QT Variability during Rest and Exercise in Patients with Implantable Cardioverter Defibrillators and Healthy Controls

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Background: Increased QT Variability (QTVI) is predictive of life threatening arrhythmias in vulnerable patients. The predictive value of QTVI is based on resting ECGs, and little is known about the effect of acute exercise on QTVI. The relation between QTVI and arrhythmic vulnerability markers such as T-wave alternans (TWA) has also not been studied. This study examined the effects of exercise on QTVI and TWA in patients with arrhythmic vulnerability.

Methods: Digitized ECGs were obtained from 47 ICD patients (43 males; age 60.9 ± 10.1) and 23 healthy controls (18 males; age 59.7 ± 9.5) during rest and bicycle exercise. QTVI was assessed using a previously validated algorithm and TWA was measured as both a continuous and a categorical variable based on a priori diagnostic criteria.

Results: QTVI increased with exercise in ICD patients (-0.79 ± 0.11 to 0.36 ± 0.08 , $P < 0.001$) and controls (-1.50 ± 0.07 to -0.19 ± 0.12 , $P < 0.001$), and QTVI levels were consistently higher in ICD patients than controls during rest and exercise ($P < 0.001$). The magnitude of QTVI increase from baseline levels was not larger among ICD patients versus controls ($P > 0.20$). Among ICD patients, elevated exercise QTVI was related to lower LV ejection fraction and inducibility of ischemia ($P < 0.05$). QTVI at rest correlated with exercise TWA ($r = 0.54$, $P = 0.0004$).

Conclusions: QT variability increases significantly with exercise, and exercise QTVI is related to other well-documented markers of arrhythmic vulnerability, including low ejection fraction, inducible ischemia, and TWA. Resting QTVI may be useful in the risk stratification of individuals incapable of performing standard exercise protocols.

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QT interval; repolarization; T-wave alternans; exercise; arrhythmia

INTRODUCTION

Instability in the repolarization phase of the action potential has received considerable attention as a manifestation of arrhythmic vulnerability in high-risk individuals.¹ Electrocardiographic variation in the amplitude of the T wave measured on an every-other-beat basis—T-wave alternans (TWA)—

has been recognized as a powerful sign of vulnerability to lethal arrhythmias, but is rarely present at rest. Therefore, TWA is typically measured during exercise or rapid atrial pacing.^{2,3} Variability in the QT interval (QTVI),⁴ which is not limited to variance at the alternans frequency, is associated with a significant increase in the incidence of ventricular tachycardia or fibrillation.⁵ It has been suggested

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that QTVI represents a lower order manifestation of myocardial vulnerability when compared to T-Wave alternans,¹ but this hypothesis has not been tested.

The role of QTVI as a marker of arrhythmic vulnerability has been evaluated at rest only, and exercise may increase the predictive power of QTVI. Furthermore, if QTVI represents a lower order form of the same phenomenon as TWA,¹ then QTVI should correlate with the magnitude of TWA during exercise. In the present study, we examined the effect of exercise on QTVI and TWA in patients with implanted cardioverter defibrillators (ICDs) and compared results with patients having coronary artery disease (CAD) (but without a history of arrhythmias) and healthy controls. This study examined the following hypotheses: (1) exercise results in increased magnitudes of QTVI; (2) ICD patients with documented risk for arrhythmias will manifest significantly greater QTVI at rest and larger QTVI increases with exercise; and (3) ICD patients with manifest TWA will have significantly higher QTVI levels.

METHODS

Patients

Patients (n = 47) with implantable cardioverter defibrillators (ICDs) and documented CAD were enrolled because of their known propensity for malignant arrhythmias (Table 1). Patients were recruited from three clinics (Arrhythmia Associates, Fairfax VA; the Veterans Affairs Medical Center, Washington DC; and St. Francis Hospital, Roslyn NY). Exclusion criteria were atrioventricular conduction defects, left bundle branch block, chronic atrial fibrillation, myocardial infarction (MI) <1 month, unstable angina, class IV congestive heart failure, critical valve pathology, primary cardiomyopathy, use of amiodarone, and age >80 years. For comparison purposes, age- and gender-matched healthy controls (n = 23) with <5% likelihood of CAD⁶ were examined using the same protocol.

