There are few clinical indices that indicate the vulnerability for atrial fibrillation (AF). Demographically, older age, hypertension, and other CHADS\textsubscript{2}V\textsubscript{A}Sc factors predict actuarial risk for AF,\textsuperscript{1–3} but poorly predict AF in individual patients in the clinic. We set out to determine if measures of atrial repolarization could provide an individualized index of AF vulnerability.

Clinical Perspective on p 867

Several lines of evidence show that human AF is predominantly a reentrant arrhythmia,\textsuperscript{4–6} and that dispersion in action potential (AP) duration (APD), which may be subtle. We hypothesized that spectral analysis would be a more sensitive and robust marker of AP alternans and thus a better clinical index of individual propensity to AF than APD alternans.

Methods and Results—In 31 patients (12 persistent AF, 15 paroxysmal AF, 4 controls with no AF), we recorded left (n=27) and right (n=6) atrial monophasic APs during incremental pacing from cycle length 500 ms (120 beats per minute) to AF onset. Alternans was measured by APD and spectral analysis. At baseline pacing (median cycle length [1st, 3rd quartiles], 500 ms [500, 500]), APD alternans was detected in only 7 of 27 AF patients (no controls), whereas spectral AP alternans was detected in 18 of 27 AF patients (no controls; $P=0.003$); AP alternans was more prevalent in persistent than paroxysmal AF, and absent in controls ($P=0.018$ APD; $P=0.042$ spectral). Spectral AP alternans magnitude at baseline was highest in persistent AF, with modest rate-dependent amplification, followed by paroxysmal AF, with marked rate dependence, and undetectable in controls until just before induced AF.

Conclusions—Spectral AP alternans near baseline rates can identify patients with, versus those without, clinical histories and pathophysiological substrates for AF. Future studies should examine whether the presence of spectral AP alternans during sinus rhythm may obviate the need to actually demonstrate AF, such as on ambulatory ECG monitoring. (Circ Arrhythm Electrophysiol. 2013;6:859-867.)

Key Words: action potentials ■ action potential duration ■ alternans ■ atrial fibrillation ■ spectral analysis

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sinus rhythm after cardioversion (before ablation). Here, we report the remaining 27 AF patients and 4 control subjects. Studied and screened patients did not differ significantly in demographics. LA thrombus was excluded by transesophageal echocardiography in AF patients. The study protocol was approved by our joint institutional review board, and all patients provided written informed consent. Some patients in this study were included in our prior reports that APD alternans tracks electric remodeling and that dynamic conduc-
tion slowing precedes AF onset.

Electrophysiology Study
Electrophysiology study was performed >5 half-lives after discon-
tinuing antiarrhythmic medications (>4 weeks after amiodarone in 8 patients; median, 284 days; Table 1). A decapolar catheter was placed in the coronary sinus. After transseptal puncture, LA geometry was reconstructed with NavX (St Jude Medical, Sylmar, CA) referenced to computed tomography (Figure 1B). A deflectable 7F MAP cath-
eter (EP Technologies, Sunnyvale, CA) was advanced to record AP in the geometry-verified antrum of superior pulmonary veins (n=27; Figure 1A) or high right atrium (n=6).

MAP Pacing and Recording Protocol
The protocol was completed before ablation. Patients in AF were electrically cardioverted up to 3 times to yield sinus rhythm, and the protocol started 10 minutes later. APs were recorded from distal poles of the MAP catheter (Figure 1A) while pacing the proximal poles for >84 beats at each cycle length (CL) of 500 (baseline), 450, 400, 350, and 300 ms, then in 10 ms steps to AF or capture failure (n=9), whichever came first.

Signal filtering was 0.05 to 500 Hz (MAPs), 30 to 500 Hz (other in-tracardiac 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 by SMN in Labview (National Instruments, Austin, TX).

Measurement of APD
We measured APD using validated software with manual verifica-
tion. After assigning AP onset as time of maximal computed upstroke (dV/dt), we determined phase II voltage and phase IV (diastolic) volt-
age as the mean voltage before and after the beat. APD is the inter-
val from AP onset to 90% voltage recovery from phase II (Figure 1B). Diastolic interval spans the interval from APD of the previous beat to AP onset.

