Utility of Treadmill Testing in Identification and Genotype Prediction in Long QT Syndrome

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Short Title: Exercise Testing to Identify Long QT Syndrome

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Abstract

Background: The clinical diagnosis of Long QT Syndrome (LQTS) remains challenging when electrocardiographic abnormalities are borderline or intermittent. In spite of issues with access, cost and heterogeneity of LQTS mutations, genetic testing remains the diagnostic gold standard for diagnosis of LQTS. We sought to develop a provocative testing strategy to unmask the LQTS phenotype and relate this to the results of genetic testing.

Methods and Results: From 1995 to 2008, 159 consecutive patients with suspected LQTS underwent provocative testing which consisted of a modified Bruce protocol treadmill exercise test, with ECGs recorded supine at rest, immediately upon standing and at 1-minute intervals during exercise, at peak exercise and at 1-minute intervals during the recovery phase. Similar testing was carried out on a stationary bike in a gradual and burst exercise fashion. LQTS was confirmed with genotyping in all 95 affected LQTS patients, and excluded with negative family screening in 64 controls. Patients were studied prior to and after initiation of beta-blockers. Of 159 patients, 50 had an LQT1 mutation and 45 had an LQT2 mutation. In the LQTS group, 44.3% of patients had a normal-to-borderline resting QTc interval. LQTS patients exhibited a greater prolongation in QTc with postural change than unaffected patients [LQT1: 40 ms (IQR 42), LQT2: 35 ms (IQR 46) and LQTS-negative: 21 ms (IQR 37), p=0.029]. During exercise, LQT1 patients had marked QTc prolongation compared to LQT2 and LQTS-negative patients [LQT1: 65 ms (60), LQT2: 3 ms (46), LQTS negative: 5 ms (41), p<0.0001]. QT hysteresis was more pronounced in patients with LQT2 mutations compared to LQT1 and LQT-negative patients [LQT2: 40 ms (10), LQT1: 15 ms (40), LQTS-negative: 20 ms (20), p<0.001]. Beta-blockade normalized the QTc changes seen with standing and QT hysteresis.

Conclusions: The presence and genotype of LQTS can be predicted by a combination of postural and exercise changes in the QT/RR relationship. Beta-blockade normalized these changes. Routine exercise testing is useful in predicting and directing genetic testing in LQTS.

Key words: exercise, QT interval, Long QT Syndrome, diagnosis
Introduction

Long QT syndrome (LQTS) is a cardiac channelopathy that is characterized by a prolonged QT interval, syncope, ventricular arrhythmias and sudden death\textsuperscript{1,2,3}. LQTS mutations are heterogeneous in their phenotypic expression\textsuperscript{4}. The great majority (over 90%) of mutations involve the LQT1 (KCNQ1) or LQT2 (KCNH2) genes, which encode for the \( I_{Ks} \) and \( I_{Kr} \) potassium channels respectively\textsuperscript{3}. In the United States, it is estimated that 4000 people die from resultant sudden cardiac death yearly, the majority of them in childhood or adolescence\textsuperscript{5,6,7}. Excellent outcomes in the management of LQTS have been achieved by lifestyle modification, beta-blocker therapy and selective ICD implantation.

The diagnosis of LQTS remains challenging in patients with borderline ECG abnormalities and a prolonged QT interval is often overlooked\textsuperscript{8}. Genetic testing has come to the forefront as a powerful tool to identify patients with LQTS. Yet, it remains expensive and unavailable to many centers. Furthermore, up to 50% of patients with LQTS can have a normal-to-borderline prolonged QT interval (“concealed” LQTS), making selection of patients for genetic testing difficult\textsuperscript{9,10}. Finally, genetic testing may identify novel LQTS mutations of unclear significance, which could represent normal variants (false positives, single nucleotide polymorphisms), and require validation\textsuperscript{11}. A provocative testing strategy is needed to help unmask the LQTS phenotype to not only guide genetic testing and assist with the diagnosis of LQTS, but also to validate the significance of genetic findings. We examined the utility of a provocative postural and exercise test protocol in identifying
patients with LQT1 and LQT2 mutations among patients referred for evaluation of LQTS at a regional Inherited Arrhythmia Clinic.

