Background—Analysis of repolarization instability, manifested by T-wave alternans (TWA), has proved useful for arrhythmia risk assessment. However, temporal relations between TWA and the spontaneous initiation of ventricular tachyarrhythmias (VTA) in humans are unknown. We examined continuous dynamics of repolarization in Holter electrocardiograms with spontaneous sustained (>30 seconds) VTA.

Methods and Results—Ambulatory electrocardiograms from 42 patients (79% with ischemic heart disease; left ventricular ejection fraction, 37±15%) were digitized, and the lead with the highest magnitude of the T wave was selected for analysis. TWA was examined by the modified moving average and intrabeat average analyses. To examine non-TWA (longer-period) oscillations in the repolarization segment, spectral energy of oscillations of consecutive T-wave amplitudes was calculated with the use of the short-time Fourier transform. Heart rate variability was assessed with the Fourier transform as well. TWA increased before the onset of VTA and reached a peak value of 23.6±11.7 μV 10 minutes before the event (P=0.0007). Spectral power of the oscillations of consecutive T-wave amplitudes increased nonuniformly, with the greatest increase in the respiratory range (2.6 μV²; P=0.005). In the TWA range, the change was smaller but highly pronounced relative to the 60- to 120-minute level (65%; P=0.003). The low-frequency and high-frequency heart rate variability power declined before the arrhythmia (P=0.04 and P=0.06, respectively).

Conclusions—the magnitude of repolarization instability, manifested by TWA and beat-to-beat oscillations of T-wave amplitudes at other frequencies, increased before the onset of VTA. Tracking of these dynamics can facilitate timely detection of high-risk periods and may be useful for initiation of preventive treatments. (Circulation. 2006;113:2880-2887.)

Key Words: arrhythmia ■ cardiac repolarization ■ electrocardiography ■ electrophysiology ■ tachyarrhythmias ■ T-wave alternans

T-wave alternans (TWA) is a beat-to-beat alternation in the magnitude of successive electrocardiogram (ECG) T waves that repeats every other beat. Over the past 2 decades, experimental, theoretical, and clinical studies have identified mechanistic and statistical relations linking this phenomenon to a heightened risk of arrhythmogenesis.1,2 In a guinea pig model, TWA led to initiation of ventricular fibrillation through a sequence of events that included the presence of spatially discordant (out-of-phase) TWA, unidirectional block of impulse propagation, and reentry.3 In a canine model of acute ischemia, TWA heralded the first step of a cascade of repolarization instabilities culminating in ventricular fibrillation.4 In humans, however, the dynamics of TWA preceding the onset of spontaneous VTA are still unknown, despite the prominent role that TWA plays in a clinical risk assessment.1 Furthermore, it is unclear whether TWA is the only form of repolarization instability that arises before the onset of arrhythmia or whether it represents a larger class of instabilities that coexist minutes to hours before the event.

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This deficit of knowledge stems in part from the technical difficulties of recording and capturing high-fidelity data during the hours that precede the onset of spontaneous VTA. Although laboratory experiments with electric stimulation can provide valuable diagnostic information about arrhythmia inducibility, they cannot fully reproduce the complex and dynamic spectrum of electrophysiological and neurohumoral perturbations that occur before the onset of spontaneous VTA.5 Analysis of implantable device data is also suboptimal because the magnitude of TWA varies spontaneously over short time intervals comparable to those that could be stored in a limited memory of the device.6 On the other hand, ambulatory (Holter) monitors have a large data-storage capacity, but the advantage is offset by the low probability of

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From the Cardiovascular Institute, University of Pittsburgh, Pittsburgh, Pa.
The online-only Data Supplement can be found at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.607895/DC1.
Correspondence to Dr Vladimir Shusterman, University of Pittsburgh, 200 Lothrop St, Room B535, Pittsburgh, PA 15213. E-mail shustermanv@msx.upmc.edu
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capturing spontaneous VTA in ambulatory recordings because of the rare occurrence of these events.

