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Original Article

Occurrence of atrial fibrillation in pacemaker patients and its association with sleep apnea and heart rate variability

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ABSTRACT

Aims: Sleep apnea (SA) is a risk factor for atrial fibrillation (AF) occurrence. Sympathovagal imbalance is a mechanism that predisposes to the development of AF and that occurs in SA. Some pacemakers can detect SA events and continuously measure a time domain measure of heart rate variability (HRV), i.e. the standard deviation of 5-min median atrial–atrial sensed intervals (SDANN). We evaluated the association between the occurrence of AF and device-detected SA and SDANN in patients who received pacemakers.

Methods: We enrolled 150 consecutive patients undergoing implantation of a dual-chamber pacemaker, capable of SA and SDANN estimation. The SA was defined as severe if the Respiratory Disturbance Index was ≥30 episodes/h for at least one night during the first week after implantation.

Results: Sixteen patients in permanent AF were excluded from our analysis. During follow-up, AF (cumulative device-detected AF duration > 6 h/day) occurred in 24(18%) patients out of the remaining 134 patients. Severe SA was detected in 84 patients. SDANN values were available in 74 patients and the median value was 76 ms [25°–75°percentile:58–77]. The risk of AF was higher in patients with severe SA (log-rank test; p = .033). The presence of either or both conditions (severe SA and SDANN < 76 ms) was associated with shorter time to AF event (p = .042) and was an independent predictor of AF (hazard ratio: 2.37; 95%CI:1.08 to 5.21; p = .033).

Conclusion: In pacemaker patients, device-diagnosed severe SA and reduced SDANN are associated with a higher risk of AF.

1. Introduction

Cardiac arrhythmias are reported more frequently in persons with sleep-related breathing disorders, and in patients with diagnosed sleep apnea (SA) they increase with the number of apneic episodes [1,2].

In particular, a higher proportion of patients with a history of atrial fibrillation (AF) have been shown to have SA in comparison with the general population [3]. In the specific setting of SA, hypoxemia [4], systemic inflammation [5] and also sympathetic activation [6] have been recognized to be involved in the complex pathophysiological mechanisms leading to development of AF.

Autonomic dysfunction and sympatho-vagal imbalance are associated with cardiovascular death. Heart rate variability (HRV) refers to the variation in time interval between consecutive heart beats, corresponding to the balance between parasympathetic and sympathetic influences on the sinoatrial node [7].

Some pacemakers are now able to monitor intrathoracic impedance for automatic detection of SA events [8]. Pacemakers are also able to continuously measure the HRV to provide indices of sympathovagal imbalance.

The aim of this study was to evaluate the association between the occurrence of AF and device-detected SA, and to investigate the possible further association with device-measured HRV in patients who received pacemakers according to standard indications for the treatment of bradyarrhythmias.

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2. Methods

2.1. Patient selection, pacemaker implantation and follow-up

We enrolled all consecutive adult patients in whom a pacemaker had been implanted from October 2015 to August 2017 in our centre. Patients were required to have standard indications for dual-chamber pacing [9–11]. The study was approved by the Local Ethics Committee and informed consent was obtained from all patients. Devices and pacing leads were implanted by means of standard techniques. Atrial leads were routinely implanted in the right atrial appendage and ventricular leads in the right apex. Baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, and echocardiographic evaluation. Optimization of pacing parameters and pharmacological treatments was based on clinical evaluation by the attending physicians. During follow-up, patients returned for regular clinic visits every 3 months. At each scheduled or unscheduled visit, the pacemaker was interrogated and stored data were retrieved.

