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Anger-Induced T-Wave Alternans Predicts Future Ventricular Arrhythmias in Patients With Implantable Cardioverter-Defibrillators

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Objectives This study sought to determine whether T-wave alternans (TWA) induced by anger in a laboratory setting predicts future ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICDs).

Background Anger can precipitate spontaneous ventricular tachycardia/ventricular fibrillation and induce TWA. Whether anger-induced TWA predicts future arrhythmias is unknown.

Methods Sixty-two patients with ICDs underwent ambulatory electrocardiography during a mental stress protocol, 3 months after the ICD was implanted. T-wave alternans was analyzed using time-domain methods. After a ≥1 year follow-up, ICD stored data was reviewed to determine incidence of ICD-terminated ventricular tachycardia/ventricular fibrillation.

Results Patients with ICD-terminated arrhythmias during follow-up (n = 10) had higher TWA induced by anger, 13.2 μV (interquartile range [IQR] 9.3 to 16 μV), compared with those patients without future ventricular arrhythmias, 9.3 μV (IQR 7.5 to 11.5 μV, $p < 0.01$). Patients in the highest quartile of anger-induced TWA (>11.9 μV, n = 15) were more likely to experience arrhythmias by 1 year than those in the lower quartiles (33% vs. 4%) and during extended follow-up (40% vs. 9%, $p < 0.01$ for both). In multivariable regression controlling for ejection fraction, prior clinical arrhythmia, and wide QRS, anger-induced TWA remained a significant predictor of arrhythmia, with likelihood in the top quartile 10.8 times that of other patients (95% confidence interval: 1.6 to 113, $p < 0.05$).

Conclusions Anger-induced TWA predicts future ventricular arrhythmias in patients with ICDs, suggesting that emotion-induced repolarization instability may be 1 mechanism linking stress and sudden death. Whether there is a clinical role for anger-induced TWA testing requires further study. (J Am Coll Cardiol 2009;53:774–8) © 2009 by the American College of Cardiology Foundation

Evidence linking strong emotion and sudden cardiac death continues to mount. Sudden death increases during emotionally devastating disasters such as earthquakes (1). In patients with implantable cardioverter-defibrillators (ICDs), ventricular tachycardia/ventricular fibrillation (VT/VF) increased in the emotional weeks following the World Trade Center attacks in 2001 (2). Further, anger precipitates spontaneous VT/VF among patients with ICDs (3). The physiologic pathways through which emotion can trigger arrhythmia, however, remain incompletely understood.

See page 779

Recently, we (4) and Kop et al. (5) demonstrated that anger, induced in a laboratory setting, can increase T-wave alternans (TWA). T-wave alternans is a marker of repolarization instability (6) that immediately precedes development of VF in animal models (6,7) and in patients (8), suggesting that TWA may be mechanistically related to arrhythmia. Further, TWA measured during exercise (9) or atrial pacing (10) predicts vulnerability to ventricular arrhythmias. To test the hypothesis

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that TWA induced by anger will similarly predict future VT/VF, we measured TWA during a laboratory mental stress protocol in patients shortly after ICD implantation and prospectively evaluated the incidence of spontaneous sustained VT/VF requiring ICD-termination in follow-up.

Methods

Patient population. Patients were recruited from the Yale Electrophysiology practice who had coronary artery disease (≥75% narrowing of ≥1 artery or documented infarction) or dilated cardiomyopathy and a standard indication for ICD implantation. Patients with atrial fibrillation, diagnosed psychiatric or cognitive disorders, inability to speak English, class IV congestive heart failure, or medical comorbidities associated with a likelihood of death within 2 years were excluded. Seventy-one appropriate patients receiving ICDs between December 2000 and September 2004 agreed to participate and underwent the protocol. In 7 patients, noise precluded TWA analysis in ≥1 stage. Two patients failed to complete 1 year of follow-up (1 death due to unknown cause, 1 heart transplant). Data from the remaining 62 are included. Clinical variables were collected through chart review. The study was approved by the Yale Human Investigation Committee, and all patients provided written informed consent.