In the present study, for the first time, we show that in a relatively large data set of ambulatory Holter ECGs collected prospectively in a uniform fashion at 14 clinical centers, TWA increased 30 minutes before the onset of spontaneous sustained VTA, and we confirm this finding by using 3 different analytical techniques.11 In addition, we show that an upsurge in the magnitude of non-TWA repolarization instabilities also preceded the onset of the arrhythmia.

Methods

Patient Characteristics

Clinical and Holter ECG data were collected in 1985–1991 in the course of a National Institutes of Health-sponsored Electrophysiological Study Versus Electrocardiographic Monitoring (ESVEM) clinical trial; protocols, methods, definitions, and patient characteristics have been described in detail.5,6,9 Patients for this study were identified by the presence of spontaneous, sustained ventricular tachycardia (duration >30 seconds, rate >100 beats per minute [bpm]) on a 24-hour Holter recording. All patients had a history of cardiac arrest, documented ventricular fibrillation, sustained ventricular tachycardia, or syncope. Enrolled patients had to have at least 10 premature ventricular complexes per hour and sustained ventricular tachyarrhythmia induced at electrophysiological study. Data were obtained at least 5 half-life periods after the discontinuation of antiarrhythmic drugs. Patients with recent myocardial infarction, the long QT syndrome, hypertrophic cardiomyopathy, or arrhythmias due to transient or reversible disorders were excluded.

Analysis of Recordings

Ambulatory recordings were obtained with the use of commercial, analog Holter monitors with 2 standard, bipolar leads.10 The recorders provide a flat frequency response and a linear phase between 0.67 and 50 Hz (±3 dB).11–13 Therefore, the recorded signals had sufficient amplitude resolution and frequency range for dynamic analysis of repolarization.95 Holter recordings from 59 of 499 patients demonstrated sustained, monomorphic ventricular tachyarrhythmia (VTA). Because subjects with multiple episodes of VTA could be different from those with a single episode of VTA, and the inclusion of all VTA episodes would favor characteristics of patients with multiple arrhythmias, the analysis was restricted to the single, longest VTA episode per patient. Forty-two recordings, which had (1) at least 2 hours of sinus rhythm preceding the arrhythmia and (2) the amplitude of T wave >0.1 mV, were included in analysis. ECG data were digitized at 400 Hz and effective resolution of 2.5 μV with the use of a custom scanning system.

Repolarization Analysis

A lead with the largest-magnitude T wave was selected for repolarization analysis. Because a single lead was used in each patient for all analyses in all time intervals, interlead differences in T-wave amplitudes would not be expected to affect the results.16 The procedures used for artifact and baseline drift control are described in the online-only Data Supplement. The QRS complexes were classified with the use of custom software and verified by an experienced technician. Fiducial points, including the onset of the Q wave, the end of the S wave, and the beginning (T-onset), peak (T-peak), and end (T-end) of the T wave were identified as described elsewhere.17

Data segments with uninterrupted streams of consecutive T waves were used for TWA analysis. The dynamics of TWA were examined with the use of 2 independent time-domain techniques; the intrabeat average (IBA) and the modified moving average (MMA) analyses (Figures 1 and 2).7,14,18 Because IBA is methodologically similar to MMA and performed similarly in previous validation studies, numerical results are presented for IBA only.9 In addition, spectral analysis was applied to examine dynamics of repolarization insta-
Heart Rate Variability Analysis
Heart rate variability (HRV) was estimated by the use of the low-frequency power (LFP) (0.04 to 0.15 Hz) and high-frequency power (HFP) (0.15 to 0.4 Hz) as previously described (in the online-only Data Supplement).5

