Prediction of Ventricular Tachyarrhythmias by Intracardiac Repolarization Variability Analysis

Larisa G. Tereshchenko, MD, PhD; Barry J. Fetics, MS; Peter P. Domitrovich, PhD; Bruce D. Lindsay, MD; Ronald D. Berger, MD, PhD

Background—Arrhythmic sudden cardiac death (SCD) is generally mediated by ventricular fibrillation (VF) or fast ventricular tachycardia (FVT). We studied the predictive value of temporal QT variability detected from various sources of cardiac electric signal: surface ECG, far-field (FF), and near-field (NF) intracardiac electrograms (EGMs) in patients with implantable cardioverter-defibrillators (ICDs).

Methods and Results—Surface ECG and FF and NF intracardiac EGMs were simultaneously recorded at rest (mean heart rate, 74±15 bpm) for 4.5±1.3 minutes in 298 patients (mean age, 59±14; 216 male [73%]) with structural heart disease and an implanted Medtronic ICD for primary (231 patients, 78%) or secondary (67 patients, 22%) prevention of SCD. During mean follow-up of 16±8 months, 52 (13.1% per person-year of follow-up) patients sustained VT/VF and received appropriate ICD therapies, but only 19 (4.8% per person-year of follow-up) patients sustained FVT/VF with cycle length ≤240 ms. The Kaplan–Meier survival analysis showed that the highest QT variability index (QTVI) quartile from all cardiac sources (surface ECG; NF and FF EGMs) is associated with event-free survival (P=0.038 for ECG; P=0.024 for FF EGM; P=0.012 for NF EGM). QTVI was a predictor of all VT/VF events and FVT/VF in the multivariate Cox model (including ischemic or nonischemic cardiomyopathy, history of revascularization procedures, LVEF, New York Heart Association class). Strong significant correlation among QTVI determined from all 3 sources was found.

Conclusion—Repolarization lability is present throughout the ventricular myocardium. Increased intracardiac QT variability predicts VT/VF events in patients with structural heart disease. (Circ Arrhythmia Electrophysiol. 2009;2:276-284.)

Key Words: heart arrest ■ tachyarrhythmias ■ defibrillation ■ prognosis ■ electrophysiology

Sudden cardiac death (SCD) remains the major cause of cardiovascular mortality. Difficulties in attempting to stratify the risk of the individual for life-threatening ventricular tachyarrhythmias have prompted the search for new approaches.

Clinical Perspective on p 284

Current implantable devices (loop recorders, pacemakers, implantable cardioverter-defibrillators [ICDs]) offer important advances in intracardiac electrogram (EGM) monitoring, storing, transmission, and analysis. Prediction of ventricular tachycardia (VT)/ventricular fibrillation (VF) could provide opportunities for timely preventive interventions that in future implantable devices could help to avoid the negative consequences of both ventricular tachyarrhythmia itself and therapy by ICD shock.

Recent work has demonstrated the feasibility and value of EGM analysis for VT/VF prediction and risk stratification despite limitations caused by required signal filtering.1-3 Several studies4-5 reported that detection of localized myocardial ischemia by far-field electrograms from ICD devices is feasible and even superior to standard surface ECG. Intracardiac T-wave alternans recorded by near-field right ventricular (RV) EGM have shown significance for prediction of ventricular tachyarrhythmias in patients with ICDs.6

Numerous studies documented that assessment of repolarization lability by the beat-to-beat QT variability7 measured from surface ECG identifies patients at risk for SCD.7-11 The predictive value of beat-to-beat QT variability measured from intracardiac EGMs compared with QT variability measured from surface ECG in VT/VF prediction is unknown. We hypothesized that repolarization lability may be present throughout the ventricular endocardium and myocardium, and intracardiac QT variability analysis may provide an important insight into mechanisms of predisposition to VT/VF and effective means for VT/VF prediction.

Methods

The study protocol was approved by the Johns Hopkins University and the Washington University Human Studies Committees, and all patients gave written informed consent before entering the study.

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Study Population
Patients with structural heart disease of either sex older than 18 years were eligible for the study if they had a Medtronic transvenous ICD device implanted for primary or secondary prevention of SCD. Exclusion criteria were pregnancy, inherited channelopathies, and concomitant conditions other than cardiac diseases that were associated with a high likelihood of death during 1 year after enrollment.

