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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

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ERP was measured 3 times at each cycle length and averaged. If ERP varied by >10 ms, an additional 2 measurements were made and the total number averaged. ERP was measured from the following sites: 1) distal coronary sinus; 2) proximal coronary sinus; 3) low-lateral RA; 4) high-lateral RA; 5) high-septal RA; 6) LA appendage; 7) midposterior LA; 8) inferior LA; 9) junction of left superior pulmonary vein with LA roof; and 10) junction of right superior pulmonary vein with LA roof. Heterogeneity of ERP was determined by the coefficient of variation of ERP at each cycle length (SD/mean × 100%). AF induced by ERP testing lasting >5 min was considered sustained; when this occurred, no further data were acquired.

ATRIAL CONDUCTION. Atrial conduction time was assessed along linearly placed catheters by pacing the distal bipole (1,2) and determining the conduction time to a proximal bipole (9,10) at the LA roof, inferior LA, coronary sinus, and lateral RA. Conduction time at each site was averaged over 10 beats during stable capture at 600 and 450 ms cycle lengths. P-wave duration was determined as a marker of global conduction by the average of 10 beats on ECG lead II.

SITE-SPECIFIC CONDUCTION ABNORMALITIES AT THE CRISTA TERMINALIS. The number of bipoles on the crista terminalis catheter with discrete double potentials separated by an isoelectric interval or complex fractionated activity of ≥50 ms duration and the maximum electrogram duration were determined during sinus rhythm, constant pacing and for the shortest-coupled captured extra-stimulus from the proximal coronary sinus, low-lateral RA, inferior LA, and LA appendage.

SINUS NODE FUNCTION. Sinus node function was evaluated as follows: 1) baseline sinus cycle length was determined over 10 consecutive sinus cycles; 2) sinoatrial conduction time (SACT) was determined after an 8-beat pacing train using the formula (SACT = [return − basic cycle length]/2) 3 times and averaged; and 3) corrected sinus node recovery time (CSNRT) was determined after a 30-s drive train at cycle lengths of 600 and 450 ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times and averaged.

Electroanatomic mapping. Electroanatomic maps were created of both atria during sinus rhythm using the CARTO mapping system and a 3.5-mm tip catheter (Navistar, Biosense-Webster). The electroanatomic mapping system has been previously described in detail; the accuracy of the sensor position has been previously validated and is 0.8 mm and 5° (16). In brief, the system records the surface ECG and bipolar electrograms filtered at 30 to 400 Hz from the mapping and reference catheters. Endocardial contact during point acquisition was facilitated by electrogram stability, fluoroscopy, and the catheter icon on the CARTO system. Points were acquired in the auto-freeze mode if the stability criteria in space (≤6 mm) and local activation time (≤5 ms) were met. Mapping was performed with an equal distribution of points using a fill-threshold of 15 mm. Editing of points was performed offline. Local activation time was manually annotated to the peak of the largest amplitude deflection on bipolar electrograms; in the presence of double potentials, this was annotated at the largest potential. If the bipolar electrogram displayed equivalent maximum positive and negative deflections, the maximum negative deflection on the simultaneously acquired unipolar electrogram was used to annotate the local activation time. Points not conforming to the surface ECG P-wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded. Regional atrial bipolar voltage and conduction velocity were analyzed as previously described and are detailed in the following text (15,17–19).

VOLTAGE ANALYSIS. For the purposes of evaluating regional voltage differences, each atrium was segmented using previously validated offline software (20). The RA was segmented as the high- and low-lateral RA, high- and low-posterior RA, high- and low-septal RA, and anterior RA. The LA was segmented as posterior LA, anterior LA, septal LA, inferior LA, lateral LA, and LA roof. The voltage of points identified by region was then exported for analysis. Low voltage points were defined as point with a bipolar voltage ≤0.5 mV and electrically silent points (scar) as the absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV (the noise level of the system).

CONDUCTION VELOCITY ANALYSIS. Isochronal activation maps (5-ms intervals) of the atria were created and regional conduction velocity determined in the direction of the wave-front propagation (least isochronal crowding). An approximation of conduction velocity was determined by expressing the distance between 2 points as a function of the difference in local activation time. Mean conduction velocity for each region was determined by averaging the conduction velocity between 5 pairs of points, as previously described (15,17–19). For the purposes of evaluating regional conduction differences, each atrium was segmented as noted in the preceding text.

COMPLEX ELECTROGRAMS. The proportion of points demonstrating complex electrograms was determined using the following definitions: 1) fractionated signals: complex activity of ≥50 ms duration; and 2) double potentials: potentials separated by an isoelectric interval where the total electrogram duration was ≥50 ms.

