QT dynamics early after exercise as a predictor of mortality

Nils P. Johnson, MD, Thomas A. Holly, MD, Jeffrey J. Goldberger, MD, FHRS

From the Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

BACKGROUND Exercise and QT dynamics during ambulatory monitoring impact mortality in a variety of populations. Heart rate recovery (HRR) after exercise is a known strong predictor of mortality.

OBJECTIVE This study assessed the independent prognostic significance of the QT response to changing heart rate (QT dynamics) during recovery from exercise.

METHODS The cohort included patients referred for treadmill exercise stress testing over a 5-year period. Patients had to have at least 4 electrocardiographic tracings within 5 minutes of peak exercise. One had to be recorded 60 seconds into recovery to calculate the HRR. Linear regression of the QT–RR relation during recovery was used to predict the QT interval at cycle lengths of 500 and 600 ms (QT-500 and QT-600). Only studies with an R² ≥ 0.9 (72%) were retained. Optimal binary cut points were chosen. All-cause mortality was determined from either the Social Security Death Index or hospital records.

RESULTS A total of 2,994 patients met inclusion criteria; 228 (7.6%) died during an average follow-up of 7.6 ± 1.9 years. Abnormal QT-500 (>316 ms) was the strongest univariate QT dynamics predictor in a Cox proportional hazards model (hazard ratio = 2.13, P < .001). It remained an independent predictor of mortality after adjustment for age, exercise capacity, medications, single photon emission computed tomography defects, and abnormal (<12 beats/min) HRR (hazard ratio = 1.46, P = .014).

CONCLUSION An abnormal predicted QT interval at 500 ms (120 beats/min) during recovery from exercise independently predicts all-cause mortality. Because QT dynamics in recovery incorporate information on both repolarization and autonomic responsiveness, its role in risk prediction for sudden cardiac death should be further explored.

KEYWORDS QT dynamics; Mortality; Exercise stress test; Heart rate recovery; Prognosis

ABBREVIATIONS ECG = electrocardiogram; EF = ejection fraction; HRR = heart rate recovery; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; SPECT = single photon emission computed tomography; SRS = summed stress score; SSS = summed stress score

Introduction

Sudden cardiac death (SCD) remains a major cause of mortality, with an estimated 184,000 to 462,000 cases occurring annually in the United States. Although patients with marked left ventricular dysfunction have the highest risk of SCD, they represent only a minority of the total. Even within populations for whom implantable cardioverter-defibrillator (ICD) devices have been shown to improve survival, many patients treated with an ICD do not experience SCD. Given the cost, procedural risk, and complications associated with ICDs, a continued need exists to improve the identification of individuals at increased risk for SCD.

Exercise and the postexercise recovery period are associated with a markedly increased relative risk of SCD, ranging from 11 in individuals who regularly exercise to 74 in those who do not. Dramatic physiologic changes occur during this time, with sympathetic excitation and parasympathetic withdrawal during exercise and then their reversal during recovery. One-minute heart rate recovery (HRR) is a simple index that is reflective of these changes and has been shown to be highly predictive of mortality.

Prolongation of the QT interval in normal and diseased populations without the long QT syndrome carries prognostic information. The QT interval varies with heart rate, requiring correction using a variety of proposed formulae that all have significant limitations. Characterizing the rate dependence of the QT interval on the RR interval as it varies naturally, so-called QT dynamics, during ambulatory monitoring has been shown to predict all-cause and arrhythmic death.

Emerging data suggest that QT dynamics during recovery from exercise may provide an integrative measure of autonomic balance under conditions of stress. Because of the increased risk of death during and after the exercise period and the risk imparted by abnormal QT dynamics during ambulatory monitoring, we hypothesized that abnormal QT dynamics during exercise recovery would independently predict all-cause mortality.
Methods

Patient population and clinical data

The institutional review board approved this study. A historical cohort was drawn from consecutive patients referred for a treadmill exercise stress study with single photon emission computed tomography (SPECT) imaging. Inclusion criteria were age at least 18 years, a study performed between August 1998 and December 2003 (to ensure availability of archived and decipherable digitized electrocardiographic [ECG] waveforms), 4 ECG tracings within 5 minutes of peak exercise (in addition to 1 at peak exercise), and 1 ECG tracing recorded 60 seconds into recovery (to compute the HRR6). Exclusion criteria were missing demographic information, a prior included study (only the first of multiple studies was included), or an increase in heart rate of more than 10% between serial tracings during recovery.