Definition of APD Alternans
We measured pairwise differences in APD (ΔAPD) as mean absolute ΔAPD for the last 10 beats at each CL. APD alternans was defined when ΔAPD alternated in polarity with magnitude \( \geq 5\% \) of mean APD (baseline APD varies \( \leq 2\% \)). Because alternans may disorganize to complex oscillations before arrhythmia onset, we also assigned alter-
ans if mean absolute ΔAPD \( \geq 5\% \) for 10 nonalternating beats.

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Persistent AF (n=12)</th>
<th>Paroxysmal AF (n=15)</th>
<th>Controls (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>65 (58, 73)</td>
<td>61 (56, 65)</td>
<td>66 (37, 69)</td>
<td>0.595</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>12/0</td>
<td>14/1</td>
<td>4/0</td>
<td>NS</td>
</tr>
<tr>
<td>Sinus CL, ms*</td>
<td>984 (660, 1306)</td>
<td>1142 (938, 1196)</td>
<td>859 (771, 948)</td>
<td>0.291</td>
</tr>
<tr>
<td>Duration of AF, mo*</td>
<td>64 (25, 67)</td>
<td>26 (11, 36)</td>
<td>...</td>
<td>0.043</td>
</tr>
<tr>
<td>Left atrial diameter, mm*</td>
<td>47 (44, 50)†‡</td>
<td>42 (36, 44)</td>
<td>35 (34, 37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %*</td>
<td>56 (45, 70)</td>
<td>58 (52, 64)</td>
<td>59 (49, 70)</td>
<td>0.638</td>
</tr>
<tr>
<td>NYHA Heart Failure Class*</td>
<td>0 (0, 1.5)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.715</td>
</tr>
<tr>
<td>Coronary disease, n</td>
<td>4 (33)</td>
<td>5 (33)</td>
<td>0</td>
<td>0.391</td>
</tr>
<tr>
<td>Medications, n</td>
<td>ACE-I/ARB</td>
<td>7</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
<td>7</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ß-Blockers</td>
<td>9</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Antiarrhythmic drugs (all discontinued before study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I agents</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0.626</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>6‡</td>
<td>2</td>
<td>0</td>
<td>0.043</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>0.272</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0.534</td>
</tr>
<tr>
<td>No. pacing segments, LA/RA</td>
<td>9/3</td>
<td>14/2</td>
<td>4/1</td>
<td>0.693</td>
</tr>
<tr>
<td>AF initiation, n</td>
<td>10</td>
<td>11</td>
<td>1</td>
<td>0.081</td>
</tr>
<tr>
<td>CL of AF initiation, ms*</td>
<td>200 (165, 225)</td>
<td>230 (190, 245)</td>
<td>180</td>
<td>0.084</td>
</tr>
</tbody>
</table>

*Median (25th, 75th); †P<0.05 vs controls; ‡P<0.05 vs paroxysmal AF.

ACE-I indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, aldosterone receptor blockers; CL, cycle length; LA, left atrium; NS, nonsignificant; NYHA, New York Heart Association; RA, right atrium.

Figure 1. Monophasic action potential (MAP) recording. A, Fluo-
roscopy (left anterior oblique 30°) showing MAP catheter in the
left atrium (LA) placed near the left superior pulmonary vein
(LSPV). B, NavX digital reconstruction of LA.
Spectral Measurement of Alternans in AP Morphology

AP alternans was computed spectrally using the method we applied to ventricular APs. Using validated software, 64 contiguous APs were selected ≥20 beats after pacing onset, baseline corrected to a 10-ms segment starting 20 ms before AP onset, and aligned to phases 0 to I (Figure 2C). Successive APs were represented as a 2-dimensional matrix \( R(n, t) \), where \( n \) indicates beat number (0≤n≤63) and \( t \) the time sample. A Fourier transform was used to compute power spectra across beats for each \( t \), and then spectra were summated across the AP.

