

Electrophysiological determinants of atrial fibrillation in sinus node dysfunction despite atrial pacing

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Aims The effectiveness of atrial pacing in reducing the incidence of atrial fibrillation in patients with sinus node dysfunction is incomplete, and the correlation between electrophysiological atrial properties and the effect of permanent atrial pacing has been poorly investigated. Accordingly, the aim of the present study was to correlate electrophysiological data, in terms of atrial refractoriness, conduction parameters, and propensity to atrial fibrillation induction, and the likelihood of atrial fibrillation after DDD device implantation.

Methods and Results The authors reviewed electrophysiological data of 41 patients with sinus node dysfunction (mean age 70 ± 8 years, who were investigated free of antiarrhythmic treatments before pacemaker implantation. At a drive cycle length of 600 ms, effective and functional refractory periods, S1–A1 and S2–A2 latency, A1 and A2 width, and latent vulnerability index (effective refractory period [ERP] A2), were measured. Atrial fibrillation induction was tested with up to three extrastimuli in 34 patients. Induction of sustained atrial fibrillation (>1 min) was considered as the end-point. P-wave duration on the surface ECG in lead II/V1 was also measured. Minimal atrial rate was programmed between 60 and 75 bpm (mean: 64 ± 4 bpm). After implantation, the patients were followed-up for 28 ± 17 months, and ECG-documented occurrence of atrial fibrillation was determined. Electrophysiological characteristics of patients with ($n=12$) or without ($n=29$) paroxysmal atrial fibrillation before implantation were similar. When comparing patients with ($n=11$) or without ($n=30$) post-pacing atrial fibrillation occurrence, no differences were found in age, underlying heart disease, left atrial size, minimal pacing rate, and follow-up duration. Additionally, between the two former groups, there was no significant difference in terms of effective refractory periods (233 ± 47 ms vs 239 ± 25 ms), functional refractory periods (280 ± 48 ms vs 272 ± 21 ms), S1–A1 (44 ± 20 ms vs 37 ± 13 ms) and S2–A2 latency (77 ± 28 ms vs 66 ± 22 ms), and A1 duration (60 ± 23 ms vs 53 ± 16 ms). In contrast, in patients with post-pacing atrial fibrillation occurrence, the P wave was more prolonged (116 ± 22 ms vs 98 ± 13 ms; $P<0.01$), A2 was longer

(116 ± 41 ms vs 87 ± 27 ms; $P<0.01$), effective refractory periods/A2 was lower (2.1 ± 0.4 cm vs 3.1 ± 1.4 cm; $P<0.05$), and rate of atrial fibrillation induction was higher (8/11 patients vs 8/23 patients; $P<0.05$). Electrophysiological characteristics of patients free of post-pacing atrial fibrillation with associated ($n=6$) or unassociated ($n=24$) paroxysmal atrial fibrillation history before implantation were quite similar. In patients with post-pacing atrial fibrillation with associated ($n=6$) or unassociated atrial fibrillation history ($n=5$) before implantation, effective refractory periods was statistically different (207 ± 23 ms vs 264 ± 46 ms; $P<0.05$). Values of effective refractory periods <220 ms were significantly more frequent in patients with post-pacing atrial fibrillation than in patients without (4/11 patients vs 2/30 patients; $P<0.05$). When comparing patients with post-pacing atrial fibrillation with effective refractory periods ≥ 220 ms ($n=7$) and <220 ms ($n=4$), A2 duration was remarkably prolonged (145 ± 42 ms vs 90 ± 11 ms; $P<0.05$) in those with effective refractory periods ≥ 220 ms. By contrast, between the two groups, effective refractory periods/A2 were identical (2.08 ± 0.6 cm vs 2.15 ± 0.3 cm; $P=n.s.$).

Conclusion Prolonged atrial refractoriness, lesser degrees of conduction disturbance and a lower rate of atrial fibrillation induction seem to be predictive of stable sinus rhythm. In contrast, patients with persistence of atrial fibrillation despite pacing have a more abnormal and inhomogeneous atrial substrate, as well as a higher rate of atrial fibrillation induction.

Prolonged P wave, shortened refractoriness, or remarkably abnormal conduction disturbances in the presence of prolonged refractoriness limit the effectiveness of standard atrial pacing in atrial fibrillation prevention. Identification of predictive criteria of failure of single-site atrial pacing may be used to consider dual-site atrial pacing in such patients with sinus node dysfunction.

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Key Words: Sinus node dysfunction, atrial fibrillation, electrophysiological study, atrial pacing.

