Arrhythmia/Electrophysiology

Intracardiac Electrogram T-Wave Alternans/Variability Increases Before Spontaneous Ventricular Tachyarrhythmias in Implantable Cardioverter-Defibrillator Patients

A Prospective, Multi-Center Study

Charles Swerdlow, MD; Theodore Chow, MD; Mithilesh Das, MD; Anne M. Gillis, MD; Xiaohong Zhou, MD; Athula Abeyratne, PhD; Raja N. Ghanem, PhD

Background—T-wave alternans (TWA) increases before ventricular tachycardia (VT) or fibrillation (VF), suggesting that it may warn of VT/VF in implantable cardioverter-defibrillator patients. Recently, we described a method for measuring alternans and nonalternans variability (TWA/V) from electrograms (EGMs) stored in implantable cardioverter-defibrillators before VT/VF. The goal of this prospective, multicenter study was to determine whether EGM TWA/V was greater before VT/VF than at baseline.

Methods and Results—We enrolled 63 implantable cardioverter-defibrillator patients. TWA/V was computed from stored EGMs before spontaneous VT/VF and from sequential windows of 8 pairs of beats using 4 different control recordings: baseline rhythm, rapid pacing at 105 bpm, segments of ambulatory Holter EGMs matched to the time of VT/VF episodes, and EGMs before spontaneous supraventricular tachycardia. During follow-up, 28 patients had 166 episodes of VT/VF. TWA/V was greater before VT/VF (62.9±3.1 μV; n=28) than during baseline rhythm (12.8±1.8 μV; P<0.0001; n=62), during rapid pacing (14.5±2.0 μV; P<0.0001; n=52), before supraventricular tachycardia (27.5±6.1 μV; P<0.0001; n=9), or during time-matched ambulatory controls (12.3±3.5 μV; P<0.0001; n=16). By logistic regression, the odds of VT/VF increased by a factor of 2.2 for each 10-μV increment in TWA/V (P<0.0001). Conclusions—In implantable cardioverter-defibrillator patients, EGM TWA/V is greater before spontaneous VT/VF than in control recordings. Future implantable cardioverter-defibrillators that measure EGM TWA/V continuously may warn patients and initiate pacing therapies to prevent VT/VF. (Circulation. 2011;123:1052-1060.)

Key Words: implantable cardioverter defibrillator ■ tachyarrhythmias ■ T-wave alternans

B eat-to-beat alternation in duration and amplitude of ventricular action potentials is a form of dynamic electric instability that predisposes to ventricular tachycardia (VT) or ventricular fibrillation (VF). 1,2 Alternans^{2–7} and nonalternating repolarization variability 1,7 increases before VT/VF under some conditions.

Clinical Perspective on p 1060

T-wave alternans (TWA), the surface ECG manifestation of action-potential repolarization alternans, is measured to estimate long-term risk of VT/VF.⁸⁻¹⁰ TWA recorded from intracardiac electrograms (EGMs) of implantable cardioverter-defibrillators (ICDs) correlates well with ECG TWA.¹¹ Investigators have hypothesized that EGM TWA can serve as a predictor of spontaneous VT/VF.^{4,6,11-14}

To test this hypothesis, we developed and validated a method that measures TWA and nonalternans T-wave variability (TWA/V) from ventricular EGMs stored in ICDs before VT/VF.¹⁵ Retrospective data indicate that EGM TWA/V is greater before spontaneous VT/VF than in limited baseline recordings¹⁵ or after ICD shocks.¹⁶ This prospective, multicenter study tested the hypothesis that high-amplitude EGM TWA/V precedes spontaneous VT/VF in ICD patients.

Methods

Each institution obtained approval from its Investigational Research Committee for this prospective, multicenter, nonrandomized study.

Patients

Patients met 4 criteria: (1) They had had a Medtronic ICD implanted for at least 1 month; (2) in the last 3 months, they either had

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From the Cedars-Sinai Heart Institute, Los Angeles, CA (C.S.); Ohio Heart and Vascular Center, Cincinnati (T.C.); Indiana University School of Medicine, Indianapolis (M.D.); Faculty of Medicine University of Calgary, Calgary, AB, Canada (A.M.G.); and Medtronic, Inc, Mounds View, MN (X.Z., A.A., R.N.G.).

