

Angerlike Behavioral State Potentiates Myocardial Ischemia-Induced T-Wave Alternans in Canines

Julie A. Kovach, MD, FACC,* Bruce D. Nearing, PhD,† Richard L. Verrier, PhD, FACC†

Ann Arbor, Michigan and Boston, Massachusetts

- OBJECTIVES** The main goal of this study was to determine whether induction of an angerlike state can result in significant levels of T-wave alternans, a marker of electrical instability, in the normal and ischemic heart.
- BACKGROUND** Outbursts of anger have been implicated in the occurrence of myocardial infarction and sudden cardiac death, but the pathophysiologic mechanisms remain unknown.
- METHODS** A standardized behavioral challenge of eliciting an angerlike state was conducted before and during a 3-min period of coronary artery occlusion in six canines.
- RESULTS** Precordial T-wave alternans increased from 0.04 ± 0.02 at baseline to 1.40 ± 0.32 mV \times ms ($p < 0.05$) during the angerlike response. When the angerlike state and myocardial ischemia were superimposed, the augmentation in T-wave alternans magnitude (to 3.27 ± 0.61 mV \times ms, $p < 0.05$) exceeded their additive effects, increasing by 130% over the angerlike state alone ($p < 0.05$) and by 390% over occlusion alone ($p < 0.05$). Adrenergic influences were reduced by the beta₁-adrenergic receptor blocking agent metoprolol (1.5 mg/kg, intravenous), which diminished T-wave alternans magnitude ($p < 0.0004$ for all) during the angerlike response (from 1.40 ± 0.32 to 0.80 ± 0.17 mV \times ms) and during the combined intervention (from 3.27 ± 0.61 to 1.23 ± 0.13 mV \times ms). In five additional normal anesthetized canines, atrial pacing at 180 beats/min did not increase T-wave alternans magnitude monitored from lead II electrocardiogram.
- CONCLUSIONS** Provocation of an angerlike state results in T-wave alternans in the normal heart and potentiates the magnitude of ischemia-induced T-wave alternans. Elevation in heart rate during arousal does not appear to be the main factor in the development of alternans in the normal heart but may be an important component during myocardial ischemia. Enhanced adrenergic activity appears to mediate the effects in both the normal and ischemic hearts. T-wave alternans may constitute a useful electrophysiologic measure for clinical use in conjunction with behavioral stress testing or ambulatory monitoring. (J Am Coll Cardiol 2001;37:1719–25) © 2001 by the American College of Cardiology

The emotional state of anger has been implicated in the precipitation of myocardial infarction (MI) (1,2), myocardial ischemia (3–6) and life-threatening ventricular arrhythmias, including sudden cardiac death (1,7,8). Mittleman et al. (1,9) reported an important association between outbursts of anger with nonfatal MI and sudden cardiac death. Reich et al. (7) determined that anger preceded episodes of arrhythmia in 15% of patients with recurring life-threatening arrhythmias. Availability of noninvasive techniques to evaluate vulnerability to malignant arrhythmias could facilitate assessment of the risk of sudden cardiac death (10).

Measurement of T-wave alternans during diverse interventions in experimental animals indicates that this noninvasive parameter offers significant promise for assessing cardiac electrical instability and risk of ventricular arrhythmias (11–15). We (13–15) demonstrated in a canine model that the magnitude of T-wave alternans parallels the inci-

dence of ventricular tachyarrhythmias during myocardial ischemia and reperfusion. Significant and consistent myocardial ischemia-induced T-wave alternans is evident in ambulatory electrocardiogram (ECG) recordings of patients with stable coronary artery disease (16) during coronary angioplasty (14) and in patients with implantable cardioverter defibrillators (ICD) during the mental challenges of anger recall and arithmetic as well as during exercise (17). During peak myocardial ischemia, alternans was sufficiently prominent as to be visible in the precordial leads. Alternation was greatest in the first half of the T-wave, coinciding with the established location of the vulnerable period of the cardiac cycle (13,14), thereby suggesting an electrophysiologic link between alternans and electrical instability (18). Promising evidence of alternans' suitability for arrhythmia risk stratification in the moderate-risk post-MI population has been provided in the ambulatory ECG-based Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study (19).

Other investigators have employed Fast Fourier Transform analysis to demonstrate that the presence of microvolt, nonvisible levels of T-wave alternans in high-risk (20–28) and moderate-risk (29,30) patient populations was predictive of arrhythmia-free survival. In these studies, myocardial ischemia was not elicited, a fact that could account, in part, for the lower levels of T-wave alternans reported than

From the *Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, Michigan; and the †Institute for Prevention of Cardiovascular Disease, Department of Medicine, Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. Supported by grant R01-HL-33567 from the National Heart, Lung and Blood Institute and grant P01-ES-08129 from the National Institutes of Environmental Sciences, National Institutes of Health, Bethesda, Maryland.

Manuscript received March 4, 1999; revised manuscript received December 11, 2000, accepted January 12, 2001.

