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# T-Wave Alternans, Restitution of Human Action Potential Duration, and Outcome

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**Objectives** Our aim was to study the relationship between T-wave alternans (TWA) and rate-response (restitution) of repolarization in subjects with and without ventricular systolic dysfunction.

**Background** T-wave alternans is a promising predictor of sudden death, yet the mechanisms linking it with human ventricular arrhythmias are unclear. From theoretic considerations, we hypothesized that abnormal TWA is linked with steep restitution of action potential duration (APD) and that both predict arrhythmic outcome.

**Methods** We studied 53 subjects with left ventricular ejection fraction (LVEF) ≤40% and 18 control subjects. At electrophysiologic study, we recorded APD at 90% repolarization ($APD_{90}$) in the right (n = 62) or left (n = 9) ventricle during pacing while measuring TWA from the body surface.

**Results** As expected, TWA (at <109 beats/min) was more likely to be abnormal in study than in control subjects ($p < 0.01$). However, study (LVEF 28 ± 8%) and control (LVEF 58 ± 12%) subjects did not differ in $APD_{90}$ restitution slope maxima (1.2 ± 0.6 vs. 1.3 ± 0.6, respectively; $p = 0.82$) or numbers with steep slope (>1; 58% vs. 67%). T-wave alternans and simultaneous APD alternans always occurred at diastolic intervals where APD restitution was not steep ($p < 0.001$), and there was no relationship between maximum restitution slope and TWA magnitude. Over 829 ± 473 days, TWA ($p = 0.02$), but not restitution slope >1, predicted ventricular arrhythmias in subjects with LVEF ≤40%.

**Conclusions** The mechanism by which TWA predicts arrhythmic mortality does not reflect the maximum slope of ventricular APD restitution. Better understanding of the mechanisms underlying TWA may enable improved prediction and prevention of ventricular arrhythmias. (J Am Coll Cardiol 2007;50:2385–92) © 2007 by the American College of Cardiology Foundation

Sudden cardiac arrest (SCA) from ventricular arrhythmias claims over 300,000 lives per year in the U.S. alone (1). T-wave alternans (TWA) is a promising electrocardiographic (ECG) predictor of SCA (2–5), yet its mechanistic link with ventricular arrhythmias is unclear. A better understanding of the pathophysiologic basis for TWA is important to enable improved predictive or preventive strategies for ventricular arrhythmias.

A substantial body of literature from animal models and computer simulations shows that rapid heart rates (e.g., during pacing) may transition to re-entrant arrhythmias if the relationship of action potential duration (APD) to its preceding diastolic interval (i.e., APD restitution) has slope >1 at these rates (2,6,7). Such "steep" APD restitution, with other mechanisms (8,9), enables APD oscillations (alternans) and may lead directly to wavebreak and re-entry. Steep APD restitution was recently shown in human subjects (10) during rapid pacing (>200 beats/min) preceding ventricular arrhythmias (11). It has thus been proposed that beta-blockers (12), class III drugs (13), and amiodarone (14) may exert part of their antiarrhythmic effects by flattening APD restitution. However, it is unclear if steep APD restitution explains TWA, which predicts ventricular arrhythmias only if present at rates ≤109 beats/min (15). As a corollary, it has yet to be shown whether steep APD restitution improves the predictive value of TWA for arrhythmic outcome in humans.

We conducted a prospective study to test the hypotheses that TWA in patients with and without systolic dysfunction indicates steep restitution of ventricular APD, measured using

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**Abbreviations and Acronyms**

**APD** = action potential duration
**DI** = diastolic interval
**ECG** = electrocardiogram/electrocardiography
**LV** = left ventricle/ventricular
**LVEF** = left ventricular ejection fraction
**MAP** = monophasic action potential
**RV** = right ventricle/ventricular
**SCA** = sudden cardiac arrest
**TWA** = T-wave alternans
**VF** = ventricular fibrillation
**VT** = ventricular tachycardia

a monophasic action potential (MAP) catheter at electrophysiologic study, and that both predict long-term arrhythmic outcome in patients with systolic dysfunction.