AP amplitude was defined for phase II or III as the height above baseline. The magnitude of AP amplitude alternans was represented by the dimensionless k-score (Figure 2D):

\[
\text{k-score} = \frac{\Sigma T - \mu_{\text{noise}}}{\sigma_{\text{noise}}}
\]

where \( \Sigma T \) is spectral magnitude at 0.5 cycles/beat (alternans, ie, every other beat), and \( \mu_{\text{noise}} \) and \( \sigma_{\text{noise}} \) are the mean and SD of spectral noise. Therefore, the k-score represents the spectral alternans magnitude as a number of SD beyond the noise bandwidth. Notably, spectral noise is not equivalent to random voltage fluctuations that are aperiodic with no spectral peak. Spectral noise represents a bandwidth outside the alternans frequency, and 0.33 to 0.49 Hz was used based on previous studies. Because atrial AP spectral alternans had not previously been applied clinically, we compared 4 cutpoints: k>0.67 (top quartile), k>1, k>2, and k>3 (top 0.1% of measurements; used in previous ventricular studies). We found that k>0.67 provided optimum clinical accuracy (P=0.008 versus k>3), representing the top quartile of values analogous to early reports of ventricular alternans.

AP amplitude was also measured as the absolute voltage of alternation \( V_{\text{alt}} \) (in \( \mu \text{V} \)), which is not scaled by noise SD, as:

\[
V_{\text{alt}} = \frac{\Sigma T - \mu_{\text{noise}}}{\text{AP duration}}
\]

We studied AP amplitude for the entire AP, that is, from the end of the alignment window (phases 0 to I) to the time of 90% repolarization (APD90; Figure 2C and 2D), and for phase II (defined as the first half of this interval) and phase III (second half).

Statistical Analysis

Continuous data are represented as median (1st, 3rd quartiles). The Kruskal–Wallis test was used to compare continuous variables between 3 patient groups, with post hoc Mann–Whitney U test to identify differences between group pairs. Paired continuous variables were compared using Wilcoxon signed-rank test. The \( \chi^2 \) test was applied to 3×2 contingency tables and Fisher exact test was applied to 2×2 contingency tables. McNemar test was used to compare different classification methods. A probability value <5% was considered statistically significant.

Results

The clinical characteristics of our population are shown in Table 1. Patients with persistent AF had larger left atria than paroxysmal AF or control patients.
APD alternans, n only 1 of 15 showed time-domain APD alternans (spectral AP alternans was present in 10 of 15 patients, yet Figure spectral analysis across the entire AP revealed only minimal measurement or visual inspection (Figure 3A). At baseline, no alternans was observed by APD measurement or visual inspection at baseline. In controls, AP alternans was absent at baseline. At rapid pacing (P<0.001), Spectral AP alternans magnitude was small at baseline and rose dramatically at fast rates to the point of AF initiation (k-score, 1.55 [−0.43, 2.43] versus 8.58 [3.32, 10.19]; P=0.003). Figure 3 demonstrates the significant increase in AP alternans with rate acceleration from baseline (CL, 500 ms) to intermediate (CL, 300 ms) and fast (CL, 280 ms) pacing rates before AF onset in this paroxysmal AF patient.

In persistent AF patients, APD alternans was present in 6 of 12 patients at baseline pacing and 9 of 12 patients at faster rates before AF onset (P=0.083). In contrast to paroxysmal AF, spectral AP alternans magnitude did not significantly change with rate acceleration to AF (k-score, 3.31 [0.15, 7.84] versus 4.79 [2.64, 9.91]; P=0.596). Figure 4 demonstrates marked spectral AP alternans in this persistent AF patient throughout incrementally faster pacing to the point of AF (CL, 450–300–180 ms).

In controls, AP alternans was absent at baseline. At rapid rates, alternans of APD was present in 2 of 4 subjects with notable increase in spectral AP alternans (k-score, −0.87 [−1.15, −0.76] versus 5.97 [0.42, 11.36]; Figure 5). Atrial spectral AP alternans was distributed evenly across the entire AP for all patient groups at baseline and fast rates, with no significant difference between AP phase II and phase III.

**Table 2. Atrial AP Alternans**

<table>
<thead>
<tr>
<th>AP Alternans</th>
<th>Persistent AF (n=12)</th>
<th>Paroxysmal AF (n=15)</th>
<th>Controls (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD alternans, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pacing</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0.018</td>
</tr>
<tr>
<td>Fast pacing</td>
<td>9</td>
<td>14</td>
<td>2</td>
<td>0.123</td>
</tr>
<tr>
<td>Spectral AP alternans, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pacing</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0.042</td>
</tr>
<tr>
<td>Fast pacing</td>
<td>11</td>
<td>15</td>
<td>3</td>
<td>0.164</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; and APD, action potential (AP) duration.

