Effects of Selective Autonomic Blockade on T-Wave Alternans in Humans

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Background—T-wave alternans (TWA) is an important noninvasive measure of ventricular arrhythmia vulnerability. This study tested the hypothesis that the autonomic nervous system influences TWA measurement in high-risk subjects with coronary artery disease.

Methods and Results—T-wave alternans was measured in 60 patients with coronary artery disease, left ventricular dysfunction, and inducible sustained ventricular tachycardia during electrophysiological studies. All patients had TWA measured at baseline with atrial pacing at 100 bpm (600 ms), 109 bpm (550 ms), and 120 bpm (500 ms). After a 10-minute recovery period, TWA was measured again after sympathetic blockade (esmolol, n=20), parasympathetic blockade (atropine, n=20), or no intervention (control subjects, n=20). The prevalence of significant TWA was unchanged compared with baseline after atropine infusion and in the control group. In contrast, the amplitude of TWA in the vector magnitude lead was significantly reduced after esmolol infusion (P<0.001), and the number of positive TWA tests was reduced by 50% (70% versus 35%, P<0.05).

Conclusions—Our findings have important implications for the use of TWA to risk-stratify patients for life-threatening ventricular arrhythmias and provide a new potential mechanism for the reduction in sudden cardiac death conferred by β-blockers among patients with coronary artery disease and congestive heart failure. (Circulation. 2002;105:837-842.)

Key Words: tachyarrhythmias ■ nervous system, sympathetic ■ electrophysiology

Abnormalities in ventricular repolarization contribute importantly to the pathogenesis of life-threatening ventricular arrhythmias among patients with coronary artery disease and left ventricular dysfunction.1 The T wave is the surface ECG representation of the ventricular repolarization process. Visible alternation in the amplitude of the T wave (T-wave alternans, TWA) is a rare but significant finding that has been associated with malignant ventricular arrhythmias.2,3 Recently, a method was developed to detect more subtle microvolt levels of TWA.4–6 Microvolt TWA was subsequently shown to be associated with inducible ventricular arrhythmias during electrophysiological studies as well as spontaneous arrhythmic events.5–12

The autonomic nervous system is also an important determinant of arrhythmia vulnerability among patients with coronary artery disease.13 Since β-blockers reduce total mortality rates and sudden cardiac death among patients with ischemic heart disease14 and congestive heart failure15 and there is strong evidence that TWA is mechanistically related to the pathogenesis of ventricular arrhythmias,16,17 we hypothesized that β-blockade would reduce TWA. Accordingly, we prospectively evaluated patients with ischemic heart disease, left ventricular dysfunction, and inducible sustained monomorphic ventricular tachycardia during electrophysiological studies to determine if selective autonomic blockade alters the sensitivity of TWA for life-threatening ventricular arrhythmias. Our results provide novel insights into the pathogenesis of TWA and have important implications for the use of TWA for arrhythmia risk stratification in contemporary clinical practice.

Methods

Patients

The inclusion criteria for this prospective study were ischemic cardiomyopathy with a left ventricular ejection fraction ≤40%, age ≥21 years, referral for invasive electrophysiological testing for standard clinical indications, and inducible sustained monomorphic ventricular tachycardia during electrophysiological testing. The exclusion criteria were current use of Vaughan-Williams class I or III antiarrhythmic drugs or amiodarone use for the past 3 months, active ischemia or myocardial infarction within the past 4 weeks, baseline rhythm other than normal sinus (eg, atrial fibrillation or flutter), and known or probable sensitivity to esmolol or atropine (eg, bronchospasm, narrow angle glaucoma). To ensure that the patients could serve as their own controls, patients were also excluded if the TWA

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test was indeterminate at baseline (see below) or if 1:1 atrioventricular conduction during atrial pacing at 109 bpm did not persist after esmolol infusion. Of the 74 consecutive patients who were screened at the University of Maryland Medical Center and the Baltimore VA Medical Center, 14 were excluded because of indeterminate test results (19%). All enrolled patients underwent baseline TWA testing followed by repeat TWA testing after either esmolol infusion (n = 20), atropine infusion (n = 20), or no intervention (n = 20, control subjects). For the initial portion of the study, the drug infusion was assigned on an alternating basis (esmolol or atropine). A separate control group of 20 consecutive patients was subsequently enrolled when spontaneous oscillations in TWA magnitude were reported during fixed rate pacing in the absence of any pharmacological intervention. The clinical characteristics of the 3 groups did not differ significantly from each other (Table 1) or from those of the excluded patients (data not shown). Written informed consent was obtained from all patients, and the study was approved by the Institutional Review Boards at both institutions. The procedures followed were in accordance with institutional guidelines.