## Methods

**Subject recruitment.** The study protocol was approved by the Institutional Review Board of the University of California and Veterans Affairs Medical Centers, San Diego, California, and all subjects provided written informed consent. We included 53 study subjects with left ventricular ejection fraction (LVEF) ≤40% undergoing programmed ventricular stimulation and 18 control subjects undergoing ablation of supraventricular tachycardias (LVEF >40%). We excluded another 10 study and 5 control subjects with poor data quality. We also excluded subjects who had experienced sustained ventricular arrhythmias or aborted SCA who were within 30 days of an acute coronary syndrome or 6 weeks of coronary revascularization or who had experienced ventricular pacing (to minimize T-wave memory effects).

**Ventricular pacing at electrophysiologic study.** Subjects were studied in the post-absorptive state, under minimal sedation. Therapy with beta-blockers was continued. In addition to clinically indicated catheters, a 7-F MAP catheter (EP Technologies, Sunnyvale, California) was advanced transvenously to the apex of the right ventricle (RV) (n = 62), or via the aorta to the apex of the left ventricle (LV) (n = 9) with heparin anticoagulation. A subgroup of subjects (n = 12) underwent dual-site simultaneous MAP recordings from the RV apex/LV apex (n = 3) or RV apex/RV outflow tract (n = 9). Electrocardiograms were recorded on a physiologic recorder (Bard, Billerica, Massachusetts) filtered at 0.05 to 100 Hz (ECG), 0.05 to 775 Hz (MAPs), and 30 to 500 Hz (other intracardiacs) and digitized at 1 kHz.

Pacing was performed from the RV or LV apex (with simultaneous atrial pacing to avoid variable V:A conduction [16]) before attempted ventricular tachycardia (VT)/ventricular fibrillation (VF) induction (study subjects) or ablation (control subjects). First, we assessed standard restitution by introducing single extrastimuli while pacing at cycle length 500 ms for 10 beats, coupled at 400 ms then progressively earlier in 20-ms steps to 300 ms, then in 10-ms steps to the effective refractory period (similar to another clinical report [11]). Second, we performed constant pacing for TWA measurement for 90 s at cycle length 600 ms (100 beats/min), 550 ms (109 beats/min), 500 ms (120 beats/min), 550 ms, then 600 ms (17). Following this protocol, the clinical procedure was performed. Programmed ventricular stimulation was considered to be "positive" if monomorphic ventricular tachycardia was induced with 1 to 3 extrastimuli, or polymorphic VT/VF was induced with 1 to 2 extrastimuli (18). Cardioverter defibrillators were implanted per clinical guidelines (18).

**Analysis of TWA.** We measured TWA from the surface ECG using HeartWave (Cambridge Heart, Bedford, Massachusetts) during ventricular pacing, then remeasured TWA immediately during right atrial pacing using the same protocol. Meticulous attention was paid to achieving excellent skin contact with HiRes electrodes (Cambridge Heart) (15).

Each TWA report was classified as positive, negative, or indeterminate (15) by consensus from 3 reviewers blinded to clinical variables, including outcome. We compared positive/negative TWA to APD metrics; for outcome analyses, we grouped positive and indeterminate TWA during atrial pacing as "abnormal" (4). Peak TWA magnitude was also measured in microvolts (19).

**Analysis of APD restitution.** Electrocardiograms were exported at 16-bit digital resolution for offline analysis using custom software written in Labview (National Instruments, Austin, Texas) by SMN. We carefully measured APD at 90% repolarization ($APD_{90}$) for each analyzed beat using our validated software (20). Briefly, MAP onset was assigned as the time of maximum rate of change of voltage (dV/dt) of the MAP upstroke. Phase 2 (plateau) and phase 4 (diastolic) voltages were identified. The $APD_{90}$ was computed automatically to span the interval from MAP onset to 90% voltage recovery from phase 2. Diastolic interval (DI) is the interval from $APD_{90}$ of the last drive-train beat to MAP onset (maximum dV/dt) of the current beat.

We created standard APD restitution curves for each subject using DI-$APD_{90}$ pairs for each extrastimulus. Slopes were 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 (11). We also determined the range of DI for which slopes were ≥1 (11). Dynamic APD restitution (21) was not studied to avoid pacing our study patients (LVEF 28 ± 8%, BNP 640 ± 825 pg/ml) at rates of >200 beats/min. We compared maximum slopes (22) and the $APD_{90}$ range (maximum to minimum) between subjects.

