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

Raymond W. Sy, MBBS*; Christian van der Werf, MD*; Ishvinder S. Chattha, MSc; Priya Chockalingam, MD; Arnon Adler, MD; Jeffrey S. Healey, MD; Mark Perrin, MBBS; Michael H. Gollob, MD; Allan C. Skanes, MD; Raymond Yee, MD; Lorne J. Gula, MD; Peter Leong-Sit, MD; Sami Viskin, MD; George J. Klein, MD; Arthur A. Wilde, MD; Andrew D. Krahn, MD

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 restratified 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 criteria[5,6]; 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]

Editorial see p 2181
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

Received February 24, 2011; accepted August 15, 2011.

From the University of Western Ontario, London, ON, Canada (R.W.S., I.S.C., A.C.S., R.Y., L.J.G., P.L.-S., G.J.K., A.D.K.); Academic Medical Center, Amsterdam, Netherlands (C.V.d.W., P.C., A.A.W.); Tel Aviv University, Tel Aviv, Israel (A.A., S.V.); McMaster University, Hamilton, ON, Canada (J.S.H.); and University of Ottawa, Ottawa, ON, Canada (M.P., M.H.G.).

*Drs Sy and van der Werf are co–primary investigators.

Correspondence to Andrew Krahn, MD, Arrhythmia Service, London Health Sciences Centre, 339 Windermere Rd, London, Ontario, Canada, N6A 5A5. E-mail akrahn@uwo.ca

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.111.028258**

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)[5] 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 ($QT_{exercise} - QT_{recovery}$).[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 leads II and V_5. The mean of 3 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 formula.[30] 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.[6,11] ECG readers also evaluated resting T-wave morphology and determined the presence of abnormalities based on specific patterns, as described previously.[31] 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, χ^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 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).

Table 1. Patient Characteristics

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

QTc indicates corrected QT interval; LQTS, long-QT syndrome; LQT1, LQTS type 1; and LQT2, LQTS type 2.

*Based on Schwartz criteria.[5]

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

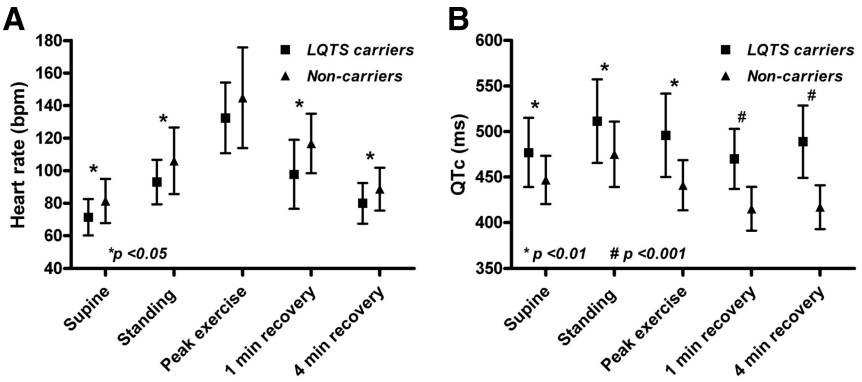

Figure 1. Comparison of heart rates (mean±SD; **A**) and corrected QT interval (QTc, mean±SD; **B**) in long-QT syndrome (LQTS) carriers and noncarriers at various stages of treadmill exercise testing. Probability values for comparisons by mixed-model analysis.

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 in noncarriers 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 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.

