Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 52, No. 15, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.07.012

Repolarization and Activation Restitution Near Human Pulmonary Veins and Atrial Fibrillation Initiation

A Mechanism for the Initiation of Atrial Fibrillation by Premature Beats

Sanjiv M. Narayan, MD, FACC,* Dhruv Kazi, MD,* David E. Krummen, MD,* Wouter-Jan Rappel, PHD†

La Jolla and San Diego, California

Objectives The authors sought to study mechanisms to explain why single premature atrial complexes (PACs) from the pulmonary veins (PVs) may initiate human atrial fibrillation (AF).

Background Theoretically, single PACs may initiate AF if the rate response of action potential duration (APD) restitution has a slope >1. However, human left atrial APD restitution and its relationship to AF have not been studied. We hypothesized that an APD restitution slope >1 near PVs explains the initiation of clinical AF.

Methods We studied 27 patients with paroxysmal and persistent (n = 13) AF. We advanced monophasic action potential catheters transseptally to superior PVs. Restitution was plotted as APD of progressively early PACs against their diastolic interval (DI) from prior beats. Activation time restitution was measured using the time from the pacing artifact to each PAC.

Results Compared with paroxysmal AF, patients with persistent AF had shorter left atrial APD and effective refractory period ($p = 0.01$). In paroxysmal AF, maximum left atrial APD restitution slope was 1.5 ± 0.4; and 12 of 13 patients had slope >1 ($p < 0.001$). In persistent AF, PACs encountered prolonged activation for a wider range of beats than in paroxysmal AF ($p = 0.01$), which prolonged DI and flattened APD restitution (slope 0.7 ± 0.2; $p < 0.001$); no patient had APD restitution slope >1. A single PAC produced AF in 5 patients; in all, an APD restitution slope >1 caused extreme APD oscillations after the PAC, then AF.

Conclusions In patients with paroxysmal AF, maximum APD restitution slope >1 near the PVs enables single PACs to initiate AF. However, patients with persistent AF show marked dynamic activation delay near PVs that flattens APD restitution. Studies should determine how regional APD and conduction dynamics contribute to the substrates of persistent AF. (J Am Coll Cardiol 2008;52:1222–30) © 2008 by the American College of Cardiology Foundation

The mechanisms separating persistent from paroxysmal atrial fibrillation (AF) remain unclear. Paroxysmal AF typically requires premature atrial complexes (PACs) (1) or sustaining mechanisms (2) from pulmonary veins (PVs) and thoracic veins, yet persistent AF often initiates and sustains after isolating such veins (3,4). Two central questions are why PACs from PVs initiate paroxysmal AF, and why they may be less important in persistent AF. Elegant computational studies (5) recently showed that steep rate-related change (restitution) in action potential duration (APD) enable single PACs to initiate AF, yet this hypothesis has not been tested in humans nor compared between paroxysmal and persistent AF.

We hypothesized that APD restitution slope should be >1 near PVs in patients with AF. Restitution relates APD to the diastolic interval (DI) from the prior beat (6), and when slope >1 (steep), explains self-amplifying APD oscillations. An early beat shortens DI, yet shortens APD to a greater extent; this further lengthens DI/APD for the next beat, to cause APD alternans and wave break. In animal (7) and human (8) ventricles, this may cause fibrillation. However, there are no data linking this mechanism with AF. Although right atrial APD restitution slope is >1 in AF patients (9), this has not been linked with AF nor studied in left atrium (LA), where most triggers arise (10). We have reported APD alternans

From the *University of California and Veterans Affairs Medical Center, San Diego, California; and the †Department of Physics and Center for Theoretical Biology, University of California, San Diego, California. Supported by grants to Dr. Narayan from the National Institutes of Health (HL70529, HL83359) and the Doris Duke Charitable Foundation, and to Dr. Krummen by an American College of Cardiology–Merck Fellowship. Francis Marchlinksi, MD, served as Guest Editor for this article.

Manuscript received February 25, 2008; revised manuscript received July 7, 2008, accepted July 8, 2008.

in the right atrium, heralding the disorganization of typical atrial flutter to AF (11), yet it is unclear whether that mechanism explains AF initiated by PV-PACs.

To test our hypothesis, we studied APD restitution and activation delay for PACs near the LA PV ostia and high right atrium, where PACs may trigger AF, vis-à-vis AF initiation in 27 patients before AF ablation.

Methods

Patient recruitment. We studied 27 patients (age 63 ± 9 years) referred for AF ablation to the Veterans Affairs Medical Center, San Diego. The study was approved by the joint Veterans Affairs/University of California at San Diego Institutional Review Board, and all patients provided written informed consent. The LA thrombus was excluded by transesophageal echocardiography in patients with persistent AF.

Catheter placement. Electrophysiology study was performed in the fasted state, >5 half-lives after discontinuing antiarrhythmic medications (>4 weeks after discontinuing amiodarone) (Table 1). A decapolar catheter was placed in the coronary sinus. After transseptal puncture, LA geometry was digitally reconstructed using NavX (St. Jude Medical, Sylmar, California) referenced to patient-specific computed tomography (Fig. 1). A deflectable 7-F monophasic action potential (MAP) catheter (Boston Scientific, Sunnyvale, California) was advanced to record action potentials (APs) adjacent to the NavX-verified antrum of the left superior PVs (Fig. 1) or right superior PVs. The APs were recorded at the high right atrium just inferior to the superior vena cava in 14 patients. Three patients (n = 2 persistent) provided only right atrial data.

Table 1 Clinical Characteristics

Characteristic	Paroxysmal AF	Persistent AF	p Value
n (male)	14 (13)	13 (13)	0.81
Age, yrs	63 ± 8	62 ± 10	0.67
Duration of AF, months	69 ± 144	77 ± 69	0.87
Left atrial diameter, mm	40 ± 5	48 ± 5	0.001
Left ventricular ejection fraction, %	60 ± 8	53 ± 12	0.12
Hypertension	8 (57)	11 (85)	0.49
Coronary disease	4 (29)	2 (17)	0.92
Diabetes mellitus	5 (36)	4 (31)	0.99
Prior cardiac surgery or PCI	5 (36)	1 (8)	0.38
Medications			
ACEI/ARB	7 (50)	7 (54)	1.00
Statins	9 (64)	6 (46)	0.83
Beta-blockers	7 (50)	10 (77)	0.55
Class I agents	2 (14)	1 (8)	0.96
Amiodarone	1 (8)	2 (15)	0.94
Sotalol	3 (21)	0	0.37
Dofetilide	2 (14)	0	0.57

Data are presented as n (%) or mean ± SD unless otherwise indicated.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF = atrial fibrillation; PCI = percutaneous coronary intervention.

