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Prevalence and predictors of atrial arrhythmias in patients with sinus node dysfunction and atrial pacing

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Abstract

Purpose—This study aimed to determine the incidence, prevalence, and predictors of atrial arrhythmias (AAs) in patients with symptomatic sinus node dysfunction (SND) who required permanent pacemaker implantation. Also, we evaluated the impact of atrial pacing (AP) on AAs.

Methods—All consecutive patients who underwent pacemaker implantation from 2005 to 2011 were included. Atrial fibrillation (AF), atrial flutter (AFL), atrial tachycardia (AT), and AV nodal reentrant tachycardia (AVNRT) were detected via pacemaker interrogation and clinical documentation.

Results—The study group included 322 patients (44% male) with mean age 68.8 ± 15 years and followed for an average of 5.6 ± 2.2 years (median 5.7 years). Overall, 61.8% were found to have any AA at follow-up. Individual prevalence of AAs was high as follows: AF 43.5%, AFL 6.5%, AT 25%, and AVNRT 6.8%. AF was documented in 23% of patients ($n = 74$) prior to pacemaker; among those, 15% ($n = 11$) had no recurrence of AF with average AP of 74%. The incidence of new-onset AF after pacemaker was 15.8%. In subgroup analysis, prevalence of AF was increased by 16% with high rate of AP (81–100%) and 17% with lower rate of AP (0–20%). Incidence of new-onset AF was not affected by AP. Diabetes, hypertension, and left atrial enlargement were predictors of AAs. White men and women had higher prevalence of AF.

Conclusions—AAs are highly prevalent in SND, particularly in white patients. Paroxysmal AF is suppressed with AP in minority, but there is no impact of AP on new-onset AF. Patients with diabetes, hypertension, and dilated atria must be monitored closely for early detection of AAs.

Keywords

Pacemaker; Atrial arrhythmias; Atrial fibrillation; Sinus node dysfunction

1 Introduction

Sinus node dysfunction (SND) describes a broad range of clinical entities including inappropriate sinus bradycardia, sinus pause, sinus arrest, sinoatrial exit block, and

tachycardia-bradycardia syndrome. The prevalence of SND is estimated to be about 1 per 1000 persons in patients above the age of 45, with incidence increasing with age [1]. SND often coincides with atrial arrhythmias (AAs), particularly atrial fibrillation (AF) [2, 3]. However, in patients with SND, the overall prevalence of AAs, predictors of this association and the impact of race and gender on the co-existence are not well characterized. Also, the relation between permanent pacing and the risk of AAs in patients with SND is not fully understood.

Symptomatic patients with SND typically require dual-chamber permanent pacemaker placement. Atrial and dual-chamber pacing have separately been shown to reduce the incidence of AF compared with single-chamber right ventricular pacing, without consistent impact on cardiovascular mortality and stroke [4–6]. Yet, there is lack of information about the impact of percent of atrial pacing (AP) on both pre-existing AF and incidence of other AAs.

In this study, we hypothesized that SND and AP may have significant impact on incidence and prevalence of AAs through atrial electroanatomical remodeling. Both SND and AAs may reflect underlying atrial disease processes, and therefore, it is important to determine the predictors of this association. Thus, we studied symptomatic patients with SND who required dual-chamber permanent pacemaker implantation for the treatment of SND. Incidence and prevalence of AAs as well as the predictors of AAs in this study group were evaluated with respect to race, gender, and comorbidities.

2 Methods

Study design

All patients who underwent dual-chamber pacemaker implantation for SND from February 2005 to December 2011 at the University of Chicago Medical Center were included in this study. The study was approved by the Institutional Review Board. Patients were identified retrospectively and followed prospectively. Patients with single-chamber pacemaker or persistent and permanent AF were not included in this study. The patients with cardiac resynchronization therapy or upgrade during the follow-up period were also excluded. Also, the six patients who were lost to follow-up beyond the first 30 days of implant were excluded from the analysis of the study population.