Statistical Analysis
Shapiro-Wilk’s W test of normality was used to assess distribution of the data. Because of substantial deviation from normal distribution, nonparametric Friedman ANOVA was applied to test the significance of changes in each variable over time. If overall changes were significant by the Friedman ANOVA, Wilcoxon test was applied to determine which data points are significantly different from baseline reference periods. The circadian changes in the frequency of VTA were analyzed with the Fisher exact test. The results are presented as mean±SD, unless indicated otherwise.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population
Participants’ demographic and clinical characteristics are summarized in Table 1. Typical of most coronary artery disease populations, the majority of subjects were male, and mean age of the patients in this study was 65.5±9.7 years. The etiology of heart disease was ischemic in 79% of the disease populations, the majority of subjects were male, and the mean ejection fraction was 37±15%. The mean duration of the index arrhythmia was 11.4±20.5 minutes (median, 2.65 minutes; range, 30 seconds to 97 minutes), and mean cycle length was 362±84 ms (median, 348 ms; range, 206 to 569 ms). Arrhythmias were more frequent in the morning and late afternoon than during the night (P=0.004).

Changes in Heart Rate and HRV
Heart rate increased 8% (P<10-7) during 30 minutes before the arrhythmia, peaking at 88±20 bpm in the last 5 minutes before the onset (Table 2, Figure 2). The LFP and HFP HRV decreased, although the changes in HFP did not reach statistical significance (P=0.04 and P=0.06, respectively; Table 2).

Changes in Repolarization
Analysis of TWA in Time Domain
Figure 1 shows 4 examples of changes in the magnitude of TWA measured by IBA and MMA during 4 hours before the onset of VTA in individual subjects. Overall in the studied group, TWA increased 10% during 30 minutes before the onset of arrhythmia and reached a peak value of 23.6±11.7 μV (a 25% increase compared with the mean value of 60 to 120 minutes before VTA; P=0.0007) 10 minutes before the event (Figure 2). Separate analyses of TWA in the first (TWAonset-peak) and second (TWApeak-end) halves of the T wave showed that 30 minutes before the arrhythmia, TWA was significantly elevated only in the first half, although the magnitude of increase in the second half was similar (Figure 3). Indeed, as the magnitude of TWA reached the peak 10 minutes before the event, TWA was increased in both halves of the T wave (26% and 22%, respectively; P<0.002 compared with 60 to 120 minutes before VTA).

Role of Heart Rate in the Upsurge of TWA Before the Onset of VTA
Because TWA is usually increased at higher heart rates, it was unclear whether the prearrhythmic upsurge in TWA was

TABLE 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Presenting event</th>
<th>Study (n=42)</th>
<th>All SpVT (n=59)</th>
<th>No SpVT (n=440)</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.5±9.7</td>
<td>64.5±10.3</td>
<td>64.5±9.7</td>
<td>0.55</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>9 (21)</td>
<td>9 (15)</td>
<td>55 (13)</td>
<td>0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>33 (79)</td>
<td>47 (80)</td>
<td>373 (85)</td>
<td>0.51</td>
<td>0.52</td>
</tr>
<tr>
<td>Years since last MI, mean (median)</td>
<td>5.7±7.1 (2.5)</td>
<td>5.9±6.8 (2.5)</td>
<td>8.3±8.3 (6.4)</td>
<td>0.057</td>
<td>0.049</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>37±15</td>
<td>35±15</td>
<td>32±12</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>PVCs/h (median)</td>
<td>316±433 (131)</td>
<td>371±505 (151)</td>
<td>304±385 (170)</td>
<td>0.22</td>
<td>0.20</td>
</tr>
<tr>
<td>Digitals</td>
<td>11 (26)</td>
<td>14 (30)</td>
<td>165 (38)</td>
<td>0.34</td>
<td>0.43</td>
</tr>
<tr>
<td>Verapamil or diltiazem</td>
<td>5 (12)</td>
<td>6 (13)</td>
<td>63 (14)</td>
<td>0.90</td>
<td>0.89</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3 (7)</td>
<td>5 (11)</td>
<td>59 (13)</td>
<td>0.77</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Percentages are in parentheses except where indicated and reflect missing data for some variables. SpVT indicates spontaneous sustained monomorphic ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; MI, myocardial infarction; SAS, Symptomatic Activity Scale; PVCs, premature ventricular complexes; and β-blocker, β-adrenergic receptor–blocking drug.

