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Cardiac Repolarization Instability during Psychological Stress in Patients with Ventricular Arrhythmias

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Abstract

Introduction—Changes in the autonomic nervous system activity (ANS) are a major trigger of life-threatening ventricular tachyarrhythmias (VTA). Mental arithmetic, a condition administered in a laboratory setting, can provide insight into the ANS effects on cardiac physiology. We examined the responses of cardiac repolarization to laboratory-induced psychological stressors in patients with implantable cardioverter defibrillators (ICDs) with the objective of identifying the indices that differentiate patients with and without subsequent VTA in follow-up.

Methods—Continuous ECG signals were recorded using 3 standard bipolar (Holter) leads in 56 patients (age: 63.6±11.9, female: 12%, LVEF: 32.3±11) with ICDs during mental arithmetic. The patients were separated into those with subsequent VTA during 3–4 years of follow-up (Group 1: N=9 pts) and those without VTA (Group 2: N=47 pts). Changes in repolarization (QT-interval, mean T-wave amplitude (Tamp), and T-wave area (Tarea) were analyzed during 5min of baseline, stress and recovery. The temporal instability of Tamp and Tarea was examined using the range (Δ) and variance (σ^2) of beat-to-beat variations of the corresponding parameters.

Results—There were no significant differences in HR between the two groups at baseline (61 vs. 63 bpm, $p=0.97$), during stress (64 vs. 65 bpm, $p=0.40$), and recovery (62 vs. 61 bpm, $p=0.88$). However, during mental stress and post-stress recovery Δ Tamp was almost 2-fold greater in Group 1 compared with Group 2 (111 (57–203) vs. 68 (44–94) μ V $p=0.04$, respectively). Changes in QT-intervals were also greater in Group 1 compared with Group 2 ($p=0.02$).

Conclusion—Among patients with ICDs, changes of T-wave amplitude after psychological stress were greater in those with subsequent arrhythmic events. This might signal proarrhythmic repolarization response and help identify patients who would benefit the most from ICD implantation and proactive management.

Keywords

Repolarization Instability; Psychological Stress Ventricular Arrhythmias; Electrocardiographic T-wave

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Introduction

Changes in the autonomic nervous system activity (ANS) are a major trigger of life-threatening ventricular tachyarrhythmias (VTA).^{1,2} Increased sympathetic nervous system activity, manifested by faster heart rate and changes in heart rate variability, has been reported prior to the onset of spontaneous VTA in humans.¹ These ANS changes were also associated with increased proarrhythmic repolarization instability,³ which provides a plausible pathophysiological mechanism linking the changes in ANS with arrhythmogenesis.

Mental arithmetic, a condition administered in a laboratory setting to elicit psychological stress, can provide insight into the ANS effects on cardiac physiology. Psychological stress activates sympathetic nervous system activity and can provoke fatal VTA and sudden cardiac death in patients with and without structural heart disease.^{4,5} It also increases T-wave alternans (TWA),^{6,7} and TWA induced by psychological stress predicts future VTA in patients with implantable cardioverter-defibrillators (ICDs).⁸

However, temporal repolarization instability is not limited to the single frequency of 0.5 cycle/beat which characterizes T-wave alternans, but can include dynamical processes oscillating at other frequencies as well.³ Recent studies have shown that such a “broad-range” repolarization instability, which includes both TWA and “non-alternans” frequencies, also increases before the onset of spontaneous VTA.^{3,9} It is plausible that some instabilities, arising at non-TWA frequencies would be missed by TWA analysis. Indeed, the clinical utility of TWA is primarily associated with its negative predictive value.¹⁰ Therefore, broad range repolarization instability (possibly, in combination with TWA) may provide a more comprehensive and sensitive indication of overall repolarization instability, with a stronger positive predictive value than the TWA analysis alone.

The relationship between stress-induced broad-range repolarization instability (BRI) and future arrhythmias has not been studied. Here, we examined the responses of BRI to laboratory-induced psychological stressors in patients with implantable cardioverter defibrillators (ICDs) with the objective of identifying the indices that differentiate patients with and without subsequent VTA in follow-up.

Methods

Patient population

The study design has been described in detail elsewhere.² Briefly, 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. Two patients failed to complete 1 year of follow-up (1 death due to unknown cause, 1 heart transplant). Clinical variables were collected through chart review. The study was approved by the Yale Human Investigation Committee, and all patients provided written informed consent.

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. For this analysis, the patients were separated into those with

subsequent VTA during the follow-up (Group 1: N=9 pts) and those without VTA (Group 2: N=47 pts).

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.⁶ Briefly, conditions included resting baseline, mental arithmetic (serial subtraction of 7) and second baseline; each stage was 5-min long.

