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Pacemaker-detected severe sleep apnea predicts new-onset atrial fibrillation

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Aims Sleep apnea (SA) diagnosed on overnight polysomnography is a risk factor for atrial fibrillation (AF). Advanced pacemakers are now able to monitor intrathoracic impedance for automatic detection of SA events.

Methods and results We enrolled 160 consecutive recipients of a dual-chamber pacemaker endowed with the ApneaScan algorithm (Boston Scientific). If the pacemaker-measured Respiratory Disturbance Index was ≥30 episodes per hour for at least one night during the first week after implantation, SA was defined as severe. Patients were considered to have experienced AF episodes if the device detected a cumulative AF burden ≥6 h in a day. Sixteen patients in AF at the time of implantation were excluded from our analysis. During follow-up, AF burden ≥6 h/day was documented in 35 (24%) of the patients included in the analysis and in 12 (13%) of the 96 patients with no history of AF. Severe SA was detected in 89 patients during the first week after implantation; 58 of these had no history of AF. Severe SA at the baseline was associated with a higher risk of AF both in the whole population (log-rank test, hazard ratio: 2.38; 95% CI: 1.21–4.66; $P = 0.025$) and among patients with no previous history of AF (log-rank test, hazard ratio: 2.80; 95% CI: 1.10–7.10; $P = 0.047$). Moreover, severe SA at the time of follow-up device interrogation predicted AF occurrence within the next 3 months (log-rank test, hazard ration: 2.13; 95% CI: 1.11–4.08; $P = 0.036$).

Conclusions In pacemaker patients, device-diagnosed severe SA was independently associated with a higher risk of AF (≥6 h/day) and new-onset AF. In particular, 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.

Keywords Sleep apnea • Pacemaker • Atrial fibrillation

Introduction

Sleep-related breathing disorders are highly prevalent in patients with established cardiovascular disease. In particular, obstructive sleep apnea (OSA) is present in a large proportion of patients with hypertension and coronary artery disease. In contrast, central sleep apnea (SA) occurs mainly in patients with heart failure.[1]

Cardiac arrhythmias are reported more frequently in persons with OSA, and increase with the number of apneic episodes.[2,3] Factors such as hypoxemia, sympathetic activation and systemic inflammation that occur in OSA may also be mechanisms that predispose to the development of atrial fibrillation (AF). Indeed, a higher proportion of patients with a history of AF have been shown to have OSA in comparison with the general population.[4]

Recently, automated pacemaker algorithms to detect advanced sleep-disordered breathing have been developed and have proved successful in detecting advanced SA.[5]

The aim of this study was to evaluate the association between the occurrence of AF and device-detected SA at the baseline and on routine follow-up interrogation in patients who received pacemakers according to standard indications for the treatment of bradyarrhythmias.

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What's new?

- In patients who received a pacemaker, severe device-detected sleep apnea at the baseline was independently associated with a higher risk of atrial fibrillation during follow-up.
- Severe sleep apnea on follow-up data review identified patients who were ~2-fold more likely to experience an atrial fibrillation episode in the next 3 months.

Methods

Patient selection, pacemaker implantation and follow-up

We enrolled all consecutive adult patients in whom a pacemaker had been implanted from October 2013 to October 2015 at the Santa Maria della Stella Hospital in Orvieto, Italy. Patients were required to have standard indications for dual-chamber pacing. Patients with evidence of systolic dysfunction (left ventricular ejection fraction $\leq$35%) or a prior diagnosis of heart failure were excluded from the analysis. 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.

Device characteristics, SA detection 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). 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 (>10 s) by measuring reductions in tidal volume. The Respiratory Disturbance Index is the average number of events per hour throughout the night.[5] Data are presented as trends on pacemaker interrogation (*Figure 1*).

As the first analysis of the present study, SA was defined as severe if the pacemaker-measured Respiratory Disturbance Index was $\geq$30 episodes per hour for at least one night during the first week after implantation.[5,6] The potential association between severe SA at the baseline and the occurrence of AF during the entire follow-up period was evaluated in each patient.