### Electrophysiological Testing

Electrophysiological testing was performed in the mildly sedated, postabsorptive state, as previously described. Sinus and atrioventricular nodal function were assessed, followed by programmed ventricular stimulation at 2 right ventricular sites with up to 3 extrastimuli at 2 drive cycle lengths (600 ms, 400 ms). All of the patients that were selected for study inclusion had inducible sustained monomorphic ventricular tachycardia that either persisted for at least 30 seconds or required earlier intervention with overdrive pacing or DC cardioversion because of hemodynamic compromise.

### TWA

TWA testing was conducted after the completion of the electrophysiological studies. β-Blockers were withheld for at least 4 hours so that the effects of selective autonomic blockade could be assessed. Careful skin preparation including mild abrasion was performed to reduce the skin-electrode impedance. Special high-resolution electrodes (High-Res, Cambridge Heart, Inc) were used to minimize noise. ECG leads were placed at the standard precordial lead positions (V1 through V6) and in an orthogonal X, Y, Z configuration, as described previously. TWA was measured with the CH2000 system (Cambridge Heart, Inc) and utilized a spectral method of analysis designed to allow detection of alternans in the microvolt range of amplitude.

TWA was measured at rest and during high right atrial pacing at cycle lengths of 600 ms (100 bpm), 550 ms (109 bpm), and 500 ms (120 bpm). Data were acquired for a minimum of 5 minutes at each paced rate. If 1:1 atrioventricular conduction was not present at a paced cycle length of 500 ms (120 bpm), then this pacing rate was not evaluated. After the first pacing protocol was completed (baseline), the patients were allowed to recover for 10 minutes. The patients then received intravenous esmolol, atropine, or no drug (control), and the same pacing protocol was repeated. Esmolol was administered as a loading dose of 500 μg/kg over 1 minute followed by a continuous intravenous infusion at 50 to 300 μg/kg per minute. The esmolol infusion was increased until a 20% decrease in heart rate was achieved or the maximum recommended intravenous infusion rate was reached (300 μg/kg per minute). Atropine was administered as a single intravenous bolus (0.02 mg/kg) over 2 minutes.

The maximal sustained TWA amplitude in the vector magnitude lead (present continuously for at least 1 minute) was recorded at each paced heart rate. TWA was considered positive at any paced rate when the alternans amplitude was >1.9 μV with the alternans ratio (signal-to-noise ratio) ≥3 for at least 1 minute in the vector magnitude lead, any orthogonal lead, or 2 consecutive precordial leads. TWA was defined as negative if the criteria for a positive test were not met, if there was no significant alternans for 1 minute during the pacing period, and if the tracing was not obscured by noise or ectopic beats. Otherwise, TWA was considered indeterminate. Each paced rate was evaluated separately for the first and second tests; in addition, an overall interpretation of each TWA test was performed. For the overall interpretation, the test was considered positive if significant TWA was present at ≥109 bpm (550 ms) and negative if no significant TWA was present and a heart rate of at least 109 bpm was attained; patients with indeterminate overall test results were excluded from this study. The TWA tests were interpreted by 2 experienced readers who were blinded with respect to the drug infusion and all clinical data including the results of the electrophysiological studies.

### Statistical Analysis

The clinical characteristics of the 3 groups were compared by means of χ² tests for categorical variables and ANOVA for continuous variables. The proportion of patients with positive TWA test results at each heart rate was compared with baseline by means of χ² tests. In addition, drug effects on TWA in the vector magnitude lead were assessed by means of 2-way, repeated-measures ANOVA. Since the proportion of patients who could be paced at 500 ms should be increased by atropine and decreased by esmolol, only paired comparisons were made at this cycle length; all patients were included for the other analyses. A value of P<0.05 was required for statistical significance.

### Results

#### Patient Demographics

The study population was 88% men, with a mean age of 65±9 years and a mean left ventricular ejection fraction of 27±7%. The majority of the patients had mild to moderate symptomatic heart failure. The indications for electrophysiological studies were asymptomatic nonsustained ventricular tachycardia in 25%, presyncope/syncope in 27%, and sustained ventricular tachycardia/ventricular fibrillation in 48%. By study design, all patients had ischemic cardiomyopathy and inducible sustained ventricular tachycardia during the electrophysiological studies. There were no significant differences between the study groups with respect to any of these clinical variables (Table 1).

### Baseline TWA Testing

As expected, TWA was rarely present during sinus rhythm (Table 2). In all 3 study groups, the prevalence of significant TWA and the maximal voltage in the vector magnitude lead increased when the heart rate was elevated with atrial pacing (P<0.01 for comparison of the 4 heart rates, Table 2 and Figure 1). The baseline TWA test was positive in 70% of patients, with no significant differences between the 3 study groups (Table 1).