To optimize electrocardiographic assessments, calcium antagonists and angiotensin-converting enzyme inhibitors were withheld for 24 hours, and

Table 1. Patient Characteristics

	Healthy Controls (n = 23)	ICD Patients (n = 47)
Age	59.7 ± 9.5	60.9 ± 10.1
Sex (male)	18 (78.3%)	43 (91.5%)
Race (Caucasian)	20 (87.0%)	41 (87.2%)
Presenting arrhythmia		
Resuscitated + inducible VT/VF		4 (8.5%)
VF/VT with syncope		15 (31.9%)
Symptomatic VT		14 (29.8%)
Asymptomatic VT		4 (8.5%)
VT on Holter monitoring		10 (11.7%)
Number of vessels diseased (n,%)*		
1vd	-	9 (19.1%)
2vd	-	15 (31.9%)
3vd	-	23 (48.9%)
Ejection fraction (%)*	-	34.3 ± 10.9
Prior coronary angioplasty	-	23 (48.9%)
Prior coronary bypass surgery	-	23 (48.9%)
History of myocardial infarction	-	40 (85.1%)
History of hypertension	-	32 (68.1%)
Diabetes mellitus	-	6 (12.7%)
Beta-adrenergic blocking agent		
Not prescribed	-	10 (21.3%)
Withheld	-	8 (17.0%)
Continued	-	29 (61.7%)

*LV ejection fraction evaluated in ICD patients only.

LV = left ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

long-acting nitrates for 6 hours.⁷ Beta-adrenergic blocking agents were withheld for > 48 hours in 8 patients, 10 patients did not receive beta blockade as part of their medical regimen, and 29 patients were tested without discontinuation of beta-adrenergic blockade. Patients tested while using beta blockade (n = 29) had similar QTVI at rest (P = 0.92) but higher QTVI at peak exercise (P = 0.008) as compared to patients tested without beta blockade (n = 18). Thus beta-adrenergic blockade did not suppress QTVI during rest and was associated with elevated QTVI during exercise. These data remained unchanged if the effects of beta-adrenergic blockade on heart rate were statistically adjusting for. The study was approved by the Institutional Review Boards of the participating study sites, all patients gave written informed consent, and institutional study guidelines were followed.

Protocol

Continuous digitized ECGs were obtained during rest, paced breathing, and bicycle exercise. High-resolution silver-silver chloride electrodes were used for noise reduction. Continuous ECGs were recorded and digitized at 1000 Hz with 16-bit resolution using the CH2000 (Cambridge Heart, Bedford, MA, USA) and were exported for blinded off-line QTVI analyses by a trained reader using a Pentium-based personal computer.

Before exercise, patients rested for 10 minutes and paced breathing (12 breath/min) for 2 minutes to examine potential biases related to inter-individual differences in breathing frequency on QTVI measures. Bicycle exercise was performed with increasing workloads of 25W in 3-min stages following the standard CH2000 protocol.³ Recovery measures were obtained for 4 min post exercise. Exercise tests were discontinued if patients reached 80% of predicted heart rate or if severe ST-segment depression, arrhythmias, angina, or fatigue occurred.

ECGs were monitored for ventricular arrhythmias and ischemia, defined as ≥ 1 mm horizontal or downsloping ST-segment depression. Systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were obtained at 90-second intervals during baseline and paced breathing, and at the end of each 3 min exercise stage (Dinamap, Critikon, Tampa, FL, USA).

Analysis of QTVI

QT Variability markers of repolarization stability were assessed blindly by measuring each QT and HR interval over equal epochs obtained from the lead with the best visualization of the QT interval (generally lead III).⁴ The QT variability index (QTVI) was derived as the log ratio of normalized QT variability to normalized HR variability (HRV). The algorithm applies a user-defined QT interval template to all the successive QT intervals. On subsequent beats, the QT template is stretched or compressed in time to match the new beat, and a new QT (as well as HR) value is derived. A power spectrum is then generated for HR and QT and the QT variability index ("QTVI") is calculated as: $\log ([QT \text{ total power}/\text{mean } QT^2]/[HR \text{ total power}/\text{mean } HR^2])$.^{4,5} We also provide the separate measures that are used to calculate QTVI (mean QT, standard deviation of QT, QTVI numerator, mean HR, SDNN, and QT denominator). Care was taken to exclude the beats preceding and following ectopy and all artifacts were removed prior to analyses. ECGs with less than 33% usable data were excluded from the analyses (4.7% of data).