**Prospective follow-up.** Subjects were followed prospectively for 829 ± 473 days (median 776 days, interquartile range 587 to 1,126 days) using 6 monthly device interrogations, a telephone questionnaire, and reviews of electronic medical records over the entire follow-up period. End points were assigned blinded to TWA and APD analyses. Arrhythmia detection was programmed uniformly in device subjects, and ECGs were verified by consensus. The primary end point was appropriate device therapy or sustained VT/VF. The secondary end point was the combined occur-

**Table 1** Baseline Clinical Characteristics

| | Study Subjects (n = 53) | Control Subjects (n = 18) | p Value |
|---|---|---|---|
| Age, yrs | 65.4 ± 13.3 | 65.8 ± 10.6 | 0.91 |
| Gender, M/F | 52/1 | 15/3 | 0.05 |
| Ejection fraction, % | 28 ± 8 | 58 ± 12 | <0.001 |
| Coronary disease, n | 47 | 4 | <0.001 |
| Hypertension, n | 11 | 3 | 1.00 |
| Diabetes mellitus, n | 8 | 2 | 1.00 |
| BNP, pg/ml | 640 ± 825 | 131 ± 282 | 0.02 |
| Medication use, n | | | |
| Beta-blockers | 39 | 7 | 0.01 |
| ACE inhibitors/ARB | 47 | 11 | 0.01 |
| Spironolactone | 10 | 1 | 0.27 |
| CCB | 11 | 4 | 1.00 |
| Digoxin | 21 | 2 | 0.04 |
| Amiodarone | 5 | 1 | 1.00 |
| Statins | 38 | 9 | 0.23 |

Categoric variables are compared using Fisher exact test, continuous variables using *t* test.
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BNP = B-type natriuretic peptide concentration; CCB = calcium-channel blockers.

rence of ventricular arrhythmias or all-cause mortality. We compared the predictive value of TWA, APD restitution slope, and inducible ventricular arrhythmias for both end points.

**Statistical analysis and sample size considerations.** Continuous data are presented as mean ± SD and were compared using the 2-tailed *t* test. Paired continuous variables were compared using the paired 2-tailed *t* test. The Fisher exact test was applied to comparisons of categoric variables. Kaplan-Meier survival curves were constructed for event-free survival. Statistics were analyzed using SPSS software (SPSS Inc., Chicago, Illinois). Significance was assessed at a 2-tailed alpha level of 0.05.

## Results

The baseline characteristics of study and control subjects are listed in Table 1.

**Ventricular action potential duration (APD).** Figure 1 illustrates ventricular MAPs during close-coupled extrastimuli in study and control subjects. We measured APD in the RV in 62 subjects (Figs. 1A and 1C) and in the LV in 9 subjects (n = 6 study and 3 control) (Fig. 1B).

**Intersite concordance of APD restitution.** In subjects with simultaneous 2-site MAPs, the concordance of APD restitution (slope <1 vs. slope ≥1) between sites was 83% (kappa statistic 0.625). Figure 2A shows a subject with RV/LV recordings in whom maximum APD restitution slopes were RV 1.58 and LV 1.19. Figure 2B shows a subject in whom dual-site MAPs showed APD restitution slopes of 1.42 (RV apex) and 1.31 (RV outflow tract).

Overall, there was no significant difference in APD restitution slope between RV and LV (1.2 ± 0.6 vs. 1.4 ± 0.6; p = 0.46), so we pooled both sites for each group. In subjects with dual-site RV recordings, we used only recordings from the RV apex for group comparisons.

**Action potential kinetics between groups.** As summarized in Table 2, $APD_{90}$ minima were longer in study than in control subjects (205 ± 38 ms vs. 183 ± 32 ms; p = 0.04). However, there was no difference between subject groups in maximum $APD_{90}$ restitution slope (1.2 ± 0.6 vs.

