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Inducibility of atrial fibrillation during electrophysiologic evaluation is associated with increased dispersion of atrial refractoriness

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Abstract

The impact of atrial dispersion of refractoriness (Disp_A) in the inducibility and maintenance of atrial fibrillation (AF) has not been fully resolved. Aim: To study the Disp_A and the vulnerability (A_Vuln) for the induction of self-limited (<60 s) and sustained episodes of AF. Methods and results: Forty-seven patients with paroxysmal AF (PAF): 29 patients without structural heart disease and 18 with hypertensive heart disease. Atrial effective refractory period (ERP) was assessed at five sites - right atrial appendage and low lateral right atrium, high interatrial septum, proximal and distal coronary sinus. We compared three groups: group A - AF not inducible ($n=13$); group B - AF inducible, self-limited ($n=18$); group C - AF inducible, sustained ($n=16$). Age, lone AF, hypertension, left atrial and left ventricular (LV) dimensions, LV systolic function, duration of AF history, atrial flutter/tachycardia, previous antiarrhythmics, and Disp_A were analysed with logistic regression to determine association with A_Vuln for AF inducibility. The ERP at different sites showed no differences among the groups. Group A had a lower Disp_A compared to group B (47±20 ms vs 82±65 ms; $p=0.002$), and when compared to group C (47±20 ms vs 80±55 ms; $p=0.008$). There was no significant difference in Disp_A between groups B and C. By means of multivariate regression analysis, the only predictor of A_Vuln was Disp_A ($p=0.04$). Conclusion: In patients with PAF, increased Disp_A represents an electrophysiological marker of A_Vuln. Inducibility of both self-limited and sustained episodes of AF is associated with similar values of Disp_A. These findings suggest that the maintenance of AF is influenced by additional factors.

Keywords: Dispersion of refractoriness; Atrial vulnerability; Non-sustained and sustained atrial fibrillation

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general practice setting. Its prevalence increases with age, from 0.4% in the general population to more than 5% over the age of 65 [1,2], and it is recognized as a potentially dangerous arrhythmia, with impact on both life expectancy and quality of life [3,4]. AF remains a considerable clinical challenge, in part due to our limitations in understanding the electrophysiological mechanisms underlying the condition. Despite the amount of recent information on management and therapeutic strategies on AF, we still have limited knowledge regarding the mechanisms of arrhythmia recurrence and progression to sustained AF. In fact, paroxysmal AF, defined as recurrent, self-terminating within 7 days of onset, progresses to persistent AF in over 18% of patients, even if there is no sign of underlying structural heart disease [5,6].

Electrical remodelling of the atrial tissue, which is associated with shortening of the atrial refractory period in a heterogeneous way, is known to be related with atrial vulnerability for the occurrence of spontaneous and inducible

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AF and to favour the maintenance and perpetuation of the arrhythmia [7]. Patients with inducible AF are at an increased risk of AF recurrence, even after pulmonary vein isolation [8,9]. Atrial effective refractory periods (ERP) and its spatial dispersion heterogeneity have been accepted to promote AF re-initiation and to provide a substrate for the re-entry of multiple wavelets to enhance the ability of the disorder to sustaining itself [10,11]. Also, an increase in the electrical homogeneity or a decrease in the dispersion of refractoriness may contribute to decrease the number of wavelets and lead to the AF termination [12]. Studies have shown that spatial dispersion of refractoriness is involved in the maintenance of AF [13,14]. Increased dispersion of atrial refractoriness and shortening of wavelength have been also correlated with initiation and maintenance of AF after its induction in a pacing-induced model of AF in the pig [15]. Nevertheless, there is lack of data concerning the impact of the degree of the non-uniformity of ERP on the vulnerability for the inducibility and for the persistence of AF among humans.

In the present study, we investigated whether the dispersion of atrial refractoriness influences the vulnerability for the induction of AF in patients with paroxysmal AF (PAF). Additionally, we evaluated the relationship between the magnitude of atrial refractoriness dispersion and inducibility of self-limited and self-sustained AF.