Abbreviations and Acronyms

ECG	=	electrocardiogram
ICD	=	implantable cardioverter defibrillator
LAD	=	left anterior descending
LV	=	left ventricular
MI	=	myocardial infarction

observed in our studies. The possibility remains that alternans was sizeable just before the onset of the arrhythmia in the follow-up months, as has been observed experimentally during transition from macroscopic alternans to ischemia-induced ventricular tachyarrhythmias (13-15,31).

In this investigation, we examined the effect of provoking an angerlike state on vulnerability to cardiac arrhythmias as tracked by T-wave alternans magnitude using a standardized experimental paradigm of confrontation by canines over access to food (32). The effect of superimposing the intense angerlike behavioral state during myocardial ischemia induced by coronary artery occlusion was also evaluated. The contributions of elevated heart rate and adrenergic influences to T-wave alternans magnitude were investigated by fixed-rate atrial pacing and administration of the β_1 -adrenergic agent metoprolol.

METHODS

Animal preparation and data acquisition. Six adult mongrel dogs (24.6 kg to 34 kg) of either gender, preselected for a positive angerlike response by simulating experimental conditions, were studied according to the principles and regulations of the National Institutes of Health and the American Heart Association, and protocols were approved by the Institutional Animal Care and Use Committee. Before the experiment, the animals were chronically instrumented under inhalation anesthesia with isoflurane after tranquilization with acepromazine (0.05 mg/kg, intramuscular) and induction of anesthesia with pentobarbital sodium (20 to 30 mg/kg, intravenous). After left thoracotomy and suspension of the heart in a pericardial cradle, a toroidal balloon occluder (R.E. Jones, Silver Spring, Maryland) was placed proximal to a rigid Doppler flow probe (Craig Hartley, Houston, Texas) on the midleft anterior descending (LAD) coronary artery. Disruption of pericoronary nerves was minimized. Electrical wires and tubing were exteriorized via a subcutaneous tunnel to the posterior aspect of the thorax. The chest was closed, and the animals were allowed to recover for at least three weeks.

On the morning of the experiment, after methohexital sodium (12 mg/kg, intravenous, Eli Lilly, Indianapolis, Indiana), an ultrashort-acting barbiturate, was administered, a solid-state arterial blood pressure catheter was introduced. Bupivacaine (0.25%), a long-acting local anesthetic, was injected subcutaneously in the inguinal area before placement of a 5F sheath in either the right or left femoral artery using a modified Seldinger technique. A 5F

Millar pressure catheter was introduced through the sheath into the descending aorta. The recovery period was 90 to 120 min. Electrocardiogram leads V_4 and V_5 , hemodynamic and Doppler flow analog signals were collected, low-pass filtered at 50 Hz and then digitized at a rate of 500 samples/s for each channel of data. Rate-pressure products were calculated on a beat-by-beat basis.

Induction of angerlike state with and without myocardial ischemia. An angerlike behavioral state was provoked according to methods previously reported (32). Briefly, the instrumented animal was restrained by a leash and presented with a dish of food that was then placed just out of the animal's reach. A "provoker" dog, similarly restrained, was brought into the room and initially allowed to eat the food, which was then placed equidistant between the animals. Typically, both animals displayed an intense, angerlike behavioral response characterized by growling, baring of teeth and piloerection that persisted for the duration of time that the animals were in each other's presence (3 min). At no time were the animals permitted to come into contact. Ten-minute rest periods followed each intervention.

Both preconditioning and control occlusions of the coronary artery were produced for 3 min by inflating the toroidal balloon occluder and documenting zero Doppler flow. No arrhythmias occurred during balloon deflation. After a 10-min rest period, the LAD was again occluded. After 1 min of coronary artery occlusion, the angerlike state was again induced, and both coronary artery occlusion and the angerlike response were continued for an additional 2 min. The confrontation was terminated and the occlusion slowly released.

Beta-adrenergic receptor blockade. Metoprolol (1.5 mg/kg, intravenous, Geigy, Ardsley, New York) was then administered, and completeness of beta-adrenergic blockade was assessed frequently with isoproterenol (2 μ g/kg, intravenous, Sanofi Winthrop, New York, New York) (33). The sequence of the angerlike response, coronary artery occlusion and coronary artery occlusion plus the angerlike state was then repeated.