Methods

Patients with suspected LQTS were referred to the Inherited Arrhythmia Clinic at the London Health Sciences Centre for assessment. Inclusion criteria included a history of syncope or cardiac arrest, and either the presence of an affected first-degree relative or a borderline-to-prolonged corrected QT-interval (≥440 ms in males and ≥460 ms in females) on their resting 12-lead ECG. Probands underwent comprehensive direct sequencing of the complete KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 genes in either a research laboratory or through PGx Health (New Haven, CT). Sequencing included PCR amplification, forward and reverse sequencing, and comparison to 500-750 normal multiethnic volunteers to detect common polymorphisms. Family members of probands with suspected disease-causing mutations underwent family-specific screening only. Consecutive patients with genetic data between the 1995 and 2008 were included in the analysis. Six LQT3 patients were excluded from the study because of insufficient numbers to permit meaningful comparison. The protocol was approved by the University of Western Ontario Ethics Review Board and all patients provided informed consent.

Provocative testing consisted of a modified Bruce protocol treadmill test and two forms of exercise on a stationary bicycle as described previously12. In the five patients with implanted devices, lower rate was temporarily programmed to as low as 40 bpm to ensure
intrinsic rhythm during exercise testing. Briefly, we obtained 12-lead ECGs of study patients while supine, immediately upon standing and at 1-minute intervals during exercise, at peak exercise, and at 1-minute intervals during the 6-minute recovery phase. Continuous ECGs were also obtained during burst and gradual bicycle exercise testing and during recovery. Blood pressure, heart rate and symptoms were monitored during testing. The QT interval was measured as the time interval in milliseconds (ms) from the beginning of the QRS complex and the end of the T-wave. The end of the T-wave was determined as the intersection point between the isoelectric baseline and the tangent line representing the maximal downward slope of the positive T-wave or maximal upward slope of the negative T-wave. The QT interval was considered the longest interval of all 12 leads, primarily measured in lead II and V5. The mean of 3 QT intervals were used. The corrected QT (QTc) was calculated using Bazett’s formula. All measurements were made manually by a single observer (AK) using a previously validated technique that has been shown to have low intraobserver variability. For males, the QTc was considered normal if it was ≤440 ms, borderline if 441-460 ms and prolonged if >460 ms. For females, a QTc of ≤460 ms, 461-480 ms and >480 ms was defined as normal, borderline and prolonged respectively.

Postural change in QTc was obtained by taking the QTc difference between rest and standing ECGs. Absolute QT shortening refers to the difference between the rest and peak exercise QT intervals (QT_{peak} – QT_{rest}). The QTc prolongation was calculated by taking the difference between the peak exercise and rest QTc intervals (QTc_{peak} – QTc_{rest}). QT hysteresis was determined by calculating the QT interval difference between exercise and 2-
minutes into the recovery phase at similar heart rates (within 10 beats per minute) as previously described\textsuperscript{15}.

Beta-blockers were recommended to all patients with a new diagnosis of LQTS, regardless of symptom status. Beta-blocker use was predominantly Atenolol titrated to 50 mg daily or Bisoprolol titrated to 5 mg daily, targeting a 30 bpm reduction in peak treadmill heart rate at peak workload. If this heart rate change was not achieved, the dose was increased and testing was repeated.

\textit{Statistics}

Continuous variables were compared by use of Mann-Whitney U tests for two-group comparisons and Kruskal-Wallis tests for multiple group comparisons. P-values for multiple comparisons were corrected using a Bonferroni adjustment. Chi-square tests were used for comparison of categorical variables. Results are shown in medians and interquartile range (IQR). Continuous variables are expressed as mean ± standard deviation. Test performance was assessed by use of Receiver Operator Characteristic (ROC) Curves and presented with a p-value testing the null hypothesis that the area under the curve is 0.5. Statistical analysis was performed using SAS software version 9.1 (SAS Institute, Cary, NC) by the authors (LG). P-values <0.05 were considered significant.

\textbf{Results}
Patients

Between 1995 and 2008, 159 patients and family members were assessed for Long QT Syndrome (Table 1). Ninety-five patients were genotype positive for LQTS, with 50 LQT1 patients (28 females; mean age 36±19 years) and 45 LQT2 patients (34 females; mean age 34.5±21 years). A total of 64 patients (39 females; mean age 38±20 years) were genotype negative, representing unaffected family members that served as the control population. The resting QTc was prolonged in patients with LQTS mutations compared to LQTS-negative patients (p<0.0001). In the LQTS group, 24.3%, 20% and 55.7% had a normal, borderline and prolonged resting QTc respectively. In the Controls, 80.5%, 13.9% and 5.6% had a normal, borderline and prolonged resting QTc respectively.

