Severity of Obstructive Sleep Apnea Influences the Effect of Genotype on Response to Anti-Arrhythmic Drug Therapy for Atrial Fibrillation

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SCIENTIFIC INVESTIGATIONS

Study Objectives: To examine the impact of genotype on the relationship between obstructive sleep apnea (OSA) and anti-arrhythmic drug (AAD) efficacy in atrial fibrillation (AF).

Design: Registry based.

Setting: Clinic-based.

Participants: Eighty-four individuals from Vanderbilt AF registry who had polysomnography, genotyping, and serial comprehensive evaluations of AF status.

Interventions: None.

Measurements and Results: Response to AADs was defined as a decrease in AF burden score by $\geq 75\%$ or the combination of sinus rhythm on follow-up EKGs, stable AAD therapy for at least 6 months, objective AF burden below an established threshold, and the absence of non-pharmacologic therapies. Participants were genotyped for common AF susceptibility alleles at chromosomes 4q25 (near *PITX2*), 16q22 (in *ZFHX3*), and 1q21 (in *KCNN3*), and common SNPs in the β 1-adrenergic

receptor (ARDB1). Wild-type status for rs10033464 at 4q25 was associated with increased success of AAD therapy in patients with no or mild OSA (odds ratio: 10.0, 95% confidence interval: 1.03 to 97.5; $p < 0.05$), but did not influence response to AAD therapy in those with moderate-severe OSA. A similar trend was observed for rs1801252 on ARDB1.

Conclusion: In this hypothesis-generating pilot study of predominantly Caucasian men, the effect on AF response to AAD therapy of rs10033464 at 4q25 varied based on OSA status. The impact of genotype on AAD efficacy may be greatest in mild OSA and attenuated in more severe disease.

Keywords: obstructive sleep apnea, atrial fibrillation, anti-arrhythmic drugs, genetics

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Obstructive sleep apnea (OSA) has been increasingly recognized as a risk factor for atrial fibrillation (AF) and has an adverse impact on therapy for AF. Individuals with OSA have a higher prevalence of AF than those without OSA, and OSA is more prevalent in those with AF than those without AF.^{1,2} Paroxysms of AF are more common during and shortly after OSA-related respiratory events compared to periods of normal breathing.³ Anti-arrhythmic drugs (AADs) are less effective in achieving rhythm control when severe OSA, as compared to milder disease, is present; similarly, electrical cardioversion and catheter ablation are less successful in those with OSA than in unaffected individuals.⁴⁻⁶

Recent genome-wide association studies have identified loci on chromosomes 4q25 (near *PITX2*),⁷ 16q22 (in *ZFHX3*),^{8,9} and 1q21 (in *KCNN3*),¹⁰ that associate with either typical or lone AF. Wild-type status for rs10033464 at 4q25 is a predictor of successful treatment of AF with AADs,¹¹ and variants in rs10033464 and rs2200733 at 4q25 increase the chance of AF recurrence after catheter ablation.^{12,13} In addition, a common β -1 adrenergic receptor (ADRB1) polymorphism at rs1801253 has been shown to predict response to rate-control therapy in AF.¹⁴ These findings indicate that variable mechanisms contribute to AF susceptibility and suggest that response to therapy is also influenced by genotype.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Individuals with OSA have a higher prevalence of AF and both genetics and OSA have been individually known to affect response to AAD therapy. Given that both OSA and common variants influence the response of AF to AAD therapy, it is plausible that the impact of OSA on AF is determined in part by genotype.

Study Impact: This study points toward the role of genetics in determination of anti-arrhythmic drug efficacy in patients with AF and OSA. This will help direct further focused research on defining exact extent of genetic influence in these patients.

Given that both OSA and common variants influence the response of AF to AAD therapy, it is plausible that the impact of OSA on AF is determined in part by genotype. Understanding the effects of common variants and OSA on the response to pharmacologic treatment of AF could influence AAD choice and may also factor into decisions to pursue non-medication-based treatment strategies, such as pulmonary vein isolation or AV nodal ablation/pacemaker placement. Therefore, we sought to explore the relationship between common AF single nucleotide polymorphisms (SNPs) and symptomatic response to AADs in a cohort with AF and OSA. Specifically, we hypothesized that common genetic variants associated with AF decrease the efficacy of AADs to a greater

degree in moderate or severe OSA as compared to no or mild OSA.

METHODS

Study Cohort and Definitions

The Vanderbilt University Medical Center institutional review board approved the study protocol. The cohort used for this study and the techniques for measuring AF symptom burden have been previously described.^{4,15} Briefly, adults with documented AF treated with at least 1 conventional AAD were prospectively enrolled in the Vanderbilt AF Registry between November 2002 and October 2005. 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 burden.¹⁵ Patients' electronic medical records were also reviewed, and an electrophysiologist blinded to genotype status of the patients ascertained AF burden during enrollment.

