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Sinus Node Dysfunction Is Associated With Higher Symptom Burden and Increased Comorbid Illness: Results From the ORBIT-AF Registry

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ABSTRACT

Background: Patients with sinus node dysfunction (SND) have increased risk of atrial tachyarrhythmias, including atrial fibrillation (AF). To date, treatment patterns and outcomes of patients with SND and AF have not been well described.

Hypothesis: Patients with SND and AF have higher risk of adverse cardiovascular outcomes.

Methods: Sinus node dysfunction was defined clinically, based on treating physician. Treatment patterns were described and logistic regression analysis performed to assess outcomes.

Results: Overall, 1710 (17.7%) out of 9631 patients had SND at enrollment. Patients with SND and AF had increased comorbid medical illnesses, more severe symptoms (European Heart Rhythm Association class IV: 17.5% vs 13.9%; $P = 0.0007$), and poorer quality of life (median 12-month Atrial Fibrillation Effect on Quality of Life score: 79.6 vs 85.2; $P = 0.0008$). There were no differences in AF management strategy between patients with SND and those without (rate control, 69.7% vs 67.7%; rhythm control, 30.0% vs 32.0%; $P = 0.11$). After adjustment, patients with SND were more likely than those without SND to progress from paroxysmal AF at baseline to persistent or permanent AF at any follow-up, or persistent AF at baseline to permanent AF at any follow-up (odds ratio: 1.23, 95% confidence interval: 1.01-1.49, $P = 0.035$). However, there was no association between SND and major risk-adjusted outcomes.

Conclusions: Sinus node dysfunction is present in 1 of 6 patients with AF and is associated with increased comorbidities and higher symptom burden. However, SND is not associated with an increase in major risk-adjusted outcomes.

Introduction

Symptomatic sinoatrial node disease represents a constellation of signs and symptoms that signify the heart's inability to perform its pacemaker function. Manifestations of disease include sinus bradycardia, sinus pauses or arrest, chronotropic incompetence, and alternating atrial bradyarrhythmias and tachyarrhythmias, referred to as the bradycardia-tachycardia syndrome.[1] Sinus node dysfunction (SND) may become manifest due to age, genetics, disease, and/or medications.

In the elderly and in patients with many types of comorbidities, most often degenerative change and/or fibrosis of the atrial myocardium and conduction system are responsible for the clinical manifestations of both atrial fibrillation (AF) and SND. In addition, AF itself can cause detrimental remodeling throughout the right atrium, including the sinus node and its vascular supply,[2−4] leading to slowed conduction, sinoatrial exit block, low-voltage amplitude signals, and myocardial scarring.[5,6] Treatment of SND in patients with AF can include permanent pacing to prevent the consequences of postconversion pauses after AF, treatment of chronotropic incompetence, prevention of the clinical sequelae of antiarrhythmic drug−induced aggravation of conduction system disease, and additional rate control in those patients with episodes of AF with rapid ventricular response.

To date, the treatment patterns and outcomes from a contemporary group of patients with AF and SND have not been well characterized. Accordingly, we used the Outcomes Registry for Better Informed Treatment−Atrial Fibrillation (ORBIT-AF) to describe the prevalence, clinical characteristics, treatment, and outcomes associated with SND. We hypothesized that patients with SND and AF would have more symptomatic AF, with higher risk of adverse cardiovascular outcomes.

Methods

Study Population

The ORBIT-AF registry is a prospective, multicenter registry of patients with AF from across the United States managed by a variety of providers including internists, general cardiologists, and electrophysiologists. The rationale and design of the ORBIT-AF registry have been previously described.[7] Briefly, eligible patients included those age ≥18 years with electrocardiographically documented AF who were able to provide written informed consent and to comply with regularly scheduled follow-up visits. As ORBIT-AF was an observational registry, all treatment decisions were left to the discretion of the individual treating physicians in accordance with practice guidelines, recommendations, and local standards of care, as was the determination as to whether SND was present.

