Repolarization Alternans Reveals Vulnerability to Human Atrial Fibrillation

Sanjiv M. Narayan, MB, MD, FRCP; Michael R. Franz, MD, PhD; Paul Clopton, MS; Etienne J. Pruvot, MD; David E. Krummen, MD

Background—The substrates for human atrial fibrillation (AF) are poorly understood, but involve abnormal repolarization (action potential duration [APD]). We hypothesized that beat-to-beat oscillations in APD may explain AF substrates, and why vulnerability to AF forms a spectrum from control subjects without AF to patients with paroxysmal then persistent AF.

Methods and Results—In 33 subjects (12 with persistent AF, 13 with paroxysmal AF, and 8 controls without AF), we recorded left (n=33) and right (n=6) atrial APD on pacing from cycle lengths 600 to 500 ms (100 to 120 bpm) up to the point where AF initiated. Action potential duration alternans required progressively faster rates for patients with persistent AF, patients with paroxysmal AF, and controls (cycle length 411±94 versus 372±72 versus 218±33 ms; \(P<0.01\)). In AF patients, APD alternans occurred at rates as slow as 100 to 120 bpm, unrelated to APD restitution (\(P>0.10\)). In this milieu, spontaneous ectopy initiated AF. At fast rates, APD alternans disorganized to complex oscillations en route to AF. Complex oscillations also arose at progressively faster rates for persistent AF, paroxysmal AF, and controls (cycle length: 316±99 versus 266±19 versus 177±16 ms; \(P=0.02\)). In paroxysmal AF, APD oscillations amplified before AF (\(P<0.001\)). In controls, APD alternans arose only at very fast rates (cycle length <250 ms; \(P<0.001\) versus AF groups) just preceding AF. In 4 AF patients in whom rapid pacing did not initiate AF, APD alternans arose transiently then extinguished.

Conclusions—Atrial APD alternans reveals dynamic substrates for AF, arising most readily (at lower rates and higher magnitudes) in persistent AF then paroxysmal AF, and least readily in controls. APD alternans preceded all AF episodes and was absent when AF did not initiate. The cellular mechanisms for APD alternans near resting heart rates require definition. (Circulation. 2011;123:2922-2930.)

Key Words: —atrium ■ fibrillation ■ action potentials ■ electrophysiology ■ remodeling

Human atrial fibrillation (AF) initiates when triggers\(^1,2\) interact with substrates.\(^3\) However, the nature of AF substrates and whether they may be detected to measure AF vulnerability remains unclear. Notably, substrates must account for AF initiation at slow sinus node rates after thoracic vein ectopy\(^1,2\) and also result from rapid tachycardia.\(^1,2\)

Clinical Perspective on p 2930

Alternans of action potential duration (APD) creates a milieu of repolarization dispersion that, in animal ventricles and in silico, may cause fibrillation directly or by interacting with slow conduction or ectopy.\(^4-6\) In humans, right atrial APD alternans\(^7,8\) explains AF transitions from typical atrial flutter\(^6\) or pacing,\(^8\) whereas left atrial APD alternans may explain AF initiation from pulmonary vein ectopy.\(^10\) However, atrial APD alternans has typically been reported only at fast rates because of APD-rate dependence (restitution)\(^1,5\) or altered cellular calcium handling.\(^5,11\) and it is unclear whether alternans differs between AF patients and individuals without AF.

We hypothesized that the remodeled atria of patients with persistent AF would exhibit APD alternans at slow heart rates, and that progressively faster rates would be required to elicit APD alternans in patients with paroxysmal AF or controls without AF. We tested this hypothesis by studying left and right atrial APD oscillations vis-à-vis AF initiation during incremental pacing from near-resting heart rates in patients with and without AF.