Introduction

In patients with sinus node dysfunction, with or without manifest atrial fibrillation, the beneficial effect of atrial pacing in the prevention of atrial fibrillation has been strongly suggested in retrospective and prospective studies, especially in comparison with VVI pacing^[1-6]. Nevertheless, the rate of atrial fibrillation occurrence during long-term follow-up has been reported to be high in some reports between 20 and 50%^[1,3]. Additionally, regardless of large populations of implanted patients for sinus node dysfunction, few data are available on the correlation between an altered atrial substrate and the effect of atrial pacing in preventing atrial fibrillation^[6]. In other words, the role of electrophysiological predictors of atrial fibrillation recurrence is still unclear. Accordingly, the purpose of the present study was to evaluate the risk of post-pacing atrial fibrillation, with reference to atrial refractoriness, conduction parameters, and atrial fibrillation induction propensity, determined by electrophysiological study performed before pacemaker implantation.

Methods

The authors analysed electrophysiological data of 41 consecutive patients with sinus node dysfunction, 22 males and 19 females, aged 70 ± 8 years, who were investigated free of antiarrhythmic treatment before DDD pacemaker implantation, from 1990 to 1998. Thirty-nine patients had primary sinus node dysfunction, with severe unexpected diurnal sinus bradycardia <40 bpm, or sino-atrial block with pauses >2500 ms in combination with fatigue, dizziness or syncope. Two other patients were included for drug-induced sinus node dysfunction, with marked aggravation of bradycardia by antiarrhythmic drugs given for the treatment of recurrent paroxysmal atrial fibrillation episodes.

Thirty patients had no detectable structural heart disease according to clinical examination, standard chest X-ray, echocardiography and exercise testing. Four patients had coronary heart disease, two patients had non-obstructive cardiomyopathy, one patient had mitral valve prolapse, and four patients had arterial hypertension. Left atrial size was measured echocardiographically in the parasternal view. Patients with abnormal thyroid function, congestive heart failure, \geq III New York Heart Association class, severe angina, and serum electrolyte disturbances at the time of the study were not included. Twelve patients had a previous history of sinus node dysfunction and associated spontaneous paroxysmal atrial fibrillation, documented by standard ECG in 11 patients and by 24 hour Holter monitoring in one patient. The frequency of atrial fibrillation attacks ranged from three episodes during the last year to one episode a week, treated unsuccessfully with one or more antiarrhythmic agents of class I-III (hydroquinidine, disopyramide, flecainide and sotalol; mean: 2 ± 0.9 treatments). The duration of each episode ranged from

some hours to 7 days, generally self-terminating. Atrial fibrillation episodes were symptomatic for palpitations in 10 patients and for chest discomfort in two patients. P-wave duration was measured in spontaneous sinus rhythm in lead II or V1, at a paper speed of $50 \text{ mm} \cdot \text{s}^{-1}$ on the surface ECG.

Informed and written consent was obtained from all patients before electrophysiological study, and all cardioactive drugs were discontinued at least five pharmacological half-lives before the electrophysiological study. Patients taking amiodarone were not included.

Two six Fr USCI (division CR Barb Inc., Billerica, MA, U.S.A.) quadripolar electrode catheters, with 10 mm interpolar spacing, were inserted percutaneously through the femoral vein and placed, under fluoroscopic guidance, in the high right atrium at the parasinus region and at the His-bundle area for the evaluation of sinus node and atrioventricular parameters. Electrical stimulation was delivered by a programmable stimulator (Savita, Paris, France) with square impulses 2 ms in duration, and at twice threshold. Right atrial electrograms were recorded using the proximal electrodes of the quadripolar catheter, whereas the impulse was delivered by the distal pair of electrodes. The recordings were filtered at 50-700 Hz by a multichannel Siemens Mingograph 82 (Siemens-Elema, Solna, Sweden), and they were analysed at a paper speed of $100 \text{ mm} \cdot \text{s}^{-1}$. Measurements were assessed by two independent observers, and an inter-observer value greater than 10 ms was considered as an exclusion criterion.

Electrophysiological parameters were evaluated at a drive cycle length of 600 ms by an incremental technique. Following eight paced cycles (S1), an extra-stimulus (S2) was introduced, incrementing the coupling interval (S1-S2) in 10-ms steps. The atrial effective refractory period (ERP) was defined as the longest S1-S2 interval that failed to result in an atrial activation (A2). The functional refractory period (FRP) was defined as the shortest obtainable A1-A2 atrial activation interval. The duration of atrial activation (A1 and A2) was defined as the time from the beginning of the earliest electrical activity that deviated from the stable baseline value to the last point of the atrial electrogram at which the baseline was crossed. Atrial latency (S1-A1 and S2-A2) was defined as the interval between the stimulus artifact and the first intrinsic deflection of the corresponding propagated response. To represent the atrial vulnerability, we took into account the latent vulnerability index proposed by Attuel *et al.*^[7]. Based on Allesie's concept of wavelength, an easily measurable electrophysiological parameter related directly to refractoriness and atrial conduction velocity was proposed. The limitations of mapping during electrophysiological study do not permit the evaluation of velocity. Consequently, it is not possible to evaluate precisely the distance covered by the activation front between two sites. Therefore, in order to estimate as accurately as possible the probable velocity, the shortest distance between two electrodes (1 cm) and the duration of bipolar electrogram A2 were examined. Velocity could