Abbreviations and Acronyms

AF = atrial fibrillation
AP = action potential
APD = action potential duration
AT = activation time
DI = diastolic interval
ERP = effective refractory period
FRP = functional refractory period
LA = left atrium/atrial
MAP = monophasic action potential
PAC = premature atrial complex
PV = pulmonary vein

Pacing protocol. The protocol was performed before ablation. Patients presenting in AF were electrically cardioverted to sinus rhythm; those who could not complete the protocol with 2 cardioversions were excluded. After ensuring stable MAP catheter positions, the protocol commenced after 18 ± 5 min. Pacing was applied at the proximal poles of the MAP catheter at twice diastolic threshold, and APs were recorded from distal poles (12). A drive train of 10 beats at cycle length 500 ms was followed by single PACs coupled at 450 ms, 400 ms, reduced in 20 ms steps to 300 ms, then in 10-ms steps to the effective refractory period (ERP).

The MAPs were filtered at 0.05 to 500 Hz and intracardiac signals between 30 and 500 Hz. Signals were digitized at 1 kHz to 16-bit resolution and exported from the recorder (Bard Pro, Billerica, Massachusetts) for analysis using custom PC software written by SMN in Labview (National Instruments, Austin, Texas). Recordings showing excessive baseline wander, artifact, or noise were excluded.

Measurement of PAC-related APD restitution. We measured APD using validated software (12) (Fig. 2). The AP onset was defined as the calculated maximal upstroke dV/dt. Phase II was defined after the AP peak, and phase IV (diastolic) voltage as the mean of voltages before and after the beat. An APD at 90% repolarization (APD_{90}) extends from AP onset to 90% voltage recovery from phase II. The DI extends from APD_{90} of the prior beat to the current AP onset (Fig. 2C). When an AP was contaminated, for example, a pacing artifact in the last drive beat (Figs. 3 to 6), we used the mean APD_{90} of the 2 prior beats. Early PACs have negative DI if ERP is shorter than APD_{90} (12).

We constructed standard APD restitution curves from (DI, APD_{90}) pairs. Maximum slope was determined from linear fits of 30-ms DI segments containing data (i.e., from 0 to 30 ms, 10 to 40 ms, and so on) without extrapolation (13,14).

Analysis of activation time (AT) restitution. We measured AT from the pacing stimulus to AP upstroke of each PAC. We used (DI, AT) pairs to plot standard restitution (14) as best-fit straight lines: 1) where AT lengthened (at short DI); and 2) at flat restitution. We report the longest DI where AT began to prolong (7).

Statistical analysis. Continuous data are represented as mean ± SD. The 2-tailed *t* test was used to compare continuous clinical variables. Paired clinical variables were compared using linear regression and the paired *t* test. The

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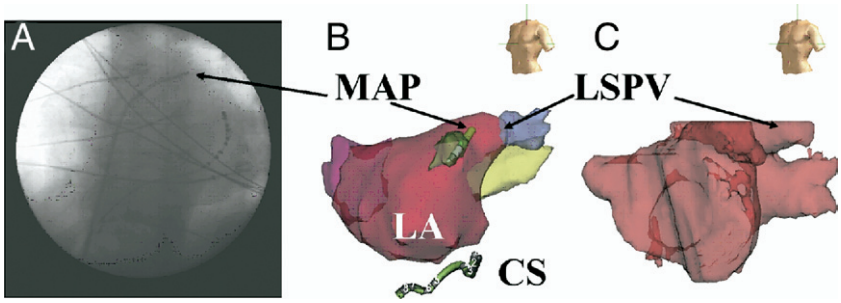

Figure 1 **LA MAP Recording Site in a 74-Year-Old Man With Persistent AF and LA Diameter 48 mm**

(A) Fluoroscopy (left anterior oblique 30°) showing the monophasic action potential (MAP) catheter within a transseptal sheath near the left superior pulmonary vein (LSPV), and the coronary sinus (CS) catheter. **(B)** Digital reconstruction of left atrial (LA) confirming the MAP catheter in the LSPV antrum (NavX, St. Jude Medical, Sylmar, California). **(C)** Segmented 64-slice computed tomogram imported into NavX for positional reference. AF = atrial fibrillation.

Mann-Whitney *U* test was used to compare repolarization and conduction parameters. The Fisher exact test was applied to contingency tables. An additional 4 patients recruited after phase I of the analysis did not appreciably alter the statistics, which are presented for the entire population. A p value <0.05 was considered statistically significant.

Results

Clinical characteristics are shown in Table 1. Patients with paroxysmal AF had smaller left atria than those with persistent AF.

LA APD dynamics in paroxysmal AF. Left atrial APD restitution had slope >1 in paroxysmal AF. Figure 3 shows LA APs near the right superior PV in a 61-year-old man with LA diameter 42 mm and paroxysmal AF for 2.5 years. For this PAC just outside ERP, AT is short and APD_{90} is markedly shortened. The APD restitution (for all PACs) has a maximal slope of 1.79.

For patients with paroxysmal AF, maximum LA APD restitution slope was 1.5 ± 0.4, and 12 of 13 had a maximum slope >1. Of these patients, the DI range for which the slope >1 was 27 ± 9 ms. Two patients presented in AF. After cardioversion, maximal LA APD restitution slopes were >1 (1.9 and 1.5), and the other parameters were similar to patients presenting in sinus rhythm.

Relevance of APD restitution slope >1 to AF initiation. A single PAC initiated AF in 5 patients with paroxysmal AF, all with maximum restitution slope >1. In each case, the PAC was followed by marked APD oscillations predicted by APD restitution, then AF (i.e., without rapid automatic firings). Figure 4A shows APs near the left superior PV in a 65-year-old man with LA diameter 38 mm and maximum APD restitution slope 1.2. The very early PAC was followed by a pause to the next beat, then a short-coupled beat, then AF. In Figure 4A, steep APD restitution predicted that this long-short-long sequence would cause extreme APD oscillations (221-139-224-158 ms for S1-S2-F1-F2), then AF (F1-F7) that continued to track APD restitution.

LA APD dynamics in persistent AF. Patients with persistent AF had shorter peri-PV baseline APD_{90} ($p < 0.001$) and shorter ERP ($p = 0.01$) than patients with paroxysmal AF (Table 2). The maximum APD_{90} restitution slope, however, was less steep than in patients with paroxysmal AF. Single PACs from the PVs did not induce AF in any patient with persistent AF.

