Exploiting Rate-Related Hysteresis in Repolarization Alternans to Improve Risk Stratification for Ventricular Tachycardia

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OBJECTIVES
We sought to study the effect of heart rate acceleration and deceleration on the ability of repolarization alternans (RPA) to stratify ventricular tachycardia (VT) risk.

BACKGROUND
Heart rate fluctuations alter arrhythmic propensity, yet it is unclear whether fluctuations, as well as absolute rate, dynamically increase VT risk. We hypothesized that repolarization heterogeneity reflected by RPA would exhibit hysteresis during rising and falling heart rate, which may reflect arrhythmic propensity.

METHODS
The RPA magnitude (absolute voltage of alternation [V\text{alt}] and T-wave alternans ratio [TWAR]) and temporal distribution were determined from the electrocardiogram (ECG) in 60 patients during paced heart rate acceleration from 100 to 150 beats/min, then deceleration to 100 beats/min at electrophysiologic study (EPS). The V\text{alt} and TWAR thresholds were varied prospectively to generate receiver-operating characteristics (ROC) for the prediction of inducible VT at EPS.

RESULTS
Thirty-six patients were induced into VT and 24 were not. Hysteresis of RPA was seen. The V\text{alt} reached steady-state within 60 beats of each rate transition and was higher in deceleration than in acceleration at matched heart rates. In induced patients, V\text{alt} rose then fell with heart rate. In noninduced patients, V\text{alt} was insensitive to acceleration, but rose on initial deceleration. The RPA distributed later within repolarization in induced patients but, on deceleration, moved earlier in both groups. By ROC analysis, V\text{alt} = 2.6 μV in late repolarization at 120 beats/min provided optimal sensitivity and specificity for VT in acceleration (87.5% and 88.7%, respectively) versus deceleration (80% and 62.5%, respectively; p = 0.004, chi-square test).

CONCLUSIONS
1) Physiologic fluctuations in heart rate may affect the clinical utility of RPA for VT risk stratification; and 2) repolarization dispersion measured by RPA is more exaggerated during deceleration than acceleration at matched heart rates (rate hysteresis).

We sought to determine whether dispersion of ventricular repolarization, as measured by the magnitude and temporal distribution of repolarization alternans (RPA), is affected by fluctuations in heart rate as well as absolute rate, and how this dynamic behavior relates to the inducibility of VT. Repolarization alternans represents microvolt-level, alternate-beat fluctuations in the electrocardiographic (ECG) JT segment, and these fluctuations have been shown to reflect temporospatial dispersion of repolarization in several experimental models (6–8) and to predict ventricular arrhythmias (9,10). Heart rate acceleration (11–13) and deceleration (12,14) may both exaggerate repolarization dispersion. During acceleration, RPA increases with repolarization dispersion to the point of onset of ventricular arrhythmias (7,9). However, this link is less clear during deceleration. Furthermore, the arrhythmic significance of repolarization dispersion varies with its timing within repolarization. Dispersion late, versus early, in repolarization...
may reflect a transmural repolarization gradient critical to re-entrant arrhythmogenesis (15), explaining the improved specificity for VT reported for RPA (16) and QT dispersion (17,18) measured in late repolarization. However, whether acceleration and deceleration may differentially alter the timing of repolarization dispersion or alter its association with VT has yet to be explored.

We hypothesized that progressive changes in heart rate may produce hysteresis in RPA, with higher magnitudes and earlier temporal redistribution within the T wave on deceleration than on acceleration. We also sought to define the optimal heart rate dynamics for applying RPA to risk stratification for inducible VT. We tested this hypothesis in patients undergoing programmed electrical stimulation (PES) of the ventricle.

METHODS

Patient recruitment and clinical ECG collection. Studies were approved by the Human Subjects Committee of the Washington University School of Medicine. Sixty consecutive consenting patients undergoing PES for evaluation of unexplained syncope or VT were recruited (the first 40 of whom were previously studied [16]), and antiarrhythmic medications were withheld for at least two days. Patients were lightly sedated using intravenous midazolam, then 6F quadripolar catheters were placed into the right atrium and right ventricle. Before PES, experimental pacing was performed simultaneously from the atrium and ventricle to maintain a constant heart rate while preventing atrial activation from contaminating late repolarization. Pacing was performed for 2 to 5 min as tolerated, at stepped cycle lengths (CLs) of 600 to 400 to 600 ms (50-ms steps). Pacing was truncated to 2 min if automated blood pressure readings (taken after 30 to 60 s of pacing at each CL and requiring 30 s) revealed hypotension. No patient experienced angina pectoris or other symptoms during pacing.