### TABLE 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Control (n=20)</th>
<th>Atropine (n=20)</th>
<th>Esmolol (n=20)</th>
</tr>
</thead>
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<tr>
<td>Age, y</td>
<td>64±10</td>
<td>64±7</td>
<td>66±10</td>
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<td>Male, %</td>
<td>90</td>
<td>85</td>
<td>90</td>
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<tr>
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<td>28±7</td>
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<td>NYHA class, %</td>
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<td>80</td>
<td>75</td>
<td>80</td>
</tr>
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<td>Baseline TWA +, %</td>
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<td>75</td>
<td>70</td>
</tr>
<tr>
<td>Drug TWA +, %</td>
<td>55</td>
<td>60</td>
<td>35*</td>
</tr>
</tbody>
</table>

*P<0.05 for esmolol vs baseline.
TWA Testing After Drug Infusion
All patients in the esmolol group received a loading dose of 500 μg/kg. The esmolol infusion was titrated to the maximum dose of 300 μg/kg per minute in 80% of the patients; the remaining patients achieved the desired 20% decrement in heart rate at lower esmolol infusion rates. The mean dose of atropine given was 1.7 mg. The mean heart rate was reduced by atropine given was 1.7/H11006, heart rate at lower esmolol infusion rates. The mean dose of remaining patients achieved the desired 20% decrement in/H9262, dose of 300/H9262, TWA was significantly reduced by esmolol (0.001). Figure 1. Effects of esmolol on TWA amplitude at each heart rate. TWA was significantly reduced after esmolol infusion (24/H11006, unchanged in control subjects (2/H11006, P/11005, Table 1). There was no significant change in the prevalence of positive TWA test results after atropine infusion or after repeat testing in the control patients. A representative example of the effects of esmolol on TWA is shown in Figure 2.

Discussion
The major findings of this study are that selective β-adrenergic blockade markedly reduces the magnitude of TWA and the prevalence of positive TWA tests among patients with ischemic cardiomyopathy and inducible sustained monomorphic ventricular tachycardia. It is notable that these large changes in TWA were observed even though most patients exhibited only partial adrenergic blockade after esmolol was infused at the maximal dose. In contrast, selective parasympathetic blockade with atropine did not affect TWA. Importantly, the short-term reproducibility of the TWA test was excellent in the control group, indicating that the effects that we observed are not attributable to spontaneous oscillations in TWA magnitude.18

TWA and the Sympathetic Nervous System
In 1975, Schwartz and Malliani2 described a child with hereditary long-QT syndrome who had visible TWA during a fright response. They subsequently observed that unilateral left stellate ganglion stimulation could also evoke visible TWA in anesthetized felines. Nearing et al4 confirmed these findings by using a complex demodulation algorithm to measure microvolt levels of TWA in anesthetized canines. In this study, coronary artery occlusion produced large increments in TWA that were abolished after bilateral surgical stellate ganglion ablation. Left stellate ganglion stimulation restored the magnitude of alternans to values that were not statistically different from predenervation levels. This same group recently reported that an anger-like behavioral state significantly increased TWA in conscious dogs and that this effect was amplified by superimposed myocardial ischemia.21 Acute β-blockade with intravenous metoprolol significantly reduced TWA during the anger-like behavioral state and during concurrent anger and myocardial ischemia.21 In contrast, stellate ganglion stimulation increases the onset heart rate that is required to elicit TWA in normal anesthetized canines.22 An important limitation of many of these studies is that they did not control for heart rate, which is an important determinant of TWA magnitude.3,4,21 It is therefore possible that chronotropic effects and not adrenergic influences per se may have mediated much of the observed effects on TWA in these animal models.

Much less information is available regarding the effects of adrenergic interventions on TWA in humans. Hohnloser et al8 reported that exercise and right atrial pacing yielded concordant TWA test results in 84% of patients. Since physical

<table>
<thead>
<tr>
<th>TWA+ in Sinus Rhythm</th>
<th>TWA+ at 600 ms</th>
<th>TWA+ at 550 ms</th>
<th>TWA+ at 500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Drug</td>
<td>Baseline Drug</td>
<td>Baseline Drug</td>
<td>Baseline Drug</td>
</tr>
<tr>
<td>Control</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Atropine</td>
<td>0 (0)</td>
<td>3 (15)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Esmolol</td>
<td>3 (15)</td>
<td>0 (0)</td>
<td>9 (47)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages. *P=0.03, baseline vs drug; †P=0.004, baseline vs drug.

