Influence of heart rate and sympathetic stimulation on arrhythmogenic T wave alternans

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Kaufman, Elizabeth S., Judith A. Mackall, Birendra Julka, Carole Drabek, and David S. Rosenbaum. Influence of heart rate and sympathetic stimulation on arrhythmogenic T wave alternans. Am J Physiol Heart Circ Physiol 279: H1248–H1255, 2000.—We determined the temporal stability of T wave alternans (TWA) during constant rate stimulation and the dependence of alternans on heart rate (HR) and β-adrenergic stimulation. Although it is established that exercise can provoke microvolt-level TWA in patients at risk for reentrant ventricular arrhythmias, the mechanisms underlying TWA in humans are not well understood. Specifically, the temporal stability of alternans at any given HR and the influence of HR vs. sympathetic activation on alternans remain unclear. TWA was measured during prolonged fixed-rate atrial pacing at multiple cycle lengths (CLs) in 10 subjects referred for electrophysiological testing and in 14 additional subjects in whom atrial pacing was performed at identical pacing CLs with and without isoproterenol. During constant CL stimulation, TWA amplitude oscillated significantly over time (typically by 10 μV) in a quasiperiodic fashion with periodicity of ~2–3 min. Alternans amplitude was strongly dependent on HR but not on adrenergic stimulation. There was a patient-specific threshold HR over which alternans appeared. At higher HR, alternans amplitude increased and oscillations were less prominent. Adrenergic stimulation was required to produce TWA that was not already elicited by moderate elevation of HR in only 2 of 14 (14%) patients. In conclusion, TWA 1) fluctuates spontaneously over 2–3 min and 2) increases monotonically with increased HR (without a major adrenergic contribution in most patients). These data suggest that increased HR rather than sympathetic activation is responsible for arrhythmogenic microvolt-level TWA measured during exercise.

electrical alternans; repolarization; Q-T interval; adrenergic stimulation; ventricular tachycardia

T WAVE ALTERNANS (TWA) is defined as the beat-to-beat oscillation of the amplitude of the T wave that repeats every other beat. Although alternans of the QRS complex was first described in the context of atrial tachycardia by Sir Thomas Lewis in 1910 (8), TWA has since been described in the absence of tachycardia (i.e., in normal sinus rhythm) in a variety of clinical conditions such as acute myocardial infarction and ischemia (13, 18), Prinzmetal’s angina (7, 17), electrolyte disorders (9), and during angioplasty (4) and drug intoxications (6). In each of these conditions, alternans was associated with malignant ventricular arrhythmias, raising the possibility that the presence of alternans at relatively normal physiological heart rates may point to underlying electrophysiological pathology in the heart. Moreover, Rosenbaum et al. (16) showed that microvolt-level TWA that is not visibly apparent on the electrocardiogram (ECG) could be detected during atrial pacing at relatively slow heart rates (100–110 beats/min) in patients with ventricular arrhythmias but not in control subjects, indicating that in humans TWA is a marker of electrical instability in the heart. TWA is also present in patients with congenitally long Q-T syndrome (LQTS) and, in these patients, is often provoked by excitement or emotional or physical stress, suggesting that sympathetic stimulation may be important to its mechanism (19, 20).

Numerous recent studies have confirmed these observations in similar and other patient groups (1, 3, 5, 12). Importantly, in these more recent investigations, microvolt-level TWA was measured without artificial pacing. Moderate heart rate elevation was achieved using low-level exercise, which is now the standard noninvasive method used to measure TWA in patients. However, the role of heart rate vs. exercise-induced sympathetic activation on the development of TWA is not well understood. Also, during exercise-induced TWA, the magnitude of alternans can vary considerably, yet it is not known whether such variation can be explained by heart rate fluctuations or other factors. If TWA is to be used as a noninvasive screening test for sudden cardiac death (SCD), it is imperative to resolve these questions. The goal of this study was to examine the roles of heart rate and β-adrenergic stimulation in the development of TWA in humans.

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METHODS

For the purpose of testing the effects of heart rate (protocol 1, n = 10) and β-adrenergic stimulation (protocol 2, n = 14) on TWA, two independent patient populations were studied. All patients referred for programmed ventricular stimulation who fulfilled the study entry criteria were consecutively enrolled after obtaining informed consent. Patients were excluded if reliable atrial pacing could not be performed because of atrial fibrillation or flutter, ventricular preexcitation, atrioventricular block, or high-grade ventricular ectopy (>20% premature ventricular complexes). For protocol 2, patients were also excluded if they were taking β-blockers or had contraindications to β-adrenergic stimulation. For each protocol, TWA was measured at the time of electrophysiological (EP) testing after insertion of standard endocardial recording-stimulating catheters and before programmed ventricular stimulation (using at least double premature stimuli from 2 ventricular sites).