Surface ECG leads I, aVF and V1 were recorded using a 16-channel analog amplifier (Bloom & Associates, Reading, Pennsylvania) with a surface ECG bandpass of 0.04 to 100 Hz. Data were sampled at 1 kHz to 12-bit resolution using an analog-to-digital board (National Instruments, Austin, Texas), then transferred to a UNIX workstation (Sun Computer, Palo Alto, California) for off-line analysis.

Spectral computation of RPA. Analysis was performed using a suite of graphic software written by the authors in C and Labview (National Instruments), as previously described (19). Sequences of 64 contiguous beats were selected to exclude ectopic depolarizations, fusion complexes or other spurious events that impair the computation of RPA. The temporal decay of RPA was analyzed using overlapping 64-beat sequences starting from the first then every fifth beat after the onset of each paced CL. Sequences were grouped into 1) immediate (commencing with beats 0, 5, 10 and 15); 2) early (beats 20 to 35); 3) middle (beats 40 to 55); 4) late (beats 60 to 75) and 5) steady-state (beats 80 to 95) epochs.

Beats were baseline-corrected then QRS-aligned to their maximal normalized dot products. Repolarization alternans was computed on each aligned beat array using multidimensional spectral analysis (9) over the entire JT segment (R, defined without knowledge of the clinical data), then using intervals of half its duration early (R₂), middle (R₄₉) and late (R₄) within the JT segment (Figure 1, left panel). Each series was represented as a two-dimensional matrix R (n, s), where n indicates the beat number (0 ≤ n ≤ 63) and s its time sample (in milliseconds). A fast Fourier transform was used to compute power spectra columnwise across all rows (arrow-wise in Fig. 1).

The RPA is represented by the 0.5-cycles/beat peak from the summated power spectra, $\Sigma T$ (in $\mu V^2$), distinct from respiratory modulation of the ECG (0.1 cycles/beat in Fig. 1). The RPA was quantified relative to spectral noise, defined over 10 preceding spectral points (0.33 to 0.48 cycles/beat), using the dimensionless T-wave alternans ratio (TWAR):

$$TWAR = \frac{\Sigma T - \mu_{noise}}{\sigma_{noise}}$$

where TWAR > 0 indicates RPA detectable above noise; TWAR ≥ 3 predicts inducible VT (9); and $\mu_{noise}$ and $\sigma_{noise}$ are mean and standard deviation of noise, respectively ($\mu V^2$). The mean absolute voltage difference of alternation ($V_{alt}$) over the series (Fig. 1A) was also estimated as:

$$V_{alt} = \frac{\Sigma T - \mu_{noise}}{\sqrt{JT \text{ duration}} (\mu V)}$$

Protocol for PES and outcome comparisons. Programmed electrical stimulation was performed by pacing at the right ventricular apex at CL 600 then 400 ms. A train-of-eight S₁ stimuli were presented, followed by single, double or triple premature extrastimuli, as required, to induce sustained monomorphic VT. If unsuccessful, this process was repeated at a second right ventricular site. Accordingly, each patient (n = 60) was labeled “inducible” or “noninducible.” The RPA data for surface ECG leads I, aVF and V1 were combined into a vector resultant using...
Pythagoras’ theorem. For each JT region in each patient, RPA was considered significant (RPA-positive) or not (RPA-negative) according to whether TWAR and $V_{alt}$ exceeded discriminants varying within ranges that encompass previously applied criteria (2 = TWAR ≤ 6 and 1 ≤ $V_{alt}$ ≤ 4 $\mu V$). These data were compared with PES outcomes to generate receiver-operating characteristic (ROC) plots of specificity versus sensitivity of $V_{alt}$ and TWAR for inducible VT.

Statistical analysis. Continuous data are presented as the mean value ± SD. The unpaired two-tailed $t$ test was used to compare TWAR and $V_{alt}$ between groups, applying the Bonferroni correction for multiple comparisons. The chi-square test was applied to contingency tables of sensitivity and specificity. A probability level of 5% (p < 0.05) was considered statistically significant.