Figure 1. Effects of esmolol on TWA amplitude at each heart rate. TWA was significantly reduced by esmolol (P<0.001). Vmag indicates maximal TWA magnitude in the vector magnitude lead.
exercise produces sympathetic activation and parasympathetic withdrawal, these data could be interpreted as indirect evidence against an important sympathetic influence on TWA. However, it should be noted that there is relatively little sympathetic activation at the levels of exercise that were used to evoke TWA and that the magnitude of alternans was in fact greater during exercise compared with the highest heart rates achieved during atrial pacing. Kaufman et al. assessed the effects of \( \beta \)-adrenergic stimulation with isoproterenol on TWA in a small series of patients during atrial pacing at 100 bpm and did not observe any consistent effects. It is possible that sympathetic stimulation did not augment TWA in these 2 studies because sympathetic tone was already high at baseline in these subjects with congestive heart failure and left ventricular dysfunction. In the present study, we evaluated the effects of selective \( \beta \)-adrenergic blockade in a homogenous patient population with coronary artery disease, left ventricular dysfunction, and inducible sustained ventricular tachycardia. Importantly, we observed a significant decrease in heart rate after esmolol infusion, suggesting that the observed effects on TWA were in fact due to sympathetic blockade. Despite only partial sympathetic blockade, there was a 50% decrease in the number of patients with positive TWA tests and a marked decrease in the TWA voltage at each paced heart rate (Figure 1, Table 2). It is now well recognized that TWA arises from repolarization alternans at the cellular level.16 Although TWA is intrinsic to the myocyte and can be evoked in the absence of sympathetic stimulation, our data clearly indicate that adrenergic blockade modulates TWA in humans by an undefined mechanism. This phenomenon is analogous to the hereditary long-QT syndrome in which the fundamental defects, mutations in cardiac ion channels, have been localized to the cellular level but the clinical phenotype is importantly influenced by the adrenergic nervous system.25

Potential Mechanisms for Adrenergic Effects on TWA

Recent evidence indicates that TWA on the surface ECG arises from alternation of repolarization at the level of the
single cell. In addition, TWA appeared to be mechanistically related to the genesis of ventricular arrhythmias in this model. When atrial pacing was performed to increase the duration of TWA, marked dispersion of repolarization was generated that created the substrate for reentrant ventricular arrhythmias. The ionic mechanism of TWA was further elucidated by Shimizu et al., who used the arterially perfused wedge model. These investigators observed that TWA was abolished by ryanodine, which blocks calcium release from the sarcoplasmic reticulum, and by low levels of extracellular calcium, suggesting a critical role for intracellular calcium cycling in the maintenance of TWA. TWA is thought to result when the pacing rate is faster than the time required for calcium release, reuptake, and transport to the junctional sarcoplasmic reticulum. β-Adrenergic blockade could reduce TWA by decreasing intracellular cAMP formation, which would decrease calcium entry into the cell via L-type calcium channels. If TWA is in fact mechanistically related to the genesis of ventricular arrhythmias in humans, then abolition of TWA by β-adrenergic blockade may be indicative of a reduced susceptibility to subsequent arrhythmic events in individuals who exhibit this response and are maintained on long-term β-blocker therapy.

TWA and the Parasympathetic Nervous System

Vagus nerve excitation is antifibrillatory during acute myocardial ischemia, and clinical markers of enhanced tonic or reflex vagal activity have been associated with an improved prognosis after myocardial infarction. There is limited evidence that vagus nerve stimulation can reduce TWA in humans, but ours is the first study to evaluate the effects of selective parasympathetic blockade on TWA while simultaneously controlling for heart rate. We did not observe any effect of atropine on TWA, suggesting that tonic vagal activity does not exert an important influence on TWA, which would decrease calcium entry into the cell via L-type calcium channels. If TWA is in fact mechanistically related to the genesis of ventricular arrhythmias in humans, then abolition of TWA by β-adrenergic blockade may be indicative of a reduced susceptibility to subsequent arrhythmic events in individuals who exhibit this response and are maintained on long-term β-blocker therapy. Limbodynamic Tone and Reflexes After Myocardial Infarction (ATRAMI) Investigators. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet. 1998;351:49–53.

Clinical Implications

It is intriguing to speculate that abolition of TWA by β-adrenergic blockade may identify patients who are at low risk for ventricular arrhythmias if they are maintained on long-term β-blocker therapy. β-Blockers reduce mortality rates and prevent sudden cardiac death among patients with coronary artery disease and congestive heart failure. β-Blockers also reduce recurrent ventricular arrhythmias among implantable cardioverter-defibrillator recipients and effectively terminate life-threatening episodes of “electrical storm” among patients with recent myocardial infarction. Additional studies are required to determine if risk stratification is optimized by performing TWA testing in the drug-free state or on optimal medical therapy with β-blockers.

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