The advantages of using QTVI include the presence of heart rate variability in the metric, the inclusion of the entire T wave, which makes the QTVI measure resistant to noise, and the assessment of repolarization variability beyond merely 1:2 changes as in TWA.^{1,5} Prior analyses from our laboratory indicates good reliability of QTVI (n = 90; r = 0.78; P < 0.001) when the same patients are measured on two consecutive days.

Analyses of TWA

TWA was measured using the Cambridge Heart software, and both the established clinical TWA diagnostic criteria (TWA-positive, TWA-negative, and indeterminate TWA), as well as continuous TWA scores were employed using software provided for research purposes by Cambridge Heart.^{2,3} Microvolt TWA levels were assessed over 128 consecutive complexes, and beat-to-beat fluctuations in electrocardiographic amplitude were represented as power spectra by calculating the squared magnitude of the fast Fourier transformation of beat-to-beat fluctuations in the amplitude of each sample point of the 128 time-aligned electrocardiographic complexes. The peak at 0.5 cycle per beat

reflects fluctuations in T-wave amplitude on every other beat; thus indicating electrical alternans, expressed as follows: TWA (microvolt) = $\sqrt{(\text{alternans peak} - \text{mean (noise)})}$. Mean noise equals the standard deviation of spectral noise estimated from a predefined noise window.³ Continuous TWA values were based on the lead with the maximum TWA value during exercise. TWA diagnosis (positive, negative, indeterminate) was based on review by two trained observers based on Cambridge Heart criteria and disagreements were settled by consensus.

Assessment of Myocardial Ischemia

To examine the potential role of exercise-induced ischemia, dual isotope single photon emission computed tomography (SPECT) was used to assess exercise-induced myocardial ischemia^{8,9} because of its suitability in patients with reduced left ventricular function.⁸⁻¹⁰ Thallium-201 (2.5–3.5 mCi) was injected at rest and SPECT images were obtained 10 min after isotope injection. Exercise sestamibi was injected at peak effort and patients continued exercise for one min following isotope injection. SPECT images were obtained at 45 minutes following the exercise test. Images were processed by a trained technologist, blinded to clinical information. Image analysis was performed with QPS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA), using a 20-segment, 5-point model (0 = normal, 1 = mildly reduced, 2 = moderately reduced uptake, 3 = severely reduced uptake and 4 = no uptake). Summed difference scores between stress and rest were used to determine stress-induced ischemia as absent (0–3), mild, moderate (4–6), or severe (≥ 7).^{8,10}

Statistical Analyses

Data are presented as mean $\pm$ standard deviation (s.d.) or percentages when appropriate. QTVI values are presented as mean $\pm$ standard error (s.e.). Stress-induced responses were examined using repeated measures analysis of variance (ANOVA) and paired *t*-tests (baseline vs exercise). Comparisons between ICD patients and controls were conducted using *t*-tests without pooling of variances across groups. Mixed model analysis of variance was used to examine group differences in response to exercise, with "groups" as a between subjects factor and "response" as a three-level within subjects fac-

tor (baseline, exercise stage 1, peak exercise). To assess differential responses in patients versus controls, the "groups $\times$ response" interaction term was evaluated. Associations of QTVI with ejection fraction, heart rate, and continuous TWA levels were calculated using product-moment correlation coefficients. Analysis of covariance was used to examine whether group differences remained significant when adjusting for covariates. Two-tailed probabilities at a P-level of <0.05 were used as cutoff for statistical significance.

RESULTS

Exercise-Induced Hemodynamic Responses

Patient characteristics are displayed in Table 1. Exercise induced significant increases in blood pressure and heart rate (P 's < 0.01). Exercise HR and BP levels were not different between ICD patients versus healthy controls ($P > 0.2$), whereas ICD patients had lower resting HR than controls ($P < 0.05$) (Table 2).