RESULTS

Thirty-six patients were induced into VT, whereas 24 were not. Induced patients had worse systolic function and a higher incidence of structural heart disease and previous MI. Of patients with structural heart disease, there was a trend for more cases to be ischemic in the inducible group versus the noninducible group (p = 0.11, chi-square test). The demographic data of both groups are shown in Table 1.

Magnitude of RPA and heart rate. The magnitude of RPA was greater in inducible than in noninducible patients at all CLs (Fig. 2), with a distinct rate hysteresis in each group. In inducible patients on acceleration, mean $V_{alt}$ (throughout repolarization, R) increased from 3.63 ± 1.32 ($n = 25$) to 4.54 ± 2.14 ($n = 26; p = 0.036, t$ test) and then to 8.03 ± 5.43 $\mu V$ ($n = 28; p = 0.001$) at 100, 120 and 150 beats/min (CLs of 600, 500 and 400 ms, respectively). Deceleration to 120 beats/min caused a slight fall in mean $V_{alt}$ to 7.74 ± 4.41 $\mu V$ ($n = 14; p = NS$), then a significant reduction to 3.49 ± 2.61 $\mu V$ at 100 beats/min ($n = 10; p = 0.004$). Notably, RPA magnitude was significantly greater ($p = 0.015$) at 120 beats/min during deceleration ($V_{alt} = 7.74 ± 4.41 \mu V$) than on acceleration ($V_{alt} = 4.54 ± 2.14 \mu V$). Relations were similar for TWAR.

In noninducible patients, $V_{alt}$ and TWAR (throughout repolarization, R) increased very little and nonsignificantly on acceleration from 100 beats/min (2.33 ± 1.67 $\mu V; n = 15$) to 120 beats/min (2.33 ± 3.43 $\mu V; n = 24$) to 150 beats/min (2.96 ± 2.98 $\mu V; n = 18$) during pacing (p = NS for all comparisons) (Fig. 2B). However, on deceleration to 120 beats/min, $V_{alt}$ increased to 6.43 ± 3.81 $\mu V$ ($n = 14; p = 0.004$) before falling to 4.21 ± 3.02 $\mu V$ at 100 beats/min ($n = 14; p = 0.049$ vs. 120 beats/min). The $V_{alt}$ was greater during deceleration than acceleration at

<table>
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<th>Criteria</th>
<th>Inducible Patients (n = 36)</th>
<th>Noninducible Patients (n = 24)</th>
<th>p Value</th>
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<tr>
<td>Male/female (n)</td>
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<td>Age (years)</td>
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<td>LVEF (%)</td>
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*By the $t$ test. †By the chi-square test. Data are presented as the number of patients or the mean value ± SD. LVEF = left ventricular ejection fraction; MI = myocardial infarction.
120 beats/min (p = 0.002) and 100 beats/min (p = 0.049), as shown in Figure 2B (comparing RPA magnitudes for matched CLs on either side of the vertical line). Similar results were found for TWAR.

Temporal decay of RPA after step changes in CL. After CL transitions in inducible patients, RPA was maximal, then decayed over the next 60 beats (three epochs). Figure 3 shows that on acceleration to 500 ms CL, the mean TWAR fell from 34.77 (immediate) to 22.34 (early; p = 0.03, t-test). Statistically, immediate TWAR exceeded that in the early (p = 0.02, Wilcoxon signed-rank) and middle (p < 0.01) phases, and exceeded the all-epoch mean (p = 0.005). Similar results were seen after deceleration for all transitions. In noninducible patients, TWAR was more uniform within sequences at each CL and did not decay after either acceleration or deceleration (e.g., decelerating to 500 ms CL; p = NS for immediate vs. early, early vs. middle and middle vs. late).

Temporal distribution of RPA during acceleration versus deceleration. Repolarization alternans became redistributed within repolarization with changes in heart rate. In inducible patients, the RPA magnitude rose in concert for all regions of repolarization. \( V_{alt} \) was significantly greater during deceleration than acceleration at 120 beats/min (R; p = 0.015), with redistribution from R\(_L\) toward R\(_E\) and R\(_M\) (R\(_M\) > R\(_L\) p = 0.045). \( V_{alt} \) resumed baseline at 100 beats/min. B. Noninducible patients showed different hysteresis without an acceleration-related increase in \( V_{alt} \), but then an increase on deceleration to 120 beats/min (p = 0.004) and to 100 beats/min (p = 0.049) with earlier redistribution of RPA (R\(_M\) > R\(_L\), p = 0.048; R\(_M\) > R\(_E\), p = 0.041).