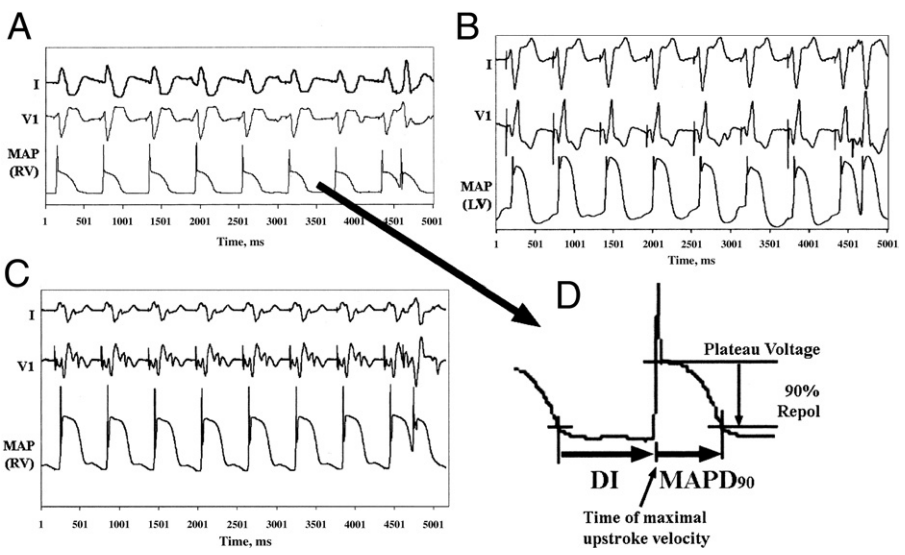


**Figure 1** MAPs During Single Ventricular Extrastimuli

Study subjects with coronary disease and left ventricular (LV) ejection fractions 26% **(A)** and 38% **(B)**. **(C)** Control subject. **(D)** Diastolic interval (DI) span from monophasic action potential duration at 90% repolarization ($MAPD_{90}$) of the preceding beat to the computed maximum rate of change of voltage of the present beat. MAP = monophasic action potential; RV = right ventricular.

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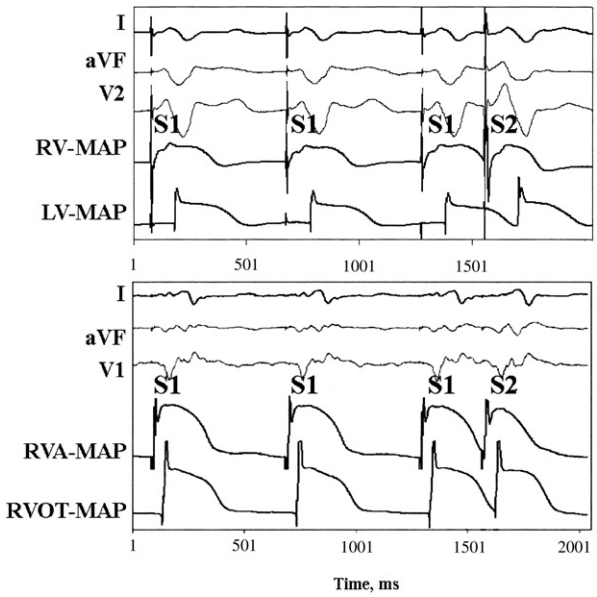


**Figure 2** Simultaneous Dual-Site MAP Recordings

**(A)** Study subject at the right ventricular (RV) apex and left ventricular (LV) apex. Maximum action potential duration (APD) restitution slopes were RV 1.58 and LV 1.19. **(B)** Study subject at the apex (RVA) and outflow tract (RVOT). Maximum APD restitution slopes were RVA 1.42 and RVOT 1.32. MAP = monophasic action potential.

1.3 ± 0.6; p = 0.82), prevalence of maximum slope ≥1 (study 58%, control 67%; p = 0.59), or $APD_{90}$ range. For subjects with steep APD restitution in each group, there was no difference in DI range for which APD restitution slope was ≥1 (Table 2). As a measure of the validity of restitution slope comparisons, the minimum DI did not differ between study and control subjects (Table 2), or between study patients with and without restitution slope ≥1 (19 ± 13 ms vs. 17 ± 12 ms; p = 0.62).

**TWA and APD.** Thirty-three study subjects had positive TWA tests during atrial pacing, compared with 4 control subjects (Fisher exact test: p = 0.006) (Table 2). Notably, each case of positive TWA arose at DI when the slope of the APD restitution curve was not steep (p < 0.001). Moreover, the presence of a steep APD restitution slope (≥1) was unrelated to positive TWA (atrial pacing) for all subjects (p = 0.58) or study subjects (p = 0.33; both using Fisher exact test). Steep restitution was also unrelated to positive TWA during ventricular pacing (p = 0.72 and 0.7, respectively). There was also no correlation between actual maximum APD restitution slope and peak TWA magnitude ($V_{alt}$) in microvolts (p = 0.50). Indeterminate TWA were excluded from all comparisons.