Intracardiac EGMs and Surface ECG Recording
Baseline recordings of far-field (FF) and near-field (NF) RV intracardiac EGMs (Figure 1) at rest during 5 to 15 minutes simultaneously with a 1-lead (lead II) surface ECG were obtained via Medtronic programmer 2090 using the NI USB-9215A portable data acquisition system, with customized LabVIEW (National Instruments, Austin, Tex) software application (1000-Hz sampling frequency with 0.3 mV/bit amplitude resolution). The right atrial ECG was simultaneously recorded in patients with dual-chamber ICD devices for the purpose of rhythm discrimination. All study patients had a dedicated bipolar ICD lead implanted with 8-mm distance from tip to ring. Bipolar endocardial NF RV EGM was recorded as difference of potentials between the tip and the ring of the dedicated bipolar ICD lead implanted in the apex of the RV. The potential difference between the ring of the RV lead and the ICD can was recorded as FF RV EGM.

Beat-to-Beat QT Variability Analysis
Temporal beat-to-beat QT variability was measured as previously described for surface ECG analysis. For QT variability index (QTVI) analysis on simultaneously recorded surface ECG, R-wave peak was automatically detected on the surface ECG channel. One investigator (L.G.T.) defined a template QT interval by selecting the beginning of QRS complex, J-point, and the end of the T wave. The algorithm then found the QT interval of all other beats by determining how much the ST-segment and T wave of each beat must be stretched or compressed in time to best match the template. For intracardiac EGM analysis, NF RV EGM was used for the automated R-wave peak detection. These fiducial points on the FF RV EGM were marked by the investigator and the algorithm run as described above. Corresponding fiducial points on the FF RV EGM were marked by the algorithm automatically without operator involvement. Appropriate selection of fiducial points was confirmed for all signals manually with the aid of a graphical display. Simultaneously recorded surface ECGs in all patients and atrial EGMs in patients with dual-chamber ICD devices allowed precise definition of rhythm and beat origin.

The heart rate mean (HRm) and variance (HRv) and QT interval mean (QTm) and variance (QTV) were computed from the respective time series (3 to 5 minutes). A normalized QTVI was derived according to equation:

$$QTVI = \log_{10}\left(\frac{QT_v}{QT_m^2}\sqrt{HR_v/HR_m^2}\right)$$

Custom software was written in MATLAB (MathWorks Inc, Natick, Mass). Only recordings with normal sinus rhythm were included in the analysis. Recordings with >15% of ectopic, paced, or noise-distorted beats were excluded.

End Points
Appropriate ICD therapies (both shocks and antitachycardia pacing [ATP]) for VT/VF were the primary end points for analysis. Programming of the ICD device was based on clinical evaluation of the attending electrophysiologist. Patients were followed up in Washington University Arrhythmia Clinic and remotely via the Internet-based CareLink remote monitoring system. All ICD interrogation data were reviewed by an ICD end point committee composed of 3 members (attending electrophysiologist and 2 of the investigators [L.T.G and R.D.B.B.]), who adjudicated each ICD event. ICD therapy occurring for VT or VF was classified as appropriate. Inappropriate therapy events were not censored, and follow-up continued. Ventricular tachycardia was differentiated from supraventricular tachycardia via standard criteria, including a change in EGM morphology, sudden onset, and the atrial-ventricular relationship if atrial EGMs were available. The event was considered in the context of other episodes for the same patient, if applicable. All sustained VT/VF events requiring ICD therapy were categorized as fast VT/VF with cycle length (CL) ≤240 ms and VT with CL >240 ms. The combination of appropriate ICD therapy for VT/VF and death, whichever came first, was analyzed as a secondary end point. Time to event was measured from the day of study enrollment, when intracardiac EGMs were acquired for analysis. Any ICD therapy before enrollment did not count as an end point.