Statistical analysis. Continuous variables are reported as mean ± SD or median and interquartile range as appropriate. Categorical variables are reported as number and percentage. Proportions were compared using the Fisher exact test. Comparisons between means were analyzed using paired or unpaired *t* tests as appropriate. Comparisons with adjustment for multiple sampling within patients were performed using a mixed linear model for continuous data or a logistic generalized estimating equation for categorical data. Statistical tests were performed using SPSS version 15

(SPSS Inc., Chicago, Illinois), and statistical significance was set at a value of $p < 0.05$.

Results

Baseline details. Baseline patient characteristics are summarized in Table 1. Groups were well matched for age, sex, left ventricular wall thickness, and function. However, patients with AF had significantly larger LA ($p < 0.001$). None of the patients with AF had atrial arrhythmias (>30 s) by continuous monitoring in the 7 days before the procedure.

Atrial refractoriness. For patients with AF, the mean ERP across all sites was greater than that of reference patients (at 600 ms: 255 ± 25 ms vs. 222 ± 16 ms, $p < 0.001$; at 450 ms: 234 ± 20 ms vs. 212 ± 14 ms, $p = 0.004$). Figure 1 demonstrates the ERP at the 10 sites tested after 600 and 450 ms drive trains in patients with AF versus reference patients, and indicates those areas where significant differences were seen. The differences in ERP between patients with AF and reference patients were not uniform across all sites ($p = 0.02$). At each site, patients with AF demonstrated either an increase or no significant change in ERP when compared with the reference group. The ERP was longer after a 600-ms drive train than after a 450-ms drive train for both patients with AF ($p < 0.001$) and reference patients ($p = 0.02$); that is, there was preservation of physiological rate-adaptation of ERP in both groups ($p = 0.1$). Heterogeneity of refractoriness, as measured by the coefficient of variation of ERP, did not differ between groups: at 600 ms 12 ± 5% versus 13 ± 3% ($p = 0.6$) and at 450 ms 13 ± 5% versus 13 ± 4% ($p = 1.0$).

Atrial conduction time. The conduction time along the catheters at the LA roof, inferior LA, coronary sinus, and lateral RA was significantly longer in patients with AF compared with that seen in the reference group (57 ± 18 ms vs. 47 ± 10 ms, $p = 0.01$). However, there was no significant interaction between patient group and site of conduction measurement ($p = 0.3$), suggesting a homogenous slowing of conduction in patients with AF.

The P-wave duration was significantly prolonged in patients with AF compared with that in reference patients (128 ± 8 ms vs. 95 ± 10 ms, $p < 0.001$).

Site-specific conduction abnormalities. Site-specific conduction abnormalities at the crista terminalis during sinus rhythm were more apparent in patients with AF than reference patients. During sinus rhythm, patients with AF had a greater number of bipoles demonstrating double potentials or fractionated signals on the crista terminalis catheter than reference patients (4.9 ± 1.8 vs. 0.7 ± 0.8, $p < 0.001$) of which the maximum electrogram duration was longer (84 ± 15 ms vs. 52 ± 11 ms, $p < 0.001$). These differences were more marked during pacing and with extrastimulus ($p < 0.001$), as illustrated in Figure 2, which describes the extent of conduction abnormalities depending on the rate and site of stimulation.

Sinus node function. Patients with AF had a longer baseline sinus cycle length (975 ± 131 ms vs. 762 ± 129 ms, $p < 0.001$), SACT (154 ± 58 ms vs. 83 ± 31 ms, $p < 0.001$), and CSNRT at 600 ms (265 ± 57 ms vs. 185 ± 60 ms, $p = 0.002$) but not 450 ms (261 ± 96 ms vs. 241 ± 76 ms, $p = 0.6$) compared with reference patients.

Electroanatomic mapping. A total of 193 ± 62 points per patient were analyzed in the LA and RA using electroanatomic mapping.

Structural and voltage abnormalities. Both RA and LA volumes by electroanatomic mapping were significantly greater in patients with AF compared with those seen in reference patients (RA: 94 ± 18 ml vs. 69 ± 9 ml, $p = 0.003$; LA: 99 ± 19 ml vs. 77 ± 17 ml, $p = 0.006$).