Data collection

Data were collected from a centralized electronic medical record that contained records of patients treated and followed at the University of Chicago Medical Center during the range of study dates. These records contained detailed histories and diagnoses for all inpatient and outpatient encounters including emergency room visits, diagnostic tests, and clinical follow-up. Medical records were reviewed for baseline characteristics including demographic information, medical history, electrocardiogram (ECG), pacemaker interrogation, remote pacemaker monitoring, Holter recording, and echocardiogram. Baseline history of arrhythmia was taken from medical record as obtained by the patient's treating cardiologist. When available, this information was confirmed with prior ECGs, rhythm strips, and

intracardiac electrograms. Total pacing requirements were determined based on the last follow-up device interrogation.

Follow-up

The follow-up period for patients began at pacemaker implantation and ended November 2016. Patients had clinic visits within 1 month of the procedure, and at regular 3 to 6 months intervals in first year followed by 6 to 12 months thereafter. Pacemaker interrogation was performed in patients during those follow-up visits. Dual-chamber pacemakers were programmed as DDDR. Patients with pacemakers from various companies were included in the study. Total lifetime pacing requirements were determined based on the last follow-up device interrogation. Incidence and prevalence of AF, atrial flutter (AFL), atrial tachycardia (AT), atrioventricular reciprocating (AVRT), and AV nodal reentrant tachycardia (AVNRT) were documented after pacemaker implantation based on device interrogation. All intracardiac electrograms of recorded supraventricular tachycardia episodes lasting 30 s were individually reviewed and adjudicated to confirm the diagnosis. Definition of AF and AAs were based on current guideline [7, 8]. Further information from ECG, medical record, and clinical electrophysiological study were used when obtainable.

Statistical analysis

Between the groups that developed new-onset AF and remained AF-free, categorical variables were compared using the chi-squared test while continuous variables compared with Student's *t* test. Univariate associations were assessed by means of chi-squared test for categorical variables and logistic regression model for continuous variables. Multivariate associations were determined with logistic regression model. Analyses were run individually for each arrhythmia and for combined AF, AFL, and AT. The following variables were considered as potential prognostic factors for both univariate and multivariate analyses: age, gender, race, comorbid conditions (hypertension, diabetes, thyroid disease, obstructive sleep apnea, chronic obstructive pulmonary disease, chronic kidney disease (CKD), and coronary artery disease), left ventricular ejection fraction, left atrial (LA) size, and AP frequency. For analysis of impact of AP, patients were separated by frequency of AP. Statistical analyses were performed using R version 3.3.2. In all testing, $p < 0.05$ was used as the level of significance.

3 Results

Baseline characteristics

A total of 322 patients (141 men and 181 women) with average age 68.8 ± 14.8 years were included in this observational study. Mean follow-up after pacemaker implantation was 5.6 ± 2.2 years (median 5.7 years, range 3 months to 11.4 years) in the total sample. Approximately 23% of patients ($n = 74$) had pre-existing AF before pacemaker, 62.7% of patients ($n = 202$) had no known AF, and 14.3% ($n = 46$) had no data on prior AF occurrence. The ethnicity of the study population was as follows: 120 White (37.2%), 177 Black (55.0%), six Hispanic (1.9%), six Asian (1.9%), and 13 mixed/other (4.0%). A total of 11 patients (3.4%) underwent electrophysiological study, and 43 patients (13.35%) underwent catheter ablation for AAs in the study population. The baseline characteristics of

the entire study sample and the patients with and without AF are summarized in Table 1. Comorbidities were common in this study population. Patients with pre-existing paroxysmal AF had higher rates of valvular disease (32.4 vs 16.3%, $p = 0.006$) and valve surgery (16.2 vs 5.5%, $p = 0.015$) than patients without AF. All other comorbidities were comparable between groups. Additionally, baseline LA size was larger in those with AF than those without AF ($p = 0.027$).