As the second analysis, we determined the potential utility of pacemaker-detected severe SA, when reviewed at routine follow-up intervals, in predicting the occurrence of AF within the next 3 months. We therefore considered the evaluations made in each patient every 3 months. For each evaluation, we included: a retrospective 1-week period, in order to assess the presence of severe SA (based on the values collected by the algorithm), and a prospective 3-month risk evaluation period, in order to observe the occurrence of the first AF event (*Figure 2*).

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 $\geq$6 h in a day, in agreement with previous studies.[7,8]

Statistical analysis

Continuous data were expressed as means $\pm$ SD. Categorical data were expressed as percentages. Differences between mean data were compared by means of a *t* test for Gaussian variables, and by the Mann–Whitney nonparametric test for non-Gaussian variables. 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 device-detected SA and the occurrence of AF during the prospective evaluation period and to estimate the hazard ratios (HRs) and the 95% confidence intervals (CIs) of an AF event in a subsequent prediction period. In the first analysis, the presence of SA at the baseline was tested as a predictor of the first episode of AF occurring over the entire follow-up period. In our evaluation of the predictive value of SA at the follow-up visit, multiple evaluation periods were considered in each patient. To account for the correlation among evaluation periods within a patient, the robust sandwich variance estimate for the HR was applied. All variables associated to a P value <0.05 on univariate analysis were entered into the multivariate regression analysis. A P value <0.05 was considered significant for all tests. All statistical analyses were performed by means of STATISTICA software, version 7.1 (StatSoft, Inc.).

Results

Study population and baseline evaluation

From October 2013 to October 2015, a total of 160 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 63 cases (39%), sinus node disease in 36 (23%), Brady–Tachy syndrome in 48 (30%), and carotid sinus syndrome in 13 (8%). On implantation, 16 (10%) patients were in AF and were excluded from the analysis, and 64 (40%) patients presented with a history of AF. On hospital discharge, 37 (23%) patients were on beta-blockers, 33 (21%) on amiodarone and 11 (7%) on other antiarrhythmic medications.

Of the 144 patients in sinus rhythm at the time of implantation and included in the analysis, severe SA was detected in 89 (62%) during the first week after implantation; 58 of these had no history of previous AF. Severe SA was detected in 34 (57%) patients with atrioventricular block, in 22 (61%) with sinus node disease, in 24 (69%) with Brady–Tachy syndrome and in 9 (69%) with carotid sinus syndrome.

Follow-up

During a mean follow-up of 8 $\pm$ 5 months, AF of at least 6 h was detected in 35 (24%) patients (*Figure 3*). Specifically, AF ($\geq$6 h) occurred in 12 (13%) of the 96 patients with no history of previous AF. Among patients with undetected severe SA at the baseline 1-week evaluation, 26 presented severe SA on follow-up device interrogation.

During follow-up, strokes were reported in two patients with severe SA. The respiratory disturbance index at the baseline was 36