2.2. Device characteristics, SA detection, HRV measurement and endpoints

Commercially available pacemakers and transvenous leads were used in this study. Pacemakers were equipped with the ApneaScan diagnostic feature (Boston Scientific Inc., Natick, MA, USA). This feature continuously measures thoracic impedance by sending a low-voltage signal from the lead and the pacemaker can. As thoracic impedance varies with respiratory movements, changes in impedance are used to create a waveform that is used to count respiratory acts. At night, the algorithm automatically detects apnea/hypopnea events (longer than 10s) by measuring reductions in tidal volume. The Respiratory Disturbance Index is the average number of events per hour throughout the night [6]. Data are presented as trends on pacemaker interrogation. For the aims of the present study, SA was defined as severe if the pacemaker-measured Respiratory Disturbance Index was ≥30 episodes/h for at least one night during the first week after implantation [8,12]. Indeed, the index value calculated by ApneaScan over a 1-week period was previously demonstrated to accurately identify patients with severe disordered breathing (87% sensitivity and 56% specificity) on a polygraphic recording subsequently performed [13]. Pacemakers also allowed continuous HRV measurements. The device calculates a time domain measure of HRV, the standard deviation of 5-min median atrial–atrial sensed intervals (SDANN). Paced atrial beats, supraventricular and ventricular premature beats, and arrhythmic episodes are automatically excluded from the analysis by the device. The values are stored for each complete 24 h period and the days during which the amount of valid sensed atrial beats fall below 67% are excluded and not shown. The technical feasibility of the SDANN measurement achieved by automatic algorithms of implanted devices has been previously demonstrated [14]. In the present analysis, the average of the first week after implantation was used as the baseline value of SDANN, if at least one day with measurable SDANN was available [15].

The incidence and duration of AF were derived from device data, which comprise the total time spent by the patient in AF on each day of the follow-up period. Patients were considered to have experienced AF episodes if the device detected a cumulative AF duration greater than or equal to 6 h in a day, which is a reasonable cut-off according to previous studies [16–19]. The potential association between the occurrence of AF during the entire follow-up period and severe SA at the baseline was evaluated in each patient. Baseline SDANN values were used to test the added value of pacemaker-measured indices of sympathovagal imbalance for the assessment of the predisposition to AF development.

2.3. Statistical analysis

Continuous data were expressed as means ± standard deviation. Categorical data were expressed as percentages. Event rates were summarized by constructing Kaplan–Meier curves, and the distributions of the groups were compared by means of a log-rank test. Cox proportional hazards models were used to determine the association between the occurrence of AF during the follow-up period and baseline characteristics and to estimate the hazard ratios (HRs) and the 95% confidence intervals (CIs) of an AF event. All variables associated to a p value $< .05$ on univariate analysis were entered into the multivariate regression analysis. A p value $< .05$ was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc.).

Table 1
Demographics, baseline clinical parameters and Pharmacological Treatment of the overall population and of the groups in analysis with and without severe SA detected during the first week after implantation.