Prevalence of AAs after pacemaker implantation

At the end of follow-up period, about 61.8% of all patients ($n = 199$) were found to have any AAs. Approximately 59% of patients ($n = 190$) had any of AF, AFL or AT. The individual prevalence of AAs in the study population was high as follows: AF 43.5%, AFL 6.5%, AT 25.2%, AVNRT 6.8%, and AVRT 1.2% (Fig. 1). Of the 202 patients with no prior history of AF, 32 patients (15.8%) developed new-onset AF resulting in an annual incidence of AF as 2.8%. The rates of AF prior to and after pacemaker are shown in Fig. 2. Pre-implant AF and new-onset AF do not equal post-implant AF because some patients had no data on if they had pre-existing AF. Thus, those patients with AF post-pacemaker but unclear history of AF ($n = 34$) were not included in the new-onset AF group. In those with new AF, the co-existing prevalence of other AAs was as follows: AFL 3%, AT 25.7%, AVNRT 7.4%, and AVRT 1.5%. In patients with documented AF prior to implantation ($n = 74$), 85% of them ($n = 63$) developed recurrences of AF during follow-up, but 15% of those patients ($n = 11$) had no documented AF after pacemaker implantation. Thus, AF was suppressed in 15% of the patients with AP (mean AP 74% in this group).

Predictors of AAs

Univariate and multivariate analysis revealed several significant predictors for AAs after pacemaker. In univariate analysis, AP was associated with AF after implantation (HR 1.01, 95% CI 1.0–1.014, $p = 0.03$), AF/AFL/AT (HR 1.01, 95% CI 1.0–1.016, $p = 0.01$), and all AAs (HR 1.01, 95% CI 1.0–1.015, $p = 0.01$). LA size was associated with AF ($p < 0.001$) and AFL ($p < 0.001$) but not associated with any other arrhythmias. AF after implant was associated with AFL ($p = 0.05$) but not any other AAs.

The multivariate predictors of AF, AFL, and AT after implant are shown in Table 2. The strongest predictor was co-existing diabetes mellitus (OR 2.14, 95% CI 1.03–4.65, $p = 0.05$) followed by LA size (OR 1.73, 95% CI 1.31–2.33, $p < 0.001$). AP was also significantly associated with AF/AFL/AT as previously mentioned. When arrhythmias were evaluated individually, AF was associated with HTN (OR 0.42, CI 0.19–0.89, $p = 0.03$) and LA size (OR 1.61, CI 1.24–2.12, $p < 0.001$). AT was significantly associated with HTN (OR 2.60, CI 1.1–7.0, $p = 0.04$), CKD (OR 0.49, CI 0.24–0.96, $p = 0.04$), and AP (OR 1.01, CI 1.00–1.02, $p = 0.03$). AVNRT was significantly associated with LA size (OR 0.51, CI 0.26–0.89, $p = 0.03$). When all AAs were taken together, predictors were LA size (OR 1.71, CI 1.28–2.33, $p < 0.001$), CKD (OR 0.43, CI 0.21–0.87, $p = 0.02$), and AP (OR 1.01, CI 1.11–1.02, $p = 0.05$). AFL and AVRT did not have any significant associations. New-onset AF was associated with LA size (OR 1.55, 1.03–2.37, $p = 0.04$). There were no other univariate associations with or multivariate predictors of new-onset AF.

Effect of race and gender on AAs

Race had a demonstrable impact on the rates of AAs. Whites had a pre-procedure AF prevalence of 33.3% and after implant AF 52.5%, AFL 6.7%, AT 26.7%, AVNRT 10%, and AVRT 2.5%. Black patients had pre-procedure AF rate as 15.8% and after implant AF 37.9%, AFL 5.7%, AT 26.6%, AVNRT 5.7%, and AVRT 0.6%. Compared to blacks, AF was more prevalent in whites before implant ($p < 0.001$) and after implant ($p = 0.01$). However, new-onset AF was comparable between whites and blacks (16.4 vs 15.3%, $p = 0.51$) and there were no other statistically significant differences in rate of AAs between races. Both HTN (85.3 vs 62.5%, $p < 0.001$) and CKD (60.9 vs 43.1%, $p = 0.004$) were more prevalent in blacks, with no other significant baseline differences between groups.