Methods

Patient Flow

We prospectively enrolled 33 patients referred for ablation to the Veterans Administration and the University of California Medical Centers in San Diego, CA, 25 for ablation of AF (12 persistent) and 8 controls (6 with accessory pathways, 1 with atrial tachycardia, and 1 with premature ventricular complexes) without AF. We approached for enrollment all consecutive patients undergoing AF ablation between December 2005 and March 2009, when research staff and catheters were available (n=54), excluding those with decompensated heart failure or coronary disease, and we report...
consecutive enrollees. Control subjects (recruited until November 2010) had a clinical indication for left-sided access but no evidence for AF or atrial flutter on Holter or event monitor recordings. AF was defined as paroxysmal if it terminated in 7 days and persistent if it lasted >7 days or required cardioversion. In AF patients, atrial thrombus was excluded by transesophageal echocardiography. The study was approved by our joint institutional review board, and all patients provided written informed consent. Some patients were included in our report that an atrial APD restitution slope explained AF initiation from ectopic beats.10

Catheter Placement

Electrophysiology study was performed >5 half-lives after discontinuing antiarrhythmic medications (3 weeks after amiodarone; Table 1). A decapolar catheter was placed in the coronary sinus. After transeptal puncture, a deflectable 7F monophasic action potential (MAP) catheter (EP Technologies, Sunnyvale, CA) was advanced to record AP in the antra of the right or left superior pulmonary vein (Figure 1) and high right atrium in 6 patients (1 control) selected because tachycardias at these sites mayinitiate AF.1,2

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Persistent AF (n=12)</th>
<th>Paroxysmal AF (n=13)</th>
<th>Controls (n=8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±11†</td>
<td>64±8†</td>
<td>48±15</td>
<td>0.010</td>
</tr>
<tr>
<td>Gender, M, F</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>0.16</td>
</tr>
<tr>
<td>Duration of AF, mo</td>
<td>71±72</td>
<td>64±132</td>
<td>62±8</td>
<td>0.87</td>
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<tr>
<td>Left atrial diameter, mm</td>
<td>47±5†</td>
<td>40±5</td>
<td>36±2</td>
<td>&lt;0.001</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>54±11</td>
<td>60±7</td>
<td>62±8</td>
<td>0.19</td>
</tr>
<tr>
<td>NYHA Class I/II</td>
<td>11</td>
<td>13</td>
<td>8</td>
<td>0.41</td>
</tr>
<tr>
<td>Coronary Disease, n (%)</td>
<td>3 (27)</td>
<td>5 (46)</td>
<td>1 (13)</td>
<td>0.42</td>
</tr>
<tr>
<td>Medications, n</td>
<td>ACEI/ARB</td>
<td>Statins</td>
<td>β-blockers</td>
<td>Class I agents</td>
</tr>
<tr>
<td></td>
<td>6†</td>
<td>6</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; NYHA, New York Heart Association functional class; ACEI, angiotensin-converting enzyme inhibitors; ARB, aldosterone receptor blockers.
*P<0.05 vs paroxysmal AF.
†P<0.05 vs controls.

Pacing Protocol

Patients in AF were electrically cardioverted to sinus rhythm and studied after 15 minutes, preceding ablation. Action potentials were recorded from the distal poles of the MAP catheter while pacing from the proximal poles or a nearby stable position. Pacing was delivered for 74 beats at cycle lengths (CL) 500 ms, 450 ms, 400 ms, 350 ms, and 300 ms, then in 10 ms steps to AF or capture failure (n=6), whichever came first. In 5 patients, pacing started at 600 ms, 550 ms, then the above sequence.

Signal filtering was 0.05 to 500 Hz (APs), 30 to 500 Hz (other intracardiac signals), and 0.05 to 100 Hz (ECG). Signals were digitized at 1 kHz to 16-bit resolution (Bard Pro, Billerica, MA) and exported for analysis using software written in Labview (National Instruments, Austin, TX).

Measurement of Action Potential Duration

We measured APD using validated methods6,10,13–16 with manual verification. We assigned AP onset as the time of maximal computed upstroke dV/dt and determined phase II voltage and phase IV (diastolic) voltage in the 5 ms preceding AP upstroke (Figure 2A). Action potential duration (APD) was measured from AP onset to 90% voltage recovery from phase II. Diastolic interval (DI) spans from APD of the prior beat to AP onset.10

Measurement of Action Potential Duration Restitution

We constructed curves of APD restitution during pacing using ≥5 (DI, APD) pairs at each pacing CL. Maximum slope was determined from linear fits for the shortest 30-ms DI segment with data (eg, 0 to 30 ms or 10 to 40 ms) as previously described.10

