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Heart Rhythm Disturbances

QT Interval Variability and Spontaneous Ventricular Tachycardia or Fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Patients

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OBJECTIVES This study aimed to determine whether increased QT interval variability is associated with an increased risk for ventricular tachycardia (VT) or ventricular fibrillation (VF), documented by interrogation of the implantable cardioverter-defibrillator (ICD), in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II.

BACKGROUND Unstable repolarization has been proposed as a risk factor for re-entrant arrhythmias, but confirmatory data from clinical trials are lacking.

METHODS The QT variability was assessed in 10-min, resting high-resolution electrocardiogram recordings at study entry using a semiautomated algorithm that measured beat-to-beat QT duration in 817 MADIT II patients. The incidence of VT/VF requiring device therapy was determined by ICD interrogation.

RESULTS Median normalized QT variability (QTVN) was 0.179 and 0.125, respectively, in patients with VT/VF versus those without VT/VF ($p = 0.001$); QTVI (QTVN adjusted for heart rate variance) also was significantly ($p < 0.05$) higher in VT/VF patients than in those without VT/VF. Either QTVN or QTVI was linked with a significantly higher probability of VT/VF: two-year risk of VT/VF from Kaplan-Meier curves was 40% in highest quartile versus 21% in lower quartiles for QTVN, and 37% versus 22% for QTVI ($p < 0.05$ for each). In multivariate Cox regression models adjusting for clinical covariates (race, New York Heart Association functional class, time after myocardial infarction), top-quartile QTVI and QTVN were independently associated with VT/VF (hazard ratio for QTVN 2.18, 95% confidence interval [CI] 1.34 to 3.55, $p = 0.002$; hazard ratio for QTVI 1.80, 95% CI 1.09 to 2.95, $p = 0.021$).

CONCLUSIONS In postinfarction patients with severe left ventricular dysfunction, increased QT variability, a marker of repolarization lability, is associated with an increased risk for VT/VF. (J Am Coll Cardiol 2004;44:1481–7) © 2004 by the American College of Cardiology Foundation

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) II demonstrated that prophylactic defibrillator implantation in patients with a prior myocardial infarction and an ejection fraction of ≤0.30 reduced the risk of death from 19.8% to 14.2% at 20 months (1). Conventional risk stratification failed to predict which patients would experience ventricular tachycardia (VT) or ventricular fibrillation (VF) necessitating either an implantable cardioverter-defibrillator (ICD) shock or antitachycardia pacing. In the Multicenter Unsustained Tachycardia Trial (MUSTT) registry, subjects with a negative electrophysiologic study experienced an unacceptably high rate of arrhythmic death or cardiac arrest (24% at 5 years) (2). Moreover, inducibility at electrophysiologic study did not predict subsequent mortality, arrhythmia recurrence, or arrhythmic death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (3). The failure of conventional approaches to arrhythmia prediction may reflect a limited understanding of the mechanism of VT/VF in post-infarction patients with significant left ventricular dysfunction.

Unstable ventricular repolarization may contribute to the development of VT/VF (4,5). The induction of T-wave alternans by atrial pacing or exercise has been found to predict subsequent spontaneous or inducible ventricular arrhythmias in several small (6–8) and two large studies (9,10). While T-wave alternans is rarely found in the absence of pacing or exercise-induced tachycardia, resting patients with dilated cardiomyopathy (11) or congenital long QT syndromes manifest increased beat-to-beat variability in the QT interval duration (12). Atiga et al. (13) studied 95 patients undergoing electrophysiologic study and

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Abbreviations and Acronyms

CI = confidence interval
HRv = heart rate variance
ICD = implantable cardioverter-defibrillator
MADIT = Multicenter Automatic Defibrillator Implantation Trial
QTVI = QT variability index
QTVN = QT variability (numerator)
VF = ventricular fibrillation
VT = ventricular tachycardia

compared both invasive and noninvasive indexes of arrhythmic risk, including T-wave alternans ratio during atrial pacing. In a stepwise multiple logistic regression, the presence of increased QT variability was the only variable associated with sudden death.