**Spectral Fibrillation Uncovers Atrial AP Alternans at Baseline**

Alternans of atrial AP was more evident using frequency- than time-domain analyses. Alternans was not observed in controls at baseline. At baseline pacing (median CL [1st, 3rd quartiles], 500 ms [500, 500]), APD alternans was present in n=7 AF patients (with small magnitude in the study population; ΔAPD, 15 ms [8, 28]; 9% [4, 18]), with greatest prevalence in persistent AF (6/12), then paroxysmal AF (1/14), and absent in controls (0/4; P=0.018; Table 2).

However, spectral analysis at this same rate revealed AP alternans in 18 of 27 AF patients versus no controls (P=0.023; Table 2). Similar to APD, spectral AP alternans was most prevalent in persistent AF (8/12), then paroxysmal AF (10/15), and absent in controls (0/4; P=0.042; Table 2). Additionally, AP amplitude alternans and k-scores were highest in magnitude in persistent AF, then paroxysmal AF, and least in controls (P=0.030 amplitude; P=0.023 k-score; Table 3).

Figure 3 shows a 61-year-old patient with paroxysmal AF. At baseline, no alternans was observed by APD measurement or visual inspection (Figure 3A). Additionally, spectral analysis across the entire AP revealed only minimal alternans compared with noise bandwidth (k-score, 0.47; Figure 3A). In paroxysmal AF patients at baseline pacing, spectral AP alternans was present in 10 of 15 patients, yet only 1 of 15 showed time-domain APD alternans (P=0.008).

**Table 3. Rate-Dependent Spectral AP Characteristics**

<table>
<thead>
<tr>
<th>Spectral AP Alternans Characteristics</th>
<th>Persistent AF (n=12)</th>
<th>Paroxysmal AF (n=15)</th>
<th>Controls (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pacing CL, ms</td>
<td>500 (463, 500)</td>
<td>500 (500, 500)</td>
<td>500 (463, 500)</td>
<td>0.522</td>
</tr>
<tr>
<td>Fast pacing CL, ms</td>
<td>215 (200, 253)</td>
<td>240 (200, 260)</td>
<td>250 (220, 295)</td>
<td>0.338</td>
</tr>
<tr>
<td>ΔCL, ms</td>
<td>275 (240, 300)</td>
<td>260 (240, 300)</td>
<td>240 (178, 280)</td>
<td>0.519</td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pacing, uV</td>
<td>4.3 (0.2, 13.8)*</td>
<td>1.5 (0.0, 3.8)*</td>
<td>0 (0, 0)</td>
<td>0.030</td>
</tr>
<tr>
<td>Fast pacing, uV</td>
<td>4.8 (2.7, 13.6)</td>
<td>4.4 (2.7, 13.7)</td>
<td>13.8 (1.1, 78.7)</td>
<td>0.881</td>
</tr>
<tr>
<td>ΔAmplitude, uV</td>
<td>−0.2 (−4.8, 13.0)</td>
<td>3.1 (1.1, 12.9)</td>
<td>13.9 (1.1, 78.7)</td>
<td>0.204</td>
</tr>
<tr>
<td>k-Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline pacing</td>
<td>3.31 (0.15, 7.84)*</td>
<td>1.55 (−0.43, 2.43)*</td>
<td>−0.87 (−1.15, −0.76)</td>
<td>0.023</td>
</tr>
<tr>
<td>Fast pacing</td>
<td>4.79 (2.64, 9.91)</td>
<td>8.58 (3.32, 10.19)</td>
<td>5.97 (0.42, 11.36)</td>
<td>0.565</td>
</tr>
<tr>
<td>Δk-Score</td>
<td>0.25 (−5.19, 9.55)</td>
<td>4.25 (2.29, 10.62)</td>
<td>7.06 (1.29, 12.19)</td>
<td>0.182</td>
</tr>
</tbody>
</table>

Median (25th, 75th). AF, atrial fibrillation; AP, action potential; and CL, cycle length.

*P<0.050 vs controls.
Alternans by APD Versus Spectral Alternans

Alternans evaluated by APD and spectral analysis were compared for each patient, at each rate. Only a weak correlation was observed between $\Delta$APD (as percentage of mean APD) and k-score ($P=0.673$; Figure 6).

