

Effects of Psychologic Stress on Repolarization and Relationship to Autonomic and Hemodynamic Factors

RACHEL LAMPERT, M.D.,* VLADIMIR SHUSTERMAN, M.D., PH.D.,†
 MATTHEW M. BURG, PH.D.,* ‡ FORRESTER A. LEE, M.D.,* CHRISTINE EARLEY, M.S.,*
 ANNA GOLDBERG, B.S.,† CRAIG A. MCPHERSON, M.D.,* WILLIAM P. BATSFORD, M.D.,*
 and ROBERT SOUFER, M.D.* ‡

*Yale University School of Medicine, New Haven, Connecticut; †PinMed, Inc., and University of Pittsburgh, Cardiovascular Institute, Pittsburgh, Pennsylvania; ‡VA Connecticut Healthcare System, New Haven, Connecticut, USA

Psychological Stress and Repolarization. *Introduction:* Psychological stress can precipitate ventricular arrhythmias in patients with ICDs, as well as sudden death. However, the physiologic pathways remain unknown. We sought to determine whether psychological stress induced in the laboratory setting alters indices of repolarization associated with arrhythmogenesis.

Methods and Results: Patients with ICDs and a history of ventricular arrhythmia underwent ambulatory ECG monitoring during a laboratory mental stress protocol (anger recall and mental arithmetic). Continuous changes in repolarization indices which have correlated with temporal and spatial myocardial heterogeneity of repolarization, including T-wave alternans (TWA), T-wave amplitude (Tamp), and T-wave area (Tarea) were analyzed in the time domain. In the 33 patients (85% male, 88% with coronary artery disease, mean ejection fraction 30%), norepinephrine, epinephrine, BP, and HR increased during mental stress. TWA increased from 22 (interquartile range 16–27) at baseline to 29 (21–38) μ V during mental stress ($P < 0.001$). Changes in TWA correlated with changes in HR, systolic BP, and catecholamines. Tamp and Tarea also increased with mental stress ($P < 0.01$) but did not correlate with changes in other variables.

Conclusion: Psychological stress increased TWA, Tamp, and Tarea. Autonomically mediated repolarization changes may be a pathophysiologic link between emotion and arrhythmia in susceptible patients. (*J Cardiovasc Electrophysiol*, Vol. 16, pp. 1-6, April 2005)

stress, catecholamines, repolarization, ventricular arrhythmia, T-wave alternans

Introduction

Psychological stress increases sudden cardiac death in populations during emotionally devastating disasters such as earthquake or war,^{1,2} alters induced arrhythmias,^{3,4} and precipitates spontaneous ventricular arrhythmias in patients with implantable cardioverter defibrillators (ICDs).⁵ However, the physiologic pathways through which stress can trigger arrhythmia remain poorly understood. Stress may alter electrophysiological properties of the myocardium, through the actions of stress hormones or via efferents descending from the CNS. One electrophysiological property necessary for ventricular arrhythmogenesis is non-uniform recovery of ventricular excitability.⁶ Indices reflecting temporal and spatial heterogeneity of repolarization, such as T-wave alternans (TWA) predict vulnerability to sudden death and ventricular arrhythmia.⁷⁻⁹ Indirect evidence suggests that autonomic fluctuations can alter TWA. For example, TWA demonstrates

circadian variation, with highest values in the morning,⁸ when catecholamine levels also peak.¹⁰ Further, beta-blockade can decrease TWA.¹¹ Eliciting an anger-like state in dogs increases TWA.¹² One previous study has demonstrated that psychological stressors can increase TWA,¹³ but evaluated only limited potentially mediating factors.

To further investigate whether and how psychological stressors may alter indices which reflect temporal and spatial heterogeneity of repolarization, we compared TWA, as well as T-wave amplitude (Tamp) and T-wave area (Tarea)¹⁴⁻¹⁷ at rest and during laboratory-induced psychological stress in a group of subjects likely to manifest repolarization heterogeneity, patients with ICDs and a history of ventricular arrhythmia, and evaluated these changes in relationship to changes in autonomic and hemodynamic factors.

Methods

Patient Population

Patients were included with ischemic or dilated cardiomyopathy and a history of spontaneous or induced ventricular arrhythmias. Patients with atrial fibrillation, diagnosed psychiatric disorders, or severe comorbidities were excluded. Thirty-three patients receiving ICDs between 12/00 and 12/02 agreed to participate and provided written informed consent. The study was approved by the Yale Human Investigation Committee.