Statistical Analysis
Results are presented as mean±standard deviation (SD) for normally distributed variables and as median and interquartile range for nonnormally distributed variables. Continuous variables were compared using the independent-samples t test if normally distributed and the Wilcoxon rank sum test if skewed. The Pearson χ² test was used to compare categorical variables. A probability value of <0.05 was considered significant. Kaplan–Meier survival analysis was used to compute mean and median survival time, with standard errors and 95% confidence intervals. The log-rank (Mantel-Cox) statistic was computed to test the equality of survival distributions in the presence of arbitrary right censorship. A Cox proportional hazards analysis was performed separately for each variable of interest (NF EGM QTVI, FF EGM QTVI, ECG QTVI). Regression models included tested clinical and demographic predictors of outcomes along with above-named beat-to-beat waveforms variability indices, SPSS 16.0.0 software package (SPSS Inc, Chicago, Ill) was used for calculations.

Results
Eligible for QT Variability Analysis Intracardiac EGM and Surface ECG Recordings
Of 500 eligible study patients, 202 were excluded from QTVI analysis if, according to stored device data, they were paced either from the right atrium or ventricle >5% during the preceding 7 to 90 days, or baseline EGM recording did not meet eligibility criteria for QT variability analysis (presence of >15% of premature beats, atrial fibrillation beats, atrial paced and/or ventricular paced beats, or noise-distorted beats as defined by the custom software algorithm). QT variability was analyzed during sinus rhythm in the remaining 298 patients who were included in the survival analysis. Excluded patients differed from those included in subsequent analysis in being slightly older (63.4±15.5 versus 58.5±14.4 years, P<0.0001), having a higher proportion of New York Heart Association (NYHA) class III heart failure (30.8% versus 13.1%, P<0.0001), and having a lesser proportion of diabetics (22% versus 34.6%, P=0.001).

Patient Population
Among the patients eligible for QT variability analysis (Table 1), 216 were men (72.5%) and 82 women (27.5%) who...
underwent ICD implantation for primary (231 patients, 77.5%) or secondary (67 patients, 22.5%) prevention of SCD. The mean age was 58.5 ± 14.1 years (range, 18 to 93).

Ischemic cardiomyopathy with history of myocardial infarction (MI) was diagnosed in 181 (60.7%) patients and nonischemic cardiomyopathy in 117 (39.3%). A transvenous Medtronic ICD device was implanted in each patient: single-chamber ICD in 221 (74.2%) and dual-chamber ICD in 77 (25.8%) patients. The patients were enrolled in the study in median time 9.4 months after ICD implantation (range, 6 days to 8 years; Figure 2).

Programming the ICD Device
Programming of the ICD device was based on the clinical evaluation of the attending electrophysiologist. ATP was programmed ON (either during charging or via FVT/VT zone) in 200 patients (68%). FVT/VT detection cutoff for ATP therapy was in the range of CL 200 to 500 ms, mean 326 ± 33 ms. Single VF zone with ICD shock only (ATP during charging disabled) was programmed in 98 patients (32%). VF detection cutoff was in the range of 280 to 370 ms (mean, 297 ± 29 ms).

End Point Events During Follow-Up
During mean follow-up of 16.8 months, 52 patients (17.4% or 13.1% per person-year of follow-up) of 298 sustained VT/VF and received appropriate ICD therapies. ATP was attempted in 27 (51.9%) of 52 patients and was successful in 17 of these (63%). Nineteen patients sustained FVT/VF with CL ≤240 ms (6.4%, or 4.8% per person-year of follow-up) with successful rescue ICD shocks. During follow-up, 20 patients (6.7%, or 5.0% per person-year of follow-up) died, and heart transplantation was performed in 5 patients (1.7%). Among 20 patients who died, cardiovascular cause of death (congestive heart failure predominantly) was determined in 14 patients, noncardiovascular in 2 patients, and undetermined in 4 patients. Three patients died after appropriate ICD shocks (median, 113 days after).

QT Variability Analysis
QTVI measured from surface ECG, FF EGM, and NF EGM was significantly higher in the patients with subsequent VT/VF (Table 2). No significant differences between groups were found in mean QT interval, mean heart rate, QT interval variance, or heart rate variance, using any source of cardiac signal. Figure 3 shows examples of heart rate variance and QT variance graphs in patients with (A) and without (B) subsequent VT/VF events during follow-up. Very few clinical differences were observed between patients with and those without VT/VF during follow-up. Patients who had VT/VF events were more likely to have had a history of percutaneous transluminal coronary angioplasty (PTCA) and were more often receiving class III antiarrhythmics (12% of patients without VT/VF versus 35% with VT/VF, P < 0.0001).