Right atrial pacing in anesthetized animals. It was not feasible to conduct rapid atrial pacing in resting conscious animals to match the heart rates achieved during arousal because of vagally mediated heart block and the possibility of disrupting the behavioral state due to hypotension and somatosensory feedback. Therefore, we studied the effects of pacing in seven normal canines pre-anesthetized with xylazine (0.237 mg/kg, subcutaneous) and anesthetized with alpha-chloralose (150 mg/kg, intravenous, with subsequent doses of 600 mg) according to standard procedures (15). Heart rate was maintained constant at 180 beats/min by fixed-rate pacing by delivering constant current stimuli from a pair of stainless steel needle electrodes inserted into the right atrial appendage through a fourth interspace thoracotomy incision. The current intensity was twice the diastolic threshold. Modified lead II ECG signals were recorded for 5 min at baseline and during pacing and were low-pass

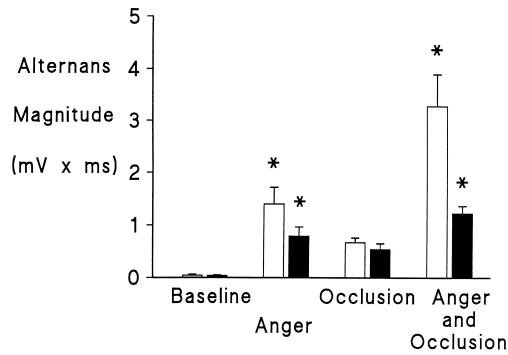


Figure 1. T-wave alternans magnitude increased significantly from baseline (0.04 ± 0.02 mV \times ms) during induction of an angerlike behavioral state alone (to 1.40 ± 0.32 , $p < 0.05$) and with simultaneous myocardial ischemia and angerlike response (to 3.27 ± 0.61 , $p < 0.05$). The 3-min periods of ischemia were insufficient to increase T-wave alternans significantly from baseline (to 0.67 ± 0.09 mV \times ms, $p = \text{NS}$). Concurrent provocation of the angerlike state and imposition of myocardial ischemia increased T-wave alternans magnitude in excess of their additive effects ($p < 0.05$). This amplification was blunted by beta-adrenergic blockade with metoprolol ($p < 0.0004$ for all), which reduced T-wave alternans at baseline (to 0.04 ± 0.01) during the angerlike state (to 0.80 ± 0.17) during myocardial ischemia (to 0.55 ± 0.11) and during simultaneous myocardial ischemia and angerlike response (to 1.23 ± 0.13). **Open bars** = no drug; **solid bars** = metoprolol. * $p < 0.05$.

filtered at 50 Hz. Because of heart block, two animals could not be paced atrially at the desired rate, leaving five animals to be included in the analysis.

T-wave alternans analysis. Complex demodulation, a type of spectral analysis that treats the T-wave as a sinusoid of slowly varying amplitude and phase, was employed to analyze T-wave alternans magnitude (13-17,34). Because this analytical method is relatively tolerant of nonstationary data, independent of phase-shift perturbations and requires <30 s of data, it is well-suited to quantifying the effects of transient events, such as surges in autonomic nervous system activity, that may last <1 min while having marked effects on cardiac electrical instability (34).

Statistical analysis. Statistical analysis with Excel and SAS by two-tailed, four-way analysis of variance (ANOVA) was used to examine the overall effects of anger, occlusion and metoprolol on each of the variables (alternans, heart rate, blood pressure and rate-pressure product) (Fig. 1, Table 1). Further comparisons between each of the experimental conditions were analyzed using a one-way ANOVA with Tukey's studentized range test to correct for multiple