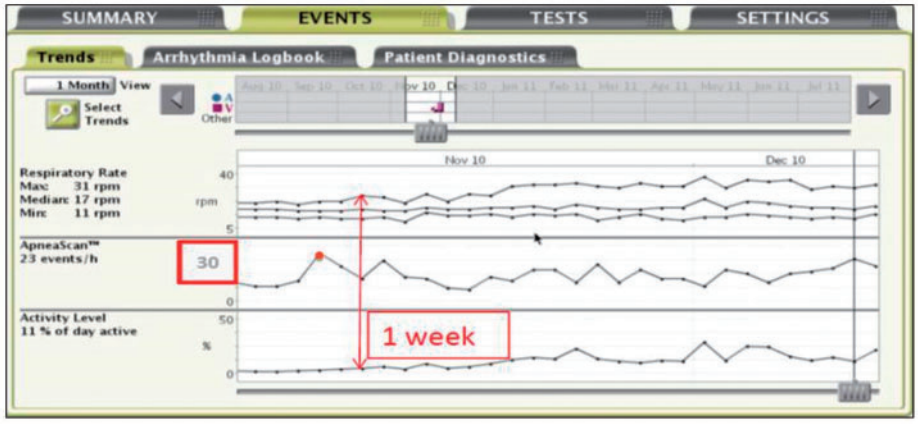

Figure 1 The Respiratory Disturbance Index is the average number of apnea/hypopnea events per hour throughout the night and is presented as a daily trend. For the aims of this analysis, SA was defined as severe if the pacemaker-measured Index was ≥30 episodes per hour for at least one night during the first week after implantation, or during the week preceding each follow-up visit.

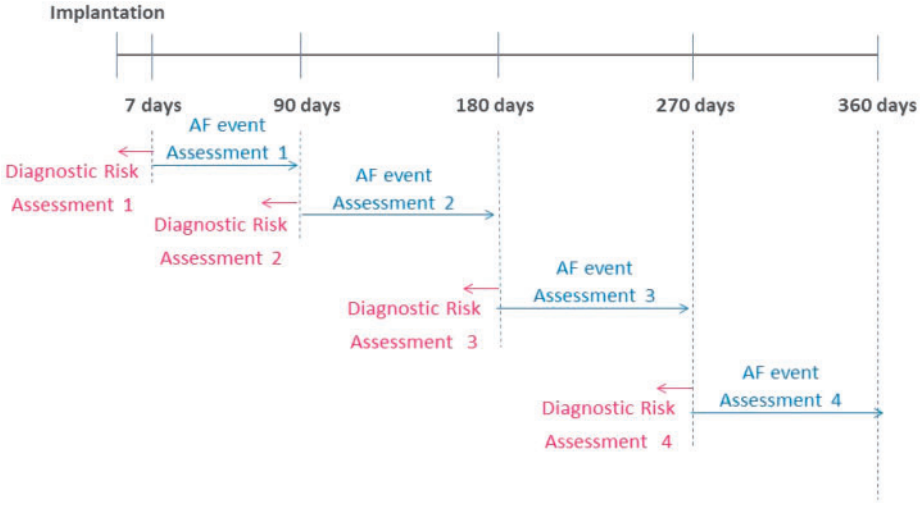

Figure 2 Every 3 months (routine visit-to-visit interval) the previous 1-week period was evaluated for SA assessment (based on the values collected by the algorithm) and the subsequent 3 months were evaluated for AF risk.

and 34, respectively. The index at the last routine follow-up visit before the stroke event was 46 and 37, respectively.

Association between SA and occurrence of AF

The mean values of the respiratory disturbance index measured at the baseline and the maximum value during follow-up are reported in *Figure 3*. The risk of AF was higher in patients with severe SA at the baseline. *Figure 4* 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, HR: 2.38; 95% CI: 1.21–4.66; $P = 0.025$). Severe SA at the baseline was also associated with a higher risk of AF in the group of patients with no history of AF (log-rank test, HR: 2.80; 95% CI: 1.10–7.10; $P = 0.047$). On multivariate analysis, severe SA at the baseline 1-week evaluation was confirmed as an independent predictor of AF occurrence during follow-up, together with previous history of paroxysmal AF (*Table 2*).

Pacemaker-detected severe SA at the time of follow-up device interrogation was predictive of AF occurrence within the next 3 months. Indeed, the risk of AF events was higher within the next 3 months (*Figure 5*; log-rank test, HR: 2.13; 95% CI: 1.11–4.08; $P = 0.036$), and multivariate analysis confirmed this as an independent predictor of AF occurrence (HR: 2.68; 95% CI: 1.28–5.60; $P = 0.009$).