Response of the QTc interval to change in posture and exercise

Patients with LQTS exhibited a greater prolongation in QTc on standing than LQTS-negative patients. [Figure 1a, p=0.029]. During exercise, patients with LQT1 mutations had an attenuated QT shortening compared to LQTS-negative and LQT2 patients [Figure 1b, p<0.0001]. In addition, LQT1 patients had a marked QTc prolongation during exercise, while only a modest change in the QTc interval was observed in LQT2 and LQT-negative patients [Figure 1c, p<0.0001]. Burst bike and gradual bike testing showed similar results, with LQT1 patients demonstrating significantly impaired shortening of their QT interval and pronounced QTc lengthening with exercise (Figure 1b,c). In contrast, LQT2 patients had greater QT hysteresis than LQT1 and LQTS-negative patients [Figure 1d, p<0.0022]. The area under the ROC curve for identifying LQT2 by hysteresis was 0.825 [95% CI (0.721 – 0.930), p<0.0001], for LQT1 by peak exercise prolongation was 0.775 [95% CI
(0.654 - 0.896), p=0.0002], and for LQTS from postural QTc change 0.666 [95% CI (0.544 – 0.789), p=0.0095, Table 2]. In the patients with “concealed” LQTS (resting QTc ≤460 msec in males, ≤480 msec in females), postural QTc increase was >30 msec in 68%.

Exercise QTc prolongation was >60 msec in 94% of concealed LQT1 patients. Hysteresis was >25 msec in 67% of concealed LQT2 patients.

Effect of beta-blocker therapy

The effect of beta-blockade is summarized in Table 3. Treated patients had significantly lower resting and peak exercise heart rates. Furthermore, beta-blockers normalized the postural QTc prolongation and QT hysteresis. Finally, there was a trend toward beta-blocker therapy reducing the QTc prolongation observed during treadmill testing in LQT1 patients [from 65 (IQR 60) to 47 (IQR 45) ms, p= 0.0785].

Discussion

The primary findings of this study of the utility of an exercise protocol to identify patients with LQT1 and LQT2 mutations were: (1) LQTS patients had a greater prolongation of their QTc interval with changes in posture than controls; (2) patients with LQT1 mutations had marked QTc prolongation with exercise; (3) LQT2 patients had an exaggerated QT hysteresis compared to LQT1 and controls; and (4) beta-blockade normalized postural and exercise-induced QTc prolongation and QT hysteresis.
The high prevalence of “concealed” LQTS patients with normal-to-borderline QTc intervals\(^9,10\) and the high degree of heterogeneity and variable penetrance of LQTS mutations\(^4\) contribute to the ongoing challenge of LQTS diagnosis. A provocative testing strategy to unmask the LQTS phenotype and point to a specific genotype would be of considerable value. In a study of 82 patients with genetically identified LQTS, Takenaka et al. showed that a modified Bruce protocol used in combination with a qualitative assessment of T-wave morphology was useful in identifying patients with LQT1 mutations, who experienced marked QTc prolongation during exercise\(^16\). The identification of LQT2 patients was much more limited in this study as it was dependent on the qualitative assessment of T-wave morphology changes during exercise. In a similar study of 147 genotyped patients, Vyas et al. showed that an increase in the QT-interval \(\geq 30\) ms during epinephrine infusion, a strategy pioneered independently by Shimizu\(^17,18\) and Ackerman\(^19\), could identify LQT1 patients with a good degree of accuracy\(^20\). Furthermore, in a study of 103 patients, Swan et al. suggested that a steep QT/RR slope may be useful in identifying patients with LQT2 mutations\(^21\). Finally, our preliminary observations suggested that postural changes in QTc\(^12\) and prolonged QT hysteresis\(^15\) during exercise testing may be helpful in identifying patients with LQTS. The current study suggests that failed QT shortening with exercise is characteristic of LQT1, and exaggerated hysteresis is characteristic of LQT2. Combining postural changes with QT/RR findings from exercise is useful in identifying LQTS patients, predicts genotype in a large proportion of patients, and may be useful in directing genetic testing.
In this study, we found that approximately 44% of patients had a “concealed” QTc interval consistent with previous data from Priori et al., highlighting the low penetrance of LQTS and diagnostic challenge these patients can present\textsuperscript{4,10}. Furthermore, we observed that postural changes in the QTc interval are useful in identifying patients with LQT1 or LQT2 mutations, and could be used as a simple, initial bedside screening test. Walker et al.\textsuperscript{12} had previously described that postural QTc changes could be utilized in the identification of patients with LQT2 mutations, and our data extends this observation to include LQT1 patients. We postulate that even the heart rate increase with posture unmasks reduced repolarization reserve, shifting borderline QT intervals into the clearly abnormal range, as illustrated in Figure 2a. Postural changes typically occur at low-to-intermediate heart rates, in which I_{Kr} is likely to play a significant role in cardiac repolarization. Furthermore, sudden changes in posture lead to a complex physiological response involving sympathetic and vagal-mediated pathways to sustain the appropriate inotropy and chronotropy that may lead to the recruitment of both I_{Ks} and I_{Kr} channels.