Response to AAD Therapy

Response to AADs was defined as a decrease in AF burden score by $\geq 75\%$ on a validated symptom scoring tool¹⁶ or the combination of sinus rhythm on follow-up EKGs, stable AAD therapy for ≥ 6 months, AF burden below the threshold for increased stroke risk described in the ASSERT trial¹⁷ on device diagnostics or ambulatory monitoring, and the absence of non-pharmacologic therapies (cardioversion, nodal ablation, AF ablation). In all participants, EKGs were obtained at enrollment and at the 1-, 3-, and 6-month follow-up visits. In the first 6 months of enrollment, one-third of participants had an assessment of AF burden by either device interrogation or ambulatory monitoring.

Polysomnography Data

The Vanderbilt AF registry was screened for participants who underwent a diagnostic overnight polysomnogram (PSG) for clinical reasons at the Vanderbilt Sleep Center.¹⁸ 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 bilevel positive airway pressure) were utilized.

Full-night PSGs were carried out using the Polysmith Sleep system (Nihon Kohden America Incorporated; Foothill Ranch, CA). Airflow was monitored using both a thermistor placed over the philtrum and a nasal pressure transducer via oronasal cannula. Respiratory effort was monitored by impedance plethysmography. Electroencephalogram, electro-oculogram, and submental electromyogram were recorded according to American Academy of Sleep Medicine standards. Single lead electrocardiographic signals, as well as oxyhemoglobin saturation via digital pulse oximetry, were continuously recorded throughout the study. Apnea was defined as $\geq 90\%$ decrease in the airflow signal from baseline for ≥ 10 seconds. For all patients, hypopneas were defined as $\geq 50\%$ reduction in airflow from baseline for ≥ 10 sec accompanied by a decrease in oxyhemoglobin saturation of $\geq 3\%$ or an associated EEG arousal.¹⁹

This definition of hypopneas was used to calculate the "standard AHI" for the entire cohort. A separate analysis was also performed for Medicare patients ($n = 44$), in which hypopneas were defined as $\geq 30\%$ reduction in airflow from baseline for ≥ 10 sec associated with $\geq 4\%$ desaturation. This definition of hypopnea was used to calculate for Medicare patients a respiratory disturbance index (RDI) that included apneas, hypopneas, and respiratory effort-related arousals (flow limitation that resolved with an arousal). The standard AHI and RDI were similar numerically; use of the RDI would have resulted in re-classification of 2 Medicare participants from "none" to "mild" and 1 Medicare participant from "mild" to "moderate." Therefore, the standard AHI was used for all participants. Individuals with an apnea-hypopnea index (AHI) (sum of apneas and hypopneas divided by the total sleep time) ≥ 5 events/h were considered to have OSA. Severity of OSA was further categorized by AHI as follows: mild: 5-15 events/h; moderate: 16-30 events/h; severe: > 30 events/h.

Genotyping

Genomic DNA was isolated from whole blood by a commercial kit (Purgene; Gentra Systems; Minneapolis, MN). Genotyping of the 4q25 SNPs (rs2200733 and rs10033464) was performed using real-time polymerase chain reaction (PCR), iPLEX single base primer extension, and MALDI-TOF mass spectrometry in a 384-well-format (Sequenom; San Diego, CA) as previously described.²⁰ Genotyping at the 16q22 SNP (rs7193343 in *ZFHX3*), the 1q21 SNP (rs13376333 in *KCNN3*), and *ADRB1* (rs1801252; rs1801253) was performed using TaqMan assays (Applied Biosystems Incorporated; Foster City, CA) as previously described^{8,10} by laboratory personnel who had no knowledge of the response to rhythm control therapy.

Statistical Analysis

Clinical 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 χ^2 test for categorical variables.

Pearson χ^2 test was also used to test for Hardy-Weinberg equilibrium. Logistical regression was used to assess the association between rhythm control and genotype, adjusting for OSA status; an interaction term between genotype and OSA status was also included. Due to expected low numbers of homozygous variants, it was defined *a priori* to include homozygous variants of all SNPs with their respective heterozygous variants.

