Rate adaptation of QT intervals during and after exercise in children with congenital long QT syndrome

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Objectives To improve the diagnostic criteria of the congenital long QT syndrome in borderline cases we examined rate adaptation of ventricular repolarization phases during exercise and subsequent recovery in children with the long QT syndrome and controls.

Methods Nineteen children with definite long QT syndrome and 19 healthy controls underwent exercise testing. QT intervals were measured to the apex (early QT), to the end (total QT) and from apex to the end of the T wave (late QT) at heart rates from 90 by steps of 10 to 150 beats. min⁻¹.

Results In 11/19 long QT syndrome patients (61%) and 2/19 controls (12%) the total QT lengthened during the recovery phase compared with exercise (P = 0.005) at the lowest comparable heart rate. No difference was found between the groups during exercise. The sensitivity of rate adaptation of repolarization intervals was analysed by calculating linear regression slopes relating the QT intervals to the heart rates. During recovery, slopes relating the total QT to heart rate were steeper in long QT syndrome patients than those in controls (−2.50 ± 0.82 vs −1.79 ± 0.47, P = 0.003). Total QT/heart rate slopes differed between exercise and recovery phases in the long QT syndrome group only (−1.77 ± 0.71 vs 2.50 ± 0.82, P = 0.009). In long QT syndrome patients, the difference in total QT/heart rate slopes was mainly because the late QT/heart rate slopes indicating inhomogeneity of repolarization were steeper during recovery (−1.27 ± 0.74) than during exercise (−0.46 ± 0.29, P < 0.0001).

Conclusions After exercise in long QT syndrome children the QT interval lengthens abnormally and inhomogeneity of repolarization increases. Evaluation of the QT interval, and especially its late portion after exercise, may help in establishing the diagnosis of long QT syndrome.

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Key Words: Long QT syndrome, children, exercise test, QT interval, repolarisation, ventricular arrhythmias

Introduction

The long QT syndrome is most often inherited as an autosomal dominant trait[1] and is associated with life threatening arrhythmias. The QT interval divided by the square root of the RR interval (QTc) >440 ms, together with stress-related syncopal spells or a family history of the long QT syndrome are the major criteria for diagnosis[2]. In borderline cases, however, additional features, such as abnormal ventricular repolarization, must be looked for[3]. Recent molecular genetic studies have increased the knowledge of the pathophysiology of the long QT syndrome. Ion channel defects are now recognised as causing alterations in the duration and morphology of the repolarization wave in the electrocardiogram[4,5]. Nevertheless, identification of genotypes has underlined the fact that the QT interval alone is not a sufficient factor to discriminate the carriers from non-carriers of the long QT syndrome[6] but is expected to be a remarkable aid in the diagnosis of borderline cases.

At present, diagnosing an individual by genetic analysis has limitations because not all mutations causing the long QT syndrome are recognised, and linkage studies are not applicable to sporadic cases. Theoretically, the dynamics of ventricular repolarization during interventions such as exercise might give additional information about the repolarization abnormality. However, studies on rate adaptation of the QT interval during exercise have yielded controversial results in long QT syndrome patients[7,8]. Using our recent approach to evaluate the phases of the QT interval during exercise testing[9] we compared the dynamics of repolarization in children with the long QT syndrome and their controls.
The hypothesis was that during exercise and subsequent recovery some phases of the QT interval behave differently in long QT syndrome and normal children.

**Patients and methods**

Nineteen children (age 12·5 ± 3·1 years) with the congenital long QT syndrome underwent an exercise test. The criterion for the diagnosis of the long QT syndrome was QTc >440 ms (Bazett’s formula) in the standard 12-lead ECG and either syncpe or a positive family history of the long QT syndrome. The mean QTc of the patients at rest was 494 ± 44 ms. Fifteen patients had a positive family history. Ten children had had syncopal spells: four lost consciousness during exercise, five had spells while awake but not exercising, and one had convulsions while asleep. In two patients, syncopal spells could not be related to sleep, awakening or any kind of stressful situation. Seven out of nine asymptomatic children had at least one family member with symptoms (syncope or sudden death) which had occurred during exercise.