Correspondence to Charles Swerdlow, MD, Cedars-Sinai Medical Towers, 8635 W Third St, Ste 1190-W, Los Angeles, CA 90048. E-mail swerdlow@ucla.edu

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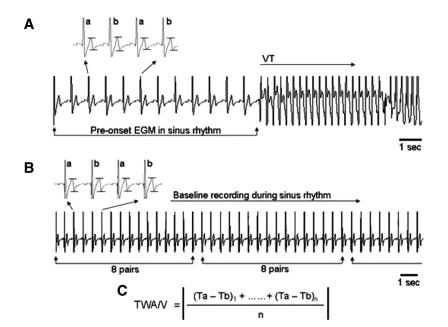


Figure 1. T-wave alternans and nonalternans variability (TWA/V) measurement for preonset electrogram before ventricular tachycardia (VT; A) and control baseline electrogram (EGM) in sinus rhythm (B). Each peak-to-peak T-wave amplitude was measured between 2 horizontal bars (enlarged tracing) and assigned to the a-b order shown. The measured value of TWA/V was the absolute value of the average beat-to-beat difference (C). Control beat-to-beat TWA/V was averaged from 8-pair, nonoverlapping sliding windows that spanned the entire recording.

spontaneous, sustained VT/VF before implantation or received ICD therapy for spontaneous VT/VF; (3) their doses of β -blockers and other heart failure medications were constant for 1 week, and no dosage changes were planned; and (4) they were likely to tolerate pacing at 105 bpm. Patients were excluded if measurement of TWA/V was not feasible (eg, permanent atrial fibrillation with rapid atrioventricular conduction).

Data Collection

ICD Programming

ICDs were programmed to store preonset EGMs before detected VT/VF. EGMs before device-detected supraventricular tachycardia (SVT) were also stored. At least 1 EGM channel recorded the right ventricular coil to active can (far-field) EGM with a range of ±2 or 4 mV to ensure adequate resolution for measurement of TWA/V. The number of intervals to detect VT or VF was ≤18 to ensure sufficient preonset EGMs for analysis. The ICD amplifier for far-field EGMs sampled at 256 Hz with a band-pass filter of 3 to 100 Hz.

Preonset EGM TWA/V

Stored EGMs before episodes of VT were recorded for 5 to 10 seconds, depending on the ICD model and duration of spontaneous VT/VF. We reviewed all stored EGMs. For analysis of EGMs before VT/VF, we included only episodes that received therapy for true VT/VF and excluded episodes of SVT, self-terminating VT, and oversensing and those with more arrhythmic preonset beats than sinus beats. ICDs were interrogated at 3 and 6 months; data were stored electronically as save-to-disk files.

Control EGM TWA/V

Four independent control data sets of EGMs were used to analyze TWA/V: (1) recordings during baseline rhythm at rest, (2) recordings during pacing at 105 bpm (rapid-pacing control), (3) recordings of ambulatory EGMs matched to the time(s) of day at which VT/VF occurred (time-matched ambulatory control), and (4) preonset stored EGMs before inappropriate detection of SVT as VT or appropriate rejection of SVT by an SVT-VT discrimination algorithm. The first 3 control data sets were recorded with telemetry Holter monitors (model DR190, Northeast Monitoring, Maynard, MA) that recorded

intracardiac EGMs and ICD marker channel. The fourth data set was composed of EGMs stored as an arrhythmia episode by the ICD.

Real-time baseline rhythm control recordings were performed for 10 minutes. Pacing was then performed at 105 bpm for 5 minutes to measure TWA/V at a higher rate (rapid-pacing control). In patients with dual- or triple-chamber ICDs and adequate conduction, we performed both atrial pacing (AAI) and atrial (right)-ventricular rapid pacing. If 1:1 atrioventricular conduction was not present during AAI pacing, only atrioventricular pacing was performed. In patients with single-chamber ICDs, we performed only ventricular (VVI) pacing.

Patients who had VT/VF during the study wore a 24-hour telemetry Holter starting within 1 week of the clinic visit at which VT/VF was identified. To control for diurnal variation in EGM TWA/V, we analyzed segments of these ambulatory Holter recordings that matched the time(s) of day at which VT/VF occurred. The start time of the time-matched ambulatory control was determined by calculating the time offset between the Holter start time and the detection of VT/VF by the ICD extracted from the save-to-disk file. In addition to the single 8-pair window that most closely matched the onset of VT/VF, we computed TWA/V from 5-minute segments beginning at the start time of the time-matched ambulatory controls. This duration was chosen to be comparable to that during baseline rhythm and rapid-pacing controls.