To further investigate the relation between repolarization lability and spontaneous VT/VF, we measured QT variability at rest in the MADIT II population. In this prospectively designed MADIT II substudy, we hypothesized that increased QT variability would be independently associated with subsequent VT/VF requiring therapy from the ICD.

METHODS

Patient population and data acquisition. The study population was derived from the 1,232 patients in the MADIT II study population. Each patient had a history of myocardial infarction and an ejection fraction of 0.30 or less (1). As part of MADIT II enrollment, patients underwent resting Holter monitoring for 10 min, using a high-resolution digital recording system (3 orthogonal leads, 1,000-Hz sampling frequency, 12-bit resolution, SpaceLab-Burdick 6632 recorder, Spacelab-Burdick, Milton, Wisconsin). The recording electrodes were standard silver-silver chloride conductors (Blue Sensor, Linthicum, Maryland) arrayed in an XYZ configuration (i.e., lead X corresponding to limb lead I, lead Y to aVF, and lead Z roughly to V_3, with the positive electrode anterior and negative pole posterior at the tip of the right scapula). This short recording period, considered adequate for measurements of heart rate variability (14) was chosen due to the practical limitations of acquiring more prolonged high-quality electrocardiogram (ECG) in such a large population. Patients were excluded if their ECG demonstrated rhythm other than sinus; bundle branch block was not an exclusion criterion. All subjects gave informed, written consent at entry, and the institutional review board at each hospital approved the study.

QT variability algorithm. We applied the QT variability algorithm described by Berger et al. (11), provided courtesy of Ronald Berger and Barry Fetics, Johns Hopkins University. Briefly, the analysis was performed offline, the operator selecting the ECG lead with the least noise and the most consistent T-wave morphology. The operator chose the X lead in 30% of subjects, the Y lead in 26%, and the Z lead in 44%. For each patient, the operator defined a template QRST configuration and a reference QT interval by selecting the beginning of the QRS complex and the end of the repolarization complex for one representative beat. A programmable blanking period removed the QRS complex. The algorithm then applied the template to each subsequent beat, and a QT interval was derived for that beat based on a "best-fit" for the entire T-wave. All deflections that might

Table 1. Clinical Characteristics of MADIT II Patients With QTVI Dichotomized at 75th Percentile (the Highest Quartile Versus Three Lower Quartiles)

	QTVI ≤75th Percentile (n = 613)	QTVI >75th Percentile (n = 204)	p Value
Clinical variables			
Mean age (yrs)	63	62	
Females	16%	24%	0.008
Diabetes	31%	48%	< 0.001
CHF NYHA functional class II–IV	59%	71%	0.002
Median time from MI until enrollment (months)	54	47	
Hypertension requiring treatment	51%	60%	0.030
Ejection fraction	23.3%	22.7%	0.182
Coronary bypass surgery	56%	58%	
Blood urea nitrogen (mg/dl)	21	25	0.012
Inducible at electrophysiologic study	39%	30%	
Mean heart rate (beats/min)	70	78	< 0.001
Left bundle branch block	16%	18%	
Medications			
Beta-blockers (baseline)	65%	66%	
Digitalis (baseline)	52%	67%	< 0.001
Ace inhibitor (baseline)	78%	77%	
Diuretic (baseline)	71%	79%	0.019
Lipid-lowering (baseline)	69%	68%	

Only p values <0.05 are shown, all other p values were nonsignificant.
CHF = congestive heart failure; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NYHA = New York Heart Association; QTVI = QT variability index.