Discussion

This study shows that spectrally measured atrial AP alternans provides a sensitive marker of propensity to AF. At baseline pacing slightly above resting heart rates, AF patients showed spectral AP alternans despite no measurable APD alternans, whereas controls showed no AP alternans. With rate acceleration, spectral AP alternans rose in all AF patients. These data suggest the role of spectral AP alternans as a patient-specific mechanistic indicator of the dynamic susceptibility to AF.

Rate-Dependent Dynamics of AP Alternans

The detection of spectral AP alternans at slow pacing separates AF patients from controls without AF. Compared with patients with persistent AF, those with paroxysmal AF showed smaller magnitudes of spectral AP alternans at baseline, with greater rate-dependent amplification. The greater sensitivity of spectral analysis contrasts with time-domain analyses of APD alternans, which were insensitive at slow rates, and may enable more precise mechanistic separation of the pro-fibrillatory atrial substrate between groups. Not surprisingly, the magnitudes of APD and
Spectral AP alternans correlate only weakly, because they measure different components of repolarization: spectral AP alternans evaluates the plateau and repolarization phases of the AP, whereas APD alternans evaluates only terminal repolarization.

**Tissue-Level Mechanisms for Rate Response in AP Alternans**

Patients with paroxysmal AF demonstrated clear rate dependence in spectral AP alternans. The presence of AP alternans at slow rates suggests a manifestation of early electric remodeling. Exaggerated spectral AP alternans with increasing rate (Figure 3), to the point where APD alternans is observed, is consistent with a restitution mechanism. APD restitution, in which the slope of APD against rate (actually, the diastolic interval between beats) >1, is well recognized to contribute to alternans, wavebreak, and the onset of fibrillation.

Patients with persistent AF, conversely, exhibited larger magnitude AP alternans at baseline that was stable with increasing rate. This is consistent with our observations using time-domain APD alternans. Such alternans may also reflect greater cellular remodeling near rest, but the lack of rate dependence reduces the likely contribution of APD restitution >1. Indeed, maximum APD

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**Figure 4.** Action potential (AP) spectral alternans at baseline in persistent atrial fibrillation (AF) in an 82-year-old man demonstrating significant spectral AP alternans at all rates from baseline to AF onset. A, Cycle length (CL) 450 ms, minimal AP duration (APD) alternans, but with high magnitude spectral AP alternans. B, CL 300 ms, spectral AP alternans persisted with APD alternans (APD alternans now apparent). C, Both spectral AP alternans and APD alternans were present at CL 190 ms before AF initiation.

---

**Figure 3.** Spectral AP alternans with increasing rate (0.5 cycles/beat) in a 77-year-old man with paroxysmal atrial fibrillation.

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**Figure 2.** Action potential (AP) spectral alternans at baseline in persistent atrial fibrillation (AF) in a 77-year-old man demonstrating significant spectral AP alternans at all rates from baseline to AF onset. A, Cycle length (CL) 450 ms, minimal AP duration (APD) alternans, but with high magnitude spectral AP alternans. B, CL 300 ms, spectral AP alternans persisted with APD alternans (APD alternans now apparent). C, Both spectral AP alternans and APD alternans were present at CL 190 ms before AF initiation.
The restitution slope was often <1 in such patients. Mechanistically, patients with persistent AF had structural remodeling (larger LA diameters in Table I in the online-only Data Supplement), which could potentially contribute to alternans via dynamic conduction slowing (restitution) as we recently reported. Alternatively, it is possible that proarrhythmic remodeling in persistent AF may reflect calcium overload. Indeed, in the ventricle, calcium overload is known to lower the rate threshold for AP alternans. Previous studies have demonstrated abnormal calcium handling in the atrium, as recently suggested by our own work using computer modeling. Further studies are required to determine whether cellular calcium overload explains the early presence of atrial AP alternans in AF patients at slower rates. At the present time, this mechanism remains speculative.

Finally, the absence of AP or APD alternans until rate accelerates to the point of AF onset may reflect a pure steep APD restitution mechanism at markedly elevated rates.

Cellular Mechanisms

It is interesting to put these data on human MAP alternans into the context of possible cellular pathology underlying alternans and arrhythmogenesis. It is now well established that APD alternans may reflect oscillations in intracellular
as recently postulated, the direct regression of atrial T-tubules these groups (Table I in the online-only Data Supplement) and, AF in clinical practice, but further studies are required. Continuous ambulatory recordings required to capture paroxysmal be an effective clinical surrogate for the often-multiple or continuous ambulatory recordings required to capture paroxysmal AF in clinical practice,34 but further studies are required.

