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Incidence of sleep apnea and association with atrial fibrillation in an unselected pacemaker population: Results of the observational RESPIRE study

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BACKGROUND Patients with atrial fibrillation (AF) often have sleep apnea (SA), but diagnosis of SA with polysomnography is costly. SA monitoring is a pacemaker feature that measures respiratory disturbance index, the sum of abnormal respiratory events divided by sleep duration.

OBJECTIVE The purpose of this study was to evaluate the incidence and severity of SA and its association with AF in an unselected population fitted with pacemakers.

METHODS RESPIRE (REgistry of Sleep APnea monItoring and Atrial Fibrillation in pacemakeR patients) was a multicenter, international, observational, open-label study following adult subjects for 18 months after implantation with an SA monitoring–enabled dual-chamber pacemaker. Severe SA was defined as average respiratory disturbance index ≥20 from implantation to follow-up visit. The first co-primary end point was the difference in significant AF (cumulative AF episodes lasting ≥24 hours over 2 consecutive days) between subjects with severe and those nonsevere SA at 12 months in the full analysis set (N = 553). The second co-primary end point was the rate of major serious adverse events at 18 months in the modified intention-to-treat set (N = 1024).

RESULTS Severe SA was detected in 31.1% (172 of 553). A higher incidence of significant AF was reported in patients with severe SA than in patients with nonsevere SA (25.0% vs 13.9%; difference 11.1%; 95% confidence interval 3.7%–18.4%; $P = .002$). Significant AF increased with time in both groups, but at a faster rate in the severe SA group. No intergroup difference in the overall rate of major serious adverse events was observed ($P = .065$).

CONCLUSION SA screening over 12 months identified severe SA in almost one-third of unselected patients fitted with pacemakers. Severe SA was associated with a higher incidence of significant AF.

KEYWORDS Atrial fibrillation; Dual-chamber pacemaker; Respiratory disturbance index; Sleep apnea; Sleep apnea monitoring

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Introduction

Sleep apnea syndrome (SAS) is a common disorder. The prevalence of moderate-to-severe SAS has been reported as 23% in middle-aged women and 49% in middle-aged men.[1] SAS is characterized by repeated episodes of reduced (hypopnea) or absent (apnea) airflow causing frequent

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arousals, oxyhemoglobin desaturation, and excessive daytime sleepiness. SAS has a potential deleterious impact on the cardiovascular system and is associated with increased morbidity and mortality.[2] In addition, patients with SAS are more likely to have a reduced quality of life than are the general population.[3]

Although overnight polysomnography is the current criterion standard for the diagnosis of sleep apnea (SA), high associated costs and a shortage of sleep laboratories render it inadequate for widespread screening. Screening questionnaires have been found to have low accuracy.[4] Thus, there is a need for affordable and reliable alternative diagnostic means and prescreening methods to improve the targeting of patients at risk of SAS.

One-third to half of pacemaker patients has SAS,[5] which is often asymptomatic. Furthermore, a high percentage of SAS patients have heart rhythm disturbances.[6] There are currently few data on the association between SAS and atrial fibrillation (AF) in pacemaker patients.[7] Pacemakers capable of detecting respiratory disturbance may be used as a screening tool for detecting SAS and provide long-term information on changes in the severity of SA over time.[8–10] The feature has the added advantage vs polysomnography of monitoring sleep continuously every night.

Recent pacemakers (MicroPort CRM, Clamart, France) feature sleep apnea monitoring (SAM), which analyzes and records abnormal breathing events such as apnea and hypopnea during sleep. In the DREAM (Evaluation of the Performances of the Sleep **D**isordered B**rea**thing **M**onitoring Function in Pacemaker) study,[11] the SAM algorithm was validated to identify severe SA with a sensitivity of 88.9% and a specificity of 84.6%. SAM can thus be considered a good screening tool for use in a wide population, for example, an unselected population fitted with pacemakers.[11]

The above considerations led to the design of RESPIRE (REgistry of Sleep APnea monItoring and Atrial Fibrillation in pacemakeR patiEnts), an 18-month multicenter observational study with the main objective to assess the association between SA and AF in a population with dual-chamber pacemakers equipped with the SAM feature.