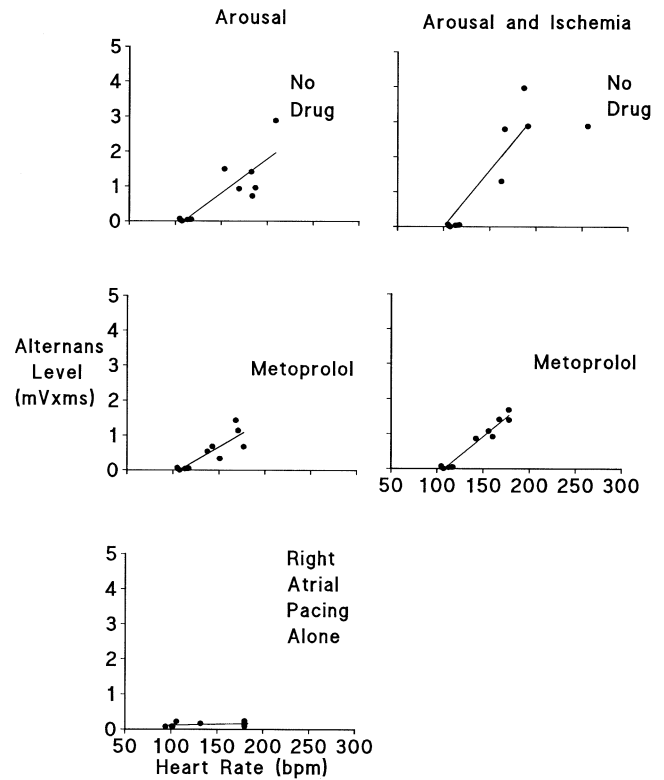


Figure 2. There is a positive, statistically significant correlation ($p < 0.01$) between increased heart rate and T-wave alternans level during induction of the angerlike state before (**upper left panel**) and during left anterior descending coronary artery occlusion (**upper right panel**). The slope of each line is significantly elevated above the horizontal ($p < 0.0003$). Beta-adrenergic blockade with metoprolol did not produce a significant decrease in the slope of the heart rate/alternans relationship (**middle panels**). Right atrial pacing did not increase T-wave alternans magnitude in lead II over baseline in five anesthetized canines (0.129 ± 0.026 mV \times ms at spontaneous baseline rate of 107 ± 6 beats/min vs. 0.158 ± 0.023 mV \times ms at 180 beats/min; slope vs. baseline, $p < 0.47$, **lowest panel**). The r^2 values are: **upper right panel** = 0.739; **upper left panel** = 0.628; **middle left panel** = 0.764; **middle right panel** = 0.959; **lowest panel** = 0.118. These results suggest an association, but not necessarily a causal relationship, between elevated rate and T-wave alternans, as discussed in the text.

comparisons (Fig. 1, Table 1). Least squares analysis was used to form the regression line for the plots of T-wave alternans magnitude against the associated heart rates, and lack of differences in the slopes of the regression lines was determined by ANOVA (Fig. 2). Values are presented as mean \pm SEM with significance at $p < 0.05$.

Table 1. Effect of Provocation of an Angerlike State on Heart Rate, Blood Pressure and Rate-Pressure Product

	Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)		Rate-Pressure Product (beats/min \times mm Hg)	
	No Drug	Metoprolol	No Drug	Metoprolol	No Drug	Metoprolol
Baseline	111 \pm 2	88 \pm 6	124 \pm 5	117 \pm 9	13,741 \pm 748	10,531 \pm 1,202
Angerlike state	181 \pm 7*	158 \pm 6*	162 \pm 8*	144 \pm 14	29,544 \pm 2,427*	22,437 \pm 2,123*
Occlusion	102 \pm 3]	94 \pm 8]	116 \pm 7]	114 \pm 9	11,931 \pm 1,087]	10,667 \pm 1,249
Angerlike state and occlusion	192 \pm 13*]	164 \pm 5*]	160 \pm 7*]	141 \pm 10	30,940 \pm 2,548*]	22,818 \pm 3,560*

* $p < 0.05$ with Tukey test correction for multiple comparisons with respect to baseline no drug, except where brackets indicate comparison. The results of the overall analysis of variance are presented in the Results section.

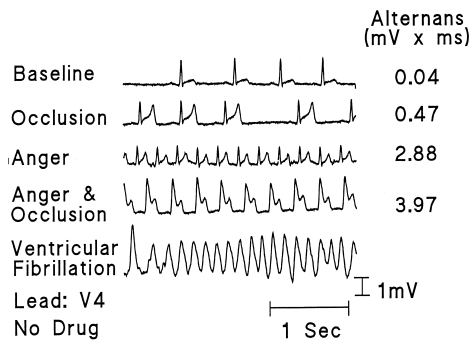


Figure 3. Segments of electrocardiogram tracings with measurements of maximum T-wave alternans magnitude at baseline, during myocardial ischemia, during angerlike state and with simultaneous angerlike state and myocardial ischemia in one dog that experienced ventricular fibrillation at 42 s after provocation of angerlike response was superimposed at 1 min of coronary artery occlusion.

RESULTS

Heart rate and arterial blood pressure response to angerlike state and myocardial ischemia. The angerlike behavioral state and the superimposition of the angerlike response during myocardial ischemia significantly increased heart rate ($p < 0.0001$) and arterial blood pressure ($p < 0.0001$) and, as a result, more than doubled the rate-pressure product ($p < 0.0001$, Table 1). Heart rate and arterial blood pressure did not increase significantly with 3 min of myocardial ischemia ($p = \text{NS}$). Metoprolol administration blunted the anger-induced increase in heart rate ($p < 0.0003$) and rate-pressure product ($p < 0.0002$), both with and without ischemia, and reduced the effect of arousal on blood pressure ($p < 0.03$).

Effect of angerlike state and myocardial ischemia on T-wave alternans magnitude. The angerlike response alone significantly increased the magnitude of T-wave alternans (Fig. 1). While alternation occurred across the ST-segment and T-wave, as in previous studies (13,14), the maximum changes in alternans level occurred during the first half of the T-wave. Induction of 3 min of the angerlike response alone increased the degree of alternans similarly to a 3-min duration of myocardial ischemia produced by coronary artery occlusion alone. The superimposition of an intense angerlike response during a brief period of occlusion-induced myocardial ischemia produced an increase in T-wave alternans that was in excess of their additive effects. These combined challenges increased alternans magnitude by 130% over the angerlike state alone ($p < 0.05$) and by 390% over occlusion alone ($p < 0.05$). The increase in heart rate correlated with the increase in T-wave alternans magnitude during arousal with and without coronary artery occlusion (Fig. 2, top panels). Striking augmentation in T-wave alternans preceded ventricular fibrillation in one animal when the angerlike response was provoked during occlusion-induced myocardial ischemia (Fig. 3). The arrhythmia did not occur during either the angerlike state or coronary artery occlusion alone or after beta-adrenergic blockade in the same dog.

