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Novel risk predictor of arrhythmias for patients with potassium channel–related congenital long QT syndrome

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See commentary on page 1572

ABSTRACT

BACKGROUND Congenital long QT syndrome (LQTS) is characterized by delayed ventricular repolarization, predisposing to potentially lethal ventricular arrhythmias. The variability in disease severity among patients remains largely unexplored, underscoring the limitations of current risk stratification methods.

OBJECTIVE We aimed to evaluate the potential utility of electrocardiographic markers from the exercise stress test (EST) in identifying patients with high-risk LQTS.

METHODS The study, which considered patients with LQTS type 1 and LQTS type 2, comprised a discovery cohort of 695 and a validation cohort of 635 patients.

RESULTS The change in corrected QT (QTc) interval between rest and recovery (between rest and 3–4 minutes into the recovery period, called recovery-rest ΔQTc) was consistently greater in symptomatic patients. Sensitivity analyses performed on EST data obtained on and off β-blockers as well as upon distinguishing between patients with a baseline QTc interval below and those above 470 ms demonstrated consistent findings. The association of recovery-rest ΔQTc with cardiac events remained significant in a subanalysis focusing on future events (ie, occurring after the EST). An optimal recovery-rest ΔQTc cutoff was determined for LQTS type 1 (35 ms) and LQTS type 2 (16 ms) separately and was shown to be significantly associated with cardiac events.

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CONCLUSION Our findings suggest that in patients with LQTS, dynamic QT interval measures obtained during the EST are associated with lifetime arrhythmic events and events after the EST. Such measures can be helpful in identifying a higher-risk subset of patients with LQTS in order to optimize their management. Further research may confirm these findings in larger cohorts and explore the potential benefit of combining genetic and EST data for more precise risk stratification.

KEYWORDS Arrhythmias; Long QT syndrome; Exercise stress test; Risk stratification; Genetics

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Introduction

Congenital long QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by delayed ventricular repolarization, resulting in a propensity for early afterdepolarizations, which in turn promote the occurrence of potentially lethal ventricular arrhythmias such as torsades de pointes.[1,2]

The discovery of the causal ion channel genes and reappraisal of gene-disease associations had a large impact on the diagnostic procedures and clinical management of patients with LQTS.[3,4] However, the low disease penetrance and variability in disease severity, even among related individuals harboring the same causal genetic variant, vary significantly and remain largely unexplained. Historically, besides symptom status, age, and sex, the corrected QT (QTc) interval on the baseline electrocardiogram (ECG) has so far been the only clinical marker for risk stratification. Breakthroughs in refinement of risk prediction for cardiac events in more recent years comprised the consideration of the genetic subtype and the location of the causal genetic variant within the ion channel structure.[5–7] Yet, the quest for additional risk factors continues to be fundamental for enhancing the personalized treatment of each patient with LQTS.[1,8] Notably, outcomes of exercise testing, which are used in clinical practice for risk stratification, have so far only been considered for diagnostic purposes in current guidelines for LQTS.[9,10]

In LQTS, cardiac events often occur during increased sympathetic activity, such as physical exertion or emotional distress.[11] Under these circumstances, α- and β-receptor activation enhances potassium currents and subsequently shortens the repolarization phase of the cardiomyocyte. LQTS-causing genetic variants that impair potassium currents make the heart particularly susceptible to the effects of adrenergic activation and increased heart rates.[12,13] Such conditions can lead to pronounced repolarization disparities across the myocardium, and when combined with increased calcium currents, in this setting, these create a risk of arrhythmias.[14] Crotti et al[15] showed that vagal reflexes, translated as heart rate reduction during EST recovery, can contribute to identify patients—in a gene-specific manner—at high or low risk of life-threatening arrhythmias. More recently, Rieder et al[16] demonstrated in a small cohort of patients with LQTS that postexercise QTc interval may be a valuable marker for distinguishing symptomatic from asymptomatic patients, also in a gene-specific manner.

The exercise stress test (EST) evokes sympathetic activation and may thus enhance impaired repolarization, thereby accentuating or unmasking QT and T-wave changes, and mimic proarrhythmic conditions.[17] This is based on the paradoxical prolongation or altered dynamics of QT intervals in response to sympathetic neural stimulation.[18]

We built on previous work describing the phenomenon of QT-RR hysteresis during exercise and recovery, comprising delayed adaptation of the QT interval to changes in heart rate,[19,20] with effects being more pronounced in patients with LQTS.[21]

Through large independent cohorts of patients with LQTS type 1 (LQT1) and LQTS type 2 (LQT2), we tested the hypothesis that not only heart rate dynamics but also measurements of QTc dynamics during the EST may hold the potential for identifying patients at high risk of cardiac events.

Abbreviations

ΔHR: delta heart rate

ΔQTc: delta corrected QT interval

BB: β-blocker

CI: confidence interval

ECG: electrocardiogram

EST: exercise stress test

HR: hazard ratio

LQTS: long QT syndrome

OR: odds ratio

ROC: receiver operating characteristic

Methods

Study population

Genotyped patients with LQTS from the Amsterdam University Medical Center (The Netherlands), University Medical Centre Groningen (The Netherlands), Istituto Auxologico Italiano IRCCS (Italy), L'institut du thorax (France), Rigshospitalet (Denmark), Mayo Clinic (United States), and University Hospital Münster (Germany) were retrospectively included in the study. Here, only probands and family members diagnosed with LQTS and who carried a rare genetic variant in *KCNQ1* (LQT1) or *KCNH2* (LQT2), reflecting the 2 major LQTS subtypes, were included. The study was approved by the medical ethics committee of Amsterdam University Medical Center (ID W19_153 # 19.188). The patients sourced from the Netherlands, Italy, France, and Denmark constituted the discovery cohort, while patients from the United States and Germany comprised the validation cohort. Genetic variant curation was conducted as per American College of Medical Genetics and Genomics and Association of Molecular Pathology guidelines.[22]

Clinical definitions

Symptomatic patients were defined as patients with LQTS who experienced a (presumed) arrhythmic syncope, documented sustained ventricular tachycardia, or (aborted)

sudden cardiac death. These were defined as explained in Online Supplemental Table S1.

