Predictive Value of Beat-to-Beat QT Variability Index Across the Continuum of Left Ventricular Dysfunction

Competing Risks of Noncardiac or Cardiovascular Death and Sudden or Nonsudden Cardiac Death

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Background—The goal of the present study was to determine the predictive value of beat-to-beat QT variability in heart failure patients across the continuum of left ventricular dysfunction.

Methods and Results—Beat-to-beat QT variability index (QTVI), log-transformed heart rate variance, normalized QT variance, and coherence between heart rate variability and QT variability have been measured at rest during sinus rhythm in 533 participants of the Muerte Subita en Insuficiencia Cardiaca heart failure study (mean age, 63.1±11.7; men, 70.6%; left ventricular ejection fraction >35% in 254 [48%]) and in 181 healthy participants from the Intercity Digital Electrocardiogram Alliance database. During a median of 3.7 years of follow-up, 116 patients died, 52 from sudden cardiac death (SCD). In multivariate competing risk analyses, the highest QTVI quartile was associated with cardiovascular death (subhazard ratio, 1.67 [95% CI, 1.14–2.47]; P=0.009) and, in particular, with non-SCD (subhazard ratio, 2.91 [1.69–5.01]; P<0.001). Elevated QTVI separated 97.5% of healthy individuals from subjects at risk for cardiovascular death (subhazard ratio, 1.57 [1.04–2.35]; P=0.031) and non-SCD in multivariate competing risk model (subhazard ratio, 2.58 [1.13–3.78]; P=0.001). No interaction between QTVI and left ventricular ejection fraction was found. QTVI predicted neither noncardiac death (P=0.546) nor SCD (P=0.945). Decreased heart rate variability rather than increased QT variability was the reason for increased QTVI in the present study.

Conclusions—Increased QTVI because of depressed heart rate variability predicts cardiovascular mortality and non-SCD but neither SCD nor extracardiac mortality in heart failure across the continuum of left ventricular dysfunction. Abnormally augmented QTVI separates 97.5% of healthy individuals from heart failure patients at risk. (Circ Arrhythm Electrophysiol. 2012;5:719-727.)

Key Words: ECG ◼ ejection fraction ◼ heart failure ◼ sudden death ◼ QT variability

An aging population with a high prevalence of obesity, diabetes mellitus, and hypertension, along with advancements in the treatment of acute cardiovascular diseases, has resulted in an increased incidence and prevalence of heart failure (HF) during the past decades.1,2 Studies estimate that 2% to 3% of the population suffer from HF.3 Despite advances in therapy and management, HF carries substantial morbidity and mortality, as well as high rates of hospitalizations and hospital readmissions, which together represent a large burden to the healthcare system.3,4

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Although mortality rates in HF with moderate and severe left ventricular (LV) systolic dysfunctions are slightly higher than those in mild HF with relatively preserved LV ejection fraction (LVEF),6,7 the absolute number of deaths attributable to mild HF with LVEF >35% is large and continues to grow.9 Although a certain amount of success has been achieved in the management of HF patients with LVEF ≤35%, resulting in improved survival over time, there are no effective therapies...
confirmed to improve the natural history of HF patients with LVEF >35%. Implantable cardioverter-defibrillators could potentially be game changers. However, strategies for effective risk stratification in the population of patients with HF and LVEF >35% have not been developed.

It was previously shown that increased beat-to-beat QT variability predicts ventricular tachyarrhythmias, sudden cardiac death (SCD), and cardiovascular and all-cause mortality in moderate and severe systolic HF. Still, data on the predictive value of QT variability in patients with LVEF >35% are limited. The threshold of abnormal QT variability is usually set at its highest quartile in a studied population. However, it is unknown whether QT variability could separate healthy individuals from subjects at risk. SCD shares many of the same risks factors as non-SCD. In addition, there are common risk factors of cardiovascular death and noncardiac death (eg, age). This creates a challenge in identifying those at risk of SCD while considering the competing risk of non-SCD and a challenge in identifying subjects at risk of cardiovascular death while considering the competing risk of noncardiac death in an aging population.

