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Electrophysiological abnormalities in patients with paroxysmal atrial fibrillation in the absence of overt structural heart disease

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ABSTRACT

Purpose: The aim of the present study was to define the atrial electrical substrate in patients with paroxysmal atrial fibrillation (AF) occurring in the absence of overt structural heart disease and to assess if electrophysiological parameters could predict AF recurrence after radiofrequency ablation in this population.

Methods and results: 45 consecutive patients (39 male, age 59 ± 10 years) with paroxysmal AF and without overt structural heart disease, referred for radiofrequency catheter ablation, were prospectively enrolled. A cohort of 12 age-matched patients without a history of AF, served as a control group. Atrial electrical substrate was assessed by P-wave signal-averaging, intracardiac conduction delays and refractory periods. Total P wave duration during signal-averaging was longer in patients with paroxysmal AF than in controls (140 ± 19 ms vs 123 ± 13 ms, $p = 0.004$). Patients with paroxysmal AF showed an increase in right intra-atrial (40.2 ± 11.3 ms vs 31.7 ± 11.8 ms, $p = 0.02$) and inter-atrial conduction delays (87.93 ± 22.0 ms vs 65.3 ± 15.6 ms, $p = 0.001$) in sinus rhythm. Refractory periods in the right atrium were longer in patients with paroxysmal AF (265 ± 44 ms vs 222 ± 32 ms, $p = 0.002$). After ablation, 22 patients had AF recurrence but showed no differences in electrophysiological parameters compared to patients without recurrence.

Conclusion: Electrophysiological abnormalities are present in patients with paroxysmal AF without overt structural heart disease. Neither signal-averaged P-wave duration nor intracardiac atrial electrophysiology could predict arrhythmia recurrence after pulmonary vein isolation.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. Although this arrhythmia is primarily seen in the elderly or in patients with heart disease, it is not exceptional to diagnose AF in patients without any overt structural heart disease or in relatively young patients [1]. This observation has lead Evans and Swann in 1954 to introduce the term "lone" atrial fibrillation, which has been used for decades by clinicians [2]. However, it has been recommended recently that the use of terms such as "idiopathic AF" or "lone AF" be avoided, because there has been a huge progress in the understanding of the pathophysiology of AF in the last 20 years; many causes of AF have been highlighted (obesity, sleep-apnea-syndrome, alcohol, vagal or adrenergic influences, excessive sporting activities, family history, genetics etc [3,4]), and abnormal electrical and anatomical substrates have been identified [5–9], including occult myocardial diseases as proven by atrial or ventricular biopsies [10,11].

In the present study we used signal-averaged P-wave analysis and intracardiac recordings to define the atrial electrical substrate of patients with paroxysmal AF occurring in the absence of overt structural heart disease and submitted to pulmonary vein isolation. We also tried to define if electrophysiological parameters could be predictive for arrhythmia recurrences after ablation in these patients.

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2. Methods

2.1. Patients

After informed consent, 45 consecutive patients (39 male, 6 female, mean age 59 ± 10 years) with paroxysmal AF referred for *de novo* radiofrequency catheter ablation (pulmonary vein isolation) were prospectively enrolled. Patients were considered eligible for catheter ablation if they had documented symptomatic AF, at least one failed antiarrhythmic drug and no history of coronary artery disease, heart failure, diabetes or pulmonary disease, with a normal physical examination, resting 12-lead ECG, transthoracic and transoesophageal echocardiogram (mild mitral regurgitation and mild atrial dilatation were not excluded). Patients were treated either with uninterrupted acenocoumarol (target INR of 2.0–3.0) or non-vitamin K oral anticoagulants (interrupted the day before the procedure). All patients underwent transoesophageal echocardiography immediately before the ablation procedure to exclude left atrial thrombi. All antiarrhythmic drugs were interrupted since at least 5 half-lives before ablation. A control group of 12 aged-matched without any history of AF, structural heart disease or hypertension and submitted to an electrophysiological study for syncope or supraventricular tachycardia was included in the study for comparison (Table 1).

