Effects of Acute Mental Stress and Exercise on T-Wave Alternans in Patients With Implantable Cardioverter Defibrillators and Controls

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Background—Malignant cardiac arrhythmias can be triggered by exercise and by mental stress in vulnerable patients. Exercise-induced T-wave alternans (TWA) is an established marker of cardiac electrical instability. However, the effects of acute mental stress on TWA have not been investigated as a vulnerability marker in humans.

Methods and Results—TWA responses to mental stress (anger recall and mental arithmetic) and bicycle ergometry were evaluated in patients with implantable cardioverter defibrillators (ICDs) and documented coronary artery disease (n=23, age 62.1±12.3 years) and controls (n=17, age 54.2±12.1 years). TWA was assessed from digitized ECGs by modified moving average analysis. Dual-isotope single photon emission computed tomography was used to assess myocardial ischemia. TWA increased during mental stress and exercise (P values <0.001), and TWA responses were higher in ICD patients than in controls (arithmetic Δ=8.9±1.4 versus 4.3±2.2 μV, P=0.043; exercise Δ=21.4±2.8 versus 13.8±3.2 μV, P=0.038). TWA increases with mental stress occurred at substantially lower heart rates (anger recall Δ=9.7±7.7 bpm, arithmetic Δ=14.3±13.3 bpm) versus exercise (Δ=53.7±22.7 bpm; P values <0.001). After adjustment for heart rate increases, mental stress and exercise provoked increased TWA in ICD patients (P values <0.05), but not in controls (P values >0.2). Ejection fraction and stress-induced myocardial ischemia were not associated with TWA.

Conclusions—Mental stress can induce cardiac electrical instability, as assessed via TWA, among patients with arrhythmic vulnerability and occurs at lower heart rates than with exercise. Pathophysiological mechanisms of mental stress–induced arrhythmias may therefore involve central and autonomic nervous system pathways that differ from exercise-induced arrhythmias. (Circulation. 2004;109:1864-1869.)

Key Words: arrhythmia ■ mental stress ■ exercise ■ ischemia ■ risk factors

The unpredictable nature of malignant arrhythmias poses a major challenge to prevention of sudden cardiac death. New noninvasive techniques for assessing arrhythmic vulnerability and increased awareness of exogenous activities as triggers of sudden death have improved risk stratification in high-risk populations.1,2 T-wave alternans (TWA), an index of beat-to-beat variation of T-wave morphology, is a marker of cardiac electrical instability and an important predictor of future arrhythmic events in vulnerable patients, including patients with implantable cardioverter defibrillators (ICDs), those referred for electrophysiological testing, and postmyocardial infarction (MI) patients.3–4

Exercise can be a potent trigger of sudden death5 and MI.6 TWA responses to exercise are related to adverse clinical outcomes in patients at high risk for arrhythmias.2,7–11 Other factors associated with TWA include myocardial ischemia12 and MI.4,7

Acute emotional arousal can trigger life-threatening arrhythmias13–15 and myocardial ischemia16–19 in vulnerable patients. Induction of anger in patients undergoing electrophysiological testing accelerates ventricular tachycardias and increases electrical termination thresholds.20 TWA can also be induced in canines by an angerlike state, and these TWA responses are increased in the presence of ischemia.21 The effects of acute mental stress on TWA have not been studied systematically in humans.

The present study examines the hypothesis that cardiac electrical instability, assessed by TWA, can be elicited by
acute mental stress in patients with coronary artery disease (CAD) and high vulnerability for malignant arrhythmias. It was further hypothesized that mental stress–induced TWA increases are independent of stress-induced heart rate (HR) responses. We also compared mental stress– and exercise-induced TWA responses and the role of left ventricular function and transient myocardial ischemia.