Data Collection and Study Endpoints

The ORBIT-AF case-report form queried each treating physician to indicate whether patients carried a clinical diagnosis of SND as determined by the treating physician. For the purpose of this analysis, patients were stratified by the presence or absence of SND and the presence or absence of a permanent pacing device, including only pacemakers and not cardiac resynchronization therapy. The purpose of stratifying patients based on the presence or absence of a permanent pacing device was to evaluate the effects of pacing on AF progression. The primary outcomes included first progression of AF, defined as having paroxysmal AF at baseline visit to persistent or permanent AF at any follow-up, or persistent AF at baseline visit to permanent AF at any follow-up; all-cause death; cardiovascular death; first rehospitalization (all cause); first major bleeding; first stroke/transient ischemic attack; first new-onset heart failure (HF); European Heart Rhythm Association (EHRA) score; and Atrial Fibrillation Effect on Quality of Life (AFEQT) score.[8] Primary outcomes were not adjudicated by a clinical events committee but reported by site investigators. All outcomes, except EHRA score, were defined from the baseline visit to the last follow-up (median, 24 months; 25th and 75th percentiles, 18 and 24 months). The EHRA score was defined at 1-year follow-up.

Statistical Analysis

Baseline characteristics were compared between the 2 groups, including demographics, medical history, CHA_2DS_2-VASc risk scores, echocardiographic assessment, procedures, and medical therapies. The data are presented as medians (interquartile range) for continuous variables and as proportions for categorical variables. For univariate analysis, the differences across 2 groups were assessed using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables. Treatment patterns at baseline for patients with and without SND are presented as proportions. Outcomes assessments by 2 groups (SND vs no SND) are presented as unadjusted and adjusted risk estimates (hazard ratio) of SND vs no SND and corresponding 95% confidence interval (CI) from a Cox frailty model. This approach allows for the inclusion of a random effect for site within a proportional hazards model, accounting for potential heterogeneities between sites. For AF progression, which was captured only at visit intervals, unadjusted and adjusted odds ratios (OR) of SND vs no SND were calculated using regression discrete time, proportional odds model. Each outcome model is adjusted for a previously identified set of significant covariates, identified from a large candidate list by backward selection, with an α for exclusion of 0.05. To assess the possibility of confounding by pacemaker status, 1 additional covariate (pacemaker) was included in each model. Missing covariate data in the regression analysis (<14%) were handled by multiple imputation using Markov chain Monte Carlo and regression methods. Final estimates and associated SEs reflect the combined analysis over 5 imputed data sets.

The ORBIT-AF study was approved by the Duke Institutional Review Board, and all participating sites obtained institutional review board approval pursuant to local requirements. All subjects provided written informed consent. All statistical analyses were performed at the Duke Clinical Research Institute using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

Between June 29, 2010, and August 09, 2011, 10 132 AF patients were enrolled in the ORBIT-AF registry. The current analysis excluded 501 patients due to incomplete follow-up. This yielded a final study population of 9631 patients with ≥1 follow-up from 174 sites. Baseline characteristics of the study cohort are shown in tables 1 and 2 according to the presence or absence of SND. Among 9631 AF patients, 1710 (17.7%) had the impression of SND as documented by the treating physician, whereas 7921 (82.2%) had no impression of SND. Patients with SND were more likely to have hypertension, coronary artery disease, valvular heart disease, heart failure (HF) thyroid disease, prior cerebrovascular events, prior interventional therapy for AF, and lower left ventricular ejection fraction. They also had higher CHA_2DS_2-VASc risk scores and higher use of oral anticoagulants (OAC), but lower AFEQT scores at 12 months. Patients without SND were less likely to have implanted devices, were of younger age, and more likely to have sinus rhythm on most recent 12-lead ECG.