ECG analysis

Twelve-lead ECGs were digitally acquired at clinical presentation for analysis of the "baseline QTc interval." The EST was performed with the modified or standard Bruce protocol treadmill test or bicycle ergometry in the upright position, during which a digital ECG was acquired. The EST was generally (but not always) performed at the first presentation in the clinic, regardless of BB use. During the EST, a digital ECG was acquired. Heart rate (in beats per minute) and QT (in milliseconds) measurements were determined uniformly at specific time points of interest selected and measured (1) in the supine resting position, referred to as "rest"; (2) at peak exercise, referred to as "peak"; and (3) at 3–4 minutes after cessation of exercise, referred to as "recovery." ECG analysis (ie, QT measurements at the prespecified time points) was performed by experienced physicians. The tangent method was used to measure the QT interval. The longest QT interval, occurring in any of the 12 leads, was considered but generally measured in leads II and V_5. The mean QT interval of 3 consecutive beats was used. When the isoelectric line was not a consistent straight line at certain heart rates, the closest heart rate was chosen to measure the QT interval to obtain correct measurements (Online Supplemental Figure S1A). Hereafter, the QT interval was corrected for heart rate (QTc) according to the Bazett formula.[23] The change in the QTc interval between (1) rest and recovery (recovery-rest ΔQTc), (2) rest and peak (peak-rest ΔQTc), and (3) peak and recovery (recovery-peak ΔQTc) was calculated for each patient and used in association analyses. An example of an ECG from patients with a large and small (negative) delta between rest and recovery QTc intervals can be seen in Online Supplemental Figures S1B and S1C. Differences in heart rate (ΔHR) were also calculated for each patient at the same time points, providing recovery-rest ΔHR, peak-rest ΔHR, and recovery-peak ΔHR for analyses. An overview of all analyses performed in discovery and validation cohorts can be seen in Figure 1.

Statistical analysis

Baseline continuous variables are presented as mean ± SD and compared between discovery and validation sets using the *t* test. Baseline categorical variables are presented as count and percentage and compared using the Pearson χ^2 test.

Lifetime cardiac events

All analyses related to lifetime cardiac events (ie, follow-up from birth) were performed in patients with LQT1 and LQT2 separately. To investigate associations between the

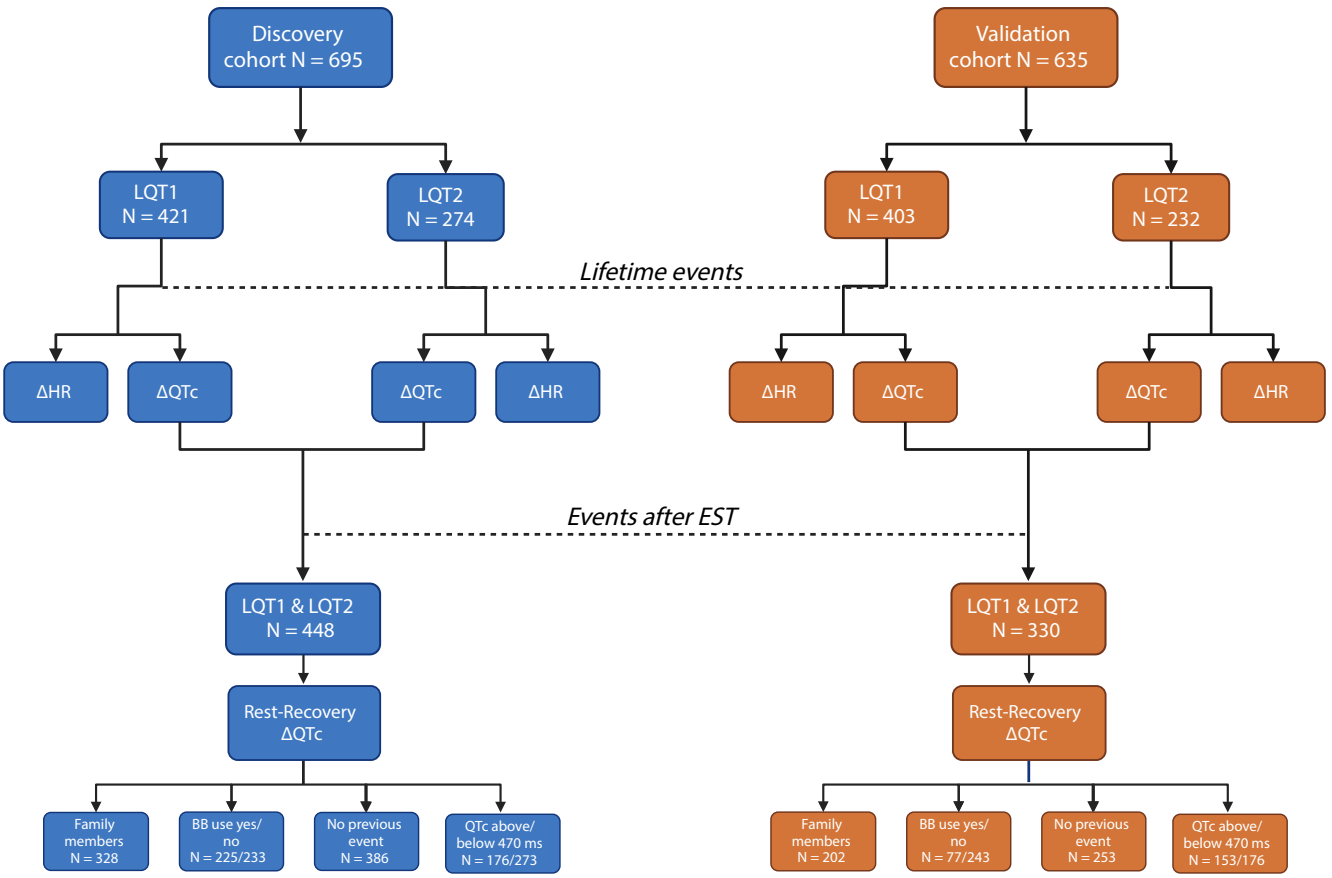

Figure 1
Flowchart of analyses performed in discovery and validation cohorts. Flowchart demonstrates which parameters were assessed for association with lifetime and future events. ΔHR = delta heart rate; ΔQTc = delta corrected QT interval; EST = exercise stress test; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2.

