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Intra-Atrial Conduction Delay Revealed by Multisite Incremental Atrial Pacing is an Independent Marker of Remodeling in Human Atrial Fibrillation

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ABSTRACT

OBJECTIVES This study sought to characterize direction-dependent and coupling interval–dependent changes in left atrial conduction and electrogram morphology in uniformly classified patients with paroxysmal atrial fibrillation (AF) and normal bipolar voltage mapping.

BACKGROUND Although AF classifications are based on arrhythmia duration, the clinical course, and treatment response vary between patients within these groups. Electrophysiological mechanisms responsible for this variability are incompletely described.

METHODS Intracardiac contact mapping during incremental atrial pacing was used to characterize atrial conduction, activation dispersion, and electrogram morphology in 15 consecutive paroxysmal AF patients undergoing first-time pulmonary vein isolation. Outcome measures were vulnerability to AF induction at electrophysiology study and 2-year follow-up for arrhythmia recurrence.

RESULTS Conduction delay showed a bimodal distribution, occurring at either long (high right atrium pacing: 326 ± 13 ms; coronary sinus pacing: 319 ± 16 ms) or short (high right atrium pacing: 275 ± 11 ms; coronary sinus pacing: 271 ± 11 ms) extrastimulus coupling intervals. Arrhythmia recurrence was found only in patients with conduction delay at long extrastimulus coupling intervals, and patients with inducible AF were characterized by increased activation dispersion (activation dispersion time: 168 ± 29 ms vs. 136 ± 11 ms). Electrogram voltage and duration varied throughout the left atrium, between patients, and with pacing site but were not correlated with AF vulnerability or arrhythmia recurrence.

CONCLUSIONS Within the single clinical entity of paroxysmal AF, incremental atrial pacing identified a spectrum of activation patterns correlating with AF vulnerability and arrhythmia recurrence. In contrast, electrogram morphology (characterized by electrogram voltage and duration) was highly variable and not associated with AF vulnerability or recurrence. An improved understanding of the electrical phenotype in AF could lead to improved mechanistic classifications. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Atrial fibrillation (AF) classifications that are used to recommend treatment decisions are based on AF episode duration (1); however, a number of observations suggest that within classification categories, AF is a structurally and electrically diverse arrhythmia. First, ablation shows variable success between apparently similar patients when controlling for comorbidities and left atrial

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ABBREVIATIONS AND ACRONYMS

ADT = activation dispersion time

AF = atrial fibrillation

CS = coronary sinus

ΔED = rate dependence of electrogram duration

ED = electrogram duration

ERP = effective refractory period

ΔEV = rate dependence of electrogram voltage

EV = electrogram voltage

HRA = high right atrium

LA = left atrial

PAF = paroxysmal AF

S1S2block = the shortest S1S2 coupling interval that conducts from pacing site to left atrium

S1S2delay = the shortest S1S2 coupling interval conducting without decrement to the left atrium

(LA) dimensions. Second, some patients require multiple ablation procedures to achieve freedom from AF despite durable pulmonary vein isolation, whereas others require only a single procedure. Finally, the natural history of AF varies, with differing rates of progression to persistent AF seen. In line with these observations, reduced conduction velocity and shortened refractoriness have been associated with increasing severity, duration or recurrence of AF in some (2), but not all (3,4), studies.

Recently, structural (5) and voltage-defined (6) targets for intervention beyond pulmonary vein isolation have been proposed. Although low voltage is correlated with the presence of magnetic resonance imaging indices of atrial fibrosis (7), preservation of normal bipolar voltage does not imply absence of fibrosis (8). Therefore, bipolar voltage measured only during sinus rhythm or fixed coupling interval pacing may fail to detect atrial structural change. Furthermore, whether LA conduction abnormalities or morphological electrogram changes occur in apparently healthy atria (with normal bipolar voltage) is unknown.

We hypothesized that direction- and coupling interval-dependent changes in electrogram morphology and timing in patients with apparently healthy atria may differentiate between truly normal atria and those with underlying substrate change. In this study, incremental atrial pacing was used to measure electrogram voltage (EV), duration, conduction, and activation dispersion in a group of uniformly classified patients with paroxysmal AF (PAF) and otherwise normal atria.

METHODS

PATIENT SELECTION AND CLINICAL PROCEDURES. Ethical approval was granted by the National Research Ethics Service (10/H0802/77), and all participants gave written informed consent for study inclusion. The research conformed to the principles described in the Declaration of Helsinki. Patients with ischemic heart disease, cardiac surgery, or structural heart disease were excluded. Antiarrhythmic drugs, including calcium channel blockers, were stopped at least 5 half-lives before ablation. Amiodarone was stopped at least 6 weeks before ablation. All clinical procedures were performed under general anesthesia. Following femoral access and trans-septal puncture, 2 8.5-F SR0 long sheaths and a PentaRay mapping catheter (Biosense Webster, Diamond Bar, California, 4-4-4 mm electrode spacing) were advanced into the left atrium. Decapolar (St Jude Medical, St. Paul, Minnesota) and pentapolar (Bard Electrophysiology, Natick, Massachusetts) catheters were positioned in the coronary sinus (CS) and high right atrium (HRA), respectively.

PACING PROTOCOL. The pacing protocol was delivered using a custom-built, institutionally approved stimulator (Online Figures 1 and 2). The protocol was designed to allow LA response to a full range of extrastimulus coupling intervals (down to atrial effective refractory period [ERP]) to be recorded at more than 100 sites per chamber. As such, the drive train was reduced to 2 beats (470 ms) followed by a single premature extrastimulus. The S1S2 coupling interval was reduced continuously without operator interference in 2% steps from 350 ms to 200 ms or loss of capture (e.g., 470-470-350, 470-470-343) (**Figure 1A**). All pacing stimuli were delivered at a voltage of at least twice threshold, with a pulse width of 2 ms. The PentaRay catheter was sequentially maneuvered to multiple sites in the body of the left atrium, and bipolar electrograms were recorded throughout in response to complete S1S1S2 pacing trains delivered from the HRA and mid-CS.

SIGNAL PROCESSING. Electrograms were digitized using LabSystem Pro-EP (Bard Electrophysiology) at 16-bit/4 kHz. Signal processing was performed offline (MATLAB 8.2, MathWorks, Natick, Massachusetts). Pacing timing was determined from the paced channel (HRA or CS). The first pacing cycle was used to determine the noise threshold and discarded from subsequent analysis. A2 electrograms were rejected from analysis if the signal was far-field, there was fusion with an atrial ectopic beat, or the 2 preceding S1 beats failed to capture the left atrium. A band-pass filter (30 to 500 Hz) was applied to bipolar recordings, and the noise threshold defined as signal mean $\pm$ 3 SD of the 100 ms preceding the S2 component of the first cycle.

ELECTROGRAM ANALYSIS. Electrogram analysis was performed to quantify electrogram morphology, conduction response, activation dispersion, and atrial refractoriness. Criteria used are summarized in **Table 1**.

Electrogram morphology. Electrogram peak-to-peak bipolar voltage (EV) and duration (ED) were determined from the longest S2 pacing cycle length analyzed at each site. The rate dependence of electrogram amplitude was quantified by calculating the gradient of the best-fit line through S1S2 versus