Figure 5A shows APs near the left superior PV in an 82-year-old man with LA diameter 44 mm and AF for 5 years. This very early PAC (coupled at 180 ms, vs. APD_{90} approximately 230 ms) was captured because of marked AT delay (93 ms) that is evident after the pacing artifact (compare against the artifact from the blocked stimulus in the lower panel). This AT delay prolonged DI (18 ms) to truncate the left-most portions of APD restitution, giving maximum slope 0.52 (i.e., <1). Figure 5B shows APs near the right superior PV in a 62-year-old man with LA diameter 50 mm and AF diagnosed 5 years ago. Again, this early PAC (coupled at 200 ms, vs. APD_{90} approximately 250 ms) captures because of AT delay (106 ms) that prolonged DI. Maximal APD restitution slope is 0.45 (i.e., <1).

Such results were typical for patients with persistent AF (Table 2), in whom the maximal APD restitution slope was significantly lower (0.7 ± 0.2) than in paroxysmal AF ($p < 0.001$), and no patient had slope >1. Accordingly, APD_{90} range was compressed compared with patients with paroxysmal AF ($p = 0.01$) (Table 2). One persistent AF patient who presented in sinus rhythm had an APD restitution slope <1 (0.64), and similar APD indexes to patients presenting in AF (who were cardioverted).

Right atrial APD dynamics. Right atrial APD restitution showed maximum slopes >1 in patients with paroxysmal

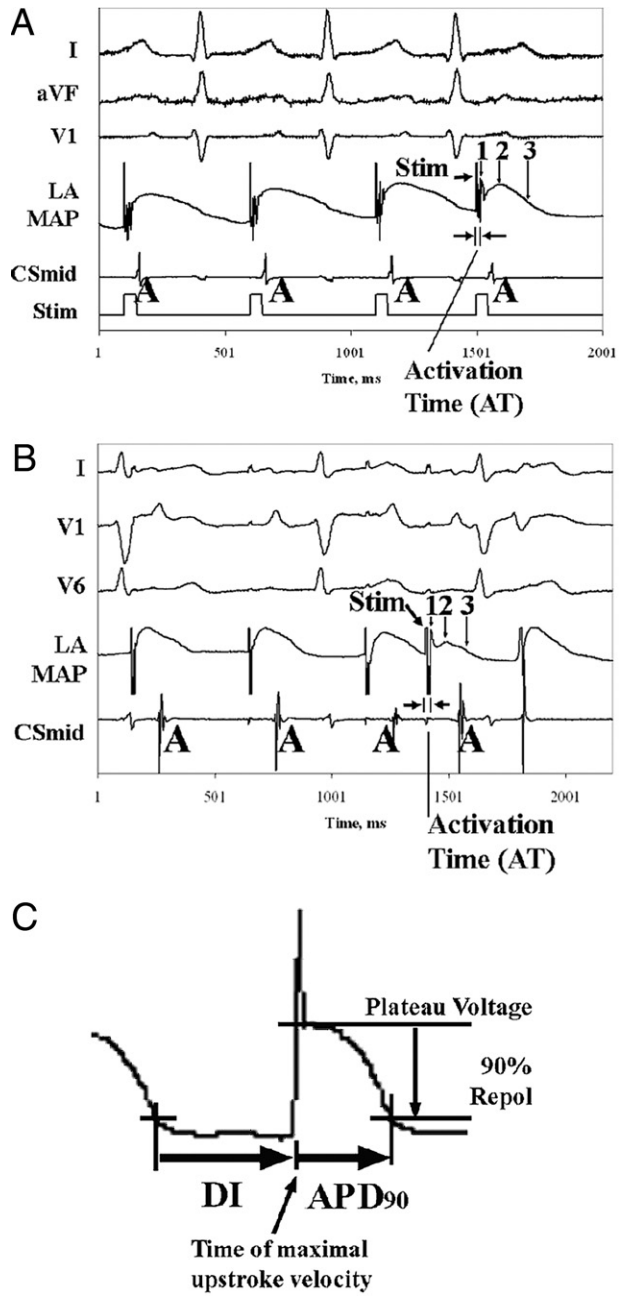

Figure 2 **LA Action Potentials During Constant Pacing (S1) and PACs (S2)**

Patients with **(A)** paroxysmal and **(B)** persistent AF. For each premature atrial complex (PAC), stimulus artifact (Stim) and phases 1, 2, and 3 of the AP are labeled. Activation time (AT) spans the time from the stimulus artifact to the computed dV/dt maximum of phase 0 (not labeled), and is 25 ms for **A** and 50 ms in **B**. Bipolar atrial electrograms are labeled **A** in the CS. **(C)** APD_{90} measurement, calculated as 90% repolarization from phase II voltage to the baseline. DI = diastolic interval; other abbreviations as in Figure 1.

and persistent AF (Table 2, Fig. 6), confirming a previous report (9).

For all patients, right atrial APD restitution slope was 1.4 ± 0.4 (Table 2) and 13 of 14 patients had a slope >1 (the exception had persistent AF). In persistent AF patients, the APD restitution slope was higher in right atrium than the LA (1.5 ± 0.3 vs. 0.7 ± 0.2; $p < 0.001$) (Table 2).

LA AT and APD restitution. Because dynamic conduction slowing may alter APD restitution (7), we measured AT restitution in both groups. Left atrial AT prolongation arose more easily (i.e., for later coupled PACs) in persistent than paroxysmal AF. This prolonged DI for early PACs and truncated the steepest portion of APD restitution.

Figure 7A shows LA AT restitution for a patient with paroxysmal AF. The AT for PACs prolongs only when DI <21 ms (i.e., very early beats). In contrast, LA AT for a patient with persistent AF prolongs for a wide PAC range (DI <98 ms) causing broad restitution (Fig. 7B) (7).