2. Methods

2.1. Patient population

The study consisted of 47 patients referred to our institution, with ≥1 year duration of clinical history of PAF, despite antiarrhythmic therapy. PAF was documented with electrocardiograms and/or Holter recordings. Patients with evidence of sick sinus syndrome, failure to remain in stable sinus rhythm while in-hospital monitoring before the electrophysiological study (EPS), permanent pacemaker implanted, bronchopulmonary disease and pregnancy or thyroid dysfunction were not included in the study. Prior to the EPS, all antiarrhythmic drugs were withdrawn for at least 5 half-life times. Patients under amiodarone stopped treatment 2 months before the EPS. The study protocol was approved by the local ethics. All subjects were required to give written informed consent.

The study protocol was performed according to the ethical guidelines of the Declaration of Helsinki.

2.2. Electrophysiological protocol

All patients underwent EPS in a non-sedated postabsorptive state. No serum electrolyte disturbances were found.

Electrical programmed stimulation and recording of electrograms were performed by using 6F catheter electrodes inserted percutaneously into the femoral and internal jugular veins. A quadripolar electrode catheter (2-mm-spaced; Daig Co) was positioned in the right atrial appendage (RAA), and moved to the low right posterolateral atrium (LRA) and high interatrial septum (IAS), a second quadripolar electrode catheter (2-mm-spaced; Daig Co) was inserted into the His bundle area (HBE), and a 2-mm-spaced decapolar electrode catheter (Daig Co) was advanced into the coronary sinus (CS). All bipolar electrograms were recorded using a multichannel electrophysiological recorder (Bard Lab System) with a frequency response of 50–500 Hz onto optical disks for later analysis. Twelve-lead surface ECGs were also simultaneously recorded. Hard copies of the electrograms were printed at a recording speed of 100 mm/s.

As a measure of local refractoriness, ERP were assessed in each patient at five different sites (RAA, LRA, IAS, proximal and distal CS). Under stable conditions, a programmed electrical stimulation using a single premature stimulus (S2) was delivered, while pacing continuously at a basic drive cycle length of 600 ms. Stimulation was performed with impulses of 2 ms duration at twice the diastolic threshold. A premature beat was introduced in late diastole, beginning at a coupling interval of 100 ms less than the basic cycle length. The coupling interval of the premature stimulation was decreased by 10 ms steps until the ERP was reached. The ERP were taken as the longest S1–S2 intervals that failed to initiate a propagation response. Dispersion of refractoriness was obtained in all patients as the difference between the longest and the shortest ERP at the five stimulation sites.

All patients underwent programmed bipolar stimulation (drive-train cycle length of 600 ms using S2–S3 extra-stimuli) and incremental pacing protocols (short-term of burst pacing range from 600 to 300 ms) during sinus rhythm by pacing from the distal electrode pairs positioned at the RAA and distal CS catheters. AF was defined as a rapid atrial rhythm (rate >350 beats/min) characterized by variability of the beat-to-beat cycle length, polarity, configuration and amplitude of the recorded atrial electrograms and lasting more than 5 cycles [16]. The concept of atrial vulnerability was based on the ability to induce AF with 1–2 extra-stimuli or with incremental atrial pacing during electrical stimulation from the RAA or distal CS. If AF was induced, an external electrical cardioversion was performed after ≥5 min of continuous AF without spontaneous termination. In patients requiring external cardioversion, a maximum of 3 shocks was delivered. The patients were separated into group A — AF not inducible, group B — AF inducible, self-limited (<60 s), and group C — AF inducible, self-sustained, terminated by therapeutic intervention.

2.3. Statistical analysis

The results are presented as mean value±standard deviation. Categorical variables are expressed as frequencies and percentages. Student's *t* test and repeated ANOVA were utilised for the analysis of continuous variables (overall comparison). The Chi-square test was used to evaluate the

Table 1
Clinical characteristics of the patients.

Characteristic	All patients (n=47)	Group A (n=13)	Group B (n=18)	Group C (n=16)
Age, years	56±14	57±13	54±15	57±14
Male gender	47%	47%	50%	44%
History of hypertension	36%	38.5%	33.3%	44%
Number of previous AA	1.7±0.8	1.6±0.9	1.4±0.8	2.0±0.5
LA≥22 mm/m^2	36%	38.5%	38.9%	31%
LV hypertrophy	12.7%	15.3%	11.1%	12.5%
LVEF<50%	11.1%	15.4%	11.1%	6.3%
Duration of AF (years)	2.3±1.9	2.0±1.5	1.9±2.0	3.0±2.2
AFL/AT	11.1%	15.4%	5.6%	12.5%