Administration of the beta₁-selective adrenergic blocker metoprolol significantly blunted the augmentation in T-wave alternans resulting from the angerlike behavioral state alone and from the superimposition of the angerlike response on myocardial ischemia (Fig. 1). Metoprolol resulted in a slight, but not statistically significant, decrease in the slope of the relationship between heart rate and T-wave alternans (Fig. 2, middle panels).

Right atrial pacing in five normal, anesthetized canines to 180 beats/min, approximating the mean heart rate change observed during arousal, did not result in a significant increase in T-wave alternans level (Fig. 2, lowest panel).

DISCUSSION

Retrospective clinical studies of ventricular arrhythmias and sudden cardiac death have identified profound emotional stress, especially anger, as a trigger of arrhythmic events (1,7,8). We employed a standardized, reproducible experimental paradigm of provocation of an intense angerlike behavioral state (32) to simulate the effect of intense behavioral arousal on T-wave alternans, a measure of cardiac electrical instability. This angerlike response elicits significant increases in the magnitude of T-wave alternans in the normal canine heart, suggesting that intense behavioral stress induces a significant increase in vulnerability to ventricular arrhythmias even without underlying myocardial ischemia. Elicitation of the angerlike state during myocardial ischemia increased T-wave alternans magnitude by 390% over that observed during myocardial ischemia alone, evidence that the angerlike state strongly potentiates the risk of ventricular fibrillation elicited by myocardial ischemia. The absolute levels of T-wave alternans observed in the present investigation are lower than those reported in our previous studies (13-15) because precordial, and not intracavitary, ECGs were recorded. This lead placement attenuates the alternans signal magnitude in parallel to one sixth (14).

The findings are in agreement with earlier studies of cardiac electrical instability in animal models of stress that showed a marked reduction in repetitive extrasystole threshold, an invasive measure of cardiac vulnerability, during induction of behavioral states simulating anger and fear in dogs with either normal or ischemic hearts (35). The fact that high-level alternans heralded the onset of ventricular fibrillation triggered by the induction of anger during myocardial ischemia in one of the six animals (Fig. 3) was anticipated by our previous finding that T-wave alternans magnitude correlates ($r^2 = 0.98$) with the incidence of ventricular tachyarrhythmias (14).

Role of heart rate. Given the significant sinus tachycardia produced by aggressive arousal, it is reasonable to question whether the heart rate elevation contributed to the observed amplification in T-wave alternans magnitude (Fig. 1). A positive, although not necessarily causal, relationship was evident when alternans magnitude was plotted against heart

rate (Fig. 2). Several atrial-pacing studies suggest that the elevation in heart rate produced by aggressive arousal in this study is unlikely to be the sole factor responsible for the sizeable increase in T-wave alternans in the normal heart. We demonstrated that increasing heart rate from a spontaneous, baseline value of 107 ± 6 beats/min to 180 beats/min with right atrial pacing does not produce significant changes in the level of T-wave alternans in normal, anesthetized canines (Fig. 2, lowest panel). Adam et al. (11) determined that rapid atrial pacing in normal, anesthetized animals to the range of 200 beats/min, a level that is beyond the 181 ± 7 beats/min average rate of the arousal-induced levels in this study, did not produce any significant change in T-wave alternans level in the surface ECG. Pastore and colleagues (36) found in the Langendorff-perfused isolated guinea pig heart that repolarization alternans could only be induced above a critical threshold heart rate of 200 beats/min. Euler et al. (37) demonstrated that alternans was induced in normal, anesthetized canines only when the rate was approximately 200 beats/min or more and was associated with mechanical pulsus alternans. The tachycardia-induced mechanical and electrical alternans were eliminated by sympathetic nerve stimulation, presumably due to the positive inotropic effect of neural release of catecholamines. Consistent with this supposition is the finding that beta-adrenergic blockade with timolol reversed the effect. In the present study, the arterial blood pressure recordings did not indicate the presence of mechanical alternans during aggressive arousal.

During myocardial ischemia, rapid heart rates could play a role in the increased T-wave alternans level and in cardiac electrical instability because of compromised coronary diastolic perfusion time and elevated cardiac metabolic requirements. In a prior study in anesthetized animals, we determined that rapid atrial pacing at 150 and 180 beats/min increased the average T-wave alternans levels during occlusion-induced myocardial ischemia by 68% and 148%, respectively, over the level observed during spontaneous rhythm, which ranged from 80 to 120 beats/min (14).

In humans, the presence of myocardial pathology results in a heart rate dependence of T-wave alternans magnitude. Hohnloser et al. (38) demonstrated that decreased pacing cycle length produced a significant and comparable dose-dependent increase in the T-wave alternans level in patients with a history of ventricular tachyarrhythmias who were referred for electrophysiologic study. They further demonstrated a concordance between T-wave alternans magnitude induced by invasive right atrial pacing and by noninvasive bicycle ergometry for submaximal exercise testing. In patients referred for electrophysiologic testing or ICD implantation, right atrial pacing (20,23,24,28) or bicycle ergometry (21,22,25-27,29,30) carries predictive significance for arrhythmia-free survival.