To propose a clinically meaningful cutoff for prospective QTVI evaluation for SCD risk stratification, we explored distribution of QTVI separately for surface ECG, FF EGM, and NF EGM and compared clinical characteristics of patients with the highest QTVI quartile (Table 3) with those in the other 3 quartiles. The highest QTVI quartile for NF EGM was characterized by QTVI ≥0.100; for FF EGM, QTVI ≥0.080; and for lead II surface ECG, QTVI ≥0.114. Patients with the highest NF and FF EGM QTVI quartile were more likely to have a history of PTCA and more likely to take class

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>58.5±14.1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>216 (72.5)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>52 (17.4)</td>
</tr>
<tr>
<td>Ischemic CM with MI history, n (%)</td>
<td>181 (60.7)</td>
</tr>
<tr>
<td>Primary prevention of SCD, n (%)</td>
<td>231 (77.5)</td>
</tr>
<tr>
<td>Single-chamber ICD, n (%)</td>
<td>221 (74.2)</td>
</tr>
<tr>
<td>Dual-chamber ICD, n (%)</td>
<td>77 (25.8)</td>
</tr>
<tr>
<td>LVEF at ICD implantation±SD, %</td>
<td>33.1±12.3</td>
</tr>
<tr>
<td>NYHA class I, n (%)</td>
<td>116 (38.9)</td>
</tr>
<tr>
<td>NYHA class II, n (%)</td>
<td>141 (47.3)</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>39 (13.1)</td>
</tr>
<tr>
<td>NYHA class IV, n (%)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>103 (34.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>224 (75.2)</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>101 (33.9)</td>
</tr>
<tr>
<td>PTCA, n (%)</td>
<td>96 (32.2)</td>
</tr>
<tr>
<td>α-blockers, n (%)</td>
<td>253 (84.9)</td>
</tr>
<tr>
<td>Aldosterone antagonists, n (%)</td>
<td>110 (36.9)</td>
</tr>
<tr>
<td>Class I antiarrhythmic medication, n (%)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Class III antiarrhythmic medication, n (%)</td>
<td>74 (24.8)</td>
</tr>
</tbody>
</table>

CM indicates cardiomyopathy; MI, myocardial infarction; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
III antiarrhythmics. No between-group differences were found in other clinical variables. No significant differences were observed when patients were grouped by highest quartile QTIV from the surface ECG.

To compare beat-to-beat QT variability measured by surface ECG with intracardiac EGMs QT variability, we studied correlations of QTIV among 3 available sources of cardiac signal and found a strong significant correlation (Figure 4). The strongest correlation was between NF EGM QTIV and FF EGM QTIV ($r = 0.705$, $P = 0.0001$). Correlation between FF QTIV and surface ECG QTIV ($r = 0.643$, $P = 0.0001$) was stronger than between NF QTIV and surface ECG QTIV; ($r = 0.593, P < 0.0001$).

**Antiarrhythmic Medication**

Seventy-five patients (25%) took class I and/or class III antiarrhythmics at least during the month before the baseline EGM recording: 50 patients (16.8%) were taking amiodarone, 29 (9.7%) were taking sotalol, 5 (1.7%) were taking mexiletine, and 1 was taking propafenone. Use of class I antiarrhythmics (mexiletine and propafenone) did not confound results of QT variability. However, QT variability was significantly different in patients taking class III medications (amiodarone and sotalol) (Table 4). NF RV EGM signal was the most sensitive to use of class III antiarrhythmics. NF RV EGM QTIV was significantly higher, and NF EGM QT interval duration was significantly longer in patients taking class III antiarrhythmics. Mean heart rate (HR) was slightly but significantly lower, and heart rate variance was significantly less in all 3 cardiac signal sources in patients taking class III antiarrhythmics. However, lengthening of QT duration was less prominent on FF RV EGM as compared with NF RV EGM and was absent on the surface ECG. There was no statistically significant difference in QT variance and QTIV from FF RV EGM and surface ECG between patients who took and those who did not take class III antiarrhythmics.

