Abnormal repolarization dynamics revealed in exercise test in long QT syndrome mutation carriers with normal resting QT interval

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Aims
The identification of affected family members with long QT syndrome (LQTS) is often difficult due to their normal—or only marginally lengthened—QT interval duration. We examined whether physical exercise test could increase the ability to detect the mutation carrier status in phenotypically normal LQTS family members.

Methods and results
Sixty-six subjects were included: 15 were carriers of KCNQ1 (LQT1); 15 of KCNH2 (LQT2); and 9 of SCN5A (LQT3) gene mutations with no, or borderline, QT lengthening; and 27 were healthy controls. Multiple electrograms over the precordial area were recorded during workload and recovery phases of exercise test. QT intervals and T peak to T end intervals (Tpe intervals) were determined using an automatic algorithm at specified heart rates (HR). The LQT1 mutation carriers had QT interval most prolonged during exercise and recovery, whereas the LQT2 carriers had QT interval longest at low exercise HR. The LQT3 carriers had QT interval longest at rest. The Tpe interval remained nearly unchanged during exercise in LQT1, but shortened in LQT2 and in LQT3 carriers. The Tpe interval was longest in LQT2 carriers at the end of the recovery phase. Tentative dichotomizing values of QT and Tpe intervals improved sensitivity and specificity in distinguishing LQTS subtypes, compared with the QT interval duration alone.

Conclusions
LQTS mutation carriers lacking diagnostic QT interval prolongation exhibit abnormal QT and Tpe interval adaptions during physical exercise test. Looking for subtype-specific adaptions might facilitate the identification of LQTS mutation carriers when molecular genetic analysis is not available.

Keywords
Exercise test • LQTS • QT interval • Tpe interval • Ventricular repolarization

Introduction
Congenital long QT syndrome (LQTS) is a familial disorder caused by mutations in different genes coding sarcolemmal ion channels. The most common subtypes LQT1 and LQT2 are caused by loss of function mutations in slow (I\(_{Ks}\)) and fast (I\(_{Kr}\)) cardiac potassium channels, whereas subtype LQT3, present in about 10% of patients, is caused by gain of function mutations in cardiac sodium channel (I\(_{Na}\)).1 The clinical outcome is prolonged and non-homogenous ventricular repolarization, exposing the patient to torsades de pointes ventricular tachycardia, leading to abrupt loss of consciousness and sudden cardiac death.2–4

Molecular screening has become an important tool for diagnosing LQTS. However, 30–40% of mutation carriers still escape molecular genetic diagnosis.4,5 and screening tests are not readily available. In the absence of molecular genetic testing the diagnosis is based on clinical characteristics.6 A considerable proportion of mutation carriers—and even symptomatic patients—present with normal (QTc <440 ms) or borderline (QTc <470 ms) QT intervals. T wave morphology and gene-specific T wave patterns5,7 and dynamic changes in ventricular repolarization8 have been looked for facilitating the diagnosis. Exercise tolerance test has been used for identifying LQTS7 and its subtypes.9,10 We characterized subtype-specific features in ventricular repolarization using
Table 1 Basic characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 27)</th>
<th>LQT1 carriers (n = 15)</th>
<th>LQT2 carriers (n = 15)</th>
<th>LQT3 carriers (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34 ± 7</td>
<td>34 ± 11</td>
<td>41 ± 10</td>
<td>35 ± 15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 3</td>
<td>24 ± 4</td>
<td>26 ± 3</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>Peak exercise level (W)</td>
<td>254 ± 74</td>
<td>221 ± 76</td>
<td>228 ± 59</td>
<td>181 ± 33*</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>60 ± 7</td>
<td>61 ± 9</td>
<td>65 ± 9</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>Achieved heart rate (bpm)</td>
<td>184 ± 9</td>
<td>164 ± 11†</td>
<td>177 ± 11</td>
<td>174 ± 17</td>
</tr>
<tr>
<td>QTc at rest (ms)</td>
<td>378 ± 22</td>
<td>420 ± 24*</td>
<td>438 ± 30‡</td>
<td>440 ± 29‡</td>
</tr>
<tr>
<td>Tpe at rest (ms)</td>
<td>78 ± 10</td>
<td>83 ± 11</td>
<td>114 ± 25‡</td>
<td>83 ± 17</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. BMI, body mass index; bpm, beats per minute; QTc, QT interval at rest, adjusted for heart rate by Bazett’s formula; Tpe, T wave peak to T wave end interval at rest. *P < 0.05, compared with controls; †P < 0.05, compared with controls and LQT2 mutation carriers; ‡P < 0.001, compared with other groups.