When stratified by gender and race, black men had less AF initially than white men (12.2 vs 41.8%, $p = 0.002$), and white women had less AF than black women (21.4 vs 37.0%, $p = 0.07$). After pacemaker placement, black men continued to have less AF than white men (35.6 vs 56.5%, $p = 0.03$) and black women less than white women (39 vs 48%, $p = 0.36$). This data is shown in Fig. 3. There was also an interaction between race and AFL ($p = 0.02$) as Asians had a significantly higher rate of AFL compared to other races, such as whites ($p = 0.04$).

Effect of AP on AA

The distribution of patients by frequency of AP is shown in Fig. 4 and are as follows: 0–20 (31.1%), 21–40 (14.6%), 41–60 (13.4%), 61–80 (11.5%), and 81–100 (29.5%). The mean rate of pacing was 49%, and median rate was 46%. In the group of patients paced at a frequency of 0–20%, the initial prevalence of AF was 20% and post-device prevalence of AF was 36%, leading to an increased prevalence of 16%. The patients paced at 81–100% had a pre-device prevalence of 31.6% and post-device prevalence of 48.4%, resulting in a difference in prevalence rate of 16.8%. The overall prevalence of AF, AFL, AT in the 0–20%-pacing group was 50%, in the 21–40%-pacing group was 55.3%, in the 41–60%-pacing group was 62.8%, in the 61–80%-pacing group was 67.6%, and in the 81–100%-group was 65.3%.

4 Discussion

Our study evaluated the incidence, prevalence, and predictors of AAs in patients with SND who required permanent pacemaker. We found that AAs including AF, AFL, AT, and AVNRT are highly prevalent in patients with SND undergoing AP. The annual incidence of new-onset AF was 2.8% during follow-up. While the majority of the patients with paroxysmal AF developed recurrence of AF episodes after pacemaker, 15% had suppression of AF in this subgroup. Diabetes, HTN, and LA enlargement were significant predictors of AAs, suggesting these traditional risk factors are important with or without pacing [9, 10]. AP frequency was weakly associated with AF post-pacemaker. There was no difference in incidence of new-onset AF between the low and higher pacing groups or between blacks and whites. However, black men had less AF initially than white men and white women had less AF than black women when stratified by gender and race.

Comparison with previous studies

In this study population, AF and other AAs frequently occurred before and after pacemaker implantation. At mean follow-up of 5.6 years, 43.5% of the study population had documented AF. Our results are similar to the work of Healey et al., who examined 445 patients (25.9% of which had pre-existing AF) who had dual-chamber pacemaker placed for multiple indications including SND. They found that at a mean of 4.3-year follow-up, 55.3% of patients had device detected AF [11]. Gillis et al. described in a smaller population of 137 patients with SND and AF prevalence decreasing from 85.4 to 67.9% at 2-year follow-up [2]. However, their study had shorter a follow-up (about 2 years) and an unusually high initial prevalence of AF. Additional studies have shown a prevalence of device-detected AF similar to what was found in our study [12].

There is limited published data regarding the device-detected prevalence of supraventricular arrhythmias in patients with SND. Defaye showed in a population of 617 patients with dual-chamber pacemaker about 46% of patients had device-detected AAs at 6-month follow-up [13]. However, this study did not differentiate among specific AAs. Here, we report the prevalence of individual AAs in long-term follow-up. We show that AT and less-so AFL and AVNRT are frequent in SND treated with pacemaker. Additionally, the distribution of AAs was comparable between subgroup of patients with new-onset AF and the overall cohort, suggesting these patients were at similar risk for development of other arrhythmias. Further evidence of this is new-onset AF was not significantly associated with any other arrhythmias. We also showed that AF post-pacemaker was associated with AFL, a link which has been well described [14, 15].