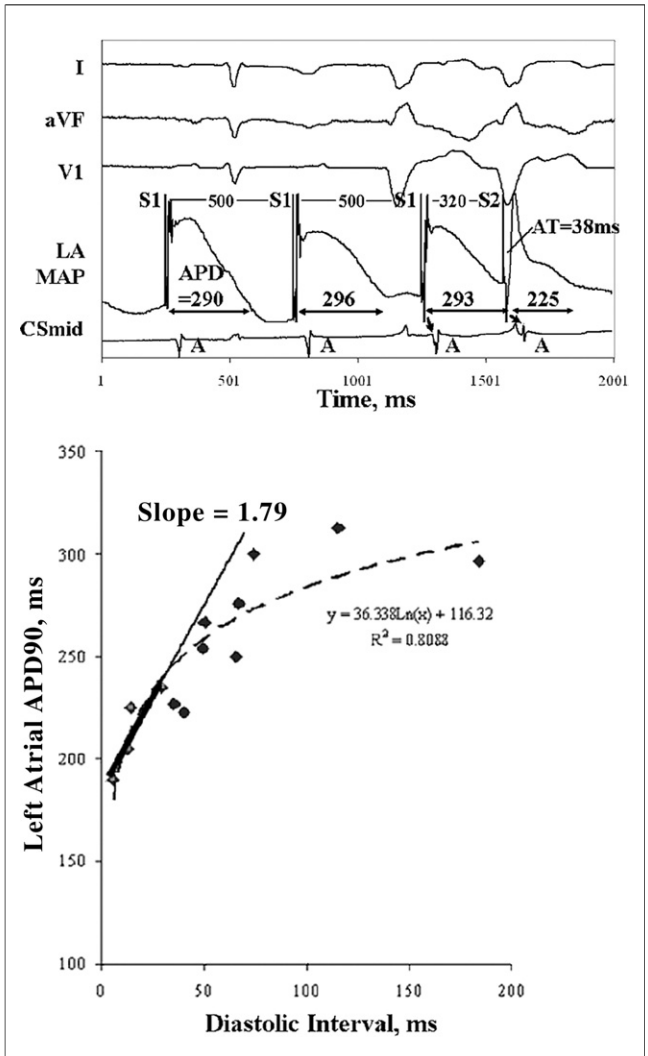

Figure 3 **Steep LA APD Restitution in Paroxysmal AF**

This PAC is delivered just outside the effective refractory period (500/320 ms) and results in DI 6 ms and APD restitution slope = 1.8 (same patient as Fig. 2A). The **thickened line** represents the DI range for which the slope was calculated. APD = action potential duration; other abbreviations as in Figure 2.

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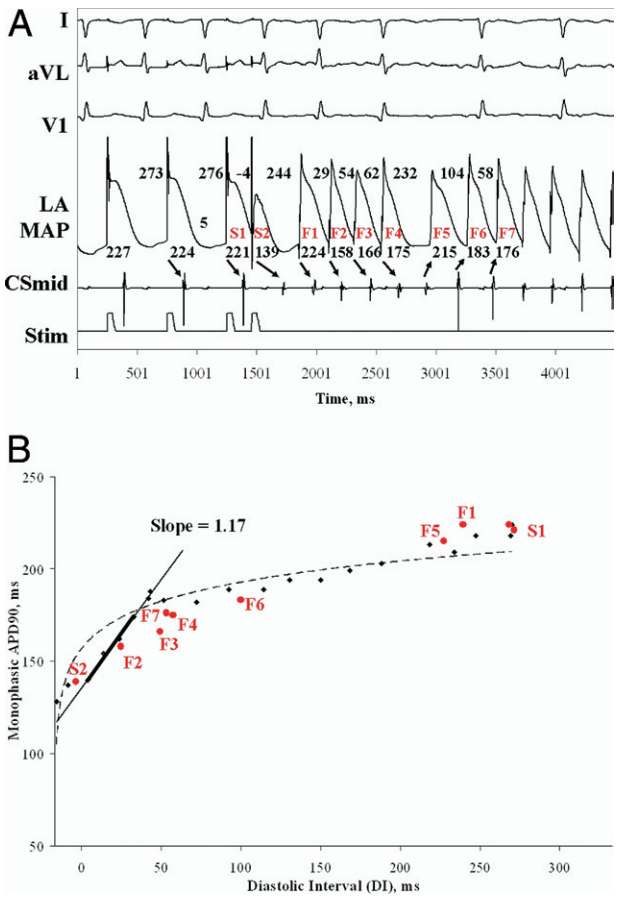

Figure 4 PAC Induces Paroxysmal AF in a Patient With Steep APD Restitution

(A) Very early PAC (DI −4 ms) followed by a pause, then AF. **(B)** Steep restitution may explain PAC-induced AF **(red)**. S1, S2, F1, and F2 show marked APD oscillations because of steep APD restitution (slope = 1.2; slope >3 by mono-exponential fit), then AF onset. The AF cycles continue to track restitution, although wavelets meander (altered activation sequence after F4). Abbreviations as in Figures 1 to 3.

Compared with paroxysmal AF, patients with persistent AF showed broader LA AT restitution ($p = 0.01$) (Table 3). In persistent AF, the functional refractory period (FRP)/APD_{90} ratio was >1 (1.12) because of delay for earliest PACs. Put another way, the earliest PAC was separated from the last drive beat (i.e., FRP) by APD_{90} + 28 ms (12% of 237 ms). In paroxysmal AF, the LA FRP/APD_{90} ratio was approximately 1 ($p < 0.01$ vs. persistent AF) (Table 2).

The clinically measurable parameter LA ERP/FRP was smaller in persistent than paroxysmal AF ($p < 0.05$) (Table 2).

Relationship of AT and APD indexes with demographic variables. For all patients, neither the minimum DI at which AT prolonged ($p = 0.17$) nor maximum APD restitution slope ($p = 0.10$) significantly related to the LA diameter.

Table 2 Bi-Atrial Repolarization Dynamics

Characteristic	Paroxysmal AF	Persistent AF	p Value
Left atrial, n	13	11	
APD_{90} (drive train), ms	295 ± 44	237 ± 35	<0.001
APD_{90} range, ms	104 ± 27	68 ± 35	0.01
ERP, ms	242 ± 34	204 ± 28	0.01
FRP, ms	285 ± 39	261 ± 25	0.06
ERP/FRP, %	85 ± 7	78 ± 8	<0.05
FRP/APD_{90}, %	97 ± 6	112 ± 14	<0.001
Maximum APD_{90} restitution slope	1.5 ± 0.4	0.7 ± 0.2	<0.001
Shortest diastolic interval, ms	5 ± 21	20 ± 21	0.10
Right atrial, n	6	8	
APD_{90} (drive train), ms	315 ± 36	271 ± 33	0.01
APD_{90} range, ms	124 ± 31	121 ± 27*	0.65
Effective refractory period, ms	252 ± 41	224 ± 37	0.24
Functional refractory period, ms	282 ± 54	264 ± 44	0.61
ERP/FRP, %	90 ± 9	85 ± 7†	0.25
FRP/APD_{90}, %	89 ± 12	97 ± 10‡	0.24
Maximum APD_{90} restitution slope	1.3 ± 0.4	1.5 ± 0.3§	0.52
Shortest diastolic interval, ms	−5 ± 16	2 ± 15‡	0.61

Compared with left atrium: *$p < 0.01$; †$p = 0.06$; ‡$p < 0.05$; §$p < 0.001$.
AF = atrial fibrillation; APD_{90} = action potential duration at 90% repolarization; ERP = effective refractory period; FRP = functional refractory period.