Measurement of EGM TWA/V

We used a previously validated, simple averaging method¹⁵ to measure EGM TWA/V on a beat-to-beat basis using custom software written in Matlab (release 7.0, version 14, Matlab Inc, Natick, MA). Briefly, after pairs with arrhythmic beats were removed, beat-to-beat alternans was calculated as the difference in T-wave amplitude of sequential beat pairs. TWA/V was determined as the absolute value of the average of these differences over an analysis window (Figure 1A). In this study, the analysis duration consisted of all analyzable pairs for stored EGMs before VT/VF or SVT.

In all control recordings, TWA/V was measured from a nonoverlapping sliding window of successive 8 pairs until all data were processed (Figure 1B). The number of pairs was selected as an approximate match to the number of preonset pairs (7) in our pilot study. Thus, the durations of the individual analyzed control windows were comparable to those of preonset EGMs, and multiple TWA/V measurements were performed during each control recording.

For time-matched ambulatory control recordings, we also measured TWA/V for the single time-matched ambulatory 8-pair window that matched the time of the detected VT/VF episode.

Data Analysis

Analyses were performed with the SAS generalized linear mixed model procedure (GLIMMIX, SAS Institute Inc, Cary, NC). Mean values, proportions, percentages, and their SEs were estimated with the fitted model (least-squares estimates). Wherever applicable, these estimates were obtained by adjusting for the correlation between repeated measurements on the same subject using the random-effects model. Values are presented as mean ± SE unless otherwise indicated, except in tables, where mean ± SDs are shown. When >1 hypothesis was tested for a given set of data (except for TWA/V demographics comparisons), P values were adjusted to keep the probability of wrongfully rejecting the null hypothesis in at least one of the tests to ≤ 0.05 .

In each patient, we determined the 90th sample percentile of the TWA/V measurements from all 8-pair windows during baseline rhythm controls, rapid-pacing controls, and time-matched ambulatory controls. This value corresponds to a false-positive rate of 10%. For preonset EGMs before VT/VF, we estimated the percentage of the TWA/V amplitude above these 90th sample percentile values for individual patients. Additionally, we compared mean TWA/V amplitude in preonset EGMs before VT/VF with mean TWA/V amplitude in each of the 4 control data sets.

For time-matched, ambulatory controls, we also compared the mean TWA/V in preonset EGMs before each VT/VF episode with the mean TWA/V in a corresponding single time-matched, 8-pair window.

To determine the short-term predictive value of TWA/V for VT/VF, we used a logistic regression model with TWA/V as the only predictor. A receiver-operating characteristic (ROC) curve was also constructed to evaluate the predictive power of TWA/V for VT/VF. For the ROC, we combined all control data sets to determine specificity and used TWA/V before VT/VF to determine sensitivity. We computed the ROC curve and the area under the ROC curve using 2 different approaches. First, we fitted a logistic regression without accounting for the correlation of multiple episodes within each patient (unadjusted ROC curve). Second, we accounted for the correlation of multiple episodes within a patient using the randomeffects model (adjusted ROC curve).

We compared TWA/V in control recordings for subgroups dichotomized for age, New York Heart Association class, and left ventricular ejection fraction. We also analyzed subgroups identified by use of β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, amiodarone, and any antiarrhythmic drug.

Results

Clinical Data

Clinical characteristics of the 63 enrolled patients are summarized in Table 1. Of these, 35 patients (56%) experienced a total of 426 appropriate VT/VF detections and therapies during follow-up. Table 1 shows that the clinical characteristics of these 35 patients did not differ significantly from those of the 28 patients (44%) who did not have VT/VF during follow-up.

TWA/V Before Spontaneous VT/VF

The flow diagram in Figure 2 shows that stored preonset EGMs before VT/VF could be analyzed before 166 episodes in 28 patients. There were 140 episodes of monomorphic VT (cycle length, 325±41 milliseconds) and 26 of polymorphic VT (cycle length 282±45 milliseconds). Overall, 6±3 pairs of beats (range, 2 to 22 pairs) were available for analysis. The number of

Table 1. Patient Baseline Demographics

Variable	Patients Without VT/VF Episodes (n=28)	Patients With VT/VF Episodes (n=35)	Р
Age, y	67±11	71±14	0.22
Male gender, n (%)	24 (86)	32 (91)	0.69
LVEF, % (n)	$36\pm15~(26)$	32±14 (34)	0.34
Heart disease			
Ischemic cardiomyopathy, n (%)	11 (39)	12 (34)	0.79
Nonischemic cardiomyopathy, n (%)	17 (61)	23 (66)	
β-blocker, n (%)	26 (93)	30 (86)	0.45

VT/VF indicates ventricular tachycardia/fibrillation.

pairs analyzed was ≤4 in 69 episodes (41.6%), 5 in 14 episodes (8.4%), 6 in 14 episodes (8.4%), 7 to 9 in 44 episodes (26.5%), and \geq 10 in 25 episodes (15.1%). Over this range of pairs, there was no significant correlation between the number of pairs and measured TWA/V amplitude (F value=0.85; P=0.3592). Overall, TWA/V amplitude was $62.9\pm3.1~\mu$ V.