Risk factors for AA development

We found multiple risk factors in development of AAs in our study population. Diabetes was strongly associated with development of AF, AFL, and AT, supporting the need for effective glycemic control in these patients. While HTN was associated with lower odds of AF, it also had significant association with higher AFL. LA size was the strongest predictor of developing AF/AFL/AT, which is consistent with prior studies. While the association between LA dimension and AF is best documented in the general population [16], Healey et al.'s early study was important in demonstrating association between LA enlargement and pacemaker-detected AF [11]. Said et al. also showed LA size as an OR 1.18 (1.07–1.29, $p = 0.001$) for new-onset AF risk in a mixed population that received pacemaker for either SND or high grade AV block [6]. Thus, treating HTN and DM are important objectives with the goal of decreasing arrhythmia-burden post-pacemaker.

Race and prevalence of AA

There were racial differences in prevalence of AAs in our cohort. White patients had higher prevalence of AF before and after pacemaker than black patients, while whites and blacks had a similar incidence of new AF. Race overall did not have a significant effect on rates of new AF, prevalence of AFL, AT, AVRNT, AVRT, or predictors of AAs. It has been reported in large-scale retrospective studies using claims data that black patients, even with more traditional risk factors, have less clinically detected AF than white patients [17, 18]. Kamel et al. studied patients after pacemaker placement and found that at mean 3.7-year follow-up,

black patients had lower rates of clinically detected AF than white patients (21.4 vs 25.5%, $p < 0.001$) [17]. Kamel et al. also found AFL rates comparable between black and white patients. Our study had a longer duration of follow-up, and we used the more sensitive modality of pacemaker-detected AF instead. The results of this study suggest that while whites are not at increased risk of newly developing AF post-pacemaker implantation, they still have a higher AF burden which requires closer monitoring.

AP and prevalence of AA

The distribution of AP frequency shows that most patients are paced at either very high or very low rates. Patients in the low-pacing group of 0–20% and those in the higher pacing group of 80–100% had similar increases in prevalence of AF. Also, while AP was statistically significant as a univariate predictor of AF prevalence post-implant, it was not associated with new-onset AF. This suggests that while AP pacing had a modest association with AAs including AF, a higher rate of pacing may have reflected greater underlying atrial disease, rather than being directly pro-arrhythmogenic. Previous studies have shown conflicting results, with some suggesting AP does not increase risk of new AF in a SND population when corrected for cofounders [19], while others show a rate-dependent increase in new AF with higher atrial and ventricular pacing [20]. In our study, AF was suppressed in a small subset of patients with average AP 74%. Prior research has shown that while the pathophysiology of AF is diverse, SND and AF share important underlying principles, such as anatomic and electrical remodeling at the cellular level. Atrial stretch and fibrosis damage both the sinus node and underlying substrates necessary for AF to form [3, 21]. In a subgroup of patients, cumulative frequent AP in the setting of SND may actually help limit or potentially reverse this electro-anatomic remodeling.

Clinical implications and potential treatments

Recently published work further highlights the clinical importance of the association between AF and SND. Inohara et al. attempted to risk-stratify a general population of patients with AF based on composite endpoint of major adverse cardiovascular or neurological events and major bleeding events [18]. Through cluster analysis, they isolated a unique phenotype of AF, specifically AF associated with tachy-brady syndrome and implanted devices, that had distinct associations and elevated risk of adverse clinical outcomes [22]. The results of our study can be thought of as applying to a similar subgroup of patients. While AP suppressed AF in some patients with prior AF, a significant number of patients developed new AF, which supports the need for further investigation of the mechanisms and prevention of AF in this population. For example, AF ablation prior to pacemaker has been studied as a therapy for patients with concomitant AF and SND with promising results—increased resting heart rates, decreased frequency of sinus pauses, and often fewer episodes of symptomatic bradycardia [23–25]. This suggests possible reversibility of SND with appropriate early treatment before pacemaker. However, it is not clear whether it is the restoration of normal sinus rhythm or the cessation of antiarrhythmic or rate-controlling drugs that provides benefit. The population that would most benefit from ablation has not yet been fully characterized [26].