Methods

Patients
Patients (n=23) with ICDs and documented CAD were recruited because of their known propensity for malignant arrhythmias and ischemia (Tables 1 and 2). A priori statistical power analysis indicated that 17 patients per group would suffice to detect a difference of 1 SD in TWA responses to mental stress at an α-level of 0.05 and power of 80%. Patients were recruited from Arrhythmia Associates, Fairfax, Va; the Veterans Affairs Medical Center, Washington, DC; and St. Francis Hospital, Roslyn, NY. Exclusion criteria were atrioventricular conduction defects, left bundle-branch block, chronic atrial fibrillation, MI <1 month, unstable angina, class IV congestive heart failure, critical valve pathology, primary cardiomyopathy, use of amiodarone, and age >80 years. Age-matched normal volunteers (n=17) with <5% likelihood of CAD were tested as controls.

To optimize assessments of TWA, calcium antagonists and ACE inhibitors were withheld for 24 hours, and long-acting nitrates were withheld for 6 hours.23 β-Adrenergic blocking agents were withheld for >48 hours in 4 patients, 6 patients did not receive β-blockade as part of their medical regimen, and 13 patients were tested without discontinuation of β-blockade. The study was approved by the participating institutional review boards, and all patients gave written informed consent.

Protocol
Mental stress and exercise tasks were performed on 2 consecutive days in randomized order. High-resolution silver–silver chloride electrodes were used for noise reduction. Continuous ECGs were recorded and digitized at 1000 Hz with 16-bit resolution with the CH2000 (Cambridge Heart) and were exported for blinded offline analyses by a trained reader using a GE Medical Systems Workstation. ECGs were monitored for ventricular arrhythmias and ischemia, defined as ≥1 mm horizontal or downsloping ST-segment depression. Systolic and diastolic blood pressure and HR were obtained at 90-second intervals (Dinamap, Critikon).

Analysis of TWA
The modified moving average (MMA) analysis was used to measure TWA.4,24 This method was validated experimentally24 and was shown to be capable of identifying post-MI patients with a >4-fold increased risk of malignant arrhythmias based on ambulatory ECG levels of TWA.4 The MMA approach builds on principles of noise reduction through filtering, exclusion of aberrant beats, and use of continuous waveform averaging to provide a robust, dynamic assessment of TWA. Briefly, preprocessing is performed by low-pass filtering and removal of baseline wander and premature and noisy beats. The next step and hallmark of the MMA process involves separating beats into odd and even groups and averaging the waveforms of each group. A weighting function in the averaging process limits undue influence from single aberrant beats. The final step is computation of TWA as the maximum difference in amplitude between the odd-beat and the even-beat average complexes from the J point to the end of the QT wave. Extensive testing has revealed that the readings are not affected by changing HRS or phase shift perturbations. As standard practice in this and previous studies, the reliability of the results was further ensured by analysis of only those intervals that were free of premature beats. In the present study, average TWA was assessed over 3- to 4-minute segments during baseline (after 10 minutes of rest), anger recall, and mental arithmetic; after mental challenge; during stage 1 exercise; and at peak exercise.

Mental Stress and Exercise Protocols
Before the mental tasks, patients relaxed in a quiet room during a 15-minute baseline phase. Mental stress consisted of 2 tasks:23,25 that elicit ischemia in 30% to 60% of CAD patients. During anger recall, patients gave a 4-minute speech about a recent anger-provoking incident.16,23 Mental arithmetic involved subtraction of serial 7’s from a 4-digit number while being interrupted and urged to improve performance.23,26,27

Bicycle exercise was performed with increasing workload by 25 W in 3-minute stages according to the standard CH2000 protocol.2,3

Exercise tests were discontinued if patients reached 80% of predicted HR or if severe ST-segment depression, arrhythmias, or angina occurred.