Demographic, clinical, and Bruce protocol variables were recorded. In contrast to prior work,6 our exercise laboratory does not use a formal 2-minute cool-down period, although patients continue on the treadmill for approximately 30 seconds after peak exercise before the belt stops. There is no laboratory policy to continue or discontinue beta-blocker medications uniformly, and this decision is left to the referring physician. Rest, stress, and recovery 12-lead ECGs were interpreted using standard criteria.12

The vast majority of SPECT studies used a single-day dual-isotope protocol.13 Rest images were acquired using intravenous thallium-201, and stress images with technetium-99m sestamibi. A minority of studies used a 2-day, high-dose Tc-99m sestamibi protocol in patients over 350 pounds to improve image quality. Images were interpreted using a 20-segment scoring system in which 0 = normal tracer activity and 4 = no tracer activity.13 Total scores for the stress and rest images determined the summed stress score (SSS) and summed rest score (SRS), respectively. The majority of stress SPECT images was ECG-gated to yield the ejection fraction (EF), although arrhythmia limited gating in a minority of patients.

QT dynamics

The ECG waveforms in digital format were extracted from our Marquette MUSE database using custom software. Tracings provide 10 seconds of data in a standard 12-lead arrangement, giving 4 groups of 3 simultaneous leads with 2.5 seconds of data each. Marquette software records the heart rate, from which the RR interval in milliseconds was calculated.

Automated QRS onset was detected using single-lead data via the auxiliary signal method.14 Two QRS onsets detected within 200 ms of each other were assumed to represent the same QRS complex and were treated as such. Automated T-wave offsets were determined by using the publicly available ECGPUWAVE.15 For each set of 3 simultaneous leads (I, II, and III, for example), 2 were chosen for analysis by ECGPUWAVE. Leads I, aVL, V1, and V6 were not used in an attempt to provide the algorithm with uniphasic and high-amplitude T-waves. Two T-wave offsets detected within 300 ms of each other were assumed to represent the same T-wave and were treated as such. QT intervals were calculated as differences between the QRS onset and T-wave offset for each beat. The QT interval for the ECG tracing as a whole was taken as the average of the 25th and 75th percentile of all intervals. Tracings from 30 patients (total of 150 tracings) were analyzed manually for QRS onset and T-wave offset. QT intervals from these tracings were compared with QT intervals determined by the automated QRS onset and T-wave offset.

Linear regression analysis was performed on the QT–RR interval pairs (minimum of 5) obtained at peak exercise and during recovery for each subject. The QT–RR relationship has often been characterized by the slope.10 However, this characterization is less complete because it excludes the intercept.11 To incorporate both components of the QT–RR relationship and provide standardized QT intervals that could be evaluated in the population, predicted QT intervals were calculated from the linear regression formula for cycle lengths of 500 ms (QT-500) and 600 ms (QT-600), corresponding to heart rates in the 100 to 120 beats/min range, using individual slope and intercept results from the regression analysis. QT-500 and QT-600 were defined as: QT-500 (or -600) = intercept + slope × 500 (or 600) ms.

Figure 1 shows raw data, results of the linear regression analysis, and the calculated QT-500 and QT-600 values for an individual patient from our cohort. The QT–RR relationship in recovery is highly linear, with a mean R² value approaching 0.9.11 Because this is the initial evaluation of QT dynamics in recovery for prognosis, to maximize the specificity of the results our primary analysis incorporated only studies with R² ≥ 0.9 and a positive QT–RR slope. However, a second analysis using R² ≥ 0.7 was performed to determine the robustness of the findings. Using the peak exercise tracing and the tracing recorded at 60 seconds, HRR was calculated as the difference between the 2 heart rates.

![Figure 1](image-url)  
Example of QT–RR analysis for an individual patient.
Survival
All-cause mortality was determined from either the Social Security Administration’s Death Master File or our hospital records of inpatient mortality. Length of survival was computed as the number of days between the treadmill exercise stress test and the date of death or the end of December 2008, whichever came first.

