Risk of Mortality Associated with QT and JT Intervals at Different Levels of QRS Duration (from the Third National Health and Nutrition Examination Survey [NHANES III])

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Abstract

QT prolongation in the setting of QRS>120 ms is believed to be triggered by prolonged depolarization rather than repolarization. Hence, JT interval is suggested as an alternative to QT interval when QRS duration is prolonged. It is unclear, however, if JT and QT intervals portend similar risk of mortality for different durations of QRS. We examined the association between QT and JT, separately, with all-cause mortality across different levels of QRS duration in 8,025 participants (60±13 years, 41% white, and 54% women) from the Third National Health and Nutrition Examination Survey. At baseline (1986–1994), 486 (6%) participants had QRS duration≥120 ms. During a follow-up of up to 18 years, 3,045 (38%) deaths occurred. There were significant non-linear relationships of QT and JT intervals with mortality (p <0.001). Hence, QT and JT were categorized as prolonged (>95th percentile), shortened (<5th percentile) and normal (reference group). In multivariate adjusted Cox regression models, prolonged JT [HR (95% CI): 4.75, (1.86, 12.11)] was associated with increased risk of mortality more than prolonged QT [HR (95%CI):1.50 (1.03, 2.17)] in participants with QRS ≥120 ms (Interaction p=0.02). In participants with QRS duration <120ms, prolonged QT and JT were equally predictive of all-cause mortality [HR (95%CI): 1.27(1.06, 1.54)] and [1.31 (1.10, 1.55)], respectively. Similar patterns were observed with shortened QT and JT intervals. In conclusion, although both QT and JT intervals are

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DISCLOSURES
None
predictive of mortality, JT is more predictive in the setting of QRS duration >120 ms supporting the use of JT interval in individuals with prolonged QRS.

Keywords
JT interval; QT interval; NHANES; mortality

INTRODUCTION
Prolonged QT interval has been shown to be one of the strongest risk factors of mortality in various populations. In patients with QRS duration ≥120 ms, QT interval increases due to prolonged duration of QRS and thus, JT interval is recommended to be used for identifying patients at higher risk of torsades de pointes. Since QT interval is considered primarily as a measure of repolarization more than the depolarization abnormality, special considerations must be taken in the presence of QRS >120 ms where depolarization abnormality becomes a significant part of QT interval. Therefore, JT interval is thought to convey better prognostic information regarding mortality risk specifically attributable to repolarization abnormalities. Because of this, the American College of Cardiology and American Heart Association recommend measuring JT interval instead of QT interval when QRS is >120 ms. Both QT and JT interval are known to be associated with mortality. However, it is not well established if QT interval mortality risk is similar for individuals with QRS duration ≥120 ms and <120 ms. If both JT and QT intervals provide similar prognostic information regardless of QRS duration, this will suggest they can interchangeably be used for risk stratification in patients with both normal and prolonged QRS duration. This may also help to simplify risk management of such patients. Thus, we aimed to examine the risk of mortality associated with QT and JT intervals in community-dwelling adults at different levels of QRS duration.

METHODS
The National Health and Nutrition Examination (NHANES) III survey was conducted using a representative sample of the non-institutionalized United States (US) population which included individuals who participated in the survey both during an in-home interview as well as subsequent visit to a mobile examination center for a period of six years from 1988 to 1994. As part of the in-home interview, data were obtained which included complete medical history encompassing individual’s smoking history and medications, demographics, body mass index, blood pressure measurements and total serum cholesterol levels. Blood pressure readings were taken during the in house evaluation and again during their visit at the mobile examination center. These blood pressure measurements were averaged for each individual for this study. Elements of history were obtained by self-report. Prior history of heart failure, prior history of cerebrovascular accident and coronary artery disease were categorized as prior history of cardiovascular disease. NHANES III participants who were 40–90 years of age with quality ECGs and had medical, anthropometric measurements and mortality data available by 2006 were included in this particular study. Trained technicians
recorded standard 12-lead ECG (using Marquette Medical Systems, Milwaukee, Wisconsin) during the study visit at mobile examination center. These ECG recordings were then analyzed digitally using computerized automated analysis of the electrocardiographic data with classification of ECG abnormalities using Minnesota ECG Code Classification. All the ECG abnormalities detected by the software were later on confirmed by an ECG coder visually. The individuals who participated in the NHANES III survey were followed up until December 31, 2006 for mortality. Probabilistic matching method was utilized as a link between the NHANES III participants and the National Death Index for identification of vital status and the cause of death in individuals who died. Gender, date of birth and social security number were part of twelve identifiers which were used to match the participating individuals. The time period between NHANES III examination and December 31, 2006 or date of death with whichever occurring first was defined as the follow up duration.

