Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population
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Chapter 3

Derivation and Validation of a Simple Exercise-Based Algorithm for Prediction of Genetic Testing in Relatives of LQTS Probands

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Abstract

Introduction: Genetic testing can diagnose Long QT Syndrome (LQTS) in asymptomatic relatives of patients with an identified mutation. However, it is costly and subject to availability. The accuracy of a simple algorithm that incorporates resting and exercise ECG parameters for screening LQTS in asymptomatic relatives was evaluated, with genetic testing as the gold standard.

Methods: Asymptomatic first-degree relatives of genetically characterized probands were recruited from 5 centers. QT intervals were measured at rest, during exercise and recovery. Receiver operating characteristics were used to establish optimal cutoffs. An algorithm for identifying LQTS carriers was developed in a derivation cohort and validated in an independent cohort.

Results: The derivation cohort consisted of 69 relatives (28 LQT1, 20 LQT2, 21 genotype-negative patients). Mean age was 35±18 years and resting QTc was 466±39 ms. Abnormal resting QTc (females ≥480 ms; males ≥470 ms) was 100% specific for gene carrier status, but was observed in only 48% of patients. However, mutations were observed in 68% and 42% of patients with a borderline or normal resting QTc, respectively. Among these patients, 4-minute recovery QTc ≥445 ms correctly re-stratified 22 of 25 patients as having LQTS and 19 of 21 patients as being genotype-negative. Combining resting and 4-minute recovery QTc in a screening algorithm yielded a sensitivity of 0.94 and specificity of 0.90 for detecting LQTS carriers. When applied to the validation cohort (n=152, 58 LQT1, 61 LQT2, 33 genotype-negative patients, QTc 443±47ms), sensitivity was 0.92 and specificity was 0.82.

Conclusions: A simple algorithm that incorporates resting and exercise-recovery QTc is useful in identifying LQTS in asymptomatic relatives.
Introduction

Congenital Long QT Syndrome (LQTS) is an inherited cardiac channelopathy characterized by abnormal ventricular repolarization manifested as QT prolongation on the surface electrocardiogram (ECG) and a predisposition to ventricular arrhythmia and sudden death.\textsuperscript{1-3} Subtypes are classified according to the gene affected, with LQTS type 1 (LQT1; \textit{KCNQ1} mutation), LQTS type 2 (LQT2; \textit{KCNH2} mutation) and LQTS type 3 (LQT3; \textit{SCN5A} mutation) accounting for ~90% of patients with identified mutations.\textsuperscript{4} Diagnosis is relatively straightforward in patients with overt QT prolongation or symptoms based on the Schwartz criteria;\textsuperscript{5,6} however, there is significant overlap in the QT range between LQTS carriers and genotype-negative patients, and 25% to 50% of LQTS carriers have a corrected QT interval (QTc) in the normal or borderline range due to a combination of variable penetrance, the effect of modifying genes, and individual variability in QT duration.\textsuperscript{7-13} The diagnosis is particularly challenging in asymptomatic relatives of patients with established LQTS, because the Schwartz criteria rely on the presence of symptoms and QT prolongation.\textsuperscript{5} Accurate identification of LQTS carriers in this subgroup is important because they remain at significant risk of life-threatening cardiac events, and β-blockade is effective for prevention.\textsuperscript{14}

Genetic testing of relatives is advocated in some centers as the gold standard for diagnosis, but it is restricted by cost and availability.\textsuperscript{6,15,16} Postural and exercise provocation have been explored as a means of amplifying phenotypic characteristics, especially in so-called silent mutation carriers with a normal or borderline resting QT interval.\textsuperscript{12,17-26} Numerous exercise parameters have been proposed, but these are limited by the lack of external validation.

The aims of the present multicenter study were to systematically explore the predictive utility of postural and exercise ECG parameters, and to derive and validate a simple exercise-based algorithm for identifying LQTS and predicting genotype in first-degree relatives of probands with established disease.