Methods

Study design

The RESPIRE study (ClinicalTrials.gov Identifier: NCT01922726) was an observational, single-arm, open-label, international, multicenter study conducted at 98 centers in Europe (Austria, Belgium, France, Germany, Italy, Portugal, Spain, Switzerland, and United Kingdom). Patients 18 years and older were included if they were eligible for a dual-chamber pacemaker implant (de novo, replacement, or upgrade) according to current available guidelines[12] and had been implanted with a SAM-equipped dual-chamber pacemaker (REPLY 200, KORA 100, or KORA 250 DR, MicroPort CRM) in the previous 4 weeks or were scheduled to be in the upcoming fortnight. Unavailability for routine follow-up, inclusion in another clinical study that could affect the results of RESPIRE, and pregnancy were exclusion criteria. Local ethics committees approved the study protocol. All patients gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki[13] and Good Clinical Practice.

SAM feature

As described previously,[11,14] the SAM algorithm detects the following events using measurement of transthoracic impedance for evaluating respiratory rate: apnea (absence of a significant respiratory cycle for $\geq$10 seconds) and marked hypopnea (sustained, $\geq$10 seconds, reduction of the respiratory amplitude by at least 50% compared to the mean minute ventilation of preceding validated respiratory cycles).

Each day, at the end of the monitoring period (a 5-hour programmable period between 22:00 and 6:00), the respiratory disturbance index (RDI) evaluated by the SAM algorithm, corresponding to the mean number of detected events per hour during sleep, was automatically computed. At the end of the night, an analysis of the total number of excluded cycles was performed; no RDI was calculated when excluded cycles exceeded 400 cycles/h overnight.

The performance of the SAM algorithm was assessed in the DREAM study.[11] RDI stored in the pacemaker memory was compared with the apnea-hypopnea index derived from polysomnography. The study showed that an RDI of $\geq$20 with the SAM feature was equivalent to an apnea-hypopnea index of $\geq$30 with polysomnography to identify severe SA patients.

Follow-up and data collection

As an observational study, treatment of patients was left to physicians' discretion with no additional examinations involved. Patients were followed up according to the routine clinical practice of individual centers, typically at 6, 12, and 18 months. At each visit, episodes of both fallback mode switch and RDI stored in the device memory were downloaded. Clinical data were retrieved and transferred to standard case report forms, as were adverse events that prompted unscheduled visits.

Objectives and end points

The primary study objective was to evaluate the association between significant AF and SA severity at 12 months on the basis of data stored in the pacemaker. Significant AF was defined as cumulative AF episodes lasting $\geq$24 hours over 2 consecutive days on the basis of the duration of fallback mode switch. SA severity was defined according to average RDI from implantation to follow-up visit (ie, 12 or 18 months): RDI $\geq$20 was classified as severe SA, and RDI $<$20 was classified as nonsevere SA. Average RDI $\geq$20 was chosen rather than a single RDI value $\geq$20 to ensure the robustness of the diagnosis of severe SA.

The first co-primary end point was to show a difference in the incidence of significant AF in patients with severe SA compared with those with nonsevere SA after 12 months.

The second co-primary end point was all major investigator-reported serious adverse events—death, myocardial infarction, stroke, and pacemaker- and/or lead-related reintervention—that occurred in patients with severe SA and in those without severe SA over the 18-month study period.

Other end points included the development of significant AF and persistent AF (defined as an AF episode lasting for more than 7 consecutive days) from implantation up to 1, 6, 12, and 18 months according to SA severity. Furthermore, SA referrals, examinations, and treatment were determined at 12 months for patients with and without severe SA. Patients already receiving SA treatment were excluded from this last analysis. Different clinical and demographic variables were examined to determine the predictors of significant AF.