Methods
We performed ad hoc analysis using the prospectively collected data of 2 studies. The multicenter prospective observational cohort study Muerte Subita en Insuficiencia Cardiaca (MUSIC; Sudden Death in Heart Failure) was designed to assess risk predictors of cardiac mortality and SCD in ambulatory patients with mild to moderate HF. To determine the threshold of abnormal QT variability that would allow us to separate 97.5% of healthy individuals from those at risk, we analyzed healthy subjects from the Intercity Digital Electrocardiogram Alliance (IDEAL) database. The study protocols were approved by the institutional investigational committees, and all participants gave written informed consent before entering the study.

MUSIC Study Population
The design of this prospective multicenter observational cohort study was previously described. Adult stable ambulatory symptomatic New York Heart Association class II to III HF patients with either depressed or preserved LVEF, either ischemic or nonischemic cardiomyopathy, were enrolled in 8 Spanish University Hospitals between April 2003 and December 2004. Study subjects were treated according to the guidelines of that time and did not have cardioverter-defibrillators or cardiac resynchronization therapy implanted. High-resolution (1000 Hz) orthogonal ECG recordings were performed using ELA Spideerview recorders (ELA Medical, Sorin Group, Paris, France) during 10 minutes at rest at the time of enrollment. Patients were followed every 6 months in outpatient HF clinics. All death cases were adjudicated by the MUSIC study core end points adjudication committee as previously described. Noncardiac mortality, cardiovascular mortality, SCD, and non-SCD served as end points in the present study.

IDEAL Healthy Subjects Database
The IDEAL database study was conducted by the University of Rochester (Rochester, NY) and was provided for this analysis by the Telemeteric and Holter ECG Warehouse. Healthy individuals were eligible for enrollment if they had no history of cardiovascular disorders, no history of blood pressure >150/90 mm Hg, no history of any chronic illness, did not take any medications, and fulfilled objective criteria of cardiovascular health: normal physical examination; no pregnancy; normal 12-lead ECG (specifically, without signs of ventricular hypertrophy, inverted T waves, and conduction abnormalities). In the presence of borderline ECG changes, normal echocardiogram and normal ECG exercise testing were required for inclusion. High-resolution (1000 Hz) orthogonal ECG recordings (SpaceLab-Burdick, Inc, Deerfield, WI) were performed at rest during 10 minutes.