Methods

Study Population

Study participants were asymptomatic first-degree relatives of consecutive LQTS probands referred to five university teaching hospitals in Canada, The Netherlands and Israel. All probands fulfilled the clinical criteria for LQTS (diagnostic score ≥4)\textsuperscript{5} and were confirmed to have disease-causing mutations in the coding exons of either \textit{KCNQ1} (LQT1) or \textit{KCNH2} (LQT2) genes according to conventional methods. We were unable to identify a sufficient number of families with LQT3 or other genotypes for meaningful inclusion in the present study. First-degree relatives underwent comprehensive clinical screening as well as family-specific genetic screening, and were assigned an LQTS diagnostic score on the basis of previously published criteria.\textsuperscript{5} Patients from a single center (London, ON, Canada) formed the derivation cohort and patients from the
other four centers formed the validation cohort. The study was approved by the ethics review committee of the University of Western Ontario.

**ECG Analysis**

Twelve-lead ECGs were digitally acquired during exercise testing, using the modified or standard Bruce protocol treadmill test or bicycle ergometry. To ensure uniformity across centers, QT measurements were determined at specific time points of interest selected on the basis of the previous exercise literature: (1) supine resting; (2) immediately on standing; (3) at peak exercise; (4) at 1-minute recovery; and (5) at 4-minute recovery.\(^{17,19,23,24,27}\) QT hysteresis was also calculated as the difference in QT interval between exercise and recovery at a heart rate of 100 bpm, as previously described (QT\(_{\text{exercise}}\) – QT\(_{\text{recovery}}\)).\(^{27,28}\) ECG analysis was performed by experienced physicians blinded to the results of genetic screening. The QT interval was measured manually from the beginning of the QRS complex to 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.\(^{28,29}\) The QT interval was considered the longest interval of all 12 leads, generally occurring in lead II and V\(_5\). The mean of three consecutive QT intervals was used. Blinded assessment of interobserver variability revealed no significant differences (r\(^2=0.98\), p<0.001).

QTc was calculated with the Bazett’s formula.\(^{30}\) The resting QTc was considered normal if it was <450 ms in males, <460 ms in females, abnormal if ≥470 ms in males, ≥480 ms in females and borderline if 450 to 469 ms in males and 460 to 479 ms in females.\(^6,11\) ECG readers also evaluated resting T wave morphology and determined the presence of abnormalities based on specific patterns as previously described.\(^{31,32}\) Quantification of T waves in terms of duration and amplitude was not performed in the current analyses.

**Statistical Analysis**

Comparisons between groups were performed using individual-samples t-test, \(\chi^2\) test, and mixed-model analysis, as appropriate. Data from the derivation cohort were used to assess the utility of various ECG parameters for predicting LQTS carrier status and LQTS subtype (LQT1 versus LQT2), with genetic testing results serving as the “gold standard”. Optimal cutoffs for continuous variables were selected to achieve a sensitivity of 90% for LQTS carrier status and >80% for LQTS subtype based on receiver operating characteristics (ROC). Generalized estimating equations were used to adjust for potential correlation between relatives within a family. A multistep screening algorithm was derived, with baseline QTc as an initial criterion because it has been previously reported to be highly specific for LQTS.\(^{11}\) Selection of parameters for subsequent steps of the algorithm was based on those parameters with maximal area under the ROC curve (confidence intervals derived by the nonparametric distribution-free method). The performance of the overall algorithm was evaluated using contingency tables and then tested externally in an independent validation cohort. An a priori decision was
made to evaluate performance of the algorithm in the following subgroups: β-blocker naïve, male and female patients. The algorithm was also tested in a third independent cohort of probands confirmed to have disease-causing mutations in the KCNQ1 or KCNH2 genes. All analyses were performed using SPSS 16.0 for Mac (SPSS Inc., Chicago, IL) and SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics and ECG Parameters

Sixty-nine first-degree relatives were recruited from 26 families. The mean age of the derivation cohort was 35±18 years, 62% of patients were female, and the mean QTc was 466±39 ms (Table 1). On the basis of the Schwartz criteria,6 46% of patients had a low probability (LQTS score ≤1), 22% had an intermediate probability (LQTS score 2-3)