Discussion

This study shows that patients with paroxysmal AF exhibit APD restitution slope >1 near PVs. This enables single PACs to cause exaggerated APD oscillations that may lead to wave break and AF. Conversely, in patients with persistent AF, early PV-PACs experience a markedly prolonged AT that flattened APD restitution (slope <1). The initiation of persistent AF may thus reflect broad conduction restitution or mechanisms unrelated to APD oscillations. Notably, differences were more marked in the left than the right atrium, and may reflect progressive atrial electrical remodeling.

APD restitution as a potential mechanism for human AF. This is the first human study to link the restitution hypothesis (6,7,15) with AF. In this population, single PACs induced AF in one-fifth of patients, all of whom had an APD restitution slope >1 (i.e., paroxysmal AF) enabling marked APD oscillations. Furthermore, because extreme APD oscillations may enable a tachycardia to

Table 3 Atrial Conduction Dynamics

Conduction Parameter	Paroxysmal AF	Persistent AF	p Value
Left atrial			
Baseline AT (in drive cycle), ms	23 ± 11	20 ± 7	0.84
Maximal AT, ms	76 ± 35	91 ± 28	0.17
DI where prolongation starts, ms	11 ± 55	71 ± 30	0.01
Right atrial			
Baseline AT (in drive cycle), ms	14 ± 6	15 ± 7	0.70
Maximal AT, ms	39 ± 45	62 ± 29	0.12
DI where prolongation starts, ms	14 ± 28	18 ± 32	0.60

AF = atrial fibrillation; AT = activation time; DI = diastolic interval.

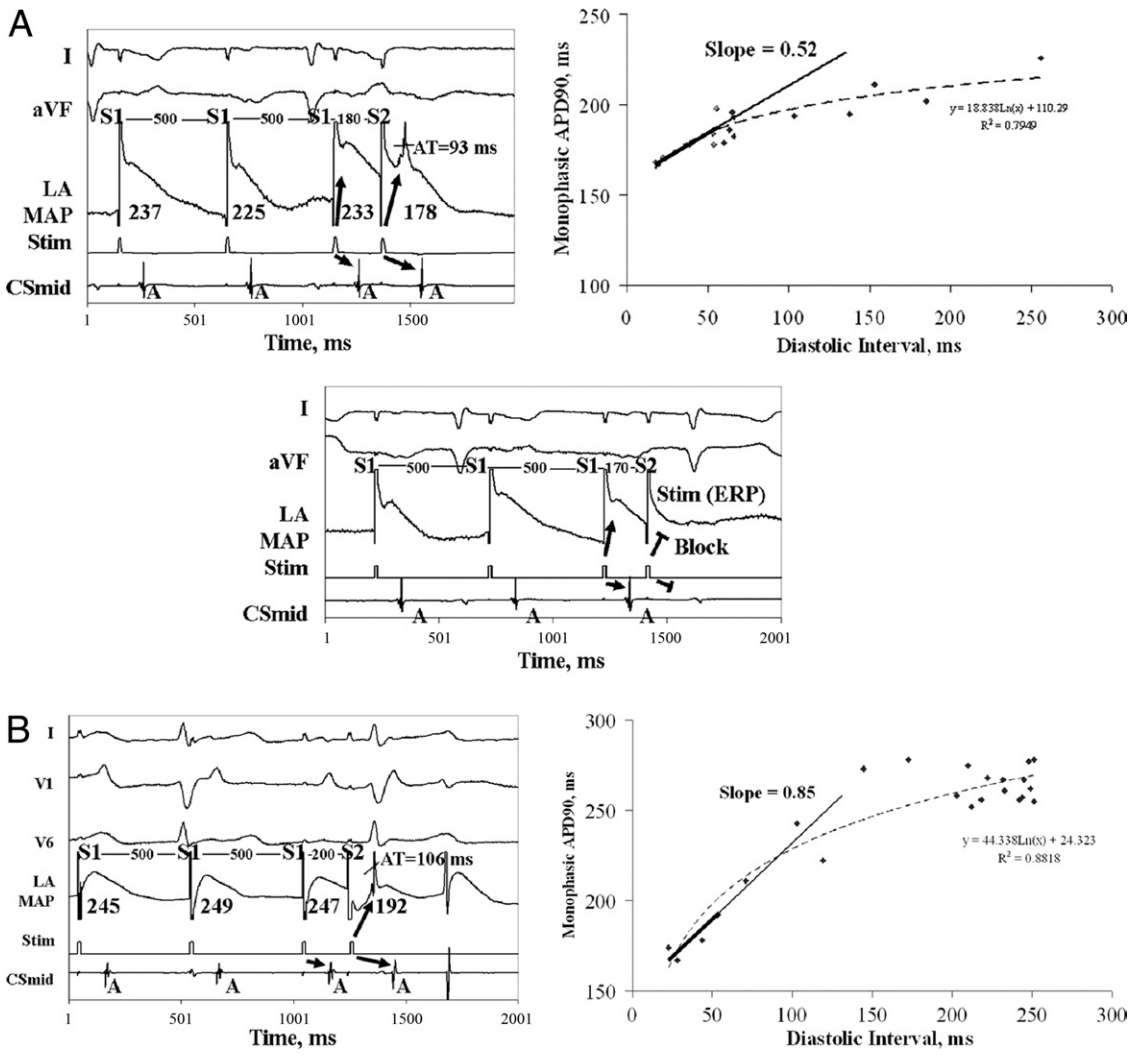

Figure 5 **LA APD Restitution Is Less Steep in Persistent AF**

(A) This PAC is early (coupling interval 180 ms), yet significant activation time (AT) delay (93 ms) enables capture (see blocked stimulus artifact at ERP, 170 ms). This prolongs DI and flattens APD restitution. **(B)** This early PAC also encounters AT delay (106 ms). The APD restitution has a maximum slope 0.85 (i.e., also not steep; same patient as in Fig. 2B). In both patients, FRP (minimum interval from prior beat to PAC) is longer than ERP (minimum distance between stimuli). See Table 2. ERP = effective refractory period; FRP = functional refractory period; other abbreviations as in Figures 1 to 3.

terminate abruptly (16), an APD restitution slope >1 may also explain why paroxysmal AF is more likely to self-terminate than persistent AF.