Sample size and statistical methods

Assuming that 58% of patients would have severe SA and that 14% of severe SA patients would have AF vs 8% of nonsevere SA patients,[7] 862 evaluable patients would be needed for 80% study power and 2.5% type I error (1-sided Z test) in order to show a difference in AF between severe and nonsevere SA patients.

The first co-primary end point was analyzed in the full analysis set (FAS) population (enrolled patients with $\geq$80% of valid nights with RDI data from SAM initiation and who underwent successful pacemaker implantation). A sensitivity analysis for the first co-primary end point was performed in the modified intention-to-treat (mITT) population. The second co-primary analysis was performed in the mITT population (enrolled patients with $\geq$1 night of SAM data who underwent successful pacemaker implantation). For both co-primary end points, differences in proportions and their 95% confidence intervals (CIs) were estimated using the Wald method and tested between the severe and nonsevere SA groups using a 1-sided Z test with significance set at $P < .025$. A multivariate analysis was performed in the mITT population to determine the predictors of significant AF using logistic regression to estimate odds ratios and 95% Wald CIs. A complementary analysis using a logistic regression model with the interaction term severe SA (yes/no)*AF (yes/no) adjusted for all cofactors in the multivariate analysis was conducted to determine the impact of the presence or absence of history of AF on severe SA as a predictor of significant AF. Quantitative parameters are presented as mean $\pm$ SD for normally distributed data or as median and interquartile range otherwise. Qualitative parameters are presented as number and percentage. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Results

Study population

Between July 22, 2013, and April 28, 2015, 1147 subjects were enrolled. The analyzed populations are reported in Figure 1. A dual-chamber pacemaker was implanted, or an implant attempt was made, in 1119 subjects, who constituted the intention-to-treat population. The previously described

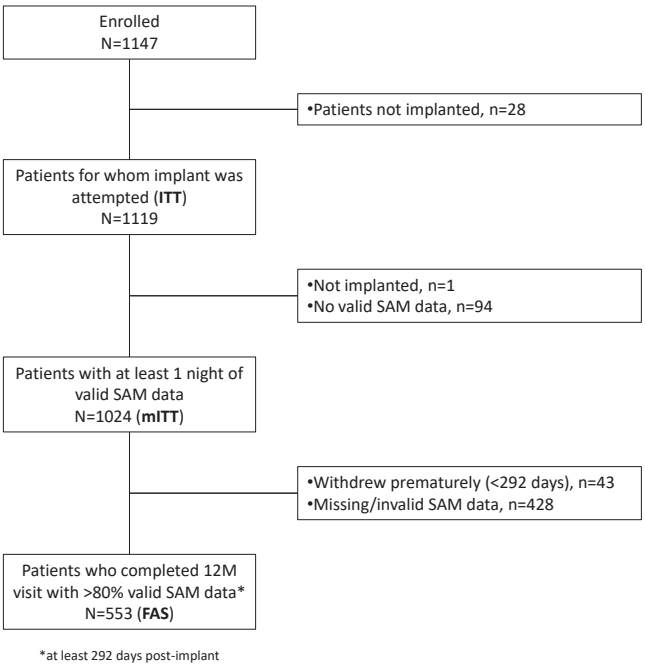

Figure 1 Patient flowchart in RESPIRE (REgistry of Sleep APnea monItoring and Atrial Fibrillation in pacemakeR patiEnts). FAS = full analysis set; ITT = intention-to-treat; mITT = modified intention-to-treat; SAM = sleep apnea monitoring.

FAS and mITT populations consisted of 553 and 1024 subjects, respectively (Figure 1). The baseline characteristics of the FAS and mITT populations are reported in Supplemental Table 1.

In the FAS population, most subjects (72.2%) were aged between 65 and 85 years and there were more men (61.5%) than women. Over two-thirds of the population (69.8%) received a pacemaker for sinus node dysfunction or AV block. About a quarter of subjects (23.9%) had a history of AF, and a history of SA was recorded in 8.0%. Patients with severe SA were more likely to be male, older, and in poorer cardiovascular health than were patients with nonsevere SA (Table 1). The baseline characteristics of the mITT population according to SA severity are presented in Supplemental Table 2.