Methods

Subjects

The study population consisted of asymptomatic LQTS mutation carriers and healthy controls. We selected randomly from our national LQTS register mutation carriers who had normal—or non-diagnostic—QT interval duration. None of them had had beta-blocker therapy prior to, or during, the study. Fifteen subjects had LQTS type 1, 15 LQTS type 2, and 9 LQTS type 3 mutations. The mutations were KCNQ1 G589D mutation in 15, KCNH2 del453C in 8, L552S in 5, R176W in 1, and G584S in 1, and SCN5A V1667I in 4, I239V in 2, KCNQ1 G589D mutation in 15, KCNH2 del453C in 8, L552S in 5, R176W in 1, and G584S in 1, and SCN5A V1667I in 4, I239V in 2, and SCN5A E1784K in 1. All these mutations are known to cause clinical disease.11,12 Twenty-seven healthy volunteers without any history of syncope or clinical evidence of cardiovascular disease, and with normal baseline QT intervals (QTc < 440 ms) served as controls. Ages are presented in Table 1. None took any regular medication during the study.

Exercise testing and analysis of electrocardiograms

Exercise was performed with bicycle ergometer starting with a load of 30 W followed by increments of 15 W for females and 20 W for males every minute until exhaustion. Blood pressure was measured at rest and subsequently every 3 min during the test. Electrocardiograms were recorded first at rest and then continuously throughout the exercise test.

A body surface potential mapping system (BSPM, BioSemi Mark-6) was used for recording 12 electrocardiograms at a 1 kHz sample rate over the precordial area (Figure 1). Usually, these leads showed positive T waves, and were not notably disturbed while exercising. The average of all selected channels was calculated to represent ventricular repolarization of the entire precordial area.

Data were analysed with an automated algorithm described previously.14 Each lead was first preprocessed by detecting QRS complexes using an amplitude trigger, determining the baseline, and creating a QRS template. Both atrial and ventricular premature complexes were rejected. Each QRS-T deflection was replaced by an averaged QRS-T deflection including two preceding and two succeeding heart beats, using a moving window. Then the QRS onset, T wave peak and T wave end were determined. The U waves were excluded using the presented guidelines.14 Bifid repolarization waves exhibiting a time interval of ≤0.15 s between first and second components were regarded as T waves.

The QT interval was determined from QRS onset to the end of T wave, and the Tpe intervals from T wave peak to T wave end. At rest the intervals were averaged at 30 s, and during the exercise test at prespecified heart rates (HR) at steps of 10 beats/min (bpm) from 90 to 150 bpm during workload, and 140–100 bpm during recovery. A tolerance of ± 2 bpm was allowed.

Intervals were corrected for HR at rest by using Bazett’s formula15 but analysed uncorrected at specified HR during the exercise test. QT interval/HR and Tpe interval/heart rate (Tpe/HR) slopes were also calculated during exercise and recovery for each group.

The repeatability of automated QT and Tpe interval measurements adapting our technique at rest and during exercise has been reported earlier. The coefficient of variation for QT wave end interval was 4.4%, and 9.3% for Tpe-interval between separate exercise test recordings. Reproducibility was comparable between healthy subjects and LQTS patients.16
Three cardiologists determined the subjects’ mutation carrier status according to ST-T wave pattern criteria in LQTS patients as presented by Zhang et al. In the study by Zhang et al., four typical LQT1 patterns (infantile pattern, broad-based T wave pattern, normal-appearing, and late-onset normal-appearing pattern); four LQT2 patterns (four sub-types of bifid T waves); and two LQT3 patterns (late-onset peaked/biphasic T wave and asymmetrical peaked T wave pattern) were described. These were compared to classifications based on intervals derived from the present study.

Statistical analyses
Statistical analyses were carried out using the SPSS 12.0.1 statistical software package (SPSS Inc., Chicago, Illinois). Data are reported as the mean ± SD. Differences between groups were assessed by analysis of variance and by Scheffe’s test, and an independent sample t-test when appropriate. A P value < 0.05 was considered to signify statistical significance.

The study was approved by the ethical review board of the Institution, and was in accordance with the Helsinki Declaration. An informed consent was obtained from all subjects.