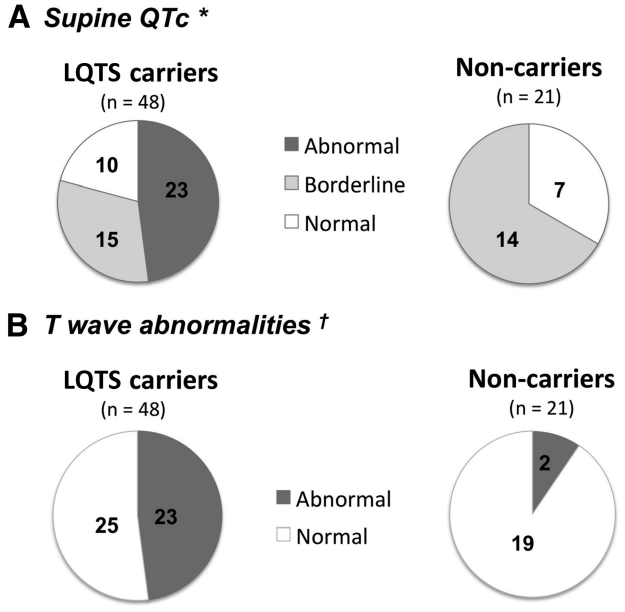

Figure 2. Frequency of baseline ECG abnormalities among long-QT syndrome (LQT) carriers and noncarriers (supine corrected QT, **A**; T wave abnormalities, **B**). *Cutoffs for supine corrected QT interval (QTc): Normal, <440 ms in males and <450 ms in females; Borderline, 440 to 470 ms in males and 450 to 480 ms in females; and Abnormal, ≥470 ms in males and ≥480 ms in females. †T-wave abnormality defined as broad-based T waves or low-amplitude T waves with notching in ≥3 leads.[32]

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,

Table 2. Predictive Utility of Baseline ECG Parameters

	AUC	Cutoff, ms*	Sensitivity	Specificity
Supine QTc	0.79†	Males ≥470 Females ≥480	0.48	1.00
T-wave abnormality‡	. . .	. . .	0.48	0.90

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]

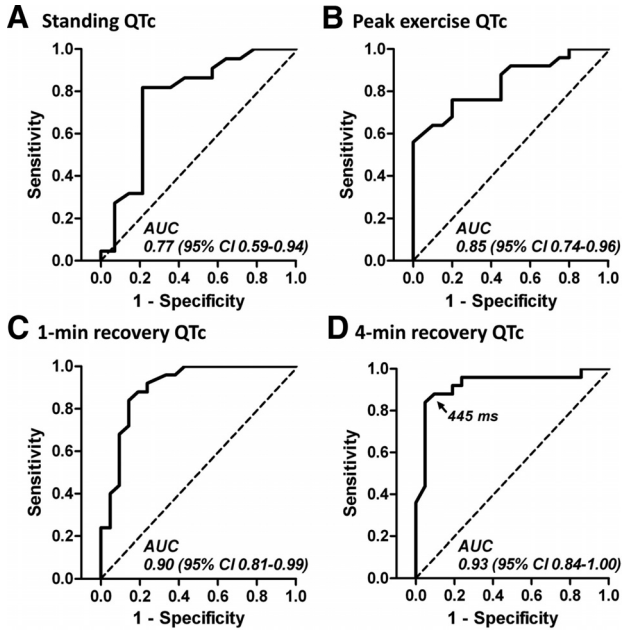

Figure 3. Receiver operating characteristics curves for detecting LQTS with standing corrected QT interval (QTc; **A**), peak exercise QTc (**B**), 1-minute recovery QTc (**C**), and 4-minute recovery QTc (**D**). Area under the curve (AUC) is presented for each parameter. 95% CI indicates 95% confidence interval.

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. 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=0.89). 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 it was applied to a subset of the validation cohort that was β-blocker naïve. Test performance was slightly inferior in male patients compared with 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.

Table 3. Predictive Utility of Exercise ECG Parameters

			90% Sensitivity	
	AUC	*P**	Cutoff, ms	Specificity
Standing QTc	0.77	0.02	445	0.43
Peak exercise QTc	0.85	0.01	441	0.45
1-min recovery QTc	0.90	0.02	426	0.76
4-min recovery QTc	0.93	0.01	445	0.90

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

*Generalized estimating equations were used to adjust for potential familial correlation.