Statistical analysis
All statistical tests were performed using STATA version 10.1 (StataCorp, College Station, Texas). The primary analysis for this study evaluated the QT–RR slope, QT-500, and QT-600. Our methods sought to facilitate exploratory data analysis because these variables have no established cutoff values. Therefore, each variable was optimally dichotomized into normal and abnormal groups by maximizing the log likelihood ratio from a Cox proportional hazards model with the limitation that each subgroup had at least 10% of the cohort. This dichotomization simplified tabular, graphical, and statistical comparison of abnormal versus normal subgroups, which seemed most appropriate for this initial exploration of these novel parameters. We also sought to maintain physiologic applicability, as the QT dynamics variables are derived from the slope and intercept values obtained by linear regression. Therefore the arbitrary, but physiologically motivated, QT-500 and QT-600 were used instead of entering both QT–RR slope and intercept as separate variables into models.

Of these variables, QT-500 proved to be most predictive. An exploratory Cox model with both QT–RR slope and intercept determined their optimal weighting. This showed both variables to be simultaneously significant ($P < .001$) with an optimal weighting corresponding to a cycle length of 487 ms, further supporting the choice of QT-500. The data are therefore displayed by normal or abnormal QT-500 subgroups.

Continuous variables were compared using a $t$-test. Categorical variables were compared using the chi-square or Fisher exact test. The unadjusted incidence of all-cause death used the incidence density because follow-up differed for each patient. A Kaplan-Meier survival analysis by QT-500 and HRR subgroups used the log-rank test. All applicable tests were 2-tailed, and $P < .05$ was considered to be statistically significant.

Cross-validation using random subsets was performed to test reproducibility. For each repetition, the entire cohort was randomly split into 2 distinct cohorts of equal size. The first (derivation) cohort was used to select optimal, binary cutoffs for QT-500 and HRR using the technique described earlier. These cutoffs were then applied to the second (validation) cohort to build univariate and multivariable models using the technique described earlier. In total, 100 repetitions were performed, and optimal cutoffs as well as univariate and multivariable hazard ratios for QT-500 and HRR were recorded. These distributions were examined using mean ± standard deviation. The frequency of $P < .05$ for the hazard ratios was recorded for QT-500 and HRR.

Results
Cohort selection and mortality
Between August 1998 and December 2003, our laboratory performed 12,780 stress SPECT studies. Of these, 6,768 (53.0%) used treadmill exercise stress. Further studies were excluded: 2,257 who did not have an ECG tracing at 60 seconds or fewer than 4 tracings within 5 minutes of peak exercise or whose heart rate increased by more than 10% between serial tracings, 284 repeat studies on patients already included, 22 with missing social security numbers, 68 with missing demographic information, 6 under 18 years of age, and 3 whose QT–RR slope was negative. Of the remaining 4,128 studies, 1,134 had least-squares regression $R^2 < 0.9$ and were not included in the primary analysis.

The final cohort consisted of 2,994 patients, which represented 44.2% of all treadmill exercise studies during this period. A total of 228 deaths (7.6%) occurred over an average of 7.6 ± 1.9 years of follow-up. Only 34 patients (1.1%) reported taking an antiarrhythmic medication. A chart review found that 39 patients (1.3%) had an ICD upon entry into the cohort.

Figure 2  Histogram of $R^2$ distribution for QT–RR fit by linear model.
A total of 150 tracings were processed both manually and in automated fashion. Automated QT interval measurements agreed with manual measurements with an overestimation of \( \frac{1}{1.015} \) (\( QT_{\text{automated}} \) vs. \( QT_{\text{manual}} \), \( R^2 = 0.998 \), \( P < .01 \)). Figure 2 shows the cumulative distribution of \( R^2 \) values for a linear fit to the QT–RR relationship, including all 4,511 studies as earlier. The vast majority have a QT–RR relationship accounted for in large part by a linear model: 85% had an \( R^2 > 0.7 \) and 72% had an \( R^2 > 0.9 \).

### Univariate QT dynamics predictors

Table 1 summarizes the results of QT dynamics and HRR univariate predictors and provides their optimal cut points. Our HRR cutoff of <12 beats/min is nearly identical to the cutoff of \( \leq 12 \) beats/min presented in the original study of its prognostic power.\(^6\)

Although all QT dynamics variables were significant predictors of survival by both models, QT-500 had the largest hazard ratio so it was selected as the best single variable to represent QT dynamics in our population. Figure 3 shows Kaplan-Meier survival curves for QT-500 subgroups, demonstrating poorer survival among those with a longer QT-500.

Table 2 shows baseline characteristics for the entire cohort and by QT-500 subgroup. In general, abnormal QT-500 status associates with markers of worse prognosis. Table 3 details the outcomes by QT-500 quartile. Note that the mortality increase clusters in the highest quartile, suggesting an abnormal threshold below which QT-500 has a smaller prognostic gradient.