Primary and secondary end points

For the first co-primary end point, evaluated after 12 months of follow-up, severe SA was identified in 172 patients (31.1%) from the FAS population (N = 553). Forty-three patients with severe SA (25.0%) had AF compared with 53 patients without severe SA (13.9%), a difference of 11.1% (95% CI 3.7%–18.4%; $P = .002$) (Table 2). In the sensitivity analysis in the mITT population, 80 patients with severe SA (24.9%) had AF compared with 92 patients without severe SA (13.2%), a difference of 11.7% (95% CI 6.4%–17.1%; $P < .001$) (Table 2). Multivariate analysis determined that severe SA (RDI >20; odds ratio 2.02; 95% CI 1.36–3.00) and AF at baseline (odds ratio 5.19; 95% CI 3.51–7.69) were the only predictors of significant AF (Table 3). Severe SA was both a predictor of significant AF in patients with a history

Table 1 Baseline characteristics in the full analysis set population (N = 553) according to severity of SA

Characteristic	Severe SA (n = 172)	Nonsevere SA (n = 381)	*P*
Age (y)	77.7 ± 8.6	74.1 ± 9.7	<.001
<65	11 (6.4)	59 (15.5)	.001
≥65 to <85	126 (73.3)	273 (71.7)	
≥85	34 (19.8)	45 (11.8)	
Sex: male	115 (66.9)	225 (59.1)	<.001
SBP (mm Hg)	142 ± 21	141 ± 22	.80
DBP (mm Hg)	73 ± 12	74 ± 12	.16
Heart rate (beats/min)	65 ± 17	64 ± 17	.54
BMI (kg/m^2)	28.4 ± 4.6	26.8 ± 4.4	.059
Cardiovascular history			
CAD	29 (16.9)	36 (9.4)	.015
Angina	11 (6.4)	15 (3.9)	.28
Cardiomyopathy	13 (7.6)	13 (3.4)	.049
Myocardial infarction	16 (9.3)	14 (3.7)	.013
Heart failure	10 (5.8)	8 (2.1)	.035
Cardiac surgery	17 (9.9)	19 (5.0)	.040
Stroke history	11 (6.4)	21 (5.5)	.70
TIA	3 (1.7)	7 (1.8)	>.99
Renal failure	8 (4.7)	12 (3.1)	.46
Implant indication			
Sinus dysfunction	30 (17.4)	92 (24.1)	.12
AV block	84 (48.8)	180 (47.2)	
Syncope	15 (8.7)	35 (9.2)	
Carotid sinus syndrome	3 (1.7)	3 (0.8)	
Brady-tachy syndrome	18 (10.5)	39 (10.2)	
Other	22 (12.8)	28 (7.3)	
Unknown	–	4 (1.0)	
History of rhythm disorders			
Atrial fibrillation	49 (28.5)	83 (21.8)	.11
Paroxysmal	38 (22.1)	73 (19.2)	
Permanent	3 (1.7)	0 (0)	
Persistent	7 (4.1)	9 (2.4)	
Unknown	1 (0.6)	1 (0.3)	
Atrial flutter	11 (6.4)	15 (3.9)	.28
Atrial extrasystole >10 per minute	3 (1.7)	2 (0.5)	.18
Ventricular extrasystole >10 per minute	4 (2.3)	5 (1.3)	.47
Long QT syndrome	–	3 (0.8)	.56
Ventricular tachycardia	2 (1.2)	4 (1.0)	1.00
Sleep apnea	11 (6.4)	33 (8.7)	.40
Light (5 ≤ AHI < 15)	–	2 (0.5)	
Moderate (15 ≤ AHI < 30)	–	3 (0.8)	
Severe (AHI ≥ 30)	4 (2.3)	14 (3.7)	
AHI unknown	7 (4.1)	14 (3.7)	
Comorbidities			
COPD	9 (5.2)	10 (2.6)	.13
Diabetes	38 (22.1)	59 (15.5)	.070
Smoking status			
Nonsmoker	96 (55.8)	258 (67.7)	.021
Smoker	13 (7.6)	28 (7.3)	
Ex-smoker	48 (27.9)	65 (17.1)	
Unknown	14 (8.1)	25 (6.6)	
Medication			
Antiarrhythmic			
Amiodarone	16 (2.9)	33 (6.0)	.87
β-Blocker	54 (9.8)	80 (14.5)	.010
Digoxin	3 (0.5)	1 (0.2)	.092
Disopyramide	1 (0.2)	1 (0.2)	.53
Dronedarone	1 (0.2)	1 (0.2)	.53
Flecainide	2 (0.4)	12 (2.2)	.24
Propafenone	0 (0)	3 (0.5)	.56
Sotalol	3 (0.5)	5 (0.9)	.71
Other antiarrhythmic	6 (1.1)	13 (2.4)	1.00