Beat-to-Beat QT Variability Analysis
QT variability analysis was performed at the Johns Hopkins Hospital by investigators (L.G.T., L.H., S.S.) fully blinded to the study population’s clinical characteristics and outcomes. Software for this analysis was developed in Tereshchenko’s laboratory. Fiducial points (beginning of Q or R wave and end of T wave) were detected automatically by a customized software application written in Matlab (MathWorks, Inc, Natick, MA) on each beat during 3-minute ECG epochs. The accuracy of automated detection was verified for each beat, included in analysis, with the aid of a graphical display. Premature atrial and ventricular beats with 1 subsequent sinus beat were excluded from analysis. Mean heart rate, heart rate variance, mean duration of QT interval, and QT variance were measured on each of the XYZ leads and averaged. Normalized by the mean QT interval, QT variance (QTVN) was calculated according to the following equation: QTVN=QT variance/mean duration of QT interval. The heart rate variance (HRV) was log-transformed (LogHRV) to normalize distribution. The QT variability index (QTVI) was calculated as previously described, according to the following equation: QTVI=log[log(1/(QTVI/mean heart rate²))]. To assess the coherence between the heart rate variability and QT variability, spectral analysis of the RR’ and QT intervals was performed, and a cross spectrum was generated using the Blackman-Tukey method. Coherence was calculated as previously reported, according to the following equation: γ(f)=|Pxy(f)/Pₓₓ(f)Pᵧᵧ(f)|. Statistical Analysis
Statistical analysis for the present study was performed in the Statistical Core Laboratory of the Heart Research Follow-up Program at the University of Rochester. Results are presented as mean±SD after confirmation of normal distribution. Continuous variables were compared using the independent samples t test. The Pearson χ² test was used to compare categorical variables. To dissect which component of the QTVI formula contributes the most to the predictive power of QTVI, we prespecified high-risk subgroups by identifying individuals in the highest quartile (≥75th percentile) of QTVI and of QTVN and in the lowest quartile (<25th percentile) of mean coherence and of LogHRV. To determine whether abnormal QTVI could robustly separate healthy individuals from HF patients at risk of death, an additional threshold of abnormal QTVI was determined at the 97.5th percentile of IDEAL healthy individuals’ QTVI values. Nelson-Aalen cumulative incidence function was used to test predictive value of QTVI in combination with LVEF for cardiovascular death, noncardiac death, SCD, and non-SCD. Cox regression analyses were performed to determine which demographic and clinical characteristics were associated with the risk of outcomes. The clinical and demographic variables that were significantly associated with end points in the MUSIC study as shown previously were included in the models. For each outcome, a backward stepwise algorithm determined the demographic and clinical characteristics significantly associated with outcome. From those, a set of covariates was selected for use in competing risk models. The univariate and multivariate Fine and Gray competing risk regression analysis was performed to determine whether the evaluated ECG predictors for the risk of SCD differed from those for the risk of non-SCD and whether ECG predictors of cardiovascular death differed from those of noncardiac death. The ECG variables were included one at a time in the multivariate competing risk models. Cumulative incidence functions were plotted after competing risk models for QTVI and LVEF groups, with remaining covariates held at their mean values. Schoenfeld-like residuals were evaluated to test an assumption of the subhazards proportionality. STATA function nlcheck, which uses a joint Wald test for the added parameters, was used to test the linearity assumption of the predictors. Interaction between LVEF and QTVI was tested in the competing risk regression.
models. \( P < 0.05 \) was considered significant. Data were analyzed using SAS 9.2 (SAS Institute Inc, Cary, NC) and STATA 12 (StataCorp LP, College Station, TX).

**Results**

**MUSIC Study Population**

Clinical characteristics of MUSIC study participants have been previously described.\(^{16}\) We analyzed high-resolution ECGs of 924 MUSIC study participants. Patients with ECGs not eligible for QT variability analysis (because of atrial fibrillation/flutter, frequent premature beats \( n=346 \), or noise \( n=45 \)) were excluded from the present study, and data of remaining 533 patients were further analyzed. Mean age was 62.8±12.0 years. The majority of patients were men \( n=377; 70.7\% \), in New York Heart Association HF class II \( n=428; 80.3\% \), with LVEF \( >35\% \) in about half \( n=254; 47.7\% \), and history of myocardial infarction in 238 \( 44.7\% \) patients. There were 125 deaths overall during the median 44-month follow-up, including 105 cardiac deaths, 20 noncardiac death, 53 non-SCDs, and 52 cases of SCD. Among 254 HF patients with LVEF \( >35\% \), 39 died during follow-up, cardiovascular cause of death was established in 32 patients, and SCD was established in 15 patients.

**IDEAL Study Population**

We analyzed data of 181 healthy subjects in the IDEAL database (mean age, 38.7±15.7; range of age, 18–82 years; men, 51%; 93.8% whites), predominantly nonsmokers \( 71.4\% \) with a mean body mass index of 24.1±4.5 kg/m\(^2\).