2.2. Radiofrequency (RF) procedure

The procedure was performed in a fasting state under light sedation with midazolam and/or fentanyl. Only the right femoral vein was used for insertion of catheters, and in the absence of a patent foramen ovale a single transseptal puncture was performed using the Brockenbrough technique and a long sheath (SL0, St Jude Medical, St Paul, MN, USA). For the conventional point-by-point approach (n = 14), 3 catheters were inserted: one duodecapolar lasso catheter for pulmonary vein (PV) recording (introduced through the SL0 long sheath and positioned at the ostium of each PV sequentially), one 4-mm irrigated-tip ablation catheter for segmental isolation, and one decapolar (2 mm spacing) steerable catheter in the distal coronary sinus. For circular irrigated radiofrequency ablation (nMARQ, Biosense Webster, n = 31), only 2 catheters were inserted: one catheter for mapping and ablation in the left atrium (nMARQ catheter) and one decapolar (2 mm spacing) steerable catheter in the distal coronary sinus. The technique has been described in detail previously [12]. After transseptal puncture, a bolus of intravenous heparin was administered to aim for an ACT of 250–350 s and 3D electro-anatomical mapping using the CARTO3 system (Biosense Webster) was performed in all cases. With the point-by-point approach, ostial segmental isolation of all 4 PVs was performed using the ablation catheter under the guidance of the circumferential mapping catheter in the PV (maximum power 30–35 Watts; maximal temperature 48°; duration of the RF application 60 s). For circular irrigated nMARQ RF ablation, maximal power was 15 Watts and RF current was applied during 40 s at each site. The endpoint of RF application was complete PV isolation, demonstrated by the absence of PV potentials during sinus rhythm or coronary sinus pacing. Reconfirmation of PV isolation was performed 30 min after ablation for each PV. Patients were followed with continuous ECG monitoring for 24 h and were discharged from the hospital the day after the procedure. Patients were prospectively followed for up to 18 months or until recurrences occurred. Recurrences were defined as documented AF (duration > 30 s) occurring after a blanking period of 2 months after the ablation procedure. To confirm AF recurrence, serial 12-lead ECG recordings were obtained as well as at least one 24-h Holter ECG or one 7-days loop recording at 3–6 months post-procedure. Anticoagulation was maintained for 3 months in the absence of recurrence and longer in the presence of recurrences.

2.3. Intracardiac recordings

Intra-atrial conduction (right atrial conduction) was evaluated by measuring the interval between the atrial component in the high right atrium (HRA) and the atrial component recorded with the His bundle electrode(HBE) or with the proximal pole of the decapolar catheter-electrode positioned inside the coronary sinus (pCS), during sinus rhythm and during right atrial pacing (at 600 ms cycle length). Inter-atrial conduction was evaluated by measuring the interval between the atrial component in the high right atrium (HRA) and the atrial component recorded with the distal pole of the decapolar catheter-electrode positioned inside the coronary sinus (dCS), during sinus rhythm and during right atrial pacing (at 600 ms cycle length). The effective refractory period (ERP) of the right and the left atrium were determined by extra-stimulation during continuous pacing at 600 ms, at twice the diastolic threshold voltage and with a pulsewidth of 2 ms.

Table 1
Clinical and electrophysiological characteristics in the control group and in patients with paroxysmal atrial fibrillation (AF) in the absence of structural heart disease.

	Control group n = 12	Paroxysmal AF n = 45	p value
Age (years)	58.6 ± 12.3	58.8 ± 9.9	0.32
Left atrial diameter (cm)	33.8 ± 3.4	38.9 ± 4.3	0.0003*
Left atrial surface (cm^2)	15.8 ± 1.5	19.9 ± 2.8	<0.0001*
Left ventricular ejection fraction (%)	70.4 ± 4.0	67.1 ± 3.7	0.008*
P wave duration (ms)	122.8 ± 12.8	140.3 ± 19.3	0.004*
RMS 20 (μV)	3.50 ± 2.61	3.95 ± 2.64	0.59
RMS 30 (μV)	4.75 ± 3.04	4.68 ± 2.77	0.94
RMS 40 (μV)	5.25 ± 3.16	5.24 ± 2.74	0.99
P wave integral (μVs)	525 ± 161	646 ± 260	0.13
HRA-HBE (ms)	31.7 ± 11.8	40.2 ± 11.3	0.02*
HRA-pCS during sinus rhythm (ms)	54.3 ± 14.9	63.9 ± 17.4	0.08
HRA-pCS during pacing 600 ms (ms)	76.2 ± 13.8	88.9 ± 18.9	0.03*
HRA-dCS during sinus rhythm (ms)	65.3 ± 15.6	87.9 ± 22.0	0.001*
HRA-dCS during pacing 600 ms (ms)	92.8 ± 16.6	118.4 ± 22.2	0.0005*
Right atrial ERP (ms)	221.7 ± 31.9	265.0 ± 43.7	0.002*
Left atrial ERP (ms)	257.5 ± 33.9	271.8 ± 26.9	0.12