Table 2. Clinical Variables Significantly Associated With High-Risk Quartile of QTVI in the Multivariate Logistic Regression Model

	Hazard Ratio*	95% CI	p Value
NYHA functional class ≥II	1.51	1.05–2.15	0.025
Diabetes	1.70	1.21–2.39	0.002
BUN >25	1.62	1.13–2.31	0.009
Digitalis	1.67	1.18–2.35	0.004

*Odds of appearing in the high-risk (highest) quartile of QTVI if the characteristic is present.

BUN = blood urea nitrogen; CI = confidence interval; NYHA = New York Heart Association; QTVI = QT variability index.

relate to repolarization were included in the template; the end of repolarization was determined by the final return to the isoelectric baseline. The U waves did not have a disproportionate effect on the QT interval determination because they were of low amplitude and had less influence than the T-wave on the sum of squared differences. Because of the blanking period, the algorithm excluded variability in QRS morphology as a source of measured QT variability.

Because QT variability in normal subjects is driven to a large degree by heart rate variability, in one analysis we used a metric incorporating assessment of heart rate variability (11). A heart rate time series was constructed from the sequence of RR intervals. The heart rate mean (HRm) and heart rate variance (HRv) and QT interval mean (QTm) and QT interval variance (QTv) were computed from the respective time series. A normalized QT variability index (QTVI) was then derived according to the equation: $QTVI = \log_{10} [(QTv/QTm^2)/(HRv/HRm^2)]$.

The QTVI, therefore, is the log ratio between the QT interval and heart rate variability, each normalized by the squared mean of the respective time series. In order to index the extent of repolarization lability without adjustment for heart rate variability, we also calculated the QT variance normalized for the mean QT (QTVN) as: $QTVN = QTv/QTm^2$. The digitized ECG recordings were analyzed by a single physician (P.J.G.), who was blinded to the treatment allocation and outcomes of the subject. Because the measure is semiautomated, selection of the QT interval is the only significant source of interobserver variability. We had two independent operators analyze 50 records randomly selected from the MADIT II database. The correlation between the results was extremely good for both QTVI (r = 0.983) and QTVN (r = 0.976).

Determination of clinical end points. The occurrence of VT or VF requiring defibrillator therapy (either antitachycardia pacing or defibrillator shock) was determined by periodic interrogation of the implanted device as determined by the trial protocol. The results of these device interrogations were reviewed by the MADIT II Data Coordinating Center, which determined the appropriateness of therapy. The appropriate therapy for VT/VF was the end point in patients randomized to ICD therapy, and all-cause mortality was the end point in patients randomized to conventional therapy.

Statistical analysis. We prespecified a high-risk subgroup of studied patients by identifying individuals in the highest quartile (>75th percentile) of distribution of QTVI and QTVN values. Dichotomized variables were compared by chi-square test, while *t* test was used for continuous variables that were normally distributed; the Wilcoxon rank-sum test was used for nonnormally distributed variables. Kaplan-Meier curves with log-transformed data were used to address our primary hypothesis testing the association between increased QT variability and probability of first appropriate defibrillator therapy for VT or VF in patients randomized to ICD therapy. The association between QT variability and end points was next tested with the Cox proportional-hazards regression model after stratification based on enrolling center, using a center-pooling algorithm. Similar analyses were performed for testing the association between QT variability and all-cause mortality in patients randomized to the conventional arm and in those randomized to ICD therapy.

RESULTS

Of 1,232 subjects in the trial, 310 Holter records were initially excluded by the core laboratory at University of Rochester; 111 were paced, 98 were in atrial fibrillation, 76 were uninterpretable due to noise, and the remainder (n = 35) had no recording performed. Of the remaining records (n = 912), 95 were excluded due to atrial fibrillation/flutter (n = 64), ventricularly paced rhythm (n = 2), excess noise (n = 8), high-degree heart block (n = 2), or ectopy, which the data-processing algorithm could not distinguish from sinus rhythm (n = 19). Of 817 subjects who were successfully analyzed, 476 (58%) were randomized to defibrillator implantation, and 341 (42%) to conventional therapy with-