Patient group 1: short-term variability and rate dependence of TWA. Alternans was measured during steady-state atrial pacing for up to 3 min at different heart rates. Atrial pacing was initially performed at a cycle length (CL) as close as possible to 700 ms. After >2 min of pacing to achieve steady state, 300 ECG complexes were recorded. In patients with high intrinsic heart rates that precluded pacing at CL of 700 ms, TWA was measured at the longest CL at which reliable atrial pacing could be performed. Recordings of TWA were then obtained over a range of steady-state CL ranging from 700 to 400 ms, in 50-ms decrements. In seven patients, alternans was also measured continuously at a constant heart rate of 100 beats/min for 10 min to assess the temporal stability of TWA.

Patient group 2: response to β-adrenergic stimulation. To control for the effects of heart rate, TWA was measured at an identical pacing CL before and after the administration of isoproterenol as follows. First, TWA was measured during steady-state (>2 min) atrial pacing at a heart rate as close to 100 beats/min as possible that would provide reliable 1:1 atrioventricular conduction. If the subject’s baseline heart rate was >80 beats/min, TWA was measured at a heart rate that was 25% above baseline so as to assure that pre- and postisoproterenol measurements were obtained at comparable rates. Patients were excluded if their baseline heart rate exceeded 90 beats/min, because under such circumstances it is possible that adrenergic tone was elevated even before isoproterenol was administered. After baseline measurements of TWA, pacing was stopped and isoproterenol (1.0–3.0 μg/min) was administered by a slowly increasing infusion rate (by 0.5 μg/min every 5 min) to achieve a target heart rate 25% above each subject’s baseline sinus rate so as to assure an adequate β-adrenergic effect. To assure that steady state had been reached, the target heart rate was observed to be stable for at least 5 min at the same dose of isoproterenol.

Finally, while the isoproterenol infusion continued, TWA was measured during steady-state atrial pacing at a heart rate as close to 100 beats/min as possible. In cases where isoproterenol increased heart rate above 100 beats/min, the slowest possible heart rate that reliably captured the atria was used. With this protocol, TWA was successfully measured at essentially identical atrial pacing CLs both before (594 ± 31 ms) and after (592 ± 32 ms) the administration of isoproterenol.

Classification of patients according to clinical and inducible arrhythmias. Patients were divided into the following groups or excluded from analysis according to their clinical characteristics and responses to programmed ventricular stimulation. Patients were defined as high risk (groups IA and 2A) if they had inducible sustained monomorphic ventricular tachycardia (SMVT) lasting >30 s or requiring termination because of hemodynamic collapse. Patients were defined as low risk or controls (groups 1B and 2B) if they had no clinical or inducible ventricular arrhythmias. A third group (group 2C) had a history of SCD but negative EP tests. Patients in whom only ventricular fibrillation or nonsustained ventricular tachycardia could be induced were considered to have nonspecific endpoints and thus uncertain arrhythmia risk. These patients were excluded from analysis.

TWA analysis. Seven silver-silver chloride electrodes were positioned in the bipolar orthogonal (XYZ) configuration. ECG signals were amplified using low-noise, high-gain amplifiers (Gould, Cleveland, OH), filtered (0.01–300 Hz), and digitized on a microcomputer (1,000 Hz with 12-bit resolution). Digitized ECG signals were transferred to UNIX workstations for offline analysis using custom software developed in the C programming language. Time-varying fluctuations of microvolt-level TWA were measured using a modification of a sensitive spectral analysis technique described previously (16, 21). Figure 1 shows a representative aggregate power spectrum that reveals the frequencies at which beat-to-beat fluctuations in the amplitude of the T wave occur (analyzed from 64 consecutive beats). The power measured at the frequency of 0.5 cycles/beat (P0.5) corresponds to alternans-specific beat-to-beat T wave fluctuations (15, 16, 21). The magnitude of TWA (Alt; in μV) was calculated from

\[
\text{Alt(μV)} = 2 \times \sqrt{P_{0.5} - P_{\text{noise}}}
\]

where \(P_{\text{noise}}\) is an estimate of average white (i.e., nonalternating) T wave fluctuations from a predefined spectral window (16). Alternans magnitude was set to zero if it was not significantly greater than noise as determined by an alternans ratio <3 (15, 16, 21). To account for temporal fluctuations, alternans was not calculated from only one series of consecutive beats at one arbitrary point of time. Instead, alternans was calculated iteratively from 64 consecutive beat segments of data after shifting each analysis segment by four beats. Consequently, short-term fluctuations in the magnitude of alternans could be monitored over time. Alternans was calculated separately at each point of time from each of three orthogonal leads, and the component of alternans magnitude contributed by each lead was summed vectorially to yield a vector magnitude trend whose median value was