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Derivation cohort (n=69)</th>
<th>Validation cohort (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>35 ± 18</td>
<td>28 ± 17</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>43 (62)</td>
<td>77 (51)</td>
</tr>
<tr>
<td>Resting QTc, ms, mean ± SD</td>
<td>466 ± 39</td>
<td>443 ± 47</td>
</tr>
<tr>
<td>LQTS score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>32 (46)</td>
<td>98 (65)</td>
</tr>
<tr>
<td>2-3</td>
<td>15 (22)</td>
<td>23 (15)</td>
</tr>
<tr>
<td>≥4</td>
<td>22 (32)</td>
<td>31 (20)</td>
</tr>
<tr>
<td>Genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1</td>
<td>28 (41)</td>
<td>58 (38)</td>
</tr>
<tr>
<td>N-terminus</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Transmembrane</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Pore</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>C-terminus</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>LQT2</td>
<td>20 (29)</td>
<td>61 (40)</td>
</tr>
<tr>
<td>N-terminus</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Transmembrane</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Pore</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>C-terminus</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Genotype-negative patients</td>
<td>21 (30)</td>
<td>33 (22)</td>
</tr>
<tr>
<td>β-blocker use, n (%)</td>
<td>23 (33)</td>
<td>45 (30)</td>
</tr>
</tbody>
</table>

QTc indicates corrected QT interval; LQTS, long QT syndrome; LQT1, LQTS type 1; and LQT2, LQTS type 2
*Based on Schwartz criteria6
and 32% had a high probability of LQTS (LQTS score ≥4). Based on genetic testing, 41% were LQT1, 29% were LQT2 and 30% were genotype-negative patients.

Heart rates were significantly lower in LQTS carriers than genotype-negative patients when resting supine, standing, and 1- and 4-minute recovery heart rates were compared (Figure 1A; p<0.05; independent of β-blocker status). QTc was consistently higher in LQTS carriers than genotype-negative patients at rest and during various phases of treadmill exercise testing (Figure 1B; p<0.01 at all time-points; independent of β-blocker status).

**Development of the Algorithm**

Patients were initially stratified as having an abnormal, borderline or normal resting supine QTc using previously published cutoffs (Figure 2A). LQTS carriers accounted for 100% of patients with an overtly abnormal resting QTc, 68% of patients with borderline QTc prolongation and 42% of those with QTc in the normal range, respectively. Notably, 52% of LQTS carriers had a resting QTc in the normal or borderline range. Qualitative T wave abnormalities were present in 36% of patients (Figure 2B). The presence of T wave abnormalities was highly suggestive of LQTS (positive predictive value=0.92) but only 48% of LQTS carriers had T wave abnormalities detected on their baseline ECG. The utility of baseline ECG parameters in predicting LQTS is summarized in Table 2. An abnormal supine QTc was selected as the initial criterion in the screening algorithm for LQTS because of its excellent specificity.

Among patients in the derivation cohort with borderline or normal resting supine QTc (n=46), the predictive value of various exercise ECG parameters was then analyzed using ROC analysis (Figure 3). Of these parameters, the 4-minute recovery QTc had the highest area under the curve (AUC), and on the basis of the ROC, a cutoff of 445 ms was selected, with a sensitivity of 0.90 and a specificity of 0.90 (Table 3). A cutoff of 445 ms appeared to be optimal for detecting LQTS carriers in both male and

![Figure 1](image.png)

**Figure 1.** Comparison of heart rates (mean ± SD; A) and QTc (mean ± SD; B) in LQTS carriers and genotype-negative patients at various stages of treadmill exercise testing. Probability values for comparisons by mixed-model analysis.
Figure 2. Frequency of baseline ECG abnormalities among LQTS carriers and genotype-negative patients (supine corrected QT, A; T wave abnormalities, B). * Cutoffs for supine QTc: Normal, <440 ms in males, <450 ms in females. Borderline, 440-470 ms in males; 450-480 ms in females. Abnormal, ≥470 ms in males; ≥480 ms in females. † T wave abnormality defined as broad-based T waves or low-amplitude T waves with notching in ≥3 leads.