Application of Algorithm in Probands

The algorithm was also evaluated in an independent cohort of probands assessed for possible LQTS who 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 the 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[11] 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.[2,8,9,11,14] 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[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.[15] 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

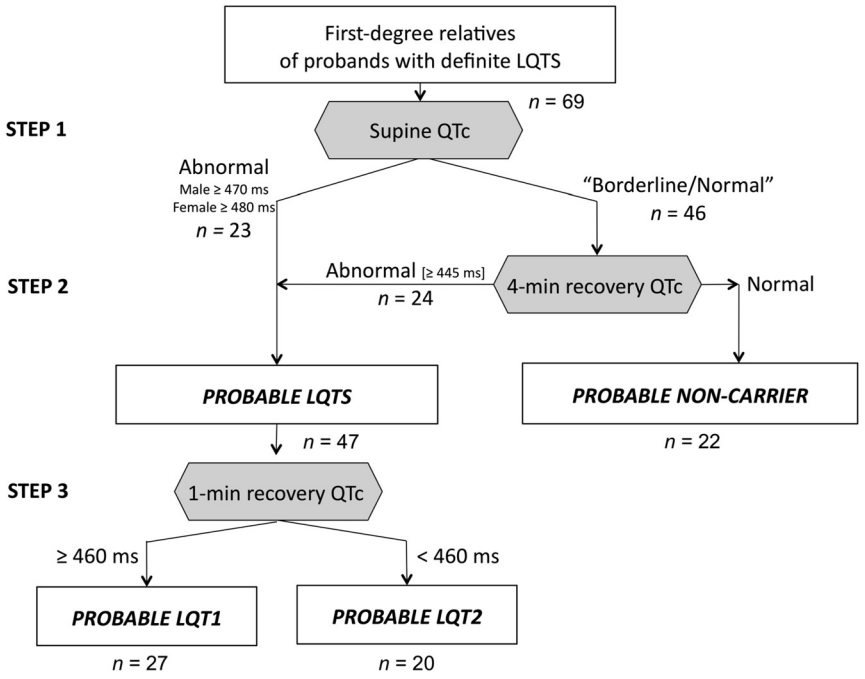

Figure 4. Screening algorithm for detecting LQTS and predicting genotype. LQTS indicates long-QT syndrome; QTc, corrected QT interval; LQT1, LQTS type 1; LQT2, LQTS type 2; and *n*, number of patients with algorithm applied to derivation cohort.

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 genotype[31,32]; however, these remain observer dependent, and significant overlap exists between LQTS subtypes and between LQTS carriers and noncarriers. For example, Zhang et al[31] reported that 67% of LQT1 patients had normal-appearing T waves, and Takenaka et al[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.[34–38]

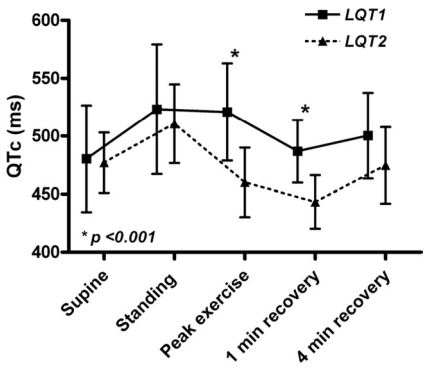

Figure 5. Comparison of corrected QT interval (QTc; mean±SD) in patients with long-QT syndrome type 1 (LQT1) and type 2 (LQT2) at various stages of treadmill exercise testing. Probability values for paired comparisons by mixed-model analysis.

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.[18–23,25,27,45] 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

Table 4. Prediction of LQTS Subtype

	AUC	P*	Cutoff, ms†	Sensitivity	Specificity
Predictive of LQT1					
Broad-based T waves	. . .	. . .	. . .	0.27	0.71
Peak exercise QTc	0.88	<0.01	486	0.81	0.90
1-min recovery QTc	0.89	<0.01	460	0.81	0.76
4-min recovery QTc	0.72	0.02	458	0.81	0.38
Predictive of LQT2					
Low-amplitude notched T waves	. . .	. . .	. . .	0.37	0.93
Standing QTc	0.58	0.54	474	0.83	0.39
QT hysteresis‡	0.82	<0.01	10	0.82	0.55

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.