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 84 individuals who underwent polysomnography and had genotype data as well as serial evaluations of AF symptoms. This cohort includes the group described in our prior work,⁴ as well as an additional ~ 25 individuals identified in the interim. As such, this study population is very similar to the previously reported cohort in terms of

demographics, cardiac history, echocardiographic characteristics, and key sleep parameters (Table 1). Briefly, the study population was primarily comprised of obese, middle-aged, Caucasian males. More than half had paroxysmal AF. Severe OSA was present in 52% of the cohort, with a mean AHI at the lower end of the severe range. Approximately 15% of those with at least mild OSA (12/79) were on continuous positive airway pressure (CPAP) therapy at the time of enrollment in the AF Registry. Three individuals initiated CPAP during the first 6 months after enrollment, and 2 participants had their CPAP therapy intensified (i.e., an up-titration of mean PAP) over that time frame. Two-thirds were taking either a β -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%) responded to AADs according to the definition used in this study. As in our prior study,⁴ when compared to responders to AADs, non-responders had higher AHIs, greater likelihood of severe OSA, and a higher prevalence of non-paroxysmal AF. There was no difference in left atrial size in non-responders as compared to responders.

The availability of genotype status was as follows: 4q25.rs2200733: 99% (83/84); 4q25.rs10033464: 95% (80/84); ZFXH3.rs7193343: 99% (83/84); KCNN3.rs13376333: 97% (81/84); ADRB1.rs1801252: 98% (82/84); ADRB1.rs1801253: 99% (83/84). The wild-type frequency across the SNPs of interest was between 40% and 75% (4q25.rs2200733: 65%; 4q25.rs10033464: 73%; ZFXH3.rs7193343: 67%; KCNN3.rs13376333: 44%; ADRB1.rs1801252: 68%; ADRB1.rs1801253: 53%).

Carriers of the 4q25.rs10033464 wild-type allele were more likely to respond to AAD therapy if they had no or mild OSA (odds ratio [OR]: 10.0, 95% confidence interval [CI]: 1.03 to 97.5; $p < 0.05$), but this genotype did not influence the success of AAD response in participants with moderate or severe OSA (OR: 0.86, 95% CI: 0.26 to 3.20). Those with the ADRB1.rs1801252 wild-type allele showed a trend towards more successful response to AAD therapy in the presence of no or mild OSA; again, there was no effect in those with moderate or severe OSA. The response to AADs stratified by OSA status for both 4q25.rs10033464 and ADRB1.rs1801252 is displayed in Figure 1. For comparison, when stratified in a similar manner by OSA level and genotype status, there was no difference in the prevalence of a given clinical AF subtype (i.e., paroxysmal, persistent, permanent) between any subgroups.

For the KCNN3, ZFXH3, 4q25.rs2200733 and ADRB1.rs1801253 variants, there was no difference in AAD response rate when stratified by OSA status.

DISCUSSION

The key finding of this study suggests that the effect of genotype on the response of AF to AAD therapy depends partially on OSA severity. The high non-response rates in more severe OSA,⁴ regardless of genotype, suggest that the impact of common variants on response to AADs may be “overwhelmed” by the increased frequency of apneic events and their pro-arrhythmic consequences.³ However, at lower levels of OSA, a favorable genotype may be able to “protect”

Table 1—Cohort characteristics stratified by response to anti-arrhythmic drugs

Characteristic	Entire cohort	Responders	Non-Responders
Patients	84	41	43
Demographics			
Age (years)	63 $\pm$ 9	62 $\pm$ 8	64 $\pm$ 9
Female	33%	34%	30%
Caucasian	90%	86%	95%
Body mass index (kg/m ²)	35 $\pm$ 7	35 $\pm$ 7	34 $\pm$ 6
Cardiac history			
Hypertension	75%	80%	70%
Coronary artery disease	28%	24%	33%
Heart failure	29%	22%	38%
Type of atrial fibrillation			
Paroxysmal *	57%	67%	44%
Persistent	27%	23%	39%
Permanent	15%	10%	17%
Echocardiographic parameters			
Left atrial dimension (mm)	45 $\pm$ 7	42 $\pm$ 5	47 $\pm$ 7
Left ventricular ejection fraction (%)	53 $\pm$ 11	53 $\pm$ 10	52 $\pm$ 11
Right ventricular systolic pressure (mm Hg)	33 $\pm$ 10	32 $\pm$ 11	34 $\pm$ 9
Polysomnogram parameters			
Apnea-hypopnea index (events/h) *	31 $\pm$ 23	23 $\pm$ 16	37 $\pm$ 26
Minimum oxygen saturation (%)	80 $\pm$ 8	82 $\pm$ 7	77 $\pm$ 8
Severe obstructive sleep apnea *	52%	31%	56%

* $p < 0.05$ for comparison between responders and non-responders.

against arrhythmogenesis given the less frequent pro-arrhythmic stimuli.