Figure 3 shows a study subject in whom TWA was positive despite the fact that $APD_{90}$ restitution was not steep (maximum slope 0.73). When TWA was positive during steady-state pacing at 109 beats/min, $APD_{90}$ alternated (for 48 of 64 beats) (Fig. 3, inset) within the range 245 to 290 ms with DI of 305 to 260 ms. However, this entire DI range fell on the flat portion of the APD restitution curve (Fig. 3), far removed from the maximum restitution slope at short DI.

Figure 4 shows a control subject in whom TWA was negative even though $APD_{90}$ restitution was steep, with maximum slope 1.82 and slope ≥1 for DI of 2 to 47 ms (range 45 ms). The $APD_{90}$ at 109 beats/min ranged from 280 to 290 ms with DI 270 to 260 ms. Again, this DI range fell on the flat portion of the restitution curve, far removed from its maximum slope at short DI. Notably, APD alternans was found inconsistently at these long diastolic intervals and when present was intermittent during pacing. This was true for both LV and RV MAP recordings.

**Inducible arrhythmias in study subjects.** Twenty patients had inducible ventricular arrhythmias and 33 patients did not. We compared steep APD restitution with arrhythmia

**Table 2** Repolarization Dynamics

| | Study Subjects | Control Subjects | p Value |
|---|---|---|---|
| T-wave alternans (RA pacing) | | | 0.01 |
| Positive | 19 | 1 | |
| Indeterminate | 14 | 3 | |
| Negative | 20 | 14 | |
| Electrical restitution of $APD_{90}$ | | | |
| Right/left ventricle | 47/6 | 15/3 | |
| Slope maximum | 1.23 ± 0.60 | 1.27 ± 0.55 | 0.82 |
| No. with maximum slope ≥1, % | 58 | 67 | 0.59 |
| Minimum DI, ms | 19 ± 13 | 16 ± 12 | 0.47 |
| DI range for which slope ≥1 | 31 ± 14 | 34 ± 12 | 0.65 |
| $APD_{90}$ maximum, ms | 272 ± 43 | 258 ± 43 | 0.27 |
| $APD_{90}$ minimum, ms | 205 ± 38 | 183 ± 32 | 0.04 |
| $APD_{90}$ range, ms | 68 ± 34 | 78 ± 38 | 0.26 |
| $APD_{90}$ range, % of baseline $APD_{90}$ | 24 ± 11 | 29 ± 11 | 0.12 |

$APD_{90}$ = action potential duration at 90% repolarization; DI = diastolic interval; RA = right atrial.