As shown in Table 2, exercise-induced ST-segment depression occurred in 5 ICD patients. Among ICD patients, exercise induced premature

Table 2. Exercise-Induced Changes in Heart Rate, Ischemia, and TWA

	Healthy Controls (n = 23)	ICD (n = 47)
Maximum heart rate	114.9 $\pm$ 15.5	112.4 $\pm$ 17.2
HR response from baseline	43.3 $\pm$ 17.1	47.3 $\pm$ 15.6
SBP response	46.4 $\pm$ 18.0	46.7 $\pm$ 18.6
DBP response	17.5 $\pm$ 15.2	17.1 $\pm$ 13.2
Maximum stage reached		
Stage 1	4 (17.4%)	8 (17.0%)
Stage 2	7 (30.4%)	20 (42.6%)
Stage 3	7 (30.4%)	17 (36.2%)
Stage ≥ 4	5 (21.7%)	2 (4.3%)
Ischemia		
ST depression	0 (0.0%)	5 (10.6%)
SPECT perfusion defect	-	23 (54.8%)
Arrhythmias	0 (0.0%)	7 (14.8%)
TWA negative	16 (69.6%)	15 (31.9%)
Indeterminate	7 (30.4%)	20 (42.6%)
Positive	1 (0.0%)	12 (25.5%)

Arrhythmias: premature ventricular complexes (PVC) were not included.
SPECT analyses were not obtained in healthy controls and 5 ICD patients.

ventricular complexes ($n = 22$), couplets ($n = 5$), supraventricular tachycardia ($n = 1$), atrial fibrillation ($n = 1$), and bigeminy ($n = 1$). At peak exercise, 34 (72.3%) patients achieved heart rates >105 beats/min (required for evaluation of exercise-induced TWA), and 14 (29.8%) patients reached 80% of age-predicted heart rate. The primary reasons for discontinuations of exercise were fatigue and lower extremity discomfort during bicycle exercise.

QTVI Responses in ICD Patients versus Controls

Among ICD patients, QTVI increased significantly from baseline (-0.79 ± 0.11) to exercise (stage I exercise: -0.08 ± 0.11 , $P < 0.001$; maximum exercise 0.36 ± 0.08 , $P < 0.001$). Figure 1 shows that QTVI levels were consistently higher in ICD patients than controls (P 's < 0.002). ICD patients had also greater QTVI levels than healthy controls when potential artifacts of breathing were controlled for by holding respiration rate constant (-0.61 ± 0.13 vs -1.31 ± 0.08 ; $P = 0.00002$). Resting QTVI levels displayed a moderate correlation with QTVI levels during exercise ($r = 0.43$, $P = 0.002$). Although the levels of QTVI were consistently elevated in ICD patients versus controls, the magnitude of QTVI responses from baseline to exercise was not larger in ICD patients than controls (P -values > 0.20).

Figure 1. QTVI levels during exercise and recovery in ICD patients with CAD (triangles) and healthy controls (open circles). QTVI levels are consistently higher in ICD patients than controls ($P < 0.002$).

Resting QTVI levels were associated with resting heart rate ($r = 0.30$, $P = 0.047$), whereas QTVI levels during exercise were not associated with exercise-induced HR levels ($r = 0.09$, $P = 0.53$) or HR responses from baseline ($r = 0.08$, $P = 0.59$). Thus, group differences in QTVI are not likely to reflect differences in HR.

Table 3 displays the differences between ICD patients and controls on QTV components. ICD patients displayed significantly elevated ($P = 0.007$) QT numerator levels (i.e., QTV unadjusted for HR power). A similar pattern was observed during peak exercise. Exercise induced a steeper increase in the QTV numerator and a stronger reduction in mean QT among ICD patients versus controls (Table 3). However, the increase in QT numerator was not paralleled by a steeper exercise-induced increase in QTVI among ICD patients versus controls. In general, exercise-induced increases in QTVI were explained by increases in the QTV numerator, and not by changes in the heart rate-based QTV denominator.

Effects of Left Ventricular Function and Stress-Induced Ischemia in ICD Patients

Left ventricular ejection fraction was inversely related to QTVI during exercise, whereas left ventricular ejection fraction (LVEF) was not related to resting QTVI (Fig. 2). The associations between low LVEF with higher QTVI levels during exercise remained significant (P 's < 0.01) when adjusting for age.