†Selected to achieve sensitivity >80% based on receiver operating characteristic curves.

‡QT hysteresis = $QT_{HR\ 100\ bpm\ during\ exercise} - QT_{HR\ 100\ bpm\ during\ recovery}$, where HR indicates heart rate.[27,28]

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.[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 0.82 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. Although augmentation of parasympathetic effects occurs rapidly, sympathetic withdrawal is not significant within the first minute of recovery.[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 *KCNQ1*/*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

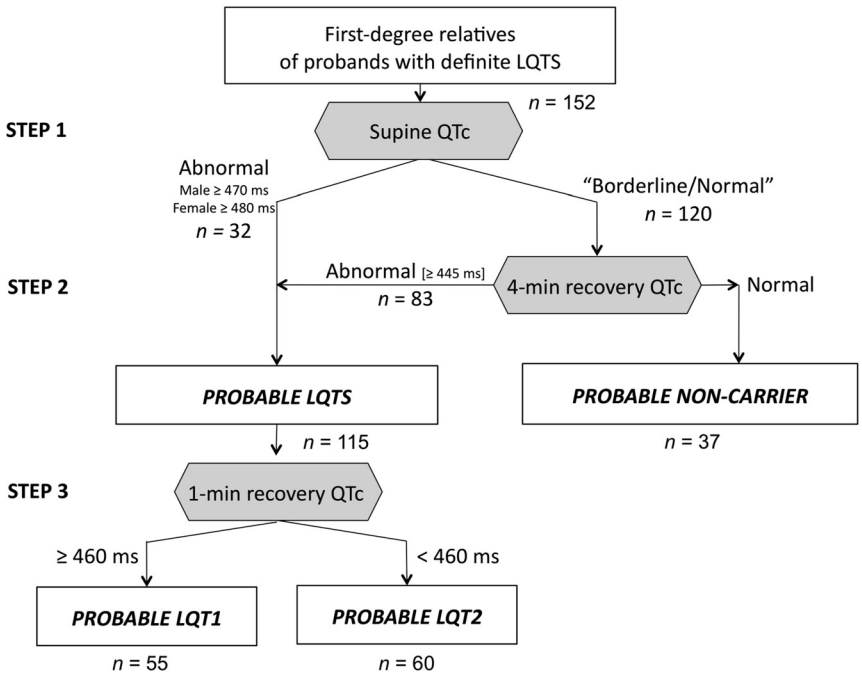

Figure 6. Application of screening algorithm to validation cohort. LQTS indicates long-QT syndrome; QTc, corrected QT interval; LQT1, LQTS type 1; and LQT2, LQTS type 2.

Table 5. Validation of Algorithm

	Accuracy	Sensitivity	Specificity	PPV	NPV
All patients (n=152)	0.89	0.92	0.82	0.95	0.73
β-blocker naïve (n=107)	0.87	0.89	0.82	0.92	0.77
Female patients (n=77)	0.92	0.94	0.87	0.97	0.76
Male patients (n=75)	0.87	0.89	0.78	0.94	0.70

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

understood to have supranormal QT adaptation to exercise.[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.[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 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[32,35,37,38] or alternative methods for measuring parameters such as the standing QT[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, 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.

Sources of Funding

Dr Krahn is a Career Investigator of the Heart and Stroke Foundation of Ontario (CI6498). The study was supported by the Heart and Stroke Foundation of Ontario (T6730). Drs Van der Werf and Wilde were supported by Zorg Onderzoek Nederland Medische Wetenschappen (Zon MW, grant No. 120610013).

Disclosures

None.