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**Fig. 1.** A representative example of an aggregate T wave power spectrum calculated from 64 consecutive beats. The aggregate spectrum is derived from the average of all spectra generated by each point of the T wave. See TWA analysis for details.
taken as the representative value of alternans for a particular stimulus rate; alternans trends are all represented in this fashion (Figs. 2, 3, and 4). This approach avoided the need for baseline correction or calculation of alternans from the vector magnitude ECG signal, both of which can introduce significant nonlinearities and potential errors. The alternans for any given heart rate was calculated from the median value measured over time at that heart rate (Figs. 5 and 6). The alternans trends were analyzed for phase resetting by examining spectra from each time point of apparent reduction in TWA magnitude. Phase resetting was evident by the emergence at that time point of a spectral peak in the frequency bin adjacent to the alternans frequency. Phase resetting was further confirmed if deleting one beat of the time series (i.e., restoring the alternans phase) caused reemergence of the spectral peak at the alternans frequency.

RESULTS

Temporal stability of TWA. Shown in Fig. 3 is a representative example demonstrating the manner in which TWA fluctuated spontaneously during fixed-rate atrial pacing in a subject with inducible SMVT. Note that although the magnitude of TWA remains persistently elevated, there are substantial oscillations in alternans magnitude (~10 μV of the 15-μV maximum or 66%). TWA constantly increased and decreased with time in a pattern that typically repeated every 2 to 3 min in a quasiperiodic fashion. Note also that despite rather marked fluctuations of TWA, it is not possible to discern from the ECG signals any TWA, let alone any changes in TWA over time, reaffirming the need for sensitive processing techniques to detect TWA in humans.

Because when the spectral technique is used it is possible that phase resetting can cause artifactual changes in alternans magnitude, we analyzed individual spectra that were calculated at different points of time for evidence of phase resetting. As shown in Fig. 4, phase resetting caused by a ventricular ectopic beat can indeed produce an apparent reduction in alternans magnitude (point C) because of spectral leakage (14) of alternans power into neighboring frequencies (Fig. 4, spectrum C). Therefore, changes in alternans magnitude that are attributable to phase resetting were easily recognized by inspection of individual spectra and were discarded. In contrast to Fig. 4, the spectra

Fig. 2. Representative example of T wave alternans (TWA) magnitude (in μV) measured from 3 orthogonal leads (XYZ) over 1,000 beats from a patient with sustained monomorphic ventricular tachycardia (SMVT; group IA). Measurement at each point of time was made from 64 beat segments, each shifted by 4 beats at a time. Three such segments (A, B, and C) are shown at top. Segments where alternans magnitude was significant (alternans ratio >3). Vector magnitude of TWA was calculated from $\sqrt{X^2 + Y^2 + Z^2}$ at each point of time, where the alternans magnitude was set to zero if alternans ratio <3. Overall TWA magnitude was calculated from the median alternans level of the vector magnitude trend.
shown in Fig. 3 illustrate true fluctuations in alternans magnitude that cannot be explained by phase resetting.

Heart rate dependence of TWA. Of the 10 patients in group 1, five satisfied high-risk (group 1A) criteria. All patients in group 1A were men (age 60 ± 10 yr) with ischemic heart disease with left ventricular ejection fraction (LVEF) 0.36 ± 0.09. Group 1B included three women and two men with mean age of 38 ± 13 yr. Patients in this group had LVEF 0.67 ± 0.09 and no clinical ventricular arrhythmias.

TWA was elicited in all the high-risk patients and in four of five low-risk patients. For each patient, there was a patient-specific heart rate threshold above which...

Fig. 3. Oscillatory nature of TWA during constant rate stimulation. TWA spectra calculated at 6 points of time (A–F) are shown in I. Note that spontaneous variations in alternans magnitude are reflected by changes in the spectral peak (arrows) registered at the alternans frequency (0.5 cycles/beat). TWA trend plot (III) demonstrates alternans magnitude at every point of time over ~9 min. Note also that despite rather marked discernible changes in T wave spectra from A to C (I), there are no visibly detectable TWA evident on the surface electrocardiograms (ECGs; II).