In agreement with previous studies, we have also observed that LQT1 patients had an attenuated QT shortening and an exaggerated QTc prolongation during exercise testing. The LQT1 gene encodes for the I_{Ks} potassium channel, which is responsible for the repolarization phase of the cardiac cycle at rapid heart rates. In the absence of functional I_{Ks}, consistent with what we observed in our LQT1 patient cohort, the QT fails to adapt (i.e. shorten) with increasing heart rate. On the other hand, we have also observed that patients with LQT2 mutations have normal QT shortening and minimal prolongation of their QTc interval during exercise. This latter observation is in agreement with previous data from
Swan et al. who proposed that LQT2 patients could be identified by their steeper QT/HR slope during exercise\textsuperscript{21}.

A unique aspect of the current study is the identification of exaggerated QT hysteresis as an LQT2 phenomenon (figure 2b). ROC curve analysis identified QT hysteresis as a good predictor of LQT2 phenotype. Prior to the era of genetic testing, we reported exaggerated RT hysteresis as a characteristic of LQTS based on a Schwartz score alone\textsuperscript{2,15}. In retrospect, the modest sized study population was subsequently found to be composed primarily of LQT2 patients. Our data thus extends these previous observations and suggests that increased QT hysteresis may be a phenomenon unique to LQT2 patients. QT hysteresis is normally measured at 1 – 2 minutes into the recovery phase, when heart rates typically return to approximately 100 beats per minute. In LQT2 patients with impaired I\textsubscript{Ks}, the QT fails to shorten at these intermediate heart rates in early exercise, a so-called “I\textsubscript{Ks} zone”. This is followed by recruitment of I\textsubscript{Ks} above 100 beats per minute through to peak exercise with concomitant appropriate QT shortening, which persists into the recovery phase. This consequently leads to an exaggerated QT difference between the exercise and recovery QT/RR curves that is manifested as increased QT hysteresis.

In agreement with our preliminary observations\textsuperscript{12,22}, beta-blockade normalized QT hysteresis and the QTc prolongation seen with assuming the standing position. In addition, beta-blockers appeared to attenuate the QTc prolongation seen with exercise. These findings suggest that beta-blockade improves QT adaptation to changes in heart rate, perhaps via a direct effect on the “abruptness” of heart rate changes, or an indirect effect on
catecholamines or potassium ion channels. Furthermore, as a result of these changes, testing of suspected LQTS patients while on beta-blockers may mask the LQTS phenotype during exercise and postural testing, limiting test utility. We did not directly address the optimal means to determine beta-blocker efficacy, but we typically target a reduction in peak treadmill heart rate of 30 bpm at peak workload as a practical target for beta-blocker effect.

Several forms of exercise were assessed, with consistent changes noted to distinguish LQTS and genotype. Since findings were consistent, we recommend gradual supine bicycle testing because signal artifact from upper body motion during exercise is minimized.

This study has several limitations. First, our observations are based on a modest sample of patients and may not apply to all genotypes of LQTS. Secondly, in determining the QT interval, identifying the end of the T-wave can be challenging, especially at rapid heart rates. QT hysteresis is determined by calculating the difference between QT intervals during recovery and exercise phases and is typically small; any errors in measuring the QT segment may under- or overestimate the true hysteresis value. Third, Bazett’s formula was used for correction of the QT interval and may be inaccurate at high heart rates. Since the same correction was applied to all groups, this should not have influenced the study results substantively. Finally, LQTS mutations vary in severity depending on the location and nature of the mutation. We analyzed mutations by affected gene and, given the small sample size, did not perform a subgroup analysis by mutation severity. Finally, a validation cohort would have strengthened the findings, which we are currently collecting data on. Despite these limitations, the current study found clear utility in combining posture and exercise
parameters in identifying and predicting genotype in suspected LQTS patients. Further validation with a larger cohort seems appropriate.

In conclusion, QT hysteresis and QTc prolongation with standing and during exercise is useful in the identification of patients with LQTS. Beta-blocker therapy normalized these parameters. Postural and exercise testing is an efficient, accessible and simple test that is a valuable adjunct to genetic testing.