Table 2. Predictive utility of baseline ECG parameters

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Cutoff, ms*</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine QTc</td>
<td>0.79†</td>
<td>Males ≥470, Females ≥480</td>
<td>0.48</td>
<td>1.00</td>
</tr>
<tr>
<td>T wave abnormality ‡</td>
<td>-</td>
<td>-</td>
<td>0.48</td>
<td>0.90</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; QTc, corrected QT interval
* Cutoffs for supine QTc were based on previous literature
† p<0.01; generalized estimating equations were used to adjust for potential familial correlation
‡ Broad-based T waves or low-amplitude T waves with notching in ≥3 leads.

Table 3. Predictive utility of exercise ECG parameters

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>p*</th>
<th>90% Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cutoff, ms</td>
</tr>
<tr>
<td>Standing QTc</td>
<td>0.77</td>
<td>0.02</td>
<td>445 ms</td>
</tr>
<tr>
<td>Peak exercise QTc</td>
<td>0.85</td>
<td>0.01</td>
<td>441 ms</td>
</tr>
<tr>
<td>1-min recovery QTc</td>
<td>0.90</td>
<td>0.02</td>
<td>426 ms</td>
</tr>
<tr>
<td>4-min recovery QTc</td>
<td>0.93</td>
<td>0.01</td>
<td>445 ms</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; QTc, corrected QT interval
* Generalized estimating equations were used to adjust for potential familial correlation.
female patients, with a sensitivity of 0.86 and specificity of 0.93 in female patients, and a sensitivity of 0.91 and specificity of 0.86 in male patients. When we combined the resting supine QTc as the first step and the 4-minute recovery QTc as the second step of a screening algorithm (Figure 4), the overall accuracy for predicting LQTS in the derivation cohort was 0.93, with a sensitivity of 0.94 and specificity of 0.90.

**Prediction of Subtype (LQT1 versus LQT2)**

The ability of ECG parameters to predict LQTS genetic subtype was then evaluated among patients that were assigned a probable diagnosis of LQTS on the basis of the screening algorithm (n=47). Differential QT adaptation during exercise was observed between LQT1 and LQT2 patients, being most pronounced at peak exercise and 1-minute recovery (Figure 5). The performance characteristics of various ECG parameters for differentiating LQTS genotype are summarized in Table 4. Peak exercise QTc and 1-minute recovery QTc had similar AUC values for prediction of LQT1. Peak exercise QTc ≥486 ms had a sensitivity of 0.81 and specificity of 0.90, whereas 1-minute recovery QTc ≥460 ms had a sensitivity of 0.81 and specificity of 0.76. QT hysteresis ≥10 ms had a sensitivity of 0.82 and specificity of 0.55 for prediction of LQT2.

**Figure 3.** Receiver operating characteristics curves for detecting LQTS with standing QTc (A), peak exercise QTc (B), 1-minute recovery QTc (C), and 4-minute recovery QTc (D). Area under the curve (AUC) is presented for each parameter. 95% CI indicates 95% confidence interval.
Figure 4. Screening algorithm for detecting LQTS and predicting genotype. LQTS indicates long QT syndrome; QTc, corrected QT interval; LQT1, LQTS type 1; LQT2, LQTS type 2; and n, number of patients with algorithm applied to derivation cohort.

Table 4. Prediction of LQTS subtype

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>p*</th>
<th>Cutoff, ms†</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive of LQT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad-based T waves</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.27</td>
<td>0.71</td>
</tr>
<tr>
<td>Peak exercise QTc</td>
<td>0.88</td>
<td>&lt;0.01</td>
<td>486</td>
<td>0.81</td>
<td>0.90</td>
</tr>
<tr>
<td>1-minute recovery QTc</td>
<td>0.89</td>
<td>&lt;0.01</td>
<td>460</td>
<td>0.81</td>
<td>0.76</td>
</tr>
<tr>
<td>4-minute recovery QTc</td>
<td>0.72</td>
<td>0.02</td>
<td>458</td>
<td>0.81</td>
<td>0.38</td>
</tr>
<tr>
<td>Predictive of LQT2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-amplitude notched T waves</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.37</td>
<td>0.93</td>
</tr>
<tr>
<td>Standing QTc</td>
<td>0.58</td>
<td>0.54</td>
<td>474</td>
<td>0.83</td>
<td>0.39</td>
</tr>
<tr>
<td>QT Hysteresis‡</td>
<td>0.82</td>
<td>&lt;0.01</td>
<td>10</td>
<td>0.82</td>
<td>0.55</td>
</tr>
</tbody>
</table>