Categorical variables were reported as frequency and percentage while continuous variables were reported as mean ± standard deviation (SD). Statistical significance for differences in the baseline characteristics between individuals with <120 ms and ≥20ms of QRS duration were tested using the chi-square for categorical data and t-test for continuous data. Due to nonlinear relationship of QT and JT intervals as evidenced by restricted cubic spline models adjusted for model 2 covariates, QT and JT intervals were divided into three groups; >95th percentile (prolonged), 5 – 95th percentile (normal) and <5th percentile (shortened). In the Cox regression models, we used 5 – 95th percentile group as the reference group. Adjusted and unadjusted Cox proportional hazard regression models were used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between QT and JT intervals with mortality. Multivariable models were adjusted as follows: Model 1 adjusted for age, sex, race, and heart rate; Model 2 adjusted for covariates in Model 1 with the addition of antihypertensive medication use, systolic blood pressure, HDL-cholesterol, total cholesterol, body mass index, smoking status, diabetes, history of previous cardiovascular disease (composite of prior history of congestive heart failure, prior history of cerebrovascular accident, prior history of coronary heart disease). Mortality rates were calculated per 1000 person years. Statistical significance was defined as p < 0.05. SAS v 9.2 (SAS Inc. Cary, NC, USA) was used for all analyses.

RESULTS

A total of 8,025 individuals were included in the analysis. The mean age was 60±13 years. There were 41% white, 27% black, and 54% women. The mean QT interval was 407±32 ms and mean JT interval was 309±31 ms. The mean QRS duration was 98±14 ms with 486 (6%) participants having QRS duration ≥20 ms. Participants with QRS duration ≥20 were more likely to be older, white, males, diabetic, ever smoker, hypertensive, had history of prior cardiovascular disease, and have higher systolic blood pressure while less likely to be black, and lower cholesterol, high density lipoprotein and heart rate (Table 1). There were no differences in BMI and diastolic blood pressure between the two groups. During a follow-up of up to 18 (median 14, interquartile range= 12–16) years, 3,045 (38%) deaths occurred, of which 286 (59%) occurred in individuals with QRS duration ≥20 ms. The mortality rate per 1000 person years for participants with normal, prolonged and shortened QT interval were 2.3, 3.5 and 4.0, respectively. For normal, prolonged and shortened JT interval, the mortality...
rates were 2.3, 3.3 and 4.1 per 1000 person years, respectively. There were significant non-linear relationships of QT and JT intervals with mortality (Figure 1 and Figure 2). In multivariable adjusted Cox proportional hazard models, prolonged and shortened QT and JT intervals (compared to normal) were associated with increased risk of mortality (Table 2). However, the magnitude for association of mortality with prolonged JT was greater than prolonged QT interval in individuals with QRS ≥120 ms vs. QRS<120 ms, with p=0.02 for the interaction between the two groups.

DISCUSSION

In this study, we examined the risk of mortality associated with QT and JT intervals in individuals with QRS duration ≥120 ms and <120 ms. We observed that prolongation of both QT and JT intervals was associated with mortality regardless of the QRS duration. However, prolonged JT interval was a stronger risk factor for mortality than prolonged QT interval in individuals with QRS ≥120 ms. We also demonstrated that there is non-linear relationship of both QT and JT intervals with risk of mortality, with shortening of JT and QT being also associated with mortality. Our findings add support to using JT instead of QT in the setting of prolonged QRS duration.