This mechanism may contribute to the focal source hypothesis for AF, in which rapid regular regions activate too quickly for the remaining atrium, causing AF via fibrillatory conduction (17,18). An APD restitution slope >1 could potentially amplify slight cycle fluctuations to cause APD alternans, wave break, and AF. We have previously reported that APD alternans heralds the disorganization from atrial flutter to AF (11), although the short pacing sequences in the current protocol prevented an analysis of alternans.

Notably, these data do not explain episodic AF—that is, why AF does not follow every early PAC. This may result from sympathovagal activity, which may variably steepen APD restitution, as in canine atria (19), or create pro-arrhythmic APD heterogeneity (20). These data also do not explain initiation of persistent AF. This could be explained by spatial heterogeneity: persistent AF initiates in regions where APD restitution slope is >1. Spatial factors are likely to be central; for example, Kim et al. (9) reported a right atrial APD restitution slope >1 in AF patients, yet very early PACs and rapid pacing (cycle length 180 ms) at these sites did not induce AF.

Dynamic LA activation delay and mechanisms for persistent AF. The AT prolongation was greater in persistent than paroxysmal AF, and in left compared with right atrium. The magnitude of this delay (≈100 ms) suggests

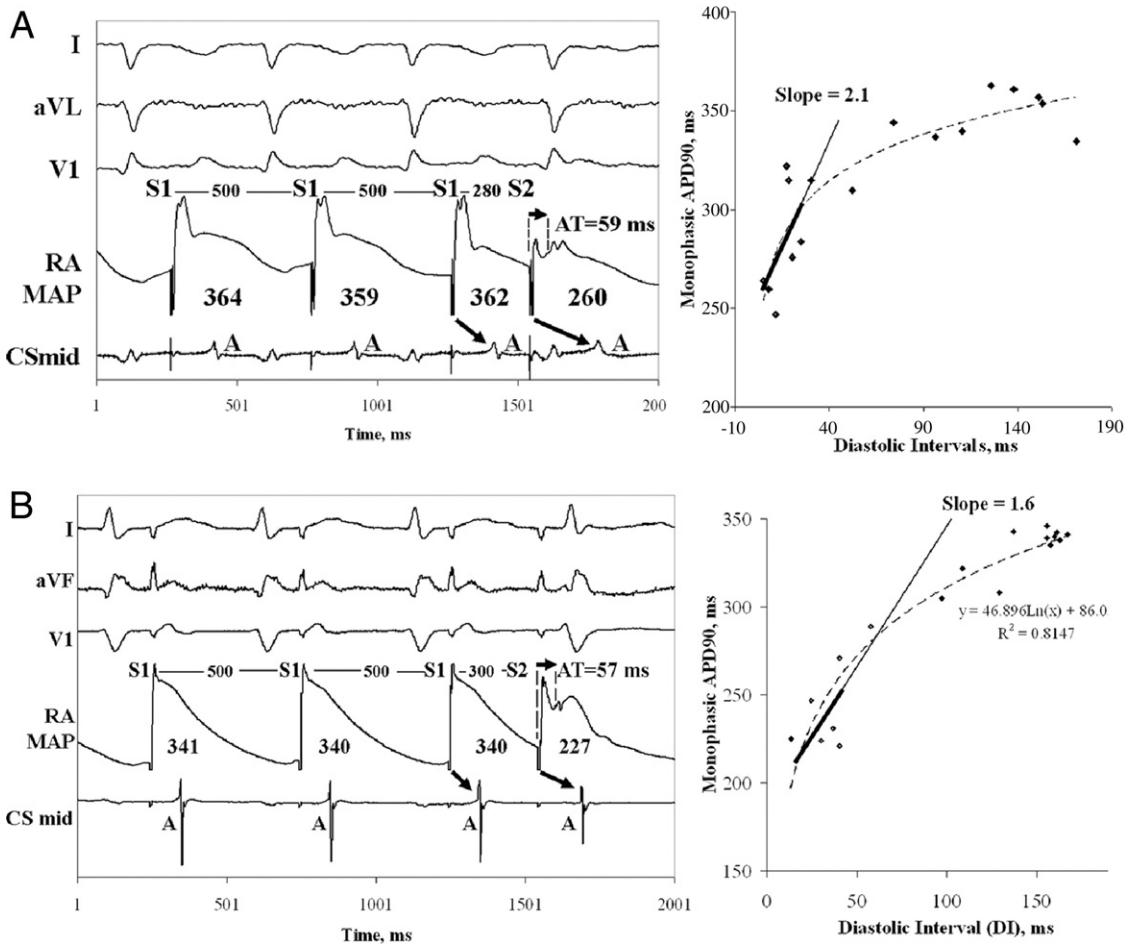

Figure 6 **Right Atrial APD Restitution Has Slope >1 Without AT Prolongation**

(A) Paroxysmal AF PACs, and APD restitution for a 74-year-old man with LA diameter 45 mm and AF for 3 years. **(B)** Persistent AF in the same patient as in Figure 5B. Compared with left atrial data in this patient, ERP (280 ms vs. 200 ms) and APD_{90} (346 ms vs. 275 ms) were longer, and AT delay (57 ms vs. 106 ms) and minimum DI (13 ms vs. 23 ms) were shorter. See Table 2. Abbreviations as in Figures 1 to 3.

that it represents dynamic conduction slowing, supported by a similar delay to distant electrodes (e.g., coronary sinus), rather than intracellular mechanisms that may explain shorter right atrial latency (≈28 ms) in patients with structurally normal atria (21).

In the ventricle, dynamic slowing enables fibrillation even if APD restitution slope <1 (7,22). In canine atria, conduction slowing from cellular uncoupling increases AF vulnerability independent of cellular electrophysiology (APD dynamics) (23). Speculatively, therefore, broad LA conduction restitution in patients with persistent AF may enable rapid tachycardias to cause APD alternans and wave break, a mechanism that we suggested in the right atrium in patients in whom typical atrial flutter disorganizes to AF (11). Recent studies confirm LA conduction slowing in patients with structural disease (24), although this requires study in patients with AF.