Myocardial ischemia measured by SPECT scans occurred in 23/42 (54.8%) ICD patients during exercise (scans for 5 patients were not analyzable). Patients with exercise-induced ischemia exhibited higher QTVI levels during exercise than patients without ischemia (0.50 ± 0.10 vs 0.16 ± 0.12 , $P = 0.031$). Within ICD patients who displayed ischemia, no significant associations were found between the number of myocardial segments with exercise-induced perfusion abnormalities and QTVI during exercise ($r = 0.12$, $P = 0.59$). Statistical adjustments for heart rate did not attenuate the association between exercise-induced ischemia and QTVI (adjusted $P = 0.032$).

Relationship to Inducibility of T-Wave Alternans

Analyses of continuous TWA levels revealed that resting QTVI levels were significantly predictive of

Table 3. QT Variability Parameters during Baseline and Peak Exercise

	Healthy Controls (n = 23)	ICD (n = 47)
Baseline		
QT mean (ms)	427.87 ± 14.33	499.20 ± 11.23***
QTVI numerator	0.07 ± 0.02	0.29 ± 0.08)*
HR (bpm)	71.63 ± 1.98	64.42 ± 1.47**
SDNN (ms)	35.78 ± 3.27	45.22 ± 4.69
QTVI denominator	1.60 ± 0.23	1.86 ± 0.35
QTVI	-1.50 ± 0.07	-0.79 ± 0.11***
Exercise (max)		
QT mean (ms)	390.15 ± 12.94)	420.03 ± 11.71
QTVI numerator	0.36 ± 0.05)	0.91 ± 0.14**
HR (bpm)	114.95 ± 3.22	112.41 ± 2.51
SDNN (ms)	35.35 ± 4.40	28.12 ± 3.28
QTVI denominator	1.74 ± 0.23	1.32 ± 0.26
QTVI	-0.19 ± 0.12	0.36 ± 0.08***
Exercise response from baseline		
QT mean (ms)	-37.73 ± 5.46†	-78.07 ± 9.65**†
QTVI numerator	0.29 ± 0.05†	0.62 ± 0.12*†
HR (bpm)	43.32 ± 3.57†	47.27 ± 2.33†
SDNN (ms)	-0.42 ± 4.83	-15.83 ± 5.54*†
QTVI denominator	0.14 ± 0.25	-0.47 ± 0.43
QTVI	1.31 ± 0.15†	1.15 ± 0.10†

SDNN = standard deviation of NN intervals.

*P < 0.05; **P < 0.01; ***P < 0.005 compared to healthy controls.

†Significant response from baseline.

TWA levels during exercise ($r = 0.54$; $P = 0.0004$; Fig. 3). No cross-sectional relationships were found for QTVI levels at rest with resting TWA levels ($r = -0.06$; $P = 0.73$). Similarly, associations between continuous QTVI and TWA levels during

exercise were not significant ($r = 0.09$; $P = 0.058$). These data suggest that resting QTVI may identify patients at risk of TWA during exercise testing, but that different physiological processes may drive QTVI and TWA during exercise.

Figure 2. Relationship between left ventricular ejection fraction (EF) and QTVI during rest, stage 1 exercise and peak exercise in ICD patients.

Figure 3. QTVI at rest as predictor of T-wave alternans (TWA) during exercise in ICD patients. Resting QTVI levels were significantly related to TWA during subsequent exercise stress testing ($P = 0.0004$).

Inducible TWA as per a priori diagnostic criteria was documented in 10 (21.2%) ICD patients, whereas one healthy control had a positive TWA response ($P = 0.002$). As shown in Figure 4, ICD patients with a positive TWA response had elevated QTVI during rest ($P = 0.081$) and peak exercise ($P = 0.014$) as compared to patients with a negative TWA response. The subgroup of ICD patients

Figure 4. Inducibility of T-wave alternans (TWA) as related to QTVI. ICD patients with inducible TWA ($n = 10$; 21.2%) have elevated QTVI at rest ($P = 0.081$) and during peak exercise ($P = 0.014$) as compared to patients with a negative TWA response ($n = 16$; 34.0%).

with indeterminate TWA responses (42.6%) did not sustain the target heart rate of >105 bpm for >1 minute to optimally assess TWA. QTVI levels for patients with an indeterminate TWA response were higher than TWA-negative patients and lower than TWA-positive patients, but these differences were not statistically significant (P 's > 0.1).