**Beat-to-Beat QT Variability**

QTVI was significantly higher in MUSIC HF patients than in healthy IDEAL participants \( -1.56 \text{ [95% CI, } -2.61 \text{ to } -0.42\] versus \(-2.23 \text{ [95% CI, } -3.39 \text{ to } -1.05\]); \( P<0.00001 \); Figure 1). To determine the threshold of abnormally amplified QTVI, which would separate healthy individuals from HF patients at risk, we compared percentiles of QTVI in HF patients and healthy subjects. The threshold of the highest QTVI quartile in HF patients (above \(-1.19\); 95% CI, \(-1.27 \text{ to } -1.13\)) corresponded to the threshold of QTVI above the 97.5th percentile of healthy individuals’ values (above \(-0.97\); 95% CI, \(-1.32 \text{ to } -0.42\)). Interestingly, HF patients with QTVI in the highest quartile had smaller LV mass and narrower QRS (Table 1). As expected, the highest QTVI quartile was characterized by significantly increased QTVN, faster heart rate, decreased mean duration of QT interval, diminished LogHRV, and reduced coherence (Table 2). Although the heart rate at rest was slower in patients with LVEF \( >35\% \), there were no significant differences in QT variability parameters between HF patients with LVEF \( \leq 35\% \) and those with LVEF \( >35\% \) (Table 2).

**Predictive Value of QT Variability: Competing Risk Analyses**

Overall mortality was almost twice as high in patients with QTVI in the highest quartile \( [42 \text{ deaths (31.6\%); mean survival time, 40.4 [95\% CI, 38.0–42.8] months}] \) versus 74 deaths.

![Figure 1. Histograms showing QT variability index (QTVI) distribution. Histograms showing the distribution of the QTVI in healthy Intercity Digital Electrocardiogram Alliance (IDEAL) subjects (empty bars) and heart failure participants of Muerte Subita en Insuficiencia Cardiaca (MUSIC) study patients (full bars).](http://circep.ahajournals.org/)

Table 1. Clinical Characteristics of MUSIC HF Patients With QTVI Dichotomized at the 75th Percentile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>QTVI &lt;75th Percentile (n=400)</th>
<th>QTVI ≥75th Percentile (n=133)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD, y</td>
<td>63.4±11.3</td>
<td>62.3±12.7</td>
<td>0.434</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>110 (27.5)</td>
<td>46 (34.6)</td>
<td>0.120</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>196 (49.0)</td>
<td>70 (52.6)</td>
<td>0.468</td>
</tr>
<tr>
<td>History of MI, n (%)</td>
<td>176 (44.0)</td>
<td>61 (45.9)</td>
<td>0.708</td>
</tr>
<tr>
<td>LVEF ≤35%, n (%)</td>
<td>213 (53.3)</td>
<td>66 (49.6)</td>
<td>0.468</td>
</tr>
<tr>
<td>Mean LVEF</td>
<td>38±13</td>
<td>40±15</td>
<td>0.291</td>
</tr>
<tr>
<td>LV mass, g/m(^2)</td>
<td>166±53</td>
<td>151±59</td>
<td>0.012</td>
</tr>
<tr>
<td>Restrictive filling pattern, n (%)</td>
<td>29 (7.3)</td>
<td>15 (11.3)</td>
<td>0.144</td>
</tr>
<tr>
<td>NYHA class II, n (%)</td>
<td>327 (81.8)</td>
<td>102 (76.7)</td>
<td>0.202</td>
</tr>
<tr>
<td>NYHA class III, n (%)</td>
<td>73 (18.3)</td>
<td>31 (23.3)</td>
<td>0.202</td>
</tr>
<tr>
<td>( -)Blockers use, n (%)</td>
<td>283 (70.8)</td>
<td>84 (63.2)</td>
<td>0.101</td>
</tr>
<tr>
<td>Heart rate±SD, bpm</td>
<td>65.5±10.9</td>
<td>78.5±13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>123±32</td>
<td>112±27</td>
<td>0.001</td>
</tr>
</tbody>
</table>