Atrial remodeling, dynamic prolongation of AT, and APD restitution. It is unclear whether observed differences between persistent and paroxysmal AF reflect electrical or structural atrial remodeling. It is tempting to conclude that structural remodeling and fibrosis (25) explain broad LA AT restitution in persistent AF. However, the DI for AT prolongation (Table 3) associated weakly with increased age or LA size, and did not differ between groups in the right atrium, which typically dilates in tandem with the LA.

In the absence of structural remodeling, conduction slowing is an inconsistent feature of electrical remodeling; for example, it is seen in dogs and sheep but not goats (25). Conduction slowing also may not fully explain flattened APD restitution in persistent AF, because minimum DI did not differ significantly from paroxysmal AF. Thus, electrical remodeling may explain these observations. In canine atria, electrical remodeling causes greater I_{Kr} current in the left

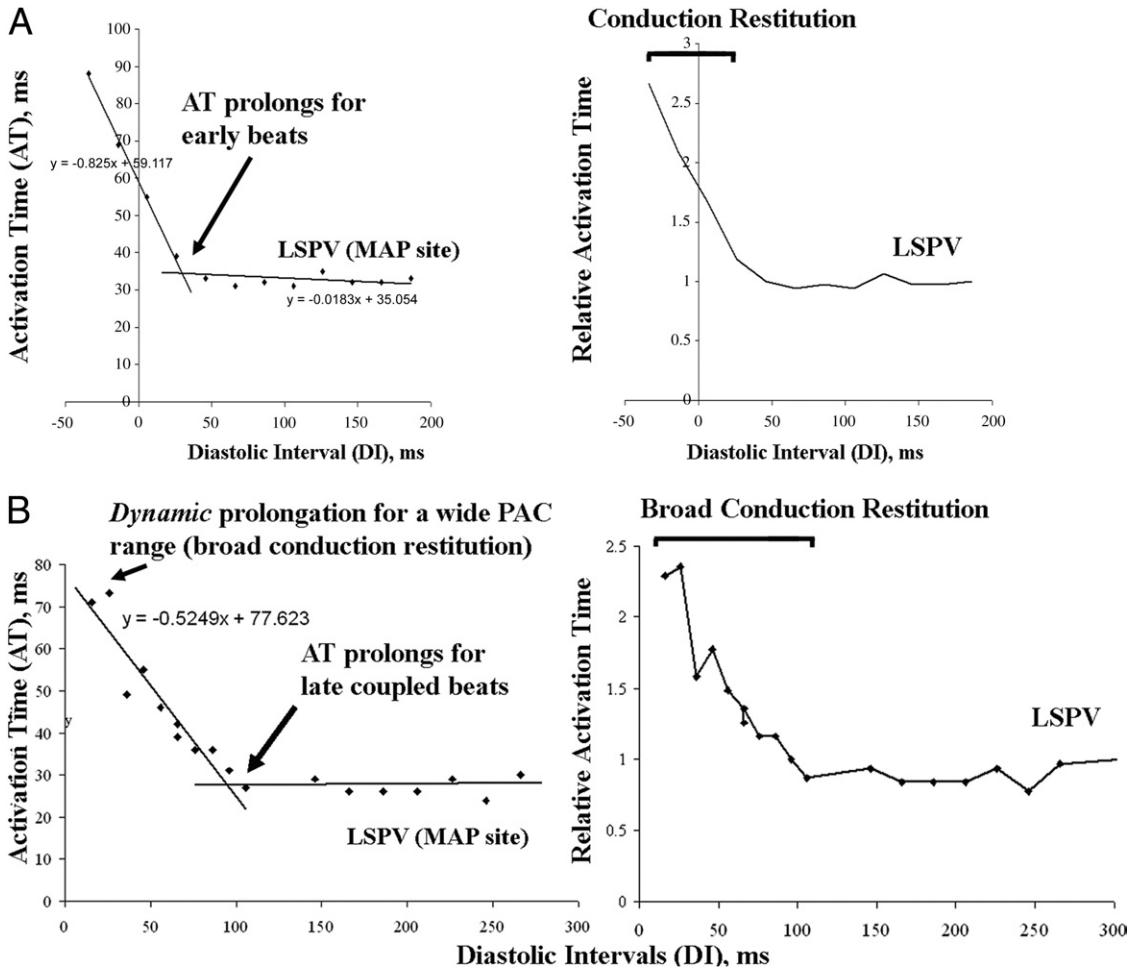

Figure 7 LA Activation Prolongs for a Wider Range of Beats in Persistent Than Paroxysmal AF

(A) Paroxysmal AF, AT prolongs only at very early DI (<20 ms; i.e., preserved conduction restitution), seen in actual and normalized plots. **(B)** Persistent AF, AT prolongs at longer DI (<108 ms; i.e., broad conduction restitution) in both plots. See Table 3. Abbreviations as in Figures 1 to 3.

than the right atrium, which compresses APD range and shortens ERP (26). Future studies must therefore examine atrial cellular electrophysiology in patients with persistent and paroxysmal AF (27).

Clinical implications. An APD restitution slope >1 provides a mechanistic rationale to isolate PVs and other trigger sites (10). On the other hand, APD restitution slope <1 and substantial AT delay may suggest a reduced dependence on triggers, and the need for additional ablation even in patients with paroxysmal AF. Clinically, this is revealed by a shorter ERP/FRP ratio (Table 2). Trials should study whether conduction slowing adds to dominant frequency or fractionation mapping (10) in guiding ablation.

Study limitations. One major limitation is lack of spatial sampling. Because of the challenges of recording stable MAPs for prolonged periods, particularly in the LA, we studied APD restitution near putative trigger sources, that is, the superior PVs and superior vena cava. Future work should study whether persistent AF patients show APD restitution slope >1 remote from PVs or exaggerated APD dispersion. We recorded right atrial MAPs only in a patient subset, yet our findings of APD restitution slope >1 without marked AT delay in either group agree with a prior report (9). Second, we had no control group, yet comparing APD restitution to induced AF in control subjects (i.e., without clinical AF) would be of unclear significance. Third, it is possible that APD restitution may be flattened in persistent AF patients, because of immediately preceding AF. However, paroxysmal AF patients presenting in AF still had an APD restitution slope >1, whereas the persistent AF patient presenting in sinus rhythm had an APD restitution slope <1, somewhat reducing this concern. In addition, persistent AF patients showed a right atrial APD restitution slope >1 despite longstanding AF (likely with remodeling). To minimize the impact of cardioversion, we waited >15 min as in prior reports (12). Fourth, these data may not apply to patients who could not remain in sinus rhythm long

enough to complete this protocol. Fifth, although MAPs could theoretically be influenced by movement, we think that this is unlikely given the consistency of MAP morphology before and after PACs (e.g., Fig. 5B). Sixth, higher spatial resolution is needed to determine whether AT delay reflects conduction restitution or intracellular mechanisms (e.g., reduced excitability). Although AT delay also occurred to the coronary sinus (Figs. 2 to 6), we did not quantify this because activation paths likely vary with PAC prematurity over this distance. In addition, our sample was too small to study whether APD or activation slowing predicts the response to AF ablation. Finally, our study lacked women, reflecting our Veterans' Affairs patient population. Although gender differences in AF are not clear, studies in both genders are required.