### Multivariable models

Table 4 explores progressive Cox proportional hazards models. Model 1 includes abnormal QT-500 as a univariate predictor and is the same as the first line of Table 1. Model 2 adjusts for abnormal HRR.

The preliminary effects model includes all univariate predictors with \( P < .25 \), in addition to abnormal QT-500 and HRR: age, male sex, diabetes, family history, hypertension, tobacco use, known coronary artery disease, coronary artery bypass graft, myocardial infarction, percutaneous transluminal coronary angioplasty, resting heart rate, all medical...
Table 3  Survival by QT-500 quartile

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
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<td>288 ± 10</td>
<td>299 ± 2</td>
<td>307 ± 3</td>
<td>325 ± 14</td>
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<tr>
<td>N</td>
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<td>748</td>
<td>749</td>
<td>748</td>
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<tr>
<td>Dead</td>
<td>46</td>
<td>44</td>
<td>52</td>
<td>86</td>
</tr>
<tr>
<td>Mortality (%)</td>
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<td>5.9</td>
<td>6.9</td>
<td>11.5</td>
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<tr>
<td>Length of survival (yrs)</td>
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<td>7.3 ± 2.0</td>
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<tr>
<td>Incidence (per 1,000 patient-years)</td>
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<td>15.7</td>
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</tbody>
</table>

Abbreviations as in Table 2.
worse prognosis than patients with an abnormal QT-500 but normal HRR.

### Sensitivity analysis for R² ≥ 0.7

To determine the robustness of QT dynamics, we expanded our original analysis by including all patients with R² ≥ 0.7 instead of the original criterion of R² ≥ 0.9. This increased the cohort size from 2,994 to 3,505 patients and the number of deaths from 228 to 309. The same analysis as described above was carried out. The results were essentially unchanged. Specifically, the hazard ratio for Model 1 was 2.48 (P < .001), 1.71 (P < .001) for Model 2, and 1.42 (P = .014) for Model 3.

### Cross-validation using random subsets

The univariate hazard ratio for QT-500 in the derivation cohorts was 2.32 ± 0.33 compared with 1.82 ± 0.29 in the validation cohorts, and its adjusted hazard ratio in the validation cohorts was 1.27 ± 0.26. This compares to a univariate hazard ratio for QT-500 in the entire cohort of 2.13 ± 0.31 (68% confidence limit to facilitate comparison with standard deviation) and an adjusted hazard ratio of 1.46 ± 0.23. The univariate hazard ratio for QT-500 had a P < .05 in 83% of the repetitions; the adjusted hazard ratio had a P < .05 in 10%. The derivation cohort cutoff was 314 ± 8 ms.

The univariate hazard ratio for HRR in the derivation cohorts was 2.85 ± 0.49 compared with 2.70 ± 0.42 in the validation cohorts, and its adjusted hazard ratio in the validation cohorts was 1.62 ± 0.38. This compares with a univariate hazard ratio for HRR in the entire cohort of 2.99 ± 0.43 and an adjusted hazard ratio of 1.81 ± 0.29. The univariate hazard ratio for HRR had a P < .05 in 100% of the repetitions; the adjusted hazard ratio had a P < .05 in 50%. The derivation cohort cutoff was 13 ± 2 beats/min.

### Discussion

We found that QT dynamics during recovery from treadmill exercise, as reflected by the predicted QT interval at 500 ms (QT-500), stratified subsequent all-cause mortality. The predictive power of an abnormal QT-500 remained significant after adjustment for abnormal 60-second HRR and important clinical variables. An abnormal QT–RR slope during the early recovery phase from exercise, which is often used to describe the QT–RR relationship, was a less significant predictor. This suggests that, at least in the recovery phase from exercise, the predominantly linear QT–RR relationship is better described by the full linear regression information incorporating both the slope and the intercept.

### Existing literature

Several studies have shown that resting QT dynamics predict outcome, although QT dynamics have been quantified using several metrics, including QT–RR slope, intercept, diurnal slope, and variability ratio. After a myocardial in-
QT dynamics

The QT interval measures the period of ventricular depolarization and repolarization. Repolarization abnormalities can play an important role in arrhythmogenesisis. However, there are a number of technical factors that limit the utility of the raw QT interval. First, the QT interval is highly dependent on heart rate, for which rate correction formulae have been developed. None are optimal, and they are particularly prone to error at extremes of heart rate, as might be observed during exercise. Second, there may be direct autonomic effects on the QT interval. To compensate for these issues, assessment of the QT–RR slope has emerged as a reliable and reproducible method to quantify QT dynamics. The prognostic significance of QT–RR slope has been demonstrated in studies using Holter monitoring in which the heart rate varies naturally throughout the day.