Study Design

Patients underwent laboratory mental stress testing in the morning immediately prior to scheduled non-invasive ICD

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Address for correspondence: Rachel Lampert, M.D., Yale School of Medicine, Section of Cardiology, 333 Cedar Street, FMP 3; New Haven, CT 06520. Tel.: 203-737-4068; Fax: 203-737-2437; E-mail: rachel.lampert@yale.edu

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testing, 3 months after implantation (standard of care at our institution), and prior to administration of sedatives or analgesics. An intravenous cannula was placed in an antecubital vein for blood sampling. Pacing was programmed to the VVI mode at 40 bpm, which allowed emergence of sinus rhythm with native AV conduction in all patients. Continuous 12-lead ECG was monitored throughout the protocol (GE CardioLab System, Milwaukee, WI).

Mental Stress Protocol

In accordance with our standard mental stress protocol,⁴ the room lights were dimmed and quiet maintained. In the baseline period, starting at least 30 minutes after IV placement, patients were encouraged to think about past relaxing situations. This was followed by the two mental stress tasks, first arithmetic and then anger recall, interspersed with a second baseline period. Each phase lasted 5–7 minutes. For the mental arithmetic task, subjects were asked to subtract 7 serially from a 3-digit number rapidly and accurately. For anger recall, patients described a recent event eliciting irritation, annoyance, or frank anger, with the insertion of frequent irritating questions by the interviewer. Two stressors were utilized because this approach provides greater generalizability to naturalistic settings.¹⁸ Consistent with previous investigations, the maximum response to the two stressors was analyzed.^{4,19}

Repolarization Analysis

Ambulatory ECGs (Holters) with modified V1 and V5 leads were recorded on GE Medical (Milwaukee, WI) Marquette Series 8500 direct (amplitude-modulated) recorders. These recorders have a flat frequency response and a linear phase between 0.67 and 50 Hz (± 3 dB).^{20,21} This range is somewhat narrower than 0.3–50 Hz recommended by Nearing et al. for TWA monitoring.²² However, since the lowest frequency components of the cardiac complexes in more than 99% of adults, 99% of the time are greater than 0.67 Hz, most ambulatory recorders (including Marquette 8500) have a 0.67 Hz (3 dB) cutoff frequency of the high-pass filter for baseline correction.²³ The frequency of the cardiac complexes can be lower than 0.67 Hz at very slow heart rates (<40 bpm), which were not observed in our study. The recordings were digitized at 400 Hz sampling frequency and effective resolution of 2.5 μ V.²²

Holter recordings were digitized at 400 Hz using a commercial scanning system (Burdick, Inc., Syracuse, NY). A single lead (that with larger magnitude T-wave) was analyzed for each repolarization index, the same lead for all stages.

A previously validated program for adaptive baseline correction²⁴ was then applied to assure accurate detection of the isoelectrical line with a minimal distortion of the repolarization waveforms. The QRS complexes were classified using custom software and verified by an experienced technician. After exclusion of ectopy, series of consecutive sinus beats were processed to identify fiducial points, including the onset of the Q-wave, the end of the S-wave, and the beginning, peak, and end of the T-wave as described elsewhere.²⁴ Because the changes in repolarization are complex and highly variable among individuals, and because no single parameter on the surface ECG can reliably represent the entire spectrum of repolarization changes, we used a set of several descriptors, including T_{amp} , T_{area} , and TWA, as previously described.²⁵

Analysis of TWA was methodologically similar to the modified moving average approach introduced by Nearing and Verrier²⁶ but computationally simpler for examining gross alternations in the T-wave, at the expense of a lower sensitivity to small-amplitude TWA.²⁴ This automated computer algorithm consisted of (1) detection of the fiducial points (T_{onset} , T_{peak} , and T_{end}), (2) calculation of the mean amplitude of the corresponding segment of the T-wave (from T_{onset} to the T_{peak} ($T_{onset-peak}$); from the T_{peak} to the T_{end} ($T_{peak-end}$); and from the T_{onset} to the T_{end} for “total” (TWA); (3) calculation of the time series of the differences between the corresponding amplitudes under consecutive even and the odd beats; (4) averaging of these time series over 5-minute intervals; and (5) calculation of the results for each test as a percent change compared to the individual baseline values. This algorithm was validated on simulated signals with various levels of TWA in the presence of random noise, spurious artifacts, and phase-shifts using the methodology described by Nearing and Verrier.²⁶ The algorithm accurately detected changes in the level of TWA both in clean signals and in signals contaminated by noise and artifacts,²⁷ with performance similar to that of modified moving average analysis.²⁶