above-mentioned 6 ECG parameters and lifetime cardiac events, we (1) compared the ECG parameters between symptomatic and asymptomatic individuals using the *t* test, (2) performed logistic regression with lifetime cardiac event (yes/no) as an outcome, and (3) performed Cox proportional hazards regression with time to the first lifetime cardiac event as an outcome. This was done separately in the discovery and validation sets. For all regression models, the ECG parameters were (initially) entered as continuous variables, resulting in effects per 1-ms or 1-beat/min increase. Quantitative covariates that were used in all models were age and QTc interval on the baseline 12-lead ECG. Categorical variables were proband or family member status, sex, BB use during the EST, and clinical center. We additionally corrected for the LQT1- and LQT2-specific type of genetic alteration (missense vs non-missense) and the location in the channel protein of the amino acid residue affected by missense variants. This was based on previous publications correlating the location of amino acid change with arrhythmia risk (see Online Supplemental Table S2).[24,25]

To evaluate the added value of including the ECG parameter, the fit of 2 nested logistic/Cox regression models (ie, ECG parameter plus covariates vs covariates only) were compared using a likelihood ratio test. In the case of multiple significantly associated ΔQTc (or ΔHR) variables, the variable with the best fit was selected, resulting in maximal ΔQTc and/or ΔHR to be evaluated in further analyses. Using receiver operating characteristic (ROC) curves based on a predicted survival at 30 years in the discovery set, the optimal cutoff for the selected ΔQTc and/or ΔHR variables was determined on the basis of the maximum Youden's index. Calibration curves were created for the models with the dichotomized ΔQTc and/or ΔHR in the discovery set.

Cardiac events after the EST

Next, we examined the association of EST markers with the incidence of cardiac events occurring *after* the EST assessment. For this, we performed Cox regression analyses focusing on the ΔQTc and/or ΔHR marker that demonstrated the most robust and consistent association with lifetime cardiac events across both the discovery and validation cohorts (see above). Kaplan-Meier curves were created using the dichotomized variables. In these analyses, patients with LQT1 and LQT2 were combined to increase statistical power.

Sensitivity analyses

Several sensitivity analyses were performed to evaluate the utility in clinically relevant scenarios: (1) Since both patients with and without β-blocker (BB) use during the EST were included (to increase statistical power), subanalyses were performed in these 2 patient groups separately. We also compared the association between the EST and events within patients who underwent an EST both on and off BB. (2) To reveal any potential differences in the risk of cardiac events depending on the baseline QTc interval and to account for patients with concealed LQTS, subanalyses were performed in 2 subsets of patients with a baseline QTc interval above or below 470 ms. (3) Subanalyses were conducted in patients who had not experienced a prior cardiac event to evaluate their risk independently of past events. (4) Subanalyses were also performed specifically in relatives of probands to assess the utility of the EST in this subgroup.

All statistical analyses were performed using R software (version 4.3.2, R Core Team, University of Auckland, Auckland, New Zealand) and rms, survival, and survival ROC packages. *P* values <.05 were regarded as statistically significant.

Results

Lifetime cardiac events

Discovery study

We collected 695 patients with LQTS (LQT1, 60.6%; LQT2, 39.4%) with available EST data from the Netherlands, France, Italy, and Denmark. Baseline and demographic characteristics can be seen in Table 1. They comprised 239 probands (34.4%) and 456 family members (65.6%).

LQT1. There were 421 patients with LQT1 who underwent both a baseline 12-lead ECG and an EST. The results of the direct comparison between symptomatic and asymptomatic patients as well as the logistic and Cox regression for association analyses of baseline QTc interval and ΔQTc with cardiac events are presented in Table 2.

Association analyses of peak-rest ΔHR, recovery-peak ΔHR, and recovery-rest ΔHR with cardiac events in patients with LQT1 demonstrated a statistically significant association for peak-rest ΔHR (Online Supplemental Table S3). We observed that symptomatic patients had a lesser degree of heart rate increase between rest and peak exercise (peak-

Table 1 Characteristics of the studied discovery and validation sets of patients with LQT1 and LQT2

	LQT1			LQT2		
Characteristic	Discovery (n = 421)	Validation (n = 403)	*P*	Discovery (n = 274)	Validation (n = 232)	*P*
Female	253 (60)	270 (67)	.204	147 (54)	145 (63)	.039
Age during the EST (y)	30 ± 18	35 ± 17	.002	29 ± 18	35 ± 18	.565
QTc interval at baseline (ms)	461 ± 40	458 ± 42	.312	463 ± 43	464 ± 37	.872
Heart rate at rest (beats/min)	73 ± 15	72 ± 14	.423	76 ± 15	74 ± 15	.817
BB use at the time of the EST	230 (57)	53 (13)	.001	131 (48)	40 (17)	.003
Lifetime cardiac events	68 (16)	74 (18)	.495	31 (11)	38 (16)	.032

Values are presented as mean ± SD or n (%).
BB = β-blocker; EST = exercise stress test; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2.

Table 2 Association analyses of rest-peak ΔQTc, peak-recovery ΔQTc, and rest-recovery ΔQTc with the occurrence of lifetime cardiac events in patients with LQT1 and LQT2