Pharmacotherapy

Unadjusted rates for both OAC and pharmacologic therapy for AF differed between groups. Current warfarin use was higher in those patients with SND and a CHA_2DS_2-VASc risk scores ≥2 compared with patients without SND and comparable CHA_2DS_2-VASc risk scores (76.2% vs 73.0%; $P = 0.0079$). In addition, OAC use (warfarin or dabigatran) was higher in patients with SND (79.2% vs 75.9%; $P = 0.0035$). Between 6% and 10% of patients with SND and AF were not treated with OACs in the absence of a perceived contraindication. Rate control therapy with β-blockers was similar for those patients with SND vs those without (64.4% vs 64.4%; $P = 0.92$), whereas calcium channel blocker use was higher in patients without SND (31.0% vs 27.3%; $P = 0.0025$). Current membrane-active antiarrhythmic drug use at baseline was not significantly different in those patients with SND vs those without SND (29.3% vs 28.7%; $P = 0.62$), whereas previous use of antiarrhythmic drugs was higher in patients with SND (55.7% vs 47.5%; $P < 0.0001$). In addition, current membrane-active antiarrhythmic drug use at baseline was not significantly different in those patients with SND without a pacemaker vs patients with SND and pacemaker (29.1% vs 29.4%; $P = 0.89$). There were no differences in the current AF management strategy between patients with SND vs those without (rate control, 69.7% vs 67.7%; rhythm control, 30.0% vs 32.0%; $P = 0.11$).

Major Risk-Adjusted Outcomes

Unadjusted rates for outcomes are shown in (Figure 1). Patients with SND had higher rates of AF progression (19.0% vs 15.6%, $P = 0.0012$; unadjusted OR: 1.18, 95% CI: 1.04-1.35) and all-cause mortality (6.7% vs 5.1%, $P = 0.0011$; unadjusted OR: 1.28, 95% CI: 1.08-1.51) than did patients without SND. For all other outcomes, except for first stroke, patients with SND had higher risk of each event than those without SND before adjustment (Figure 1). After adjustment for differences in baseline variables, SND was associated with a higher risk of AF progression (adjusted OR: 1.23, 95% CI: 1.01-1.49), but there was no association between SND and any of the other outcomes assessed (Figure 2) (See supporting information, Table 1, in the online version of this article).

To assess for the possibility of confounding, 1 additional covariate (pacemaker) was added in each final model. After adjustment, we found that the association between SND and AF progression was no longer significant after adjusting for pacemaker implantation (adjusted OR: 1.11, 95% CI: 0.86-1.43; Table 3). In addition, after adjusting for pacemaker implantation, there was no statistically significant difference between patients with SND and those without SND for all other outcomes.

In comparing outcomes of patients with SND between 2 treatment groups (pacemaker vs no pacemaker), both unadjusted and adjusted rates of each outcome failed to show a statistically significant difference (Figure 3).

Discussion

This study examined the differences in patient characteristics, treatment patterns, and outcomes among a large sample of patients with clinically determined SND. Our analysis yielded several important findings: (1) SND is common among patients with AF; (2) SND is accompanied by increased comorbid illnesses, including risk factors for AF progression such as hypertension, coronary artery disease, HF, valvular heart disease, and older age; (3) SND is associated with higher symptom burden; (4) AF progression is associated with SND; and (5) SND is not associated with worse CV outcomes.

The ORBIT-AF registry represents the largest contemporary registry of patients with SND. The findings that patients with SND have higher rates of comorbid medical illness as well as more symptoms related to AF suggest that this population is older, with higher comorbidities (tables 1 and 2). We also observed an increase in mortality of 28% for patients with SND and AF (vs no SND; hazard ratio: 1.28, 95% CI: 1.08-1.51, $P = 0.0011$). Although these data are unadjusted for confounding and demonstrate no difference after adjustment, it suggests that this subgroup constitutes a population, as expected, that is less healthy, with an increased number of comorbid illnesses and increased risk of mortality.