Table 1 (*Continued*)

Characteristic	Severe SA (n = 172)	Nonsevere SA (n = 381)	*P*
Anticoagulant			
Anti–vitamin K*	31 (5.6)	49 (8.9)	.12
NOAC†	18 (3.3)	29 (5.2)	.32
Other anticoagulant	10 (1.8)	13 (2.4)	.25
Antiplatelet drug	46 (8.3)	85 (15.4)	.28

Values are presented as mean ± SD or as n (%).

AHI = apnea-hypopnea index; AV = atrioventricular; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; NOAC = non–vitamin K oral anticoagulant; SA = sleep apnea; SBP = systolic blood pressure; TIA = transient ischemic attack.

*For example, coumadin, warfarin, and acenocoumarol.

†For example, dabigatran, rivaroxaban, apixaban, and edoxaban.

of AF (odds ratio 2.46; 95% CI 1.36–4.45) and a predictor of new-onset significant AF in patients without a history of AF (odds ratio 1.72; 95% CI 1.01–2.93).

The second co-primary end point was evaluated at 18-month follow-up in 312 subjects with severe SA and 712 subjects without. Overall rates of major serious adverse events were no different in the group with severe SA compared with the group with nonsevere SA (difference 2.8%; 95% CI −0.8% to 6.3%; $P = .065$) (Table 2). Analysis of the components of the second co-primary end point found no intergroup differences in myocardial infarction (0.2%; $P = .33$), stroke (0.7%; $P = .12$), or reintervention (−0.2%; $P = .59$) but did find a significant difference in death (2.7% [5.1% severe SA vs 2.4% nonsevere SA]; 95% CI 0.05%–5.4%; $P = .023$) (Table 2).

Other analyses

The evolution of the incidence of significant AF from implantation up to 1, 6, 12, and 18 months according to SA severity in the mITT population is shown in Figure 2. The percentage of patients with significant AF increased in both groups, with a higher rate of increase in the group with severe SA. The mean differences between the groups in the incidence of significant AF at 1, 6, 12, and 18 months were 4.0% (95% CI −0.3% to 8.3%), 9.1% (95% CI 3.2%–15.0%), 11.7% (95% CI 6.4%–17.1%), and 15.0% (95% CI 5.7%–24.3%), respectively. The differences increased throughout the follow-up period. The relative risk of significant AF in severe SA vs nonsevere SA patients was 1.53 (95% CI 0.99–2.35), 1.87 (95% CI 1.28–2.72), 1.89 (95% CI 1.45–2.47), and 1.92 (95% CI 1.33–2.77) at 1, 6, 12, and 18 months, respectively.