The mean bipolar voltage was reduced in patients with AF compared with that in reference patients (RA: 1.7 ± 0.4 mV vs. 2.9 ± 0.4 mV; LA: 1.7 ± 0.7 mV vs. 3.3 ± 0.7 mV, $p < 0.001$). The difference in mean log bipolar voltage between patients with AF and reference patients varied significantly by mixed linear model according to the region of measurement (RA: $p = 0.002$; LA: $p = 0.03$). Regional differences in bipolar voltage with significant differences indicated are illustrated in Figure 3. Additionally, points in patients with AF at the high-lateral RA, posterior LA, and the LA roof were more likely to be low voltage (≤0.5 mV) (odds ratio [OR]: 2.9, 95% confidence interval [CI]: 1.4 to 6.3; OR: 1.7, 95% CI: 1.1 to 2.6; and OR: 3.3, 95% CI: 1.8 to 6.3, respectively). No significant areas of electrical scar (≤0.05 mV) were observed in this cohort of patients. Representative examples of electroanatomic maps in representative patients are shown in Figure 4.

Abnormalities in conduction velocity. Patients with AF had a significantly slower mean conduction velocity during sinus rhythm compared with reference patients (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, $p < 0.001$). Regional differences in conduction velocity with significant differences indicated are illustrated in Figure 5. The total atrial activation time was significantly prolonged in patients with AF compared with that in reference patients (128 ± 17 ms vs. 89 ± 10 ms, $p < 0.001$).

Complex electrograms. Patients with AF demonstrated a significantly greater number of points with double potentials or fractionated signals than reference patients (27 ± 8% vs. 8 ± 5%, $p < 0.001$). Patients with AF were more likely to have a point with a double potential or fractionated signal in

Table 1 Baseline Characteristics

	AF (n = 25)	Reference (n = 25)	p Value
Age (yrs)	53 ± 8	49 ± 9	0.2
Male sex (%)	80	60	0.2
Median AF history (months)	60	0	N/A
Longest AF duration (days)	3.0 ± 2.2	0	N/A
Left atrial parasternal size (mm)	41 ± 7	34 ± 4	<0.001
Interventricular septum (mm)	11 ± 2	11 ± 1	0.6
Left ventricular ejection fraction (%)	55 ± 9	58 ± 7	0.7

AF = atrial fibrillation.