Catecholamine Collection and Analysis

Blood for catecholamine assay was withdrawn continuously by exfusion pump (Dakmed, Buffalo, NY) at a rate of 1 ml/min. Samples were immediately placed on ice and brought to the Yale General Clinical Research Center within 30 minutes where they were spun and stored at -70° C. Levels of epinephrine (EPI) and norepinephrine (NE) were determined by high-performance liquid chromatography (ESA, Inc., Chelmsford, MA) using electrochemical detection (Coulchem II) after alumina extraction. Samples from each patient were run in the same batch in duplicate. Four patients were not included in the analysis of catecholamines due to the inability to gain or maintain adequate intravenous access.

Heart Rate Variability Analysis

After editing as above, an annotated list of R-R intervals was analyzed using customized software. The R-R interval data were edited to remove ectopic beats and noise, and gaps were filled in by interpolated linear splines.²⁸ Holter recordings with >20% interpolated R-R intervals were excluded from further analysis ($N = 2$). The R-R interval time series was sampled using a boxcar window²⁹ to obtain 1024 samples per 5 minutes (3.41333 Hz). The power spectrum was computed using a fast Fourier transform with a Parzen window on 4-minute segments with a 1-minute sliding window, corrected for attenuation due to windowing and sampling³⁰ and integrated over five standard frequency bands.³¹ High-frequency power (HF, 0.15–0.40 Hz), a marker of parasympathetic activity,^{32,33} was compared between experimental conditions.

Statistical Analysis

Changes in TWA, T_{amp} , and T_{area} and in catecholamines, from baseline to mental stress showed a highly skewed distribution (Shapiro–Wilk $W < 0.05$) and hence were analyzed by the paired non-parametric Wilcoxon signed-rank test. Other variables were compared using paired t -test. Relationships

TABLE 1
Demographic and Clinical Characteristics

Age (years)	64 ± 12
Male	28 (85%)
Coronary artery disease	29 (88%)
Ejection fraction (%)	30 ± 10
Indication	
VF	7 (21%)
VT	3 (9%)
Syncope*	7 (21%)
High risk†	16 (48%)
Medications	
Beta-blockers‡	29 (88%)
Amiodarone	2 (6%)
Sotalol	3 (9%)
Other anti-arrhythmic	1 (3%)
ACE or ARB	24 (73%)
Digoxin	10 (30%)
Benzodiazepines	2 (6%)

*With VT induced at electrophysiology study.

†CAD, EF < 35%, inducible VT ‡including sotalol.

between mental-stress induced changes in repolarization indices, autonomic factors, and heart rate were evaluated using Pearson product-moment correlation coefficients. Relationship between TWA change and factors with significant correlations was further evaluated with standard least-squares regression. In addition, because NE and EPI response to stress was highly skewed, patients were dichotomized into high and low NE and EPI responders at the top quartile (top 7 of 29 patients). Mental-stress induced changes in repolarization were compared between these groups.

Results

Patient Population

Participants' demographic and clinical characteristics are shown in Table 1. Typical of most ICD populations, the majority of subjects were male and had coronary artery disease. The mean ejection fraction was 30%. Most were on beta-blockers and few on anti-arrhythmic medications.

Autonomic, Hemodynamic, and Electrocardiographic Effects of Mental Stress

NE and EPI rose significantly from baseline to mental stress (Table 2), implying sympathetic activation, and HF power decreased, indicating parasympathetic withdrawal. The increase in heart rate was consistent, although of small magnitude. Systolic and diastolic BP rose during stress. No ischemic changes in ST segment or T wave were seen on continuous 12-lead ECG monitoring.