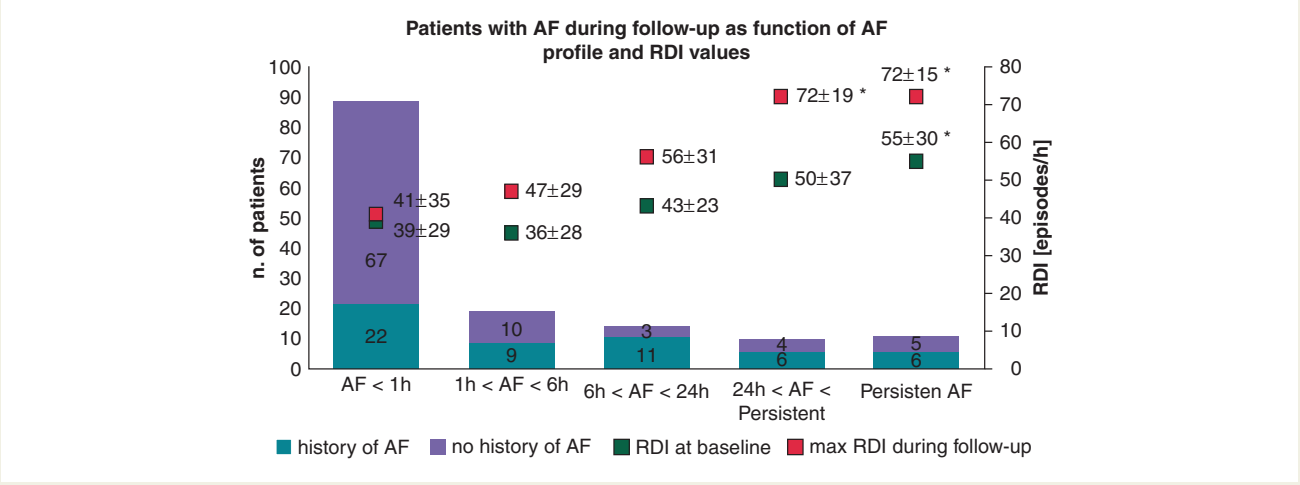

Figure 3 Patients with AF during follow-up, as a function of the duration of the longest arrhythmic episode. In blue, patients with known history of AF; in red, patients with new-onset AF. For each group, we reported the mean values of the respiratory disturbance index (at the baseline and the maximum during follow-up). *$P < 0.05$ vs. AF < 1 h.

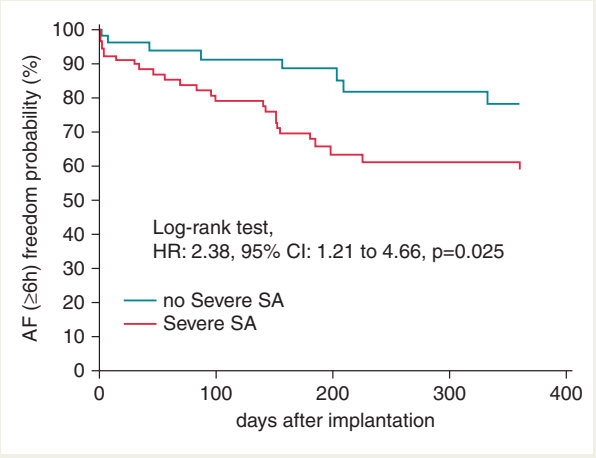

Figure 4 Kaplan–Meier estimates of time to AF (≥6 h in a day) over the entire follow-up period, stratified by presence or absence of severe SA at baseline.

Table 1 Demographics and baseline clinical parameters

Parameter	*N* = 160
Male gender, *n* (%)	90 (56)
Age (years)	80±8
Ejection fraction (%)	58±8
Left atrial diameter (mm)	41±6
NYHA class	
NYHA I, *n* (%)	105 (66)
NYHA II, *n* (%)	53 (33)
NYHA III, *n* (%)	2 (1)
Coronary artery disease, *n* (%)	24 (15)
Hypertrophic cardiomyopathy, *n* (%)	2 (1)
Hypertension, *n* (%)	124 (78)
Diabetes, *n* (%)	42 (26)
Chronic obstructive pulmonary disease, *n* (%)	16 (10)
Chronic kidney disease, *n* (%)	29 (18)
Peripheral arterial disease, *n* (%)	15 (9)
$CHADS_2$ score	1.5±1.2
CHA_2DS_2-VASc score	3.0±1.5
Atrial fibrillation on implantation, *n* (%)	16 (10)
History of atrial fibrillation, *n* (%)	
Paroxysmal, *n* (%)	34 (21)
Persistent, *n* (%)	30 (19)

NYHA, New York Heart Association.