Table 3. Comparison of Studied Electrocardiogram Parameters in Subjects With and Without Appropriate ICD Therapy for VT/VF

	No VT/VF (n = 359)		VT/VF (n = 104)		
	Mean ± SD	Median (25th; 75th percentile)	Mean	Median (25th; 75th Percentile)	p Value
HR	70 ± 14	69 (59; 80)	71 ± 13	71 (64; 80)	0.276
SDNN	42 ± 35	31 (20; 49)	41 ± 31	35 (19; 50)	0.620
QTVI	−0.94 ± 0.60	−0.97 (−1.37; −0.55)	−0.80 ± 0.56	−0.85 (−1.24; −0.36)	0.037
QTVN	0.25 ± 0.56	0.13 (0.06; 0.23)	0.39 ± 0.59	0.18 (0.08; 0.38)	0.001

HR = heart rate; ICD = implantable cardioverter defibrillator; QTVI = QT variability index; QTVN = QT variability; SDNN = standard deviation of normal RR intervals; VF = ventricular fibrillation; VT = ventricular tachycardia.

out defibrillator. The univariate comparisons of important clinical variables between the highest quartile for QTVI and the remaining three quartiles in these 817 subjects are summarized in Table 1. In a multivariate logistic regression (Table 2), patients with increased QT variability (the highest quartile) manifested evidence of more severe disease with more frequent New York Heart Association functional class ≥II, higher blood urea nitrogen levels, more frequent diabetes, and more frequent digoxin use.

QT variability and ICD therapy. Of 742 subjects randomized to defibrillator implantation in the trial, 476 had digital ECG recordings that were successfully analyzed. Defibrillator interrogations were not available for 13 subjects. The mean QTVI was significantly higher in the 104 subjects subsequently requiring an appropriate therapy for VT/VF during a mean 21 ± 12 month follow-up, consistent with a higher degree of instability in repolarization (Table 3). Interestingly, the normalized HRv was not different between those who experienced VT/VF and those 359 who did not, suggesting that the difference in the QTVI was driven by an increase in the unadjusted QT variability, QTVN. Indeed, mean and median QTVN were significantly higher in the VT/VF group compared with those who did not experience VT/VF.

Of the subjects in the highest quartile for QTVI (>−0.52 log units), 37% experienced an episode of VT/VF by two years, compared with 22% in the lower three quartiles. The time until first appropriate therapy for VT/VF was significantly shorter in the top quartile for QTVI (p = 0.01) (Fig. 1, top panel). Even greater separation in the Kaplan-Meier curves is found when comparing the time until first therapy between the highest quartile for QTVN versus the lower quartiles (>0.257 U, p = 0.001) (Fig. 1, bottom panel). Although most of the arrhythmic events in these subjects represented VT, those in the top quartile for QTVN were also more likely to experience VF compared with those in the lower quartiles (p = 0.046 by Kaplan-Meier analysis). In the multivariate Cox proportional-hazards regression model, a QTVI >−0.52 log units was an independent risk factor for VT/VF, with a hazard ratio of 1.80 (95% confidence interval [CI] 1.09 to 2.95, p = 0.021) after adjusting for relevant and significant clinical covariates (race, New York Heart Association functional class, time after myocardial infarction); QTVN was a somewhat stronger predictor using the same model, with a hazard ratio for VT/VF of 2.18 (95% CI 1.34 to 3.55, p = 0.002). Table 4 shows results of additional Cox analysis after adjustment for clinical factors differentiating patients with higher and lower levels of QTVN. Again, QTVN was significantly associated with VT/VF during a long-term follow-up. Finally, neither ejection fraction (dichotomized at > or <25%; hazard ratio 1.12, 95% CI 0.79 to 1.57, p = 0.53) nor inducibility of VT/VF during programmed ventricular stimulation (hazard ratio 1.26, 95% CI 0.86 to 1.86, p = 0.24) was a significant predictor of spontaneous VT/VF resulting in ICD therapy.