TWA/V in Control Recordings

TWA/V during baseline rhythm controls was $12.8\pm1.8~\mu\text{V}$ (n=62). The baseline rhythm was sinus rhythm in 34 patients (55%), atrial pacing in 13 patients (21%), right ventricular pacing in 7 patients (11%), and atrial-sensed, biventricular pacing in 8 patients (13%). TWA/V was not significantly different among baseline rhythm controls measured in sinus rhythm $(13.0\pm1.0 \mu V)$, AAI pacing $(14.5\pm1.5 \mu V)$, or DDD/VVI pacing (14.5±1.0) (P>0.5 for all pairwise comparisons). TWA/V during rapid-pacing controls was $14.5\pm2.0 \ \mu V \ (n=52).$

Table 2 shows that TWA/V did not differ significantly among the analyzed clinical subgroups for baseline or rapidpacing control recordings. Specifically, there were no significant differences between patients who had VT/VF during the study and those who did not or between patients taking and those not taking analyzed drugs. There were no significant differences in the distributions of control TWA/V between

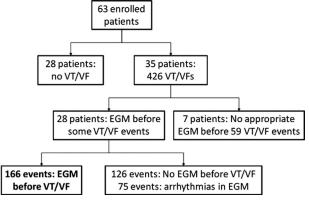


Figure 2. Flow diagram shows the distribution of spontaneous ventricular tachycardia/fibrillation (VT/VF) events in study patients. EGM indicates electrogram.

Table 2. TWA/V Comparisons by Demographics

Variable	Categories (n)	TWA/V Baseline Rhythm, μV	HR Baseline Rhythm, bpm	TWA/V Pacing at 105 bpm, μ V
Age	≤70 y (31)	12.6±10.8	64.8±10.2	15.2±15.8 (26)
	>70 y (31)	13.1 ± 12.0	67.7 ± 12.1	13.8±12.2 (26)
P		0.6809	0.2361	0.4846
Gender	Male (56)	12.5 ± 11.1	66.3 ± 10.6	14.1±13.9 (45)
	Female (6)	15.7 ± 12.9	65.9 ± 15.3	17.2±15.1 (7)
P		0.0992	0.9310	0.2690
LVEF	≤35% (37)	13.6 ± 12.0	67.2 ± 12.4	14.5±13.8 (31)
	>35% (22)	11.4±10.1	65.3±8.1	12.5±10.2 (18)
P		0.0733	0.4890	0.2846
NYHA class	I+II (28)	13.0 ± 11.4	66.2±11.5	14.3±12.5 (23)
	III + IV (16)	13.3 ± 12.2	66.4±11.6	14.8±15.3 (15)
Р		0.8456	0.9479	0.8340
eta-blocker	On BB (56)	12.8 ± 11.1	66.1 ± 10.3	14.8±14.5 (48)
	No BB (6)	12.7 ± 13.1	67.9 ± 16.4	11.1 ± 8.3 (4)
P		0.9627	0.6657	0.3031
ACE-I or ARB	On ACE-I (45)	13.0 ± 11.3	66.6±10.9	15.5±14.9 (38)
	No ACE-I (17)	12.4 ± 11.3	65.4±11.9	11.8±10.6 (14)
Р		0.6785	0.6680	0.0885
Any antiarrhythmic drug	On AA (26)	13.0 ± 11.6	66.7 ± 12.4	13.2 ± 13.3 (22)
	No AA (36)	12.6 ± 11.1	65.9 ± 9.9	15.5±14.6 (30)
Р		0.7457	0.7480	0.2338
Amiodarone	On amiodarone (17)	12.7 ± 11.3	66.6 ± 14.5	12.2±12.0 (13)
	No amiodarone (45)	12.9 ± 11.3	66.1 ± 9.6	15.3±14.6 (39)
Р		0.8998	0.8660	0.1568
VT/VF episodes	Episodes (34)	13.0 ± 12.1	66.4±11.9	14.0±13.2 (28)
	No episodes	12.6 ± 10.3	66.1 ± 10.1	15.1 ± 15.5 (24)
P	(28)	0.7517	0.9166	0.5839

TWA/V indicates T-wave alternans and nonalternans variability; HR, heart rate; LVEF, left ventricular ejection fraction, NYHA, New York Heart Association class; BB, β -blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AA, antiarrhythmic; VT/VF, ventricular tachycardia/fibrillation.

enrollment and 6-month follow-up recordings (baseline rhythm, P=0.16; rapid pacing, P=0.08).