LQTS indicates long QT syndrome; AUC, are under the curve; LQT1, LQTS type 1; QTc, corrected QT interval; and LQT2, LQTS type 2

*Generalized estimating equations were used to adjust for potential familial correlation
†Selected to achieve sensitivity >80% based on receiver operating characteristics curves
‡QT Hysteresis = QT<sub>HR 100 bpm during exercise</sub> – QT<sub>HR 100 bpm during recovery</sub>
wave abnormalities were present in 22 (47%) of 47 LQTS patients (47%). Specifically, only 27% of LQT1 carriers had broad T waves, and 37% of LQT2 carriers had low-amplitude notched T waves. Nevertheless, low-amplitude notched T waves were a relatively specific marker of LQT2 (specificity=0.93).

External Validation of Algorithm
The mean age of the independent validation cohort was 28±17 years and 51% of patients were female (Table 1). On the basis of genetic testing, 38% had LQT1, 40% had LQT2 and 22% were genotype-negative patients. The screening algorithm was applied to the validation cohort (Figure 6; Table 5). The algorithm correctly predicted LQTS carrier status in 136 of 152 patients (overall accuracy=0.89). The sensitivity was 0.92, specificity was 0.82, positive predictive value was 0.95, and negative predictive value was 0.73. The performance of the screening algorithm was similar when applied to a subset of the validation cohort that was β-blocker naïve. Test performance was slightly inferior in male patients compared to female patients. In terms of predicting genetic subtype, abnormal prolongation of 1-minute recovery QTc ≥460 ms correctly differentiated LQT1 subtype in 86 of 115 patients (overall accuracy=0.75), with sensitivity of 0.73 and specificity of 0.76. Peak-exercise QTc ≥486 ms had an inferior performance in the validation cohort with an accuracy of 0.63, sensitivity of 0.48, and specificity of 0.76.

Application of Algorithm in Probands
The algorithm was also evaluated in an independent cohort of probands assessed for possible LQTS that were subsequently confirmed to have disease-causing mutations in the KCNQ1 or KCNH2 genes (n=45). The mean age was 34±15 years; 64% were female; and 23 had LQT1, whereas 22 had LQT2. The mean resting supine QTc was 470±37 ms and mean 4-minute recovery QTc was 509±52 ms. An abnormally prolonged resting QTc (females ≥480 ms; males ≥ 470 ms) was observed in only 38% of patients. Among patients with normal or borderline resting QTc, 4-minute recovery QTc ≥445 ms
correctly identified 25 of 28 patients as having LQTS. The combined diagnostic algorithm had an overall sensitivity of 0.93 for identifying mutation-positive probands.

**Discussion**

In the present study, differential QT response during exercise was exploited to predict LQTS carriers among first-degree relatives of probands with an established diagnosis of LQTS. A simple 3-step screening algorithm was derived based on resting QTc,
4-minute recovery QTc and 1-minute recovery QTc. Subsequent external validation in an independent cohort demonstrated a high degree of accuracy for predicting LQTS carriers, and a moderate degree of accuracy for predicting LQTS subtype.