All symptomatic patients were using beta-blocking medication during the time of examination. No other medications were in use. The clinical characteristics are presented in Table 1. Nineteen healthy relatives of the patients (age 11·6 ± 3·5) were studied as controls. Nine of them had any symptoms or medications and the QTc in the standard 12-lead ECG at rest did not exceed 440 ms.

One of the children had bundle branch block in the baseline ECG. Echocardiography was carried out to disclose any structural heart diseases. An exercise test was performed with a bicycle ergometer with continuous ECG recording. The initial load was 30 W and the load was increased by 15 W per minute until exhaustion. When patients could no longer continue exercising, they immediately laid down and the continuous ECG was recorded in the supine position for 7 min.

The total QT interval was measured manually by the tangent method from the beginning of the Q wave to the end of the T wave, and the early QT interval from the peak of the T wave. The tangent method was chosen to enable uniform measuring of the QT interval even at high heart rates when the end of the T wave merges into the P wave. It should be noted, however, that this method may result in somewhat shorter QT intervals than when measured to the point where the terminal limb of the T wave is joined to the TP baseline. Both total and early QT intervals were measured from lead V3 at specified heart rates from 80 to 150 in steps of 10 beats whenever available. Lead V3 was chosen because it often has the largest T-wave amplitudes.[10] The registered measurement was a mean of at least four consecutive QRS complexes. In cases of notched or double-peaked T waves, the first peak of the T wave was used for measurements. If the interval between the peaks was longer than 150 ms, the second was considered as a U wave and was not included in the measurements. The late QT was the sum of subtracting the early QT from the total QT. Maximum load and heart rate attained during exercise were recorded.

To analyse the sensitivity of the rate adaptation of the repolarization intervals we studied the behaviour of total, early and late QT by plotting the measurements against the heart rate and calculating the slopes by least squares linear regression analysis in each individual. At least three measurements in each phase were required for each patient or control person in order to create a slope for the individual. These slopes of the QT to heart rate relationship were used to assess the differences in repolarization phenomenon between the groups and to evaluate the intra-individual changes between physical effort and recovery. We used QT/heart rate slopes and not QT/RR slopes because the relationship between QT intervals and heart rate appeared to be linear, whereas the relationship between QT and RR intervals is curvilinear[9]. Slopes with correlation coefficients less than 0·50 were excluded (8·8% of all slopes). Student’s t-test, paired t-test for intra-individual comparisons and chi-square test for categorized parameters were used for statistical analysis.

**Results**

The maximal load achieved was 161 ± 50 W in the long QT syndrome group and 172 ± 48 W in the control group (ns). In the long QT syndrome group without beta-blocking medication the maximal heart rate attained was 172 ± 20 beats min⁻¹ and in the control group 195 ± 11 beats min⁻¹ (P = 0·003). Long QT syndrome patients with beta-blocking medication had a maximal heart rate 146 ± 17 beats min⁻¹. Transthoracic 2-D and Doppler echocardiography revealed no abnormalities in any of the children.

**Comparison between groups**

Total and early QT of the long QT syndrome patients were statistically significantly longer than those of the
controls at any measured heart rate during exercise and recovery (Tables 2 and 3, all P values ≤ 0.03, not shown in the tables). The late QT interval was significantly longer in the long QT syndrome patients than in the controls at the heart rate of 100 beats·min⁻¹ after exercise, 115 ± 40 vs 85 ± 15 ms, P = 0.05.

