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# Paroxysmal Lone Atrial Fibrillation Is Associated With an Abnormal Atrial Substrate

## Characterizing the "Second Factor"

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**Objectives** The purpose of this study was to determine whether patients with paroxysmal "lone" atrial fibrillation (AF) have an abnormal atrial substrate.

**Background** While "AF begets AF," prompt termination to prevent electrical remodeling does not prevent disease progression.

**Methods** Twenty-five patients with paroxysmal lone AF, without arrhythmia in the week prior, and 25 reference patients with left-sided accessory pathways were studied. Multipolar catheters placed at the lateral right atrium (RA), crista terminalis, coronary sinus, septal RA, and sequentially within the left atrium (LA) determined the effective refractory period (ERP) at 10 sites, conduction time along linear catheters, and conduction characteristics at the crista terminalis. Bi-atrial electroanatomic maps were created to determine regional differences in conduction velocity and voltage.

**Results** Patients with AF demonstrated the following compared with reference patients: larger atrial volumes (RA: 94 ± 18 ml vs. 69 ± 9 ml, $p = 0.003$; LA: 99 ± 19 ml vs. 77 ± 17 ml, $p = 0.006$); longer ERP (at 600 ms: 255 ± 25 ms vs. 222 ± 16 ms, $p < 0.001$; at 450 ms: 234 ± 20 ms vs. 212 ± 14 ms, $p = 0.004$); longer conduction time along linear catheters (57 ± 18 ms vs. 47 ± 10 ms, $p = 0.01$); longer bi-atrial activation time (128 ± 17 ms vs. 89 ± 10 ms, $p < 0.001$); slower conduction velocity (RA: 1.3 ± 0.3 mm/ms vs. 2.1 ± 0.5 mm/ms; LA: 1.2 ± 0.2 mm/ms vs. 2.2 ± 0.4 mm/ms, $p < 0.001$); greater proportion of fractionated electrograms (27 ± 8% vs. 8 ± 5%, $p < 0.001$); longer corrected sinus node recovery time (265 ± 57 ms vs. 185 ± 60 ms, $p = 0.002$); and lower voltage (RA: 1.7 ± 0.4 mV vs. 2.9 ± 0.4 mV; LA: 1.7 ± 0.7 mV vs. 3.3 ± 0.7 mV, $p < 0.001$).

**Conclusions** Patients with paroxysmal lone AF, remote from arrhythmia, demonstrate bi-atrial abnormalities characterized by structural change, conduction abnormalities, and sinus node dysfunction. These factors are likely contributors to the "second factor" that predisposes to the development and progression of AF. (J Am Coll Cardiol 2009;53:1182–91) © 2009 by the American College of Cardiology Foundation

Atrial fibrillation (AF) arises as a result of a complex interaction of triggers, perpetuators, and substrate (1). Experimental studies of AF have demonstrated shortening of the effective refractory period (ERP) and slowing of conduction as a result of AF and have suggested that these factors combine to promote continuing AF, giving rise to the concept that "AF begets AF" (2–6). Clinical studies have shown reversal of electrical remodeling over time after termi-

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nation of arrhythmia (7,8). However, strategies of prompt termination of AF to avoid this cycle of adverse remodeling have failed to show benefit (9). In fact, the natural history of paroxysmal AF is one of increasing frequency and duration of episodes (10). These observations have led to the search for a "second factor" integral to the development and progression of AF (11).

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We hypothesized that patients with paroxysmal "lone" AF have an abnormal atrial substrate that determines disease progression. In order to evaluate the substrate predisposing to AF, free of the electrical remodeling effects of the arrhythmia itself, we evaluated the electrophysiological and electroanatomic characteristics of atria in patients with paroxysmal "lone" AF, remote in time from arrhythmia.