Data acquisition

Data acquisition has been previously described.⁶ In brief, ambulatory ECGs with modified V1 and V5 leads were recorded on GE Medical (Milwaukee, WI) Marquette Series 8500 direct recorders. The recordings were digitized at 400-Hz sampling frequency and effective resolution of 2.5 μ V.⁶

Signal Processing and Data Analysis

A previously validated method for ECG baseline correction was applied.¹¹ In addition; the level of baseline instability was estimated using the standard deviation of the baseline segment. If the amplitude of baseline instability exceeded 50 μ V or its standard deviation was > 25 μ V, those beats were excluded.^{3,12} To exclude possible spurious artifacts superimposed on the repolarization segment, each T wave was compared to the average of all T waves in the corresponding 5-min interval (referred to as the average T wave) using a cross-correlation. If the correlation coefficient was < 0.85 or the peak amplitude of the T wave was more than two times greater than that in the average T wave, the waveform was excluded from analysis.³

The fiducial points, including the R-peak, Q-wave onset, S-wave end, T-wave peak and end, were identified using custom software and verified by an experienced technician. The QT-interval was automatically computed from the Q-wave onset to T-wave end. The mean T-wave amplitude was calculated as the mean amplitude of the entire T-wave; T-wave area was estimated using the integral of the area under the T-wave from T-onset to T-end.^{3,13} The lead with the largest T wave was used for analysis. Because a single lead was used in each patient for all analyses inter-lead differences in T-wave amplitude are not expected to affect the results. The time series of RR-intervals were re-sampled at 1 Hz using cubic spline interpolation. To eliminate the high-frequency noise and respiratory variations in the RR-intervals, the signal was low-pass filtered at 0.03 Hz using a 2nd-order Butterworth filter.¹⁴ The data values for RR, QT, QTp, Tamp, Tarea, and the time of R-peak were divided into three 5-min segments corresponding to baseline, stress and recovery periods. The heart rate, QT-interval, QRS-duration, T-wave amplitude (Tamp), T-wave integral (Tarea) were calculated during baseline, stress and recovery. The broad-range repolarization instability was examined using the range (Δ) and variance (σ^2) of beat-to-beat variations of Tamp and Tarea.

Catecholamine Collection and analysis

Catecholamine collection and analysis has been previously described.⁶ In summary, blood for catecholamine assay was withdrawn continuously using an exfusion pump (Dakmed, Buffalo, NY) at a rate of 1ml/min. Samples were immediately placed on ice and brought to the research laboratory within 30mins of collection, 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. Chemsford, MA), using electrochemical detection (coulochem II) after alumina extraction.⁵

Statistical Analysis

The data distributions were tested using Shapiro-Wilks W test. Because the distributions were significantly different from normal for a number of variables, nonparametric tests were applied. Baseline data were compared to stress and recovery data using Wilcoxon matched pairs test. Repolarization parameters and catecholamine levels were compared between groups of patients with and without arrhythmias using Mann-Whitney U test. Categorical variables were compared using Fischer's exact test. The analyses were performed using SPSS for Windows version 19 (SPSS Inc., Chicago, IL) and Statistica (StatSoft, Tulsa, OK). The results are presented as median (25–75%) range except where indicated otherwise.

Results

Patient Characteristics

Clinical and demographic characteristics of patients participating in this study are shown in Table 1. There were 56 patients (age: 63.6±11.9, female: 12%, LVEF: 32.3±11) in the study group. The majority of the patients had coronary artery disease and >90% were on β -blocker therapy. During a median follow-up of 37 months (interquartile range 25 to 47 months, range 12 to 75 months), 10 patients experienced ICD-terminated VT/VF. There were no significant differences between the clinical characteristics of patients with and without ventricular tachyarrhythmias.

Changes in catecholamines during stress

Both epinephrine and norepinephrine increased by 30 % and 1.2%, respectively from baseline to stress and remained elevated during the recovery phase (Table 2).

Changes in cardiac rhythm and repolarization during stress

Heart rate increased from 60(54–65) to 65 (59–70) $p < 10^{-5}$ and QT interval shortened from 447(411–476) to 441(409–465) ms $p = 0.006$ during stress (Figure 1, Table 2). There were no significant differences in HR, mean or median T_{amp}, and T_{area} between the two groups at baseline, during stress or post-stress recovery (Table 2).

Δ T_{amp} was similar at baseline in the two groups; however, it became approximately 2-fold greater in Group 1 compared with Group 2 during stress and post-stress recovery ($p = 0.04$ and 0.008, respectively; Table 3). Δ QT was greater in Group 1 compared with Group 2 during baseline, stress and recovery (Table 3). The variance, σ^2 , of T_{amp} was also greater in Group 1 compared with Group 2 during stress and post-stress recovery ($p = 0.02$ and 0.007 respectively, Table 3).