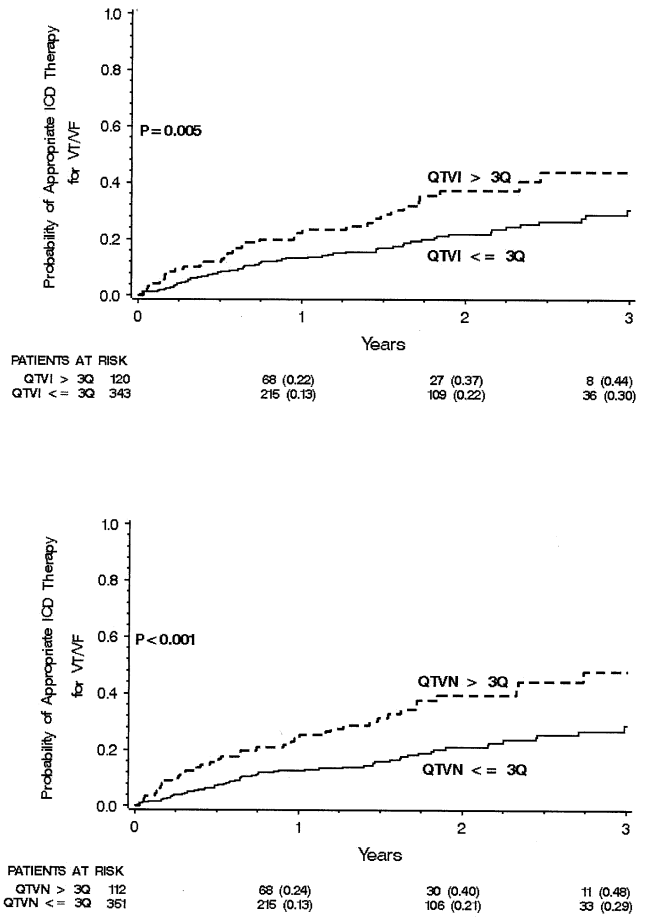

Figure 1. Cumulative probability of first appropriate defibrillator therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with QT variability (QTVN) in the highest quartile versus lower three quartiles for QT variability index (QTVI) **(top panel)** and QTVN **(bottom panel)**. P value from log-rank statistics. ICD = implantable cardioverter defibrillator.

Because the identification of the high-risk subset was prespecified before the data analysis, we also tested whether distribution of QTVN by quartile might influence the results. As shown in Figure 2, patients with QTVN in the lower three quartiles were at very similar risk of VT/VF, significantly lower than patients with QTVN in the high-risk quartile.

Table 4. High-Risk Quartile of QTVN in the Multivariate Cox Model Predicting Appropriate Therapy for VT/VF After Adjustment for Relevant Clinical Covariates*

	Hazard Ratio	95% CI	p Value
NYHA functional class ≥II	1.28	0.77–2.16	0.339
Diabetes	0.61	0.37–0.99	0.049
BUN >25	1.48	0.88–2.51	0.140
Digitalis	1.07	0.66–1.75	0.785
QTVN (HRQ)	2.20	1.36–3.56	0.001

*Clinical covariates that were significantly different in patients with QT variability (QTVN) in the high-risk quartile (HRQ) than those having lower QTVN values were forced in the model.

Abbreviations as in Tables 2 and 3.