	Discovery cohort				Validation cohort			
Analysis	Peak-rest ΔQTc	Recovery-peak ΔQTc	Recovery-rest ΔQTc	Baseline QTc	Peak-rest ΔQTc	Recovery-peak ΔQTc	Recovery-rest ΔQTc	Baseline QTc
Patients with LQT1								
Symptomatic vs asymptomatic	20 ± 55 vs 18 ± 38; P = .804	25 ± 55 vs 11 ± 38; P = .058	47 ± 39 vs 24 ± 35; P < .001*	482 ± 45 vs 460 ± 38; P .001*	34 ± 45 vs 23 ± 47; P = .074	-3 ± 53 vs -4 ± 45; P = .852	47 ± 43 vs 34 ± 42; P = .018*	472 ± 43 vs 455 ± 32; P = .002*
Logistic regression	OR 1.005 (95% CI 0.996–1.014)	OR 1.007 (95% CI 0.998–1.016)	OR 1.034 (95% CI 1.023–1.047)*	OR 1.016 (95% CI 1.010–1.023)*	OR 1.010 (95% CI 1.003–1.017)*	OR 1.001 (95% CI 0.994–1.008).	OR 1.010 (95% CI 1.002–1.018)*	OR 1.011 (95% CI 1.002–1.020)*
Survival analysis	HR 1.005 (95% CI 0.998–1.013)	HR 1.005 (95% CI 0.999–1.011)	HR 1.022 (95% CI 1.015–1.030)*	HR 1.006 (95% CI 1.001–1.011)*	HR 1.007 (95% CI 1.002–1.013)*	HR 0.998 (95% CI 0.994–1.005)	HR 1.009 (95% CI 1.003–1.015)*	HR 1.015 (95% CI 1.007–1.023)*
Patients with LQT2								
Symptomatic vs asymptomatic	-13 ± 45 vs -12 ± 38; P = .933	39 ± 46 vs 20 ± 37; P = .082	43 ± 39 vs 6 ± 32; P < .001*	494 ± 55 vs 460 ± 39; P = .002*	-13 ± 50 vs -20 ± 51; P = .461	1 ± 58 vs 5 ± 55; P = .734	10 ± 34 vs -7 ± 47; P = .008*	497 ± 52 vs 461 ± 35; P < .001*
Logistic regression	OR 1.018 (95% CI 1.001–1.038)*	OR 0.998 (95% CI 0.983–1.013).	OR 1.040 (95% CI 1.023–1.059)*	OR 1.017 (95% CI 1.004–1.030)*	OR 1.004 (95% CI 0.948–1.014)	OR 0.997 (95% CI 0.988–1.005).	OR 1.009 (95% CI 0.998–1.021)	OR 1.022 (95% CI 1.010–1.035)*
Survival analysis	HR 1.017 (95% CI 1.000–1.035)*	HR 0.987 (95% CI 0.974–0.9996)	HR 1.011 (95% CI 1.001–1.024)*	HR 1.011 (95% CI 1.001–1.021)*	HR 1.003, (95% CI 0.996–1.009)	HR 0.998 (95% CI 0.994–1.006)	HR 1.008 (95% CI 1.000–1.016)*	HR 1.017 (95% CI 1.010–1.025)*

All QTc and ΔQTc values are expressed as milliseconds. Odds ratio (OR) and hazard ratio (HR) are expressed as per 1-ms increase. Direct comparison between symptomatic and asymptomatic.
ΔQTc = delta corrected QT; CI = confidence interval; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; QTc = corrected QT;.
*P < .05.

rest ΔHR) than did asymptomatic patients (59 ± 25 beats/min vs 67 ± 18 beats/min; P = .008). Logistic regression showed similar results, demonstrating an OR per beat/min increase of 0.984 (95% confidence interval [CI] 0.970–0.999). However, Cox regression did not reveal significant association (hazard ratio [HR] 0.989; 95% CI 0.977–1.001).

As expected, symptomatic patients had a higher baseline QTc interval than did asymptomatic patients (482 ± 45 ms vs 460 ± 38 ms; P < .001). Logistic regression showed an odds ratio (OR) per ms increase in QTc interval of 1.016 (95% CI 1.010–1.023), and survival analysis demonstrated an HR per ms increase in QTc interval of 1.006 (95% CI 1.001–1.011).

Association analyses of peak-rest ΔQTc, recovery-peak ΔQTc, and recovery-rest ΔQTc with cardiac events in patients with LQT1 demonstrated a statistically significant association for recovery-rest ΔQTc (Table 2). The mean recovery-rest ΔQTc was 28 ± 37 ms. Recovery-rest ΔQTc was significantly higher in symptomatic patients than in asymptomatic patients (47 ± 39 ms vs 24 ± 35 ms; P < .001) (see Figure 2A). Logistic and Cox regression demonstrated an association between recovery-rest ΔQTc and the occurrence of lifetime cardiac events (OR per ms recovery-rest ΔQTc 1.034; 95% CI 1.023–1.047; C-statistic 88.4%; HR per ms recovery-rest ΔQTc 1.022; 95% CI 1.015–1.030; concordance 0.87).

A recovery-rest ΔQTc cutoff of 35 ms was calculated for the optimal area under the ROC curve (0.84) in Cox regression at 30 years of follow-up from birth. The cutoff was determined on the basis of logistic regression for cardiac events occurring by age 30 (ie, cardiac events at this age may be reported later during the first evaluation). This gave an HR of 3.3 for patients above this cutoff compared with those below (95% CI 1.96–5.57). The positive predictive value was 0.288 (95% CI 0.217–0.360), and the negative predictive value was 0.911 (95% CI 0.875–0.946). Moreover, the inclusion of this recovery-rest ΔQTc cutoff in the Cox proportional hazards model with baseline QTc interval and the aforementioned covariates revealed a significant enhancement in model fit compared with the basic model (P < .001) (see Figure 2B).

LQT2. Recovery-rest ΔHR was significantly higher in symptomatic patients and associated with events in both logistic (OR per beats/min 1.076) and Cox (HR 1.040) regression analyses, but adding it to a model with recovery-rest ΔQTc did not improve predictive power, and no association was found for peak ΔHR or recovery-peak ΔHR.

The mean QTc interval at baseline was higher in symptomatic patients than in asymptomatic patients (494 ± 55 ms vs 460 ± 39 ms; P = .002). Similar findings were observed for logistic (OR per ms 1.017; 95% CI 1.004–1.030) and Cox (HR per ms 1.011; 95% CI 1.001–1.021) regression, as reported in Table 2.