Parameter	N = 150	Severe SA (N = 84)	No severe SA (N = 50)
Male gender, n (%)	88 (59)	50 (60)	26 (52)
Age, years	81 ± 7	80 ± 7	82 ± 7
Ejection fraction, %	58 ± 6	58 ± 7	58 ± 6
Left atrial diameter, mm	42 ± 5	41 ± 5	42 ± 5
NYHA class			
NYHA I, n (%)	91 (61)	52 (62)	29 (58)
NYHA II, n (%)	56 (37)	21 (25)	21 (42)
NYHA III, n (%)	3 (2)	0 (0)	0 (0)
Coronary artery disease, n (%)	17 (11)	9 (11)	6 (12)
Hypertrophic cardiomyopathy, n (%)	2 (1)	2 (2)	0 (0)
Hypertension, n (%)	116 (77)	64 (76)	40 (80)
Diabetes, n (%)	31 (21)	20 (24)	8 (16)
Chronic obstructive pulmonary disease, n (%)	13 (9)	6 (7)	5 (10)
Chronic kidney disease, n (%)	26 (17)	18 (21)	5 (10)
Peripheral arterial disease, n (%)	18 (12)	12 (14)	5 (10)
$CHADS_2$ score	1.8 ± 0.8	1.9 ± 0.8	1.8 ± 0.7
CHA_2DS_2-VASc score	3.4 ± 0.9	3.4 ± 1.0	3.4 ± 0.8
Atrial fibrillation on implantation, n (%)	16 (11)	0 (0)	0 (0)
History of atrial fibrillation, n (%)	55 (37)	28 (33)	11 (22)
Clinical indication for pacing:			
Atrioventricular block	57 (38)	34 (40)	21 (42)
Sinus node disease	29 (19)	16 (19)	12 (24)
Brady-tachy syndrome	51 (34)	27 (32)	11 (22)
Carotid sinus syndrome	13 (9)	7 (8)	6 (12)
Ventricular pacing percentage (first week), %	42 ± 42	42 ± 42	39 ± 43
Atrial pacing percentage (first week), %	38 ± 34	36 ± 33	50 ± 34
Angiotensin-converting-enzyme-inhibitor use, n (%)	63 (42)	35 (42)	24 (48)
Angiotensin receptor blockers use, n (%)	30 (20)	16 (19)	13 (26)
Beta-blockers use, n (%)	45 (30)	30 (36)	13 (26)
Amiodarone use, n (%)	23 (15)	13 (15)	8 (16)
Other antiarrhythmics use, n (%)	16 (11)	13 (15)	3 (6)

NYHA: New York Heart Association.

3. Results

3.1. Study population and baseline evaluation

From October 2015 to August 2017, a total of 150 consecutive patients with a standard indication for permanent pacing underwent dual-chamber pacemaker implantation in our center. Table 1 shows baseline clinical variables. The pacemaker was implanted in response to atrioventricular block in 57 cases (38%), sinus node disease in 29 (19%), brady-tachy syndrome in 51 (34%), and carotid sinus syndrome in 13 (9%). At implantation, 16 (11%) patients were in AF and were excluded from the analysis. At hospital discharge, 45 (30%) patients were on beta-blockers, 23 (15%) on amiodarone and 16 (11%) on other antiarrhythmic medications.

Of the 134 patients in sinus rhythm at the time of implantation and included in the analysis, severe SA was detected in 84 (63%) during the first week after implantation. The comparison of baseline clinical variables of patients with and without severe SA is reported in Table 1 (no significant differences detected). At the first post implantation week SDANN values could be measured in 74 (55%) patients, with a median value of 76 ms [25°–75° percentile: 58–77].

3.2. Follow-up

During a mean follow-up of 7 ± 5 months, AF of at least 6 h was detected in 24 (18%) patients. The risk of AF was higher in patients with severe SA at the baseline. Fig. 1 shows the Kaplan–Meier event-free curves regarding AF (≥6 h in a day) over the entire follow-up period for the overall population, stratified by the presence or absence of severe SA at the baseline (log-rank test, p = .033). Online Fig. 1 shows the Kaplan-Meier analysis of the study population stratified according the SDANN value (SDANN > 76 ms, SDANN < 76 ms, no value available). In Fig. 1, patients of the two groups are further stratified according to SDANN value. In this analysis, patients with SDANN < 76 ms and with no SDANN available are grouped together. The presence of either (severe SA or SDANN < 76 ms, n = 61) or both conditions (severe SA and SDANN < 76 ms, n = 60) was associated with shorter time to AF event (p = .042, Fig. 2). Similar results were obtained by excluding patients with no SDANN available (Online Fig. 2).

On multivariate analysis (Table 2), history of previous AF (hazard ratio: 3.20; 95%CI: 1.39 to 7.38; p = .007) and the categorical SA/SDANN variable (no conditions = 0; either conditions = 1; both conditions = 2) (hazard ratio: 2.37; 95%CI: 1.08 to 5.21; p = .003) were confirmed as independent predictors of AF occurrence.