dCS = distal coronary sinus; ERP = effective refractory period; FRP = functional refractory period; HBE = atrial electrogram on the His bundle electrode; HRA = high right atrium; pCS = proximal coronary sinus; ms = milliseconds; RMS = root mean square; μV = microvolt. * = statistically significant.

2.4. P-wave signal averaging

A P-wave signal averaged recording was obtained within 1 h after the ablation procedure in all patients using the Phi-Res analysis module from Marquette Medical system (GE Healthcare, Waukesha, WI, USA). This recording was obtained after the procedure for homogeneity purposes, as some patients were in AF before the procedure. The system has a sampling frequency of 1000 Hz. The software provides filtering and automatic delineation of the averaged P-wave. Automatic measurements include total unfiltered and filtered P-wave duration (FPD), P-wave integral, and Root Mean Squared (RMS) voltages of the terminal 20, 30, and 40 ms. Electrocardiographic data were obtained using three orthogonal bipolar leads (X, Y, Z) and the three leads were combined into a vector magnitude VM ($VM = \sqrt{(X^2+Y^2+Z^2)}$). The P-wave was used as a trigger for the averaging process. Qualified P-waves were correlated with a P-wave template (generated on the first 10 beats), and only P-waves with a correlation coefficient >0.95 were taken into account for the averaging process, for filtering (Fast Fourier Transform filters; high-pass filter of 40 Hz, low-pass filter of 250 Hz) and for analysis. The endpoint for the averaging process was predetermined (250 beats) and only recordings with a residual noise level < 0.5 μV were used. All tracings were verified by two independent observers and automatic measurements were corrected according to visual delineation of the beginning and of the end of the P-wave.

2.5. Statistical analysis

Data are expressed as mean ± standard deviation. after testing for normality of distribution, differences in continuous variables were performed using Student's unpaired *t*-test. Differences in categorical data were performed using Chi-square or Fischer's exact test. A p value of less than 0.05 was considered significant. The correlation between P-wave duration and parameters of intra or inter-atrial conduction was assessed using Pearson's correlation coefficient.

3. Results

The clinical and electrophysiological characteristics of the patients are summarized in Table 1. Ten patients had mild and well-controlled hypertension without any sign of left ventricular hypertrophy or diastolic dysfunction on echocardiography.

Total P wave duration measured by signal-averaging was significantly longer in patients with paroxysmal AF than in controls, but no other signal-averaged parameters were different between the 2 groups. Intracavitary measurements showed a significant increase in intra- and inter-atrial conduction times in paroxysmal AF patients compared to controls. Refractory periods measured in the right atrium were longer in patients with paroxysmal AF, but there was no significant difference between the 2 groups for the refractory periods measured in the left atrium. A weak but significant correlation was observed between age and P-wave duration during signal-averaging ($r^2 = 0.16$, $p = 0.006$), between age and left atrial size ($r^2 = 0.15$, $p = 0.006$), between P-wave duration and left atrial size ($r^2 = 0.30$, $p < 0.0001$), between P-wave duration and intra-atrial conduction time ($r^2 = 0.23$, $p = 0.0008$), or inter-atrial conduction time ($r^2 = 0.24$, $p = 0.0005$), but only during pacing. No correlation was found between P-wave duration and values of refractory periods.

Analysis was also performed for the subgroup of so-called “lone” AF (exclusion of patients > 60 years of age and/or patients with hypertension even if well controlled). Results were similar as for the analysis if the entire AF group (Table 2).

