Heart Rhythm Disorders

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

Rachel Lampert, MD, FACC,* Vladimir Shusterman, MD, PhD,† Matthew Burg, PhD,*‡ Craig McPherson, MD, FACC,* William Batsford, MD,* Anna Goldberg, BS,† Robert Soufer, MD, FACC*‡

New Haven and West Haven, Connecticut; and Pittsburgh, Pennsylvania

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 μ V (interquartile range [IQR] 9.3 to 16 μ V), compared with those patients without future ventricular arrhythmias, 9.3 μ V (IQR 7.5 to 11.5 μ V, p < 0.01). Patients in the highest quartile of anger-induced TWA (>11.9 μ V, 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),

From the *Yale University School of Medicine, New Haven, Connecticut; †PinMed Inc. and University of Pittsburgh, Cardiovascular Institute, Pittsburgh, Pennsylvania; and the ‡Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut. PinMed Inc. provided the repolarization analysis software used in this study. Dr. Lampert receives funding from the American Heart Association (Dallas, Texas) Scientist Development Grant (#0030190) and research grants from Boston Scientific, Medtronic, and St. Jude (minimally relevant to current study). Dr. Shusterman receives funding from the American Heart Association Scientist Development Grant (#0030248N) and National Institutes of Health (#1R43HL077116-01); he also has a significant (>5%) ownership interest in PinMed Inc. Dr. Soufer receives funding from the National Institutes of Health (R01# HL59619-01 and HL071116-01), a Yale Institutional Clinical and Translational Science Award Grant (#UL1 RR024139), and the National Center for Research Resources (NCRR/NIH).

Manuscript received February 29, 2008; revised manuscript received October 14, 2008, accepted October 19, 2008.

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

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

Abbreviations and Acronyms

ICD = implantable cardioverter-defibrillator

IQR = interquartile range TWA = T-wave alternans

VT/VF = ventricular

tachycardia/ventricular fibrillation

was 0.72, and results of analyses were similar, only intrabeat analysis results are presented.

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 ICDterminated 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 μ V), compared with 9.3 μ V (IQR 7.5 to 11.5 μ V, 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-

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 $(\geq 75\%$ 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 V₁ and V₅ leads were recorded (bipolar pairs) on GE Medical (Milwaukee, Wisconsin) Marquette Series 8500 direct (amplitudemodulated) recorders (flat frequency response; linear phase between 0.67 and 50 Hz [±3 dB]; digitized at 400-Hz sampling frequency, effective resolution 2.5 μ V). 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

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	$\textbf{32} \pm \textbf{2}$		
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		$\textbf{145} \pm \textbf{10}$	$\textbf{133} \pm \textbf{6}$		
Heart rate with anger, beats/min		68 ± 2	69 ± 1		
Heart rate change with anger, beats/min		4 ± 1	7 ± 1		
ICD rate cut	off for therapy, beats/min	$\textbf{172} \pm \textbf{4}$	175 \pm 2		
Follow-up, n	nonths	40 ± 4	37 ± 2		

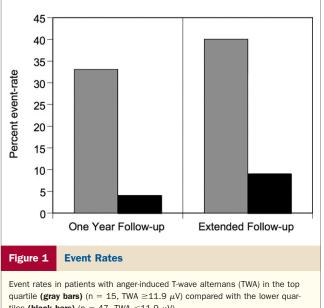
Values expressed as mean \pm standard error or n (%). *Defined in Methods section; †sustained ventricular tachycardia or fibrillation; ‡excluding sotalol or amiodarone; §amiodarone, sotalol, and/or other beta-blockers; $\|p<0.05$ with all other p values nonsignificant (>0.15).

 $\label{eq:continuous} \mbox{ICD} = \mbox{implantable cardioverter-defibrillator; TWA} = \mbox{T-wave alternans; VT/VF} = \mbox{ventricular tachycardia/ventricular fibrillation.}$

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 \geq 11.9 μ V, 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.



quartile (gray bars) (n = 15, TWA \ge 11.9 μ V) compared with the lower quartiles (black bars) (n = 47, TWA <11.9 μ V).

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).

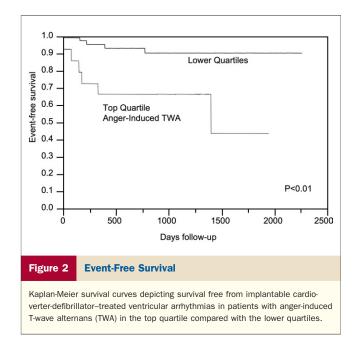
Discussion

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, \pm p < 0.05 for between-group comparison of those with versus without VT/VF in follow-up.

Abbreviations as in Table 1.