Discussion

In the present study of patients who received a pacemaker endowed with the ApneaScan algorithm, severe device-detected SA at the baseline was independently associated with a higher risk of AF (cumulative daily AF burden >6 h) 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.

In 2004, Gami *et al.*[4] studied consecutive patients undergoing cardioversion for AF and patients without past or current AF, and showed that OSA, as detected by conventional polysomnography, was more prevalent in patients with AF. More recently, the same authors performed a second analysis,[9] which involved a retrospective cohort of patients without AF who were referred for a diagnostic

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	1.71	0.88–3.31	0.116	–	–	–
Age >75 years	0.94	0.44–2.01	0.881	–	–	–
Ejection fraction	1.01	0.97–1.06	0.519	–	–	–
Left atrial diameter	1.01	0.94–1.08	0.879	–	–	–
NYHA class	0.77	0.37–1.58	0.470	–	–	–
Body mass index	1.05	0.97–1.13	0.225	–	–	–
History of paroxysmal AF	2.87	1.45–5.70	0.003	2.70	1.22–5.97	0.015
History of persistent AF	1.25	0.49–3.21	0.646	–	–	–
Coronary artery disease	1.36	0.59–3.09	0.472	–	–	–
Hypertension	1.71	0.67–4.38	0.267	–	–	–
Diabetes	0.80	0.38–1.66	0.549	–	–	–
COPD	1.52	0.66–3.48	0.324	–	–	–
Chronic kidney disease	1.92	0.92–4.00	0.082	–	–	–
Peripheral arterial disease	0.54	0.17–1.75	0.305	–	–	–
High sensitivity C-reactive protein on implantation	0.96	0.85–1.08	0.530	–	–	–
$CHADS_2$ score	0.85	0.65–1.11	0.236	–	–	–
CHA_2DS_2-VASc score	0.95	0.79–1.15	0.613	–	–	–
Severe sleep apnea at the baseline 1-week evaluation	2.36	1.07–5.18	0.033	2.78	1.24–6.26	0.014
Antiarrhythmic medications	3.00	1.55–5.84	0.001	2.04	0.96–4.31	0.064

NYHA, New York Heart Association; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

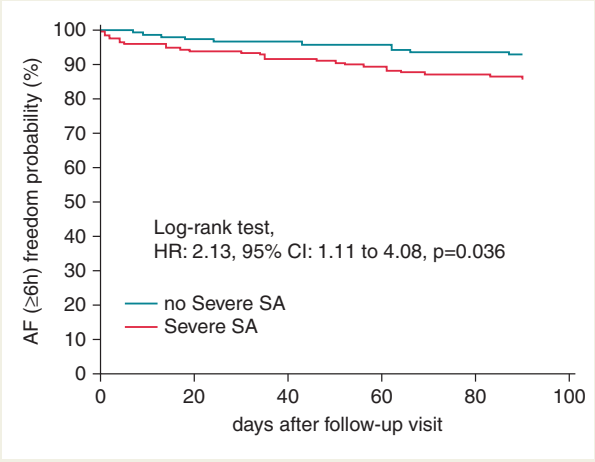

Figure 5 Kaplan–Meier estimates of time to AF (≥6 h in a day) over the 3-month period after routine follow-up visit, stratified by presence or absence of severe SA diagnosed during the week before follow-up visit.

polysomnogram. They recognized OSA as an independent risk factor for AF occurrence over a follow-up of 4 years.