AA=antiarrhythmics; LA=left atrium (M-mode measurements); LV=left ventricle; LVEF=left ventricular ejection fraction; AF=atrial fibrillation; AFL=atrial flutter; AT=atrial tachycardia.
None of the variables differed significantly between the groups.

differences in categorical variables. Logistic regression analysis was used to assess the relation of variables with atrial vulnerability for the induction of AF. We tested the following variables for all patients: age, sex, diagnosis of lone PAF, history of systemic hypertension, left atrial dimension, left ventricular ejection fraction, presence or absence of left ventricular hypertrophy, duration of clinical paroxysmal AF, number of previous antiarrhythmics, documentation of atrial flutter, and dispersion of atrial ERP. For all tests a value of $p<0.05$ was considered statistically significant. Data were analyzed using GraphPAD Instruments (GraphPad Software, Inc., California, USA).

3. Results

3.1. Patient characteristics

Forty-seven patients (47% male) with a mean age of 56±14 years (range, 18 to 76 years) were subjected to this study. The average duration of the history of PAF was 2.3±1.9 years (median 1 year; range, 1 to 8 years).The population included 29 patients without structural heart disease and 18 with hypertensive heart disease. AF was inducible in 72% of the patients and non-inducible in 28%. The patients with atrial vulnerability for arrhythmia induction showed self-limited AF in 53% and self-sustained AF requiring electric intervention in 47%. Group A included 13 patients (8 men and 5 women with a mean age of 57±13 years). These patients had a 2.0±1.5 years of clinical history of PAF, refractory to 1.6±0.9 antiarrhythmic drugs. Group B consisted of 18 patients (11 men and 7 women with a mean age of 54±15 years), who had 1.4±0.8 years of PAF, refractory to 1.9±2.0 antiarrhythmic drugs. Group C was composed of 16 patients (10 men and 6 women with a mean age of 57±14 years), who had 2.0±0.5 years of history of paroxysmal AF episodes, refractory to 3.0±2.2 antiarrhythmic drugs. There were no significant differences regarding clinical and echocardiographic data among the three groups (Table 1).

Table 2
Effective refractory periods (ERP) measured at five atrial sites.

ERP (ms)	Group A (n=13)	Group B (n=18)	Group C (n=16)
RAA	216±24	204±9	215±22
LRA (lateral)	218±24	217±24	210±14
IAS (high)	232±40	235±40	220±15
pCS	245±33*	270±24*	260±40*
dCS	242±34*	340±126*	256±35*

Data are expressed as mean±SD. RAA=right atrial appendage; LRA=low right atrium; IAS=interatrial septum; pCS=proximal coronary sinus; dCS=distal coronary sinus. $p>0.05$ for comparisons between the groups. * $p<0.01$ for comparisons between ERP in the pCS and dCS vs RAA and LRA.