Among the 45 patients with paroxysmal AF, 22 had AF recurrence after RF ablation, 5 (36%) in the point-by-point ablation group, and 17 (55%) in the nMARQ ablation group. Compared to patients who had no AF recurrence during a mean FU of 11.9 ± 4.6 months, patients with recurrences showed no differences in terms of clinical data, signal-averaged parameters or intracavitary recordings (Table 3). Among the 22 patients who had recurrences after the first ablation, 12 underwent a second ablation procedure, and in all cases focal pulmonary vein reconduction was observed as the mechanism for recurrence.

4. Discussion

The main results of the present study are:

a) Patients with paroxysmal AF without overt structural heart disease have electrical remodeling. Compared to age-matched control individuals, these patients have larger atria, longer P-wave durations measured by signal-averaging, impaired intra- and inter-atrial conduction, and longer refractory periods in the right atrium. The same findings apply when analysis is restricted to “lone” paroxysmal AF patients, suggesting that even in this specific subgroup, some electrical abnormalities are present making the term “lone” inadequate and obsolete. These results are in agreement with previous studies showing significant modifications in P-wave morphology [8], altered atrial conductive properties [6,13–16], prolonged regional refractoriness [14], increased atrial dispersion of refractoriness [17] and shortening of atrial refractory periods [18], in patients with paroxysmal “lone” AF. It has also been shown that these patients have evidence of atrial fibrosis on magnetic resonance imaging [19].
b) Total P-wave duration measured using signal-averaging, is correlated with atrial size and with intra and inter-atrial conduction times. It is established that the P-wave duration reflects inter- and intra-atrial conduction time and a prolonged P-wave implies atrial conduction delay, often not recognized on a standard electrocardiogram [20]. This electrical abnormality is generally associated with subclinical structural abnormalities, such as fibrosis and left atrial enlargement [21] which cause mechanical atrial dysfunction [22]. This electro-anatomic remodeling is involved in the initiation and perpetuation of AF [23,24], apparently even in patients with no detectable structural heart disease.
c) None of the electrophysiological parameters measured in this study (using P-wave signal-averaging or by intracavitary recordings) was useful to predict AF recurrence after RF catheter ablation. A few studies [25–28] have used the SAECG to study the effect of RF catheter ablation on the P-wave and to predict the risk of recurrences after ablation. The results of these studies are conflicting. Some studies showed that is the technique was useful to predict recurrences [25–27] whereas other data did not [28], probably because of different study design, small numbers of patients, various SAECG methodologies and variable definition of recurrences. The high recurrence rate in our study was essentially due to use of the nMARQ catheter with low power settings, which was probably a confounding factor with reconnection of the pulmonary veins. The patients included in the present study were part of a series of 50 patients ablated with this circular multipolar ablation catheter in whom we reported a recurrence rate of 54% after a follow-up of 15 ± 4 months [12].

5. Limitations

The sample size is relatively small. The present results may not

Table 2
Clinical and electrophysiological characteristics in the control group and in patients with true "lone" paroxysmal atrial fibrillation (AF).

	Control group n = 12	Lone AF patients n = 23	p value
Age (years)	58.6 ± 12.3	51.5 ± 6.7	0.03*
Left atrial diameter (cm)	33.8 ± 3.4	37.5 ± 3.1	0.002*
Left atrial surface (cm^2)	15.8 ± 1.5	19.1 ± 2.1	<0.0001*
Left ventricular ejection fraction (%)	70.4 ± 4.0	68.0 ± 3.3	0.06
P wave duration (ms)	122.8 ± 12.8	133.2 ± 15.4	0.053
RMS 20 (μV)	3.50 ± 2.61	4.34 ± 2.80	0.39
RMS 30 (μV)	4.75 ± 3.04	5.43 ± 2.79	0.50
RMS 40 (μV)	5.25 ± 3.16	6.01 ± 2.62	0.46
P wave integral (μVs)	525 ± 161	664 ± 236	0.07
HRA-HBE (ms)	31.7 ± 11.8	40.1 ± 12.4	0.06
HRA-pCS during sinus rhythm (ms)	54.3 ± 14.9	61.9 ± 19.1	0.23
HRA-pCS during pacing 600 ms (ms)	76.2 ± 13.8	81.7 ± 12.0	0.22
HRA-dCS during sinus rhythm (ms)	65.3 ± 15.6	85.1 ± 21.4	0.008*
HRA-dCS during pacing 600 ms (ms)	92.8 ± 16.6	110.9 ± 13.5	0.001*
Right atrial ERP (ms)	221.7 ± 31.9	253.7 ± 47.6	0.004*
Left atrial ERP (ms)	257.5 ± 33.9	271.7 ± 25.3	0.16