Measurement of Action Potential Duration Alternans and Complex Oscillations

We measured pairwise differences in APD (ΔAPD, Figure 2A), summarized by mean absolute ΔAPD for the last 10 beats at each CL. Alternans was assigned if ΔAPD alternated in polarity with magnitude ≥5% of mean APD (baseline APD varies ±2%/7). Because APD alternans may disorganize to complex oscillations preceding arrhythmia onset17,18 via phase reversals (eg, Long-Short-Long→Short-Long (LSLSL) proceeding to LSLS; Figure 2) or AP shape changes (Figure 3), we also report mean absolute ΔAPD for 10 nonalternating beats (if ≥5% mean APD).

Statistical Analysis

Continuous data are represented as mean±SD. ANOVA was used to compare variables among 3 patient groups, such as APD alternans magnitude or onset CL, with posthoc Tukey-Kramer tests to identify differences between group pairs. Paired continuous variables, such as the DI of APD alternans and APD restitution slope, were compared using linear regression and the paired t test. Group differences in APD90 at selected CLs were evaluated with separate ANOVAs using a Bonferroni correction for testing multiple CL bins. Action potential duration restitution slope was also compared between groups using a mixed-effects model with an unstructured covariance matrix that incorporated all observations with DIs in the range 0 to 550 ms, then the above sequence.

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ms < DI < 100 ms. This model adjusts for correlated observations within individuals. A log transform of DI was applied to account for the nonlinear relationship over this broader DI range. The Fisher exact test was applied to contingency tables. Biatrial data were primarily analyzed; right versus left atrial data are presented separately. $P<5\%$ was considered statistically significant.

**Results**

Our patient sample is described in Table 1. Patients with persistent AF had larger left atria than those with paroxysmal AF or controls. We performed 39 incremental pacing experiments in left (n=33) and right (n=6) atria, recording their transitions to AF.

**Action Potential Duration Alternans Preceded Atrial Fibrillation Transitions in Different Patterns Between Groups**

Action potential duration alternans preceded every AF initiation and arose at slower rates (ie, more easily) in patients with persistent AF than in those with paroxysmal AF and controls (Table 2). With continued incremental pacing, APD alternans transitioned to complex oscillations (Figures 2 through 4), also at slower rates in persistent AF than in paroxysmal AF and controls (ANOVA $P=0.03$). Sinus rhythm rates did not differ between groups.
In a patient with persistent AF, Figure 2 shows left atrial APD alternans at slow rates that disorganized at faster rates to complex APD oscillations en route to AF. At CL 500 ms (120 bpm), APD alternans had magnitude 58 ms (22% of mean APD), increasing to 120 ms (44% of APD) at CL 450 ms (130 bpm) that continued at CL 400 ms (150 bpm) during atrioventricular (AV) block (21% of APD; phase reversals marked * in Figure 2B) and CL 290 ms (207 bpm; 20% of APD, Figure 2C). At CL 210 ms (286 bpm), complex APD oscillations led directly to AF (Figure 2D).

In patients with paroxysmal AF, Figures 3 and 4 show APD alternans at intermediate rates en route to AF. In Figure 3A, pacing CL 500 ms (120 bpm) showed APD 309±8 ms without alternans (< 5% of APD). At CL 320 ms (188 bpm), APD alternans had magnitude 25 ms during 4:1 and 2:1 AV conduction (10% of APD 243 ms; Figure 3B), increasing at CL 280 ms (214 bpm) to 67 ms (34% of APD 198 ms; Figure 3C) immediately preceding AF. Figure 4 shows no APD alternans at CL 500 ms (120 bpm, Figure 4A), small amplitude APD alternans at CL 300 ms (200 bpm, Figure 4B) that increased at CL 250 ms (240 bpm) to magnitude 14 ms...
(7% of APD=213 ms) during 3:1 AV conduction just preceding AF. The small MAP signal (asterisk) preceding AF may indicate a far-field signal or an after-depolarization.

Although paroxysmal AF patients typically present in sinus rhythm and persistent AF patients in AF, 2 paroxysmal AF patients presenting in AF developed APD alternans at CL/H11005 400 ms and 300 ms that increased with rate just before AF. One persistent AF patient presented in sinus rhythm with APD alternans at CL 500 ms (7% of mean APD) transitioning via complex oscillations to AF.