The diagnosis of LQTS is straightforward in patients with overt QT prolongation. Vincent et al found that a QTc of ≥480 ms in women and ≥470 ms in men was 100% specific for the diagnosis of LQTS.\textsuperscript{11} In our study, using the same criteria, abnormal resting QTc prolongation was 100% specific for LQTS carriers in both cohorts, justifying its selection as the initial step in identifying LQTS carriers in our algorithm. Similar to Vincent et al, we also found that its sensitivity was approximately 50%. Other studies have also shown that up to 25% of patients with genetically-proven LQTS have a normal resting QTc because of low penetrance and the dynamic nature of QT prolongation.\textsuperscript{2,8,9,11,14} Clearly, there is a need for additional criteria in patients with normal or borderline QTc prolongation. The Schwartz criteria combines ECG and clinical parameters and remains a useful tool for diagnosing LQTS;\textsuperscript{5} however, the score relies heavily on resting QTc prolongation and the presence of symptoms which may limit its application in asymptomatic carriers. It has been demonstrated that up to 40% of relatives with LQTS may be missed by clinical assessment.\textsuperscript{15} Indeed, based on the existing guidelines, 73% of patients in our cohort with an intermediate probability of LQTS, and 50% of those with a low probability of LQTS were in fact LQTS carriers. Moreover, such “silent mutation carriers” may not have a benign prognosis as previously thought. A recent study has shown that they are exposed to a 4% risk of aborted cardiac arrest or sudden cardiac death by 40 years of age, which represents a 10-fold increase in risk compared to unaffected family members.\textsuperscript{14}

Although genetic testing for first-degree relatives of patients with LQTS is the gold standard for diagnosis and as such has been advocated in some centers,\textsuperscript{6,15} it remains unavailable to many. Even when available, there is often a significant time delay before results are available. Alternative and more readily available clinical parameters have been explored for detecting LQTS in patients with a nondiagnostic resting QTc. T wave abnormalities are frequently observed in patients with LQTS and specific patterns may be predictive of genotype;\textsuperscript{31,32} however, these remain observer dependent and significant overlap exists between LQTS subtypes and between LQTS carriers and genotype-negative patients. For example, Zhang et al\textsuperscript{31} reported that 67% of LQT1 patients had normal-appearing T waves and Takenaka et al\textsuperscript{18} reported the same in 23% of LQT1 patients. The present data support the relatively modest sensitivity but high specificity of T wave abnormalities in detecting LQTS carriers, particularly LQT2. Improvements in sensitivity may be achieved by the use of quantitative T wave parameters, epinephrine infusion, Holter monitoring and more complex mathematical computations.\textsuperscript{33-37}

The differential QT response of LQTS carriers and genotype-negative patients to adrenergic stimulation has also been extensively explored. Genotype prediction may be possible based on differential effects of adrenergic stimulation in LQT1, LQT2 and LQT3 models of congenital LQTS.\textsuperscript{38,39} Prolongation of the QT interval during epinephrine infusion has been shown to be suggestive of LQTS, especially LQT1.\textsuperscript{40-43} QTc prolongation during brief sinus tachycardia induced by standing has also been
proposed as a useful test for identifying LQTS.\textsuperscript{17,26,27} Exaggerated QTc prolongation during exercise and recovery is characteristic of LQTS and may also be useful for differentiating genotype.\textsuperscript{18-23,25,27,44} In summary, QTc prolongation is seen in both LQT1 and LQT2 in early exercise but at peak exercise, QTc prolongation is persistent in LQT1 whereas it normalizes in LQT2.\textsuperscript{22} In addition, T wave abnormalities may be induced at peak exercise.\textsuperscript{18} QTc prolongation during recovery has also been reported as a sensitive and specific marker of LQTS and may be superior to resting and stress QTc.\textsuperscript{12,19,24} In particular, QTc prolongation during late recovery may be a specific marker for LQT1 and LQT2 whereas QTc prolongation during early recovery is specific to LQT1.\textsuperscript{23} In LQT2 patients, QT adaptation is disparate during exercise and recovery with QTc prolongation being greater during early exercise compared to early recovery.\textsuperscript{19} Hence, QT hysteresis is abnormally prolonged in LQT2 patients.\textsuperscript{27} However, a major challenge in the application of exercise parameters in diagnosing LQTS has been the fact that most were derived in single-centre studies and have not been subjected to the rigors of external validation in an independent cohort.