MUSIC indicates Muerte Subita en Insuficiencia Cardiaca; HF, heart failure; QTVI, QT variability index; MI, myocardial infarction; LVEF, left ventricular ejection fraction; LV left ventricular; NYHA class, New York Heart Association HF class; bpm, beats per minute.
Table 2. ECG Parameters of MUSIC HF Patients With QTVI Dichotomized at the 75th Percentile and LVEF Dichotomized at 35%

<table>
<thead>
<tr>
<th>Predictor</th>
<th>QTVI &lt;75th Percentile (n=400)</th>
<th>QTVI ≥75th Percentile (n=133)</th>
<th>P Value</th>
<th>LVEF ≤35% (n=279)</th>
<th>LVEF &gt;35% (n=254)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRm±SD, bpm</td>
<td>65.5±10.9</td>
<td>78.5±13.5</td>
<td>&lt;0.00001</td>
<td>70.3±12.7</td>
<td>66.9±13.0</td>
<td>0.001</td>
</tr>
<tr>
<td>LogHRV±SD</td>
<td>6.60±0.95</td>
<td>5.00±0.79</td>
<td>&lt;0.00001</td>
<td>6.21±1.14</td>
<td>6.22±1.16</td>
<td>0.932</td>
</tr>
<tr>
<td>QTm±SD, ms</td>
<td>439.7±47.8</td>
<td>413.4±46.7</td>
<td>&lt;0.00001</td>
<td>432.3±48.4</td>
<td>434.1±49.4</td>
<td>0.528</td>
</tr>
<tr>
<td>QTVN±SD</td>
<td>0.230±0.024</td>
<td>0.245±0.027</td>
<td>&lt;0.00001</td>
<td>0.234±0.025</td>
<td>0.233±0.027</td>
<td>0.528</td>
</tr>
<tr>
<td>Coherence±SD</td>
<td>0.297±0.111</td>
<td>0.252±0.090</td>
<td>&lt;0.00001</td>
<td>0.283±0.109</td>
<td>0.288±0.107</td>
<td>0.414</td>
</tr>
<tr>
<td>QT±SD</td>
<td>−1.83±0.50</td>
<td>−0.66±0.37</td>
<td>&lt;0.00001</td>
<td>−1.56±0.71</td>
<td>−1.52±0.66</td>
<td>0.328</td>
</tr>
</tbody>
</table>

(18.5%; mean survival time, 44.8 [95% CI, 43.6–46.0] months; P=0.002). In competing risk analysis after adjustment for significant predictors of outcomes (Table 3), neither QT variability nor HRV predicted noncardiac death (Table 4). However, QTVI was a strong, independent predictor of cardiovascular mortality (Figures 2A and 3A). In competing risk analysis, QT and HRV strongly predicted non-SCD (Figures 2D and 3D). However, no association between SCD and QTVI was found (Figure 3C; Table 4). There was no significant interaction found between the highest QTVI quartile and LVEF above or below 35% (P=0.162 for non-SCD and P=0.426 for cardiovascular mortality), which confirmed that QTVI predicts cardiac death across the continuum of LV dysfunction equally well.

Additional analysis was performed to assess whether combination of the predictors (QTVI and LVEF) would further improve risk stratification. As expected, patients with the highest QTVI quartile and LVEF ≤35% had the highest risk (Figures 2A–2D and 3A–3D), whereas patients with QTVI in 3 lower quartiles and LVEF >35% had the lowest risk.

To separately examine the predictive value of the numerator and denominator in the QTVI formula one by one, we evaluated the predictive values of QTVI, QTVN, LogHRV, and coherence in univariate and multivariable competing risk analyses. Surprisingly, even in univariate analysis the highest quartile of QTVN did not predict any end point (Table 4), whereas the lowest quartile of LogHRV was significantly associated with cardiovascular mortality and, specifically, non-SCD. Therefore, in the present study, the predictive value of QTVI was because of the denominator in the QTVI formula, as a result of decreased heart rate variability. Importantly, we have found a similar risk for HF patients with the highest QTVI quartile and for patients with QTVI above the 97.5th percentile of healthy individuals’ values (Table 4).