The classification of patients with AF into SND and non-SND groups is important because of the limitations on the type of medical therapies that can be used in patients with SND without a pacemaker and the likelihood of future pacemaker requirements. Management of symptoms with pharmacologic therapy for patients with AF and SND did not differ from that of patients with AF alone (Table 2). These results are unexpected, as we hypothesized a higher use of antiarrhythmic drug (AAD) therapy for rhythm control in those patients with pacemakers implanted for SND. These results are concerning, because the current AF guidelines consider pharmacological therapy in patients with AF and advanced sinus-node disease a class III recommendation, unless a functioning cardiac pacemaker has been implanted.[9] We present a total cohort of 1710 patients in the ORBIT-AF registry with SND, of which 519 (30%) were not treated with a pacing system (Table 1). The fact that approximately 30% of patients with SND, not treated

Table 1. Baseline Characteristics by the Presence or Absence of SND

	Overall, N = 9631	Without SND, n = 7921	With SND, n = 1710	*P* Value
Age, y	75 (67–82)	74 (66–81)	79 (72–84)	<0.0001
Male sex	57	58	56	0.15
Race				<0.0001
White	89	89	93	
African American	4.9	5.2	3.5	
Hispanic	4.1	4.5	2.2	
Asian	0.6	0.7	0.4	
Other	0.3	0.3	0.2	
Medical history				
HTN	83	83	86	0.0002
Hyperlipidemia	72	71	77	<0.0001
Smoking	49	48	50	0.1
Thyroid disease	23	22	26	<0.0001
OSA	18	18	19	0.7
DM	29	29	30	0.4
CAD	36	34	45	<0.0001
HF	33	31	42	<0.0001
Implanted device	28	16	83	<0.0001
Pacemaker	19	7.6	70	<0.0001
Significant valvular disease	26	24	33	<0.0001
Prior cerebrovascular events	16	15	20	<0.0001
Stroke (all cause)	8.9	8.3	11	0.0001
Nonhemorrhagic	8.0	7.5	10	0.0003
Hemorrhagic	0.8	0.7	1.0	0.2
TIA	8.2	7.7	11	<0.0001
Cognitive impairment/dementia	3.0	2.8	4.0	0.01
Frailty	5.9	5.4	8.6	<0.0001
GI bleeding	9.2	8.9	11	0.03
BMI, kg/m²	29 (25–34)	29 (26–34)	28 (25–33)	<0.0001
HR, bpm	70 (63–80)	70 (62–80)	70 (64–78)	0.3
SBP, mm Hg	126 (116–138)	126 (116–138)	126 (116–136)	0.7
DBP, mm Hg	72 (66–80)	72 (66–80)	70 (64–80)	<0.0001
CrCl[a], mL/min/1.73 m²	69 (50–96)	72 (51–99)	60 (44–81)	<0.0001
LA diameter, cm	4.4 (3.9–5)	4.4 (3.9–5)	4.4 (4–5)	0.9
LVEF, %	55 (50–61)	57 (50–62)	55 (48–60)	<0.0001

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CrCl, creatinine clearance; DBP, diastolic blood pressure; DM, diabetes mellitus; GI, gastrointestinal; HF, heart failure; HR, heart rate; HTN, hypertension; IQR, interquartile range; LA, left atrium; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; SBP, systolic blood pressure; SND, sinus node dysfunction; TIA, transient ischemic attack.
Values are presented as % or median (IQR).
[a]Calculated by Cockcroft-Gault formula.

Table 2. AF History by Presence or Absence of SND

	Overall, N = 9631	Without SND, n = 7921	With SND, n = 1710	*P* Value
AF type				<0.0001
First detected/new onset	4.5	5.2	1.1	
Paroxysmal	51	50	56	
Persistent	17	17	14	
Permanent	28	28	29	
Duration of AF diagnosis, mo	48 (18–94)	44 (16–91)	60 (30–109)	<0.0001
Sinus rhythm on most recent ECG	34	36	25	<0.0001
EHRA symptom level				
No symptoms	38	39	36	0.0007
Mild	45	45	45	
Severe	15	14	17	
Disabling	1.8	1.8	1.5	
$CHADS_2$ risk groups				<0.001
0	6.3	7.1	2.6	
1	22	23	15	
≥2	72	70	82	
CHA_2DS_2-VASc score	4 (3–5)	4 (3–5)	5 (3–6)	<0.0001
ATRIA score >4	17.3	16.2	22.2	<0.0001
Current warfarin use	72	71	76	<0.0001
Dabigatran[a]	4.9	5.2	3.4	0.002
ASA	44	44	45	0.8
Current AAD	29	29	29	0.6
Prior treatment with AAD	54	56	47	<0.0001
Prior cardioversions	30	31	29	0.1
Current AF management strategy				0.1
Rate control	68	68	70	
Rhythm control	32	32	30	
AF symptoms				
Syncope/fainting	4.4	4.1	6.1	0.0003
Lightheadedness/dizziness	20	20	23	0.0007
Prior interventional therapy for AF	11	10	16	<0.0001
Catheter ablation of AF	5.6	5.5	6.0	0.5
Atrial flutter ablation	2.7	2.4	3.8	0.001
AV node/His bundle ablation	2.3	1.7	4.6	<0.0001
Surgical/maze/hybrid maze procedure	2.0	1.8	2.9	0.003
AFEQT score at 12 mo	84 (70–94)	85 (72–94)	80 (67–93)	0.0008