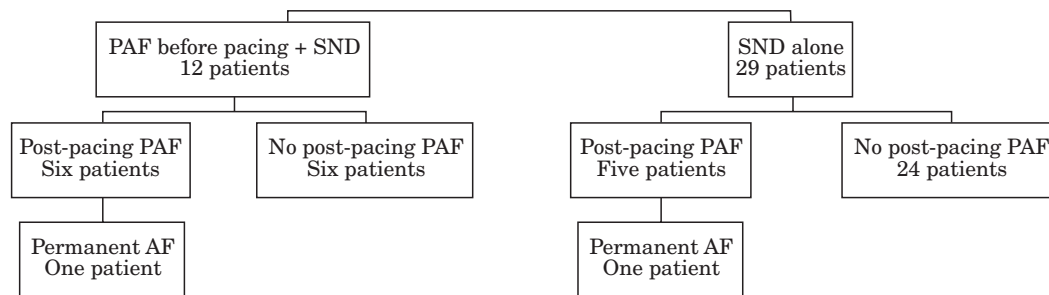


Figure 1. Sinus node dysfunction (SND) (n=41). PAF=paroxysmal atrial fibrillation; AF=atrial fibrillation.

be represented by the ratio $1 \text{ cm}/A_2$, from which it was deduced that a vulnerability parameter, such as Allesie's wavelength, could be represented in terms of the same formula, i. e. the product of refractoriness and the ratio $1 \text{ cm}/A_2$ [effective refractory periods (ms) $\times 1 \text{ cm}/A_2$ (ms)=effective refractory periods/ A_2 cm].

Assessment of atrial vulnerability was performed by programmed atrial stimulation with up to three extrastimuli at a paced atrial cycle length of 600 and 400 ms in 34 patients (10 with a previous history of atrial fibrillation before pacing and 24 without). Induction of sustained atrial fibrillation (>1 min) was considered as the end-point. A first extrastimulus (S2) was introduced late in diastole and the coupling interval was shortened by steps of 10 ms until the effective refractory period of the right atrium was reached, or sustained atrial fibrillation was induced. When sustained atrial fibrillation could not be initiated by increasing the coupling interval of the first extrastimulus by 20 ms more than effective refractory period, a second extrastimulus (S3) was introduced, shortening the coupling interval again until no atrial depolarization was observed. When two extrastimuli failed to induce sustained atrial fibrillation, a third (S4) extrastimulus was introduced following two identical coupling intervals (S1–S2=S2–S3), with the same method and end-point. The shortest coupling interval used was 160 ms. Before hospital discharge, the pacemaker was programmed in DDD mode with bipolar atrial and ventricular sensing. Atrial and ventricular pacing were programmed in unipolar mode. The lower atrial rate was programmed between 60 and 70 bpm in 39 patients. It was programmed at 75 bpm in the remaining two patients to suppress frequent premature atrial beats by overdrive atrial pacing. After discharge, seven patients with a pre-existing history of atrial fibrillation were treated by the same antiarrhythmic agents ineffective before pacing, temporarily suspended for electrophysiological study, and at the same dosage as used previously before implantation. Digoxin, calcium and beta-blocking agents were not prescribed.

The patients were followed-up and periodically evaluated clinically, by standard electrocardiograms and Holter monitoring, taking into account only ECG-documented occurrence of atrial fibrillation episodes. The minimal duration of follow-up was 6 months.

Statistical analysis

Continuous variables were expressed as mean \pm 1 standard deviation. Comparisons between groups were made by the unpaired two-tailed Student's t-test for continuous variables and the χ^2 test for discrete variables. Continuous variables among groups were analysed by one-way ANOVA, and the differences were validated by unpaired two-tailed Student's t-test. The level of significance was set at a value of $P < 0.05$.

Results

After a mean follow-up of 28 ± 17 months, paroxysmal atrial fibrillation was documented in 11 patients and did not occur in 30 patients. Paroxysmal atrial fibrillation recurred in six of 12 patients with a previous history of atrial fibrillation before pacemaker implantation. In patients with sinus node dysfunction alone, 'new-onset' atrial fibrillation occurred in five patients and not in the remaining 24. Two of these 11 patients with atrial fibrillation during follow-up developed permanent atrial fibrillation following at least one episode of paroxysmal atrial fibrillation (Fig. 1).