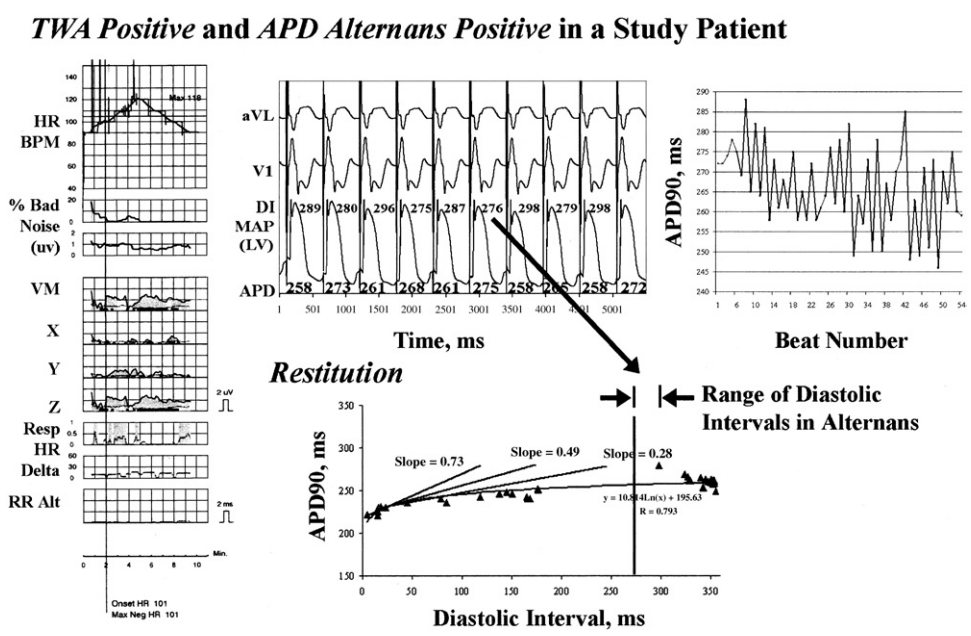


**Figure 3** **Discordance of TWA (Positive) and APD Restitution (Maximum Slope <1) for Study Subject B in Figure 1**

Despite positive T-wave alternans (TWA) at 109 beats/min (BPM) (cycle length 550 ms) and action potential duration (APD) alternans (shown in beat plot), the APD restitution was flat (maximum slope 0.73 from sequential linear plots). Importantly, note that diastolic intervals during alternans lie on the flat portion of the APD restitution curve at this rate. HR = heart rate; LV = left ventricular; Neg = negative; Resp = respiratory alternans; RR Alt = heart rate alternans; VM = voltage of alternation; other abbreviations as in Figure 1.

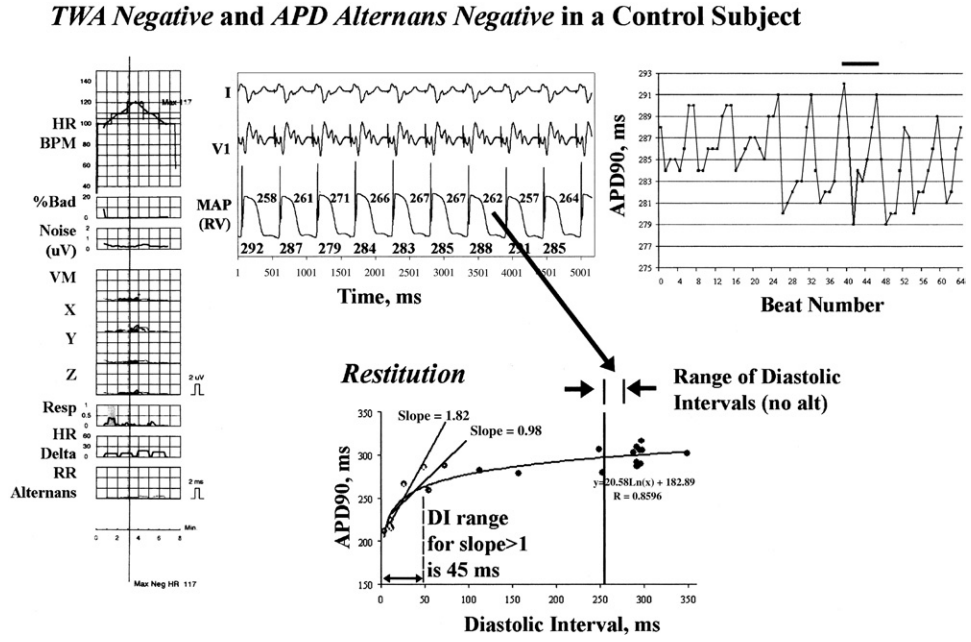


**Figure 4** **Discordance of TWA (Negative) and APD Restitution (Maximum Slope >1) for Control Subject B in Figure 1**

T-wave alternans is negative, corresponding to the absence of APD alternans. However, APD restitution is steep (maximum slope 1.82). Note that diastolic intervals at this rate (109 beats/min) interact with the flat portion of the APD restitution curve, even though the left-hand portion is steep. Alt = alternans; other abbreviations as in Figures 1 and 3.

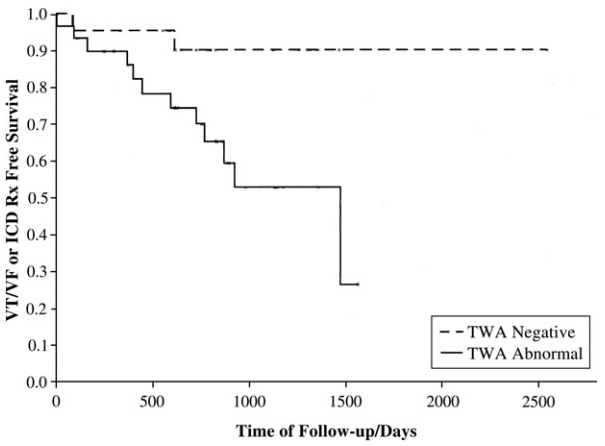


**Figure 5** Kaplan-Meier Survival Curves Using TWA as the Primary End Point (Study Subjects)

Abnormal T-wave alternans (TWA) separates patients who meet versus those who do not meet the primary end point (p = 0.024). ICD = implantable cardioverter-defibrillator; Rx = treatment; VT/VF = ventricular tachycardia/ventricular fibrillation.