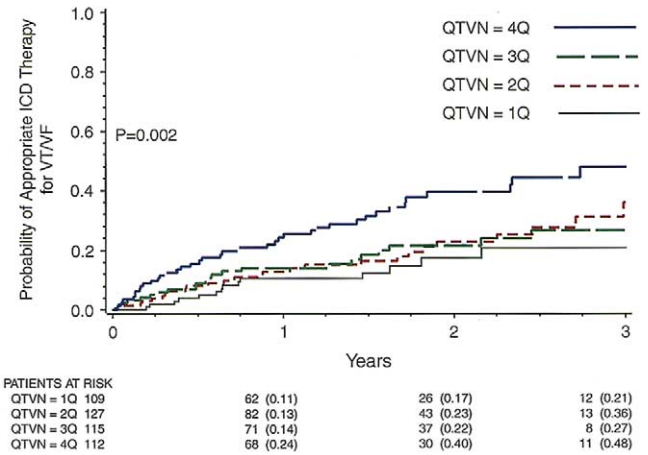

Figure 2. Cumulative probability of first appropriate defibrillator therapy for ventricular tachycardia or fibrillation in patients with QT variability (QTVN) by quartile of QTVN. P value from log-rank statistics. ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Subjects with bundle branch block were not excluded from this analysis. Because such individuals may be at higher risk for arrhythmia, we reanalyzed the time until first episode of VT/VF after removing all individuals with QRS >120 ms. The remaining subjects in the top quartile for QTVN experienced VT/VF significantly sooner than those in the lower quartiles (p = 0.001) (Fig. 3).

Survival in the conventional and defibrillator arms. Adequate digital ECG recordings were available in 341 subjects randomized to conventional therapy. There was no difference in the survival of subjects in the highest quartile and the lower quartiles for either QTVI or QTVN. There was a trend towards an increase in presumed arrhythmic mortality in the highest quartile for QTVN (13% vs. 8.5%, p = 0.23); the total number of events, however, was low (n = 32).

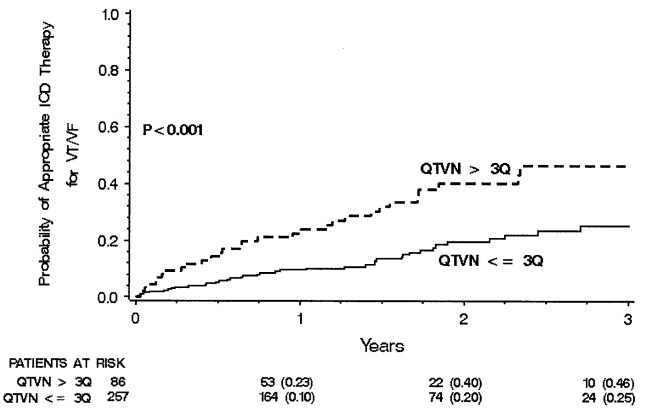

Figure 3. Cumulative probability of first appropriate defibrillator therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients without bundle branch block with QT variability (QTVN) in the highest quartile versus lower three quartiles. P value from log-rank statistics. ICD = implantable cardioverter defibrillator.