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality of Life; ASA, aspirin; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; AV, AV node; $CHADS_2$, congestive heart failure, HTN, age ≥75 y, DM, prior stroke/TIA/TE; CHA_2DS_2-VASc, congestive heart failure, HTN, age ≥75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (women); DM, diabetes mellitus; ECG, electrocardiogram; EHRA, European Heart Rhythm Association; HTN, hypertension; IQR, interquartile range; OAC, oral anticoagulant; ORBIT-AF, Outcomes Registry for Better Informed Treatment–Atrial Fibrillation; SND, sinus node dysfunction; TE, thromboembolism; TIA, transient ischemic attack.
Values are presented as % or median (IQR).
[a] ORBIT-AF registry participation began prior to dabigatran approval, which reflects the small number of patients treated with dabigatran and no patients treated with other non–vitamin K antagonist oral antagonist such as rivaroxaban or apixaban.
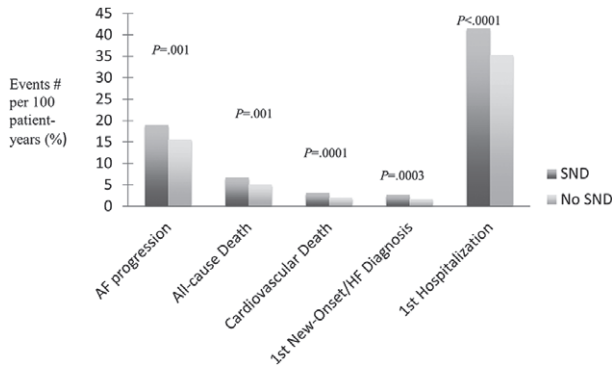
Figure 1. Unadjusted outcomes for patients with SND vs no SND. Abbreviations: AF, atrial fibrillation; HF, heart failure; SND, sinus node dysfunction.

Table 3. HR of SND (vs no SND) and Pacemaker (vs no Pacemaker) and 95% CI by Adjusting for Pacemaker Status in Final Adjusted Models

Outcome		Adjusted OR (95% CI)[a]	P Value
AF progression[b]	SND	1.11 (0.86-1.43)	0.4250
	Pacemaker	1.19 (0.97-1.45)	0.0916
AF progression[c]	SND	1.08 (0.87-1.33)	0.4934
	Pacemaker	1.08 (0.90-1.29)	0.3944

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; OR, odds ratio; SND, sinus node dysfunction.
[a]For AF progression, we presented OR and corresponding robust 95% CI. [b]Final risk factors including ECG-AF (atrial flutter/atrial fibrillation) were adjusted for. [c]Final risk factors excluding ECG-AF were adjusted for.
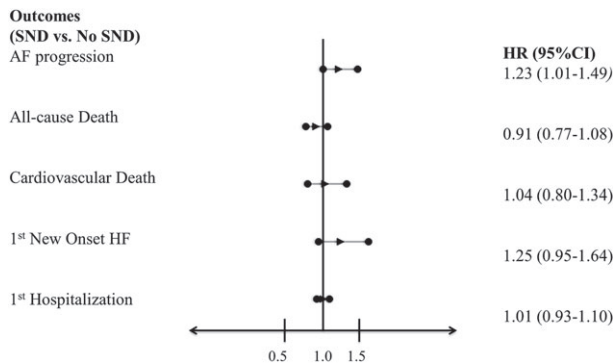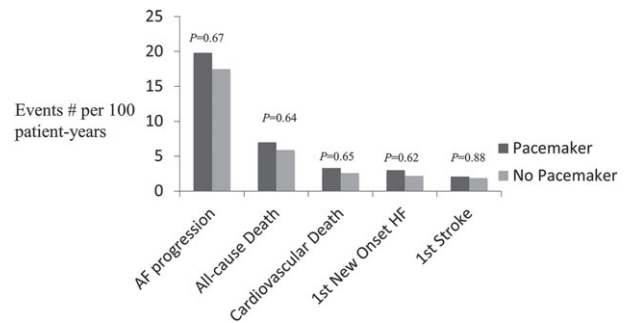