Ambulatory recordings were performed for 26 of the 28 patients who had VT/VF during follow-up. Time-matched ambulatory controls could be analyzed for 111 episodes of VT/VF in 16 of these 26 patients (median, 3.5 per patient; range, 1 to 27). TWA/V during these recordings was $12.3\pm3.5 \,\mu\text{V}$.

Stored preonset EGMs before SVT could be analyzed for 17 episodes in 9 patients. TWA/V was $27.5\pm6.1~\mu$ V. Overall, TWA/V was not statistically different across all types of control recordings (P>0.1 for all pairwise comparisons).

TWA/V Before Spontaneous VT/VF Versus Controls

Figure 3 shows an example of a preonset EGM before VT and baseline rhythm EGM from an individual patient. The magnitude of TWA/V is much greater in the preonset EGM than in the control EGM.

Comparison of Mean Values

Using unpaired comparisons, we found that TWA/V in preonset EGMs before VT/VF (n=28) was significantly greater than the

mean values during baseline rhythm controls (n=62; P<0.0001), rapid-pacing controls (n=52; P<0.0001), time-matched ambulatory controls (n=16; P<0.0001), or preonset EGMs before SVT (n=9; P<0.0001). The histogram in Figure 4 shows generalized estimating equation—adjusted proportions of TWA/V measurements as a function of TWA/V amplitude for EGMs before VT/VF and all 4 control data sets.

Using paired comparisons and adjusting for multiple measurements, we compared TWA/V before the 111 VT/VF episodes with time-matched, individual 8-pair control windows in 16 patients. TWA/V was significantly greater in preonset EGMs than controls (51.7 \pm 3.3 versus 10.9 \pm 3.4 μ V; P<0.0001). In addition, with the use of paired comparisons, TWA/V was significantly greater before VT/VF than before SVT (64.7 \pm 3.6 versus 25.6 \pm 5.1 μ V; P<0.0001; n=9). Figure 5A shows this comparison on an individual-patient basis.

ROC Curve and Logistic Regression

Figure 6 shows an ROC curve describing the predictive power of TWA/V for discriminating between preonset VT/VF EGMs and the 4 control data sets. The areas under the

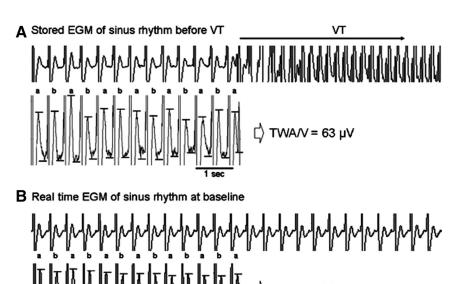


Figure 3. Example of T-wave alternans and nonalternans variability (TWA/V) before ventricular tachycardia (VT) and at baseline. A, Preonset electrogram (EGM) before VT shows TWA/V as indicated in the enlarged tracing (beat "a" T wave is larger than beat "b" T wave, except the last pair). B, Baseline EGM in the same patient shows small differences in beatto-beat T-wave amplitudes.

unadjusted and adjusted ROC curves were 0.818 and 0.916, respectively. ROC curve analysis permits optimizing the TWA/V cutoff for a specific performance objective. For example, a threshold of 29.0 µV corresponds to an unadjusted specificity of 90% and sensitivity of 61%.

We analyzed a logistic regression model adjusted for multiple episodes per patient that included baseline rhythm controls, rapid-pacing controls, time-matched ambulatory controls, preonset SVT controls, and preonset VT/VF. Greater TWA/V was a significant predictor of VT/VF (P<0.0001). The odds of developing VT/VF increased by a factor of 2.2 (95% confidence interval, 2.0 to 2.4; P<0.0001) for each 10-μV increment in TWA/V over the range of TWA/V analyzed (0 to 218 μ V).

Ventricular Rate During Control Versus Pre-VT/VF Recordings

The ventricular rate before VT/VF (n=28; 86.2±2.6 bpm) was faster than that during baseline rhythm controls (n=62; 66.3 ± 1.7 bpm; P<0.0001) or time-matched ambulatory controls (n=16; 66.9 ± 3.3 bpm; P<0.0001) but slower than that during rapid pacing (n=52; 105 bpm) or in EGMs stored before SVT (n=9; 132.4 \pm 4.8 bpm; P<0.0001).