Mental stress protocol. Patients underwent laboratory mental stress testing in the morning, before their first scheduled ICD follow-up, which was 3 months after implantation. Patients took all usual medications. Pacing was programmed VVI, 40 beats/min, with subsequent sinus rhythm with native atrial to ventricular conduction in all patients. Our mental stress protocol was described in detail previously (4). Briefly, conditions included resting baseline, mental arithmetic (serial subtraction of 7), second baseline, and anger recall.

Repolarization analysis. Methods for repolarization analysis were described in detail previously (8). Ambulatory electrocardiographs with modified V_1 and V_5 leads were recorded (bipolar pairs) on GE Medical (Milwaukee, Wisconsin) Marquette Series 8500 direct (amplitude-modulated) recorders (flat frequency response; linear phase between 0.67 and 50 Hz [±3 dB]; digitized at 400-Hz sampling frequency, effective resolution 2.5 μV). A single lead (with largest magnitude T-wave) was analyzed for each subject throughout.

A previously validated program for adaptive baseline correction (8) was applied to assure accurate detection of the isoelectrical line. The QRS complexes were classified using custom software and verified by an experienced technician. After exclusion of ectopics, series of consecutive sinus beats were processed to identify fiducial points (8).

The dynamics of TWA were examined using 2 independent time-domain techniques: intrabeat average and modified moving average analyses (7,8). Modified moving average reports a maximum difference during repolarization between beats, whereas intrabeat average reports the average differences and hence, results in lower absolute values for TWA. Although not identical, these algorithms have performed similarly in previous validation studies (8). Because the correlation coefficient between modified moving average–derived and intrabeat average–derived TWA was 0.72, and results of analyses were similar, only intrabeat analysis results are presented.

Abbreviations and Acronyms

ICD = implantable cardioverter-defibrillator
IQR = interquartile range
TWA = T-wave alternans
VT/VF = ventricular tachycardia/ventricular fibrillation

Follow-up. Each patient's ICD was interrogated at least every 3 to 6 months by telephone and/or in clinic. Review of stored electrograms and event details identified occurrence of ICD-treated sustained VT/VF episodes.

Statistical analysis. Patients with ICD-treated, confirmed VT/VF during follow-up were compared by *t* test with those without VT/VF on the magnitude of TWA during baseline, anger, and arithmetic. The relationship between TWA at each stage and incidence of VT/VF in follow-up was evaluated with logistic regression. Subsequent models included clinical variables. All models included adjustment for heart rate during the TWA analysis period and length of follow-up.

Because anger-induced TWA showed the strongest associations with future VT/VF, in further analyses we compared patients in the top quartile of anger-induced TWA with all other patients on incidence of ICD-treated, confirmed VT/VF during follow-up using the chi-square test and by construction of Kaplan-Meier survival curves. This approach was used in previous studies of TWA (11) and in analogous studies of other stress-induced cardiac changes (12). Logistic regression was also performed to adjust for clinical variables demonstrating associations with higher anger-induced TWA and/or future VT/VF.

All analyses were performed with JMP 5.0 software (SAS Institute, Cary, North Carolina).

Results

Patient population. Patient characteristics are shown in Table 1. During a median follow-up of 37 months (interquartile range [IQR] 25 to 47 months, range 12 to 75 months), 10 patients experienced ICD-terminated VT/VF.