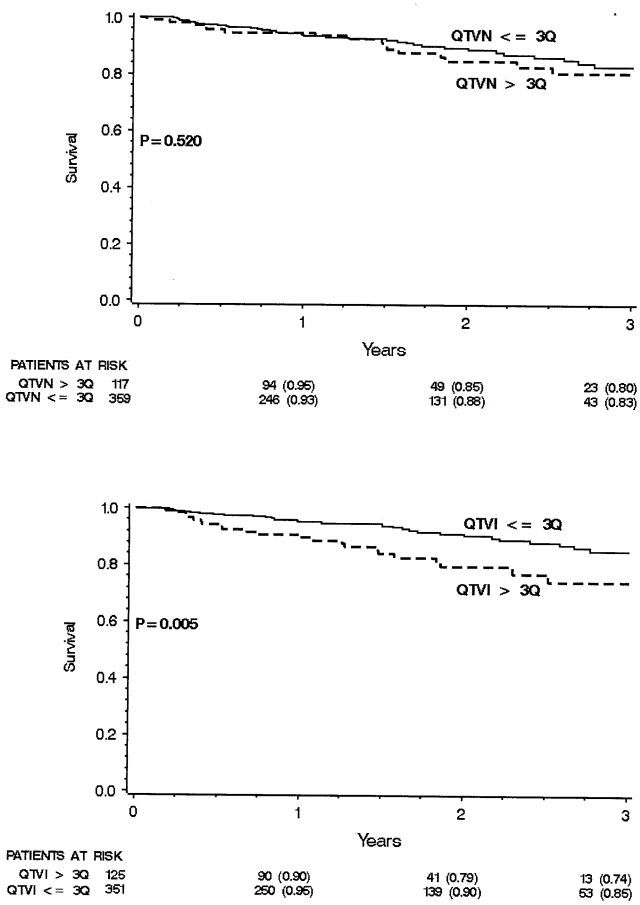

Figure 4. Cumulative probability of survival in patients randomized to defibrillator implantation with QT variability (QTVN) in the highest quartile versus lower three quartiles for QT variability index (QTVI) **(top panel)** and QTVN **(bottom panel)**. P value from log-rank statistics.

Within the defibrillator arm of the study, the survival in the highest quartile for QTVN did not differ from the lower quartiles (Fig. 4, top panel). However, the subjects in the highest quartile for QTVI demonstrated a significantly higher incidence of death compared with the other quartiles (Fig. 4, bottom panel). The increased deaths in this group were predominately due to cardiac causes that were not associated with sudden demise (19 of 109 vs. 9 of 330 for the combined lower quartiles, $p < 0.02$ by chi-square). The top quartile for QTVN was not associated with an increase in nonsudden cardiac deaths (5 of 105 vs. 13 of 334, p = 0.70). These findings suggest that HRv, the denominator in the QTVI formula, is responsible for the association between QTVI and mortality in ICD patients; QTVN, which is not adjusted for HRv, appears to be more specific for arrhythmic events.

DISCUSSION

The principle findings of this study are: 1) that varying degrees of repolarization lability are present at rest in patients with previous myocardial infarction and reduced ejection fraction; 2) those subjects in the highest quartile for

repolarization instability also had evidence of significantly more advanced disease, manifesting higher New York Heart Association functional class and more digoxin use, as well as a greater prevalence of diabetes; 3) despite these confounding factors, increased QTVI was associated with an independent risk for VT or VF resulting in defibrillator therapy with a hazard ratio of 1.80; 4) normalized QT variability unadjusted for heart rate variability (QTVN) was associated with an even greater risk for combined VT/VF with a hazard ratio of 2.18; and 5) increased QTVN, as opposed to QTVI, was not associated with higher mortality in the defibrillator arm, suggesting that QTVN is somewhat more specific for identifying vulnerability to reentrant ventricular arrhythmias (which are interrupted by an ICD therapy).

QT variability and reentrant arrhythmias. Heterogeneity of repolarization (and excitability) is necessary for the initiation and maintenance of reentrant arrhythmias. Our finding that increased QT variability is associated with spontaneous VT/VF supports the interpretation that temporal instability coexists with regional heterogeneity in repolarization. Further study will be required to determine whether temporal variability represents a causal factor for arrhythmia generation or merely an epiphenomenon.

QT variability and mortality. The QT variability in the highest quartile was not associated with greater mortality in the conventionally treated arm, although there was a trend towards an increase in deaths thought to be arrhythmic in this group. In the defibrillator arm, an increase in mortality was seen in those subjects with increased QTVI but not QTVN. These "defibrillator-resistant" deaths are presumably due to progressive heart failure rather than arrhythmias. In a recent prospective study of outpatients with heart failure, reduced heart rate variability was an independent predictor of death due to progressive pump dysfunction rather than sudden death (15). Because the QTVI includes a term for heart rate variability, an increase in QTVI may predict heart failure progression, while the QTVN appears to be more clearly associated with risk for VT/VF.