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**Conflict of Interest Disclosures:** none
References


Table 1: Study Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Gene Negative (n = 64)</th>
<th>LQT1 (n = 50)</th>
<th>LQT2 (n = 45)</th>
<th>P</th>
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<tbody>
<tr>
<td>Females, %</td>
<td>61</td>
<td>56</td>
<td>76</td>
<td>0.1214</td>
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<tr>
<td>Age, years</td>
<td>27 (27)</td>
<td>26 (31)</td>
<td>26 (32)</td>
<td>0.9985</td>
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<tr>
<td>Rest HR, bpm</td>
<td>79 (25)</td>
<td>71 (15)</td>
<td>71 (20)</td>
<td>0.2454</td>
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<td>Rest QT, msec</td>
<td>380 (45)</td>
<td>430 (50)</td>
<td>440 (70)</td>
<td>&lt;.0001</td>
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<tr>
<td>Rest QTc, msec</td>
<td>426 (33)</td>
<td>461 (43)</td>
<td>482 (39)</td>
<td>&lt;.0001</td>
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</table>

Median (interquartile range)

Table 2: Test performance of the baseline, postural and peak exercise QTc, and hysteresis in identifying LQTS and predicting genotype.

<table>
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<th>Test</th>
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<tr>
<td><strong>QTc</strong></td>
<td></td>
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</tr>
<tr>
<td>440 msec</td>
<td>89%</td>
<td>66%</td>
</tr>
<tr>
<td>460 msec</td>
<td>67%</td>
<td>89%</td>
</tr>
<tr>
<td>480 msec</td>
<td>37%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Postural QTc increase (LQTS vs. Control)</strong></td>
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</tr>
<tr>
<td>10 msec</td>
<td>84%</td>
<td>33%</td>
</tr>
<tr>
<td>20 msec</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>30 msec</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td><strong>Peak Exercise Delta QTc (LQT1 vs. LQT2/Control)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 msec</td>
<td>90%</td>
<td>44%</td>
</tr>
<tr>
<td>20 msec</td>
<td>80%</td>
<td>61%</td>
</tr>
<tr>
<td>40 msec</td>
<td>73%</td>
<td>83%</td>
</tr>
<tr>
<td>60 msec</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Hysteresis (LQT2 vs. LQT1/Control)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 msec</td>
<td>87%</td>
<td>46%</td>
</tr>
<tr>
<td>25 msec</td>
<td>73%</td>
<td>68%</td>
</tr>
<tr>
<td>35 msec</td>
<td>50%</td>
<td>81%</td>
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</table>
Table 3. Effect of beta blockade on LQT1 and LQT2 patients. P values compare patients on and off beta blockers. Baseline values of LQT negative patients are included for comparison. Values are expressed as medians (interquartile range).

<table>
<thead>
<tr>
<th>Gene Negative (n = 64)</th>
<th>LQT1 (n = 50)</th>
<th>LQT2 (n = 45)</th>
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<tr>
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<td>No Beta-Blocker (n=33)</td>
<td>Beta-Blocker (n=35)</td>
</tr>
<tr>
<td>Rest HR</td>
<td>79 (25)</td>
<td>71 (15)</td>
</tr>
<tr>
<td>Rest QTc</td>
<td>426 (33)</td>
<td>461 (43)</td>
</tr>
<tr>
<td>Stand HR</td>
<td>100 (23)</td>
<td>92 (20)</td>
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<tr>
<td>Stand QTc</td>
<td>454 (54)</td>
<td>521 (76)</td>
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<tr>
<td>Delta Postural QTc</td>
<td>21 (37)</td>
<td>40 (42)</td>
</tr>
<tr>
<td>Peak Treadmill HR</td>
<td>163 (25)</td>
<td>146 (19)</td>
</tr>
<tr>
<td>Peak Treadmill QTc</td>
<td>446 (31)</td>
<td>547 (40)</td>
</tr>
<tr>
<td>Delta Peak Exercise QTc</td>
<td>5 (41)</td>
<td>65 (60)</td>
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<tr>
<td>QT hysteresis</td>
<td>20 (20)</td>
<td>15 (40)</td>
</tr>
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</table>

Figure Legends:

Figure 1: Effect of posture and exercise on QT, QTc and QT hysteresis. A, Change in QTc interval with postural change. B, Change in QT interval with treadmill, burst bike and gradual bike exercise testing. C, Change in QTc interval with treadmill, burst bike and gradual bike testing. D, QT hysteresis. Values expressed as medians and interquartile range.

Figure 2: Effect on posture on QTc and QT hysteresis. A, ECGs showing QTc prolongation with postural change in an LQT1 patient. B, ECGs showing QT hysteresis in an LQT2 patient.
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