inducibility, both measured using extrasystoles. The APD restitution maximum slope did not differ for study subjects with and without inducible arrhythmias (1.2 ± 0.4 vs. 1.3 ± 0.7; p = 0.70), and there was no significant relationship between APD restitution slope ≥1 and inducible arrhythmias (p = 0.21).

**Relationship of repolarization indexes to outcome.** Of the 53 study patients (LVEF ≤40%), 14 experienced the primary end point and 13 died. Neither maximum APD restitution slope (1.26 ± 0.59 vs. 1.21 ± 0.61; p = 0.87) nor the DI range for slope ≥1 (27 ± 13 ms vs. 33 ± 15 ms; p = 0.36) differed for patients with or without the primary end point. Restitution indexes also did not correlate with the secondary end point. Implantable cardioverter defibrillators were placed in a similar proportion of study patients with (64%) and without (59%; p = 0.76) APD restitution slope ≥1.

On Kaplan-Meier analysis, the primary end point was predicted by positive (p = 0.03) and abnormal (p = 0.02) (Fig. 5) TWA during atrial pacing. Abnormal TWA also predicted the secondary end point (p = 0.03). However, steep APD restitution (slope ≥1) did not predict the primary end point (p = 0.85) (Fig. 6) or the secondary end point.

## Discussion

This human study is the first to relate TWA to ventricular APD restitution and clinical outcome. We found that at the relatively slow heart rates at which TWA predicts outcome, APD restitution was flat in all patients regardless of its maximum slope at shorter diastolic intervals. As a result, the presence or absence of TWA did not result from the maximum slope of APD restitution, measured at 1 to 2 ventricular sites in subjects with and without systolic dysfunction. We also found that although maximum APD restitution slope >1 is an important theoretical component of arrhythmogenesis, TWA but not standard APD restitution slope >1 alone predicted spontaneous ventricular arrhythmias on 2.5-year follow-up.

**Alternans at rapid rates and ventricular tachyarrhythmias.** Many mechanisms combine to initiate ventricular arrhythmias (6). Tissue heterogeneity, both physiologic and pathologic from scar, exaggerates repolarization dispersion that may cause wavefront fractionation and re-entry. Repolarization dispersion may be further exaggerated by an altered activation sequence from a premature beat or by the dynamics of conduction or repolarization. Fast heart rates (short DI) interact with the left-hand portion of the APD restitution curve (Figs. 3 and 4), where slope is maximal. A maximum slope of >1 has been shown to cause APD alternans and lead directly to wavebreak and re-entry (13). In humans, Koller et al. (11) recently showed steep APD restitution for a wide range of fast rates in patients with structural disease, and at rates >200 beats/min, slope >1 immediately preceded alternans and/or VT. Animal models also suggest that spatial gradients of restitution (7,8), conduction slowing (8), and the dynamics of calcium cycling (23) contribute to APD alternans at rapid rates.

**TWA at slow rates and APD restitution.** Notwithstanding that substantial body of work, it remains unclear how TWA relates to arrhythmic substrates (2). Notably, TWA is predictive of events only at slow rates ≤109 beats/min (15) and is most specific at <90 beats/min (19). Results from the present human study support emerging theoretic arguments (24) that steep maximum APD restitution slope, even if observed, does not easily explain alternans at slow rates where restitution is typically flat (Figs. 3 and 4).