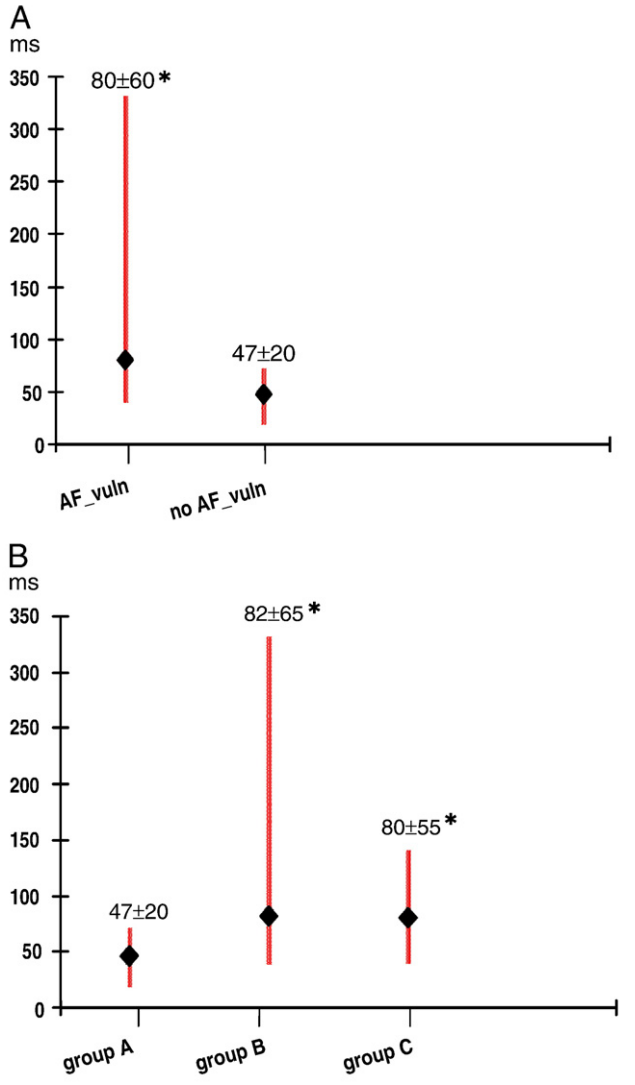

Fig. 1. The line graphs summarize the dispersion of effective atrial refractory periods for all the groups. Data are expressed as mean±SD. The lines represent the mean, minimum and maximum values for each group. A. AF_vuln=patients with vulnerability for AF induction (n=34); no AF_vuln=patients without AF induction (n=13). B. group A=AF not inducible (n=13); group B=AF inducible, self-limited (<60 s) (n=18); group C=AF inducible, self-sustained (n=16). Asterisks represent statistical significance (AF_vuln vs no AF_vuln, p=0.01; group A vs group B, p=0.002; group A vs group C, p=0.008).

3.2. Atrial refractoriness

ERP values measured at the CS (proximal and distal) were significantly higher when compared with the other evaluated sites (Table 2). The mean ERP increased progressively from the RAA, LRA, and IAS to the proximal and distal CS (212±18 ms, 213±20 ms, 228±31 ms, 256±33 ms and 273±73 ms respectively; ERP at the RAA vs distal CS, $p<0.01$). There were no significant differences among the ERP values measured in the three groups of patients at any of the five sites that were assessed (Table 2). However, dispersion of ERP was significantly higher in the group of 34 patients who had atrial vulnerability for the induction of AF compared with those who remained in sinus rhythm during the EPS (80±60 ms vs 47±20 ms; $p=0.01$) (Fig. 1). Moreover, the group A had a significant lower dispersion of the mean ERP compared to the group B (47±20 ms vs 82±65 ms; $p=0.002$) and when compared to the group C (47±20 ms vs 80±55 ms; $p=0.008$). There was no significant difference in dispersion of ERP between the patients with AF lasting ≤60 s and those with self-sustained AF (Fig. 1). By means of multivariate logistic regression, the only predictor of atrial vulnerability for the induction of AF was dispersion of atrial ERP ($p=0{\cdot}04$).

4. Discussion

4.1. Major findings

This study was designed to evaluate the impact of the degree of dispersion of atrial ERP on the vulnerability for the induction and maintenance of AF. The results have demonstrated that ERP dispersion values are determinants of atrial vulnerability. Increased dispersion of refractoriness facilitated AF induction, but the ability to sustain AF may be influenced by other factors in addition to the degree of the non-uniformity of local ERP. In fact, despite a greater dispersion of refractoriness in both groups with inducible AF, the ERP dispersion was similar in patients with inducibility of self-limited AF and in those patients who have induction of AF lasting ≥5 min. This suggests that the electrophysiological substrate that creates the conditions for the maintenance of AF is more complex, probably resulting from the combination of different underlying mechanisms in addition to the magnitude of atrial refractoriness dispersion. It is more likely that multiple variables, including the effects of autonomic nervous system, catecholamines, presence of stretched segments of the atria, ischemia and electrolyte imbalance, conduction abnormalities and other electrophysiological characteristics, contribute to the maintenance of AF.

4.2. Atrial refractory periods

Shortening of the atrial ERP has been reported as one of the main underlying electrophysiological changes in patients with sustained AF [17]. Nevertheless, in our study the ERP measurements at different sites where not different between groups. Previous studies have demonstrated that AF lead to a decrease in atrial ERP, without a significant change in conduction velocity [18,19]. A shorter ERP can create a shorter wavelength (ERP × conduction velocity), which significantly contributes to the maintenance of AF [20]. In our study, the ERP was gradually prolonged from the right to the left side, with higher determinations in the proximal CS and distal CS when compared with the RAA, LRA and IAS. Those patients with induction of AF showed a larger dispersion of refractoriness due to a marked difference between ERP at the right atrium and those obtained along the CS. These findings are in accordance with other authors, who reported shorter ERP in the high right atrium when compared with distal CS in patients with AF [7,21]. This may be explained by a non-uniform distribution of vagal nerve endings, which seems to cause greater changes in refractory period in the RAA than in left atrium [22].