The present study extends knowledge in this field by demonstrating an association between pacemaker-detected AF burden and a transthoracic impedance-derived index of SA, which is automatically and continuously measured by the implanted device. The ability of the automated algorithm to detect advanced sleep-disordered breathing from the thoracic impedance sensor of a pacemaker was previously demonstrated,[5] but no association with device-detected AF was reported. Moreover, in our study, the dedicated algorithm for respiratory disturbance monitoring was successful in detecting previously unrecognized advanced SA, which appeared to remain highly under-diagnosed in the populations of patients who had undergone pacemaker implantation for bradyarrhythmias.

Our finding that severe SA was independently predictive of AF occurrence (cumulative AF burden ≥6 h in a day) extends to the specific field of device-detected subclinical AF, and supports previous findings of an association between the magnitude of the decrease in nocturnal oxygen saturation and the onset of clinical AF.[9,10] Multiple mechanisms have been proposed to explain the link between OSA and AF. A consequence of apnea is hypoxemia, and a previous study found that a high rate of recurrent AF after cardioversion in patients with untreated OSA was directly related to the magnitude and duration of nocturnal oxygen desaturation.[11] Other studies have postulated that the diastolic dysfunction might have a role. Actually, the independent association between the magnitude of oxygen desaturation in patients with OSA and the degree of their diastolic dysfunction has been demonstrated.[12] Indeed, during obstructive apneic sleep, the attempted inspirations generate changes in cardiac transmural pressures and increase cardiac wall stress.[13] The consequent diastolic dysfunction may lead to increases in left atrial size, which has been shown to powerfully predict AF occurrence.[14] However, in the present study we did not see any association between left atrial diameter and AF occurrence. Another potential mechanism is the association between SA and systemic inflammation,[15] which may increase

the risk of AF;[10] again, however, we did not find an association between the level of high-sensitivity C-reactive protein and AF occurrence. Lastly, AF could be facilitated by the marked autonomic imbalance that has been seen to occur during SA.[16] The advanced capabilities of modern pacemakers to record heart rate variability indexes over the long term could help to better investigate this point, which was not analysed in the present study.

Understanding the link between AF occurrence and SA may have implications for targeted therapeutic strategies. Indeed, appropriate treatment with continuous positive airway pressure in OSA patients has been associated with lower recurrence of AF.[11] Although this effect was not confirmed in a more recent study,[9] other interventions, such as treatments targeting obesity, could have a role in preventing or treating AF.

Atrial fibrillation is common in patients with pacemakers.[17] Pacemakers frequently detect silent episodes in patients without a clinical history of AF,[18] but the exact amount of AF that may increase the risk of stroke is still a matter of investigation.[19,20] Our results confirm previous findings, in that we detected AF ($\geq$6 h in a day) in 24% of all patients in sinus rhythm on implantation and in 13% of patients with no history of previous AF. The capability of implanted cardiac devices to monitor the atrial rhythm is an opportunity to stratify patients for the risk of ischemic stroke, and may constitute an effective tool for ensuring correct antithrombotic treatment.[8] It has previously been found that, for every additional 1-h increase in the maximum daily AF burden, the relative risk of stroke increases by ~3%.[8] In particular, a maximum daily burden of 6 h has been shown to imply a 17% increase in the risk of stroke. More recently, the temporal relationship between AF and stroke risk was evaluated in individuals with ischemic stroke who also had implanted cardiac devices.[19] In patients who had episodes of AF, a burden of $\geq$5.5 h in a given day raised the short-term risk of stroke 4- to 5-fold. This risk was highest in the initial 5–10 days after the episode of AF and rapidly declined over longer periods.