Potential confounders: filtering and T-wave polarity

To examine the effects of filtering, we analyzed a subset of 19 patients using unfiltered data (without a 0.03-Hz low-pass filter). We found that the changes in T_{amp} were still approximately 2 times higher in patients prone to arrhythmic events compared to those without future events (Figure 2A).

To examine the effects of T-wave polarity, we also analyzed the differences in range of T_{amp} between the groups in the subgroup of patients with negative T-waves (158 (100–214) and 75 (44–111) μ V $p = 0.02$ in Group 1 and 2, respectively) and found that the trends were similar to those in the entire groups (Figure 2B).

In addition, the inter-group differences were examined with respect to an absolute magnitude of T_{amp} and found that Group 1 had a higher change in T_{amp} compared to Group 2 (Figures 2C).

Discussion

The main finding of this study is that the broad-range beat-to-beat repolarization instability during psychological stress and post-stress recovery was greater in patients with subsequent arrhythmic events compared to those without arrhythmias during 47-month follow-up. Because heart rate was similar in the two studied groups during the stress and recovery phases, the differences in the T-wave variability could not be explained by the differences in heart rate.

Previous studies

Psychological stress is a potent stimulator of the sympathetic nervous system activity, which can be proarrhythmic.^{4,6,7} The changes in cardiac rhythm and repolarization during psychological stress are similar to those observed prior to the initiation of spontaneous tachyarrhythmias.^{1,2,8} It has been previously shown that psychological stress increases T_{amp} and Tarea in this patient population.⁶ Furthermore, intensive sympathetic stimulation with a combination of isoproterenol infusion and head-up tilt or rapid atrial pacing may increase T-wave amplitude in some patients.¹⁵

Beat-to-beat variability of the T-wave amplitudes at rest has been used for arrhythmia risk stratification in patients with LQTS¹⁶, dilated cardiomyopathy¹⁷, ischemic cardiomyopathy¹⁸, and Chagas disease.¹⁹ Coudrec et al. have shown the variability of T-wave amplitudes $>59 \mu V$ was predictive of future arrhythmic events in patients with ICDs.²⁰ However, the broad-range beat-to-beat repolarization instability during the autonomic perturbations of psychological stress and its relationship to the risk of arrhythmias has not been previously studied.

Analysis of potential confounders

We investigated the potential confounding effects of noise and low-pass filtering by comparing the results of analysis performed with and without the 0.03-Hz low-pass filtering.¹⁴ In both analyses, ΔT_{amp} was consistently greater in patients with VTA, which confirms the validity of our main finding (Figure 2C).

To examine the impact of T-wave polarity, we also analyzed the changes in repolarization using both signed and unsigned (absolute) values. In addition, the inter-group differences were examined in a subset of for patients with negative T-waves (figure 2B). In all these analyses, ΔT_{amp} was consistently greater in patients with arrhythmic events compared with patients without arrhythmic events.

Physiological mechanisms of T-wave instability

Although the analysis of cellular mechanisms that could contribute to the observed increase in broad-range repolarization instability lies beyond the scope of our study, several known electrophysiological mechanisms could play some role in our findings.

Repolarization instability has been linked to both spatial (transmural and interventricular (apical-basal)) and temporal (beat-to-beat) heterogeneity of repolarization.^{21,22,23} Shimizu and Antzelevitch showed that beat-to-beat alternations in action potential duration (APD) of epicardium and endocardium leads to dynamic changes of transmural voltage gradients which manifests as microvolts alternation in T wave amplitude.²⁴ They also have shown that

beat-to-beat intracellular calcium cycling plays crucial role in the maintenance of both mechanical and electrical T wave alternans.²⁴ The differences in ΔT_{amp} between the groups of patients with and without VTA could be also related to higher prevalence of fibrosis and scar tissue in these patients. However, the exact mechanisms of the enhanced broad-range repolarization instability require further investigation.

Limitations

The size of patient population was relatively small, and some patients were on β -blockers, which could have blunted the repolarization response to psychological stress. Yet, the proportion of patients on β -blockers was similar in both groups, suggesting that the intake of β -blockers did not bias the main findings of our study that patients with future VTA have a greater broad-range beat-to-beat repolarization instability during psychological stress.

Conclusions

The broad-range beat-to-beat repolarization instability was significantly higher during psychological stress in patients with future arrhythmic events compared to those without arrhythmias. This can be useful for risk stratification and selection of patients at high risk of arrhythmic events, who would benefit the most from an ICD implantation.

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Figure 1.

A representative example of the Heart Rate (HR) and QT-interval (QT) response to psychological stress in one of the studied patients. HR increased in response to stress, whereas QT interval shortened. * $p < 0.001$ for the comparison of HR between baseline and stress and between baseline and recovery $< 10^{-4}$, ¥ $p = 0.005$ for the comparison of QT intervals at baseline and during stress.