Figure 2. Adjusted outcomes for patients with SND vs no SND. Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio; SND, sinus node dysfunction.

Figure 3. Unadjusted outcomes for patients with SND (pacemaker vs no pacemaker). Abbreviations: SND, sinus node dysfunction.

with a pacing system, were treated with AAD, highlights several points: (1) there is a continuum of severity and symptom presentation for patients with SND; (2) improved implementation of evidence-based guidelines is needed for those patients with severe symptoms attributable to SND, treated with pharmacological drug therapy without a pacemaker, a class III indication; and (3) the definition of SND in the ORBIT-AF registry may be overly inclusive, selecting for patients with objective signs of SND but with minimal to no symptoms of disease.

Prior to multivariable adjustment, SND was associated with AF progression (Figure 1). After adjustment for the presence of a pacemaker, the association between patients with SND and AF progression was no longer significant (Table 3). There are several possibilities from these findings: (1) patients with SND may experience progression of AF due to increased comorbid medical illnesses; and (2) the addition of a pacemaker helped define a population of patients with SND and severe disease who would be expected to have increased risk factors for AF, including degenerative disease and fibrosis of the atrial myocardium, and subsequently, adjusting for the presence of a pacemaker negated its overall impact. Our results regarding the effect on pacing on SND, and in particular on AF progression, should be interpreted cautiously. Physiologic DDD pacing, in conjunction with

treatment with atrioventricular nodal blocking agents and membrane-active AAD, may have prevented AF progression. Conversely, VVI pacing, which can lead to the progression to more persistent forms of AF and increase the risk of HF,[10,11] may have provoked AF progression; and hence, after adjustment for pacemaker, the detrimental effects of SND on AF progression were negated. The findings of no difference in the rate of AF progression between patients with SND and a pacemaker vs patients with SND without a pacing system (Figure 3), in conjunction with no difference in the use of membrane-active AAD between the 2 groups, suggest that the electrical and mechanical alterations caused by pacing may not be the primary determinant in AF progression. Undoubtedly, AF progression in patients with SND is a complex process that is multifactorial in its etiology, stemming from the interplay between drug therapy, pacing, and comorbid medical illness.

Study Limitations

Several limitations need to be acknowledged in the interpretation of these data. The data presented are derived from a voluntary, observational cohort, and thus are susceptible to residual unmeasured confounding that may impact the validity of our results. Reporting and sampling bias may have affected the designation of SND. The lack of a definition that encompassed the nuances of severity or types of SND may have led to an overinclusive selection of patients with few symptoms related to SND, as evidenced

by the high percentage of patients with SND (17%) in this registry. We were unable to conclude whether a specific type of rate- or rhythm-control agent affected AF progression. Adjusting for pacemaker in a multivariate fashion may have attenuated the results with respect to the findings that there was no evidence of an association between SND and AF progression. In addition, AF progression could not be assessed based on different manifestations of SND. The inability to characterize the mode of pacing limits the ability to interpret whether pacing mode affects AF progression.

Conclusion

In the ORBIT-AF registry, patients with SND were common and more likely to have increased medical comorbidities and higher symptom burden. Our study did not find any difference in major risk-adjusted outcomes between patients with SND and AF compared with patients with AF alone.

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