Exercise, in contrast, is an established stimulus that alters the heart rate (and consequently repolarization) and has also been shown to be associated with an increased risk for SCD. Therefore, there is pathophysiologic rationale to evaluate whether exercise-induced abnormalities in repolarization are predictive of SCD. In fact, other parameters of repolarization during exercise, such as T-wave alternans, have been shown to predict SCD. However, that test requires that the target heart rate be achieved with regular R-R intervals, which renders a significant percentage of tests indeterminate. In addition, the test requires special electrodes and recording equipment.

Studying the QT interval during exercise requires some adjustment for the heart rate. Measures such as the QT–RR slope or QT-500 allow for individualized analysis and make fewer assumptions about the QT–RR relationship than do standard correction methods such as the Bazett formula. Using a population-based formula to adjust the QT interval will be limited by the substantial variability among even healthy subjects. In particular, correction formulae may be less reliable at high heart rates.

The present study demonstrates that the QT–RR relationship in recovery is predominantly linear. Although QT–RR slope has been shown to provide important prognostic information when obtained under nonexercise conditions, the QT–RR slope measured in recovery was not an independent predictor in our cohort after adjusting for covariates. As QT–RR slope does not fully characterize the entire QT–RR relationship, use of the linear regression formula to generate a predicted QT interval at a fixed cycle length improved prognostic power in our cohort. Importantly, the predicted QT interval incorporates both the slope and intercept information from the linear regression.

Study limitations

Several limitations in our study should be noted. First, all-cause mortality does not distinguish arrhythmic or cardiac death from other mechanisms. Abnormal QT dynamics would be expected to manifest clinically by sudden cardiac death, although our data could not test this association directly.

Second, we assumed a linear model of QT dynamics during the exercise recovery period. The complete relationship between the QT and RR intervals is complex, and a linear model is only one of several possibilities. However, the generally high R² values in Figure 2 support the concept that most of the QT–RR relationship in early exercise recovery can be explained by a linear relationship. Additionally, the same results hold in Table 4 if a cutoff of R² ≥ 0.7 is chosen instead.

Third, the 60-second HRR is much simpler to compute than QT dynamics and has already been validated as an important prognostic factor during exercise recovery. Further studies will need to evaluate the relative contributions of these parameters for risk prediction of SCD and cardiac-specific mortality.

Fourth, we were not able to include baseline QRS duration in our analysis. Our laboratory strongly encourages adenosine stress in patients with a baseline left bundle branch block or pacemaker activity, due to the rate of false-positive SPECT defects in the septum. Only 17 patients (0.6%) had a baseline left bundle branch block or pacemaker. However, QT interval dependence on the QRS duration may have been affected by other intraventricular conduction delays.

Fifth, we do not have a large, independent cohort to validate our findings. The cutoff values and hazard ratios in the cross-validation cohorts have a similar distribution to the cutoff value and estimated hazard ratio from the cohort when taken as a whole. The lower adjusted hazard ratio in the validation cohorts and less frequent P < .05 for the hazard ratio in any repetition are expected due to the smaller size of the cohort and resulting loss of events, which is a well-known and inherent drawback to cross-validation by random subsets. This is seen more prominently for QT-500 than for HRR, as QT-500 is a weaker predictor than HRR in both univariate and adjusted models.

Finally, only 31% of the population had an EF ≤ 40%, and 1.0% had heart failure. Thus, the predictive value of the QT-500 in these generally higher risk groups will need to be further assessed.
Conclusion
Because risk for SCD is dramatically increased during exercise and recovery, and repolarization abnormalities have also been related to SCD, a strong rationale exists for evaluating exercise-induced abnormalities in repolarization as a predictor of mortality and/or SCD. This is the first large-scale evaluation of QT dynamics during recovery from exercise. We found that QT dynamics during recovery from treadmill exercise stress as reflected by an abnormal predicted QT-500 independently stratified subsequent all-cause mortality.

Further work is necessary to evaluate whether abnormal QT dynamics in recovery are more predictive of sudden versus nonsudden death. In addition, exercise QT dynamics should be applied to populations enriched for SCD, such as those with left ventricular dysfunction.

References