*Study group vs patients without spontaneous VT (column 1 vs 3).
†All patients with spontaneous VT (All SpVT) vs patients without spontaneous VT (column 2 vs 3).
driven solely by an increase in heart rate or by a combination of several factors. To answer this question, we compared the magnitude of TWA during 15 minutes before the onset of VTA with that during 15-minute, arrhythmia-free (control) periods, which (1) had heart rate in sinus rhythm greater than or equal to the heart rate 15 minutes before the onset of VTA and (2) were >1 hour before the onset of VTA or >1 hour after termination of the arrhythmia. Data containing such control periods were available in a subset of 38 recordings (average interval of 6.9±5.0 hours from the onset of VTA). Although during control periods, heart rate was higher than 85.0±17.5 bpm; P<0.006; TWA was 5% lower during these periods than before the onset of the arrhythmia (P=0.006; Figure 4).

Spectral Analysis of Beat-to-Beat Oscillations in Consecutive T Waves at TWA and Non-TWA Frequencies
Spectral power of the oscillations of consecutive T-wave amplitudes increased nonuniformly before VTA, with the maximum increase of 2.57 \( \mu \text{V}^2 \) concentrated in the respira-
The main finding of this study was evidence of a significant increase in repolarization instability preceding the onset of VTA. To the best of our knowledge, this is the first demonstration of a direct temporal relation between repolarization instability and initiation of spontaneous VTA obtained in a relatively large data set of continuous ambulatory recordings in humans. Data for this study were collected prospectively in 14 medical centers, which reduces the probability of biases in patient selection. The increase in TWA was confirmed by 3 independent methods: MMA, and spectral analyses (Figures 2 and 5). In addition, we found that the increase in repolarization instability was not limited to the TWA frequency of 0.5 c/b but included a range of non-TWA frequencies as well.

Previous Studies
TWA is a well-established risk factor related to long-term susceptibility to VTA. However, little is known about the temporal relationship between the dynamics of TWA and the onset of spontaneous VTA in humans. Because of the technical difficulties of capturing ECG dynamics preceding imminent VTA, human data are scarce and consist of anecdotal, few-minute-long recordings made before the onset of spontaneous VTA. For example, a recent single-case study of an 8-minute-long implanted cardioverter/defibrillator record before the onset of ventricular tachyarrhythmia has found some variation in the level of TWA but no definitive trend. Such variations in the magnitude of TWA, however, occur spontaneously over 2- to 3-minute periods and could be found even at a fixed heart rate independent of population-specific or clinical context. Therefore, as Kaufman et al pointed out, caution is required when inferences are made from such short-term records; analysis of longer data segments is more appropriate for reliable estimation of changes in the magnitude of TWA. Indeed, our study found that the increase in the magnitude of TWA preceding the onset of arrhythmia can be found as early as 30 minutes before the event. To determine the duration and the time course of these changes, the analysis had to include relatively long segments of continuous data.

In a canine model of acute ischemia, Nearing and Verrier have shown that an increase in TWA precedes the onset of ventricular fibrillation. This group also showed that the increase occurred predominantly in the early half of the T wave. Although patients enrolled in our study did not show any signs of acute ischemia during the time of ambulatory monitoring and there were no changes in the amplitude and slope of ST segment or T wave, our results were remarkably similar to those experimental findings. Not only did we observe a direct temporal relation between the upsurge in TWA and the onset of spontaneous VTA in humans, but the increase in the magnitude of TWA was greater in the early portion of the T wave. Several mechanisms can be suggested to explain these similarities that were present despite the important differences between the 2 studies with respect to the underlying pathophysiology (acute ischemia versus chronic heart disease) and the type of arrhythmia (ventricular fibrillation versus sustained VTA). First, most patients in our study population had coronary artery disease and thus could have experienced an episode of silent, focal ischemia in a small region of the myocardial tissue that went undetected in ambulatory ECG recordings. The second alternative is that electrophysiologic mechanisms linking TWA to the initiation of arrhythmias can be similar for the settings of acute ischemia and chronic structural heart disease, which promotes cell uncoupling by developing fibrous barriers.