**Survival Analysis**

A Kaplan–Meier survival analysis was performed to assess the ability of the QTIV to predict subsequent VT/VF events. The highest QTIV quartile from all 3 sources of cardiac signal predicted VT/VF events and appropriate ICD therapies (Figure 5). Highest surface ECG QTIV predicted FVT/VF events (Figure 6A), and both NF EGM QTIV and FF EGM QTIV demonstrated borderline level of differences for FVT/VF prediction. Because QT variability on NF RV EGM was confounded by use of class III antiarrhythmic medications,
survival analysis for FVT/VF events was performed again after exclusion of those patients. NF RV EGM QTVI predicted FVT/VF events in patients who did not take class III antiarrhythmics (Figure 6B).

Results of the survival analysis for the combined end points VT/VF and death were very similar to the results of survival analysis for VT/VF events only. The highest QTVI quartile from all cardiac sources predicted combined event-free survival (Mantel-Cox log-rank test, $P=0.011$ for ECG; $P=0.049$ for FF EGM; $P=0.019$ for NF EGM). Kaplan–Meyer survival analysis did not show significant association between baseline highest QTVI quartile and all-cause death (Mantel-Cox log-rank test, $P=0.216$ for NF EGM; $P=0.526$ for FF EGM; $P=0.056$ for surface ECG QTVI).

In the multivariate Cox regression models for all VT/VF events, all QTVI indices, tested separately, were the only significant predictors in the model. The model included cardiomyopathy, history of PTCA, LVEF, and NYHA class. The hazard (Figure 7) for patients with the highest quartile of NF EGM QTVI, FF EGM QTVI, and surface ECG QTVI is $\approx 2$ times that of the patients with 3 lower quartiles of QTVI from all 3 sources of cardiac signal.

For FVT/VF events, after exclusion of patients taking class III antiarrhythmic medication, NF RV EGM QTVI was the only significant predictor in the model (HR, 4.195; 95% CI, 1.165 to 15.107; $P=0.028$). Surface ECG QTVI also remained the only predictor in the model (HR, 4.175; 95% CI 1.398 to 12.460; $P=0.010$). FF RV EGM QTVI was not predictive for FVT/VF events.

Discussion
This study showed that beat-to-beat QT variability is detectable from the NF and FF EGMs in patients with implanted ICD and that quantification of QT variability allows for prediction of ventricular arrhythmias. To our knowledge, this is the first prospective study to show that QTVI measured from bipolar endocardial NF RV EGM Vtip-to-Vring, FF RV EGM, and lead II surface ECG, has similar predictive value of sustained VT/VF events requiring appropriate ICD therapy.

Repolarization Lability Assessment From Intracardiac ECGs
Our study is consistent with others showing the utility of NF and FF EGMs for repolarization assessment.12 Paz et al,2 in a validation simulation study, confirmed that T-wave alternans (TWA) is measurable from the FF ICD EGMs. Swerdlow et al3 showed that high-amplitude TWA measured from coil-can FF EGMs precedes spontaneous VT/VF events in patients with ICDs. Similarly, our data demonstrate that patients in the highest QTVI quartile measured from both NF and FF EGMs have significantly higher risk for sustained VT/VF events.

Sandhu et al6 compared TWA measured in intracardiac EGMs with that of surface ECG, finding high concordance. They reported that both intracardiac and surface TWA were predictive of VT/VF, although, in fact, the event rate was the same in those who were TWA positive as in those who were TWA negative.

| Table 3. Clinical Characteristics of Patients With NF EGM QTVI Dichotomized at 75th Percentile |
|-----------------|-----------------|-----------------|-----------------|
|                 | QTVI <75th Percentile (n=224) | QTVI ≥75th Percentile (n=74) | $P$ |
| Age±SD, y       | 59±14            | 59±12            | 0.849           |
| Females, n (%)  | 58 (25)          | 24 (28)          | 0.660           |
| Black, n (%)    | 40 (18)          | 12 (15)          | 0.537           |
| CHF NYHA class III, n (%) | 26 (13) | 13 (21) | 0.047 |
| Ischemic CM with MI history, n (%) | 132 (60) | 49 (69) | 0.188 |
| Primary prevention of SCD, n (%) | 175 (80) | 56 (81) | 0.821 |
| Single-chamber ICD, n (%) | 162 (72) | 59 (74) | 0.715 |
| LVEF±SD, %      | 33.2±12          | 31.0±9           | 0.113           |
| Diabetes mellitus, n (%) | 73 (33) | 30 (41) | 0.221 |
| Hypertension, n (%) | 168 (75) | 56 (79) | 0.483 |
| CABG, n (%)     | 80 (37)          | 21 (29)          | 0.234           |
| PTCA, n (%)     | 63 (28)          | 33 (47)          | 0.04            |
| ß-blockers, n (%) | 190 (86) | 63 (84) | 0.394 |
| Aldosterone antagonists, n (%) | 80 (36) | 30 (41) | 0.626 |
| Class 1 antiarrhythmic medication, n (%) | 4 (2) | 2 (2.9) | 0.625 |
| Class III antiarrhythmic medication, n (%) | 47 (22) | 27 (35) | 0.019 |