Comparisons With the 90th Percentile of Control Data

Figure 5B through 5D compares TWA/V in preonset EGMs before VT/VF with the 90th sample percentile of each type of control on an individual-patient basis, corresponding to a false-positive rate of 10%. Figure 5B shows the comparison with baseline rhythm control recordings in 28 patients. TWA/V before VT/VF exceeded the 90th percentile for controls in 108 of 166 episodes (65.1%). The generalized estimating equation-adjusted estimate of TWA/V before VT/VF exceeded the 90th sample percentile in 68.5% of episodes (95% confidence interval, 58.5 to 77.1). Figure 5C shows the comparison for rapid-pacing controls in 23 patients. TWA/V before VT/VF exceeded the 90th sample

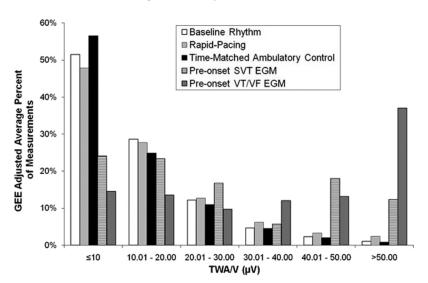


Figure 4. Histogram plots of generalized estimating equation (GEE)-adjusted average percent of T-wave alternans and nonalternans variability (TWA/V) measurements in each interval with 10-μV increment of TWA/V amplitude for each type of control and preonset ventricular tachycardia/fibrillation (VT/VF) electrograms (EGMs). SVT indicates supraventricular tachycardia.

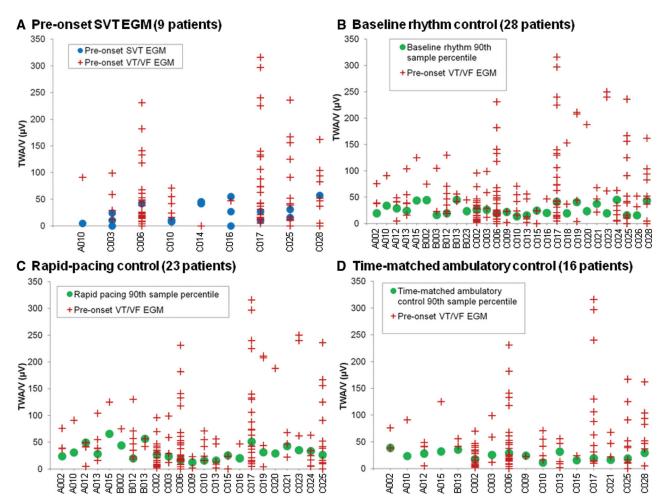


Figure 5. Distribution of individual T-wave alternans and nonalternans variability (TWA/V) measurements in preonset electrograms (EGMs) before ventricular tachycardia/fibrillation (VT/VF) vs measurements in control data sets. In all panels, each category on the horizontal axis denotes an individual patient by that patient's identification number; the vertical axis represents TWA/V amplitude in microvolts; each red cross corresponds to TWA/V for an individual preonset VT/VF episode. In A, each blue circle corresponds to measured TWA/V for a single control preonset supraventricular tachycardia (SVT) episode. Thus, in A, each patient may have multiple data points corresponding to individual preonset VT/VF and individual control preonset SVT episodes. In B through D, each green circle indicates a control data point that represents the patient-specific 90th sample percentile of all TWA/V measurements for 8-pair control windows. TWA/V values greater than those shown by the green circles correspond to false-positive rates <10%. Thus, in B through D, each patient may have multiple preonset VT/VF data points but only one 90th sample percentile control data point as described above. Controls represent baseline rhythm (B), rapid-pacing (C), and time-matched ambulatory (D) recordings. The number of 8-pair windows represented by each control recording (mean±SD) is 48.4±21.6 in B, 42.6±15.1 in C, and 112.9±123.4 in D.

percentile for controls in 89 of 148 episodes (60.1%). The generalized estimating equation—adjusted estimate of TWA/V before VT/VF exceeded the 90th sample percentile in 62.1% (95% confidence interval, 50.1 to 72.8) of episodes. Figure 5D shows the comparison with time-matched ambulatory controls in 16 patients. TWA/V before VT/VF exceeded the 90th sample percentile of the corresponding time-matched ambulatory control segment in 72 of 111 episodes (64.9%). The generalized estimating equation—adjusted estimate of TWA/V before VT/VF exceeded the 90th sample percentile in 68.2% of episodes (95% confidence interval, 55.2 to 78.9).