The mean recovery-rest ΔQTc was 10 ± 35 ms. Similar to patients with LQT1, we observed that recovery-rest ΔQTc was significantly higher in symptomatic patients than in asymptomatic patients (43 ± 39 ms vs 6 ± 32 ms; P < .001) (see also Figure 2D). Similarly, logistic and Cox regression demonstrated an association between recovery-rest ΔQTc and the occurrence of lifetime cardiac events (OR per ms

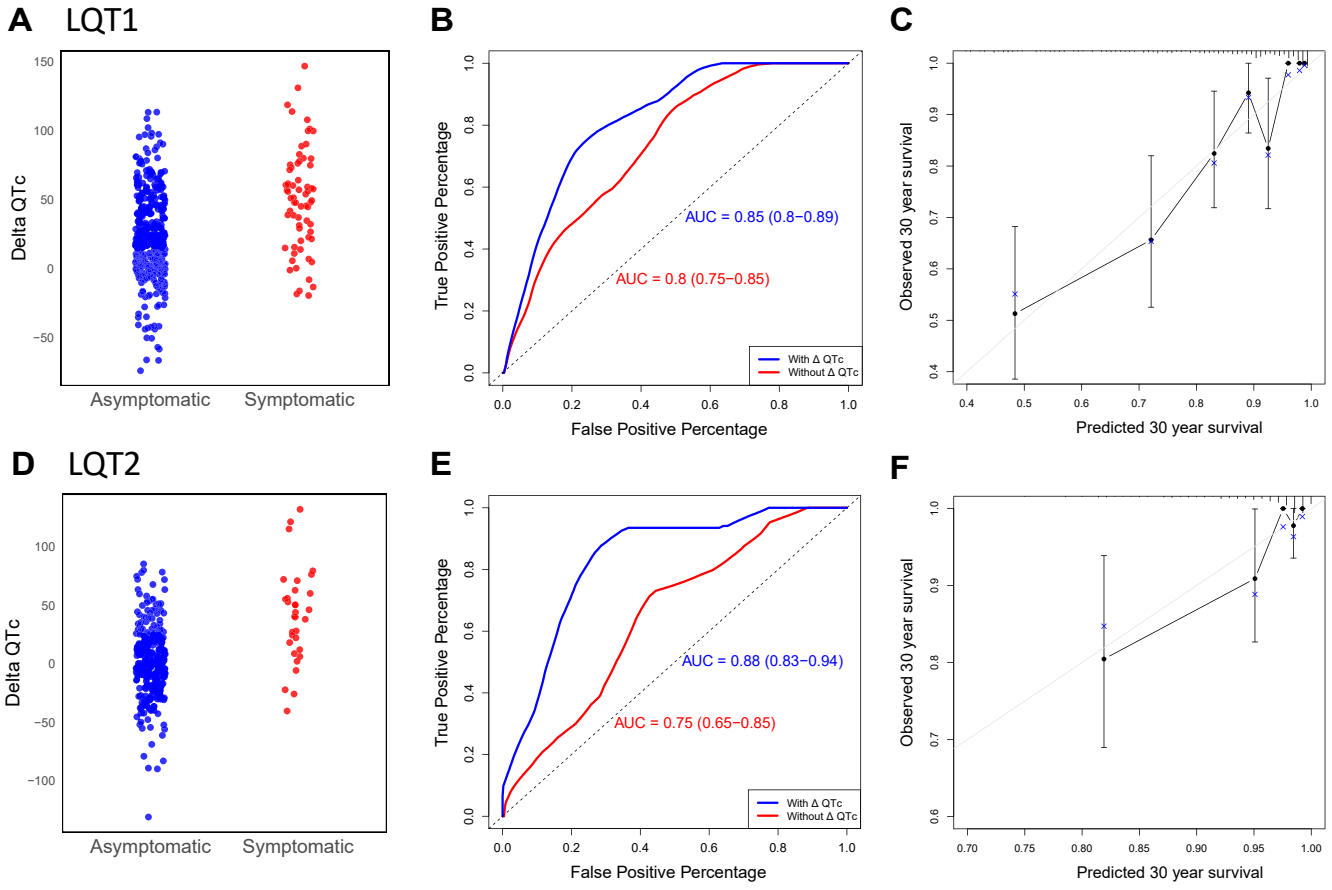

Figure 2
Analysis of patients with long QT sybdrome type 1 (LQT1) and type 2 (LQT2) in the discovery and validation cohorts uncovers an association of delta corrected QT (ΔQTc) with lifetime cardiac events. **A:** Comparison of recovery-rest ΔQTc between asymptomatic and symptomatic patients with LQT1. **B:** Receiver operating characteristic (ROC) curve (*blue line*) from predicted survival at 30 years (model 1) with baseline QTc interval + covariates as described in Methods. ROC curve (*red line*) from model 1 with the addition of rest-recovery ΔQTc, increasing the area under the ROC curve (AUROC) from 80% to 85% in patients with LQT1. **C:** Calibration plot for patients with LQT1 at the optimal ΔQTc cutoff value (35 ms). **D:** Comparison of recovery-rest ΔQTc in patients with LQT2. **E:** ROC curve (*blue line*) from model 1 with baseline QTc interval + covariates. ROC curve (*red line*) from model 1 with the addition of rest-recovery ΔQTc, increasing the AUROC from 75% to 88% in patients with LQT2. **F:** Calibration plot for patients with LQT2 at the optimal ΔQTc cutoff value (16 ms).

1.040; 95% CI 1.023–1.059; C-statistic 92.1%; HR per ms 1.011; 95% CI 1.001–1.024; concordance 0.96).

A recovery-rest ΔQTc cutoff of 16 ms was calculated for the optimal area under the ROC curve (0.87) in Cox regression at 30 years of follow-up from birth. This gave an HR of 4.8 for patients above this cutoff compared with those below (95% CI 2.00–11.72). The positive predictive value was 0.288 (95% CI 0.217–0.360), and the negative predictive value was 0.911 (95% CI 0.875–0.946). Moreover, the inclusion of this recovery-rest ΔQTc cutoff in the Cox proportional hazards model with baseline QTc interval and the aforementioned covariates revealed a significant enhancement in model fit compared with the basic model (P = .004) (see Figure 2E).