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 betaadrenergic 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) de-

scribes 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 betablocking 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.

Reprint requests and correspondence: Dr. Rachel Lampert, Yale Cardiology, 333 Cedar Street, FMP 3, New Haven, Connecticut 06520. E-mail: rachel.lampert@yale.edu.

REFERENCES

- 1. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996;334:413–9.
- Steinberg JS, Arshad A, Kowalski M, et al. Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack. J Am Coll Cardiol 2004;44:1261–4.
- Lampert R, Joska T, Burg M, Batsford W, McPherson C, Jain D. Emotional and physical precipitants of ventricular arrhythmia. Circulation 2002;106:1800-5.
- Lampert R, Shusterman V, Burg M, et al. Effects of psychological stress on repolarization and relationship to autonomic and hemodynamic factors. J Cardiovasc Electrophysiol 2005;16:372–7.
- Kop WJ, Krantz DS, Nearing BD, et al. Effects of acute mental stress and exercise on T-wave alternans in patients with implantable cardioverter defibrillators and controls. Circulation 2004;109:1864–9.
- Pastore JM, Girouard SD, Laurita KR, Akar FG, Rosenbaum DS. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 1999;99:1385–94.
- Nearing BD, Verrier RL. Modified moving average analysis of T-wave alternans to predict ventricular fibrillation with high accuracy. J Appl Physiol 2002;92:541–9.
- Shusterman V, Goldberg A, London B. Upsurge in T-wave alternans and non-alternating repolarization instability precedes spontaneous initiation of ventricular tachyarrhythmias in humans. Circulation 2006;113:2880-7.
- 9. Gehi AK, Stein RH, Metz LD, Gomes A. Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: a meta-analysis. J Am Coll Cardiol 2005;46:75–82.
- Cantillon DJ, Stein KM, Markowitz SM, et al. Predictive value of microvolt T-wave alternans in patients with left ventricular dysfunction. J Am Coll Cardiol 2007;50:166-73.
- 11. Verrier RL, Nearing BD, La Rovere M, et al. Ambulatory electrocardiogram-based tracking of T wave alternans in postmyocar-

- dial infarction patients to assess risk of cardiac arrest or arrhythmic death. J Cardiovasc Electrophysiol 2003;14:705–11.
- 12. Kral BG, Becker LC, Blumenthal RS, et al. Exaggerated reactivity to mental stress is associated with exercise-induced myocardial ischemia in an asymptomatic high-risk population. Circulation 1997;96:4246–53.
- Nearing BD, Huang AH, Verrier RL. Dynamic tracking of cardiac vulnerability by complex demodulation of the T wave. Science 1991; 252:437–40.
- Hohnloser SH, Klingenheben T, Zabel M, Li YG, Albrecht P, Cohen RJ. T wave alternans during exercise and atrial pacing in humans. J Cardiovasc Electrophysiol 1997;8:987–93.
- Kovach JA, Nearing BD, Verrier RL. Angerlike behavioral state potentiates myocardial ischemia-induced T-wave alternans in canines. J Am Coll Cardiol 2001;37:1719–25.
- Rashba EJ, Cooklin M, MacMurdy K, et al. Effects of selective autonomic blockade on T-wave alternans in humans. Circulation 2002;105:837–42.
- 17. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull 1984;96:435–64.
- Russo A, Marchlinski FE. Should microvolt T-wave alternans be used routinely in the selecting patients for prophylactic implantable cardioverter-defibrillator insertion in the setting of ischemic heart disease? J Am Coll Cardiol 2007;49:59-61.
- 19. Sheps D, McMahon R, Becker L, et al. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: results from the Psychophysiological Investigations of Myocardial Ischemia study. Circulation 2002;105:1780–4.
- Rashba E, Osman AF, MacMurdy K, et al. Exercise is superior to pacing for T-wave alternans measurement in subjects with chronic coronary artery disease and left ventricular dysfunction. J Cardiovasc Electrophysiol 2002;13:845–50.
- 21. Coumel P. Cardiac arrhythmias and the autonomic nervous system. J Cardiovasc Electrophysiol 1993;4:338–55.
- Martinez JP, Olmos S. Methodological principles of T-wave alternans analysis: a unified framework. IEEE Trans Biomed Eng 2005;52:599–613.
- Nieminen T, Lehtimaki T, Viik J, et al. T-wave alternans predicts mortality in a population undergoing a clinically-indicated exercise test. Eur Heart J 2007;28:2332–7.
- Narayan SM. T-wave alternans and susceptibility to ventricular arrhythmias. J Am Coll Cardiol 2006;47:269–81.

Key Words: tachyarrhythmias (ventricular) ■ anger ■ implantable cardioverter-defibrillator.