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International Journal of Cardiology 136 (2009) 130–135

International Journal of Cardiology

www.elsevier.com/locate/ijcard

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

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Received 7 September 2007; received in revised form 20 March 2008; accepted 23 April 2008
Available online 3 August 2008

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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doi:10.1016/j.ijcard.2008.04.097

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