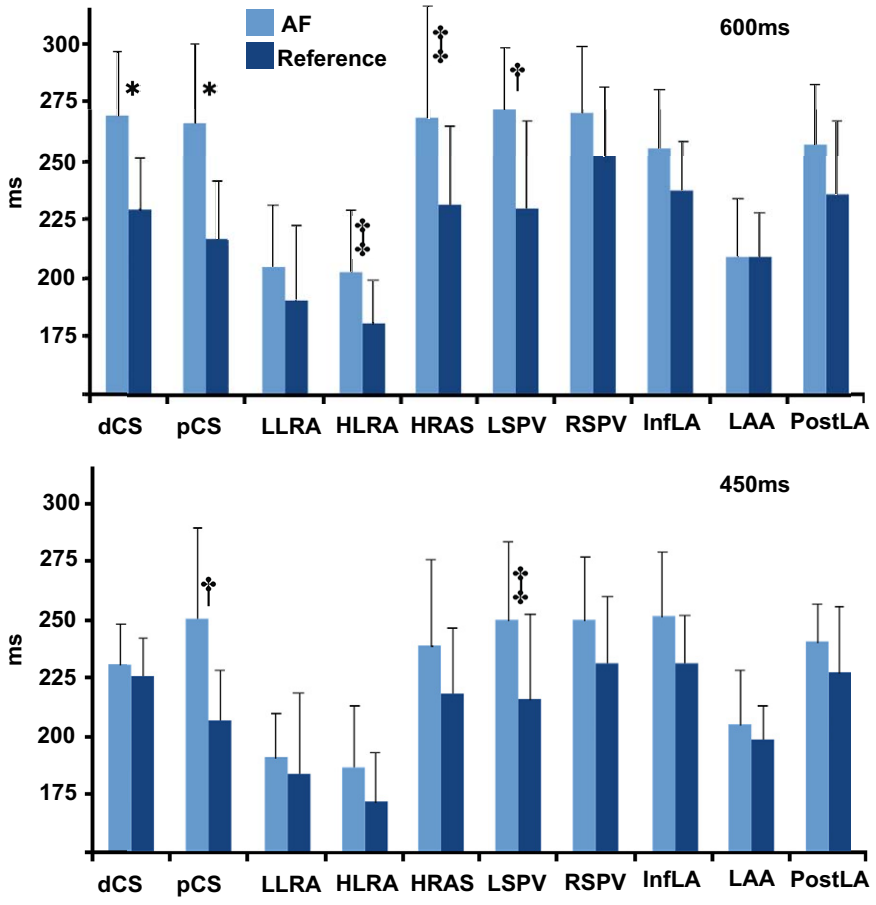

Figure 1 Regional Effective Refractoriness

Mean (±SD) effective refractory period at the 10 sites tested after a 600-ms drive train **(top)** and a 450-ms drive train **(bottom)** in patients with atrial fibrillation (AF) and reference patients. All values for 600 ms are longer than the same patient group and site value for 450 ms. The difference in mean effective refractory period between patients with AF and reference patients varied significantly according to the region of measurement ($p = 0.02$ for group by region interaction). *$p < 0.001$; †$p = 0.01$; ‡$p < 0.05$ for post-hoc comparisons (unadjusted). dCS = distal coronary sinus; HLRA = high lateral right atrium; HRAS = high right atrial septum; InfLA = inferior left atrium; LAA = left atrial appendage; LLRA = low lateral right atrium; LSPV = junction of left superior pulmonary vein with left atrium; pCS = proximal coronary sinus; PostLA = posterior left atrium; RSPV = junction of right superior pulmonary vein with left atrium.

any region than reference patients ($p < 0.02$). These points were distributed throughout both atria with a clustering at the high-posterior and -septal regions of the RA, and the LA septum and roof (Fig. 4).

Discussion

Major findings. This study utilized electrophysiological and electroanatomic mapping to demonstrate new information on the nature of abnormalities within the atria of patients with paroxysmal "lone" AF, remote from an arrhythmic event. The major findings are as follows:

1. Structural abnormalities characterized by atrial dilation and lower mean atrial voltage, suggesting the loss of atrial myocardium;
2. Conduction abnormalities, characterized by prolongation of conduction times, longer P-wave duration, slower conduction velocity, site-specific conduction delay, and an increase in the proportion of complex electrograms;
3. Impaired sinus node function; and
4. An increase in ERP consistent with prior studies evaluating clinical substrates for AF but in contrast to the remodeling attributed to AF itself.

Thus, the present study suggests that patients with paroxysmal lone AF have an abnormal atrial substrate. We posit that these abnormalities are essential contributors to the "second factor" that promotes progression of AF and why *sinus rhythm does not beget sinus rhythm* in patients with AF.

Rate-related electrical remodeling. The seminal observations by Wijffels et al. (3) that "AF begets AF" has as its central tenet the observation of reduction in atrial ERP by repeated induction of AF thereby allowing AF to sustain itself. Many experimental studies have confirmed this find-