Polymorphisms in ADRB1 are associated with differences in resting hemodynamics and response to positive airway pressure therapy in those with OSA^{21,22} and also track with a higher prevalence of OSA in hypertensive individuals.²³ Our findings provide additional support for a link between OSA and ADRB1 polymorphisms. One such connection could be increased downstream changes in sympathetic tone induced by OSA-related respiratory events, which, in turn, could contribute to a more pro-arrhythmic milieu. Correspondingly, although perhaps even more speculative, it appears plausible that *PITX2*, the closest gene to rs10033464 at 4q25 and a regulator of development of pulmonary venous myocardium, could influence susceptibility to AF based on OSA-related local fluctuations in intrathoracic pressure, oxygen tension, and sympathetic tone.²⁴ These factors may contribute to electroanatomical remodeling in the atria, which has been observed in those with OSA compared to unaffected individuals.²⁵ Whether a synergistic effect of common genetic variants and OSA on resistance of AF to treatment may contribute to the observed decrease in procedural success of electrical cardioversion⁵ or catheter ablation⁶ for AF when severe OSA is present (and increased success when OSA is treated²⁶) remains to be determined.

The current results extend recent work from our group that established rs10033464 status as a predictor of AF response

Figure 1—Response to anti-arrhythmic drugs (AADs) by genotype and OSA status.

Responder rates to AAD therapy are displayed as a function of OSA status for 4q25.rs10033464 (A), and ADRB1.rs1801252 (B). In those with no or mild OSA ($n = 22$), the prevalence of responders is higher in the wild-type (WT) than in minor allele carriers (MAC) for both SNPs. For moderate or severe OSA ($n = 59$), the responder rate does not vary based on WT vs. MAC status for either SNP.

to AAD therapy¹¹ and an ADRB1 receptor polymorphism as a modulator of response to a rate-control strategy.¹⁴ In addition to using genotype as a guide when selecting AF treatment, consideration of OSA status when formulating therapeutic plans may be reasonable as well.

Limitations

Our cohort includes detailed longitudinal follow up of AF burden and symptoms, availability of sleep-lab overnight PSGs, and detailed genotyping data. Changes in OSA therapy (i.e., initiation or titration of CPAP) over the course of the study were infrequent, suggesting that effects of OSA treatment on AAD efficacy did not unduly influence the results.

The study population primarily consisted of a Caucasian male population; therefore, the results may not be generalizable to other groups. A large percentage of our cohort had severe OSA, which may be expected in a population with numerous risk factors for OSA referred for PSG. AAD therapy was recorded at the time of enrollment into the AF Registry, and changes in pharmacotherapy over time were noted; however, detailed information regarding the rationale behind AAD choices was not available. Variation in AAD use could influence the relationship between OSA, AF, and genotype, but disparate effects of AADs would be expected to dilute the main association; for the present cohort, the small sample size does not permit investigation of this hypothesis. The low rate of recorded CPAP use among the cohort may reflect a time lag between enrollment in the AF Registry, recognition of OSA, and initiation of therapy, which could have occurred (or have been recorded) outside the follow-up period examined in this study. However, the relative paucity of OSA therapy does minimize the potentially heterogeneous and confounding effects of CPAP treatment on our analyses and permits evaluation of the “natural history” of OSA in this context. Furthermore, non-uniform treatment with CPAP of a larger portion of the cohort may have decreased the association between response to AAD therapy and OSA, thus diminishing the magnitude of our main finding.

The overall sample size is small, due to lack of PSG data in the majority of AF Registry patients; this is reflected in the wide confidence intervals associated with the main result. Although the cohort included only AF Registry participants who had a PSG, this “selection bias” should not confound the results. It is unlikely that the decision to obtain a PSG (made independent of the patient’s participation in the AF Registry) was related to genotype or efficacy of AAD therapy for AF, although it is possible that some of the referrals for PSG were prompted by unsuccessful attempts at AF treatment. The analytical limitations stemming from the size of the cohort include: (1) pooling of AADs as a single group and (2) inability to perform multivariate regression. However, the emergence of a relationship between efficacy of AAD therapy for AF, OSA, and genotype, despite the small cohort, suggests it is reasonable to pursue larger studies of the impact on this relationship of individual AADs and other potential confounders, such as AF subtype (i.e., paroxysmal, persistent, permanent, lone, familial), choice of AAD, and OSA treatment.

CONCLUSIONS

The results of this hypothesis-generating pilot study raise the possibility that the impact of common AF susceptibility alleles on the efficacy of AAD therapy for AF may be influenced by OSA severity. Future research will focus on further characterizing the interaction of genotype and OSA status on AF pathogenesis and treatment as part of the effort to personalize therapy for this common and morbid arrhythmia.

ABBREVIATIONS

OSA, obstructive sleep apnea
 AF, atrial fibrillation
 AAD, anti-arrhythmic drug
 SNPs, single nucleotide polymorphisms
 PSG, polysomnogram
 PCR, polymerase chain reaction

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