120 beats/min (p = 0.002) and 100 beats/min (p = 0.049), as shown in Figure 2B (comparing RPA magnitudes for matched CLs on either side of the vertical line). Similar results were found for TWAR.
on deceleration from 150 to 120 beats/min, \( R_E, R_M \) and \( R_L \) increased significantly in tandem \((p = 0.009, p = 0.003 \) and \( p = 0.026, \) respectively), then, on further deceleration to 100 beats/min, reduced in tandem \((p = 0.049, p = 0.050 \) and \( p = \text{NS}, \) respectively). There was a redistribution of RPA toward mid-repolarization, with \( R_M \) being greater than \( R_E \) \((p = 0.041) \) and \( R_L \) \((p = 0.048) \) at 120 beats/min \((p = 0.048) \).

**Sensitivity and specificity of RPA in late versus whole repolarization with heart rate.** Clinical sensitivity and specificity of RPA for inducible VT varied asymmetrically with heart rate between acceleration and deceleration at matched heart rates. As shown in Table 2, for the discriminant \( V_{alt} = 1.9 \, \mu\text{V} \) \((20)\), the best sensitivity and specificity resulted when late RPA was examined at 120 beats/min \((CL = 500 \, \text{ms})\) during acceleration versus deceleration. Similar results were found for TWAR \(\geq 1.9 \, \mu\text{V} \) for VT.

**Receiver-operating characteristics of \( V_{alt} \) and TWAR for VT.** The ROC relation at 120 beats/min \((CL = 500 \, \text{ms} \text{ pacing})\) is represented in Figure 4 during (A) acceleration and (B) deceleration for \( V_{alt} \) in the range \(1 \leq V_{alt} \leq 4 \, \mu\text{V} \) and TWAR in the range \(2 \leq \text{6 applied over late (} R_L \) or the entire \( R \) repolarization interval.

The optimal discriminant in this study was \( V_{alt} = 2.6 \, \mu\text{V} \) examined in late repolarization during acceleration, providing 85.7% sensitivity and 86.3% specificity for inducible VT \((\text{Fig. 4})\). The ROC plots were more favorable \((\text{curves displaced upward and to the right})\) for \( V_{alt} \) versus TWAR, for late versus whole repolarization and for acceleration \((\text{Fig. 4A})\) versus deceleration \((\text{Fig 4B})\). Raising the discriminant threshold increased specificity and reduced sensitivity.

**DISCUSSION**

To our knowledge, this study is the first to examine the contributions of heart rate deceleration and acceleration, as well as absolute rate, to the repolarization dynamics that may predispose to VT. In inducible patients, repolarization dispersion measured by RPA rose and fell with heart rate, whereas in noninducible patients, RPA rose during deceleration. In both groups, RPA exhibited rate-related hysteresis of magnitude, as well as distribution within the T wave. This hysteresis significantly altered the sensitivity and specificity of RPA for VT and best separated inducible from noninducible patients when analyzed in late repolarization during heart rate acceleration to 120 beats/min.

**Pathophysiologic bases of RPA.** The term “repolarization alternans” acknowledges that alternation may be seen in the ST segment \((9,10)\), T wave and U wave \((21)\), all of which have been included in descriptions of “T-wave” alternans. Two competing mechanisms may underly RPA, reflecting the primacy of either repolarization or conduction \((9,20)\).

First, intrinsic dispersion of refractoriness may prevent complete depolarization of myocytes with the longest recovery times or alter their action potential morphology \((8)\), producing 2:1 depolarization. This may be facilitated by the steep restitution of ventricular myocardium, wherein small differences in the diastolic interval produce widely disparate action potential durations \((\text{APDs})\) \((22)\), which has been demonstrated under nonischemic conditions. The second mechanism invokes 2:1 conduction from tissue heterogeneity—triggered or automatic mechanisms that again lead to the discordant generation of action potentials. This has been demonstrated during ischemia \((23)\). In either case, the resulting dispersion of repolarization may result in evanescent barriers to propagation, wave front fractionation and a predisposition to re-entry \((8,24)\). The extent to which RPA reflects different mechanisms and, therefore, different arrhythmic predispositions under ischemic \((6,23)\) versus non-ischemic \((8,25)\) conditions remains unresolved.