Heart rate and inducible ischemia may be important confounding factors in the relationship between TWA and QTVI. However, no differences in TWA-positive versus TWA-negative patients were found in baseline HR (66.9 ± 9.9 vs 66.2 ± 8.1 bpm) or peak exercise HR (112.6 ± 12.8 vs 119.7 ± 15.9). Patients with TWA had lower LVEF (27.9 ± 6.6 vs $35.3 \pm 12.2\%$, $P = 0.088$) and tended to be older (60.6 ± 10.2 vs 54.3 ± 9.1 yrs, $P = 0.068$). The significance of the difference between TWA-positive versus TWA-negative patients in QTVI at rest and during exercise remained unchanged when adjusting for HR at baseline, HR responses to exercise, age, and LVEF (P 's 0.06 and 0.025, respectively).

DISCUSSION

The principal finding of this study is that QT variability is significantly greater at rest in ICD patients with arrhythmic vulnerability than healthy controls. QTVI increases significantly with exercise, but exercise does not disproportionately increase QTVI among patients with arrhythmic vulnerability. QTVI is indexed for changes in the heart rate variability, and when QT variability was evaluated without correcting for heart rate variability (QT numerator), elevated responses in ICD patients versus controls were found. We further document that resting QTVI levels were predictive of T-Wave alternans during exercise. QTVI during resting conditions may therefore be a useful indicator of arrhythmic vulnerability, and variability of the QT interval, unadjusted for changes in heart period variability, may be a useful indicator of arrhythmic vulnerability in patients who are not able to complete a sub-maximal exercise test.

Effect of Exercise on QTVI

QTVI increased in all three groups with exercise. Patient with manifested exercise-induced ischemia also displayed significantly greater QTVI than those without ischemia, suggesting that the induction of ischemia with exercise may influence the prognostic utility of QTVI. While the presence

of inducible ischemia predicts an increased risk of cardiovascular death, the significance of exercise-induced ischemia in predicting arrhythmic death is uncertain as ST segment depression rarely occurs prior to VT/VF.¹¹ These observations are consistent with the present study where only 11% patients displayed ST-segment depression compared with 54% with perfusion defects. The present observation that ischemia is associated with elevated QTVI measures extends prior observations that acute MI is associated with increased repolarization variability.¹²

The exercise-induced increase in heart rate may interfere with the diagnostic utility of the QTVI. Ventricular repolarization as well as heart rate are strongly influenced by sympathovagal balance.¹³ The present study demonstrates, however, that HR is not a likely confounding factor when examining exercise-induced QTVI. The QTVI represents a log ratio of normalized QT variability to heart rate variability normalized to the mean heart rate. An increase in heart rate, then, would tend to increase the QTVI even if QT and heart rate variability were unchanged. A reduction in heart rate variability (SDNN), expected during exercise when autonomic tone favors sympathetic over parasympathetic effects, would further increase the QTVI irrespective of the QT variability. In this study, the normalized QT variability (QTVN) increased with exercise in all groups but less significantly than the QTVI. This effect may partially reflect the fact that the QTVN is normalized to the square of the mean QT. Other groups have used a simplified measure of QT variability, i.e. the ratio of the standard deviation of the QT over the standard deviation of the RR interval, and found a strong association with mortality.¹⁴ The present data show that although heart rate at rest is moderately associated with QTVI, the exercise-induced QTVI increases are not related to increases in HR with exercise.

Markers of Myocardial Vulnerability

The MADIT II¹⁵ and SCD-hEFT¹⁶ studies have demonstrated that reduced ejection fraction, a marker of abnormal myocardial substrate, has significant prognostic value in identifying patients who will develop VT/VF, and poor LV ejection fraction also predicts therapeutic efficacy following prophylactic ICD implantation. Nevertheless, the majority of participants in these trials never developed VT/VF during follow-up, and additional non-

invasive strategies to better identify those at highest and lowest risk for arrhythmic events are desirable. The present study shows that ejection fraction is inversely related to both QTVI and TWA during exercise, which is consistent with recent observations in heart failure patients.¹⁷ Thus, these ECG-derived measures may serve as additional noninvasive metrics to assess the presence of arrhythmic vulnerability during exercise. Unique to QTVI is that assessments obtained during resting conditions are of prognostic value and that exercise or other perturbations are not needed for QTVI-based risk stratification for arrhythmic vulnerability.