Results

General measures
Baseline characteristics, HR and QT and Tpe intervals at rest are presented in Table 1. There were no differences between groups in age, resting HR or blood pressure (data not shown). LQT1 mutation carriers achieved lower HR in exercise than controls or LQT2 carriers. All LQTS groups had a slightly but statistically significantly longer QTc interval than the control group. At rest, LQT2 mutation carriers had a longer Tpe interval than others.

Among LQT5 mutation carriers, the QTc interval was 440 ms in 4 of 18 males and 460 ms in 5 of 21 females. These limits yielded a sensitivity of 26%.

QT interval in exercise test
During workload of exercise test
QT intervals during exercise and recovery periods are presented in Figure 2. At the beginning of exercise, at low HRs of 90–100 bpm, LQTS mutation carriers had longer QT interval than healthy controls (P < 0.01). At a HR 90 bpm, most LQTS carriers, but only one control subject, had QT interval above 370 ms, yielding a diagnostic sensitivity of 72% and specificity of 96%. Nearly all LQT3 carriers exhibited over a 30 ms shortening in QT interval from a HR of 90 to 100 bpm. In separating LQT3 carriers from healthy controls, this yielded a sensitivity of 86% and specificity of 96%.

At higher HR of 120–150 bpm, LQT1 mutation carriers had longer QT interval than carriers of other LQTS subtypes (P < 0.01), or healthy controls (P < 0.001). At a HR of 150 bpm, 86% of LQT1 carriers had QT interval above 300 ms. In separating LQT1 carriers from others, this limit had an 86% sensitivity and 96% specificity. In separating LQT1 carriers from other LQTS subtypes, sensitivity was 86% and specificity 91%. LQT1 mutation carriers had a less steep QT/HR slope (−1.8 ± 0.4) than LQT2 (−1.5 ± 0.3; P < 0.01) or LQT3 (−1.8 ± 0.4; P < 0.001) carriers.

During recovery phase of exercise test
During the recovery period, LQT1 mutation carriers had a significantly longer QT interval than healthy controls or LQT3 carriers (P < 0.01). LQT2 carriers had longer QT interval than LQT3 carriers or controls at low HR (P < 0.05). At a HR of 100 bpm during recovery, QT interval >340 ms showed 96% sensitivity and 85% specificity for the combined LQT1 and LQT2 groups.

Tpe interval in exercise test
During workload of exercise test
Tpe intervals during exercise and recovery are presented in Figure 3. At low HR, LQT2 mutation carriers had longer Tpe interval than other LQT type carriers or controls (P < 0.001). Above a HR of 110 bpm they did not differ from LQT1 carriers. At a HR of 90 bpm most LQT2 carriers had Tpe interval over 90 ms, showing 83% sensitivity and 71% specificity among others, and 83% and 70% among LQT5 carriers, respectively. LQT2 carriers had a steeper
**Table 2** QT and Tpe interval profiles in exercise test in LQTS subgroups

<table>
<thead>
<tr>
<th></th>
<th>Start of exercise, 90 bpm</th>
<th></th>
<th>Peak exercise, 150 bpm</th>
<th></th>
<th>Post-exercise, 100 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QT (ms)</td>
<td>△QT (ms)</td>
<td>Tpe (ms)</td>
<td>QT (ms)</td>
<td>Tpe (ms)</td>
</tr>
<tr>
<td>LQT1 carriers</td>
<td>↑ (&gt;370)</td>
<td>–</td>
<td>–</td>
<td>↑ (&gt;300)</td>
<td>–</td>
</tr>
<tr>
<td>LQT2 carriers</td>
<td>↑ (&gt;370)</td>
<td>–</td>
<td>↑ (&gt;90)</td>
<td>–</td>
<td>↑ (&gt;340)</td>
</tr>
<tr>
<td>LQT3 carriers</td>
<td>↑ (&gt;370)</td>
<td>↓ (&gt;30)</td>
<td>–</td>
<td>–</td>
<td>↓ (&lt;70)</td>
</tr>
</tbody>
</table>

Sensitivity and specificity of the given interval values are presented in text. Arrows signify noticeable changes from normal subjects. ↑, lengthened; ↓, shortened; bpm, beats per minute; △QT, change in QT interval length from heart rate 90 to 100 bpm.

At low HR, and, showed proper shortening of QT and Tpe intervals during effort. LQT3 carriers had remarkably short Tpe intervals at high HRs compared with other subtypes (P < 0.05), but not to controls. The Tpe value <70 ms showed 100% sensitivity and 75% specificity thus identifying the LQT3 subtype among LQTS carriers.