**Hysteresis of RPA magnitude versus heart rate differs between patient subsets.** Repolarization alternans demonstrated distinct hysteresis between patients with and those without the substrates for inducible VT.

**INDUCIBLE PATIENTS.** The rise and fall in RPA magnitude, in concert with heart rate, is consistent in studies of human \((26)\) as well as hypothermic \((9)\) and ischemic \((7,11)\) canine ventricles and may reflect an increased dispersion of repolarization, or repolarization effects secondary to CL-related

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**Table 2.** Acceleration- and Deceleration-Dependent Sensitivity and Specificity of \( V_{alt} \geq 1.9 \, \mu\text{V} \) in Late Versus Throughout Repolarization for VT

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<thead>
<tr>
<th>Region</th>
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<td>Whole JT segment</td>
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*Chi-square test.

\( CL = \) cycle length; \( V_{alt} = \) absolute voltage of alternation.

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**FIGURE 4.** Receiver-operating characteristics of \( V_{alt} \) versus deceleration at 120 beats/min (CL 500 ms). The ROC relation at 120 beats/min (CL 500 ms) during acceleration versus deceleration at matched heart rates. As shown in Table 2, for the discriminant \( V_{alt} = 1.9 \, \mu\text{V} \) \((20)\), the best sensitivity and specificity resulted when late RPA was examined at 120 beats/min \((CL = 500 \, \text{ms})\) during acceleration versus deceleration. Similar results were found for TWAR \(\geq 1.9 \, \mu\text{V} \) for VT. The optimal discriminant in this study was \( V_{alt} = 2.6 \, \mu\text{V} \) examined in late repolarization during acceleration, providing 85.7% sensitivity and 86.3% specificity for inducible VT. The ROC plots were more favorable \((\text{curves displaced upward and to the right})\) for \( V_{alt} \) versus TWAR, for late versus whole repolarization and for acceleration versus deceleration. Raising the discriminant threshold increased specificity and reduced sensitivity.

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**TABLE 2.** Acceleration- and Deceleration-Dependent Sensitivity and Specificity of \( V_{alt} \geq 1.9 \, \mu\text{V} \) in Late Versus Throughout Repolarization for VT

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changes in activation (which follow CL alterations of 70 to 78 ms [27]). The relative contribution of these mechanisms has important implications and requires further study.

Although the RPA magnitude fell on rate deceleration, it remained significantly higher on acceleration at matched heart rates (120 beats/min) ($p = 0.018$ for $V_{alt}$). This may

Figure 4. Receiver-operating characteristics of $V_{alt}$ and TWAR (discriminant levels indicated on curves) for VT at 120 beats/min, showing markedly superior specificity of (A) acceleration over (B) deceleration. Improved specificity and specificity (curves upward and to the right) follow the use of $V_{alt}$ over TWAR, late over whole JT segment analysis and acceleration over deceleration sequences at 500 ms CL pacing. Similar trends were evident at other CLs.
represents persistence from intervening shorter CL pacing (13) or the actual deceleration process; our analyses suggest that this effect dissipates before steady-state (60 beats; Fig. 3). Deceleration-related alternans in these patients may reflect restitution, wherein APD lengthening from deceleration causes a shorter diastolic interval (DI, phase 4 duration), resulting in a reciprocally shorter DI and APD in the next beat, and so on (28).

**NONINDUCIBLE PATIENTS.** The RPA hysteresis in noninducible patients was quite different from that in inducible patients. First, RPA at a steady-state rate was insensitive to heart rate acceleration (as noted previously [16,26]), which may, speculatively, reflect a less easily perturbed physiologic dispersion of repolarization. Second, deceleration from 150 to 120 beats/min markedly increased the RPA magnitude ($p = 0.004$ for $V_{alt}$) (Fig. 2B). Clearly, this RPA augmentation directly follows deceleration. Such deceleration-induced alternans has been reported in APD (in similar patients [12]) and in the refractory period (in canine hearts [14]). Prolonging a single cycle (a postmature stimulus) can also induce alternans in APD (in canine [29] and feline [25] myocytes) and in the refractory period (in canine hearts [29]). Conduction alterations may contribute less to RPA in deceleration, because QRS morphology is less sensitive to CL lengthening than shortening (27). Furthermore, the observation that RPA was augmented to a lesser extent immediately after abrupt CL changes hints that restitution kinetics may be less operative in noninducible patients.