Notably, control subjects showed APD alternans of small magnitude (13/H11006 5 ms, 8/H11006 4% of APD), developing only at very rapid rates (CL 218/H11006 30 ms, \( P < 0.001 \) against either AF group) just before AF. Figure 5 shows a control patient in whom APD alternans was absent at CL between 500 ms and CL 250 ms. Alternans developed at CL 240 ms (200 bpm; 8% of APD) immediately before AF. No control subject had APD alternans at CL/H11005 250 ms (\( P < 0.001 \) versus either AF group).

Onset of Action Potential Duration Alternans Did Not Correlate With Action Potential Duration Restitution Slope or Atrioventricular Conduction

Figure 6A shows the atrial APD-CL curve (Figure 6A) for each group. In AF patients, APD was shorter for those with persistent than paroxysmal AF at CL 500 ms and 400 ms (\( P < 0.0125 \), using Bonferroni corrections) but not CL 300 ms or 200 ms.

Notably, the CL of onset and CL range for which APD oscillations were observed differed markedly between groups. Figure 6B illustrates the magnitude of APD oscillations (pair-wise APD range over 10 beats, centered at APD mean) for each CL. Action potential duration oscillations spanned all rates in persistent AF (red envelope) and paroxysmal AF (blue envelope) patients, but occurred only at fast rates in controls (green envelope). In 3 AF patients paced at 100 bpm (CL 600 ms; not plotted), APD oscillations occurred with magnitude 13±10% of mean APD=297±74 ms. Considering only patients whose APD alternans arose without 2:1 AV conduction, alternans onset CL was 444±80 ms (persis-
tent AF), 418±59 (paroxysmal AF), and 245±49 (controls; \( P = 0.004 \), ANOVA).

Figure 6C summarizes the magnitude of APD oscillations (as a percentage of APD) against CL for each group. Persistent AF exhibited APD oscillations for all rates, whereas paroxysmal AF exhibited rate-dependent increases in APD oscillations (\( P < 0.001 \)). Controls showed small magnitude APD alternans only at very rapid rates. Relative to AF initiation, patients with paroxysmal AF showed amplified APD oscillations as CL shortened to AF initiation (\( P < 0.001 \)); patients with persistent AF showed a weak negative relationship (\( P < 0.05 \)).

**APD Dynamics vis-à-vis Atrial Fibrillation Vulnerability and Atrial Fibrillation Initiation**

APD oscillations separated patients at different stages of remodeling (Figure 6). Unlike controls, AF patients showed APD oscillations \( > 5\% \) of APD between 120 bpm (CL 500 ms) and 240 bpm (CL 250 ms). Paroxysmal AF patients differed from persistent AF patients by amplification in APD oscillations with rate and APD \( > 303 \) ms at CL 500 ms.

Action potential duration oscillations led to AF via 2 mechanisms. Figure 7A illustrates APD alternans at slow rates (CL 450 ms illustrated; also at CL 500 ms) when a spontaneous premature atrial complex (asterisked) triggered AF. Of note, APD restitution from single extra-systoles in this patient (S2-restitution) had maximum slope \( > 1 \) (1.79). Figures 2 through 5 show transitions to AF after amplified APD alternans (Figures 3 through 5) or via complex APD oscillations (Figure 2).

**Action Potential Duration Dynamics When Atrial Fibrillation Was Not Induced**

Rapid pacing failed to initiate AF in 4 patients. All patients initially exhibited atrial APD alternans, although 2:1 atrial capture then intervened to suppress alternans. This is shown for a persistent AF patient with APD restitution slope \(< 1\) (Figure 7B) but was also seen in paroxysmal AF and in patients with maximum APD restitution slope \( > 1\).

**Right Versus Left Atrial Action Potential Duration Dynamics**

Quantitatively, there were no differences between atria in APD alternans onset CL (\( P = 0.81 \)) or magnitude as a percentage of APD (\( P = 0.26 \)). Qualitatively, APD alternans in the right atrium was also marked at slow rates in AF patients. For instance, at CL 450 ms, APD alternans had a range of 1.8 to 120 ms (0.6% to 44% of APD) in left atrium and 8.2 to 32 ms (3.4% to 14% of APD) in right atrium. Biatrial APD statistics were similar when right atrial data were excluded from analysis.