Patients with and without paroxysmal atrial fibrillation before pacing: clinical and electrophysiological variables

Comparison between patients with (n=12) and without (n=29) previously documented paroxysmal atrial fibrillation did not show any significant statistical differences in clinical parameters such as age, left atrial size, minimal pacing rate, and follow-up duration. Only cardiac disease was prevalent in patients with previous atrial fibrillation (6/12 patients vs 5/29 patients; $P < 0.05$). Additionally, no significant differences were found in any electrophysiological parameters such as P-wave duration (109 ± 19 ms vs 101 ± 16 ms), effective refractory periods (225 ± 35 ms vs 243 ± 30 ms), functional refractory periods (265 ± 38 ms vs 277 ± 27 ms), S1–A1 (39 ± 8 ms vs 39 ± 17 ms) and S2–A2 latency (73 ± 29 ms vs 68 ± 24 ms), A1 (57 ± 16 ms vs 58 ± 21 ms) and

Table 1 Patients with and without AF before pacing: clinical and electrophysiological variables

Variables	Previous AF	No previous AF	P
Patients (n)	12	29	
Age (years)	68 ± 9	72 ± 7	n.s.
Heart disease (patients)	6/12	5/29	<0.05
Left atrial size (mm)	38 ± 6	38 ± 5	n.s.
P wave duration (ms)	109 ± 19	101 ± 1	n.s.
ERP (ms)	225 ± 35	243 ± 30	n.s.
FRP (ms)	265 ± 38	277 ± 27	n.s.
S1–A1 (ms)	39 ± 8	39 ± 17	n.s.
S2–A2 (ms)	73 ± 29	68 ± 24	n.s.
A1 (ms)	57 ± 16	58 ± 21	n.s.
A2 (ms)	94 ± 19	96 ± 37	n.s.
ERP/A2 (cm)	2.5 ± 0.7	2.9 ± 1.4	n.s.
AF Induction (patients)	7/10	9/24	n.s.
Minimal pacing rate (bpm)	65 ± 4	64 ± 5	n.s.
Follow-up (months)	27 ± 14	28 ± 19	n.s.

AF=atrial fibrillation; ERP=effective refractory periods; FRP=functional refractory periods.

A2 width (94 ± 19 ms vs 96 ± 37 ms), and effective refractory periods/A2 (2.5 ± 0.7 cm vs 2.9 ± 1.4 cm). Sustained atrial fibrillation was induced in seven of 10 patients with previous paroxysmal atrial fibrillation and in nine of 24 patients without (P =n.s.) (Table 1).

Predictive parameters of atrial fibrillation after atrial pacing

When comparing patients with ($n=11$) and without ($n=30$) post-pacing atrial fibrillation occurrence, the two groups were quite similar in terms of age, prevalence of heart disease, left atrial size, minimal pacing rate, and follow-up duration. Additionally, no statistically significant differences were found in many electrophysiological parameters as effective refractory periods (233 ± 47 ms vs 239 ± 25 ms), functional refractory periods (280 ± 48 ms vs 272 ± 21 ms), S1–A1 (44 ± 20 ms vs 37 ± 13 ms) and S2–A2 latency (77 ± 28 ms vs 66 ± 22 ms), and A1 width (60 ± 23 ms vs 53 ± 16 ms).

By contrast, in patients with post-pacing atrial fibrillation occurrence, P-wave duration was longer (114 ± 21 ms vs 98 ± 13 ms; $P<0.01$), A2 was longer (116 ± 41 ms vs 87 ± 26 ms; $P<0.01$), and effective refractory periods/A2 was lower (2.1 ± 0.4 cm vs 3.1 ± 1.4 cm; $P<0.05$).

Sustained atrial fibrillation was induced in eight of 11 patients with post-pacing atrial fibrillation and in eight of 23 patients without post-pacing atrial fibrillation ($P<0.05$) (Table 2).

Correlation between electrophysiological parameters and atrial fibrillation inducibility

No statistically significant difference was observed between patients with ($n=16$) or without ($n=18$) atrial

Table 2 Patients with and without post-pacing AF: clinical and electrophysiological variables

Variables	Post-pacing AF	No post-pacing AF	P
Patients (n)	11	30	
Age (years)	68 ± 9	71 ± 7	n.s.
Heart disease (patients)	4/11	4/30	n.s.
Left atrial size (mm)	38 ± 6	38 ± 5	n.s.
P wave duration (ms)	114 ± 21	98 ± 13	<0.01
ERP (ms)	233 ± 47	239 ± 25	n.s.
FRP (ms)	280 ± 48	272 ± 21	n.s.
S1–A1 (ms)	44 ± 20	37 ± 13	n.s.
S2–A2 (ms)	77 ± 28	66 ± 22	n.s.
A1 (ms)	60 ± 23	53 ± 16	n.s.
A2 (ms)	116 ± 41	87 ± 26	<0.01
ERP/A2 (cm)	2.1 ± 0.4	3.1 ± 1.4	<0.05
AF Induction (patients)	8/11	8/23	<0.05
Minimal pacing rate (bpm)	65 ± 4	64 ± 5	n.s.
Follow-up (months)	29 ± 16	27 ± 18	n.s.