The main emphasis of the present study was to systematically explore the utility of previously reported exercise parameters in detecting LQTS among relatives with a normal or borderline resting QTc interval. In these patients, we found that QTc prolongation during late recovery (4 minutes after exercise) was the best predictor of LQTS. It also has the advantage of being a relatively easy parameter to record and measure since patient movement is minimized and heart rate is usually stable. That late-recovery QTc prolongation is a more sensitive marker of LQTS than resting QTc prolongation has also been observed by other investigators.\textsuperscript{12,19} This may reflect the persisting effect of adrenergic hormones released during exercise in exaggerating the underlying repolarization abnormality in LQTS carriers compared to genotype-negative patients, given that the half-life of the hormones is approximately 3 to 4 minutes, in addition to rate of normal reuptake. The combination of resting and late-recovery QTc had a sensitivity of 0.92 and specificity of 0.82 for detecting LQTS when applied to an independent validation cohort. As a single parameter for predicting genotype, QTc prolongation during early recovery (1 minute after exercise) was the best predictor of LQT1 with a sensitivity of 0.73 and specificity of 0.76. While augmentation of parasympathetic effects occurs rapidly, sympathetic withdrawal is not significant within the first minute of recovery.\textsuperscript{45} Hence, it is not surprising that the differential QTc response typically observed at peak exercise between LQT1 and LQT2 patients is maintained at 1-minute recovery. Interestingly, although QTc prolongation at peak exercise was a robust predictor of LQT1 in the derivation cohort, its utility was only modest in the validation cohort, perhaps reflecting the difficulty of measuring QT accurately at peak exercise.

The generalizability of the screening algorithm in other LQTS populations warrants further exploration. Although we have demonstrated that the algorithm was also sensitive in KCNQ1 and KCNH2 mutation-positive probands, further characterization of the repolarization response to exercise in LQT3 and genotype-negative patients is required. For example, LQT3 patients are understood to have supranormal QT...
adaptation to exercise.\textsuperscript{14} Mutation-specific responses were also not considered. In addition, it would be interesting to evaluate whether the repolarization response to exercise is a useful metric when interpreting genetic testing involving variants of unknown significance. It must also be stressed that the performance of the algorithm may to some degree reflect the enriched sample of the present study.

The study had several limitations, including the use of the Bazett’s formula that overcorrects the QT interval at heart rates >100 bpm, although this should be less of a concern at the time points that were selected in the final algorithm. Treadmill testing was used predominantly for validation. However, data from the single derivation centre suggests that the same cutoffs can be used with upright burst and gradual bicycle exercise protocols.\textsuperscript{23} Patients taking β-blockers at the time of exercise testing were not excluded from the study, but a subgroup analysis demonstrated that the algorithm performed satisfactorily in patients who were β-blocker naïve. The proportion of genotype-negative patients in both cohorts was surprisingly low, suggesting a degree of referral bias in exercise testing. The judgment of a normal versus abnormal result on the basis of a dichotomous measure may produce difficulties when the measurement is within a few milliseconds of the proposed cutoff. Quantification of T wave abnormalities\textsuperscript{32,34,36,37} or alternate methods for measuring parameters such as the standing QT\textsuperscript{17} may have improved the performance of individual parameters. Finally, serial exercise testing was not performed to assess the reproducibility of results within individual patients.

The proposed algorithm is readily applied to clinical practice. In principle, the cutoffs may be adjusted to achieve higher specificity (eg, 4-minute recovery ≥480 ms had a 100% specificity) to identify those patients who almost certainly have LQTS and reserve genetic testing for those patients with a residual normal or borderline result. Finally, we would caution against the use of the algorithm in isolation since other clinical findings should always be taken into account including the presence of specific T wave abnormalities or symptoms such as syncope.

Conclusions

In LQTS, asymptomatic mutation carriers often lack the characteristic resting QTc prolongation, which leads to a diagnostic dilemma. The screening algorithm to identify and predict genotype in relatives of LQTS probands presented in the present study is a simple, readily accessible and accurate tool. It may be useful as an interim test while one awaits formal genetic results or as a diagnostic test in centers where genetic testing is unavailable.

References