Similarly, there was a higher incidence of persistent AF in patients with severe SA than in patients without severe SA at 12 months (16.9% vs 7.3%). The percentages also increased over time in both groups, with a higher rate of increase in the group with severe SA (Figure 3). The differences increased throughout the follow-up period, with the mean intergroup differences at 1, 6, 12, and 18 months of 3.8% (95% CI 0.2%–7.4%), 8.2% (95% CI 2.8%–13.5%), 9.5% (95% CI 2.5%–16.6%), and 13.4% (95% CI 4.1%–22.7%), respectively. The relative risk of persistent AF in severe SA vs nonsevere SA patients was 2.33 (95% CI 1.21–4.47), 2.83 (95%

Table 2 Co-primary end points

Variable	Patients with severe sleep apnea	Patients without severe sleep apnea	Difference (95% CI) (%); *P*
Main analysis—first co-primary end point (FAS)	n = 172	n = 381	
Significant AF at 12 mo	43 (25.0)	53 (13.9)	11.1 (3.7 to 18.4); $P = .002$
Sensitivity analysis—first co-primary end point (mITT)*†	n = 321	n = 698	
Significant AF at 12 mo	80 (24.9)	92 (13.2)	11.7 (6.4 to 17.1); $P < .001$
Main analysis—second co-primary end point (mITT)†	(n = 312)	(n = 712)	
Major serious adverse events at 18 mo‡	27 (8.7%)	42 (5.9)	2.8 (−0.8 to 6.3); $P = .065$§
Death	16 (5.1)	17 (2.4)	2.7 (0.05 to 5.4); $P = .023$§
Myocardial infarction	2 (0.6)	3 (0.4)	0.2 (−0.8 to 1.2); $P = .33$
Stroke	3 (1.0)	2 (0.3)	0.7 (−0.5 to 1.8); $P = .12$
Reintervention	8 (2.6)	20 (2.8)	−0.2 (−2.4 to 1.9); $P = .59$

Values are presented as n (%) unless otherwise indicated.

AF = atrial fibrillation; CI = confidence interval; FAS = full analysis set; mITT = modified intention-to-treat.

*In the mITT population, 5 patients were not yet evaluable at 12 mo because they did not have a valid night of sleep apnea monitoring data.

†Number of patients with severe sleep apnea varied between 12 mo and 18 mo because sleep apnea severity was based on an average measurement of respiratory disturbance index, which fluctuated.

‡First-event analysis; for information, in the severe sleep apnea group, 2 patients who suffered a stroke subsequently died.

§One-sided *Z* test with significance set at $P < .025$.

Table 3 Multivariate analysis of potential predictors of atrial fibrillation in the mITT population (N = 1024) of the RESPIRE study

Variable	Odds ratio	95% Wald confidence limits	
		Lower limit	Upper limit
Severe sleep apnea* (yes vs no)	2.02	1.36	3.00
SBP > 140 mm Hg (yes vs no)	1.16	0.79	1.70
Cardiac surgery (yes vs no)	0.66	0.29	1.53
CAD, angina, or myocardial infarction (yes vs no)	0.81	0.49	1.34
Cardiomyopathy or heart failure (yes vs no)	0.97	0.52	1.84
COPD (yes vs no)	0.40	0.11	1.45
Atrial fibrillation at baseline (yes vs no)	5.19	3.51	7.69
Sex (male vs female)	1.32	0.88	1.96
Diabetes (yes vs no)	1.02	0.60	1.72
Age†	1.02	0.998	1.04
BMI†	1.01	0.97	1.06

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; mITT = modified intention-to-treat; RDI = respiratory disturbance index; RESPIRE = REgistry of Sleep APnea monItoring and Atrial Fibrillation in pacemakeR; SBP = systolic blood pressure.
*RDI >20.
†Age and BMI were treated as continuous variables.

CI 1.64–4.89), 2.29 (95% CI 1.41–3.73), and 2.55 (95% CI 1.55–4.18) at 1, 6, 12, and 18 months, respectively.

No significant differences were observed at 12 months with a lower burden of AF than significant AF (Supplemental Table 3 and Supplemental Figure 1). A quarter of patients with severe SA (24.6%) were referred to a sleep specialist during 12-month follow-up; 21.7% were referred for SA screening and 15.3% were treated for SA at 12 months (Supplemental Table 4).