Fig. 4. Example of artifactual reduction of TWA magnitude caused by phase resetting from a ventricular premature beat. Spectra in I were calculated from 64 beat segments before (A, B), centered on (C), and after (D, E) the occurrence of a ventricular premature beat (*) in the ECG recording (II). Abrupt diminution in measured TWA (III) was caused by resetting of the phase of T wave alternation. This is evident from the spectra where the apparent reduction in TWA magnitude (arrows) is associated with significant leakage of spectral energy into frequencies just below the alternans frequency (0.5 cycles/beat).
significant TWA occurred and below which it disappeared. This threshold heart rate was lower in high-risk (98 ± 12 beats/min) compared with low-risk (120 ± 25 beats/min) patients, consistent with previous observations (5), although this did not reach statistical significance in our small sample. Figure 5 illustrates the increase in alternans magnitude with increase in heart rate over the threshold heart rate for representative high- and low-risk patients. In all patients, the magnitude of TWA increased with heart rate. However, the maximum magnitude of TWA was significantly greater in group 1A patients (26.0 ± 10.0 μV) compared with controls (5.9 ± 5.0 μV; P < 0.01). As illustrated by the example shown in Fig. 6, control subjects (group 1B) were characterized by only transient increases in alternans, whereas in the patients with SMVT (group 1A), alternans remained persistently elevated over longer time periods (min) and over a broad range of heart rates. Figure 7 summarizes the alternans magnitude data for all patients.

Effect of β-adrenergic stimulation on TWA. Fourteen of the patients who completed protocol 2 met criteria for inclusion in analysis. All six patients in group 2A

Fig. 5. A representative ventricular tachycardia (VT) and control patient illustrate the dependence of TWA magnitude on heart rate. Note that in both cases, TWA occurs above a patient-specific threshold heart rate (arrows). BPM, beats/min.

Fig. 6. Representative TWA magnitude trend plots demonstrate characteristic changes in TWA levels that occur at different heart rates. Note that the in the control patient (B), TWA was only elicited at fast heart rate and was transient in nature, whereas in the SMVT patient (A), TWA occurred at a slower heart rate threshold and remained persistently elevated.

Fig. 7. The magnitude of alternans in μV is shown for VT patients and for control subjects.
were men with mean age of 65 ± 8 yr, ischemic heart
disease, left ventricular dysfunction, and SMVT at EP
testing. The three patients in group 2B (controls) in-
cluded two men and one woman, with mean age of 51 ±
16 yr. These patients had no arrhythmias induced at
EP testing, no clinical ventricular tachycardia, and
normal left ventricular function. All patients in group
2C (2 men and 3 women, mean age 58 ± 11 yr) had
documented clinical SCD but no inducible SMVT (Ta-
ble 1). The rate-corrected Q-T interval measured at
baseline was normal and did not change in response to
isoproterenol.

During adrenergic stimulation, intrinsic heart rate
increased by 26.6 ± 11.5%. Table 2 demonstrates the
mean alternans magnitude for each patient before
(baseline) and after the infusion of isoproterenol and
characterizes the response of TWA to β-adrenergic
stimulation. Patients were identified as positive re-
ponders to β-adrenergic stimulation if, as a result of
isoproterenol, they converted from alternans negative
(alternans ratio <3) to alternans positive (alternans
ratio >3) or if there was a significant (P < 0.05, paired
t-test) increase in the magnitude of alternans. Patients
were defined as negative responders if they converted
from alternans positive to alternans negative or had a
significant decrease in alternans magnitude. Other pa-
tients were classified as nonresponders.

TWA was not enhanced by isoproterenol in any of the
nine patients in group 2A or 2B (Table 2). In fact, three
of these patients were negative responders, indicating
that β-stimulation actually attenuated or eradicated
TWA in selected patients. In contrast, four of five pa-
tients in group 2C were positive responders to isopro-
terenol. However, β-stimulation induced TWA that
was not already present at baseline in only 2 of 14
patients.