Comparison between exercise and recovery

When comparing exercise and recovery phases at lowest individual heart rates, the total QT of controls was longer during exercise than recovery (328 ± 26 vs 309 ± 23 ms, P = 0.001). Long QT syndrome patients demonstrated the opposite behaviour (402 ± 50 vs 421 ± 53 ms, P = ns). In 11 long QT syndrome patients (61%) and two controls (12%) there was lengthening of the total QT during recovery compared to measurements during exercise (P = 0.005).

A biphasic or double-peaked T-wave in any of the precordial leads was observed at rest in 10, during exercise in eight and after exercise in 10 long QT syndrome patients. In the control group, a double-peaked T wave was exhibited at rest by eight, during exercise by one and during the recovery phase by none. In the long QT syndrome group, three out of 11 cases showing prolongation of the total QT from exercise to recovery did not exhibit double-peaked T waves at rest, during or after exercise. Early QT was significantly shorter in the early recovery phase than during exercise at the same heart rate in both groups (Table 3). In the long QT syndrome patients, late QT was longer during recovery than during exercise at most heart rates and the difference was significant at a heart rate of 90 beats·min⁻¹ (125 ± 38 ms and 88 ± 32 ms, respectively, P < 0.05). In the control group, late QT was shorter during recovery than during exercise.

Heart rate adaptation of QT intervals

In the study groups, the average correlation coefficients of the total QT/heart rate slopes ranged from 0.93 to 0.98. The corresponding numbers for the early QT/heart rate slopes and late QT/heart rate slopes were from 0.94 to 0.97 and from 0.54 to 0.89, respectively. During exercise, the total QT/heart rate slopes did not differ between the groups (Fig. 1 middle panel). In contrast to this, during the recovery phase the total QT/heart rate slopes of the long QT syndrome patients were steeper than those of the controls (−2.50 ± 0.82 and −1.79 ± 0.47, respectively, P = 0.003). In the long QT syndrome patients the total QT/heart rate slope was steeper during recovery than exercise (−2.50 ± 0.82 vs −1.77 ± 0.71, P = 0.009) whereas no difference was noted between the phases in the control group (−1.79 ± 0.47 vs −1.61 ± 0.56, ns) (Fig. 1 middle panel). The early QT/heart rate slopes did not differ between the groups or phases (Fig. 1 upper panel). The late QT/heart rate slopes were steeper in the long QT syndrome group than in controls during recovery (−1.27 ± 0.74 and −0.46 ± 0.29, respectively P < 0.0001) (Fig. 1 lower panel).

The nine long QT syndrome patients without beta-blocking medication exhibited steeper total QT/heart rate slopes than the controls during recovery, −2.25 ± 0.43 and −1.62 ± 0.31, respectively (P = 0.02). The corresponding values of the late QT/heart rate slopes were −1.02 ± 0.49 and −0.46 ± 0.29, respectively, P = 0.002.

Discussion

The present study shows that ventricular repolarization shortens in children with the long QT syndrome, as it does in healthy individuals during exercise. However, after exercise the QT interval and especially its late portion lengthen abnormally and these phenomena can be used in the diagnosis of the long QT syndrome in borderline cases.

Repolarization duration is the most important criterion of the clinical diagnosis of the long QT syndrome[3]. However, there is considerable overlapping between affected and non-affected family members in the length of the QT interval[6]. The Bazett's method, to
adjust QT intervals to the heart rate while under-correcting the QT values at low heart rates and over-correcting them at high heart rates\[11\], gives additional problems in borderline cases. Recently, emphasis has been put on the inappropriate shortening of the QT interval during exercise\[7,12\], and on the morphological variation of the repolarization wave as diagnostic tools in the long QT syndrome\[13\]. In the present study, an exercise-induced increase in the heart rate produced similar relative QT interval shortening both in children with the long QT syndrome and in normal children. However, during recovery in the long QT syndrome group, the QT values became longer than during the exercise phase at the same heart rates. Previously Locati et al. observed lengthening of QTc intervals in long QT syndrome patients after exercise but QT intervals were measured at different heart rates before and after exercise\[14\]. Weintraub et al. reported that the longest QTc intervals occurred after exercise in children with the long QT syndrome, but they included no control subjects as a reference\[15\].