The effects of elevating heart rate on T-wave alternans in definitively normal humans by right atrial pacing without

the confounding physiologic influences of exercise have not been studied to our knowledge.

Role of beta-adrenergic receptors. This study implicates a primary role for enhanced adrenergic input to the heart in augmenting arousal-induced T-wave alternans and cardiac electrical instability. The cardioselective beta₁-adrenergic antagonist metoprolol reduced the magnitude of T-wave alternans during provocation of the angerlike response both with and without concomitant myocardial ischemia by 62.4% and 42.9%, respectively. Only a 15% reduction in heart rate accompanied this significant decrease in T-wave alternans, suggesting that alternans magnitude is, at least in part, attributable to influences other than heart rate. Partial beta-adrenergic blockade with esmolol reduces the level of T-wave alternans by 35% in individuals with inducible sustained ventricular tachycardia during constant-rate atrial pacing (39).

It is uncertain why metoprolol did not entirely eliminate the augmentation in heart rate and T-wave alternans magnitude that occurred with myocardial ischemia or with the angerlike response, despite demonstration of completeness of beta₁-adrenergic receptor blockade by the absence of an increase in heart rate in response to isoproterenol administration. One possibility is that the dose of metoprolol given did not completely block the effect of adrenergic influences on T-wave alternans, and the absence of a heart rate response to isoproterenol did not provide an accurate measure of the incompleteness of beta₁-adrenergic receptor blockade. Since metoprolol is a competitive antagonist, the pronounced release of norepinephrine at the beta-adrenergic receptors during intense arousal may have overridden the receptor blockade. An alternative explanation is that factors in addition to sympathetic nerve activity contributed to the development of T-wave alternans during the angerlike state. One likely possibility is that aggressive arousal resulted in a decrease in cardiac vagal tone. As vagus nerve activation has been shown to suppress T-wave alternans in animals and humans (18,40), reduction in vagal tone by behavioral stress might conduce to T-wave alternans as well as to the residual sinus tachycardia.

When sympathetic nerve stimulation is superimposed on myocardial ischemia during fixed-rate atrial pacing at 150 beats/min, T-wave alternans magnitude and incidence of myocardial ischemia-induced ventricular tachyarrhythmias are increased beyond levels achieved by myocardial ischemia alone (13-15). Similarly, the effects of sympathetic nerve stimulation or behavioral arousal on the vulnerable period threshold (41,42) and on the increased dispersion of repolarization (41) also appear to be independent of heart rate, as they are manifest during fixed-rate pacing. Since there is evidence that alternans provides a measure of temporospatial heterogeneity of repolarization (31), it is reasonable to anticipate that this phenomenon also exhibits a degree of independence from rate in response to adrenergic influences in both the normal and ischemic hearts (13,41). Recently, covariance analysis disclosed that mental stress exerts an

increase in T-wave alternans in humans with ICDs that is partially independent of heart rate (17). This result differed from the effects of exercise on alternans level (17), which appeared to be largely rate-dependent, presumably due to the fact that, until the exercise challenge exceeds rates of 120 beats/min, the release of catecholamines is relatively minor (43).

Study limitations. Although the evidence provided indicates that both enhanced adrenergic activity and sinus tachycardia contribute to arousal-induced T-wave alternans level, their relative contributions are unknown. The difficulty in establishing the precise role of heart rate relates, in part, to the inherent problem of heart block, which can occur when the atrial-pacing rate is increased in the resting animal to the high levels achieved during aggressive arousal. There is also concern regarding the possibility of disrupting the behavioral state due to hypotension and other somatosensory feedback mechanisms.

The electrophysiologic mechanisms responsible for T-wave alternans and arrhythmias are complex and differ as a function of the clinical conditions, ranging from ischemic syndromes to heart failure, cardiomyopathy and chronic left ventricular (LV) dysfunction (10,18,44,45). The present experimental model does not incorporate chronic LV dysfunction which, when it occurs with or without ischemic heart disease, is highly conducive to life-threatening arrhythmias, a relationship that can be assessed by T-wave alternans measurement (20-30). Because the electrophysiologic basis for alternans in the context of chronic LV dysfunction differs from that associated with acute myocardial ischemia, the precise mechanisms involved probably differ.

Conclusions and clinical implications. Provocation of an intense angerlike state in canines increases the magnitude of T-wave alternans to a greater degree than does a brief period of myocardial ischemia. Superimposition of the angerlike response during occlusion-induced myocardial ischemia potentiates the increase in the magnitude of T-wave alternans elicited by myocardial ischemia alone, further magnifying the risk of ventricular arrhythmias in this setting. The cardioselective beta₁-adrenergic blocker metoprolol blunts the magnitude of this increase in behavioral stress-induced alternans, suggesting that adrenergic factors are, in part, responsible for T-wave alternans during the angerlike response. However, arousal-induced increases in heart rate are likely to contribute in the setting of myocardial ischemia.