Table 1. Clinical characteristics of group 2 patients

<table>
<thead>
<tr>
<th></th>
<th>Group 2A (SMVT)</th>
<th>Group 2B (Control)</th>
<th>Group 2C (SCD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Age, yr (means ± SD)</td>
<td>65 ± 8</td>
<td>51 ± 16</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>Type of heart disease</td>
<td>Coronary artery disease</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Valvular heart disease</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No organic heart disease</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>(means ± SD)</td>
<td>0.53 ± 0.17</td>
<td>0.56 ± 0.05</td>
</tr>
<tr>
<td>Indications for study</td>
<td>Sustained ventricular tachycardia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrest</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Symptomatic ventricular ectopy</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Supraventricular arrhythmias</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

SMVT, sustained monomorphic ventricular tachycardia; SCD, sudden cardiac death.

Table 2. Effect of β-adrenergic stimulation on TWA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Group</th>
<th>Baseline TWA Magnitude, μV</th>
<th>β-Stimulation TWA Magnitude, μV</th>
<th>ΔAlternans, μV</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2A</td>
<td>1.5 ± 0.3</td>
<td>1.4 ± 3.2</td>
<td>-0.1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2A</td>
<td>9.8 ± 5.9</td>
<td>4.3 ± 4.6</td>
<td>-5.5</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>2A</td>
<td>19.3 ± 5.2</td>
<td>0.6 ± 1.6</td>
<td>-18.7</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>2A</td>
<td>0.5 ± 1.5</td>
<td>1.3 ± 1.8</td>
<td>0.8 ± 0.7</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>2A</td>
<td>7.6 ± 8.7</td>
<td>6.1 ± 9.7</td>
<td>1.5 ± 1.4</td>
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</tr>
<tr>
<td>6</td>
<td>2A</td>
<td>3.8 ± 6.3</td>
<td>3.5 ± 4.3</td>
<td>-0.3</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>2B</td>
<td>7.8 ± 3.8</td>
<td>1.6 ± 2.1</td>
<td>-6.2</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>2B</td>
<td>0.4 ± 0.8</td>
<td>0.9 ± 1.4</td>
<td>0.5 ± 0.5</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>2B</td>
<td>3.7 ± 7.1</td>
<td>3.9 ± 3.7</td>
<td>0.2 ± 0.2</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>2C</td>
<td>1.9 ± 4.1</td>
<td>3.3 ± 3.5</td>
<td>1.4 ± 3.5</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>2C</td>
<td>4.7 ± 3.5</td>
<td>7.5 ± 2.1</td>
<td>2.8 ± 5.5</td>
<td>Positive</td>
</tr>
<tr>
<td>12</td>
<td>2C</td>
<td>2.6 ± 3.9</td>
<td>17.1 ± 6.1</td>
<td>-14.5</td>
<td>Positive</td>
</tr>
<tr>
<td>13</td>
<td>2C</td>
<td>10.9 ± 6.8</td>
<td>28.1 ± 5.8</td>
<td>-17.2</td>
<td>Positive</td>
</tr>
<tr>
<td>14</td>
<td>2C</td>
<td>2.1 ± 4.1</td>
<td>6.2 ± 6.3</td>
<td>4.1 ± 4.1</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Values are means ± SD. Change in T wave alternans (TWA) magnitude in response to β-adrenergic stimulation with isoprotere-
on in patients with SMVT (group 2A), control patients with negative electrophysiologic tests and no history of ventricular arrhyth-
ms (group 2B), and patients with SCD but no inducible SMVT (group 2C). Positive, Negative, and None indicate patients who were posi-
tive, negative, and nonresponders to β-adrenergic stimulation. Note
that TWA was measured at essentially identical atrial pacing cycle
lengths before (594 ± 31 ms) and after (592 ± 32 ms) administration of
isoproterenol.