Excluded From QT Variability Analysis

ECG Recordings

In univariate survival analysis, risk of all-cause death was higher in patients excluded from QTVI analysis because of arrhythmia at baseline (Figure 4A). However, in multivariate Cox regression after adjustment for age, sex, history of myocardial infarction, and New York Heart Association HF class, the status of analyzable ECG did not carry independent predictive value (hazard ratio, 0.79 [95%CI, 0.60–1.03];
Cardiovascular mortality (Figure 4B) and SCD (Figure 4C) outcomes did not differ in subjects included and excluded from QT variability analysis.

**Discussion**

To the best of our knowledge, this is the first study that showed that increased QT variability (QTVI) predicts cardiovascular mortality and, in particular, non-SCD but neither noncardiac death nor SCD across a continuum of left ventricular dysfunction in HF patients with LVEF either below or above 35%. For the first time, we showed that abnormally amplified QTVI separates 97.5% of healthy individuals from HF patients at risk and, therefore, could be considered in future investigations to develop strategy of the screening of cardiovascular death risk in the general population. In addition, we demonstrated incremental improvement of risk stratification if QTVI was combined with LVEF.

**Increased QT Variability Index: Absolute Increase in Repolarization Lability or Predominantly Decreased Heart Rate Variability?**

Berger et al.\(^{12}\) in 1997 proposed QTVI as a measure of repolarization lability. During the next 15 years, increased QTVI was shown to be a strong predictor of increased risk of cardiovascular death, SCD, and ventricular arrhythmia in patients with ischemic and nonischemic cardiomyopathy.\(^{13-15}\) Elevated QTVI has also been shown in ischemia,\(^{26}\) hypertrophic cardiomyopathy,\(^{27}\) and long-QT syndrome.\(^{28}\) Importantly, marked elevation of QT variance, rather than a drop in HRV, was responsible for increased QTVI in these conditions. At the same time, increased QTVI was observed in a wide variety of other conditions. Unfortunately, not every study reported data of QTVI formula numerator and denominator. Two scenarios could result in increased QTVI:

1. True dramatic increase in absolute beat-to-beat QT variability (eg, as reported in MADIT II men),\(^{13}\) and
2. Predominantly decreased HRV and out-of-proportion unchanged or mildly increased QT variance (eg, as reported in MADIT II women).\(^{29}\)

**Table 4. Competing Risk Subhazard Ratios of the QT Variability and Heart Rate Variability Parameters in MUSIC HF Patients**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted Subhazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Adjusted Subhazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>1.94 (1.32–2.85)</td>
<td>0.001</td>
<td>1.67 (1.14–2.47)*</td>
<td>0.009</td>
</tr>
<tr>
<td>97.5% QTVI</td>
<td>1.80 (1.21–2.68)</td>
<td>0.004</td>
<td>1.57 (1.04–2.35)*</td>
<td>0.031</td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>1.05 (0.68–1.62)</td>
<td>0.832</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>1.99 (1.33–2.97)</td>
<td>0.001</td>
<td>1.67 (1.11–2.49)*</td>
<td>0.013</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.57 (1.03–2.39)</td>
<td>0.035</td>
<td>2.25 (0.81–1.92)*</td>
<td>0.309</td>
</tr>
<tr>
<td><strong>Extracardiac death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>0.76 (0.28–2.09)</td>
<td>0.596</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>1.09 (0.36–2.71)</td>
<td>0.980</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.10 (0.40–2.06)</td>
<td>0.504</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Nonsudden cardiac death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 QTVI</td>
<td>2.31 (1.87–5.51)</td>
<td>&lt;0.001</td>
<td>2.91 (1.69–5.01)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>2.83 (1.65–4.84)</td>
<td>&lt;0.001</td>
<td>2.58 (1.13–3.78)†</td>
<td>0.001</td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>0.92 (0.51–1.67)</td>
<td>0.786</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>2.30 (1.33–4.00)</td>
<td>0.003</td>
<td>2.00 (1.15–3.48)†</td>
<td>0.014</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.90 (1.08–3.35)</td>
<td>0.026</td>
<td>1.52 (0.85–2.72)†</td>
<td>0.157</td>
</tr>
<tr>
<td><strong>SCD</strong></td>
<td>Q4 QTVI</td>
<td>1.02 (0.57–1.84)</td>
<td>0.945</td>
<td>...</td>
</tr>
<tr>
<td>Q4 QTVN</td>
<td>0.99 (0.53–1.85)</td>
<td>0.971</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 LogHRV</td>
<td>1.22 (0.64–2.33)</td>
<td>0.542</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Q1 Coherence</td>
<td>1.53 (0.85–2.77)</td>
<td>0.157</td>
<td>...</td>
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<tr>
<td><strong>Q1 Coherence</strong></td>
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<tr>
<td>Q1 Coherence</td>
<td>1.20 (0.64–2.25)</td>
<td>0.569</td>
<td>...</td>
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</tr>
</tbody>
</table>