## Methods

**Study population.** This study comprised 25 patients undergoing first-time ablation for paroxysmal AF and a reference group of 25 patients with structurally normal hearts undergoing radiofrequency ablation for atrioventricular re-entry tachycardia with left-sided accessory pathways and no history of AF. A total of 215 consecutive highly symptomatic patients undergoing AF ablation procedures were screened to obtain the 25 fulfilling the study criteria. Patients for the study group were excluded if they had AF during the week before ablation (established by continuous monitoring) or any of the criteria that would prohibit the diagnosis of "lone" AF, previously defined as the absence of structural heart disease or stroke based on history, physical examination, chest X-ray, routine blood chemistry, and transthoracic as well as transesophageal echocardiography (10,12,13). Coronary artery disease was excluded by clinical, electrocardiogram (ECG), or stress test criteria. Pulmonary disease, hypertension, hyperthyroidism, and diabetes were eliminated by appropriate tests. Paroxysmal AF was defined according to the expert consensus statement as recurrent AF that terminates spontaneously within 7 days (14).

All antiarrhythmic medication was ceased ≥5 half-lives before the study. No patient had received amiodarone or digoxin. All patients provided written informed consent to the study protocol, which was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

**Electrophysiological study and ablation.** Electrophysiological study was performed in the post-absorptive state with sedation utilizing midazolam and fentanyl. In patients with AF, the study protocol was performed before ablation, while in the reference group this was done after accessory pathway ablation. The left atrium (LA) was accessed using a single transseptal puncture after which repeated bolus unfractionated heparin was utilized to maintain the activated clotting time between 300 to 350 s.

**Abbreviations and Acronyms**

AF = atrial fibrillation
CI = confidence interval
CSNRT = corrected sinus node recovery time
ERP = effective refractory period
LA = left atrium/atrial
OR = odds ratio
RA = right atrium/atrial
SACT = sinoatrial conduction time

After the study protocol, patients with AF underwent circumferential pulmonary vein ablation with an end point of isolation confirmed by circumferential mapping (Lasso, Biosense-Webster, Diamond Bar, California) with either elimination or dissociation of pulmonary venous potentials. Ablation of the pulmonary veins was performed using a delivered power of 30 W with irrigation rates of 30 ml/min (Thermocool, Biosense-Webster). Additional substrate modification was performed in patients with an episode of AF ≥48 h or with an LA size ≥57 mm (longest diameter). This took the form of linear ablation along the LA roof with an end point of conduction block demonstrated by linear double potentials and an activation detour during pacing of the LA appendage. Cavo-tricuspid isthmus ablation with an end point of bidirectional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. Linear ablation was performed with a delivered power of 30 to 35 W with irrigation rates of 30 to 60 ml/min.

**Study protocol.** ELECTROPHYSIOLOGY STUDY. The following catheters were positioned for the study protocol: 1) a 10-pole catheter (2-5-2 mm interelectrode spacing, Daig Electrophysiology, Minnetonka, Minnesota) within the coronary sinus with the proximal bipole at the coronary sinus ostium as determined in the best septal left anterior oblique position; 2) a 20-pole "crista" catheter (1-3-1 mm interelectrode spacing, Biosense-Webster) placed along the crista terminalis with the distal tip superiorly such that the second bipole lay at the junction of the superior vena cava and right atrium (RA), stabilized by a long sheath (CSTA, Daig Electrophysiology) to ensure close apposition to this structure; 3) a 20-pole catheter (2-5-2 mm interelectrode spacing, Daig Electrophysiology) placed along the lateral RA; and 4) a roving 10-pole catheter (2-5-2 mm interelectrode spacing, Biosense-Webster) positioned within the LA via transseptal puncture. This catheter was stabilized with the use of a long sheath (Preface, Biosense-Webster or SL0, Daig Electrophysiology) and sequentially positioned as follows at the: 1) LA roof; 2) inferior LA; 3) midposterior LA; 4) LA appendage; and 5) high RA septum, as previously described (15). Electrophysiological evaluation was performed as detailed in the following text.

EFFECTIVE REFRACTORINESS. Atrial ERP was evaluated at twice diastolic threshold at cycle lengths of 600 and 450 ms using an 8-beat drive followed by an extrastimulus, starting with a coupling interval of 150 ms increasing in 10-ms increments. ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site the