Peak-rest ΔQTc was associated with cardiac events in both logistic (OR per ms 1.018; 95% CI 1.001–1.038) and Cox (HR per ms 1.017; 95% CI 1.000–1.035) regression. However, a direct comparison did not show significant differences between symptomatic and asymptomatic patients for this parameter (−13 ± 45 ms vs −12 ± 38 ms; P = .933). Peak-recovery ΔQTc did not display any association (Table 2).

Validation study

Heart rate dynamics. The association between peak-rest ΔHR and cardiac events observed in patients with LQT1 was replicated, with symptomatic patients from the validation set exhibiting a smaller increase in heart rate from rest to peak exercise, as detailed in Online Supplemental Table S3. However, this analysis did not show a significant difference in BB use between symptomatic and asymptomatic patients (P = .13). The association between recovery-rest ΔHR in patients with LQT2 was not replicated.

QTc dynamics. Given the consistent association of rest-recovery ΔQTc with cardiac events in the LQT1 and LQT2 discovery sets, we aimed to validate this in independent cohorts of patients with LQT1 (n = 403) and LQT2 (n = 232) with available baseline ECG and EST data (Table 1).

In both LQT1 and LQT2, mean recovery-rest ΔQTc was higher in symptomatic patients than in asymptomatic patients (LQT1: symptomatic, 47 ± 43 ms vs asymptomatic, 34 ± 42 ms; P = .018; LQT2: symptomatic, 10 ± 34 ms vs asymptomatic, −7 ± 47 ms; P = .008). Recovery-rest ΔQTc was

significantly associated with lifetime events in both patients with LQT1 (HR per ms 1.009; 95% CI 1.003–1.015; concordance 0.77) and those with LQT2 (HR per ms 1.008; 95% CI 1.000–1.016; concordance 0.83), thus validating the findings in the discovery set. The association of peak-rest ΔQTc with lifetime events observed in patients with LQT2 did not replicate (see also Table 2).

For LQT1 and LQT2 together, when applying their gene-specific recovery-rest ΔQTc cutoff (LQT1, 35 ms; LQT2, 16 ms), we were able to validate the significant association with lifetime events in both a single predictor and a multivariable and Cox regression model (Online Supplemental Table S4).

Sensitivity analysis

Symptomatic patients were more likely to be on BB therapy at the time of the EST than asymptomatic patients, with 76% of symptomatic patients and 38% of asymptomatic patients taking BB ($P < .001$). In a sensitivity analysis, we combined patients with LQT1 from the discovery and validation cohorts, as well as patients with LQT2. Cox regression showed a significant association for recovery-rest ΔQTc in both patients on BB and those not (Online Supplemental Table S5). In a subpopulation of 122 patients with LQTS for whom EST data on and off BB therapy were available, we found that recovery-rest ΔQTc was higher in symptomatic patients in both analyses (off BB, 56 ms vs 14 ms; $P < .001$; on BB, 49 ms vs 19 ms; $P = .047$) (see also Online Supplemental Figure S2).

Similarly, an analysis performed separately in patients with a baseline QTc interval below 470 ms and in those with a QTc interval above 470 ms showed a significant association for recovery-rest ΔQTc in both groups (Online Supplemental Table S5).

A sensitivity analysis of rest-peak ΔHR confirmed that the association with cardiac events remained significant when stratifying the cohorts on the basis of BB use at the time of the EST (Online Supplemental Table S6).

In addition to baseline QTc interval, we analyzed the 4-minute recovery QTc interval for LQT1 and LQT2 in both the discovery and the validation cohort, demonstrating similar associations as those of the baseline QTc interval (Online Supplemental Table S7).

Cardiac events after the EST

The above-mentioned analyses demonstrated the relationship between recovery-rest ΔQTc and lifetime cardiac events, not distinguishing between events before or after the EST assessment. We thus performed an analysis, focusing specifically on events after the EST evaluation until the date of last follow-up, to gauge the potential utility of incorporating recovery-rest ΔQTc into a prediction model for future risk.

The LQT1 and LQT2 discovery patient groups were combined to ensure adequate statistical power (n = 448 patients; n = 18 cardiac events). The mean follow-up time was 5.1 years. Multivariable Cox regression analysis accounting for all aforementioned covariates demonstrated an association between recovery-rest ΔQTc and future cardiac events (Table 3). Specifically, the HR per ms for a cardiac event after the EST was 1.025 (95% CI 1.010–1.041; concordance 0.90). To prevent overfitting due to limited events, a Cox model with only recovery-rest ΔQTc showed an HR per ms of 1.017 (95% CI 1.005–1.028). Similar findings were made in the LQT1 and LQT2 validation sets combined (n = 330 patients; n = 15 cardiac events), where the mean follow-up time was 4.3 years. Recovery-rest ΔQTc was associated with the prospective occurrence of a cardiac event in a Cox regression model both with and without inclusion of covariates, with HRs similar to the discovery set (covariate model: HR 1.020; 95% CI 1.003–1.038; concordance 0.88).

The previously calculated recovery-rest ΔQTc cutoff for the optimal area under the ROC curve in LQT1 and LQT2 was also significantly associated with future events (Table 3). Although both groups were analyzed together, each patient group retained its LQT type–specific cutoff values for the Cox regression analysis.

To better determine the potential clinical applicability, we next restricted the analysis (combining LQT1 and LQT2 from the discovery and validation cohorts) to the family members of probands, patients (probands and relatives) who had never suffered from cardiac events before, patients with and without BB therapy at the time of the EST, and patients with a QTc interval above and below 470 ms (Online Supplemental Table S8). A significant association between recovery-rest ΔQTc and future cardiac events was observed in all these subcategories.

Finally, we assessed the association between the previously calculated recovery-rest ΔQTc cutoff for the optimal area under the ROC curve in LQT1 and LQT2 and the occurrence of future cardiac events (Figure 3). This demonstrated a significant association for future events in patients above the QTc interval cutoff compared with patients below (Table 3).