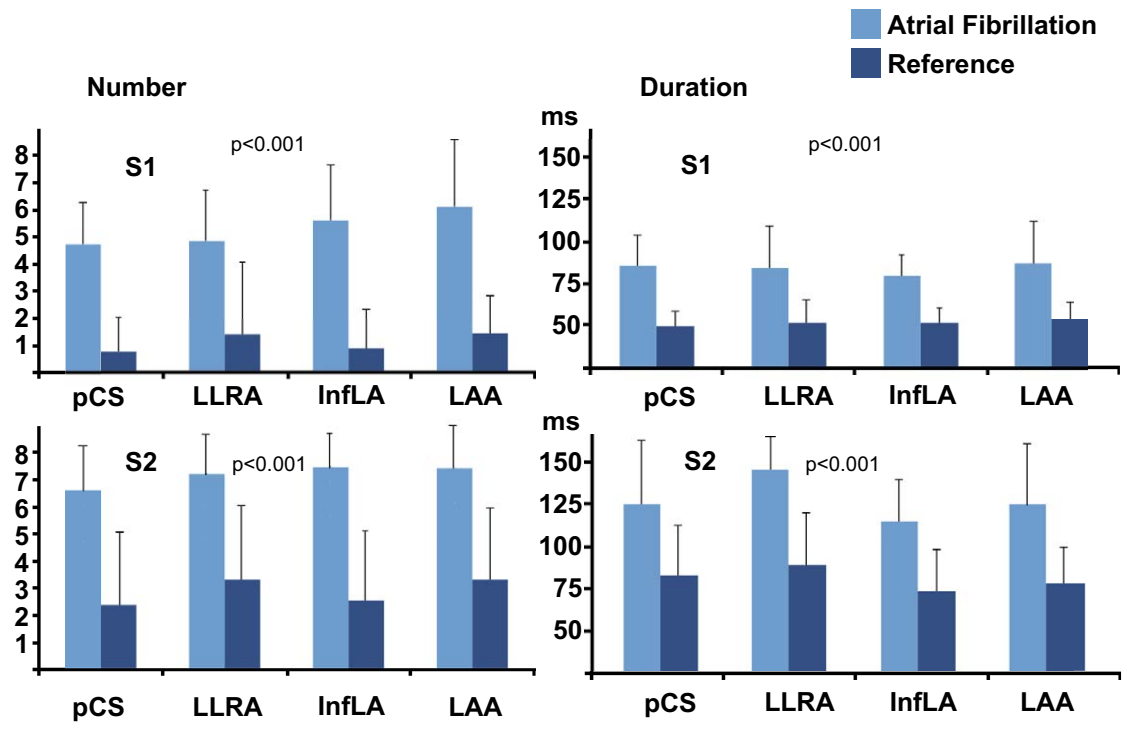

Figure 2 **Conduction Characteristics at the Crista Terminalis**

Mean (±SD) number **(left)** and maximum duration **(right)** of double potentials or fractionated signals along the crista terminalis during pacing at 600 ms (S1) and with the earliest captured extrastimulus (S2) from 4 sites in the atria in patients with atrial fibrillation and reference patients. Data at 450 ms pacing were comparable. Abbreviations as in Figure 1.

ing (2,4,6,21,22). While these initial studies fail to observe any conduction abnormalities, subsequent studies by Gaspo et al. (5) demonstrated that progressively longer episodes of AF also resulted in conduction slowing. Thus, the electrical remodeling of the atria in response to AF results in the perpetuation of arrhythmia by a shortening of the re-entrant "wavelength." In addition, several investigators have also observed remodeling of the sinus node that develops soon after the initiation of arrhythmia and reverses after restoration of sinus rhythm (13,22,23).

Interestingly, despite the early occurrence and reversible changes in electrical remodeling of the atria in response to rate, Ausma et al. (24) have observed that ultrastructural changes evolve over a much longer time frame and are not completely resolved as late as 4 months after return to sinus rhythm. These slow-to-resolve alterations have been characterized as an increase in myolysis and the fraction of extracellular matrix per myocyte, as well as changes in the expression of structural proteins.

Clinical studies have also observed similar effects of rate on the atria. Patients with recent AF have been shown to have shorter ERP than the control groups, as well as sinus node dysfunction and conduction delay (13,25). Yu et al. (8) demonstrated shorter ERP with impaired rate adaptation and depressed conduction after cardioversion for long-standing AF, with the ERP gradually increasing after 4 days of sinus rhythm. Kojodjojo et al. (26) studied patients with paroxysmal and persistent AF at their ablation procedure and demonstrated a reduction in ERP at 3 sites and conduction slowing compared with that seen in patients with no AF. In this study, patients with persistent AF had just 10 min of sinus rhythm before study, and those with paroxysmal AF had a mean AF burden of 3.2 ± 3.7 h in the preceding 72 h. Recent studies in patients with AF undergoing ablation have demonstrated the presence of areas of low voltage and scar (27,28), and have implicated this substrate as a marker of a worse outcome after an ablation procedure (29). However, with the known experimental evidence of rate-related remodeling, it is unclear if the abnormalities observed in these patients with AF form the underlying substrate for arrhythmia or whether they are indeed a consequence of the arrhythmia itself.

Progression of AF. Garratt et al. (11) evaluated the effect of repeated episodes of AF on atrial electrical remodeling. While marked remodeling was observed with 5 days of AF, 2 days of sinus rhythm was adequate to reverse all abnormalities. Despite repetitive episodes of AF, there were no additive changes observed in atrial electrical remodeling. Fynn et al. (9) evaluated the strategy of repeated cardioversion of AF in the clinical setting. Early and repeated