**Discussion**

This study shows that alternans of APD in human left and right atria indicate progressive substrates for, and susceptibility to, AF. We observed APD alternans of large amplitude near resting rate in patients with persistent AF, at intermediate amplitude and rates in patients with paroxysmal AF; and of small amplitude only at very rapid rates (\( > 230 \) bpm) just before AF was induced in control subjects. Action potential duration oscillations preceded all transitions to AF. In patients with APD alternans at slow rates, ectopy initiated AF.
In patients with APD alternans at faster rates, oscillations became complex just preceding AF. In the few patients in whom AF was not induced by pacing, activation delay led to capture failure that quenched APD alternans. Thus, atrial APD alternans may be a clinical marker of susceptibility to AF and, in AF patients, arose at markedly slower rates than those observed in experimental models.

**Differential Onset and Dynamics of Action Potential Duration Alternans**

The magnitude and onset rate of APD alternans paralleled the progressive susceptibility to AF observed in control subjects and in patients with paroxysmal and persistent AF. In control subjects, APD alternans occurred only at rapid rates, agreeing with a vast literature of computational and animal studies. However, marked APD alternans in AF patients near resting heart rates (Figure 2, summarized in Figure 6) stands in sharp contrast and points to potentially important differences in AF between humans and prior experimental models.

At rapid rates, APD alternans may be explained by the restitution hypothesis. Restitution is the relationship of APD to rate, and a maximum slope >1 leads to APD alternans at rapid rates and wavebreak.

**Cellular calcium overload is also a potential mechanism for APD alternans in the atrium, given that it has been shown to lower the onset rate of APD alternans in remodeled versus control animal** and human ventricles. In animal models, diminished L-type calcium current and abnormal intracellular calcium handling from electric remodeling causes calcium overload. Human atrial myocytes also exhibit altered calcium handling, which explains AF in computational models and may explain reduced right atrial APD alternans by verapamil. Nevertheless, direct human evidence for calcium abnormalities as a cause for APD alternans or AF is lacking.

Atrial APD alternans may also be explained by electric remodeling of membrane ion currents. In canine atria, remodeling elevates potassium currents, compounding the effects of calcium overload to shorten the effective refractory period and compress APD range. Myocytes from remodeled human atria also exhibit increased inward repolarizing currents that shorten APD. This study confirms in vivo that left atrial APD has a flattened rate-response in patients with persistent AF compared with paroxysmal AF or controls (Figure 6A and Table 2). However, because APD shortening lengthens DI, it remains unclear how this explains APD alternans at slow rates.

Finally, atrial conduction slowing may theoretically cause APD alternans and transitions to AF, and is a feature of structural remodeling. As expected, structural remodeling was more evident in patients with persistent than paroxysmal AF (Table 1). However, we recently showed that AF patients show broad left atrial conduction restitution (slowing) for premature beats only for DIs \(<\approx 50 \text{ ms}\). Thus, conduction restitution may not plausibly explain APD alternans at the longer DIs in this study (Table 2).

**Action Potential Duration Alternans and Onset of Fibrillation**

Action potential duration alternans preceded AF initiation across a wide range of rates and may provide a clinical index of AF susceptibility. These data are the first to characterize biatrial APD dynamics en route to clinical AF and suggest that APD alternans may also be mechanistically involved in transitions to AF.

In animal ventricles and in silico, beat-to-beat repolarization dispersion (alternans) may cause wavebreak and fibrillation after ectopic beats or directly. First, during APD alternans at slow rates, spontaneous premature atrial complexes were observed to trigger AF (Figure 7A). In Figure 4, the small MAP deflection after a long APD (asterisked) may potentially indicate an after-depolarization induced by APD alternans that triggers AF, although further mapping is required to exclude far-field AF signals or noise (although these signals are relatively noise free). Second, APD altern-
ans at fast rates in AF patients transitioned to AF via amplified alternans or complex oscillations. This may represent period multiplying in nonlinear systems,\textsuperscript{17,18} which heralds ventricular fibrillation in canine ventricles\textsuperscript{18} or human ECG T-waves.\textsuperscript{27,28} Complex oscillations are consistent with the findings of Mironov et al.,\textsuperscript{29} who found nodal lines during APD alternans that spanned the heart to cause phase reversals, reduce APD variability, and herald fibrillation. Higher spatial resolution mapping is required to confirm whether complex APD oscillations represent nodal lines within the MAP field of view.