Relationship between anger-induced TWA and arrhythmias in follow-up. Overall, TWA during anger was greater than baseline (Table 2). Patients with ICD-terminated VT/VF during follow-up had higher TWA than those without at all stages, a difference greatest during anger, with a median anger-induced TWA of 13.2 μV (IQR 9.3 to 16 μV), compared with 9.3 μV (IQR 7.5 to 11.5 μV, $p < 0.01$) in those without future VT/VF. In regression analysis, TWA induced with anger predicted the incidence of ventricular arrhythmias requiring ICD termi-

JACC Vol. 53, No. 9, 2009
March 3, 2009:774–8

Table 1 Demographic and Clinical Characteristics in Top and in Lower Quartiles of Anger-Induced TWA

	Top Quartile (n = 15)	Lower Quartiles (n = 47)
Age, yrs	65 ± 3	62 ± 2
Male sex	12 (80%)	41 (87%)
Coronary artery disease*	14 (93%)	42 (89%)
Ejection fraction, %	29 ± 3	32 ± 2
Ejection fraction ≤35%	12 (80%)	32 (68%)
History of prior clinical VT/VF†	6 (40%)	17 (36%)
Use of beta-blocker‡	13 (87%)	41 (87%)
Use of sotalol	0	4 (9%)
Use of amiodarone	1 (7%)	6 (13%)
Use of any beta-blocking medication§	14 (93%)	45 (96%)
QRS duration, ms	145 ± 10	133 ± 6
Heart rate with anger, beats/min	68 ± 2	69 ± 1
Heart rate change with anger, beats/min	4 ± 1	7 ± 1‖
ICD rate cutoff for therapy, beats/min	172 ± 4	175 ± 2
Follow-up, months	40 ± 4	37 ± 2

Values expressed as mean ± standard error or n (%). *Defined in Methods section; †sustained ventricular tachycardia or fibrillation; ‡excluding sotalol or amiodarone; §amiodarone, sotalol, and/or other beta-blockers; ‖$p < 0.05$ with all other p values nonsignificant (>0.15).

ICD = implantable cardioverter-defibrillator; TWA = T-wave alternans; VT/VF = ventricular tachycardia/ventricular fibrillation.

nation ($R^2 = 0.13$, $p = 0.01$). Baseline TWA and arithmetic-induced TWA also predicted future VT/VF but less strongly ($R^2 = 0.081$, $p < 0.05$ and $R^2 = 0.07$, $p < 0.05$, respectively).

Patients in the top quartile of anger-induced TWA (TWA ≥11.9 μV, n = 15) were more likely to experience ICD-terminated VT/VF at 1 year than other patients (33% vs. 4%) and during extended follow-up (40% vs. 9%, $p < 0.01$ for both comparisons) (Fig. 1). After controlling for length of follow-up, the likelihood of ICD-terminated VT/VF for those in the top quartile was 11 times that of the other patients (95% confidence interval [CI]: 2 to 98, $p < 0.01$). Kaplan-Meier analysis is shown in Figure 2. The sensitivity of anger-induced TWA was 60%, specificity 83%, positive predictive value 40%, and negative predictive value 92%. In analogous analyses of arithmetic-induced TWA, effects were similar but of smaller magnitude and/or statistical significance (data not shown).

Relationship to heart rate and clinical variables. Heart rate during anger did not differ between those in the top versus lower quartiles of anger-induced TWA (Table 1) and did not predict future arrhythmia. Controlling for this factor did not influence the relationship between anger-induced TWA and future VT/VF.

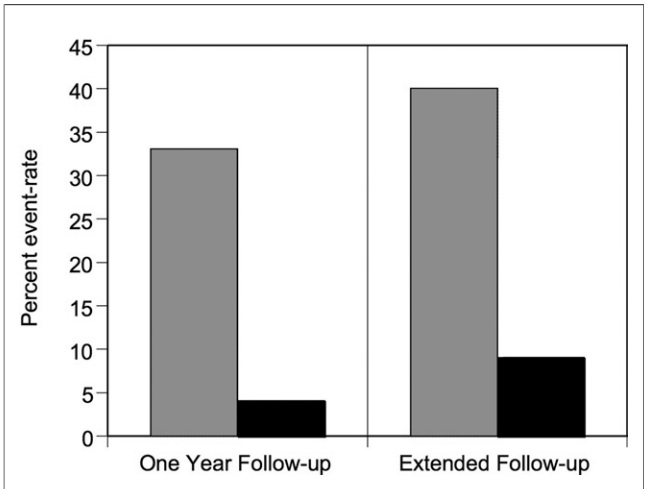

Figure 1 Event Rates

Event rates in patients with anger-induced T-wave alternans (TWA) in the top quartile **(gray bars)** (n = 15, TWA ≥11.9 μV) compared with the lower quartiles **(black bars)** (n = 47, TWA <11.9 μV).