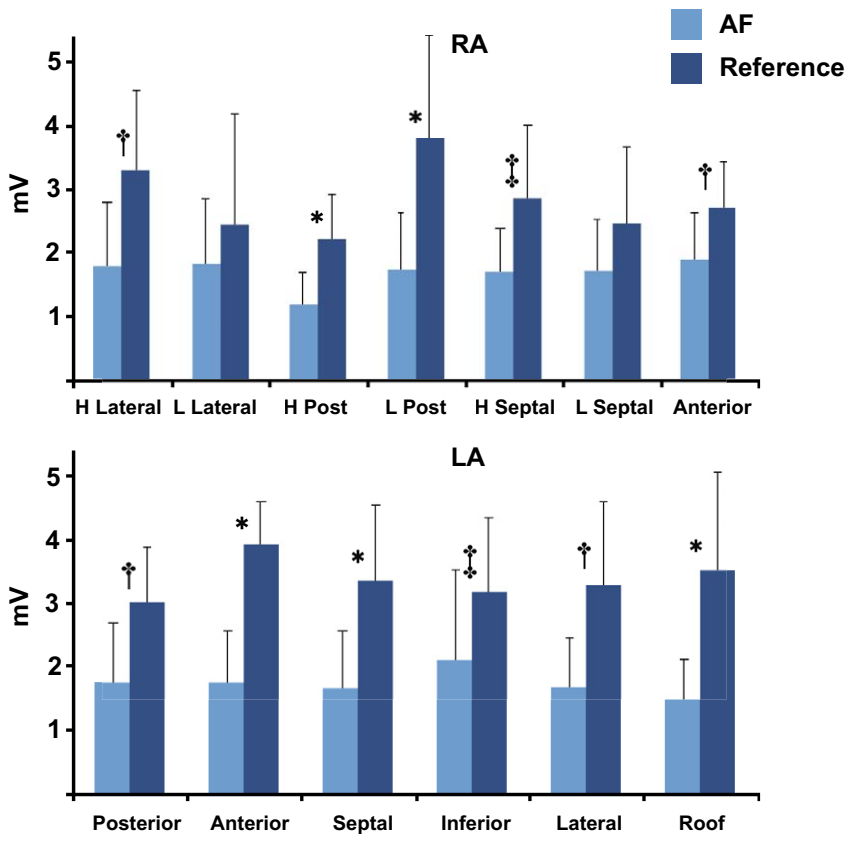

Figure 3 Regional Bipolar Voltage

Mean (±SD) bipolar voltage of the 7 right atrium (RA) and 6 left atrium (LA) regions from the electroanatomic map. The difference in mean log bipolar voltage between patients with atrial fibrillation (AF) and reference patients varied significantly by mixed linear model according to the region of measurement (RA: $p = 0.002$ for group by region interaction; LA: $p = 0.03$). *$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$ for post-hoc comparisons (unadjusted). H = high; L = low; Post = posterior.

cardioversion was performed to maintain sinus rhythm but failed to prevent the progression to more AF. Indeed, their findings suggest that sinus rhythm does not beget sinus rhythm in patients with a history of AF.

These findings have led the laboratory/group of Allessie (11) to propose the existence of a "second factor" for the initial substrate and subsequent progression of AF. To identify this factor, we studied patients with paroxysmal lone AF who were remote from an episode of AF (thereby removing the effects of acute rate-related remodeling). When studied distant from an arrhythmic event, patients with lone AF demonstrated an increase in atrial refractoriness, widespread and site-specific conduction abnormalities, and evidence of sinus node remodeling, which were associated with structural changes.

We posit that these changes in structure and conduction seen in lone paroxysmal AF, remote from arrhythmia, represent essential contributors to the "second factor," which has an important role in the development and progression of AF.

Substrate predisposing to the development of AF. Although the abnormalities that have been observed to result from AF itself have been proposed as the mechanisms by which AF begets AF, it is not likely that rate-related remodeling forms the substrate predisposing to the development of AF in the first place. This has led several investigators to evaluate the atrial abnormalities in conditions predisposed to the development of AF.

Li et al. (30) developed a canine model of congestive heart failure to evaluate effects on atrial remodeling and demonstrated "atrial remodeling of a different sort" from that seen due to AF alone. A significant increase in ERP at short cycle lengths associated with an increase in the heterogeneity of conduction and marked interstitial fibrosis was seen. Despite the increase in ERP, these abnormalities resulted in a significant increase in the duration of AF. Verheule et al. (31) observed a propensity for AF despite an increase in ERP in a canine model of mitral regurgitation, again due to abnormalities in conduction and profound structural remodeling.

Clinical studies of the atrial substrate in patients known to be predisposed to AF but without antecedent arrhythmia have demonstrated similar observations. Morton et al. (32) studied the RA substrate in patients with atrial septal defects and observed prolonged ERP and delayed conduction across the crista terminalis compared with that seen in