Assessment of Myocardial Ischemia
Dual-isotope single photon emission computed tomography (SPECT) was used to assess mental and physical stress–induced myocardial ischemia28 because of its suitability in patients with reduced left ventricular function.29-30 Thallium-201 (2.5 to 3.5 mCi) was injected at rest, and SPECT images were obtained 10 minutes after isotope injection. Two minutes into mental stress, 20 to 30 mCi

<p>| TABLE 1. Characteristics of Patients With ICDs (n=23) |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resuscitated and inducible VT/VF</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>VF/VT with syncope</td>
<td>9 (39)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic VT</td>
<td>11 (48)</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic VT</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT with syncope</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>No. of vessels diseased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (30)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>13 (57)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>32.2±8.3</td>
<td></td>
</tr>
<tr>
<td>Prior coronary angioplasty</td>
<td>8 (35)</td>
<td></td>
</tr>
<tr>
<td>Prior coronary bypass surgery</td>
<td>11 (48)</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>16 (70)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>4 (17)</td>
<td></td>
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<tr>
<td>History of hypertension</td>
<td>17 (74)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (17)</td>
<td></td>
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<tr>
<td>β-Adrenergic blocking agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not prescribed</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>Withheld</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Continued</td>
<td>13 (57)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are n (%) unless otherwise indicated.

VT indicates ventricular tachycardia; VF, ventricular fibrillation.

<p>| TABLE 2. Characteristics of Patients With ICDs (n=23) |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.8±12.7</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>30 (75)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>36 (90)</td>
<td>15 (88)</td>
</tr>
</tbody>
</table>

*P<0.01, ICD vs control.
of 99mTc sestamibi was injected. Exercise sestamibi was injected at peak effort, and patients continued exercise for 1 minute after isotope injection. SPECT images were obtained at 45 minutes after the mental and exercise tests. Images were processed by a trained technologist blinded to clinical information and type of stress. Image analysis was performed with QPS software (Cedars-Sinai Medical Center) with a 20-segment, 5-point model (0 = normal, 1 = mildly reduced uptake, 2 = moderately reduced uptake, 3 = severely reduced uptake, and 4 = no uptake). Summed difference scores between stress and rest were used to determine stress-induced ischemia as absent (0 to 3), mild, moderate (4 to 6), or severe (≥7).

**Statistical Analyses**

Data are presented as mean ± SE or percentages when appropriate. TWA values are presented as mean ± SE and were transformed logarithmically for statistical analyses because values displayed a nonnormal, positively skewed distribution. Stress-induced responses were examined with paired t tests. Comparisons between ICD patients and controls were conducted with t tests. Mixed-model ANOVA was used to examine group differences across tasks, with “groups” as a between-subjects factor and “tasks” as a within-subjects factor that consisted of baseline, anger recall, mental arithmetic, post–mental challenge, exercise stage 1, and peak exercise. To assess differential responses in patients versus controls, the groups × tasks interaction term was evaluated.

To determine TWA values with adjustment for HR changes with mental stress and exercise, regression analysis was used to predict TWA levels (y) from concomitant HR measures (n = 260), where y = a + b × HR; values of a and b were based on the regression equation. HR-adjusted residualized TWA values were then calculated as the difference between the observed (y) and predicted (ŷ) TWA levels: y - ŷ. Thus, positive residualized values occur when TWA levels are higher than expected on the basis of the relationship between HR and TWA. HR correction is important because stress-induced HR increases may contribute to elevations in TWA and are lower during mental stress than with exercise.

**Results**

**Hemodynamic and ECG Responses to Mental Stress and Exercise**

Mental stress and exercise induced significant increases in blood pressure and HR (P values < 0.01; Figure 1). Baseline levels and responses to mental stress and exercise were not different between ICD patients and controls, except that ICD patients had higher post–mental stress systolic and diastolic blood pressures than controls (P < 0.05), which indicates delayed recovery.

In ICD patients, exercise induced ST-segment depression (n = 3), premature ventricular complexes (n = 11), couplets (n = 2), and bigeminy (n = 1). Mental stress did not elicit arrhythmias or ST-segment depression. At peak exercise, all patients achieved HRs > 100 bpm, and 16 (69.6%) of 23 patients reached 80% of age-predicted HR.

**Comparison of TWA Responses in ICD Patients Versus Controls**

Among ICD patients, TWA increased significantly from baseline (15.8 ± 0.8 μV) in response to mental stress (anger recall 21.3 ± 1.6 μV, P < 0.001; mental arithmetic 24.7 ± 1.7 μV, P < 0.001; Figure 2) and remained elevated for 4 minutes after mental stress (25.4 ± 3.4 μV, P = 0.009). Low-grade exercise provoked significantly higher TWA levels (31.1 ± 2.6 μV) than mental stress (P values < 0.01), TWA levels were highest during peak exercise (35.5 ± 3.1 μV, P < 0.0001).