Effects of Mental Stress on Repolarization

All heterogeneity-related T-wave measurements, TWA, Tamp, and Tarea, increased significantly from baseline to mental stress (Fig. 1 and Table 3). Median increase in TWA was 78% (interquartile range 43–107%, $P < 0.001$), and in 10% of patients, TWA at least doubled with stress. In patients with CAD, median increase in TWA with stress was 79%, and in those without CAD, 66% ($P > 0.5$). TWA increased during both $T_{\text{onset-peak}}$ and $T_{\text{peak-end}}$ (Table 3 and Fig. 1). TWA increased during arithmetic by 67% (42–146%, $P < 0.001$) and

TABLE 2
Autonomic and Hemodynamic Changes with Mental Stress

	Baseline	Mental Stress	P
Norepinephrine (nmol/L)	1.55 ± 0.12	1.89 ± 0.15	<0.01
Epinephrine (pmol/L)	147 ± 22	322 ± 60	<0.05
High frequency power (ln msec ²)	5.34 ± 0.35	4.72 ± 0.37	<0.05
Systolic BP (mmHg)	131 ± 3	146 ± 4	<0.001
Diastolic BP (mmHg)	70 ± 2	83 ± 2	<0.001
Heart rate (bpm)	64 (±2)	67 (±2)	<0.001

during anger by 78% (50–140%, $P < 0.001$). Responses to arithmetic and anger did not differ significantly. About half of subjects showed greater response to anger (53–59% for Tamp, Tarea, and TWA) and half to arithmetic.

Median increase in Tamp was 9% (1–26%, $P = 0.001$), and in Tarea, 11% (0–24%, $P < 0.001$). QT interval decreased.

Relationship of Repolarization Changes to Autonomic and Hemodynamic Changes

The rise in TWA during mental stress was significantly correlated with increases in EPI, systolic BP, and HR (Table 4). In a multivariable model including EPI, BP, and HR, only EPI independently predicted increase in TWA ($P < 0.01$). The relationship between changes in catecholamines and in repolarization indices was further evaluated by comparing TWA changes between subjects with high versus low-normal NE and EPI responses. While TWA increased with stress in patients with both high and low-normal catecholamine response, those with greater rise in NE and in EPI showed significantly greater increases in TWA (Fig. 2). Changes in Tamp and Tarea did not correlate with heart rate change or with other variables.

Discussion

In patients with heart disease and a history of ventricular arrhythmia, laboratory-induced psychological stress increased temporal and spatial heterogeneity of repolarization as measured by TWA, Tamp, and Tarea in association with changes in catecholamines as well as in hemodynamic parameters. Thus, stress-induced sympathetic activation may be one pathway through which stress increases heterogeneity of repolarization.

TWA not only predicts both induced^{7,9} and spontaneous ventricular arrhythmia,^{7,8} but also immediately precedes development of ventricular fibrillation in animal models,^{14,26,34,35} suggesting that TWA may be mechanistically related to arrhythmia. In 10% of our patients, the stress-induced increase in TWA was similar to that previously associated with vulnerability to ventricular fibrillation.²⁶ Tamp, which also increased in response to stress, increases prior to spontaneous sustained monomorphic VT,³⁶ suggesting that an increase in Tamp may also reflect an arrhythmogenic process. Thus, changes in repolarization may be one mechanism through which psychological stress may trigger ventricular arrhythmia.

Physiologic Correlations of Repolarization Measurements

The importance of non-uniform recovery of excitability to developing ventricular fibrillation is well