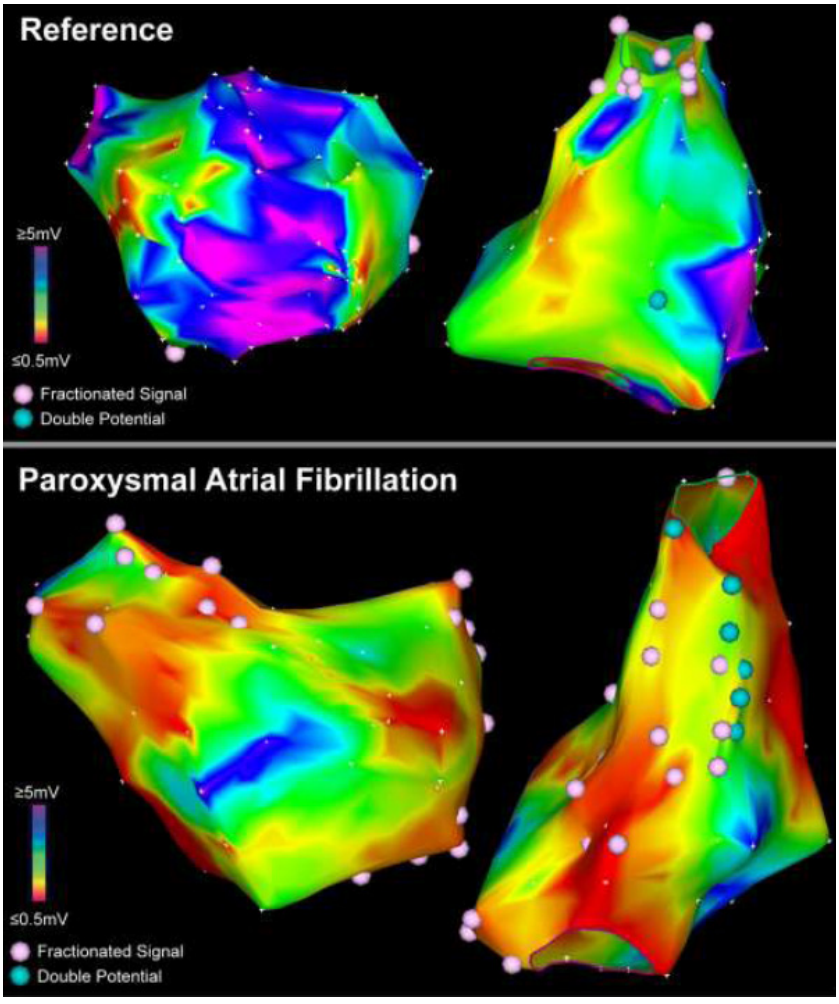

Figure 4 **Example Electroanatomic Bipolar Voltage Maps**

Representative CARTO maps of a patient with atrial fibrillation **(bottom)** and a reference patient **(top)**. Both atria are oriented in the posterior-anterior projection and are of the same scale. The color scale is identical in both images with **red** representing low voltage ≤0.5 mV and **purple** being voltage ≥5 mV. In addition to having greater regions of low voltage **(red)**, the patient with atrial fibrillation has more evidence of conduction abnormalities in the form of fractionated signals **(pink tags)** and double potentials **(blue tags)**.

reference patients. Sanders et al. (17,18) extended these findings by demonstrating significant electroanatomic remodeling with areas of low voltage and electrical scar in association with prolonged ERP with widespread and site-specific conduction abnormalities in patients with congestive heart failure and sinus node disease. Kistler et al. (19) demonstrated such changes in a progressive manner with increasing age. While these findings have been restricted to the RA, recently similar manifestations have been observed in the LA in patients with mitral stenosis (15).

In patients with AF, there is a paucity of clinical mapping that has been performed outside the context of recent arrhythmia. In order to minimize the confounding effects of electrical remodeling, we have undertaken meticulous screening to identify patients who were in sinus rhythm for a minimum of 7 days before their ablation procedure. Indeed, of 215 consecutive procedures performed on highly symptomatic patients presenting for ablation of AF, only 25 were suitable to be studied. Using such stringent enrollment criteria, the observations of the current study are remarkably consistent with the findings observed in the above conditions on the substrate predisposing to AF. Taken together, these studies provide compelling evidence that the predominant contributors to the substrate underlying AF are the structural and associated conduction abnormalities rather than changes in refractoriness.

Previous studies implicating abnormalities in "lone" AF. Although patients with lone AF are defined as a group with no structural heart disease, there is accumulating evidence of occult abnormalities. Frustaci et al. (33) found abnormal atrial histology including patchy fibrosis and inflammatory infiltrates in all of 12 patients with paroxysmal lone AF, and in none of 11 control patients. The fibrosis has