ICD patients had larger TWA increases than controls with mental arithmetic (Δ = 8.9 ± 1.4 versus 4.3 ± 2.2 μV; P = 0.043), low-grade exercise (Δ = 17.1 ± 2.2 versus 6.6 ± 1.9 μV; P = 0.0004), and peak exercise (Δ = 21.4 ± 2.8 versus 13.8 ± 3.2 μV; P = 0.038; Figure 2). Among controls, TWA responses were not statistically different between men and women (P values > 0.10), and therefore, data for men and women were combined. ANOVA confirmed that TWA responses to mental stress and exercise tasks were higher in ICD patients than in controls (P for groups = 0.013); TWA responses differed significantly between the mental and physical tasks (P for tasks < 0.001), and the ICD versus control groups displayed a differential response to the tasks (P for tasks-by-group interaction = 0.037; Figure 2).

**Adjustments for HR**

HR increases during exercise (Δ = 53.7 ± 22.7 bpm) were substantially larger than those during anger recall (9.7 ± 7.7 bpm) or mental arithmetic (14.3 ± 13.3 bpm; P values...
HR was correlated positively with TWA magnitude during rest, mental stress, and exercise for ICD patients ($r=0.46$, $P<0.001$) and controls ($r=0.32$, $P<0.001$). We used residualized TWA values to adjust for effects of HR on TWA. Among controls, HR-adjusted TWA responses to exercise or mental stress were nonsignificant (Figure 3; $P$ values $>0.20$). In contrast, ICD patients displayed significant HR-adjusted TWA responses from baseline to anger recall ($P=0.022$), mental arithmetic ($P=0.0002$), post–mental stress ($P=0.014$), exercise stage 1 ($P=0.0001$), and peak exercise ($P=0.001$). HR-adjusted TWA responses of ICD patients remained significantly higher than controls ($P$ for mental arithmetic $=0.032$, $P$ for exercise stage 1 $=0.0002$, and $P$ for peak exercise $=0.008$; Figure 3). Exercise-induced adjusted TWA increases were greater than with anger recall ($P=0.016$) and mental arithmetic ($P=0.087$).

**Effects of Left Ventricular Function and Stress-Induced Ischemia**

Patients with poor left ventricular function (ejection fraction $\leq 30\%$; $n=11$) displayed similar TWA responses as patients with preserved left ventricular function (ejection fraction $>30\%$; $n=28$).

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Figure 2. Comparison of ICD patients with controls in TWA responses to mental stress and exercise ($\Delta$=change from baseline). Increases in TWA were higher in ICD patients than in controls during mental arithmetic ($P=0.043$), exercise stage 1 ($P=0.0004$), and peak exercise ($P=0.038$). *$P<0.05$, **$P<0.01$ (ICD vs control).

Figure 3. HR-adjusted TWA responses were significant in ICD patients ($P$ values $<0.05$) but not in controls ($P$ values $>0.2$). $\Delta$=Change from baseline. HR-adjusted TWA increases were higher in ICD patients than in controls ($P$ for mental arithmetic $=0.032$, $P$ for exercise stage 1 $=0.0002$; and $P$ for peak exercise $=0.008$). *$P<0.05$, **$P<0.01$ (ICD vs control).
Discussion
This study demonstrates that acute mental stress elicits increases in TWA, a marker of cardiac electrical instability, in patients with documented coronary disease and known vulnerability to cardiac arrhythmias. The increases in TWA with mental stress are impressive given the relatively small increase in HR. TWA responses to mental arithmetic stress and exercise were higher in ICD patients than in controls. The observed increases in cardiac electrical instability induced by acute mental stress may explain clinically and experimentally documented relationships between emotional arousal and life-threatening cardiac arrhythmias.