CHF indicates congestive heart failure; CM, cardiomyopathy; MI, myocardial infarction; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

Figure 4. Scatterplots of correlations between NF EGM QTVI, FF EGM QTVI, and surface ECG QTVI. Scatterplots highlight the relationships between NF RV EGM QTVI and FF RV EGM QTVI (A); surface ECG QTVI and NF RV EGM QTVI (B); and surface ECG QTVI and FF RV EGM QTVI (C) by plotting the actual values along 2 axes.
Comparison of Intracardiac to Surface QT Variability

Results of our study confirm strong correlation among QTVI measured from various sources of cardiac signal. According to our data, the group of patients susceptible to life-threatening ventricular tachyarrhythmias is characterized by increased beat-to-beat QT variability from all available intracardiac EGMs and surface ECGs. The level of QT variability and predictive value is similar for NF, FF EGMs, and ECG, but it is not completely identical.

There are several major differences between intracardiac EGMs and surface ECG: (1) different filter settings for surface ECG (0.05 to 200 Hz) and intracardiac EGMs (2 to 100 Hz); (2) different position of lead axis for NF EGM, FF EGM, and lead II surface ECG; (3) different spatial scale of assessment of repolarization lability from local action potential duration (APD) variability in the case of endocardial NF RV EGM to the whole-heart level repolarization heterogeneity in the case of surface ECG and FF RV EGM. Despite these differences, our results confirmed significant positive correlation among QTVI measured from NF EGM, FF EGM, and lead II surface ECG.

It may seem somewhat surprising that NF EGM is at least as predictive as FF EGM despite the fact that NF EGM samples only a small section of the myocardium. Experiments have shown that QT interval measured on NF RV EGM corresponds to the action potential duration.13,14 We speculate that the NF EGM performs well because it is more closely associated with local action potential and is less affected by geometric considerations.

We have found that the 25th percentile cutoff value for QTVI is close to zero for NF EGM, FF EGM, and the surface ECG. This finding represents a particularly meaningful landmark and confirms a universal character of repolarization lability and specifically of the QTVI. From the QTVI formula (see Methods), we see that QTVI implies that the coefficient of variation in QT interval equals that in heart rate.

Prognostic Utility of Intracardiac QT Variability

Multiple previous studies confirmed the significance of surface ECG beat-to-beat QT variability for VT/VF risk stratification. Atiga et al8 reported that elevated QTVI identified sudden death survivors more accurately than TWA or EPS in a group of 98 subjects with arrhythmic complains. After this work, QT variability (with and without normalization by heart rate variability) was measured in supine 10-minute Holter recordings in 476 subjects enrolled in the MADIT II study. Table 4 shows the comparison of QT variability and clinical characteristics of patients with and those without Class III antiarrhythmic medication therapy.

