, $p < 0.05$) than did responders. There was no difference in BMI between responders and non-responders suggesting that obesity itself did not influence the response to AADs in this cohort.

Table 2 displays cohort characteristics based on OSA severity. Less than one-third of those with severe OSA responded to AAD therapy, but the response rate was twice as high in those with non-severe OSA (61 vs 30%; $p = 0.02$). There are modest differences in the distributions of paroxysmal, persistent, and permanent AF when stratified by OSA status that do not reach statistical significance. This finding suggests that the response to AADs is not confounded by a disproportionately high prevalence of 'resistant' AF. The prevalence of hypertension and coronary artery disease, both implicated in the pathogenesis of AF, are higher in the severe OSA group compared to the non-severe group raising the possibility that the higher non-response rate observed in the severe OSA group is confounded by higher rates of these conditions. However, OSA is a known risk factor for both hypertension^{9–10} and coronary disease¹¹. Therefore, the increased prevalence of these conditions in the severe OSA group is not entirely unexpected and could be partially attributable to the increased OSA burden.

DISCUSSION

This study provides data suggesting that severe OSA adversely impacts the response to AADs in patients with symptomatic AF. Our findings that non-responders to AADs (1) are more common in severe OSA than in milder disease and (2) have higher AHI than responders are consistent with prior work in this area. A study from the Mayo Clinic showed analogous results for treatment of AF with elective cardioversion; specifically, those with OSA were more likely to have a recurrence of AF than those without OSA¹. The current study extends those findings to include a reduced rate of symptomatic improvement when treated with AADs in those with severe OSA relative to those with non-severe OSA. A

recent report from the Sleep Heart Health Study demonstrated that paroxysms of AF are much more likely to occur shortly after OSA events compared to during normal breathing¹². The finding that non-responders to AADs have higher AHI than responders suggests that those individuals are subject to more respiratory events during a given sleep period, thus providing more exposure to the pathophysiologic stimuli (arousals, wide swings in intra-thoracic pressure, inflammation, left atrial stretch)¹³ that promote arrhythmogenesis. This increased exposure may lead to a greater degree of atrial remodeling and contribute to increased resistance of AF to therapy¹⁴. The similarities in % REM sleep time and minimum nocturnal oxygen saturation between non-responders and responders suggests that neither hypoxia nor non-apneic-related sympathetic stimulation (more frequent in REM sleep than in non-REM sleep) are primarily responsible for the difference in response to AADs between these groups.

This study includes a robustly phenotyped cohort, both in terms of symptomatic response to AF and OSA data. Sleep parameters were obtained from overnight PSGs, the gold standard for diagnosis and evaluation of OSA. The small sample size, due to the relatively low prevalence of PSG data in the overall cohort, requires that the findings be interpreted cautiously and indicates that larger studies, with a dedicated PSG component, are needed. Such studies can focus on whether the effects of OSA on AAD therapy for AF differ by AAD class as well as whether treatment of OSA influences the outcome of therapy for AF.

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Table 1

Cohort characteristics stratified by response to anti-arrhythmic drugs

Characteristic	Entire cohort (n = 61)	Non-responders (n = 31)	Responders (n = 30)
Age (years)	64 ± 9	65 ± 8	64 ± 10
Female	34%	35%	33%
Caucasian	89%	77%	100%
Body mass index (kg/m ²)	34 ± 7	34 ± 8	34 ± 7
Hypertension	66%	65%	67%
Coronary artery disease	31%	25%	38%
Heart failure	20%	22%	17%
Atrial fibrillation			
Paroxysmal *	61%	50%	72%
Persistent *	26%	39%	14%
Permanent	12%	11%	14%
Baseline AF burden score	19 ± 8	20 ± 9	18 ± 8
Echocardiographic parameters			
Left atrial dimension (mm)	46 ± 8	47 ± 7	45 ± 9
Left ventricular ejection fraction (%)	50 ± 11	49 ± 12	52 ± 11
Left ventricular hypertrophy	47%	48%	45%
Right ventricular systolic pressure (mmHg)	38 ± 12	38 ± 12	38 ± 11
Polysomnogram parameters			
Apnea-hypopnea index (events/hour) *	28 ± 22	34 ± 25	22 ± 18
Minimum oxygen saturation (%)	81 ± 8	80 ± 8	82 ± 9
Portion of total sleep time in REM (%)	13 ± 8	15 ± 9	12 ± 7
Severe obstructive sleep apnea *	38%	52%	23%

* p = 0.05 for comparison between non-responders and responders

Table 2

Cohort characteristics and response to anti-arrhythmic drugs stratified by obstructive sleep apnea status

Characteristic	Entire cohort (n = 61)	Non-severe OSA (n = 38)	Severe OSA (n = 23)
Age (years)	64 ± 9	64 ± 11	65 ± 7
Female *	34%	42%	22%
Caucasian	89%	90%	87%
Body mass index (kg/m ²)	34 ± 7	33 ± 8	36 ± 6
Hypertension *	66%	58%	78%
Coronary artery disease **	31%	18%	52%
Heart failure	20%	15%	26%
Atrial fibrillation			
Paroxysmal	61%	63%	57%
Persistent	25%	21%	30%
Permanent	15%	16%	13%
Baseline AF burden score	19 ± 8	18 ± 9	20 ± 8
Response to AADs ***	49%	61%	30%
Echocardiographic parameters			
Left atrial dimension (mm)	46 ± 8	46 ± 8	47 ± 8
Left ventricular ejection fraction (%)	50 ± 11	52 ± 10	47 ± 14
Left ventricular hypertrophy	47%	43%	52%
Right ventricular systolic pressure (mmHg)	38 ± 12	38 ± 12	38 ± 12
Polysomnogram parameters			
Apnea-hypopnea index (events/hour) **	28 ± 22	14 ± 8	51 ± 19
Minimum oxygen saturation (%) **	81 ± 8	84 ± 8	77 ± 6
Portion of total sleep time in REM (%) ***	13 ± 8	15 ± 8	7 ± 5

AF:atrial fibrillation

AAD: anti-arrhythmic drug

REM: rapid-eye movement

*
p < 0.05**
p < 0.001***
p < 0.02