Clinical Implications Spectrally measured AP alternans near rest, and then at higher rates, may provide a predictive tool for AF vulnerability. Spectral AP alternans at baseline may indicate remodeling from clinical AF, whereas small baseline amplitude AP alternans with rate amplification may indicate paroxysmal rather than persistent AF. Unipolar intra-atrial electrograms from implanted pacemaker leads may provide surrogate measures of AP alternans, as shown in animal models.32,33 If robust, detection of spectral AP alternans near resting heart rates may be an effective clinical surrogate for the often-multiple or continuous ambulatory recordings required to capture paroxysmal AF in clinical practice,34 but further studies are required. These findings could direct pacemaker-initiated therapies for prevention of paroxysms of AF, even those with no previous AF history. Other therapies directed to attenuate these oscillations, such as medical suppression of abnormal calcium handling,11 may reduce AF vulnerability.

Limitations The major limitation of this study is our small number of control patients, reflecting difficulties in enrolling patients without AF for this potentially prolonged pacing protocol, as well as difficulties in obtaining MAP catheters. Nevertheless, despite the limited number, all control patients demonstrated absence of alternans (spectral and APD) at baseline. Second, we did not study multisite pacing or MAP recordings. Third, our study focused on slow pacing, rather than sinus rhythm. Studies to improve spectral AP alternans detection during sinus rhythm are planned. Fourth, cardiac motion, respiration, or baseline wander could theoretically affect our recordings, although these artifacts may not alternate beat to beat. Furthermore, alternans during pacing often showed a high signal-to-noise ratio. Fifth, to avoid ectopy during long pacing runs for spectral analysis in this study, we used pacing cycle length 500 ms as the slowest rate. Sixth, we defined atrial spectral AP alternans as k-score >0.67, which was optimal compared with k-score cutpoints of 1, 2, and 3, and represents the top 25% of alternans values. Of note, k>0.67 is a comparison to a control bandwidth, rather than noise from random voltage fluctuations (that are aperiodic). Seventh, although pacing may distort phase III and IV of the AP, AP alternans was clearly present at baseline pacing, and analysis of phase II at fast rates demonstrated alternans. Eighth, and lastly, our study patients were predominantly male, reflecting our Veterans Affairs population. It is not clear that atrial repolarization dynamics has a difference between sexes, but further studies are required.

Conclusions The measurement of atrial AP alternans by spectral analysis provides sensitive clinical index for propensity to AF. Spectral AP alternans was present in AF patients at baseline pacing, even when APD alternans was absent. The differences in the presence and magnitude of AP alternans at baseline and the progressive abnormalities with faster pacing revealed a spectrum of atrial substrates and AF vulnerability. Further studies should examine whether detection of spectral AP alternans when not in AF may be an effective clinical surrogate for the often-multiple or continuous ambulatory recordings required to capture paroxysmal AF in clinical practice.

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References


CLINICAL PERSPECTIVE

Few risk factors for the development of human atrial fibrillation (AF) predict an individual’s propensity to AF. Recent clinical and translational studies show that AF is a predominantly reentrant arrhythmia and that dispersion in action potential (AP) duration (APD) leads to wavebreak and AF onset. However, measures of APD focus only on the AP terminus, ignoring changes in the AP shape that may reflect important components of atrial remodeling. We hypothesized that spectrally measured alternans of atrial AP shape may be a more sensitive marker of AF vulnerability in patients than alternans of APD. We found that although alternans of APD was present in few AF patients at slow (baseline) heart rates, spectrally detected AP alternans was present in the majority, yet absent in controls. The prevalence and the magnitude of spectrally detected AP alternans was greatest in patients with persistent AF, in whom it showed minimal amplification at increasing heart rates, followed by paroxysmal AF patients, who showed marked rate amplification, and was absent in control patients until fast rates just before AF induction. In conclusion, spectrally measured atrial AP alternans at slow rates is a sensitive marker of AF vulnerability and may help identify patients with functional substrates for AF.
Frequency Analysis of Atrial Action Potential Alternans: A Sensitive Clinical Index of Individual Propensity to Atrial Fibrillation
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