References

1. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol*. 2008; 51:2291–2300.
2. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348: 1866–1874.
3. Roden DM. Clinical practice: long-QT syndrome. *N Engl J Med*. 2008; 358:169–176.
4. Ruan Y, Liu N, Napolitano C, Priori S. Therapeutic strategies for long-QT syndrome: does the molecular substrate matter? *Circ Arrhythm Electrophysiol*. 2008;1:290–297.
5. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. *Circulation*. 1993;88:782–784.
6. Hofman N, Wilde AA, Kaab S, van Langen IM, Tanck MW, Mannens MM, Hinterseer M, Beckmann BM, Tan HL. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? *Eur Heart J*. 2007;28:575–580.
7. Zareba W. Challenges of diagnosing long QT syndrome in patients with nondiagnostic resting QTc. *J Am Coll Cardiol*. 2010;55:1962–1964.
8. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation*. 1999;99:529–533.
9. Goldenberg I, Mathew J, Moss AJ, McNitt S, Peterson DR, Zareba W, Benhorin J, Zhang L, Vincent GM, Andrews ML, Robinson JL, Morray B. Corrected QT variability in serial electrocardiograms in long QT syndrome: the importance of the maximum corrected QT for risk stratification. *J Am Coll Cardiol*. 2006;48:1047–1052.
10. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. *Heart*. 2002;87:220–228.
11. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med*. 1992;327:846–852.
12. Kaufman ES, Priori SG, Napolitano C, Schwartz PJ, Iyengar S, Elston RC, Schnell AH, Gorodeski EZ, Rammohan G, Bahhur NO, Connuck D, Verrilli L, Rosenbaum DS, Brown AM. Electrocardiographic prediction of abnormal genotype in congenital long QT syndrome: experience in 101 related family members. *J Cardiovasc Electrophysiol*. 2001;12:455–461.
13. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol*. 1993;72:23B–25B.
14. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Platonov PG, Priori SG, Qi M, Schwartz PJ, Shimizu W, Towbin JA, Vincent GM, Wilde AA, Zhang L. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol*. 2011;57:51–59.
15. Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, Bottelli G, Cerrone M, Leonardi S. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA*. 2005;294:2975–2980.
16. Roden DM. Genetic testing in subjects with no clinical abnormality: the tip of a huge iceberg. *J Am Coll Cardiol*. 2011;57:60–62.
17. Viskin S, Postema PG, Bhuiyan ZA, Rosso R, Kalman JM, Vohra JK, Guevara-Valdivia ME, Marquez MF, Kogan E, Belhassen B, Glikson M, Strasberg B, Antzelevitch C, Wilde AA. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. *J Am Coll Cardiol*. 2010;55:1955–1961.
18. Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, Kubota T, Takaki H, Kamakura S, Horie M. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation*. 2003;107:838–844.