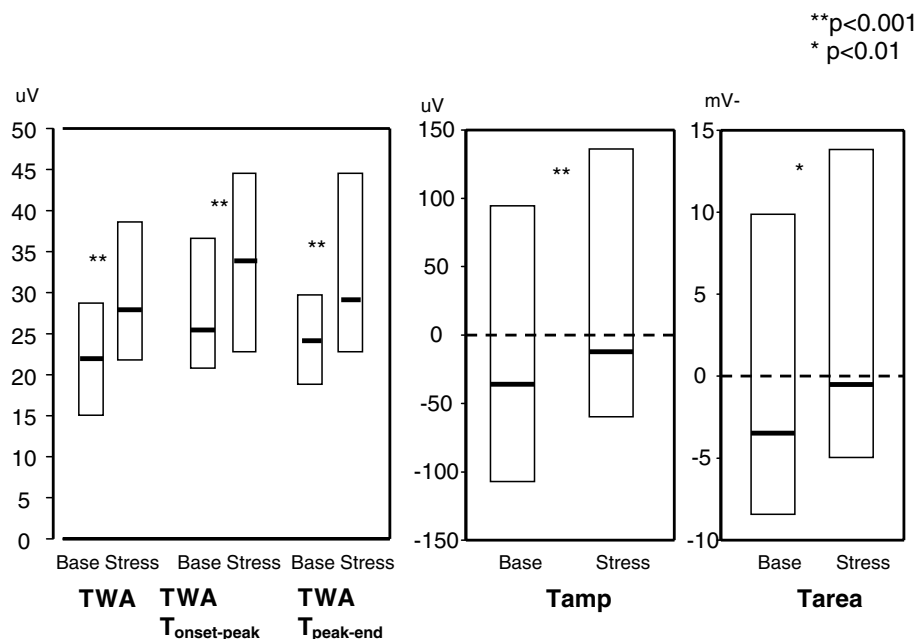


Figure 1. Repolarization changes with mental stress. Box plots represent median and interquartile range. Tamp = T-wave amplitude; TWA = T-wave alternans; Tarea = T-wave area.

recognized.^{6,14,26,34,35} However, the specific electrophysiologic perturbations responsible for repolarization heterogeneity are not well understood. In experimental models, heterogeneity of repolarization associated with the development of arrhythmia has been demonstrated at multiple levels: first, between myocardial regions epicardially,¹⁷ next, transmurally across the myocardium,^{15,16,37} and finally, between neighboring cells.¹⁴ Each of these mechanisms may be important in clinical arrhythmia.

Each of the indices used here—Tarea, Tamp, and TWA—has been correlated with heterogeneity. For example,¹⁷ in multisite epicardial recordings, regional dispersion of recovery times correlates with the width of the root-mean-square T-wave (similar to Tarea). Whether Tamp also correlates with epicardial dispersion is controversial.³⁸⁻⁴⁰ However, T-wave height does reflect transmural voltage differences.¹⁶ While TWA measures temporal changes in action potential duration at the level of single cells, cells differ in the timing and/or extent of these changes, creating spatial heterogeneity.^{14,15} Transmural heterogeneity of repolarization, with epicardial cells displaying the shortest, and subendocardial M-cells the longest, action potential duration, correlates with TWA.¹⁵ TWA also correlates with cell-to-cell heterogeneity.¹⁴

Potential Pathways Linking Psychological Stress and Repolarization Changes

The pathways through which stress alters repolarization are unknown. TWA increases with heart rate,^{7,14,41} as also seen here. However, sympathetic activation may increase TWA beyond the effects of heart rate. Experimentally, stellectomy abolishes, while stellate ganglion stimulation increases, TWA.³⁴ In clinical studies, intravenous beta-blockade¹¹ decreased the magnitude of TWA, and TWA induced with exercise is greater than that with atrial pacing at the same heart rate.⁴¹ In this study, HR increase was minimal, and EPI independently predicted TWA changes, further supporting a role of catecholamines in increasing heterogeneity of repolarization beyond effects of HR.

Whether the parasympathetic nervous system influences repolarization is unclear. With atrial pacing to control heart rate, while vagal stimulation reduced TWA induced by coronary occlusion in one study,⁴² in another, atropine did not alter TWA.¹¹ In this study, while HF power decreased overall with mental stress, as expected,⁴³ there was no correlation between vagal withdrawal and changes in repolarization.

TABLE 3

Effects of Mental Stress on Repolarization

	Baseline	Mental Stress	P
TWA* (uV)†	22 (16–27)	29 (21–38)	<0.001
TWA-T _{onset-peak} ‡	25 (21–37)	33 (23–45)	<0.001
TWA-T _{peak-end} ‡	23 (17–29)	28 (21–44)	<0.001
Tamp‡ (uV)†	-40 (-110–90)	-20 (-80–130)	<0.001
Tarea§ (mV*msec)†	-3.73 (-9.32–10.37)	-1.67 (-6.22–13.11)	<0.01
QT (msec)	442 (±9)	427 (±8)	<0.001

*TWA = T-wave alternans; †Data expressed as median (interquartile range) (distribution highly skewed); ‡Tamp = T-wave amplitude; §Tarea = T-wave area.

TABLE 4

Correlations of Changes in T-wave Alternans with Changes in Autonomic and Hemodynamic Factors in Response to Mental Stress

	Correlation Coefficient	P
Norepinephrine	0.3479	0.09
Epinephrine	0.5462	<0.01
High frequency power	0.2679	0.38
Systolic BP	0.4386	<0.02
Diastolic BP	-0.0057	0.9
R-R interval	-0.4484	<0.02

TWA changes also correlated strongly with increases in systolic BP. It is possible that mental stress affected TWA in part through mechano-electrical feedback, as changes in afterload can alter ventricular refractoriness.⁴⁴

While ischemia invokes TWA in animals,⁴⁵ as well as humans during coronary angioplasty,^{45,46} in this study no ECG changes were seen, and a recent study¹³ showed no correlation between stress-induced TWA changes and ischemia on SPECT. This suggests that mental stress-induced TWA is not ischemically mediated. Determining mechanisms through which stress increases TWA remains an important avenue of future investigation.