Relation between QTVI and TWA

The present data suggest that QTVI and TWA may be independent risk indicators for arrhythmic vulnerability. Atiga et al. reported that elevated QTVI identified sudden death survivors more accurately than TWA,¹⁸ whereas Hohnloser and Cohen came to the opposite conclusion, documenting that TWA was a better predictor of ICD-treated VT/VF than QTVI.¹⁹ Zareba has suggested that these measures may be examining similar phenomena but different degrees of severity.¹ This would suggest that individuals with moderate vulnerability will manifest increased QT variability, but as their phenotype worsens as a consequence of adverse remodeling and progression of disease, T-Wave alternans may develop. When resting measures are considered this is undoubtedly true, because some degree of QT variability at rest is physiological,^{1,4} whereas only those at highest risk for imminent VT/VF have TWA at rest.^{19,20} However, in patients at moderate to high risk, exercise is required to elicit even microvolt levels of TWA. The relationship between these measures during exercise has not been previously analyzed. In this study we examined whether QTVI and TWA are correlated and the extent to which these indices measure the same phenomenon. The absence of substantial correlations of simultaneously measured QTVI and TWA measures suggests that in fact they are not duplicative measures. Thus, QTVI and TWA may offer complementary information regarding the presence of myocardial vulnerability to arrhythmia. From a mechanistic viewpoint this seems reasonable, as it appears TWA reflects beat to beat variation in calcium handling dynamics resulting in alternating amplitude of the plateau phase of the action potential.²¹ QT variability, on the other

hand (as measured in the method previously validated by Berger and colleagues⁴), appears to reflect beat to beat changes in the terminal phase of repolarization of the cells with the longest action potentials, found in the mid-myocardial cell layer.^{22,23} Furthermore, QTVI measures variance in repolarization occurring at frequencies in addition to the alternans frequency of 0.5 Hz. A recent study found that episodes of ventricular tachycardia recorded on Holter monitors were preceded by an increase in T wave variability at both the alternans and other frequencies.²⁴ The electrophysiological source of this variation still requires systematic investigation. Finally, this study suggests that resting QTVI levels are predictive of TWA during exercise.

Study Limitations

This study compared ICD patients with known arrhythmic vulnerability to healthy controls. Associations with clinical events were not examined because we aimed to examine changes in QTVI with exercise, and whether these exercise-induced QTVI responses were related to other known markers of arrhythmic vulnerability, such as TWA, poor ejection fraction, and myocardial ischemia. The present data indicate that resting QTVI measures are less influenced by clinical variables compared with exercise-induced QTVI. Prognostic studies examining ECG-derived arrhythmic vulnerability markers therefore need to control for these important confounding factors.

A second limitation of this study is that only 30% of ICD patients reached 80% of their age-based target heart rate. This could have attenuated our ability to detect maximal QTVI measures and inducibility of TWA. Fatigue was the main reason for discontinuation of the exercise protocol, and future studies may benefit from adding a pharmacological challenge test, to ensure consistent increases in cardiac demand. Additionally, we did not withhold beta-adrenergic blocking agents for all patients (62% were tested on medication), and this may have reduced both the ability of subjects to achieve their target heart rates as well as decreased the impact of exercise on QT variability.

Clinical Implications

We provisionally conclude that resting levels of QTVI may be better suited to assessing arrhythmic

risk than QTVI with exercise because exercise-based QTVI measures are related to a range of clinical parameters such as poor LV function and inducibility of ischemia. Resting QTVI is not substantially affected by clinical parameters and is significantly elevated in ICD patients as compared to healthy controls. Further research is needed to document the utility of QTVI responses in settings with modest heart rate increases such as during mental stress or pharmacological challenges. Finally, we found that QTVI was significantly elevated in subjects who manifested significant TWA when assessed as a dichotomous variable, and that while resting QTVI was strongly correlated with exercise TWA (when measured as a continuous variable), exercise QTVI did not correlate with exercise TWA. Since many subjects fail to reach or maintain criterion heart rates for measurement of TWA, QTVI may prove to be a useful adjunct for risk stratification of those with "indeterminate" TWA studies. Future investigations will determine whether combining these measures into a composite vulnerability index will enhance the ability for clinicians to correctly identify those at highest and lowest risk of life threatening arrhythmic events.

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