**Clinical Implications**

First, APD oscillations detected invasively (eg, from implanted device leads) or potentially from the ECG\textsuperscript{30} may provide a tool of dynamic susceptibility to AF, to monitor the efficacy of therapy, or to identify patients’ risk of progression from paroxysmal to persistent AF.\textsuperscript{31} Second, therapy to prevent APD alternans, as recently shown for sarcoplasmic endoplasmic reticulum Ca\textsuperscript{2+}-ATPase gene therapy in guinea pig ventricles,\textsuperscript{32} may reduce AF vulnerability. Christini et al showed that ventricular APD alternans can be controlled clinically,\textsuperscript{33} which, with our findings, opens the possibility of preventing AF initiation. Indeed, when APD alternans was suppressed in the present study, AF was noninducible by rapid pacing (Figure 7B).

**Limitations**

A limitation of this study is that multiple sites were studied in only 6 patients because of the time required to pace into AF, cardiovert, wait 15 minutes, reposition the MAP catheter, and repeat the protocol. For this reason, we have limited statistical power to separate right and left atrial APD dynamics. Second, our sample sizes were small, largely because of the lack of availability of MAP catheters, although this remains the largest study of human left atrial APD dynamics to date. Control subjects were younger than AF patients, because patients aged 60 to 65 years who required left-sided access but did not have AF nor flutter were relatively uncommon and difficult to recruit. Third, although we focus on pacing-induced AF, this mimics atrial tachycardias that trigger AF and reliably initiates AF without the impracticalities of waiting for spontaneous AF. Moreover, we also observed spontaneous premature atrial complex–triggered AF (Figure 7A). Fourth, although pacing may distort end-repolarization, APD alternans onset occurred at slow enough rates for pacing to fall after APD (at least of the short beat, Figures 2A, 2B, 3B, 3C, and 4B). At faster rates, alternans often affected AP shape (Figures 2, 3C, and 4C), and its detection therefore remained robust. Fifth, the presence (persistent AF) or absence (paroxysmal AF) of AF just preceding the protocol may influence group differences. One persistent AF patient presenting in sinus rhythm and 2 paroxysmal AF patients presenting in AF displayed APD alternans in accordance with their groups. Sixth, we cannot categorically exclude an effect of aging, because it was challenging to enroll older patients with clinical indications for left-sided mapping without AF/ flutter. Nevertheless, 3 controls (aged 67, 64, and 69 years) showed APD dynamics that were similar to those of younger controls and distinct from AF patients. Seventh, statistically, although posthoc analyses were used after omnibus ANOVA tests, no adjustments were made for testing multiple variables. Eighth, our study had few women, reflecting our Veterans Affairs patients. Although sex differences in AF are unclear, studies in both genders are required.

**Conclusions**

Action potential duration alternans reveals a spectrum of substrates for and susceptibility to clinical AF. Control subjects and patients with paroxysmal and persistent AF showed progressive abnormalities in the onset rate, magnitude, and rate-response of APD alternans, in tandem with easier transitions to AF. When present at slow rates, APD alternans enabled ectopy to initiate AF, and at faster rates, APD alternans amplified or disorganized directly to AF. Cellular studies are required to explain the mechanisms enabling AF patients to exhibit APD oscillations at near-resting heart rates.

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**References**


Human atrial fibrillation (AF) is a highly prevalent disease whose mechanisms are poorly understood. Ectopic beats from the pulmonary veins may trigger AF, but this likely also requires substrate, because ectopy rarely triggers AF in control subjects without AF. Action potential duration alternans preceded every AF episode, yet was absent in control subjects without AF. Accordingly, APD alternans indicates dynamic substrates for AF and arises most readily in patients with persistent AF and heart failure. APD alternans provides a clinical tool to identify AF vulnerability and may be useful in refining diagnosis or monitoring the effectiveness of AF therapy.
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