Conclusions

Human LA APD restitution has slope >1 near the PVs in patients with paroxysmal AF. Through this mechanism, early PACs may cause exaggerated APD oscillations to initiate AF. In patients with persistent AF, PACs encounter prolonged ATs and flattened APD restitution. The initiation of persistent AF may thus reflect broad conduction restitution or mechanisms unrelated to APD oscillations. Therapeutically, steep APD restitution provides a mechanistic rationale to isolate triggers, whereas further studies should define how regional conduction slowing may impact the substrates for persistent AF and approaches to ablation.

Acknowledgments

The authors thank Kathleen Mills, BA, for coordinating this study and Elizabeth Greer, RN, Stephanie Yoakum, RNP, and Stanley Keys, RCVT, for helping with clinical data collection.

Reprint requests and correspondence: Dr. Sanjiv M. Narayan, Cardiology/111A, 3350 La Jolla Village Drive, San Diego, California 92161. E-mail: snarayan@ucsd.edu.

REFERENCES

1. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.
2. Haissaguerre M, Sanders P, Hocini M, et al. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. Circulation 2004;109:3007–13.
3. Gerstenfeld EP, Sauer W, Callans DJ, et al. Predictors of success after selective pulmonary vein isolation of arrhythmogenic pulmonary veins for treatment of atrial fibrillation. Heart Rhythm 2006;3:165–70.
4. Haissaguerre M, Sanders P, Hocini M, et al. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. J Cardiovasc Electrophysiol 2005;16:1125–37.
5. Gong Y, Xie F, Stein K, et al. Mechanism underlying initiation of paroxysmal atrial flutter/atrial fibrillation by ectopic foci: a simulation study. Circulation 2007;115:2094–102.
6. Franz MR. The electrical restitution curve revisited: steep or flat slope—which is better? J Cardiovasc Electrophysiol 2003;14:S140–7.
7. Weiss JN, Karma A, Shiferaw Y, Chen P-S, Garfinkel A, Qu Z. From pulsus to pulseless: the saga of cardiac alternans (review). Circ Res 2006;98:1244.
8. Koller ML, Maier SKG, Gelzer AR, Bauer WR, Meesmann M, Gilmour RF Jr. Altered dynamics of action potential restitution and alternans in humans with structural heart disease. Circulation 2005;112:1542–8.
9. Kim B-S, Kim Y-H, Hwang G-S, et al. Action potential duration restitution kinetics in human atrial fibrillation. J Am Coll Cardiol 2002;39:1329–36.
10. Calkins H, Brugada J, Packer D, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS); American College of Cardiology (ACC); American Heart Association (AHA); Society of Thoracic Surgeons (STS). Heart Rhythm 2007;4:816–61.
11. Narayan SM, Bode F, Karasik PL, Franz MR. Alternans of atrial action potentials as a precursor of atrial fibrillation. Circulation 2002;106:1968–73.
12. Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with chronic atrial fibrillation and atrial flutter. J Am Coll Cardiol 1997;30:1785–92.
13. Yue AM, Franz MR, Roberts PR, Morgan JM. Global endocardial electrical restitution in human right and left ventricles determined by noncontact mapping. J Am Coll Cardiol 2005;46:1067–75.
14. Narayan SM, Franz MR, Kim J, Lalani G, Sastry A. T-wave alternans, restitution of ventricular action potential duration and outcome. J Am Coll Cardiol 2007;50:2385–92.
15. Walker ML, Rosenbaum DS. Cellular alternans as mechanism of cardiac arrhythmogenesis. Heart Rhythm 2005;2:1383–6.
16. Frame LH, Simson MB. Oscillations of conduction, action potential duration and refractoriness. A mechanism for spontaneous termination of re-entrant tachycardias. Circulation 1988;78:1277–87.
17. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. Circulation 1998;98:1236–48.
18. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J Am Coll Cardiol 2008;51:779–86.
19. Patterson E, Lazzara R, Szabo B, et al. Sodium-calcium exchange initiated by the Ca2+ transient: an arrhythmia trigger within pulmonary veins. J Am Coll Cardiol 2006;47:1196–206.
20. Miyauchi Y, Zhou S, Okuyama Y, et al. Altered atrial electrical restitution and heterogeneous sympathetic hyperinnervation in hearts with chronic left ventricular myocardial infarction: implications for atrial fibrillation. Circulation 2003;108:360–6.
21. Koller B, Karasik PL, Solomon AJ, Franz MR. Prolongation of conduction time during premature stimulation in the human atrium is primarily caused by local stimulus response latency. Eur Heart J 1995;16:1920–4.
22. Banville I, Gray RA. Effect of action potential duration and conduction velocity restitution and their spatial dispersion on alternans and the stability of arrhythmias. J Cardiovasc Electrophysiol 2002;13:1141–9.
23. Ohara T, Qu Z, Lee MH, et al. Increased vulnerability to inducible atrial fibrillation caused by partial cellular uncoupling with heptanol. Am J Physiol Heart Circ Physiol 2002;283:H1116–22.
24. Roberts-Thomson KC, Stevenson IH, Kistler PM, et al. Anatomically determined functional conduction delay in the posterior left atrium relationship to structural heart disease. J Am Coll Cardiol 2008;51:856–62.
25. Allessie MA, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230–46.
26. Li D, Zhang L, Kneller J, Nattel S. Potential ionic mechanism for repolarization differences between canine right and left atrium. Circ Res 2001;88:1168–75.
27. Workman AJ, Kane KA, Rankin AC. Characterisation of the Na, K pump current in atrial cells from patients with and without chronic atrial fibrillation. Cardiovasc Res 2003;59:593–602.

Key Words: atrial fibrillation ■ human ■ action potential duration ■ conduction velocity ■ electrical restitution ■ monophasic action potentials ■ electrical remodeling ■ alternans.