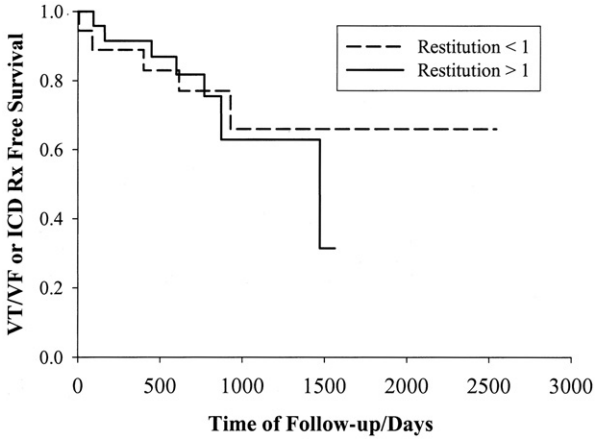


**Figure 6** Kaplan-Meier Survival Curves Using Maximum APD Restitution Slope >1 as the Primary End Point

Slope >1 did not separate study patients who did and did not meet the primary end point (p = 0.85). APD = action potential duration; other abbreviations as in Figure 5.

As alternans of APD was only inconsistently detected with TWA at <110 beats/min, the present results may reflect an inability to sample regions exhibiting MAP alternans, because limited sites were available for measurement. Alternatively, it is possible that TWA reflects spatial gradients of repolarization, abnormal conduction restitution, or mechanisms such as abnormal calcium cycling (9,23) rather than alternans of APD. Notably, although unmeasured sites (e.g., small regions of the LV) may exhibit APD restitution steep enough to facilitate arrhythmias it is unclear that this itself would lead to alternans at the long diastolic intervals corresponding to <110 beats/min.

**APD restitution, inducible VT/VF, and outcome in humans.** To the best of our knowledge, this is the first human study examining APD restitution and outcome. Earlier studies have studied APD restitution vis-à-vis results from clinical electrophysiologic studies.

An important study showed that steep restitution of unipolar activation-recovery interval (a surrogate for APD) correlated with inducible VT in 18 subjects (10). However, because some noninducible subjects had a slope >1 (group slope 0.97 ± 0.37), the predictive value of slope >1 was unclear, and the study did not report follow-up (10). The present study revealed no relationship between APD restitution slope >1 and inducible VT/VF. Our work agrees with Koller et al. (11), who, in 36 subjects, showed that neither standard nor dynamic APD restitution slopes differed between subjects with and without structural disease, and confirms studies that maximum APD restitution slope in control subjects may lie below or above unity (22).

**Clinical implications.** The present results suggest that the dependence of APD on DI (restitution) does not produce clinical TWA and may not predict future arrhythmias. Accordingly, our results have implications for therapeutic approaches to stabilize DIs via pacing (25) or to flatten APD restitution. Future clinical studies should use multielectrode mapping to investigate whether TWA and future arrhythmias are related to spatial dispersion in APD restitution (7,11), conduction dynamics (8,26), myocardial stretch (27), and abnormal calcium cycling (23).

**Study limitations.** A major limitation of this study is that we measured APD at only 1 to 2 RV/LV sites for technical and patient-care considerations. Because spatial heterogeneity in restitution is arrhythmogenic in animals (7), and spatial nonuniformities have been reported in human activation-recovery intervals (28) and TWA (29), future work should study APD at multiple biventricular sites in patients with LV dysfunction. A second limitation is that we examined only standard APD restitution. Steep dynamic restitution (via pacing as fast as 240 beats/min) (11,21) may explain wavebreak (i.e., transitions to VF), yet even such curves are flat at the long diastolic intervals corresponding to ≤109 beats/min (11). We did not perform such pacing, owing to safety concerns.

We measured APD restitution during ventricular pacing, because our preliminary studies showed that the earliest premature beats needed to define the steep portion of APD restitution often blocked at the atrioventricular node when delivered in atrial pacing. For consistency, we thus reported alternans during ventricular pacing, as previously validated by ourselves (2) and others. Although beta-blocker therapy may flatten the slope of APD restitution (12), we did observe steep APD restitution in this study, and TWA remains predictive of clinical events under such conditions (30). The 15 patients excluded owing to poor data quality are unlikely to have influenced our results, because exclusion was not based on demographic or outcome data. Finally, our study population reflects the male preponderance of Veterans Affairs populations. Although gender differences in TWA have not been reported, future studies should include more women, who have longer QT intervals and may differ in APD kinetics.

## Conclusions

T-wave alternans was not related to the maximum slope of APD restitution in patients with or without systolic dysfunction. The APD restitution slope exceeded 1 in many subjects, but did not comigrate with TWA or predict outcome in the present prospective study. Future studies should address alternative mechanisms linking TWA with ventricular arrhythmias to open avenues for improved predictive or preventive measures for arrhythmic death.

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