There were no significant clinical differences between top-quartile patients and all others (Table 1). Also, there were no significant associations between these variables and the magnitude of anger-induced TWA, although ejection fraction ≤35%, QRS width ≥120 ms, and a history of prior clinical VT/VF showed nonsignificant associations. Among clinical variables, only prior clinical VT/VF was associated with ICD-terminated VT/VF (nonsignificant trend with lower ejection fraction).

In multivariable regression analysis controlling for ejection fraction, VT/VF history, and wide QRS (and heart rate and length follow-up), anger-induced TWA remained a significant predictor of ICD-terminated VT/VF (Table 3), with the odds of ICD-terminated VT/VF in follow-up in the top-quartile group 10.8 times that of other patients (95% CI: 1.6 to 113, $p < 0.05$).

Discussion

In this study, higher magnitudes of TWA during laboratory anger-recall predicted future VT/VF requiring ICD termination in a population at risk for sudden death. This association was independent of clinical factors predisposing patients to higher levels of TWA, and/or higher risk of VT/VF. Emotion can precipitate ventricular arrhythmias (2,3), and these findings suggest that emotion-induced

Table 2 TWA During Laboratory Mental Stress

	Baseline 1	Arithmetic	Baseline 2	Anger
All subjects	9.7 (7.6–11.2)	9.8 (7.2–12.4)	9.5 (6.5–11.6)	10.4 (8.1–11.9)*
With VT/VF	12.9 (8.5–16.4)†	13 (11.7–14.8)‡	12.4 (7.9–14)‡	13.2 (9.3–16)†
No VT/VF	9.2 (7.4–11.0)	9.3 (7.1–11.3)	9.1 (6.1–11.3)	9.3 (7.5–11.5)

Data are presented as median (interquartile range). *$p < 0.001$ for comparison anger versus baseline 2 for all subjects (paired comparison); †$p < 0.01$, ‡$p < 0.05$ for between-group comparison of those with versus without VT/VF in follow-up.

Abbreviations as in Table 1.

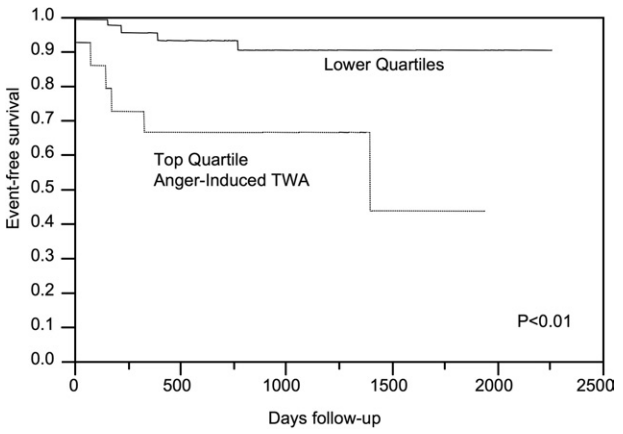

Figure 2 Event-Free Survival

Kaplan-Meier survival curves depicting survival free from implantable cardioverter-defibrillator–treated ventricular arrhythmias in patients with anger-induced T-wave alternans (TWA) in the top quartile compared with the lower quartiles.

increases in repolarization instability may link psychological stress to sudden death.