4. Discussion

In the present study, pacemaker-diagnosed severe SA was associated with a higher risk of AF. Moreover, device-measured indices of sympathovagal imbalance seemed to further stratify patients in terms of risk of AF episodes.

The association between AF and SA has been previously investigated [20]. Obstructive SA was shown to be more prevalent in patients with AF [3]. More recently, Gami et al. also recognized obstructive SA as an independent risk factor for AF occurrence over long-term follow-up [21].

An automated algorithm for SA detection based on the thoracic impedance sensor of a pacemaker was developed [8], and its ability to detect advanced sleep-disordered breathing was demonstrated [13]. In a previous analysis [22], we recently demonstrated an association between pacemaker-detected AF burden and the pacemaker-measured index of SA. In particular, in a population of 160 consecutive recipients of a dual-chamber pacemaker endowed with the ApneaScan algorithm we showed that severe SA at the baseline was independently associated with a higher risk of AF and new-onset AF during follow-up. Moreover, device-diagnosed SA was able to dynamically stratify patients in terms of risk of AF episodes. Indeed, severe SA on follow-up data review identified patients who were 2-fold more likely to experience an AF episode in the next 3 months. With the present analysis, conducted in a subsequent and non-overlapping group of patients, we confirmed those results and we further investigated the mechanisms that facilitate AF, taking advantage of the capability of modern pacemakers to record HRV indexes over the long term. Indeed, it has been previously hypothesized that the marked autonomic imbalance that has been seen to occur during SA could facilitate AF [6] and that alterations in autonomic regulation could modulate sleep-disordered breathing-related atrial arrhythmogenesis [23]. In patients who received pacemakers according to standard indications for the treatment of bradyarrhythmias we found that the risk of AF was higher in those with severe SA at the baseline, and that SDANN value further risk stratified patients. Pacemakers measure SA events through intrathoracic impedance monitoring and HRV through SDANN evaluation. When the Respiratory Disturbance Index was ≥30 episodes/h and/or when SDANN values were < 76 ms during the first week after implantation, patients were at higher risk of AF during follow-up. Multivariate analysis confirmed these pacemaker-measured indices as independent predictors of AF occurrence. In line with that, a recent work identified polysomnographic measures of HRV as predictors of incident AF and showed that obstructive SA modulates the relationship of HRV and incident AF [24]. In particular, a progressive reduction in the low-to-high frequency power ratio (i.e., a reflection of lower sympathetic to parasympathetic activity) was associated with increased AF incidence over 8-year follow-up. Moreover, indices of obstructive SA modified the relationship of HRV and incident AF, and the association between increased AF risk and autonomic imbalance was only observed in presence of severe SA.

Other mechanisms have been proposed to explain the link between SA and AF. Apnea induced hypoxemia may have a role in AF development, since the rate of recurrent AF in patients with SA was shown to be related to the magnitude of nocturnal oxygen desaturation [4]. Other studies have postulated that the diastolic dysfunction might have a role. Indeed, during obstructive apneic sleep, the attempted inspirations generate changes in cardiac transmural pressures and increase cardiac wall stress [25]. The consequent diastolic dysfunction may lead to increases in left atrial size, which has been shown to powerfully predict AF occurrence [26]. However, in the present study we did not see any