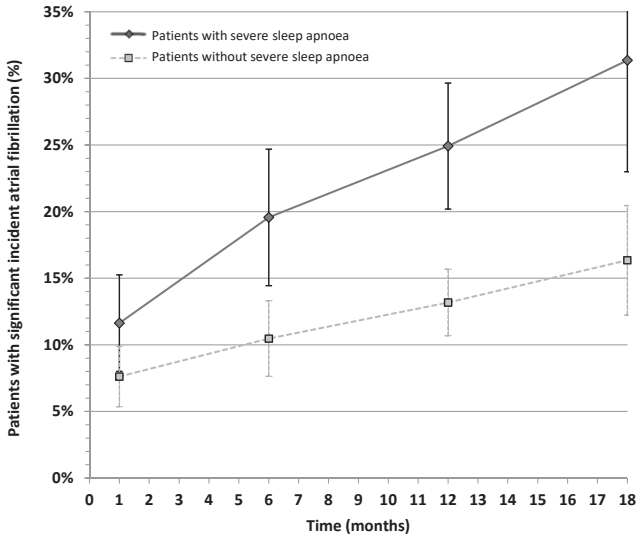

Figure 2 Identification of significant AF (cumulative AF episodes lasting ≥24 hours over 2 consecutive days) over time in patients with or without severe sleep apnea in the modified intention-to-treat population. AF = atrial fibrillation.

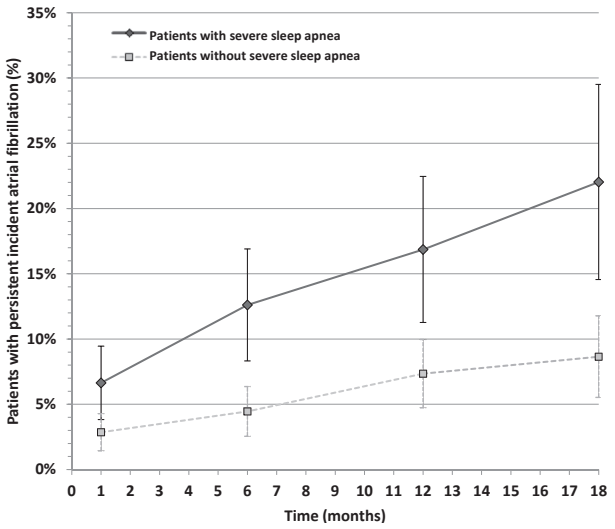

Figure 3 Identification of persistent AF (AF episode lasting >7 days) over time in patients with or without severe sleep apnea in the modified intention-to-treat population. AF = atrial fibrillation.

Discussion

To our knowledge, RESPIRE is the largest study to date that has used the SAM algorithm to investigate the association between SA and AF in a dual-chamber pacemaker population. The main findings are that severe SA is associated with close to double the risk of significant AF and with an increased risk of persistent AF, and the incidence of these atrial arrhythmias increases more rapidly in severe SA patients over time. Symptoms relating to SA should be sought in patients with severe SA identified by an RDI of ≥20, and further diagnostic tests performed when deemed necessary. Whether early intervention in these patients provides protection against AF remains speculative and merits further study.

The large sample size may explain why the RESPIRE study showed a statistically significant association between increased severity of SA and AF, which was not found in the smaller 6-month pilot study by Moubarak et al.[9] The findings of RESPIRE, however, confirm those of a recent study by Mazza et al,[15] which showed that pacemaker patients with device-diagnosed severe SA at baseline have twice the risk of AF compared with pacemaker patients with nonsevere SA (hazard ratio 2.38; 95% CI 1.21–4.66; $P = .025$). Severe SA at baseline and history of AF (paroxysmal) were also found to be independent predictors of AF. The association between severe SA and AF is not new. In the Sleep Heart Health Study published in 2006,[16] the risk of AF was 5-fold higher in patients with severe SA than in those without severe SA. Among the suggested pathophysiological mechanisms, we should consider the persistent increase in sympathetic tone due to chemoreceptor activation and arousals, which can generate abnormal electrical remodeling of the atrium, facilitating AF.[17] The increased risk of AF with