**During recovery phase of exercise test**

During recovery, the Tpe interval at low HRs of 100–110 bpm was longer in LQT2 carriers than in LQT1 carriers (P < 0.05), and in LQT3 carriers or healthy controls (both P < 0.001). During recovery at a HR of 100 bpm, all LQT2 carriers had Tpe interval longer than 90 ms. This limit had 100% sensitivity and 60% specificity in separating LQT2 carriers from other subtype carriers. LQT2 carriers had a steeper Tpe/HR slope (−0.90 ± 0.50) than LQT1 (−0.45 ± 0.38; P < 0.05) or LQT3 (−0.31 ± 0.42; P < 0.01) carriers.

Table 2 summarizes the typical observations during the course of the exercise test and indicates noticeable cut-off point values in this population. The test specificity was similar to Zhang’s criteria in distinguishing LQTS subgroups in these mutation carriers. However, our cut-off point values improved test sensitivity: in separating LQT1 carriers 67% compared with 42% using Zhang’s criteria, and in LQT2 and LQT3 the sensitivities were 73 and 56% as compared with Zhang’s 56 and 22% for LQTS carriers who mostly had diagnostic QT interval lengthening.

**Discussion**

**Main findings**

The study evaluated the modification of ventricular repolarization times during a standardized physical exercise test in LQTS gene mutation carriers with normal or non-diagnostic QT interval duration. During effort and recovery the adaptations of the QT interval and the end part of the T wave, the Tpe interval, were different for the three major LQTS subtypes. These genetic subtype-specific patterns could help in distinguishing carriers from normal subjects, thus increasing diagnostic sensitivity. During the exercise test, LQT1 mutation carriers had their longest QT interval during effort and recovery, and the Tpe interval did not shorten during effort. LQT2 carriers had a longer Tpe interval than other subtypes at low HR, and, showed proper shortening of QT and Tpe intervals during effort. LQT3 carriers had remarkably short Tpe intervals at high HRs compared with other subtypes (P < 0.05), but not to controls. The Tpe value <70 ms showed 100% sensitivity and 75% specificity thus identifying the LQT3 subtype among LQTS carriers.

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The Tpe intervals are known to be longer in LQT2 than in LQT1 in resting ECG. In the controlled physiological setting of our study, weak or an almost absent shortening of the Tpe interval was demonstrated in LQT1, whereas in LQT2 the magnitude of the Tpe interval shortening was even greater than normal. At rest the LQT3 mutation carriers had a relatively short Tpe interval already, and it shortened progressively during exercise. LQT2 carriers had long Tpe interval during the late recovery phase, even though there were no grossly abnormal bifid T waves, and the U waves were excluded.

**Observations on QT interval**

Our results extend some earlier observations on QT interval adaptation during the exercise test to LQTS mutation carriers with normal QT interval. Poor shortening of the QT interval principally concerns the LQT1 subtype. However, in LQT2, whilst the shortening is better, it is not necessarily normal. In LQT3, the QT interval shortening is greater than in LQT2. The present study demonstrates that the QT interval in LQT1 is particularly lengthened during the late recovery phase, whereas QT interval shortens during exercise in LQT3 even more than in normal subjects. That most subjects in LQTS groups had normal or non-diagnostic QT interval durations at rest indicates that dynamic characteristics of ventricular repolarization are determined by the molecular genotype even when disease is electrocardiographically hidden.

**Observations on Tpe interval**

The Tpe intervals are known to be longer in LQT2 than in LQT1 in resting ECG. In the controlled physiological setting of our study, weak or an almost absent shortening of the Tpe interval was demonstrated in LQT1, whereas in LQT2 the magnitude of the Tpe interval shortening was even greater than normal. At rest the LQT3 mutation carriers had a relatively short Tpe interval already, and it shortened progressively during exercise. LQT2 carriers had long Tpe interval during the late recovery phase, even though there were no grossly abnormal bifid T waves, and the U waves were excluded.

Takenaka et al. using a physical exercise test, found the rate-corrected Tpe interval increased in LQT1 and remain unchanged in LQT2, thus allowing separation of these subtypes. Their study is not fully comparable to ours, because more than 50% of their
subjects were symptomatic with markedly prolonged QTc intervals and the Tpe intervals were corrected to HR. Our method of determining repolarization intervals at specified HR eliminates the need for rate correction, which is useful only over a narrow band of HR. This method also avoids rate correction of Tpe interval, which, generally, has not proven to be useful.