The MADIT II study has resulted in a significant broadening of the indications for prophylactic defibrillator implantation, making more than one million Americans eligible (16). Clinical indexes that could identify subjects at highest (or lowest) risk for life-threatening ventricular arrhythmias are lacking, perhaps reflecting our incomplete understanding of the mechanisms leading to VT/VF. A recent prospective study of 700 postinfarction patients found that measures of autonomic tone and conventional ECG variables did not predict sudden cardiac death. Ejection fraction, the presence of unsustained VT, and an abnormal signal-average ECG only weakly predicted sudden death (17). The use of defibrillator interrogation in the MADIT II, however, allowed the accurate identification of arrhythmic events and was not reliant on presumptive diagnoses. Markedly increased QT variability (unadjusted for heart rate variability) is strongly associated with a significant increase in risk for VT/VF in the MADIT II population; this finding needs to be tested further in subjects with less severe myocardial disease. Unfortunately, the converse does not appear to be true; presence of low QT variability does not predict freedom from serious ventricular arrhythmias in a postinfarction subject with significant left ventricular dysfunction, at least when measured at rest in a single session. So while QT variability appears to identify significant arrhythmic vulnerability, it cannot be used to identify the individual who will not benefit from defibrillator implantation. The negative predictive power of the QTVN may be improved by combining it with a measure of depolarization function, such as QRS duration or signal-averaged ECG, or perhaps by repeating the assessment at periodic intervals or during an exercise challenge.

In conclusion, increased QT variability, a marker of repolarization lability, is associated with a substantially increased risk for arrhythmic events (documented by interrogating implanted defibrillators) in postinfarction patients with severe left ventricular dysfunction.

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REFERENCES

1. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
2. Buxton AE, Lee KL, Di Carlo I, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937–45.
3. Brodsky MA, Mitchell LB, Halperin BD, et al. Prognostic value of baseline electrophysiology studies in patients with sustained ventricular tachyarrhythmia: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Am Heart J 2002;144:478–84.
4. Tomaselli GF, Beuckelmann DJ, Calkins HG, et al. Sudden cardiac death in heart failure: the role of abnormal repolarization. Circulation 1994;90:2534–9.
5. Berger RD. Repolarization alternans: toward a unifying theory of reentrant arrhythmia induction. Circ Res 2000;87:1083–4.
6. Rosenbaum DS, Jackson LE, Smith JM, et al. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994; 330:235–41.
7. Hohnloser SH, Klingenheben T, Li Y-G, et al. 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.
8. Klingenheben T, Zabel M, D'Agostino RB, et al. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. Lancet 2000;356:651–2.
9. Gold MR, Bloomfield DM, Anderson KP, et al. A comparison of

T-wave alternans, signal averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol 2000;36:2247–53.
10. Ikeda T, Saito H, Tanno K, et al. T-wave alternans as a predictor for sudden death after myocardial infarction. Am J Cardiol 2002;89:79–82.
11. Berger R, Kasper E, Baughman KL, et al. Beat-to-beat QT interval variability: novel evidence for repolarization lability in dilated cardiomyopathy. Circulation 1997;96:1557–65.
12. Couderc JP, Zareba W, Burattini L, et al. Beat-to-beat repolarization variability in amplitude and duration in LQTS patients with the SCN5A sodium channel gene mutation. J Electrocardiol 1998;31:134.
13. Atiga WL, Calkins H, Lawrence JH, et al. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. J Cardiovasc Electrophysiol 1998;9:899–908.
14. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–65.
15. Nolan J, Batin PD, Andrews A, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom Heart Failure Evaluation and Assessment of Risk trial (UK-Heart). Circulation 1998;98:1510–6.
16. Essebag V, Eisenberg MJ. Expanding indications for defibrillators after myocardial infarction: risk stratification and cost effectiveness. Card Electrophysiol Rev 2003;7:43–8.
17. Huikuri HV, Tapanainen JM, Lindgren K, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003;42:652–8.