**Table 4. Comparison of QT Variability and Clinical Characteristics of Patients With and Those Without Class III Antiarrhythmic Medication Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Without Class III Antiarrhythmics (n=224)</th>
<th>With Class III Antiarrhythmics (n=74)</th>
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<tbody>
<tr>
<td>Mean heart rate±SD, bpm</td>
<td>76±16</td>
<td>69±14</td>
<td>0.006</td>
</tr>
<tr>
<td>Heart rate variance median (interquartile range), bpm²</td>
<td>34.0 (5.4–76.1)</td>
<td>15.3 (2.4–55.4)</td>
<td>0.029</td>
</tr>
<tr>
<td>NF EGM mean QT±SD, ms</td>
<td>482±84</td>
<td>527±90</td>
<td>0.001</td>
</tr>
<tr>
<td>NF EGM QT variance median (interquartile range), ms²</td>
<td>540 (96–1344)</td>
<td>383 (94–1193)</td>
<td>0.643</td>
</tr>
<tr>
<td>NF EGM QTVI±SD</td>
<td>−0.315±0.489</td>
<td>−0.151±0.541</td>
<td>0.020</td>
</tr>
<tr>
<td>FF EGM mean QT±SD, ms</td>
<td>482.5±89</td>
<td>523±92</td>
<td>0.015</td>
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<tr>
<td>FF EGM QT±SD</td>
<td>−0.343±0.463</td>
<td>−0.303±0.644</td>
<td>0.601</td>
</tr>
<tr>
<td>Surface ECG mean QT±SD, ms</td>
<td>497±83</td>
<td>498±76</td>
<td>0.946</td>
</tr>
<tr>
<td>Surface ECG QTVI±SD</td>
<td>−0.223±0.485</td>
<td>−0.123±0.716</td>
<td>0.351</td>
</tr>
</tbody>
</table>

**Figure 5.** Kaplan–Meier curves for freedom from all VT/VF events in patients with the highest QTVI quartile and those with the lower 3 QTVI quartiles on NF RV EGM (A), FF RV EGM (B), and surface ECG (C).
study who also received an ICD. QTVI was an independent predictor of VT/VF in a multivariate Cox regression model, whereas there was no significant difference in HRV (measured as SDNN) between either the high-risk and low-risk quartiles or the VT/VF (+) and VT/VF (−) groups. Similarly, in 396 nonischemic patients with ejection fraction between 35% and 40%, Piccirillo et al. found that QTVI dichotomized at the 80th percentile was a significant predictor of both total mortality and sudden death in a multivariate comparison. In 481 postinfarction patients with a high proportion of noncardiomyopathic subjects, Jensen et al. examined a broad spectrum of measures derived from 24-hour Holter recordings. In a multivariate comparison, they found that the ratio of the standard deviation of QT to the standard deviation of R-R intervals was the most powerful predictor of total mortality and cardiovascular mortality and was the only predictor of sudden death, outperforming QT/RR slope, EF, SDNN, PVCs per hour, and QRS duration. Consistent with results of previous studies, our Kaplan-Meyer analysis showed statistically significant differences in survival between the highest QTVI quartile and the other 3 quartiles for all sources of cardiac signal.

Importantly, addition of all-cause mortality as a secondary endpoint to survival analysis does not increase the predictive power of QTVI, in either intracardiac EGMs or surface ECG. This finding confirms the value of QTVI as a marker of life-threatening ventricular arrhythmia specifically. This is especially important information because other markers of VT/VF risk, such as LVEF and heart rate variability, work to identify individuals at risk for both SCD and death from heart pump failure. Assessment of beat-to-beat QT variability could potentially allow better discrimination between patients prone to VT/VF and patients prone to pump function deterioration, but this possibility requires further prospective studies.

ICD therapy for VT/VF events as a surrogate end point of SCD events overestimates the incidence of SCD. Thus it is extremely important to determine whether a marker proposed for VT/VF prediction works to predict FVT/VF events with CL ≤240 ms. The results of our study show that endocardial NF RV EGM and surface ECG QTVI significantly discriminate risk of FVT/VF.

**Cellular Basis of Repolarization Lability and Mechanisms Predisposing to Ventricular Tachyarrhythmias**

Several mechanisms on cellular and myocardial tissue levels could be implicated in repolarization lability. First, a combination of instabilities in action potential duration restitution and intracellular calcium dynamics, as well as anatomic and dynamically generated instabilities as a response of a nonlinear medium to periodic excitation, may produce both alternating and nonalternating repolarization lability and have been shown before the onset of VT/VF both in experiments and in humans. Second, gating kinetics of Kv channels can vary between subtypes of channels over several orders of magnitude even within the same cell. Gating kinetics together with the relative expression levels of each Kv channel type in a particular cell could be major determinants of the temporal variability of the action potential because they control the relative repolarizing force at specific time points during the action potential. Third, autonomic fluctuations may modify repolarization on a beat-to-beat basis. In animal studies, electric stimulation of the left stellate ganglion produced lengthening of corrected QT interval, and
spontaneously increased stellate ganglion nerve activity was observed before VT/VF events in dogs.24

Understanding the mechanisms predisposing to VT/VF is key to developing effective tools for VT/VF prediction. From experiments on different species, it is known that prolongation of APD, produced for example by β-adrenergic stimulation, leads to the occurrence of early afterdepolarization (EAD) that is thought to be a possible trigger for development of VT/VF.25 Recent cardiac myocyte modeling studies26 have shown that the rate of EAD occurrence is increased by a specific stochastic mechanism of L-type Ca channel gating, an important mechanism predisposing to VT/VF.