Noninvasive tracking of cardiac electrical instability using T-wave alternans during behavioral stress testing or ambulatory monitoring may provide a means for screening or monitoring individuals at risk for life-threatening arrhythmias. This concept is supported by clinical literature indicating that standardized clinical tasks including anger recall and mental arithmetic, which exert profound influences including myocardial ischemia and decreases in LV ejection fraction in individuals with coronary artery disease (3,4,46,47), also induce significant T-wave alternans in

patients with a history of tachyarrhythmias (17). T-wave alternans testing could provide the additional dimension of assessment of electrical instability in individuals known to be at heightened risk for sudden cardiac death.

Acknowledgment

The authors thank Murray A. Mittleman, MD, DrPH, for advice on statistical analyses.

Reprint requests and correspondence: Dr. Richard L. Verrier, Institute for Prevention of Cardiovascular Disease, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, W/AK-521, Boston, Massachusetts 02215. E-mail: rverrier@caregroup.harvard.edu.

REFERENCES

1. Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. *Circulation* 1995;92:1720-5.
2. Mendes de Leon CF, Kop WJ, de Swart HB, Bar FW, Appels AP. Psychosocial characteristics and recurrent events after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1996;77:252-5.
3. Ironson G, Taylor CB, Boltwood M, et al. Effects of anger on left ventricular ejection fraction in coronary artery disease. *Am J Cardiol* 1992;70:281-5.
4. Boltwood MD, Taylor CB, Burke MB, Grogan H, Giacomini J. Anger report predicts coronary artery vasomotor response to mental stress in atherosclerotic segments. *Am J Cardiol* 1993;72:1361-5.
5. Burg MM, Jain D, Soufer R, Kerns RD, Zaret BL. Role of behavioral and psychological factors in mental stress-induced silent left ventricular dysfunction in coronary artery disease. *J Am Coll Cardiol* 1993;22:440-8.
6. Gabbay FH, Krantz DS, Kop WJ, et al. Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. *J Am Coll Cardiol* 1996;27:585-92.
7. Reich P, DeSilva RA, Lown B, Murawski BJ. Acute psychological disturbances preceding life-threatening ventricular arrhythmias. *JAMA* 1981;246:233-5.
8. Kawachi I, Sparrow D, Spiro A, III, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease: the Normative Aging study. *Circulation* 1996;94:2090-5.
9. Verrier RL, Mittleman MA. Life-threatening cardiovascular consequences of anger in patients with coronary heart disease. In: Deedwania PC, Tofler GH, editors. *Triggers and Timing of Cardiac Events*. *Cardiol Clin* 1996;14:289-307.
10. Verrier RL, Cohen RJ. Risk identification by noninvasive markers of cardiac vulnerability. In: Spooner P, Rosen MR, editors. *Foundations of Cardiac Arrhythmias*. New York, NY: Marcel Dekker, 2000:745-77.
11. Adam DR, Smith JM, Akselrod S, Nyberg S, Powell AO, Cohen RJ. Fluctuations in T-wave morphology and susceptibility to ventricular fibrillation. *J Electrocardiol* 1984;17:209-18.
12. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac instability. *Circulation* 1988;77:110-21.
13. Nearing BD, Huang AH, Verrier RL. Dynamic tracking of cardiac vulnerability by complex demodulation of the T-wave. *Science* 1991;252:437-40.
14. Nearing BD, Oesterle SN, Verrier RL. Quantification of ischemia induced vulnerability by precordial T-wave alternans analysis in dog and human. *Cardiovasc Res* 1994;28:1440-9.
15. Nearing BD, Hutter JJ, Verrier RL. Potent antifibrillatory effect of combined blockade of calcium channels and 5-HT₂ receptors with nexopamil during myocardial ischemia and reperfusion in dogs: comparison to diltiazem. *J Cardiovasc Pharmacol* 1996;27:778-87.
16. Verrier RL, Nearing BD, MacCallum G, Stone PH. T-wave alternans during ambulatory ischemia in patients with coronary heart disease. *Ann Noninvasive Electrocardiol* 1996;1:113-20.