It is widely accepted that heterogeneity of electrophysiological properties may play a major role in favouring re-entry waves, and hence the initiation of AF [13,23]. Experimental studies also suggested that ERP dispersion is an important factor in determining the ability to sustain AF [24,25]. Our results showed that dispersion of refractoriness is a suitable indicator of atrial vulnerability for the induction of AF. However, dispersion of atrial refractoriness was not significantly increased in patients with self-sustained AF when compared with the group with inducible non-sustained AF.

4.3. Self-limited vs self-sustained atrial fibrillation

AF is generally considered to be maintained by multiple re-entrant wavelets of excitation that propagate in different directions around the atrial myocardium [26,27]. The maintenance of AF seems to depend on the presence of a sufficient number of small wavefronts while undergoing fractionation, collisions and coalescence over the atrial surface. To allow multiple re-entrant wavelets to propagate resulting in a self-perpetuating activity, a critical mass of excitable atrial tissue must exist [28]. Re-entry within the atria is associated with shortening of the ERP with increased dispersion of refractoriness, thereby providing a substrate for initiation of AF. The concept of dispersion of refractoriness is based on the non-uniformity of local atrial refractory periods. This results in the coexistence of regions of the atria with relatively short ERP in close proximity to areas with much longer ERP, instead of a gradual transition. Also, re-entrant wavelets must never encounter refractory tissue left over by a previous wavelet, otherwise the wavelets will be extinguished and the arrhythmia will not be sustained. Thus, non-uniform changes in refractoriness are associated with an increased frequency of induction of AF. However, when the dispersion of refractoriness is too large, re-entrant wavelets may be extinguished due to a slower recovery of adjacent

atrial myocardium. If this tissue cannot recover before the wavelet arrives, the critical number of existing wavelets, essential for the AF maintenance, will not be achieved. Moreover, a larger number of circulating wavelets can exist on the surface of larger atria. So, to accommodate the maximum number of wavelets in a constant area, several factors including atrial size, velocity of conduction and dispersion of atrial refractory periods need to be adequately combined.

Recently, in human studies, the presence of shorter ERP in the pulmonary veins, when compared to left atrial refractoriness, was considered to provide a favourable milieu for the initiation of AF and possibly to sustain fibrillatory activity [29,30]. In addition, experimental evidence suggests that certain cases of AF are maintained by small re-entrant dominant frequency sources (rotors) [31,32]. Despite different concepts to explain the perpetuation of AF, dispersion of atrial refractoriness has been consistently associated with vulnerability to the initiation and maintenance of AF.

4.4. Study limitations

First, the lack of a control group without history of AF makes the comparison of the dispersion of ERP between our patients and a population without the arrhythmia impossible. However, the aim of this study was to assess the relationship between the intensity of atrial refractoriness dispersion and the vulnerability for the induction of self-limited and self-sustained AF in a population with PAF. Second, the protocol did not include measurements of the ERP from the pulmonary veins and different left atrial sites. Therefore, it is not possible to compare ERP to the right atrium and pulmonary veins in this population. Nevertheless, in previous studies, the distal CS ERP was accepted as reflecting the ERP of the local left atrial tissue [21,33]. Finally, although the number of subjects included in the study allowed for the identification of significant differences in the dispersion of atrial refractoriness, the resulting sample was relatively small, representing only a subpopulation of patients with PAF and absent or minimal structural heart disease. Thus, further studies in a larger group may be needed to confirm these findings.

5. Conclusions

Increased atrial ERP dispersion enhances the propensity for the inducibility of AF during electrophysiologic evaluation. Nevertheless, patients with vulnerability for the induction of AF lasting less than 1 min and those with inducibility of self-sustained AF had similar and significant increases in atrial dispersion of refractoriness. These results emphasize the importance of the dispersion of ERP as an electrophysiological marker of vulnerability for the induction of AF, and suggest that the maintenance of AF induced during EPS is influenced by additional factors beyond the degree of the non-uniformity of ERP.

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