Strong emotion increases sympathetic arousal (4), which influences TWA. For example, stellectomy abolishes, while stellate ganglion stimulation increases, TWA (13). Although heart rate is 1 important determinant of TWA, TWA induced with exercise (14) or with anger (15), which increases heart rate due to autonomic effects, is greater than that with atrial pacing, implying non-heart rate–dependent effects of autonomic activity on repolarization. Intravenous beta-blockade (16) decreases TWA magnitude, particularly in the setting of an anger-like state (as shown experimentally in dogs) (15), further emphasizing the role of beta-adrenergic receptors. In daily life, TWA on ambulatory monitoring peaks at 8 AM (11), when catecholamine levels are highest. Cardiovascular reactivity to stress in the laboratory reflects reactivity in daily life (17); thus, those patients with the highest anger-induced TWA in the laboratory are most likely to experience similar emotionally mediated TWA increases during daily life. As TWA precedes spontaneously occurring ventricular arrhythmias (8), these patients may have an increased likelihood of spontaneous VT/VF.

In many studies, exercise-induced TWA predicts subsequent arrhythmias (9), and TWA has been proposed as an index for risk stratification for ICD implantation (18). This is the first study demonstrating the prognostic significance of anger-induced TWA, showing a negative predictive value similar to that for exercise-induced TWA (9). Analogously, laboratory mental stress–induced ischemia predicts subsequent clinical ischemia with predictive values similar to exercise (19). Thus, mental stress could provide an alternative to atrial pacing for patients unable to exercise.

T-wave alternans induced by atrial pacing shows poorer predictive value than exercise (10,20). Coumel (21) describes that arrhythmogenesis involves the interaction of myocardial substrate, triggering factors, and modulation by the autonomic nervous system. Measurements of TWA involving autonomic stimulation such as exercise or anger, which characterize the myocardial substrate in the presence of these modulating factors, may thus more accurately reflect arrhythmic risk. The ability to mimic the real-life combination of emotional trigger and autonomic modulation with substrate may also be why TWA induced by anger, a common emotion previously shown to trigger spontaneous VT/VF (3), was more closely associated with future VT/VF than baseline or arithmetic-induced TWA.

Few prospective studies have examined the predictive value of TWA using time-domain methodology. Although absolute values differ between time-domain and spectral analysis, results correlate closely (8,22). T-wave alternans measured in the time-domain during exercise-testing predicts arrhythmic, cardiovascular, and all-cause mortality (23). Time-domain analysis, robust in the presence of signal nonstationarity, heart rate changes, and noise, can quantify TWA from ambulatory recordings (7,8) and thus may broaden the scope of TWA testing (24).

Study limitations. Most patients were taking beta-blocking medications, possibly blunting the magnitudes of anger-induced TWA (15,16). However, performing the anger protocol in the presence of chronic medications may more accurately characterize the daily life interaction of trigger, milieu, and substrate. Also, the sample size and number of events was small, and these data should be viewed as hypothesis generating. Whether patients who agreed to participate may differ from the overall population, creating a selection bias, cannot be determined. Larger studies may more definitively establish the predictive value of anger-induced TWA. Further, the programming of ICDs was not uniform. Although the rate cutoffs did not differ between high- and low-anger TWA groups, the possibility that differences in detection times or programmed treatment may have contributed to the findings cannot be excluded.

Conclusions

Anger-induced TWA predicts future VT/VF in patients with ICDs, suggesting that emotion-induced repolarization instability may be 1 mechanism linking stress and sudden

Table 3 Predictive Value of Anger-Induced TWA and Clinical Variables for Occurrence of VT/VF

	Odds Ratio	p Value	95% Confidence Interval
Anger-induced TWA, top quartile	10.8	<0.05	1.6–113
Ejection fraction ≤35%	2.4	0.49	0.3–52
QRS ≥120 ms	0.11	0.02	0.02–1.3
History of prior clinical VT/VF	5.8	0.15	0.6–83

The model included adjustment for heart rate and length of follow-up.
Abbreviations as in Table 1.

death. Whether there is a clinical role for anger-induced TWA testing requires further study.

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