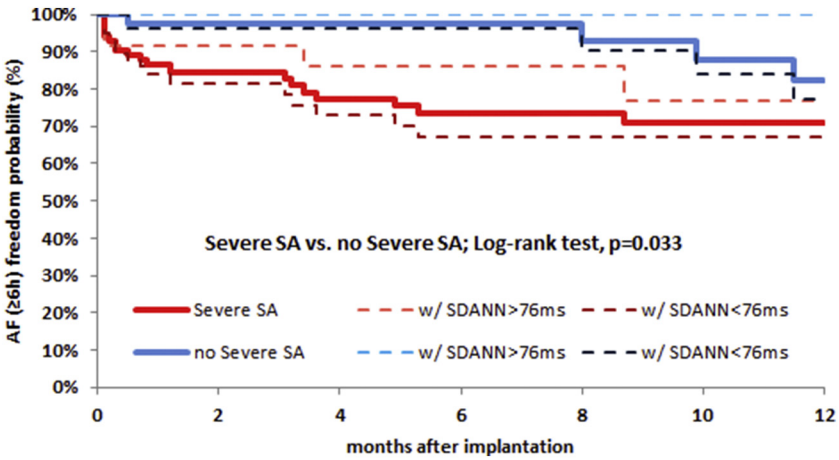

Fig. 1. Kaplan–Meier estimates of time to AF (≥6 h in a day), stratified by presence or absence of severe SA at baseline, and further stratification according to SDANN value.

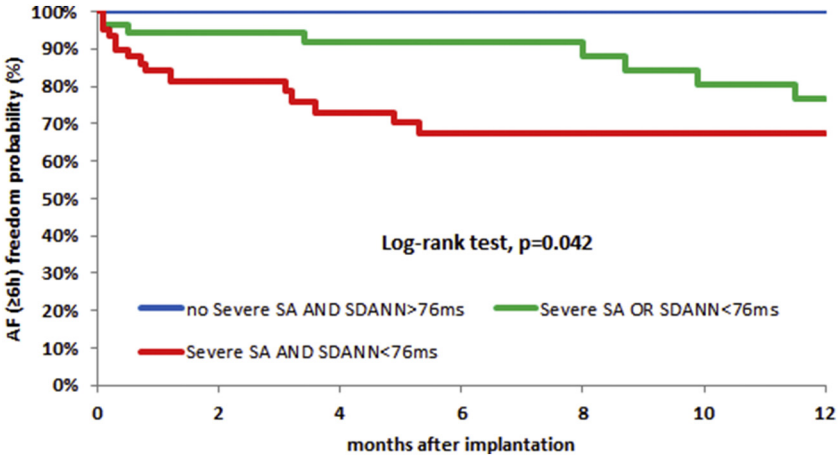

Fig. 2. Kaplan–Meier estimates of time to AF (≥6 h in a day), stratified by presence of one or two conditions: presence or absence of severe SA and SDANN < 76 ms or > 76 ms at baseline. (134 patients in analysis).

Table 2
Univariate and multivariate analysis of baseline factors associated with AF occurrence.

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Male gender	1.07	0.47–2.44	0.868	–	–	–
Age > 75 years	1.11	0.38–3.25	0.847	–	–	–
Ejection fraction	0.98	0.92–1.05	0.594	–	–	–
Left atrial diameter	1.04	0.97–1.13	0.255	–	–	–
NYHA Class	1.29	0.62–2.72	0.499	–	–	–
Body mass index	0.99	0.89–1.10	0.845	–	–	–
History of AF	3.51	1.52–8.07	0.003	3.20	1.39–7.38	0.007
Coronary artery disease	0.86	0.20–3.66	0.843	–	–	–
Hypertension	5.72	0.78–42.00	0.088	–	–	–
Diabetes	0.86	0.29–2.51	0.784	–	–	–
COPD	1.21	0.29–5.14	0.794	–	–	–
Chronic kidney disease	1.43	0.49–4.19	0.518	–	–	–
Peripheral arterial disease	1.29	0.39–4.34	0.679	–	–	–
High sensitivity C-reactive protein on implantation	1.09	0.91–1.31	0.349	–	–	–
$CHADS_2$ score	1.59	0.88–2.88	0.130	–	–	–
CHA_2DS_2-VASc score	1.26	0.80–1.98	0.317	–	–	–
Antiarrhythmic medications	1.50	0.56–4.03	0.420	–	–	–
(a) Severe sleep apnea	*2.76*	*1.04–8.06*	*0.043*	–	–	–
(b) SDANN < 76 ms or no value available	*2.13*	*1.01–6.22*	*0.047*	–	–	–
Combined conditions: No conditions [0], severe SA or SDANN < 76 ms [1], severe SA and SDANN < 76 ms [2]	2.53	1.17–5.48	0.019	2.37	1.08–5.21	0.003

