Arrhythmia/Electrophysiology

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

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Background—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 and Results—Asymptomatic first-degree relatives of genetically characterized probands were recruited from 5 centers. QT intervals were measured at rest, during exercise, and during 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. The derivation cohort consisted of 69 relatives (28 with LQT1, 20 with LQT2, and 21 noncarriers). Mean age was 35 ± 18 years, and resting corrected QT interval (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 reclassified 22 of 25 patients as having LQTS and 19 of 21 patients as being noncarriers. The combination of 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 with LQT1, 61 with LQT2, and 33 noncarriers; QTc = 443 ± 47 ms), 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. (Circulation. 2011;124:2187-2194.)

Key Words: diagnosis ■ QT interval ■ genetic testing ■ exercise test

Congenital long-QT syndrome (LQTS) is an inherited cardiac channelopathy characterized by abnormal ventricular repolarization manifested as QT prolongation on the surface ECG and a predisposition to ventricular arrhythmia and sudden death.1–3 Subtypes are classified according to the gene affected, with LQTS type 1 (LQT1; KCNQ1 mutation), LQTS type 2 (LQT2; KCNH2 mutation), and LQTS type 3 (LQT3; SCN5A mutation) accounting for > 90% of patients with identified mutations.4 Diagnosis is relatively straightforward in patients with overt QT prolongation or symptoms based on the Schwartz criteria5,6; however, there is significant overlap in the QT range between LQTS carriers and noncarriers, and 25% to 50% of LQTS carriers have a corrected QT interval (QTc) in the normal or borderline range because of a combination of variable penetrance, the effect of modifying genes, and individual variability in QT duration.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.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.14

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Clinical Perspective on p 2194

Genetic testing of relatives is advocated in some centers as the gold standard for diagnosis, but it is restricted by cost and availability.6,15,16 Postural and exercise provocation has been
explored as a means of amplifying phenotypic characteristics, especially in so-called silent mutation carriers with a normal or borderline resting QT interval.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 5 university teaching hospitals in Canada, the Netherlands, and Israel. All probands fulfilled the clinical criteria for LQTS (diagnostic score ≥4)3 and were confirmed to have disease-causing mutations in the coding exons of either KCNQ1 (LQT1) or 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 and family-specific genetic screening and were assigned an LQTS diagnostic score on the basis of previously published criteria.5 Patients from a single center (London, ON, Canada) formed the derivation cohort, and patients from the other 4 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 with 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 described previously (QT_{exercise} − QT_{recovery}).17–20 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 positive T wave or maximal upward slope of the negative T wave. The QTc was calculated with the Bazett formula.28 The resting QTc was considered normal if it was <450 ms in males or <460 ms in females, abnormal if ≥470 ms in males or ≥480 ms in females, and borderline if 450 to 469 ms in males or 460 to 479 ms in females.3 Noncarriers also evaluated resting T-wave morphology and determined the presence of abnormalities based on specific patterns, as described previously.3 Quantification of T waves in terms of duration and amplitude was not performed in the present analyses.

Statistical Analysis

Comparisons between groups were performed with individual-samples t test, χ² 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 used as an initial criterion because it has been 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 by use of 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 with 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,5 46% of patients had a low probability of having LQTS (LQTS score ≤1), 22% had an intermediate probability (LQTS score 2–3), and 32% had a high probability (LQTS score ≥4).5 On the basis of genetic testing, 41% had LQT1, 29% had LQT2, and 30% were noncarriers.

Heart rates were significantly lower in LQTS carriers than in noncarriers when resting supine, standing, and 1- and

<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>
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<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>Noncarriers</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 criteria.5
4-minute recovery heart rates were compared (Figure 1A; \( P < 0.05 \), independent of \( \beta \)-blocker status). QTc was consistently higher in LQTS carriers than in noncarriers at rest and during various phases of treadmill exercise testing (Figure 1B; \( P < 0.01 \) at all time points, independent of \( \beta \)-blocker status).

**Development of the Algorithm**

Patients were initially stratified as having an abnormal, borderline, or normal resting supine QTc according to previously published cutoffs (Figure 2A).\(^{11,13,32}\) 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 by ROC analysis (Figure 3). Of these parameters, the 4-minute recovery QTc had the highest area under the curve, 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 among both male and 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 who were assigned a probable diagnosis of LQTS based on 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 area under the curve values for prediction of LQT1. Peak exercise QTc ≥ 486 ms had a sensitivity of 0.81 and specificity of 0.90.

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### Table 2. Predictive Utility of Baseline ECG Parameters

<table>
<thead>
<tr>
<th>Parameter</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</td>
<td>0.48</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females ≥ 480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-wave abnormality†</td>
<td>. . . . . . . . .</td>
<td>0.48</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; QTc, corrected QT interval.

* Cutoffs for supine QTc were based on previous literature.\(^{11}\)

† \( P < 0.01 \); 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.\(^{32}\)
whereas 1-minute recovery QTc $\geq 460$ ms had a sensitivity of 0.81 and specificity of 0.76. QT hysteresis $\geq 10$ ms had a sensitivity of 0.82 and specificity of 0.55 for prediction of LQTS.

Qualitative T-wave abnormalities were present in 22 (47%) of 47 LQTS patients. 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 noncarriers. 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=0.73). The performance of the screening algorithm was tested in an independent cohort, was 0.76. The positive predictive value was 0.95, and negative predictive value was 0.92, specificity was 0.82, and sensitivity was 0.81.