DISCUSSION

Because TWA is a marker of electrical instability in the heart that is now used increasingly to stratify risk of
arrhythmias in patients, it is essential to develop
greater understanding of its underlying mechanistic
relation to SCD. Experimental studies in animals have
suggested that in some circumstances sympathetic
stimulation is an important mechanism of TWA. Schwartz and Malliani (19) showed that the alterna-
tion of the T wave may depend on abrupt increases in
sympathetic discharge. In dogs, stellate ganglion stim-
ulation produces a moderate increase in TWA, and
stelllectomy can significantly reduce alternans levels
(10). However, recent experimental data have chal-
lenged the notion that sympathetic stimulation plays
an important contributing role in TWA (2). Another
important physiological factor that may influence the
development of TWA is heart rate. We recently used
high-resolution optical mapping techniques to estab-
lish a link between TWA and the underlying mecha-
nism of reentry (11). According to this mechanism,
above a critical threshold heart rate, action potentials
from neighboring regions of cells alternate with oppo-
site phase that greatly amplifies spatial dispersions of
repolarization, which, in turn, form the substrate for
unidirectional block and reentry. Previously, Smith et
al. (21) showed that faster atrial pacing rates were
associated with decreased ventricular fibrillation
threshold and increased T wave alternation. Therefore,
current techniques used to measure TWA noninva-
sively involve exercise to elevate heart rate to moder-
ate levels. However, the extent to which elevated heart
rate vs. sympathetic tone during exercise contributes
to TWA was previously unknown.
The present study demonstrated the short-term variability and heart rate dependence of microvolt-level TWA, as well as the separate effects of heart rate and β-adrenergic stimulation on its development. We observed that patients exhibit spontaneous variations in TWA amplitude despite having a constant heart rate. These variations were greater at lower heart rates and less pronounced at higher heart rates as the average amplitude of TWA increased (Fig. 6). This oscillation occurred in all subgroups regardless of clinical presentation. The mechanism for this cyclic variation is unknown, although one might speculate that autonomic modulation or relatively slow intracellular processes affecting repolarization such as calcium handling might be involved. The finding that alternans amplitude increases and decreases approximately every 2–3 min contradicts the notion that TWA remains constant at a given heart rate. Because of the oscillatory variations of alternans, TWA should be measured iteratively over longer time intervals (≥3 min) and one should use appropriate caution when attempting to determine the heart rate threshold for TWA during exercise where heart rate may be fluctuating rapidly over time. This is an important practical consideration, because it is the heart rate threshold for TWA and not simply the ability to induce TWA that distinguishes high- from low-risk patients (3, 11, 16).

TWA appeared at a patient-specific heart rate threshold and rose in amplitude at higher heart rates. These findings are consistent with those of Hohnloser et al. (3) who described a patient-specific heart rate threshold for alternans in patients with ventricular tachycardia. It is known from previous studies that the threshold heart rate over which significant TWA occurs is higher in controls than in high-risk patients; Kavesh et al. (5) demonstrated that at higher heart rates TWA becomes a more sensitive but less specific test for arrhythmia vulnerability. In our study also, the threshold heart rate for TWA was higher in control subjects, but, because of the small sample size, this failed to reach statistical significance.

When heart rate was elevated to the same extent by isoproterenol instead of atrial pacing, the same TWA results (including oscillations) were found in most patients, indicating that elevation of heart rate by any means may be all that is required to elicit TWA. Ideally, we would have preferred to use more than one dose of isoproterenol. We were limited to a narrow range of heart rate by the need to perform atrial pacing at a target heart rate 25% higher than the baseline sinus rate (so as to ensure an adequate drug effect) without development of atrioventricular Wenckebach (which limited us even in the presence of isoproterenol). By using only one isoproterenol dose in each subject, we were able to achieve our goal of controlling for heart rate (i.e., the heart rate with pacing was identical before and after isoproterenol). We cannot rule out the possibility that a higher concentration of isoproterenol might have caused a significant increase in alternans, but, at the level of sympathetic stimulation achieved (enough to produce a substantial heart rate increase), there was no significant increase in alternans magnitude.

Hohnloser et al. (3) compared exercise (a combination of vagal withdrawal and sympathetic stimulation) with atrial pacing as a means of raising heart rate for the detection of TWA. They found a concordance rate of 84% for detecting abnormal alternans using the two methods. Because 77% of their patients had underlying coronary artery disease and most presented with SMVT, their findings are consistent with ours of minimal adrenergic effect on TWA in such patients and are also consistent with recent experimental studies that suggest that sympathetic stimulation is not a requirement for TWA of the surface ECG or alternans of repolarization at the level of the single cell (5, 11). In contrast, we found that sympathetic stimulation with isoproterenol did cause increased TWA amplitude in four of five patients with a history of SCD but no inducible SMVT. Thus the influence of sympathetic stimulation on TWA may depend on the population studied. Patients with fixed ventricular scar and reentrant SMVT may be relatively insensitive to an effect of sympathetic stimulation on TWA. Patients at high risk of SCD but without inducible SMVT (or any other reliable risk indicator), a heterogeneous group that often includes patients with nonspecific cardiomyopathy or LQTS, may be more susceptible to sympathetic stimulation. These findings may have important practical implications to arrhythmia risk assessment in patients.

We are extremely grateful for the assistance received from the nursing and technical staff in the clinical electrophysiology laboratories at MetroHealth Medical Center and the Cleveland Veterans Affairs Medical Center.

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