NYHA: New York Heart Association; AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease.

association between left atrial diameter and AF occurrence. Another potential mechanism is the association between SA and systemic inflammation [5], which may increase the risk of AF [27]; again, however, we did not find an association between the level of high-sensitivity C-reactive protein and AF occurrence.

The ability of modern pacemakers to monitor sleep-related breathing disorders, that frequently remain undiagnosed [28], and indices of sympathovagal imbalance represents an opportunity to allow for risk quantification and stratification. Use of these markers may provide an early warning for AF risk and possibly the ability to tailor effective treatment to mitigate risk. Moreover, normalization of these indices measured over long-term may serve as a marker of treatment efficacy and compliance. Appropriate treatment with continuous positive airway pressure in obstructive SA patients [29,30] has been associated with lower recurrence of AF [4]. Although this effect was not confirmed in a more recent study [21], other interventions, such as treatments targeting obesity, could have a role in preventing or treating AF. Pacemakers frequently detect silent episodes in patients without a clinical history of AF [31], and this represents an opportunity to stratify patients for the risk of ischemic stroke, and to ensure correct antithrombotic treatment [16,32]. In particular, a daily burden of 6 h has been shown to imply a 17% increase in the risk of stroke. Future studies are needed in order to determine the possible link between AF, pacemaker-measured indices and increased risk of stroke. Moreover, additional studies are needed to confirm our findings in patients with no history of AF, to specifically assess the association between pacemaker-measured indices and new-onset AF during follow-up.

4.1. Limitations

The main limitation of the present study is the observational design of the analysis. Indeed, some variability in the selection or management of patients during the inclusion period may have influenced the results. However, the study was carried out in a single center, the operators in charge of patient selection, device implantation and clinical management did not change during the study period, and all the patients included were consecutive. Moreover, in our analysis patients were considered to have experienced AF if the device detected a cumulative daily AF burden was ≥6 h. By using this threshold of AF burden we were therefore not able to distinguish between patients with shorter AF duration and those with no AF. However, this threshold of AF burden has been used in other previous studies [18,33]. In addition, although the ability of the ApneaScan algorithm to detect advanced sleep-disordered breathing was demonstrated [8,13], a severely deranged Respiratory Disturbance Index is not equivalent to a diagnosis of severe SA. Moreover, the algorithm does not distinguish between obstructive SA and central SA. Nonetheless, central SA is most commonly present in heart failure patients with systolic dysfunction, who were not included in the present analysis. Lastly, as a time domain measure of autonomic activity we used the SDANN, that is linked more to the ultra-low frequency spectral component in the frequency domain [34]. Although the high frequency component is known to mainly reflect vagal activity and the low-to-high frequency power ratio is considered to mirror sympathovagal balance, disagreement exists on the physiological interpretation of lower-frequency components of HRV. Therefore, our HRV assessment does not allow to draw any conclusion about the tone of the 2 limbs of the autonomic nervous system, but rather provides an overall

picture of the sympathovagal balance. Finally, HRV can be measured in patients implanted with a pacemaker when the rate of atrial pacing is relatively low, thus excluding patients with the most severe forms of sinus node disease.

5. Conclusions

In patients who received pacemakers according to standard indications for the treatment of bradyarrhythmias we found that pacemaker-diagnosed severe SA was associated with a higher risk of AF, and that SDANN value further risk stratified patients.

Disclosures

M. Lovecchio and S. Valsecchi are employees of Boston Scientific, Inc. G. Boriani reported speaker's fees of small amount from Boston, Biotronik and Medtronic. No other conflicts of interest exist.

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