Discussion

We investigated the association between dynamic changes in QTc interval and heart rate during the EST and the occurrence of cardiac events in patients with LQT1 and LQT2. We demonstrated that the change in QTc interval between rest and the 3- to 4-minute postexercise recovery period (recovery-rest ΔQTc) was independently associated with lifetime cardiac events in both patients with LQT1 and LQT2, a finding that was replicated in independent patient sets sourced from different clinical centers. Similarly, recovery-rest ΔQTc was associated with prospective cardiac events, despite management by clinical experts, occurring after the EST assessment. This underscores its potential for clinical utility, particularly in the subcategories that were assessed, as well as the potential use of a cutoff value for recommendations of therapy adjustment.

According to our findings, patients with LQT1 and LQT2 have an increased relative risk of ~1%–2% to develop cardiac events over time for every millisecond increase in recovery-rest ΔQTc. Previous research has demonstrated that repolarization markers on the baseline ECG, such as baseline QTc

Table 3 Association of recovery-rest ΔQTc with occurrence of future events in LQT1 and LQT2 patients combined

	Discovery cohort		Validation cohort		Discovery and validation cohorts together	
Variable	Single predictor	Multivariable model	Single predictor	Multivariable model	Single predictor	Multivariable model
Per 1-ms increase	1.017 (95% CI 1.005–1.028)* n = 448; 18 events	1.025 (95% CI 1.010–1.041)*	1.010 (95% CI 1.000–1.022)* n = 330; 15 events	1.020 (95% CI 1.003–1.038)*	1.014 (95% CI 1.005–1.022)* n = 778; 33 events	1.021 (95% CI 1.010–1.032)*
Above vs below the optimal ΔQTc cutoff	4.11 (95% CI 1.46–11.52)* n = 448; 18 events	5.47 (95% CI 1.69–17.69)*	4.21 (95% CI 1.18–15.00)* n = 330; 15 events	4.45 (95% CI 1.13–17.81)*	3.47 (95% CI 1.61–7.47* n = 778; 33 events	3.13 (95% CI 1.36–7.23)*

HRs shown for Cox regression models testing recovery-rest ΔQTc as a single predictor as well as with other covariates (multivariable model) as described in Methods. HRs are expressed as per 1-ms increase, or above vs below the ΔQTc cutoff previously calculated (LQT1, 35 ms; LQT2, 16 ms). n = number of patients, followed by number of events in that specific subpopulation.
Abbreviations as in Table 2.
*$P < .05$.

interval and T-wave morphology, are closely linked to cardiac events, making them crucial for risk stratification.[5,26] Our findings build on this foundation, suggesting that dynamic QTc responses to exercise stress offer a window into the arrhythmic potential not visible under resting conditions.

Until now, the QTc interval in the 3- to 4-minute recovery period has been used exclusively for diagnostic purposes and is included in the LQTS diagnostic criteria (Schwartz score).[27] However, to date, no studies have focused on ΔQTc in patients with LQTS as a predictor of risk of cardiac events, although 1 study demonstrated a longer QTc interval at 4 minutes postexercise in 4 symptomatic patients with LQT1 than in 4 asymptomatic patients.[16] In our study, a likelihood ratio test indicated that adding recovery-rest ΔQTc to both the logistic and Cox regression models with baseline QTc interval improved the model significantly. This improvement in model performance can be applied to more accurately stratify patient risk, enabling targeted interventions and monitoring for individuals at higher risk.

An approach that incorporates novel markers of risk could potentially lead to a reevaluation of current treatment paradigms, such as the indications for BB therapy (adjustment). For example, patients exhibiting marked ΔQTc changes during the EST might benefit from more aggressive management strategies, even if their resting QTc interval does not indicate high risk (Online Supplemental Table S5). Such a shift toward dynamic risk assessment could optimize treatment efficacy, minimize unnecessary interventions, and ultimately improve patient outcomes. Our focused subanalysis, particularly in family members of probands, emphasizes the predictive value of recovery-rest ΔQTc, reinforcing its utility in risk stratification. This finding is particularly relevant for family screening and management in LQTS, where genetic predisposition plays a crucial role.

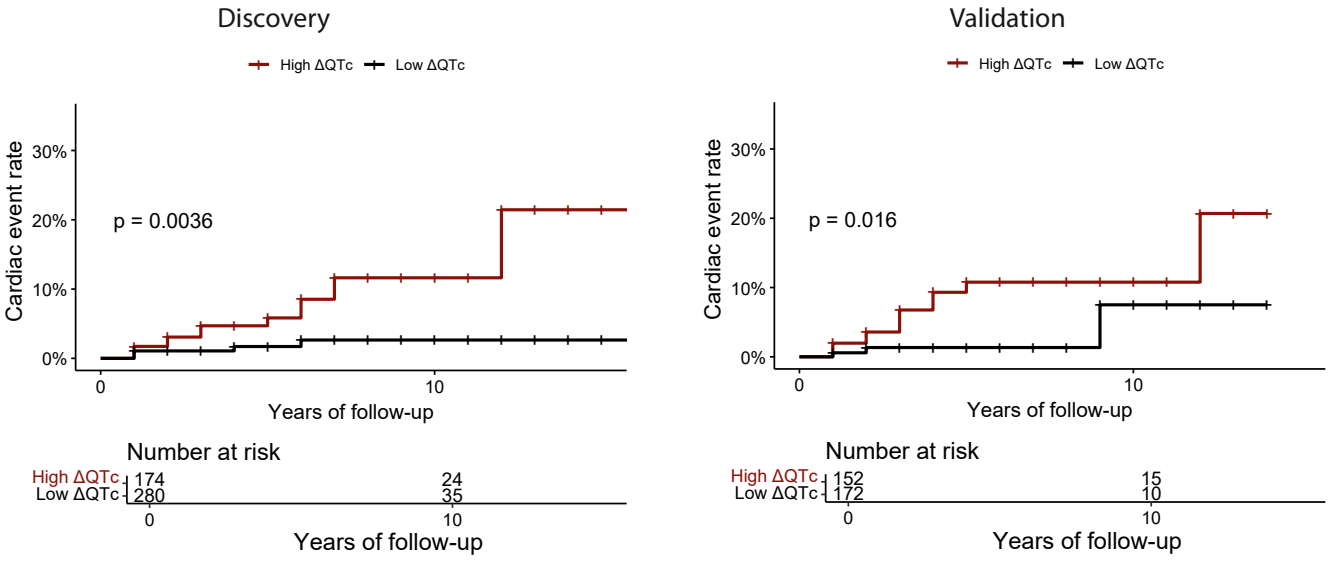

Figure 3
Analysis of patients with long QT syndrome type 1 (LQT1) and type 2 (LQT2) combined in the discovery and validation cohorts uncovers an association of delta corrected QT (ΔQTc) with future cardiac events. This figure illustrates our findings demonstrating the relationship between ΔQTc and future (ie, after the exercise stress test) arrhythmic events for patients with LQT1 and LQT2 combined. A Kaplan-Meier curve shows the difference in future cardiac events between patients classified as those having high and low rest-recovery ΔQTc (LQT1, >35 ms; LQT2, >16 ms).