Study limitations

There are several limitations in our study. The retrospective study design introduces limitations as selection of patients is not random, and causation can be difficult to determine. Patients were enrolled consecutively which is intended to limit selection bias. Some patients did not have prior history of AF documented, and silent AF prior to implant may have been undetected until continuous monitoring was available. There was a small number of patients with AVNRT and AVRT, limiting conclusions that can be drawn from these subgroups. Black patients made up a much larger share of our patient cohort than in the general population, and as previously discussed, there is known to be a significant disparity of arrhythmia prevalence by ethnicity. To minimize this, comparison and analysis were made between white and black patients. The use of beta blockers, calcium channel blockers, and antiarrhythmics was also not followed in the population. Lastly, we studied cumulative lifetime percent of pacing in our patients without cataloging the yearly percentage.

5 Conclusions

In conclusion, AAs, particularly AF and AT, are highly prevalent in patients with SND undergoing AP and remain a greater burden for white patients. High AP shows no significant impact on the incidence of new AF and actually suppresses paroxysmal AF in a subgroup of patients. Patients with diabetes, hypertension, and dilated atria have higher risk of developing AAs in association with SND and AP and, therefore, should be followed closely for early detection and treatment of AAs.

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Fig. 1.
Prevalence of atrial arrhythmias after implantation

Fig. 2.
Prevalence of atrial fibrillation before and after implantation

Fig. 3.
Prevalence of atrial fibrillation by gender and race

Fig. 4.
Proportion of patients separated by frequency of atrial pacing

Table 1

Baseline characteristics of the study cohort

Characteristic	All patients (n = 322)	Without AF (n = 202)	With AF (n = 74)	p value
Age at implant (years)	68.8 ± 14.8	67.5 ± 15.6	71.1 ± 12.7	0.53
Duration of follow-up (years)	5.6 ± 2.2	7.2 ± 1.7	6.5 ± 1.4	0.26
Male (%)	43.8	42.1	39.2	0.93
Hypertension (%)	76.4	79.2	78.4	1
Diabetes (%)	26.4	26.2	27.0	1
COPD (%)	10.9	9.4	14.9	0.30
Chronic kidney disease (%)	52.5	52.5	54.1	0.99
Obstructive sleep apnea (%)	11.2	9.9	13.5	0.55
Thyroid disease (%)	15.8	14.9	17.6	0.65
Coronary artery disease (%)	40.4	38.1	47.3	0.35
Smoker (%)	53.7	55.0	55.4	0.77
Valvular disease (%)	20.8	16.3	32.4	0.006
Valve surgery (%)	8.7	5.5	16.2	0.015
LVEF initial (%)	54.5	54.3	55.3	0.52
LA size (%)				0.027
Normal	21.4	25.2	14.9	
Mild	12.7	12.4	12.2	
Moderate	11.2	12.4	12.2	
Severe	22.4	16.8	33.8	

Patients with and without AF do not equal all patients as some patients were missing prior AF data LVEF, left ventricular ejection fraction; LA, left atria

Table 2

Multivariate predictors of atrial arrhythmias after pacemaker implantation

Variable	Odds ratio	<i>p</i> value
Left atrial size	1.73 (1.31–2.33)	<0.001
Right atrial pacing	1.01 (1.00–1.02)	0.04
Diabetes mellitus	2.14 (1.03–4.65)	0.05