AF=atrial fibrillation; ERP=effective refractory periods; FRP=functional refractory periods.

fibrillation induction during electrophysiological study in clinical variables before pacing, and in electrophysiological parameters such as P-wave duration, effective refractory periods, functional refractory periods, S1–A1, and effective refractory periods/A2. Patients with inducible atrial fibrillation had a longer S2–A2 latency (83 ± 20 ms vs 61 ± 21 ms; $P<0.01$), A1 (68 ± 18 ms vs 47 ± 13 ms; $P<0.001$) and A2 (110 ± 36 ms vs 86 ± 27 ms; $P<0.05$) duration. Post-pacing atrial fibrillation occurred in eight of 16 patients with inducible atrial fibrillation and in three of 18 patients without inducible atrial fibrillation ($P<0.05$) (Table 3).

Comparison between patients with or without previous history of paroxysmal atrial fibrillation and with or without atrial fibrillation during DDD pacing

Analysis of variance of continuous variables among the four groups showed significant differences in P-wave duration ($P<0.01$), effective refractory periods ($P=0.01$), A2 duration ($P<0.05$) and effective refractory periods/A2 ($P=0.01$).

Patients free of post-pacing atrial fibrillation with associated ($n=6$) or unassociated ($n=24$) paroxysmal atrial fibrillation history before implantation

Electrophysiological characteristics between the two groups were quite similar. However, in patients with previous paroxysmal atrial fibrillation before implantation, underlying heart disease was more common (4/6 patients vs 3/24 patients; $P<0.01$).

Table 3 Patients with and without induction of sustained AF: clinical and electrophysiological variables

Variables	AF induction	No AF induction	P
Patients (n)	16	18	
Age (years)	71 ± 8	71 ± 15	n.s.
Heart disease (patients)	4/16	2/18	n.s.
Left atrial size (ms)	38 ± 6	37 ± 6	n.s.
AF before pacing (patients)	7/16	3/18	n.s.
P wave duration (ms)	107 ± 18	100 ± 17	n.s.
ERP (ms)	231 ± 40	235 ± 30	n.s.
FRP (ms)	280 ± 46	271 ± 17	n.s.
S1-A1 (ms)	41 ± 19	39 ± 14	n.s.
S2-A2 (ms)	83 ± 20	61 ± 21	<0.01
A1 (ms)	68 ± 18	47 ± 13	<0.001
A2 (ms)	110 ± 36	86 ± 27	<0.05
ERP/A2 (cm)	2.3 ± 0.6	3.1 ± 1.5	n.s.
Minimal pacing rate (bpm)	65 ± 4	64 ± 5	n.s.
AF in follow-up (patients)	8/16	3/18	<0.05

AF=atrial fibrillation; ERP=effective refractory periods; FRP=functional refractory periods.

Patients without documented paroxysmal atrial fibrillation before implantation with (n=5) or without (n=24) post-pacing atrial fibrillation

In those with post-pacing atrial fibrillation occurrence, A1 (79 ± 25 ms vs 53 ± 16 ms; $P<0.01$) and A2 width (137 ± 51 ms vs 86 ± 27 ms; $P<0.01$) were more altered, effective refractory periods/A2 was lower (2.05 ± 0.5 cm

vs 3.1 ± 1.4 cm; $P<0.05$), and atrial fibrillation induction incidence was higher (4/5 patients vs 5/19 patients; $P<0.05$).

Patients with previous paroxysmal atrial fibrillation with (n=6) or without (n=6) atrial fibrillation recurrence after DDD pacing

Only P-wave duration was significantly prolonged in the group with atrial fibrillation recurrence (122 ± 20 ms vs 98 ± 7 ms; $P<0.05$). During follow-up, patients with previous paroxysmal atrial fibrillation before pacing were treated by the same antiarrhythmic drugs, temporarily omitted from the electrophysiological study (3/6 patients with atrial fibrillation recurrence and 4/6 patients without; $P=n.s.$).

Patients with post-pacing atrial fibrillation with associated (n=6) or unassociated (n=5) paroxysmal atrial fibrillation history before implantation

Only effective refractory periods was significantly lower (207 ± 23 ms vs 264 ± 46 ms; $P<0.05$) in those with previous atrial fibrillation.

These results are presented in Table 4.