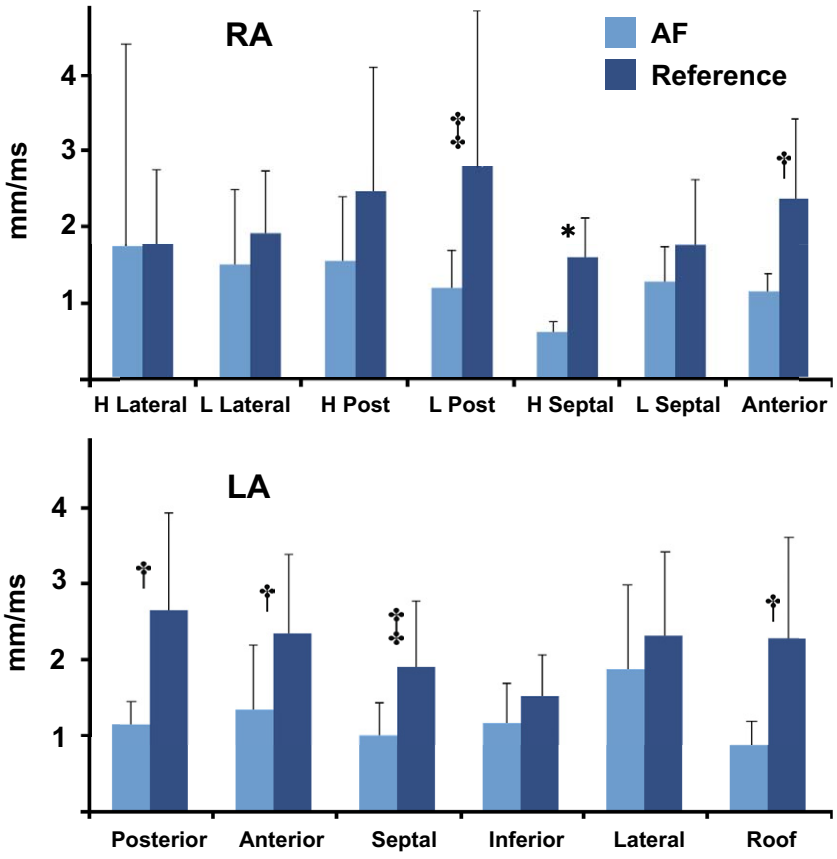

Figure 5 Regional Conduction Velocity

Mean (±SD) conduction velocity in the 7 RA and 6 LA regions from the electroanatomic map. *$p < 0.001$; †$p = 0.01$; ‡$p < 0.05$. Abbreviations as in Figure 3.

been characterized as an increased concentration of collagen type I in patients with lone AF compared with that seen in reference subjects, and this increase has been observed to be attenuated in those patients receiving angiotensin-converting enzyme inhibitors (34). There is further evidence that inflammation plays a role in AF, with the observation that C-reactive protein is elevated in patients with lone AF (35). Jaïs et al. (12) have demonstrated by transseptal hemodynamic evaluation that diastolic dysfunction is present in patients with lone AF. Finally, there is some evidence to suggest that patients with lone AF have microvascular dysfunction in the coronary circulation (36). Thus, it is feasible that patients without overt structural heart disease may have fibrosis, inflammation, structural change, and vascular dysfunction, all features that are consistent with and contribute to our observations of an abnormal substrate in lone AF.

Implications. The electrical remodeling seen in conjunction with ongoing arrhythmia and thought to perpetuate AF is known to normalize within days of sinus rhythm (11). However, strategies of repeated cardioversion have not been successful in retarding progression of disease (9). By studying patients remote in time from the arrhythmia itself, we have been able to show that the predominant underlying substrate in patients with AF is structural change is associated with conduction slowing, perhaps accounting for the progression of the AF disease. Future strategies to treat AF should, therefore, focus on atrial myocardial structure and conduction. Finally, while pulmonary vein isolation is currently considered to be highly successful for the majority of patients with paroxysmal AF, there is not yet definitive long-term data on outcome. This study showing an abnormal substrate in lone AF raises the possibility of progressive disease continuing despite early procedural success.

Study limitations. While the abnormalities observed in this study are proposed to constitute the substrate predisposing to AF, the development of clinical AF is complex and depends not only on substrate but also on other factors such as triggers and perpetuators that were not addressed by this study. Patients with persistent AF were not studied and may differ in substrate; however, many patients with persistent AF start with paroxysms initially. Finally, while we monitored patients for a week before the procedure to ensure our evaluation was remote from an episode of AF, we cannot exclude an effect of rate-related remodeling from previous episodes. However, prior studies have demon-

strated no additive effects of episodic AF and resolution of remodeling within days (11).

Conclusions

Patients with paroxysmal lone AF, remote from an arrhythmic episode, demonstrate structural abnormalities characterized by loss of myocardial voltage, conduction slowing, altered sinus node function, and prolonged atrial refractoriness. These abnormalities contribute to the "second factor" critical to the development and progression of AF.

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Key Words: atrial fibrillation ■ arrhythmia ■ electrophysiology ■ atrial remodeling ■ atrial substrate.