Our results suggest that a device-based respiratory disturbance index may be helpful in stratifying pacemaker patients for AF risk. More importantly, the index showed the ability to dynamically stratify patients at the time of follow-up interrogation in terms of their AF risk in the next 3 months. This finding suggests the importance of reviewing these automated diagnostic data during routine in-office or remote interrogation. Future studies are needed in order to determine whether clinical interventions based on this diagnostics will improve outcomes, and to determine the possible link between AF, SA and increased risk of stroke.[21]

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. Although the device measured the Respiratory Disturbance Index every night, for the sake of simplicity we only considered the evaluations made during 1-week periods early after implantation and every 3 months. Therefore, we may have underestimated the number of patients with severe SA episodes. Moreover, the algorithm for SA detection does not distinguish between OSA 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. In addition, in our analysis patients were considered to have experienced AF if the device detected a cumulative daily AF burden was $\geq$6 h. This threshold of AF burden has been used in other previous studies.[22,23] 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. In agreement with previous analyses,[7,8,23] the 6-h cut-off was chosen as an approximation of the 5.5-h value identified in one of the studies evaluating the association between pacemaker-detected AF and thromboembolic risk.[22,23] In addition, an ECG analysis was not performed to include specific variables (e.g. P-wave duration) in our analysis of predictors of AF occurrence.

Conclusions

In the present study of patients who received a pacemaker endowed with the ApneaScan algorithm, severe device-detected SA at the baseline was independently associated with a higher burden of new-onset AF (cumulative daily AF burden $\geq$6 h).

Conflict of interest: M.L. and S.V. are employees of Boston Scientific, Inc. G.B. reported speaker's fees from Medtronic, Boston Scientific and Boehringer Ingelheim. No other conflicts of interest exist.

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Transient complete atrioventricular block during catheter balloon cryoablation of atrial fibrillation: a case report

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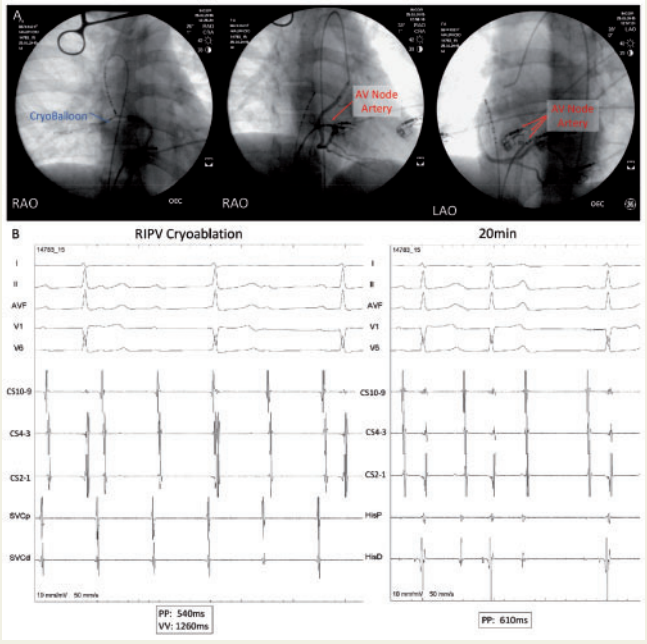
A 27-year-old man with normal heart and paroxysmal atrial fibrillation was referred for AF cryoablation. At first, the left pulmonary veins (PVs) were isolated with two 180 s cryoenergy applications in each vein. Then, the balloon was moved to the right inferior PV (RIPV) and two consecutive applications of cryoenergy, reaching a minimum temperature of −38 °C and −35 °C, were unable to isolate RIPV. The balloon was positioned in the right superior PV and isolation was obtained with two cryoenergy applications at −57°C and −56°C. The balloon was then repositioned in the RIPV and a third application was delivered, reaching a minimum temperature of −42°C. During this application, patient presented complete atrioventricular (AV) block (*Figure*) and the cryoablation was interrupted. The block persisted despite 2 mg atropine. Conduction recovered progressively 23 min after cryoablation. Coronary angiography performed 30 min after AV block showed a patent AV node artery originating from the right coronary artery.



We hypothesize that AV node ischaemia was the most probable mechanism. Artery supply of the AV node usually originates from the right coronary artery at the level of the crux cordis. The artery travels through the atrial septum at the base of the Koch triangle and the freezing of RIVP could have promoted transient AV nodal artery occlusion.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.