Inhomogeneous electrophysiological pattern in patients with atrial fibrillation despite pacing

Analysis of variance of continuous variables showed inhomogeneity in the distribution of duration of

Table 4 Patients with and without post-pacing AF occurrence and with or without clinical history of previous AF: electrophysiological profile

Variables	AF+/H+	AF+/H-	AF-/H+	AF-/H-	P (by ANOVA)
Age (years)	66 ± 9	71 ± 8	1 ± 8	72 ± 7	n.s.
Heart disease (n)	2/6	1/5	4/6	3/24¶	
Left atrial size (mm)	38 ± 8	38 ± 3	39 ± 2	38 ± 5	n.s.
P wave duration (ms)	122 ± 20	110 ± 21	98 ± 7§	98 ± 14	<0.01
ERP (ms)	207 ± 23*	264 ± 46	243 ± 36	239 ± 22	=0.01
FRP (ms)	255 ± 42	300 ± 46	275 ± 38	272 ± 17	n.s.
S1-A1 (ms)	49 ± 9	41 ± 28	32 ± 4	38 ± 14	n.s.
S2-A2 (ms)	87 ± 25	62 ± 23	60 ± 28	68 ± 22	n.s.
A1 (ms)	59 ± 15	79 ± 25‡	55 ± 19	53 ± 16	n.s.
A2 (ms)	96 ± 16	137 ± 51‡	92 ± 25	86 ± 27	<0.05
ERP/A2 (cm)	2.1 ± 0.4	2.05 ± 0.5	2.8 ± 1.1	3.1 ± 1.4	=0.01
AF Induction (patients)	4/6	4/5†	3/4	5/19	
Minimal rate (bpm)	65 ± 5	64 ± 4	64 ± 4	64 ± 6	n.s.
Follow-up (months)	29 ± 13	30 ± 20	25 ± 16	27 ± 19	n.s.

AF+/H+=patients with both AF before and after pacing (n=6).

AF+/H-=patients with AF occurrence without previous history of AF (n=5).

AF-/H+=patients without AF occurrence with previous history of AF (n=6).

AF-/H-=patients without both AF before and after pacing (n=24).

* $P<0.05$ AF+/H+ vs AF+/H-.

† $P<0.05$; ‡ $P<0.01$ AF+/H- vs AF-/H-.

§ $P<0.05$ AF+/H+ vs AF+/H-.

¶ $P<0.01$ AF-/H+ vs AF-/H- (by unpaired t-test and χ^2 test).

AF=atrial fibrillation; ERP=effective refractory periods; FRP=functional refractory periods.

Table 5 Patients with post-pacing AF: comparison between patients with ERP <220 ms and \geq 220 ms. Clinical and electrophysiological variables

Variables	<220 ms ERP	\geq 220 ms ERP	P
Patients (n)	4	7	
Age (years)	65 \pm 12	70 \pm 8	n.s.
Heart disease (patients)	2/4	2/7	n.s.
Left atrial size (mm)	41 \pm 6	37 \pm 6	n.s.
P wave duration (ms)	110 \pm 20	120 \pm 40	n.s.
ERP (ms)	194 \pm 18	255 \pm 44	<0.05
FRP (ms)	252 \pm 41	305 \pm 45	n.s.
S1-A1 (ms)	45 \pm 10	44 \pm 27	n.s.
S2-A2 (ms)	92 \pm 19	65 \pm 31	n.s.
A1 (ms)	66 \pm 17	73 \pm 28	n.s.
A2 (ms)	90 \pm 11	145 \pm 42	<0.05
ERP/A2 (cm)	2.15 \pm 0.3	2.08 \pm 0.6	n.s.
AF Induction (patients)	3/4	5/7	n.s.
Minimal pacing rate (bpm)	65 \pm 4	64 \pm 5	n.s.
Follow-up (months)	38 \pm 16	25 \pm 17	n.s.
Permanent AF (patients)	1	1	n.s.

AF=atrial fibrillation; ERP=effective refractory periods; FRP=functional refractory periods.

effective refractory periods among the four groups ($P=0.01$). In addition, it was observed that values of effective refractory periods <220 ms were significantly more frequent in patients with post-pacing atrial fibrillation than in patients without (4/11 patients vs 2/30 patients; $P<0.05$).

Based on these observations, patients with post-pacing atrial fibrillation with effective refractory periods \geq 220 ms ($n=7$) and <220 ms ($n=4$), were compared. In patients with effective refractory periods \geq 220 ms, A2 duration was remarkably prolonged (145 \pm 42 ms vs 90 \pm 11 ms; $P<0.05$). In contrast, between the two groups, effective refractory periods/A2 was identical (2.08 \pm 0.6 cm vs 2.15 \pm 0.3 cm; $P=n.s.$) (Table 5).