**Redistribution of RPA within the T wave.** Repolarization alternans became dynamically redistributed from late to early repolarization with heart rate deceleration in both patient groups (Fig. 2). Because RPA was markedly less specific for VT during deceleration (Fig. 4), such dispersion of early repolarization may be less indicative of arrhythmic substrates. Studies have recently emphasized the late T wave in re-entrant arrhythmogenesis, representing, as it does, a transmural gradient between full repolarization of the epicardium (T-wave peak), M cells (T-wave offset) and endocardium (T-wave descent) (15,30). This explains recent reports of a relationship between late QT dispersion, post-myocardial infarction survival (18) and arrhythmic tendency (in the rabbit heart [17]), and between late RPA and VT (16). In contrast, the significance of early RPA remains unclear. Under ischemic conditions, alternans in early repolarization (ST segment) may portend ventricular fibrillation (7,31,32). However, our study patients did not exhibit active ischemia, and early RPA predominated in noninducible patients (see Fig. 2 and our previous observations [16]), in whom subclinical ischemia would be particularly unlikely (Table 1).

**Implications for VT risk stratification.** This study demonstrates that RPA is sensitive to heart rate and its preceding rate dynamics, both of which significantly alter its sensitivity and specificity for VT. The optimal discriminant in our study was $V_{alt} \geq 2.6 \mu V$ measured in late repolarization after acceleration to a paced heart rate of 120 beats/min, providing a sensitivity of 85.7% and a specificity of 86.3% for inducible VT. However, Bayesian principles require that risk-screening algorithms be tailored to pretest likelihood. Therefore, in lower risk populations, a more specific discriminant (a higher level of $V_{alt}$) may be required to minimize the detection of false positive results (Fig. 4A).

Although the patients in this study differ from those comprising a typical screening population, our findings may extend previously described RPA discriminants for VT risk stratification. The earliest clinical RPA studies (9,10) suggest that TWAR $\geq 2.5$ to 3.0 effectively separated patients with and without VT. However, the TWAR calculation is greatly influenced by spectral noise, explaining the enhanced ROC of $V_{alt}$ versus TWAR in our study (Fig. 4). Recent reports using $V_{alt} \geq 1.9 \mu V$ and TWAR $\geq 2.5$ (sequences $\geq 1$ min duration; heart rate $\geq 110$ beats/min [20]) have not examined alternative discriminants and may not be optimal.

More fundamentally, however, rate threshold criteria effectively ignore the very heart rate variations that so significantly affect the predictive value of RPA for VT at any heart rate. From this study of repolarization dynamics, fixed-rate pacing during progressive acceleration may provide one strategy for better applying RPA to detect the substrates for VT. Studies of this nature may effectively calibrate the effects of rate fluctuations on RPA magnitude, thereby enhancing the interpretation of RPA measured during physiologic nonfixed heart rates.

**Study limitations.** Our use of simultaneous atrial and ventricular pacing precludes direct comparisons with studies by other investigators. Ventricular pacing may permit ventricular repolarization to be examined in isolation from the distinct response of Purkinje cells (13), whereas simultaneous atrial pacing permits the analysis of late repolarization, which may otherwise be distorted by atrial activity that may be dissociated or even cause artifactual alternans through retrograde conduction (33).

A notable issue relates to whether RPA co-migrates with other cardiac pathologic mechanisms, and therefore whether the mechanisms underlying RPA may vary as a function of substrate. Inducible patients in our study had worse cardiac systolic function and a higher incidence of previous myocardial infarction than did noninducible patients (Table 1). Although one previous study failed to correlate RPA with the presence of organic heart disease (10), structural disease can theoretically contribute to ventricular arrhythmias through infarct-related scar, repolarization effects of myocardial stretch (34) or slippage (35) and neurohumoral effects (7). The direct impact of myocardial pathology on RPA is being explored further in large observational studies currently under way (36).

Finally, we acknowledge that this is a small study, and its conclusions must be considered in this perspective. Addi-
tional studies in larger patient populations are required to validate our results.

Conclusions. The magnitude and temporal distribution of repolarization dispersion are sensitive to the direction of heart rate change as well as to absolute rate. Deceleration-related repolarization heterogeneity is timed earlier within repolarization, which may explain its less clear association with VT, as compared with acceleration-related changes. In this group, optimal separation of inducible from noninducible patients was found for $V_{tu} = 2.6 \, \mu V$ in late repolarization during acceleration to 120 beats/min.

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