17. Kop WJ, Nearing BD, Krantz DS, et al. Increased T-wave alternans with mental stress and exercise in implantable cardioverter defibrillator patients (abstr). *Circulation* 1999;100:1581.
18. Verrier RL, Nearing BD. Electrophysiologic bases for T-wave alternans as an index of vulnerability to ventricular fibrillation. *J Cardiovasc Electrophysiol* 1994;5:445-61.
19. Verrier RL, Nearing BD, LaRovere MT, et al. Median beat analysis of T-wave alternans to predict arrhythmic death after myocardial infarction: results from the Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) study (abstr). *Circulation* 2000;102:II713.
20. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994;330:235-41.
21. Estes NAM, Michaud G, Zipes DP, et al. Electrical alternans during rest and exercise as predictors of vulnerability to ventricular arrhythmias. *Am J Cardiol* 1997;80:1314-8.
22. Momiyama Y, Hartikainen J, Nagayoshi H, et al. Exercise-induced T-wave alternans as a marker of high risk in patients with hypertrophic cardiomyopathy. *Jpn Circ J* 1997;61:650-6.
23. Hohnloser SH, Klingenhoben T, Yi-Gang L, Zabel M, Peetermans J, Cohen RJ. T-wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. *J Cardiovasc Electrophysiol* 1998;9:1258-68.
24. Kavesh NG, Shorofsky SR, Sarang SE, Gold MR. The effect of heart rate on T-wave alternans. *J Cardiovasc Electrophysiol* 1998;9:703-8.
25. Adachi K, Ohnishi Y, Shima T, et al. Determinant of microvolt-level T-wave alternans in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1999;34:374-80.
26. Berul CI, Michaud GF, Lee VC, Hill SL, Estes M, Wang PJ. A comparison of T-wave alternans and QT dispersion as noninvasive predictors of ventricular arrhythmias. *Ann Noninvasive Electrocardiol* 1999;4:274-80.
27. Groh WJ, Shinn TS, Engelstein EE, Zipes DP. Amiodarone reduces the prevalence of T-wave alternans in a population with ventricular tachyarrhythmias. *J Cardiovasc Electrophysiol* 1999;10:1335-9.
28. Kavesh NG, Shorofsky SR, Sarang SE, Gold MR. The effect of procainamide on T-wave alternans. *J Cardiovasc Electrophysiol* 1999;10:649-54.
29. Ikeda T, Sakata T, Takami M, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction. *J Am Coll Cardiol* 2000;35:722-30.
30. Klingenhoben T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet* 2000;356:651-2.
31. Konta T, Ikeda K, Yamaki M, et al. Significance of discordant ST alternans in ventricular fibrillation. *Circulation* 1990;82:2185-9.
32. Verrier RL, Hagestad EL, Lown B. Delayed myocardial ischemia induced by anger. *Circulation* 1987;75:249-54.
33. Billman GE, Randall DC. Mechanisms mediating the coronary vascular response to behavioral stress in the dog. *Circ Res* 1981;48:214-33.
34. Nearing BD, Verrier RL. Personal computer system for tracking cardiac vulnerability by complex demodulation of the T wave. *J Appl Physiol* 1993;74:2606-12.
35. Verrier RL, Lown B. Behavioral stress and cardiac arrhythmias. *Ann Rev Physiol* 1984;46:155-76.
36. 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.
37. Euler DE, Guo H, Olshansky B. Sympathetic influences on electrical and mechanical alternans in the canine heart. *Cardiovasc Res* 1996;32:854-60.
38. Hohnloser SH, Klingenhoben T, Zabel M, Li Y-G, Albrecht P, Cohen RJ. T-wave alternans during exercise and atrial pacing in humans. *J Cardiovasc Electrophysiol* 1997;8:987-93.
39. MacMurdy KS, Kirk MM, Cooklin M, Shorofsky SR, Gold MR. The effect of selective autonomic blockade on T-wave alternans (abstr). *Circulation* 1999;100:1509.
40. Navarro-Lopez F, Cinca J, Sanz G, Periz A, Magrina J, Betriu A. Isolated T-wave alternans. *Am Heart J* 1978;95:369-74.
41. Han J, Garcia de Jalon P, Moe GK. Adrenergic effects on ventricular vulnerability. *Circ Res* 1964;14:516-24.
42. Verrier RL, Thompson PL, Lown B. Ventricular vulnerability during sympathetic stimulation: role of heart rate and blood pressure. *Cardiovasc Res* 1974;8:602-10.
43. Tidgren B, Hjemdahl P, Theodorsson E, Nussberger J. Renal neuro-hormonal and vascular responses to dynamic exercise in humans. *J Appl Physiol* 1991;70:2279-86.
44. Surawicz B, Fisch C. Cardiac alternans: mechanisms and clinical manifestations. *J Am Coll Cardiol* 1992;20:483-99.
45. Myerburg RJ, Kessler KM, Kimura S, et al. Life-threatening ventricular arrhythmias: the link between epidemiology and pathophysiology. In: Zipes DP, Jalife J, editors. *Cardiac Electrophysiology From Cells to Bedside*. Philadelphia, PA: W.B. Saunders, 1995:723-31.
46. Gottdiener JS, Krantz DS, Howell RH, et al. Induction of silent myocardial ischemia with mental stress testing: relation to the triggers of ischemia during daily life activities and to ischemic functional severity. *J Am Coll Cardiol* 1992;24:1645-51.
47. Deedwania PC. Hemodynamic changes as triggers of cardiovascular events. In: Deedwania PC, Tofler GH, editors. *Triggers and Timing of Cardiac Events*. *Cardiol Clin* 1996;14:229-38.