MUSIC indicates Muerte Subita en Insuficiencia Cardiaca; HF, heart failure; QTVI, QT variability index; QTVN, QT variance, normalized by mean QT interval; LogHRV, log-transformed heart rate variability; SCD, sudden cardiac death.

Q4 QTVI is the highest quartile of QTVI.

97.5% QTVI is QTVI above the 97.5th percentile of healthy individuals’ values.

Q4 QTVN is the highest quartile of normalized QT variance.

Q1 LogHRV is the lowest quartile of LogHRV.

Q1 Coherence is the lowest quartile of coherence between heart rate variability and QT variability. *Adjusted for left ventricular ejection fraction <35%, New York Heart Association HF class, N-terminal pro-B-type natriuretic peptide >1000 ng/L, positive Troponin, nonsustained ventricular tachycardia, and frequent premature ventricular contractions.

†Adjusted for age >65 years, left ventricular ejection fraction <35%, New York Heart Association HF class, and N-terminal pro-B-type natriuretic peptide >1000 ng/L.

**P value 0.085.** Cardiovascular mortality (Figure 4B) and SCD (Figure 4C) outcomes did not differ in subjects included and excluded from QT variability analysis.
Mechanisms of Repolarization Lability

The mechanisms and arrhythmogenic potential of elevated QT variability have been recently reviewed. An experimental and theoretical study showed that stochastic fluctuations of $I_{Ks}$ gating in the presence of $I_{Kr}$ block and cell-to-cell uncoupling lead to beat-to-beat variability of QT interval on pseudo-ECG. In another experiment, QTVI correlated directly with integrated left stellate-ganglion nervous activity in an HF dog model. In the study of hypertensive patients, QT variability significantly correlated with cardiac norepinephrine spillover into the coronary sinus. Increased intracardiac QT variability on bipolar near-field cardioverter-defibrillator electrogram confirmed that repolarization lability is present throughout the ventricles. Degree of beat-to-beat QT variability in humans observed in experiments is modest. In our study, QTVN was not elevated in HF patients with SCD outcome.

Methods of QT Variability Measurement

A previous study by Haigney et al underscored the importance of the U-wave inclusion in the repolarization template. QT variability method by Berger measures repolarization lability by stretching or compressing the JT interval (from the J point to the end of the U wave) but does not precisely delineate the end of the T wave. In the present study, we used a slightly different approach developed in Tereshchenko’s laboratory. Importantly, U wave is included in analysis by both methods. The U wave is an arch of the T loop and has to be analyzed accordingly, as a part of repolarization.