QT interval prolongation has been shown to be an independent predictor of mortality in different populations\(^\text{9-12}\), in patients with metabolic syndrome\(^\text{13}\), end stage renal disease\(^\text{14}\) and as a predictor of sudden cardiac death in patients with left ventricular hypertrophy\(^\text{15}\) and myocardial infarction\(^\text{16}\). Another study evaluated 11,739 subjects with normal conduction and 1,251 subjects with ventricular conduction defects\(^\text{17}\). This particular study included men and women from three population studies including the Cardiovascular Health Study\(^\text{18}\), Atherosclerosis Research in Communities Study\(^\text{19}\) and the Third National Health and Nutrition Examination Survey, and concluded that assessment of prolonged repolarization abnormalities requires the use of JT interval or a bivariate model for QT, with utilizing RR and QRS intervals as covariates. JT has shown to have a prognostic value in a group of patients with Wolff-Parkinsons-White syndrome pre- and post-ablation\(^\text{20}\). Surface ECGs of 29 patients including 16 males and 13 females with WPW pre and post ablation were assessed. Both the QRS and the QT intervals were found to have shortened on the post ablation ECGs compared to preablation ECGs (QRS: 115 ± 23 ms vs 89 ± 15 ms, respectively; P < 0.001), QT: 454 ± 26 ms vs 423 ± 23 ms, respectively; P < 0.001). The preablation JT interval did not change, post ablation (319 ± 21 ms vs 323 ± 23 ms, respectively; P > 0.05). Another study evaluated QT and JT intervals as monitoring tools for drug induced repolarization changes in the setting of ventricular pacing\(^\text{21}\). Results revealed that mean percent increase in peak QT interval during native conduction was significantly greater than during ventricular pacing (12% vs 7%, P = .003). In contrast, peak JT interval during drug loading was not significantly different between native conduction and ventricular pacing (P = .67). This showed that JT interval is a valid assessment for repolarization changes as the JT interval during ventricular pacing correlated with JT interval during native conduction.

The influence of QRS duration on the QT and JT intervals was evaluated by Zhou et al. in 20,687 normal individuals and 2,865 individuals with various ventricular conduction defects.
Variation in QRS duration resulted in 16% of total QT variation but had a negligible effect on JT interval \(^{22}\). It is proposed that if the QRS complex duration is increased, it will result in an increase in QT interval but JT interval will remain unaffected as it does not involve ventricular depolarization.

Prolonged QT interval in individuals with wide QRS complex can be associated with normal repolarization or prolonged repolarization times,\(^ {23}\) and is therefore non-specific. Prolonged QT interval results in abnormal depolarization before the completion of repolarization resulting in premature action potentials\(^ {24}\). As a result, altered ventricular repolarization dynamics predispose to serious ventricular arrhythmias and sudden cardiac death\(^ {25}\). These observations support the idea that JT interval is the true measure of ventricular repolarization\(^ {26}\).

Normal QT interval corrected for heart rate in men ranges from 350–450 ms and in women from 360 to 460 ms \(^ {27}\). QRS duration impacts the QT interval and as a result the prediction of all-cause mortality. An analysis of QT and JT intervals in patients with QRS intervals of more than 120, 120 to 150 and more than 150 ms revealed that JT interval remained relatively stable over a wide range of QRS durations, however QT interval increased with increased QRS duration\(^ {28}\). This creates a potential dilemma as to the validity of the prolonged QT interval in predicting all-cause mortality in the presence of prolonged QRS duration. Our study highlights that both QT and JT intervals are associated with all-cause mortality regardless of QRS duration, with some advantage of using JT in the setting of prolonged QRS duration. In addition, we also observed an increased risk of mortality associated with shortened QT interval (<359 ms) and JT interval (<261 ms). This suggests that short need repolarization is also associated with increased risk of mortality. Previously this was only observed for individuals with short QT syndromes. The present study establishes the importance of JT interval in community dwelling individuals. It also suggests its inclusion in risk stratification algorithms for all-cause mortality.

The strengths of our study include centralized interpretation of ECGs, long term follow up which in turn increases the reliability of the results, large sample size with better generalizability of the United States population. Limitations of our study include self-report of several variables and thus there is a potential for recall or interviewer bias. Single ECG measurements were taken and these intervals may change with subsequent measurements. Information regarding use of QT prolonging medications was not included in the analysis, in which case there might a differential effect of JT and QT intervals in predicting mortality risk.