Tamp and Tarea also increased with stress, but changes did not correlate with measured potential mediators. These indices may measure different electrophysiologic phenomena than does TWA. In normals, Tamp decreases with stress.⁴⁷ Similarly, with sympathetic activation by upright tilt, Tamp increases in patients with heart disease but decreases in normals.²⁵

Methodology

While time-domain methods to quantify TWA are less frequently used than spectral, the clinical predictive value does not differ,^{8,9} and time domain analysis may provide significant advantages.²⁶ In clinical ECG recordings, TWA estimation has been limited by signal non-stationarity and the presence of noise and artifacts,²⁶ rendering spectral methods inaccurate. However, the differences between consecutive even and odd beats calculated in the time domain provide a more accurate dynamic estimate of the TWA changes over time.²⁶ Methodology used here further enhances the specificity of TWA in settings of noise.²⁷ First, serial analysis of changes in the averaged amplitude of the T-wave³⁵ (or its segment) provides an averaged (over the corresponding segment) estimate of the changes in the T-wave energy.²⁴ While this method is not as sensitive to subtle TWA as spectral methods or modified moving average analysis,²⁶ the use of averaging renders this method less sensitive to spurious spikes or artifacts, which often contaminate clinical ECG recordings.²⁶ To further decrease noise, patients were supine, and recordings were carefully corrected for artifacts and baseline wander.²⁴ Finally, each individual served as his own control, and a percent change in TWA calculated. The use of normalized units (percent change) is relatively insensitive to inter-individual variations in spatial electrophysiologic properties.³⁵

Limitations

Most patients were taking beta-blocking medications, which decreased the magnitude of TWA in pharmacological studies.¹¹ It is thus likely that mental stress alters TWA,

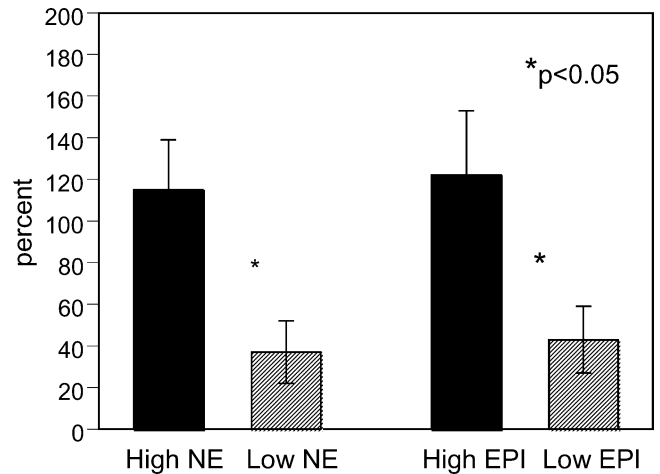


Figure 2. Increase in TWA with stress based on catecholamine response to stress. High NE, subjects whose NE (norepinephrine) response to stress fell in the top quartile; High EPI (epinephrine) similarly.

Tamp, and Tarea to a greater degree than demonstrated in this study.

To evaluate potential electrophysiological changes linking stress to arrhythmia, patients having a history of arrhythmia were studied, who were most likely to manifest repolarization abnormalities. Without a control group, this study cannot state definitively whether the relationship between stress, catecholamines, and TWA is abnormal. However, as development of TWA with exercise or pacing is clearly pathologic, stress-induced TWA most likely represents a pathologic process also. Whether vulnerability to mental-stress-induced changes in repolarization in the laboratory is associated with vulnerability to ventricular arrhythmia is an important avenue of future research.

Conclusions

Psychological stress induced in a laboratory setting increased indices associated with temporal instability and spatial heterogeneity of repolarization including TWA, Tamp, and Tarea in individuals with heart disease and a history of arrhythmia. Stress-induced changes in TWA were associated with sympathetic activation. These findings suggest that autonomically mediated repolarization changes may be one pathophysiologic link between emotion and arrhythmia.

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