The present findings are consistent with observations in canines that demonstrated TWA in response to an anger-like state.21 Lampert and colleagues also reported that mental stress results in ventricular arrhythmias resistant to termination (ie, requiring shock) during electrophysiological testing and that ICD discharges are preceded by episodes of self-reported anger.15 Mental stress–induced cardiac electrical instability, which can be measured noninvasively with TWA, may therefore prove useful as a marker of vulnerability to malignant arrhythmias and sudden death in vulnerable patients.

Pathophysiological Mechanisms of Mental Stress–Induced TWA
The role of myocardial ischemia in TWA is well established at the cellular level, in large animals, and in clinical settings such as coronary angioplasty.12 We cannot rule out that ischemia played a role in mental stress–induced TWA because of the small sample size and the possibility of low-level ischemia undetected by SPECT. However, it appears unlikely that ischemia played a major role in the observed stress-induced TWA responses, because no associations were found between TWA and presence or severity of ischemia. The observation that ischemia was unrelated to TWA may reflect the elevated arrhythmic vulnerability, which is high in ICD patients with CAD.

Adrenergic and autonomic nervous system pathways are involved in exercise-induced and mental stress–induced TWA. Patients tested while using β-blockade (n=13) had similar TWA responses to mental stress as patients tested without β-blockade but displayed attenuated TWA levels during rest (P=0.03) and exercise (P=0.02). Because of the nonrandom assignment, no conclusions can be drawn regarding the efficacy of β-blockade for mental stress–induced TWA. Further investigations are needed to examine the biobehavioral pathways by which mental stress induces arrhythmic vulnerability.

Role of HR in TWA Responses
HR may affect TWA through both metabolic and nonmetabolic actions. The effects of mental stress and exercise on TWA remained significant after adjustment for stress-induced HR responses, and TWA responses to mental stress occurred with modest HR increases (<15 bpm). Therefore, the pathophysiological mechanisms of mental stress–induced electrical instability and malignant arrhythmias may differ from those involved in exercise-induced arrhythmias, reflecting differential autonomic and central nervous system responses. This discrepancy between mental stress and exercise has also been observed in the inducibility of myocardial ischemia.

Study Limitations
The present findings may be generalizable only to patients with low arrhythmic thresholds and significant underlying CAD. The present sample size was sufficient to address the study’s main hypothesis of increased TWA responses among ICD patients versus controls, but the study was not adequately powered to address gender differences or subgroup analyses. Studies with larger samples are needed to allow multivariate analyses with adjustment for age and gender and to assess the role of compromised left ventricular function and stress-induced ischemia.

Statistical techniques were used, rather than cardiac pacing, to address potential bias due to HR. Increases in TWA with pacing occur primarily at high (>200 bpm) rates, and lower rates affect beat-to-beat alterations of the QRS complex but not the T wave.2 TWA is expected to be partially independent of HR because it reflects the temporospatial repolarization heterogeneity that is a marker of cardiac electrical instability under conditions of arrhythmic vulnerability.24,31 The present study demonstrates that adjustments for HR resulted in eradication of the TWA response in controls, whereas alternans responses in ICD patients remained significant.

Clinical Implications
Accurate identification of patients at risk of sudden cardiac death is an important goal in the prevention of life-threatening arrhythmias. Anger and emotional distress may precede arrhythmic episodes in a substantial number of individuals, and controlled laboratory stress tasks can be used to assess susceptibility to electrophysiological markers of arrhythmic vulnerability. TWA is predictive of future arrhythmic events.2,3,7–11 Recently, we documented that daily activities exert a significant impact on TWA levels in post-MI patients, which suggests a potential role of mental activity as an arrhythmogenic trigger.4 The observation that TWA can be induced by mental stress at relatively low HRs has important clinical implications, particularly for sedentary patients in...
whom ambulatory HR responses are generally low. Thus, mental stress may trigger arrhythmias in vulnerable patients by adversely affecting cardiac electrical stability. Such measures of mental stress–induced cardiac electrical instability may prove to be predictive of future cardiac arrhythmias and sudden death, as have measures of mental stress–induced myocardial ischemia in patients with CAD.19

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References
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