**Acknowledgments**

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References


Figure 1. Risk of mortality across JT interval
Cubic regression model adjusted for age, sex, race, heart rate, systolic blood pressure, anti-hypertensive medications, diabetes, HDL, body mass index, total cholesterol, ever smoker, history of cardiovascular disease (history of congestive heart failure, previous stroke, and previous coronary artery disease). Knots were placed at 5th, 50th and 95th percentiles. The non-linear relationship was significant (p <0.001)
Figure 2. Risk of mortality across QT interval
Cubic regression model adjusted for age, sex, race, heart rate, systolic blood pressure, antihypertensive medications, diabetes, HDL, body mass index, total cholesterol, ever smoker, history of cardiovascular disease (history of congestive heart failure, previous stroke, and previous coronary artery disease). Knots were placed at 5th, 50th and 95th percentiles. The non-linear relationship was significant (p < 0.001)
Table 1
Baseline characteristics of the study cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>QRS duration (ms)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;120 (n = 7539)</td>
<td>≥ 120 (n = 486)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60±13</td>
<td>67±12</td>
</tr>
<tr>
<td>Males</td>
<td>3369 (45%)</td>
<td>313 (64%)</td>
</tr>
<tr>
<td>White</td>
<td>2916 (39%)</td>
<td>301 (62%)</td>
</tr>
<tr>
<td>Black</td>
<td>2007 (27%)</td>
<td>112 (23%)</td>
</tr>
<tr>
<td>Mexican</td>
<td>2394 (32%)</td>
<td>69 (14%)</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>1720 (23%)</td>
<td>145 (29%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133±20</td>
<td>139±21</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75±9</td>
<td>74±11</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>217±44</td>
<td>211±42</td>
</tr>
<tr>
<td>High Density Lipoprotein Cholesterol (mg/dl)</td>
<td>51±16</td>
<td>48±15</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>28±6</td>
<td>28±6</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)</td>
<td>68±12</td>
<td>67±11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>855 (11%)</td>
<td>73 (15%)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>4541 (60%)</td>
<td>319 (65%)</td>
</tr>
<tr>
<td>Previous cardiovascular disease *</td>
<td>238 (3.2%)</td>
<td>62 (13%)</td>
</tr>
</tbody>
</table>

* Previous cardiovascular disease includes history of congestive heart failure, previous stroke and previous coronary artery disease; Continuous variables are expressed as mean ± standard deviations, while categorical as frequency (percentages)
Table 2
Risk of mortality associated with QT and JT intervals stratified by QRS duration

<table>
<thead>
<tr>
<th>Events</th>
<th>Models</th>
<th>QRS duration (ms)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;120</td>
<td>≥120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2759/7539)</td>
<td>(286/486)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval (&gt;462 ms)</td>
<td>Model 1 *</td>
<td>1.34 (1.13, 1.60)</td>
<td>1.48 (1.04, 2.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2 †</td>
<td>1.27 (1.06, 1.54)</td>
<td>1.50 (1.03, 2.17)</td>
<td></td>
</tr>
<tr>
<td>Prolonged JT interval (&gt;362 ms)</td>
<td>Model 1 *</td>
<td>1.36 (1.16, 1.60)</td>
<td>5.53 (2.21, 13.87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2 †</td>
<td>1.31 (1.10, 1.55)</td>
<td>4.75 (1.86, 12.11)</td>
<td></td>
</tr>
<tr>
<td>Shortened QT interval (&lt;359 ms)</td>
<td>Model 1 *</td>
<td>1.30 (1.09, 1.53)</td>
<td>1.64 (1.32, 2.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2 †</td>
<td>1.26 (1.06, 1.50)</td>
<td>1.65 (1.31, 2.07)</td>
<td></td>
</tr>
<tr>
<td>Shortened JT interval (&lt;261 ms)</td>
<td>Model 1 *</td>
<td>1.42 (1.22, 1.66)</td>
<td>1.16 (0.85, 1.57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2 †</td>
<td>1.41 (1.21, 1.66)</td>
<td>1.18 (0.85, 1.63)</td>
<td></td>
</tr>
</tbody>
</table>

QT and JT were categorized as prolonged (>95th percentile), shortened (<5th percentile) and normal (reference group in the models).

* Model 1: adjusted for heart rate, age, sex and race

† Model 2: adjusted for model 1 variables and systolic blood pressure, anti-hypertensive medications, diabetes, HDL, body mass index, total cholesterol, ever smoker, and history of cardiovascular disease (history of congestive heart failure, previous stroke, and previous coronary artery disease)