In our previous study, we showed that both QTVI and short-term variability (STV) of QT interval have similar predictive values for ventricular arrhythmia. There is a minor difference in QTVI and STV methodologies: although STV quantifies absolute differences in QT interval duration between consecutive beats, QTVI quantifies normalized QT variance during a time epoch. Importantly, in the present study we showed that risk of cardiovascular death and SCD is similar in patients eligible and noneligible for QT variability analysis ECGs.

QTVI Separates 97.5% of Healthy Individuals From HF Patients at Risk

Our study showed that QTVI separates 97.5% of healthy individuals from HF patients at risk of cardiovascular and,
Tereshchenko et al. QT variability in LVEF >35%

in particular, non-SCD. The predictive value of QTVI is independent of LVEF. Therefore, assessment of repolarization lability could be a valuable tool in future for screening for the risk of cardiovascular death in the general population. Additional studies are needed to confirm its predictive value.

Prediction of Mortality in Patients With LVEF >35%

Very few studies have explored the predictive value of ECG parameters in HF patients with LVEF >35%. In a Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca-Heart Failure trial (GISSI-HF) study, QTVI predicted cardiovascular and all-cause death. The prognostic significance of clinical and ECG parameters for SCD was previously investigated in the MUSIC study. A decreased heart rate turbulence slope was shown to be associated with an increased risk of SCD in multivariate Cox regression analysis, after adjustment for sex, LVEF, New York Heart Association class, and history of myocardial infarction. A combination of ≥2 abnormal markers (turbulence slope, QT/RR slope, or standard deviation of NN intervals (SDNN) was associated with increased SCD risk. In the "Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function" (ISAR-Risk) study, severe autonomic failure predicted SCD in patients with LVEF above and below 30%. In contrast with successful prediction of SCD by markers of autonomic failure, markers of repolarization heterogeneity were not always helpful in the prediction of SCD in HF with LVEF >35%. Contradictory results of T-wave alternans (TWA) predictive power in HF patients with LVEF >35% were previously reported, although recent analysis of the MUSIC study showed predictive value of TWA for SCD.

Limitations

This was an ad hoc analysis of a prospectively conducted cohort study. Difficulties in adjudication of SCD are well recognized. It was previously shown that in HF patients with relatively preserved LVEF, cases of nonarrhythmic death are frequent. The racial and ethnic composition of the MUSIC study may affect extrapolation of study findings to the entire US population. Specific characteristics of SCD in a Mediterranean Spanish population were recently described.

Disclosures

Ronald Berger holds a patent on the technology for QT variability analysis. The Telemetric and Holter ECG Warehouse initiative is supported by National Institutes of Health grant U24HL096556 (J-P.C.). MUSIC study was supported by the grant G03/078 from the Instituto de Salud Carlos III, Madrid, Spain.
Figure 4. Kaplan-Meier curves for the probabilities of all-cause death (A), cardiovascular death (B), and sudden cardiac death (SCD; C) in patients with available QT variability results (included) and those who were excluded from QT variability analysis as nonanalyzable.

References
CLINICAL PERSPECTIVE

Increased QT variability index predicts cardiovascular mortality and, specifically, nonsudden cardiac death but not sudden cardiac death and noncardiac death in heart failure across a continuum of left ventricular dysfunction. Abnormally elevated QT variability index separates 97.5% of healthy individuals from subjects at risk. Further investigation of QT variability index as a potential screening tool in the general population is warranted.
Predictive Value of Beat-to-Beat QT Variability Index Across the Continuum of Left Ventricular Dysfunction: Competing Risks of Noncardiac or Cardiovascular Death and Sudden or Nonsudden Cardiac Death

Larisa G. Tereshchenko, Iwona Cygankiewicz, Scott McNitt, Rafael Vazquez, Antoni Bayes-Genis, Lichy Han, Sanjoli Sur, Jean-Philippe Couderc, Ronald D. Berger, Antoni Bayes de Luna and Wojciech Zareba

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