Patients with permanent atrial fibrillation in follow-up: electrophysiological characteristics

Two patients developed permanent atrial fibrillation following at least one episode of paroxysmal atrial fibrillation. In one patient (atrial fibrillation before and after pacing; no haemodynamically significant mitral valve prolapse), effective refractory period was 165 ms, A2 width was 80 ms, latent vulnerability index was 2 cm, and P-wave duration was 140 ms. In the other patient (atrial fibrillation in follow-up, never previously documented; no heart disease), effective refractory period was 250 ms, A2 width was 180 ms, effective refractory period/A2 was 1.38 cm, and P-wave duration was 90 ms. In these patients, digoxin and beta-blocking agents were prescribed for heart rate control.

Discussion

Electrophysiological mechanisms and abnormal atrial properties responsible for atrial fibrillation in sinus node dysfunction have received little attention from investigators in spite of atrial fibrillation being a part of its natural history^[1-4,8]. Experimental and clinical data have emphasized the relationship between bradycardia and an increased risk of atrial fibrillation^[9-11], but atrial fibrillation recurs in a significant subset of patients despite atrial pacing. Thus, if atrial pacing excludes or limits the brady-related mechanisms responsible for atrial fibrillation development, the prevention of atrial fibrillation appears incomplete, suggesting the importance of other electrophysiological mechanisms. Some authors have investigated the atrial electrophysiological characteristics of patients with sinus node dysfunction, stressing the importance of localized conduction disturbances, evaluated during sinus rhythm or after premature extrastimuli^[12-14]. In addition, long atrial refractory periods have been described in some reports, regardless of the fact that this finding has never been taken into account^[10,13,15]. More recently, it has been shown that more prolonged basal and post-extrastimulus right atrial electrograms, prolonged P-wave duration, and a lower latent vulnerability index are distinctive findings of sinus node dysfunction, whereas atrial refractoriness is not significantly different when comparing sinus node dysfunction patients with control subjects. In contrast, atrial electrophysiological characteristics of patients with or without associated paroxysmal atrial fibrillation were quite similar^[16], as found in the present study. The present study found that, in patients with sinus node dysfunction and inducible sustained atrial fibrillation during electrophysiological study, S2-A2 latency, and A1 and A2 duration were more abnormal. On the other hand, the rate of atrial fibrillation induction was not significantly different, whatever the previous atrial fibrillation history. Thus, induction of sustained atrial fibrillation, also in patients without prior documented atrial fibrillation, confirms the hypothesis of more diseased atria in patients with sinus node dysfunction, and its tendency to develop atrial fibrillation based mainly on atrial conduction disturbances. However, in patients with sinus node dysfunction, the correlation between atrial fibrillation induction and more abnormal right atrial electrograms, has been well described by some authors^[17].

Regardless of large populations of implanted patients for sinus node dysfunction, with or without manifest atrial fibrillation, the correlation between electrophysiological atrial properties and the effect of permanent atrial pacing is still undetermined. Thus, the purpose of this study was to evaluate the risk of post-pacing atrial fibrillation, with reference to atrial refractoriness, conduction parameters and atrial fibrillation induction propensity, determined before pacemaker implantation.

The present results show that prolonged atrial refractoriness, lesser degrees of atrial conduction disturbance, and a lower frequency of atrial fibrillation induction

predict maintenance of sinus rhythm during DDD pacing. In these patients, electrophysiological characteristics appear homogeneous, whatever the previous atrial fibrillation history. Thus, it could be conceived that this electrophysiological profile might have a protective effect on the maintenance of a stable sinus rhythm, if atrial pacing prevents the brady-related mechanisms responsible for atrial fibrillation. By contrast, a longer P-wave and A2 duration, as well as a lower latent vulnerability index and a higher rate of atrial fibrillation induction, appear to be predictive findings of atrial fibrillation occurrence despite DDD pacing, still significantly altered in patients with 'new-onset' atrial fibrillation in follow-up, when compared with patients without atrial fibrillation both before and after pacing. When comparing patients with previous paroxysmal atrial fibrillation, with or without atrial fibrillation recurrence during DDD pacing, only P-wave duration was significantly longer in those with atrial fibrillation despite pacing. More recently, the present authors have confirmed this observation in a large series of patients with sinus node dysfunction and previous atrial fibrillation^[18]. Finally, in patients with post-pacing atrial fibrillation, an inhomogeneous electrophysiological pattern was shown. In a limited subset of patients, short refractoriness seems to contribute to the development of atrial fibrillation, while a remarkably prolonged A2 duration in the presence of prolonged refractoriness, appears to characterize the remaining patients. In other words, consistent with the Allesie theory of wavelength^[19], when refractoriness is not short, an important degree of conduction disturbance is needed to develop atrial fibrillation. Not surprisingly, the latent vulnerability index was very low and identical in the two groups, explaining atrial fibrillation recurrence/occurrence in terms of short wavelength.