Discussion

The major finding of this prospective, multicenter study is that the amplitude of EGM TWA/V is significantly greater immediately before spontaneous VT/VF in ICD patients than during 4 different types of control recordings.

Prior Studies of TWA

The potential value of TWA recorded from ICD EGMs is as an immediate antecedent of VT/VF. Computer simulations,^{2,3} animal studies,^{4–6} case reports,^{17,18} and ECG-TWA from Holter recordings⁷ indicate that TWA increases before some episodes of VT/VF.

Previously, we developed and validated a method for measuring TWA/V from the limited preonset EGMs stored in ICDs. 15 This simple averaging method takes advantage of 2 observations. First, the magnitude of TWA recorded from ICD shock EGMs is much greater than ECG TWA 11 and sufficient to permit beat-to-beat measurement without preprocessing the signal. Second, the simple difference between T-wave amplitudes of sequential beats is insensitive to noise. 15 We refer to the simple averaging method as a measure of TWA/V because it can be influenced by nonal-ternans T-wave variability but does not reflect monotonic changes in T-wave amplitude. 15 Because our method mea-

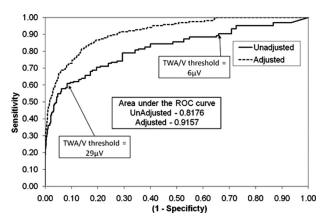


Figure 6. Receiver-operating characteristic (ROC) curves and associated area under the curve for unadjusted and adjusted data. See text for details. TWA/V indicates T-wave alternans and nonalternans variability.

sures both alternans and nonalternans variability, it may be less specific than methods designed to measure alternans alone. However, complex nonalternating patterns of repolarization variability precede ischemic VF in an animal model, and ECG repolarization variability at nonalternating frequencies precedes sustained VT in humans. This suggests that measuring both alternating and nonalternating T-wave variability may increase sensitivity for predicting VT/VF.

We did not apply the spectral analysis¹⁴ or modified moving average¹⁹ methods used clinically for measuring ECG TWA. Their potential limitations for analyzing ICD EGMs have been reported.^{15,20} The spectral method requires analysis of a minimum of 20 pairs,^{15,20} more beats than were recorded for preonset EGMs in the present study, although not more than could be analyzed in real time by an ICD. The modified moving average method has been applied to ECG segments as short as 8 pairs.^{21,22} Without signal preprocessing, however, it did not accurately reproduce simulated EGM TWA filtered by ICD sensing circuits with background noise levels typical of ICDs.^{15,20}

EGM TWA/V Preceding Human VT/VF

Limited retrospective data support the hypothesis that EGM TWA/V can predict VT/VF in ICD patients. In our retrospective pilot study of 6 patients using the simple averaging method, TWA/V was greater before VT/VF than in posthoc recordings made at rest. ¹⁵ Using the same method, Kim et al. ¹⁶ performed a retrospective study of printed strips from ICD programmers. They found that TWA/V was greater before VT/VF than in postshock (and hence potentially distorted) EGMs at ICD implantation (17 patients) or in postshock EGMs after unspecified inappropriate shocks (5 patients). In contrast to the study by Kim et al, ¹⁶ all control EGMs in the present study were recorded from long-term leads, in ambulatory patients, and before shocks.

The present study provides the first prospective, multicenter evidence that high-amplitude EGM TWA/V immediately precedes spontaneous VT/VF in humans. The mean value of TWA/V before VT/VF exceeded that of 4 independent types of control recordings by a factor of 2 to 4. The area under the adjusted ROC curve was 0.916 with TWA/V as the only predictor of VT/VF. In addition to control recordings in baseline and paced rhythms, we analyzed EGMs recorded before spontaneous SVT and EGMs matched for time of day at which VT/VF occurred to account for possible diurnal variation.²³ The mean pre-VT value of TWA/V in the present study (63 μ V) was similar to that reported by Kim et al¹⁶ (61 μ V) and slightly less than that in our pilot study (78 μ V).¹⁵ The range of baseline rhythm, rapid-pacing, and timematched control TWA/V in the present study (12 to 15 μ V) was similar to that of posthoc baseline rhythm and atrial paced controls in our pilot study (12 to 15 μ V). The 90% specificity threshold in the unadjusted ROC curve of 29.0 μ V is also similar to the threshold of 30 μ V proposed in our pilot study.15