TWA was not the only form of repolarization instability that existed before the onset of ventricular fibrillation in the aforementioned canine model of acute ischemia. Consistent with these findings, our results also show that the increase in repolarization instability preceding imminent VTA spreads into several frequency ranges. Thus, our results suggest that in the presence of a chronic structural heart disease, multiple forms of repolarization instabilities may be prevalent in addition to TWA.

Changes in Cardiac Rhythm and Repolarization Instabilities Before the Onset of VTA
The multiformal repolarization instabilities observed in our study could also be a result of complex and profound changes...
in the pattern of cardiac rhythm that occurred in the studied population during the 1 to 2 hours before the onset of VTA. Because changes in the pattern of cardiac rhythm spanned multiple frequency ranges, they could have led to the development of multiformal repolarization instabilities spanning different frequencies as well. Further support for this hypothesis comes from the experimental studies and computer simulations that demonstrated a delayed, exponentially decaying adaptation of repolarization to changes in cardiac cycle lengths. When the dynamic pattern of cardiac rhythm exhibits complex changes, the delays of adaptation can gradually accumulate and give rise to a multitude of repolarization instabilities.

An increase in heart rate is known to be a major factor affecting the level of TWA. In this study, the magnitude of changes in heart rate was modest (10%) but highly statistically significant, showing that the pre-VTA increase in heart rate was consistent across subjects. The maximum heart rate achieved minutes before the onset in the studied group was lower than the established cutoff (95 to 100 bpm) for detection of TWA during laboratory tests. Because the magnitude of increase in heart rate in our study was relatively small, it is unlikely to be a major factor determining upsurge in repolarization instability. Additional support for this notion is provided by the observation that during arrhythmia-free periods, the magnitude of TWA was often lower at similar or faster heart rates (Figure 4). This is not in disagreement with previous investigations, which also found that dynamics of TWA cannot be completely explained by changes in heart rate in patients with coronary artery disease.

Consistent with the relatively small changes in heart rate, there was also a small shortening of QT intervals before the onset of VTA (2.5%). Although correction of QT intervals with the use of Bazett’s formula resulted in prolongation of QTc-B before the onset, this effect could be due to overestimation of QT intervals at faster heart rates. Therefore, a second, independent (Hodges’s) correction formula has also been applied. The Hodges’s correction did not show any significant changes in QT intervals before the onset of VTA.

**Autonomic Nervous System Activity and Repolarization Instability**

We previously reported increased sympathetic activity manifested by increased heart rate and changes in the spectral power of HRV before the onset of VTA in the same patient population. The HRV values 30 minutes before the onset, this effect could be due to overestimation of QT intervals at faster heart rates. Therefore, a second, independent (Hodges’s) correction formula has also been applied. The Hodges’s correction did not show any significant changes in QT intervals before the onset of VTA.

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**Repolarization Analysis in Ambulatory ECG Recordings**

To ensure reliability and consistency of our findings, the results have been confirmed by 2 independent time-domain techniques, the MMA and the IBA analyses (Figures 1 and 2). In addition, spectral analysis has been applied to examine nonalternating repolarization instabilities and to confirm the dynamics of TWA. Note that the spectral analysis used in this study has been modified to reduce the impact of high-frequency artifacts by averaging all points over the entire T wave (or over the first and second halves of the T wave for analysis of the corresponding segments). To eliminate the low-frequency artifacts caused by baseline wander, a previously validated, adaptive algorithm for accurate removal of baseline drifts with a minimal distortion of repolarization complexes has been used.

Theoretically, the dynamics of TWA at 0.5 c/b could be influenced by a subharmonic of the fundamental frequency at 0.25 c/b. To rule out this possibility, the increase in the magnitude of TWA has been confirmed by 3 independent methods. Furthermore, the magnitude of the subharmonics for weakly oscillating, free of spurious spikes, and discontinuities time series of consecutive, mean T-wave amplitudes must decay at a rate \(\sim 1/n\), where \(n\) is the order number of the subharmonic. In our study, however, the magnitude of the TWA power constitutes 79% of the magnitude of TRR power (after normalizing the power for the duration of the frequency band).