**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. In the present study, using the same criteria, abnormal resting QTc prolongation was 100% specific for LQTS carriers in both cohorts, which justifies 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. Clearly, there is a need for additional criteria in patients with normal or borderline QTc prolongation. The Schwartz criteria combine ECG and clinical parameters and remain a useful tool for diagnosing LQTS; 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. Indeed, based on the existing guidelines, 73% of patients in the present study 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 with unaffected family members.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,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 detection of 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 genotype31,32; however, these remain observer dependent, and significant overlap exists between LQTS subtypes and between LQTS carriers and noncarriers. For example, Zhang et al31 reported that 67% of LQT1 patients had normal-appearing T waves, and Takenaka et al18 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.34–38

The differential QT response of LQTS carriers and noncarriers to adrenergic stimulation has also been explored extensively. Genotype prediction may be possible on the basis of differential effects of adrenergic stimulation in LQT1, LQT2, and LQT3 models of congenital LQTS.39,40 Prolongation of the QT interval during epinephrine infusion has been shown to be suggestive of LQTS, especially LQT1.41–44 QTc prolongation during brief sinus tachycardia induced by standing has also been proposed as a useful test for identifying LQTS.17,26,27 Exaggerated QTc prolongation during exercise and recovery is characteristic of LQTS and may also be useful to differentiate genotype.18–23,25,27 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 LQT2.22 In addition, T-wave abnormalities may be induced at peak exercise.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.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 LQT1.23 In LQT2 patients, QT adaptation is disparate during exercise and recovery, with QTc prolongation being greater during early exercise compared with early recovery.19 Hence, QT hysteresis is abnormally prolonged in LQT2 patients.27 However, a major challenge in the application of exercise parameters in the diagnosis of LQTS has been the fact that most were derived in single-center 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

![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.](http://circ.ahajournals.org/)

![Figure 5. Comparison of corrected QT interval (QTc; mean±SD) in patients with long-QT syndrome type 1 (LQT1) and type 2 (LQT2) at various stages of treadmill exercise testing. Probability values for paired comparisons by mixed-model analysis.](http://circ.ahajournals.org/)
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, because 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 with noncarriers, 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 0.81 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. Although augmentation of parasympathetic effects occurs rapidly, sympathetic withdrawal is not significant within the first minute of recovery.\textsuperscript{46} 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 of 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, which perhaps reflects 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 \textit{KCNQ1}/\textit{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...

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**Table 4. Prediction of LQTS Subtype**

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>(P^*)</th>
<th>Cutoff, ms(\dagger)</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-min 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-min 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(\ddagger)</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, area 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.

\(\dagger\)Selected to achieve sensitivity >80% based on receiver operating characteristic curves.

\(\ddagger\)QT hysteresis=QT\(_{100}\) bpm during exercise−QT\(_{100}\) bpm during recovery, where HR indicates heart rate.\textsuperscript{27,28}

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**Figure 6.** Application of screening algorithm to validation cohort. LQTS indicates long-QT syndrome; QTc, corrected QT interval; LQT1, LQTS type 1; and LQT2, LQTS type 2.
understood to have supranormal QT adaptation to exercise.\textsuperscript{45} 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 one interprets 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 formula, which 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 center suggest that the same cutoffs can be used with upright burst and gradual bicycle exercise protocols.\textsuperscript{23} Patients taking $\beta$-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 $\beta$-blocker naive. The proportion of noncarriers in both cohorts was surprisingly low, which suggests 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{3,12,35,37,38} or alternative 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 $\approx480$ 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, because 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.

**Table 5. Validation of Algorithm**

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=152)</td>
<td>0.89</td>
<td>0.92</td>
<td>0.82</td>
<td>0.95</td>
<td>0.73</td>
</tr>
<tr>
<td>$\beta$-blocker naïve (n=107)</td>
<td>0.87</td>
<td>0.89</td>
<td>0.82</td>
<td>0.92</td>
<td>0.77</td>
</tr>
<tr>
<td>Female patients (n=77)</td>
<td>0.92</td>
<td>0.94</td>
<td>0.87</td>
<td>0.97</td>
<td>0.76</td>
</tr>
<tr>
<td>Male patients (n=75)</td>
<td>0.87</td>
<td>0.89</td>
<td>0.78</td>
<td>0.94</td>
<td>0.70</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value.

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**Disclosures**

None.

**References**

Diagnosis of long-QT syndrome (LQTS) is relatively straightforward in patients with overt QT prolongation or symptoms based on existing clinical criteria; however, diagnosis may be challenging in asymptomatic relatives of patients with established LQTS, especially in the context of normal or borderline QT prolongation. Accurate identification of LQTS carriers in this subgroup is important because they remain at significant risk of life-threatening cardiac events. Although genetic testing can identify LQTS carriers where there is a known familial mutation, such an approach may be costly and subject to availability. Postural and exercise provocation has been explored as a means of amplifying phenotypic characteristics, especially in so-called silent mutation carriers where there is a known familial mutation, such an approach may be costly and subject to availability. Postural and exercise facilitates diagnosis of latent long QT syndrome. Am Heart J. 2005;150:1059–1063.

Deletion in proof.

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

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