According to the data reported by Attuel *et al.*^[7], evaluated in patients with paroxysmal atrial fibrillation without sinus node dysfunction, a duration of A2 >100 ms and a latent vulnerability index <2.5 cm are good predictors of atrial fibrillation, and the present results are consistent with these values. In addition, the role of prolonged of P-wave duration as a predictor of atrial fibrillation has been well described in the literature^[20-21]. More recently, Stabile *et al.*^[22] have demonstrated decreased effectiveness of single-site atrial pacing in preventing atrial fibrillation in patients with a greater right atrial conduction delay and a wider dispersion of refractoriness; sinus node dysfunction with associated atrial fibrillation was the primary indication to implant in 60% of these patients.

Limitation of the study

Of course, the present study was limited by its retrospective nature. Evaluation of refractory periods at more than one site, adaptation of refractoriness at higher frequencies, and intra- and inter-atrial conduction times were parameters which were not constantly

evaluated and, therefore, not included in this study. Also, atrial fibrillation induction by provocative methods was not constantly evaluated in all patients. In two patients with frequent long-lasting and drug refractory atrial fibrillation, induction of atrial fibrillation was not tested to avoid the risk of electrical cardioversion.

Despite a large number of patients with sinus node dysfunction referred to the authors' centre, only a limited group was evaluated. Many patients were not included because of immediate pacemaker implantation or lack of consent for electrophysiological study. In addition, patients treated with amiodarone were not included, because they did not meet the inclusion criteria with reference to pharmacological wash-out. Despite the limited number of patients, the analysis of variance among groups showed highly significant differences in terms of effective refractory periods. This observation allowed the authors to differentiate two different electrophysiological patterns in patients with atrial fibrillation despite DDD pacing. In addition, a careful ECG survey during follow-up enabled better individualization of patients with atrial fibrillation which may not have been previously documented.

The clinical evaluation of atrial fibrillation recurrence presents some difficulties in common with all the other studies. It has been well established that asymptomatic episodes are common in patients with atrial fibrillation^[23], and the clinical evaluation, based on the presence or absence of documented atrial fibrillation, may be of limited value. In any case, an ECG-documented episode of atrial fibrillation is surely significant because it represents a duration long enough to be detected and, furthermore, Holter monitoring and device-stored data are incomplete tools for identifying paroxysmal atrial fibrillation episodes^[24,25].

Clinical implications

In patients with prolonged atrial refractoriness, lesser degrees of atrial conduction disturbance and a lower frequency of atrial fibrillation induction, single-site atrial pacing as usually performed, seems to be sufficient to maintain stable sinus rhythm. In contrast, an abnormal electrophysiological profile and a higher rate of atrial fibrillation induction appear to be predictive of atrial fibrillation despite single-site atrial pacing. Additionally, two different electrophysiological patterns in patients developing atrial fibrillation after pacing were defined, focusing on inhomogeneity in electrophysiological abnormalities responsible for atrial fibrillation. More recently, dual-site atrial pacing has been proposed in patients with drug-resistant atrial fibrillation and bradycardia^[5,6]. The experimental effect of biatrial (right atrial lateral wall and coronary sinus) or interatrial septal pacing have shown improvement of conduction disturbances and lesser degrees of arrhythmogenic effect in terms of atrial fibrillation induction, without changing effective refractory periods^[26-28]. At present, the mechanisms of favourable effects of dual-site atrial pacing are not completely

established and, therefore, the effectiveness of these procedures in patients with short atrial refractoriness or pronounced conduction disturbances or both is not known. In other words, the choice of site and/or pacing modalities, based on the predictive value of the electrophysiological study, is still undetermined.

Unfortunately, a large overlap of values was observed between groups, which limits the predictive value of common basal electrophysiological parameters, and points out the need for extensive and prospective electrophysiological investigations.

Conclusion

Standard atrial pacing may be able to modify the natural history of sinus node dysfunction in reducing the incidence of atrial fibrillation. Prolonged atrial refractoriness, lesser degrees of atrial conduction disturbance and a lower rate of atrial fibrillation induction seem to be predictive of stable sinus rhythm after pacing. In contrast, patients with persistence of atrial fibrillation despite pacing had a more abnormal and inhomogeneous atrial substrate, as well as a higher rate of atrial fibrillation induction. Prolonged P-wave shortened refractoriness, or remarkably abnormal conduction in the case of prolonged refractoriness limit the effectiveness of standard atrial pacing in atrial fibrillation prevention. Identification of predictive criteria of failure of single-site atrial pacing may be useful in consideration of dual-site atrial pacing in such patients with sinus node dysfunction.

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