Figure 2.

Panel A: Δ T-wave amplitude in the raw data (prior to the application of a low-pass filter). Panel B: Δ T-wave amplitude during baseline, stress and recovery in a subset of patients with negative T-wave. Panel C: Comparison of the Δ in T-wave amplitude during post-stress recovery phase for: i) unfiltered (raw) data, ii) filtered using a 0.03-Hz low-pass filter, iii) a subset of patients with negative T-wave and iv) the T-wave amplitudes presented in absolute values.

Table 1

Clinical characteristics

	Group 1(N=9)	Group 2 (11=47)	P value
Age(y)	66±8.9	63.2±12.2	0.60
% Males	9(100%)	41(85%)	0.30
CAD, n (%)	9(100%)	45 (94%)	0.70
Ejection Fraction, %	33.6 ±11.5	32.3±12	0.80
β-blockers	8(89%)	40 (83%)	0.60

Data are presented as mean ± SD

Table 2

Stress induced changes in cardiac rhythm, repolarization and catecholamines in the studied group (N=56 patients).

	Baseline	Stress	p [*]	Recovery	p [§]
Heart Rate (bpm)	60 (54–65)	65(59–70)	<10 ⁻⁵	62(55–67)	0.009
QRS-interval (ms)	126(109–153)	127(110–152)	0.67	122(110–151)	0.92
QT-interval (ms)	447(411–476)	441(409–465)	0.006	446(406–465)	0.50
ΔQT-interval (ms)	19(15–37)	18(12–27)	0.37	17(12–28)	0.71
Tamp (μV)	-23(-70–39)	-30(-79–34)	0.92	-24(-74–35)	0.80
Δ Tamp (μV)	56(47–98)	69(48–107)	0.20	72(43–99)	0.85
σ ² Tamp (μV) ²	85(54–172)	106(55–263)	0.28	102(47–243)	0.90
Tarea (mV.ms)	-4.5(-16.3–7.9)	-4(-14.9–7.5)	0.79	-4.7(-15.1–7.4)	0.95
Δ Tarea (mV.ms)	13.6(9.1–20.6)	14.7(9.8–24.9)	0.27	14.3(8.4–22.9)	0.76
Epinephrine (pmol/L)	126(71–175)	164(76–268)	<10 ⁻⁵	147(87–213)	<10 ⁻⁴
Norepinephrine [nmol/L]	1.65(0.98–2.25)	1.67(1.18–2.57)	0.08	1.79(1.08–2.56)	<0.001

Δ = range of variations of the corresponding parameter; σ² = variance; Tamp = T-wave amplitude; Tarea = Area under the T-wave; Data are presented as median [25–75%];

* baseline vs. stress;

§ baseline vs. recovery.

Table 3
Stress induced changes in patients with (Group 1; N=9) and without (Group 2; N=47) ventricular tachyarrhythmias

	Baseline			Stress			Recovery		
	Group 1	Group 2	p	Group 1	Group 2	p	Group 1	Group 2	p
HR (bpm)	61(56-70)	63(56-66)	0.97	64(62-73)	65(59-67)	0.40	62(58-70)	61(57-63)	0.88
Tamp ((μ V)	-31(-107-(-1.4))	-10.2(-65-52)	0.33	-30.5(-107-6.4)	-24.5(-68-51)	0.34	-28.9 (-91-(-3))	-8.5(-70.5-50.3)	0.42
Δ Tamp (μ V)	64(51-118)	55 (45-87)	0.50	111(57-203)	68(44-94)	0.04	103(75-202)	58(42-81)	0.008
σ^2 Tamp (μ V) ²	167(65-389)	83(49-148)	0.20	557(81-948)	93(49-239)	0.02	244(180-550)	93(42-161)	0.007
Tarea (mV.ms)	-5.5(-18.4-(-0.14))	-2.6 (-12.8-9.6))	0.40	-5.9(-18.4-1.0)	-3.5(-12.7-9.9)	0.36	-5.6(-18.4-(-0.17))	-1.8(-15.1-10.7)	0.38
Δ Tarea (mV.ms)	14(3.5-24.5)	13.8(9.1-20.1)	0.95	17(10.2-38.3)	13.8(9.3-24.8)	0.33	22.3(10.6-26.3)	14(7.6-19.8)	0.11
QT-interval (ms)	421(410-465)	448(411-478)	0.34	417(408-428)	444(397-469)	0.15	421(403-434)	454(403-478)	0.08
Δ QT-interval (ms)	43(17-92)	19(15-28)	0.05	50(12-131)	17(21-24)	0.12	60(14-112)	16(12-21)	0.02

Δ = range of variations- of the corresponding parameter, σ^2 = variance; Tamp = T-wave amplitude; Tarea = Area under the T-wave; data are presented as median (25%-75%) range.