Proposed addition to diagnostic tools

As gene-specific therapy remains an ambitious goal in the management of LQTS, it is essential to use available techniques for distinguishing the LQTS subtypes. Besides molecular genetic analyses, evaluation of ST segment and T wave patterns, and pharmacological challenges have been used for LQTS subtype diagnostics. However, the present findings support the use of a routine exercise tolerance test not only for its informative value and availability, but for its safe, non-pharmacological nature. Along with QT interval the Tpe interval should be examined also.

In Table 2, we present characteristics of ventricular repolarization intervals during the formal exercise test, which could be regarded as supporting evidence for the diagnosis of a particular LQTS subtype, when screening family members with non-diagnostic ECG phenotypes. In the initial phase of the exercise, LQTS carriers have longer QT interval than controls. Later, LQTS carriers behave in a subtype-specific manner. The QT interval continues to be prolonged during the peak exercise only in LQT1. Conversely in LQT3, the shortening of QT interval is particularly pronounced. Tpe is long only in LQT2 during early exercise and on recovery. LQT3 mutation carriers have remarkably short Tpe intervals during peak exercise and this tends to persist during recovery. The dichotomizing values represent the studied cohorts and their generalizability likely depends on molecular genetic background of the population in concern. In our study population with normal or only marginally prolonged resting QTc intervals, the cut-off point values distinguished LQTS subtypes better than the ST-T wave patterns of Zhang et al.

Differences in populations studied may explain the disparity in sensitivity. In the study by Zhang et al., 33% of patients had QTc interval <460 ms, compared with 79% in our study. We neither had subjects with grossly abnormal QT intervals. In the former study, a variety of LQTS patients was included, whereas all the subjects in our study were asymptomatic. Thus, criteria derived from distinctly abnormal T waves cannot be applied directly to subjects with normal QT intervals, and so, additional tools are needed.

Relationship to pathophysiology of arrhythmias

Ventricular repolarization is most abnormal during peak exercise, or soon after, in LQT1 patients, coinciding with the circumstances of clinical arrhythmia events. LQT2 patients are particularly vulnerable to sympathetic arousal at rest when QT and Tpe intervals are at their longest. LQT3 patients have shortened QT and Tpe intervals upon exertion, the phase where they are least prone to arrhythmias. Experimental work by Shimizu and Antzelevitch showed that beta-adrenergic stimulation induced torsades de pointes ventricular tachycardia by increasing Tpe interval in LQT1 and LQT2 models. In the LQT3 model, such stimulation decreased Tpe interval and suppressed the tachycardia. Epinephrine stimulation is known to increase Tpe interval more in LQT1 than in LQT2, as did the physiologic sympathetic stress in our study.

During exercise, QT and Tpe intervals adapt most unfavourably in LQT1 subjects, which may also explain why beta-adrenergic antagonists are therapeutically most efficacious in this subtype. At elevated HR beta-blockers are shown to decrease sudden increases in the duration of the QT and Tpe intervals in LQT1. However, exercise notably shortens QT and Tpe intervals in the LQT3 group, supporting a favorable effect of sympathetic stimulation, which could be negatively affected by using beta-blockers. Measuring repolarization variables both during and after physical effort might potentially help in the implementation of therapy.

Limitations

Instead of the standard 12-lead ECG, we utilized precordial multichannel mapping, which provided certain advantages, such as, rejecting non-optimal ECG signals and fully automatic analysis. The technique has been shown to yield accurate and reproducible QT interval values—even during physical exercise. The characteristics of ventricular repolarization would probably be similar when using a high-quality standard ECG recorder. Although the entire subset of LQT1 subjects carried the most common KCNQ1 gene mutation in Finland, they came from nine unrelated families, possibly with different genetic modifiers. Unfortunately, our small group size restricts the application of the numerical values of Table 2 in clinical practice, as well as any gender-specific sub-analysis.

Conclusions

The adaptations of the QT and the Tpe intervals during the workload and recovery phases of the exercise test help in identifying three major LQTS subtypes, even in asymptomatic mutation carriers with non-diagnostic ECG phenotypes. Information obtained from the exercise test may help in directing mutational screening and provide putative subclass allocation for therapeutic decisions until molecular genetic diagnosis is available.

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References

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