Another major source of error in spectral estimation is the influence of spectral power on that in adjacent frequency ranges, referred to as the power leakage. This error is particularly prominent when the power is computed over narrow frequency ranges, such as that of TWA. The TWA and the adjacent high-frequency ranges, therefore, were separated by the “buffer zones” (0.4 to 0.45 c/b and 0.25 to 0.3 c/b) that should have absorbed the potential power leakage.

**Limitations**

Data for this study were obtained with the use of standard ambulatory recordings. Therefore, regional information about spatial distribution of repolarization instabilities or presence of discordant TWA is unavailable. Furthermore, analog Holter recorders used for the data collection could not...
provide the quality and resolution of contemporary digital recorders. Nevertheless, our analysis still detected an increase in repolarization instability preceding VTA. Because the analysis was designed to examine relative changes in repolarization, with each subject’s data used as an individual reference, the main results would not have been affected by some variability in recorders’ characteristics or lead placement, which are unavoidable in the setting of a multicenter clinical trial.

Prediction of the time of onset of VTA with the dynamics of repolarization has not been performed in this study. Analysis of the predictive value would require a different analytical approach, which includes selection of a training and test groups, determining the cutoff values in the training group, and testing these cutoffs in the test group. The present investigation has been designed as a feasibility study; the results reported here suggest that further research into the predictive value of repolarization instability is warranted.

Implications and Conclusions

TWA and non-TWA forms of repolarization instability increased before the onset of VTA. An increase in TWA in the setting of a structural heart disease is likely to be driven by nonautonomic mechanisms, whereas the increase in slower periodicities can be modulated, at least in part, by changes in the autonomic nervous system activity. Tracking the entire spectrum of repolarization instabilities in real-life ambulatory recordings can provide further insights into both autonomic and nonautonomic mechanisms of spontaneous arrhythmogenesis. If confirmed in larger studies, the combined analysis of TWA and non-TWA instabilities can improve identification of subjects who are prone to development of ventricular tachyarrhythmias and sudden death and facilitate timely detection of high-risk periods. Our results also suggest that dynamic repolarization analysis adds a new, emerging dimension to the quest for understanding the complex mechanisms involved in arrhythmogenesis.

Source of Funding

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Disclosures

Dr Shusterman has a significant (>5%) ownership interest in PinMed, Inc (Pittsburgh, Pa). PinMed, Inc has provided the software used in this study. The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE

Analysis of repolarization instability, manifested by T-wave alternans (TWA), has proved useful for arrhythmia risk assessment during long-term follow-up. However, the temporal relations between TWA and the spontaneous initiation of ventricular tachyarrhythmias (VTA) in humans are unknown. We hypothesized that repolarization instability increases before initiation of VTA. We examined continuous dynamics of repolarization in Holter electrocardiograms with spontaneous sustained (>30 seconds) VTA. The magnitude of repolarization instability, manifested by TWA and beat-to-beat oscillations of T-wave amplitudes at other frequencies, increased before the onset of VTA. The combined analysis of TWA and non-TWA instabilities can potentially improve identification of subjects who are prone to development of VTA and sudden death and facilitate timely detection of increasing risk that might require proactive management. An increase in TWA in the setting of a structural heart disease might be driven by nonautonomic mechanisms, whereas the increase in slower periodicities of repolarization instabilities might be modulated, at least in part, by autonomic nervous system activity. Tracking the entire spectrum of repolarization instabilities in ambulatory recordings can provide further insights into both autonomic and nonautonomic mechanisms of spontaneous arrhythmogenesis.
Upsurge in T-Wave Alternans and Nonalternating Repolarization Instability Precedes Spontaneous Initiation of Ventricular Tachyarrhythmias in Humans
Vladimir Shusterman, Anna Goldberg and Barry London

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