dCS = distal coronary sinus; ERP = effective refractory period; HBE = atrial electrogram on the His bundle electrode; HRA = high right atrium; pCS = proximal coronary sinus; ms = milliseconds; RMS = root mean square; μV = microvolt. * = statistically significant.

Table 3
Clinical and electrophysiological characteristics of patients with paroxysmal atrial fibrillation (AF) in the absence of structural heart disease who had recurrences versus those who had no AF recurrence after pulmonary vein isolation.

	Pts with recurrences n = 22	Pts without recurrence n = 23	p value
Age (years)	59.3 ± 10.4	58.3 ± 9.8	0.78
Left atrial diameter (cm)	39.5 ± 4.6	38.4 ± 4.1	0.56
Left atrial surface (cm^2)	20.6 ± 3.0	19.4 ± 2.6	0.15
Left ventricular ejection fraction (%)	66.5 ± 4.0	67.7 ± 3.3	0.24
P wave duration (ms)	141.9 ± 21.3	138.7 ± 17.4	0.57
RMS 20 (μV)	4.36 ± 2.96	3.56 ± 2.29	0.31
RMS 30 (μV)	4.59 ± 2.64	4.78 ± 2.95	0.82
RMS 40 (μV)	5.18 ± 2.32	5.30 ± 3.15	0.88
P wave integral (μVs)	663 ± 262	630 ± 262	0.66
HRA-HBE (ms)	37.0 ± 8.2	43.1 ± 13.0	0.06
HRA-pCS during sinus rhythm (ms)	61.1 ± 15.9	66.7 ± 18.7	0.29
HRA-pCS during pacing 600 ms (ms)	91.0 ± 20.9	86.9 ± 16.9	0.47
HRA-dCS during sinus rhythm (ms)	86.9 ± 24.0	88.8 ± 20.4	0.77
HRA-dCS during pacing 600 ms (ms)	119.3 ± 25.2	117.5 ± 19.4	0.78
Right atrial ERP (ms)	263.9 ± 44.5	266.1 ± 43.9	0.86
Left atrial ERP (ms)	268.2 ± 32.2	275.2 ± 20.9	0.38

dCS = distal coronary sinus; ERP = effective refractory period; HBE = atrial electrogram on the His bundle electrode; HRA = high right atrium; pCS = proximal coronary sinus; ms = milliseconds; RMS = root mean square; μV = microvolt.

be applicable to other methods of P-wave signal averaging. P-wave signal averaged recording were performed after pulmonary vein isolation, which may induced differences between the AF and control groups. However, as we performed segmental ostial isolation, with non-circumferential lesions and limited numbers of applications, this is unlikely to have led to atrial conduction delay. Our results are only applicable to AF patients undergoing PV isolation using the techniques described in this paper and may not be applicable to patients undergoing wide circumferential ablation (WACA), CFAE ablation or posterior left atrial isolation. Finally, the control group was comprised of patients without detectable structural heart disease, but who nevertheless had an indication for an electrophysiological study or supra-ventricular arrhythmia ablation, and therefore was not a "normal" population. However, atrial abnormalities in these patients would have served to reduce differences between the groups.

6. Conclusion

Electrophysiological abnormalities are present in patients with paroxysmal AF without any structural heart disease, probably reflecting the presence of a primary atrial disease and/or the extent of remodeling. P-wave signal-averaged parameters correlate with left atrial size and intra- or inter-atrial conduction. Neither signal-averaged P-wave duration nor intracardiac atrial electrophysiology are useful to predict arrhythmia recurrence after an initially successful pulmonary vein isolation using the ablation techniques described in our series.

Conflict of interest

None declared in relation to the present study.

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