In summary, our results indicate that repolarization lability may be present throughout the ventricular endocardium and myocardium. Chronic use of class III antiarrhythmic medications may confound intracardiac QT variability. Increased intracardiac QT variability may provide evidence of mechanisms predisposing to VT/VF, such as increased stochastic APD variability and EAD occurrence. At the same time, increased FF EGM and surface ECG QT variability reflect increased temporal dispersion of repolarization on the tissue and whole-heart scale.

Limitations
Detection of intracardiac QT variability from NF and FF RV EGMs is limited by the position of the implanted RV lead in the heart and available configuration of FF EGM, which may be device-specific. Only lead II surface ECG was recorded, which is not necessarily the best surface ECG lead for all patients to assess repolarization. Further studies are needed to compare various combinations of available FF EGM configuration and surface ECG leads.

VT/VF detection cutoff was programmed at the discretion of the attending electrophysiologist and varied significantly. However, categorization of VT/VF events based on CL and separate analysis of FVT/VF events eliminates risk of biased analysis.

Variable time from ICD implantation to study enrollment could be a confounding factor. Some secondary prevention patients had appropriate therapy after ICD implantation but before being enrolled in the study. Cox proportional hazards models were adjusted to correct for this confounding factor.

Roughly 40% of study participants were excluded from QTVI analysis because of non–sinus rhythm or frequent ectopy at baseline. A few baseline clinical characteristics (age, NYHA class, diabetes mellitus) were statistically significantly different between excluded and included subjects. This study represents a real-world patient population, but future studies are needed to assess the possibility of meaningful analysis in some subgroups of excluded patients.

A high percentage of participants were taking class III antiarrhythmic medications at baseline EGM recording and a majority of patients were taking β-blockers, which modify repolarization.

Finally, filter characteristics were different for surface ECG (0.05 to 200 Hz) and intracardiac EGMs (2 to 100 Hz). The filter settings for NF and FF EGMs in ICDs produced by other manufacturers may differ, precluding simple extrapolation of our results on EGM analysis to other ICD manufacturers.

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Disclosures
Dr Berger holds a patent on the technology for QT variability analysis.

References
CLINICAL PERSPECTIVE

Implantable cardioverter-defibrillators (ICDs) reduce mortality rates in patients with left ventricular systolic dysfunction. However, prediction of life-threatening ventricular tachyarrhythmias remains difficult, and new approaches are needed. Clinical trials have demonstrated the predictive value of QT variability measurement in assessing the risk of malignant ventricular arrhythmias. We tested whether repolarization lability can be similarly assessed by analysis of intracardiac electrograms obtained in patients with ICDs. We found increased repolarization lability in near-field and far-field intracardiac electrograms among patients with subsequent arrhythmias, suggesting that repolarization lability is a local as well as a global phenomenon in the diseased myocardium. We found that intracardiac repolarization variability predicted the subsequent occurrence of all ventricular tachycardia (VT) and ventricular fibrillation (VF) episodes. Importantly, the results of our study show that endocardial near-field electrograms and surface ECG QT variability significantly discriminate the risk of fast VT/VF with cycle length ≤240 ms. At the same time, addition of all-cause mortality as a secondary end point to survival analysis did not increase the predictive power of the QT variability index (QTVI), which confirms the value of QTVI as a marker of life-threatening ventricular arrhythmia specifically. Assessment of beat-to-beat QT variability could potentially allow better discrimination between patients prone to VT/VF and patients prone to pump function deterioration. Prediction of life-threatening ventricular tachyarrhythmias could provide opportunities for timely preventive interventions in future implantable devices.
Prediction of Ventricular Tachyarrhythmias by Intracardiac Repolarization Variability Analysis
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