19. Swan H, Viitasalo M, Piippo K, Laitinen P, Kontula K, Toivonen L. Sinus node function and ventricular repolarization during exercise stress test in long QT syndrome patients with KVLQT1 and HERG potassium channel defects. *J Am Coll Cardiol*. 1999;34:823–829.
20. Shimizu W, Ohe T, Kurita T, Shimomura K. Differential response of QTU interval to exercise, isoproterenol, and atrial pacing in patients with congenital long QT syndrome. *Pacing Clin Electrophysiol*. 1991;14:1966–1970.
21. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QTc and QT/QS2 in the Romano-Ward inherited long QT syndrome. *Am J Cardiol*. 1991;68:498–503.
22. Sy RW, Chattha IS, Klein GJ, Gula LJ, Skanes AC, Yee R, Bennett MT, Krahn AD. Repolarization dynamics during exercise discriminate between LQT1 and LQT2 genotypes. *J Cardiovasc Electrophysiol*. 2010;21:1242–1246.
23. Chattha IS, Sy RW, Yee R, Gula LJ, Skanes AC, Klein GJ, Bennett MT, Krahn AD. Utility of the recovery electrocardiogram after exercise: a novel indicator for the diagnosis and genotyping of long QT syndrome? *Heart Rhythm*. 2010;7:906–911.
24. Dillenburg RF, Hamilton RM. Is exercise testing useful in identifying congenital long QT syndrome? *Am J Cardiol*. 2002;89:233–236.
25. Walker BD, Krahn AD, Klein GJ, Skanes AC, Yee R. Burst bicycle exercise facilitates diagnosis of latent long QT syndrome. *Am Heart J*. 2005;150:1059–1063.
26. Walker BD, Krahn AD, Klein GJ, Skanes AC, Yee R, Wang J, Hegele RA. Effect of change in posture and exercise on repolarization in patients with long QT syndrome with HERG channel mutations. *Can J Cardiol*. 2005;21:33–38.
27. Wong JA, Gula LJ, Klein GJ, Yee R, Skanes AC, Krahn AD. Utility of treadmill testing in identification and genotype prediction in long-QT syndrome. *Circ Arrhythm Electrophysiol*. 2010;3:120–125.
28. Krahn AD, Klein GJ, Yee R. Hysteresis of the RT interval with exercise: a new marker for the long-QT syndrome? *Circulation*. 1997;96:1551–1556.
29. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm*. 2008;5:1015–1018.
30. Bazett H. An analysis of the time relations of electrocardiograms. *Heart*. 1920;7:353–370.
31. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, Shen J, Splawski I, Priori SG, Compton SJ, Yanowitz F, Benhorin J, Moss AJ, Schwartz PJ, Robinson JL, Wang Q, Zareba W, Keating MT, Towbin JA, Napolitano C, Medina A. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation*. 2000;102:2849–2855.
32. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation*. 1995;92:2929–2934.
33. Deleted in proof.
34. Khositseth A, Hejlik J, Shen WK, Ackerman MJ. Epinephrine-induced t-wave notching in congenital long QT syndrome. *Heart Rhythm*. 2005;2:141–146.
35. Kanters JK, Fanoe S, Larsen LA, Bloch Thomsen PE, Toft E, Christiansen M. T wave morphology analysis distinguishes between KVLQT1 and HERG mutations in long QT syndrome. *Heart Rhythm*. 2004;1:285–292.
36. Kanters JK, Graff C, Andersen MP, Hardahl T, Toft E, Christiansen M, Bloch Thomsen PE, Struijk JJ. Long QT syndrome genotyping by electrocardiography: fact, fiction, or something in between? *J Electrocardiol*. 2006;39:S119–S122.
37. Struijk JJ, Kanters JK, Andersen MP, Hardahl T, Graff C, Christiansen M, Toft E. Classification of the long-QT syndrome based on discriminant analysis of T-wave morphology. *Med Biol Eng Comput*. 2006;44:543–549.
38. Vaglio M, Couderc JP, McNitt S, Xia X, Moss AJ, Zareba W. A quantitative assessment of T-wave morphology in LQT1, LQT2, and healthy individuals based on Holter recording technology. *Heart Rhythm*. 2008;5:11–18.
39. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol*. 2000;35:778–786.
40. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation*. 1998;98:2314–2322.
41. Tanabe Y, Inagaki M, Kurita T, Nagaya N, Taguchi A, Suyama K, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Shimizu W. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol*. 2001;37:911–919.
42. Noda T, Takaki H, Kurita T, Suyama K, Nagaya N, Taguchi A, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Horie M, Napolitano C, Towbin JA, Priori SG, Shimizu W. Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur Heart J*. 2002;23:975–983.
43. Vyas H, Ackerman MJ. Epinephrine QT stress testing in congenital long QT syndrome. *J Electrocardiol*. 2006;39:S107–S113.
44. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc*. 2002;77:413–421.
45. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, Keating MT, Hammoude H, Brown AM, Chen LS. Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate: implications for gene-specific therapy. *Circulation*. 1995;92:3381–3386.
46. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol*. 2008;51:1725–1733.

CLINICAL PERSPECTIVE

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. 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 corrected QT interval, 4-minute recovery corrected QT interval, and 1-minute recovery corrected QT interval. 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 compared with genetic testing as a gold standard. The screening algorithm appears useful as an interim test while formal genetic results are awaited, or as a diagnostic test in centers where genetic testing is unavailable.