In this study, values of TWA/V were not statistically different across control recordings: resting baseline rhythm, pacing at 105 bpm, before SVT, and time-matched ambulatory controls. However, the ventricular rates before ICDdetected SVT were approximately twice as high as during baseline rhythm or time-matched controls. This finding reflects the operation of ICD algorithms that detect sinus tachycardia when it crosses the programmed VT detection boundary rather than at its physiological onset. Previous studies report inconsistent correlations between ECG TWA in ventricular-paced rhythm and atrial-paced rhythm or exercise, as well as inconsistent long-term predictive value for risk stratification with ventricular pacing.24-26 Given the prevalence of ventricular pacing in ICD patients, a TWA/V algorithm that predicts VT/VF on a minute-to-minute basis would be of greater value if it were independent of the control rhythm. We found that the short-term predictive value of high-amplitude TWA/V did not depend significantly on whether control TWA/V was measured during conducted or ventricular-paced rhythms.

Limitations

The short duration of preonset EGMs may have limited the accuracy with which TWA/V was measured before VT/VF. Real-time measurement of TWA/V in future ICDs will not be limited to such brief segments and could thus perform with greater specificity using a trending algorithm. Control recordings were temporally remote from episodes of VT/VF, and most were short. However, control TWA/V was not significantly different between enrollment and 6-month follow-up recordings, suggesting that it is relatively stable. Furthermore, there were no significant differences among TWA/V across all 4 control data sets taken on different days under varying conditions. Limitations of the simple averaging method for measuring TWA/V have been described above and in a previous report,15 including the fact that it does not detect phase reversal after an arrhythmic beat.27 We do not know how well this method or the spectral analysis and modified moving average methods would predict VT/VF if applied to real-time EGM TWA in an ICD. Because of the short duration of preonset EGMs, we cannot determine if the

nonalternans variability that preceded (mostly) nonischemic VT/VF in our study corresponds to the transition from alternans to complex patterns of repolarization variability that precedes ischemic VF in an animal model. In addition, we do not know if our results apply to ICD patients who have not had previous VT/VF.

Clinical Implications

Our prospective results are consistent with the hypothesis that EGM TWA/V is an antecedent of most episodes of VT/VF in ICD patients. However, improved specificity is required to apply EGM TWA/V as a clinical tool. ICD software that measures EGM TWA/V on a continuous, real-time basis will be necessary to determine the duration of the temporal analysis window that optimizes specificity. Such software could be downloaded into presently implanted ICDs. Ideally, TWA/V would be measured with a modified far-field sensing amplifier that permits high-resolution measurements of TWA/V without truncating the ventricular EGM. If VT/VF can be predicted with sufficient accuracy, even with a warning as short as ≈ 15 seconds, adaptive pacing algorithms could be initiated and potentially prevent VT/VF.28 Warning times of several minutes would permit patients to cease activities such as driving and to avoid fall-related injuries or other accidents. Longer warnings might permit titration of antiarrhythmic drugs during periods of greater vulnerability to VT/VF.

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Disclosures

Drs Swerdlow and Gillis are consultants to Medtronic. Dr Chow has ownership interest in Medtronic. Drs Zhou, Abeyratne, and Ghanem have ownership interest in and intellectual property of and are employees of Medtronic. Drs Das and Gillis report no conflicts.

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CLINICAL PERSPECTIVE

Clinically, T-wave alternans (TWA), the surface ECG manifestation of action-potential repolarization alternans, is measured to estimate long-term risk of VT/VF. TWA and nonalternans variability (TWA/V) also increases immediately before ventricular tachycardia (VT) or fibrillation (VF) under some conditions. This suggests that TWA/V may warn of VT/VF in implantable cardioverter-defibrillator patients. Recently, we described a method for measuring TWA/V from intracardiac electrograms stored in implantable cardioverter-defibrillators (ICDs) before VT/VF. In the present prospective, multicenter study, we found that electrogram TWA/V was greater (by a factor of 2 to 4) before VT/VF than during 4 independent types of control recordings. However, improved specificity is required before electrogram TWA/V can be applied as a clinical tool in ICDs. Software that measures electrogram TWA/V on a continuous, real-time basis in ICDs is necessary to optimize specificity of electrogram TWA/V. If VT/VF can be predicted with sufficient accuracy, even with a warning as short as ≈ 15 seconds, adaptive pacing algorithms could be initiated to prevent VT/VF. Warning times of several minutes would permit patients to cease activities such as driving and to avoid fall-related injuries or other accidents. Longer warnings might permit titration of antiarrhythmic drugs during periods of greater vulnerability to VT/VF.