In our analysis of heart rate dynamics, we accounted for the presence or absence of BB use in patients. Our analysis revealed some associations, and symptomatic patients in the discovery cohort were more likely to be prescribed BB than asymptomatic patients ($P < .001$). This was not observed in the validation cohort ($P = .130$). There were no consistent findings across the discovery and validation sets, with the exception of peak-rest ΔHR in LQT1. These findings suggest some nuanced interplay between autonomic regulation and arrhythmic risk. This is consistent with the broader literature, where Crotti et al identified the autonomic nervous system's role in modulating arrhythmic risk in LQTS. In this study, they identified that a greater heart rate reduction in the first minute of recovery from exercise was able to stratify arrhythmia risk for patients with LQT1, independently of BB therapy.[15] Such insights into the autonomic underpinnings of LQTS provide a compelling rationale for incorporating heart rate dynamics into risk assessment models, alongside the traditional marker.

Recent literature indicates that patients with LQT1 may exhibit chronotropic insufficiency, highlighting the importance of adjusting for BB use in risk assessment.[28] Owing to data availability, especially for patients who had not been seen in the last years, we were able to retrieve more data on exercise tests while on BB use in the discovery cohort than in the validation cohort. To address this, a subanalysis was performed to assess the association between ΔQTc and cardiac events in ESTs conducted on and off BB, revealing a consistent effect in both groups.

Our findings reveal a clear link between the extent of QTc prolongation after exercise and an increased risk of cardiac events. Rare large-effect genetic variants that disrupt repolarizing potassium currents render the heart especially vulnerable to the effects of adrenergic activation. It is well-established that β-adrenergic receptor activation enhances the slow delayed rectifier potassium current (I_{Ks}), leading to action potential shortening.[29] The impairment of I_{Ks} in patients with LQT1 undermines the effect of β-adrenergic stimulation, preventing proper shortening of repolarization with increasing heart rate. This leads to exaggerated regional dispersion of repolarization and premature ventricular beats, which may precipitate torsades de pointes ventricular tachycardia.[30–32] We propose that compromised augmentation of I_{Ks}, and the resultant QTc prolongation, remains significant in the 3- to 4-minute recovery period. Patients with a more pronounced QTc prolongation postexercise may harbor either more severe mutations (associated with a greater loss of channel function) or a constellation of modifiers, including genetic modifiers that act to delay repolarization.[33–36] Future studies should aim to correlate the extent of QTc prolongation in patients with LQTS after exercise with ion channel functionality or to identify distinct adrenergic response variations within these channels.

Prior research has shown that unlike I_{Ks}, the rapid delayed rectifier potassium current, which is compromised in patients with LQT2, predominates at rest. However, it experiences a moderate reduction during adrenergic stimulation.[37] Our results identify a significant association between recovery-rest ΔQTc and cardiac events in patients with LQT2 as well, suggesting that 3–4 minutes postexercise, the rapid delayed rectifier potassium current fails to regain its dominance, resulting in QTc prolongation. Again, this observation could imply the presence of more severe mutations affecting ion channel functionality or the influence of other factors exacerbating this condition.

Limitations and future directions

Despite the strengths of our study, we acknowledge several limitations. The focus on LQT1 and LQT2 subtypes, while clinically relevant, leaves unanswered questions regarding the applicability of our findings to other LQTS subtypes. In addition, the relatively low event rate observed in our cohort underscores the need for larger multicenter studies to validate our findings and explore their applicability to broader populations with LQTS.

The exercise tests were conducted using either a treadmill or a bicycle. While the majority of patients concluded the test owing to exhaustion, there were instances where the test was stopped upon reaching the target heart rate.

The results for LQT2, although the association is statistically significant, are less compelling than for LQT1. A smaller ΔQTc may be difficult for nonexperts to detect, potentially resulting in difficulties in achieving reliable or accurate findings.

Moreover, it has been previously suggested that in children, later evaluation in recovery predicts better LQTS,[38] and it is known that children have a more gradual heart rate deceleration.[39] In our study we measured QTc interval at the 4th minute of recovery. Future studies focusing on children may investigate the value of measuring QTc interval in the 7th minute of recovery.

The integration of novel markers, such as genetic modifiers, serum biomarkers, and imaging parameters, could further refine risk stratification models. Longitudinal studies assessing the predictive value of dynamic EST parameters over time would also provide valuable insights into their role in guiding therapeutic interventions and monitoring disease progression, according to the concept of yearly therapeutic optimization.[40]

The implementation of dynamic QTc measurements in clinical practice will require standardized EST protocols and clinician training to ensure accurate and consistent interpretation of results. Investigating the integration of these parameters into existing clinical workflows and guidelines will be an essential step forward. Moreover, with the expanding use of artificial intelligence in health care,[41,42] ΔQTc could be leveraged in artificial intelligence–driven risk stratification models, providing a valuable tool for enhancing risk assessment and decision making in the near future.

Conclusion

In summary, our study highlights for the first time the clinical utility of the dynamic QTc interval during the EST for potential

risk stratification of lifetime and future cardiac events in LQT1 and LQT2. The validation of these findings in an external cohort strengthens the case for their integration into clinical practice. By moving beyond traditional static measurements to embrace the dynamic responses of the heart to exercise stress, we can achieve a more comprehensive and personalized approach to managing LQTS. As we advance toward this goal, continued research and collaboration across the field will be essential in translating these insights into improved clinical outcomes for patients with LQTS.

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