severe SA may have contributed to a 2.7% intergroup difference (5.1% severe SA vs 2.4% nonsevere SA) in death at 18 months (Table 2), even though there was no overall intergroup difference in major serious adverse events. Recent meta-analyses have shown that severe obstructive SA is associated with an approximate doubling of the risk of all-cause mortality.[18,19]

The RESPIRE patient population had a high incidence of severe SA (31.1%), which may have been related to the risk profile of the pacemaker patients included in the trial. In subjects 65 years and older, it has been shown that the prevalence of SAS is >20%,[20] and the mean age of the RESPIRE population was high (75 years). Moreover, the way the SAM feature identifies SA differs from the clinical definition used with polysomnography in that it does not take into account variations in blood oxygen or microarousals during sleep. This makes comparisons with polysomnography-derived prevalence rates imprecise.

The need to screen for sleep disorders in patients with AF has already been pointed out,[21] and a plea for wider screening of SA in the cardiology outpatient setting has been made.[22] However, screening for cardiovascular risk factors and for AF in a population with SA has received less attention. One reason may be the cost and limited availability of polysomnography. Given the high rates of SA in pacemaker patients[5,21] and the association between SA and AF (up to 25% of the RESPIRE population with severe SA had clinically relevant AF), using pacemaker algorithms to identify both SA and arrhythmia seems an appealing initial screening option.

The rate of identified AF increases over time in patients monitored for AF after a cryptogenic stroke.[23,24] It still remains unclear whether there is a plateau, but in the CRYSTAL-AF (**CRY**ptogenic **ST**roke **A**nd under**L**ying **A**trial **F**ibrillation) study, rates of identified AF were still increasing at 12 months.[23] The study cohorts differ consistently, but there was likewise no plateau of AF rates in RESPIRE, which indicates that similar underlying factors may play a primary role in both populations.

In RESPIRE, less than a quarter of patients identified with severe SA was referred to a sleep specialist by the 12-month follow-up and only 15% were treated (Supplemental Table 4). Given the increased risk of AF in these patients, these numbers are disconcertingly low. Although the benefits of treating SA remain a subject of discussion,[25,26] patients at risk of arrhythmias need to be identified and receive attention from specialists. It was also interesting to note that 9% of patients without severe SA were treated for SA at 12 months, which may be related to differences in the way that SAS was diagnosed. Diagnosis with SAM is based on mean RDI for all nights, while other methods only take 1 night into account.

As RESPIRE was not an outcome trial, clinical consequences were not assessed and causal connections between SA severity and AF cannot be demonstrated on the basis of the data. Furthermore, there was no adjustment for confounders and polysomnography was not used in our study to confirm the presence and severity of SA disorders. Polysomnography remains the criterion standard for SA diagnosis, and more confirmatory studies are necessary to establish the role of SA monitoring by implantable devices. Nevertheless, as shown by the results in the DREAM study,[11] SAM can be a good screening tool as a first approach to diagnosing severe SA in unselected patients fitted with pacemakers. Moreover, it is worth emphasizing that device-based monitoring allows regular nightly screening of SA and may thus better reflect the real prevalence of severe SA. The analysis did not distinguish between obstructive and central SA, which may have different impacts on the risk of arrhythmias and cardiovascular events.

Conclusion

RESPIRE found an approximate doubling of the rate of clinically significant AF in pacemaker patients with severe SA compared with patients without severe SA. These results indicate that pacemakers with SA detection algorithms may have a useful role as a screening tool in pacemaker patients at risk of arrhythmia-associated events. The clinical benefit of such screening would need to be demonstrated in a specifically designed outcome trial.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.09.001.

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