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

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. Retrospective data indicate that EGM TWA/V is greater before spontaneous VT/VF than in limited baseline recordings or after ICD shocks. 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
Far-field EGMs sampled at 256 Hz with a band-pass filter of 3 to 4 mV to ensure adequate resolution for measurement of TWA/V.

The number of intervals to detect VT or VF was 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.

**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 VT/VF 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 method 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.

**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**

The ICD amplifier for far-field EGMs sampled at 256 Hz with a band-pass filter of 3 to 100 Hz.

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).

**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.

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.

**Measurement of EGM TWA/V**

We used a previously validated, simple averaging method 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 individuals. 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 random-effects 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 antiarrhythm 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 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 ≥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±3.1 μV.

TWA/V in Control Recordings
TWA/V during baseline rhythm controls was 12.8±1.8 μV (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±1.0 μV), AA pacing (14.5±1.5 μV), or DDD/VVI pacing (14.5±1.0 μV) (P>0.5 for all pairwise comparisons). TWA/V during rapid-pacing controls was 14.5±2.0 μV (n=52).

Table 2 shows that TWA/V did not differ significantly among the analyzed clinical subgroups for baseline or rapid-pacing 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

Table 1. Patient Baseline Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Without VT/VF Episodes (n=28)</th>
<th>Patients With VT/VF Episodes (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67±11</td>
<td>71±14</td>
<td>0.22</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>24 (86)</td>
<td>32 (91)</td>
<td>0.69</td>
</tr>
<tr>
<td>LVEF, % (n)</td>
<td>36±15 (26)</td>
<td>32±14 (34)</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>11 (39)</td>
<td>12 (34)</td>
<td>0.79</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy, n (%)</td>
<td>17 (61)</td>
<td>23 (66)</td>
<td></td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>26 (93)</td>
<td>30 (86)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

VT/VF indicates ventricular tachycardia/fibrillation.

Figure 2. Flow diagram shows the distribution of spontaneous ventricular tachycardia/fibrillation (VT/VF) events in study patients. EGM indicates electrogram.
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 ± 3.5 \( \mu \)V.

Stored preonset EGMs before SVT could be analyzed for 17 episodes in 9 patients. TWA/V was 27.5 ± 6.1 \( \mu \)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 ± 3.3 versus 10.9 ± 3.4 \( \mu \)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 ± 3.6 versus 25.6 ± 5.1 \( \mu \)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

### Table 2. TWA/V Comparisons by Demographics

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

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

**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±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 sample 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 percentile in 68.5% of episodes (95% confidence interval, 58.5 to 77.1). Figure 5D shows the comparison for time-matched ambulatory controls in 28 patients. TWA/V before VT/VF exceeded the 90th sample percentile in 68.5% of episodes (95% confidence interval, 58.5 to 77.1).

![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 beat-to-beat T-wave amplitudes.](http://circ.ahajournals.org/)

![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.](http://circ.ahajournals.org/)
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, animal studies, case reports, and ECG-TWA from Holter recordings 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. 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 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. We refer to the simple averaging method as a measure of TWA/V because it can be influenced by nonalternans T-wave variability but does not reflect monotonic changes in T-wave amplitude. Because our method mea-
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 postshock recordings made at rest.\textsuperscript{15} Using the same method, Kim et al\textsuperscript{16} performed a retrospective study of printed strips from ICD programmers. They found that TWA/V was greater before VT/VF than in postshock 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\textsuperscript{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.\textsuperscript{23} The mean pre-VT value of TWA/V in the present study (63 μV) was similar to that reported by Kim et al\textsuperscript{16} (61 μV) and slightly less than that in our pilot study (78 μV).\textsuperscript{15} The range of baseline rhythm, rapid-pacing, and time-matched control TWA/V in the present study (12 to 15 μV) was similar to that of postshock baseline rhythm and atrial paced controls in our pilot study (12 to 15 μV). The 90% specificity threshold in the unadjusted ROC curve of 29.0 μV is also similar to the threshold of 30 μV proposed in our pilot study.\textsuperscript{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 ICD-detected 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.\textsuperscript{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,\textsuperscript{15} including the fact that it does not detect phase reversal after an arrhythmic beat.\textsuperscript{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...
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.

Acknowledgments

We acknowledge Haresh Sachanandani for data analysis. We also acknowledge David White at the Ohio Heart and Vascular Center, Susan Straka at the Indiana University School of Medicine, Nancy Massee at the University of Calgary School of Medicine, and Annie Titmass at Cedars-Sinai Medical Center for their role as research coordinators.

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.

References

22. Slawnych MP, Nieminen T, Kahonen M, Kavanagh KM, Lehtimaki T,table references


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.
Intracardiac Electrogram T-Wave Alternans/Variability Increases Before Spontaneous Ventricular Tachyarrhythmias in Implantable Cardioverter-Defibrillator Patients: A Prospective, Multi-Center Study
Charles Swerdlow, Theodore Chow, Mithilesh Das, Anne M. Gillis, Xiaohong Zhou, Athula Abeyratne and Raja N. Ghanem

Circulation. 2011;123:1052-1060; originally published online February 28, 2011; doi: 10.1161/CIRCULATIONAHA.110.986364
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/123/10/1052

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/