The behaviour of the early QT was the same in both study groups during exercise and recovery. Thus, measuring of the early QT does not increase the power of the exercise test in the diagnosis of the long QT syndrome. On the contrary, the late QT behaved differently between patients with the long QT syndrome and the control children. The observation of longer late QT after exercise than during exercise may improve the diagnosis in some suspected cases with the long QT syndrome.

Besides its duration, the dynamics of the repolarization time, determined in relation to the heart rate (QT/heart rate slope), may help in diagnosing the long QT syndrome\[16\]. We observed that after exercise the total QT/heart rate slopes and the late QT/heart rate slopes were steeper in children with the long QT syndrome than in the control group. These slopes in the long QT syndrome children were also steeper than the corresponding slopes during exercise. The steeper slopes show exaggerated delay in repolarization with decreasing heart rate. In this study, an additional diagnostic criteria for the long QT syndrome appeared to be steeper total QT/heart rate and late QT/heart rate slopes during recovery than corresponding slopes during exercise. Although the relationship between QT intervals and the heart rate becomes less steep after beta-blockade\[17,18\], the common use of beta-blocking medication in our long QT syndrome patients did not eliminate the difference between the study groups.

Previously Merri et al. using Holter recordings, reported steeper early QT slopes in long QT syndrome patients than in healthy controls\[17\]. Our method showed no differences between the groups or between test phases in the early QT/heart rate slopes. We measured the early QT intervals to the first peak of T waves. The rationale of our decision rests on the hypothesis that the second component of the T wave may be the manifestation of after-depolarizations\[19,20\]. Merri et al. measured the

![Figure 1](image-url)  
**Figure 1** Mean slopes of long QT syndrome children and controls showing the relationship of early QT (QTm) (upper panel), total QT (QTc) (middle panel) and late QT (TmTo) (lower panel) to heart rate (HR) during and after exercise.
early the QT interval to the maximum amplitude of the T wave. It follows that in the method of Merri et al. the maximal amplitude of the T wave could be the first or the second peak of the T waves. This may explain why Merri et al. had steeper early QT slopes in long QT syndrome patients.

Molecular genetics has revealed the heterogeneous nature of the long QT syndrome. Recently Schwartz et al. reported differences in repolarization behaviour in one long QT syndrome subtype caused by a mutation in the cardiac potassium channel gene HERG on chromosome 7 (LQT2) compared with another caused by a mutation in the cardiac sodium channel gene SCN5A on chromosome 3 (LQT3). In their study, an increase in heart rate shortened the QT interval further in patients with LQT3 than in LQT1 and LQT2. Despite the ion channel abnormality, however, the unifying feature in all long QT syndrome patients is a propensity to torsades de pointes ventricular tachycardia. One of the electrophysiological mechanisms for torsades de pointes is the heterogeneity of the repolarization. It has also been shown, that the duration of the late phase of repolarization correlates with the dispersion of repolarization.

The above-mentioned study by Schwartz and co-workers also suggested that the adrenergic mechanisms were critical in LQT2, whereas slow heart rates meant a risk of arrhythmia events in LQT3. By monitoring the repolarization dynamics during exercise and subsequent recovery, both the adrenergic and vagal activation and inactivation sequences are included. Thus, despite the possibly different triggering autonomic events in the long QT syndrome subtypes, exercise testing may reveal the abnormality in the repolarization dynamics. It might be possible to find a typical abnormality in different long QT syndrome subtypes by analysing repolarization behaviour. As many of our studied families were small, we could link only a few of the presented long QT syndrome patients to chromosome 11, while others remained of an unknown genotype. Therefore, the variation of the QT/heart rate slopes in the long QT syndrome group in our material may be explained by genetic heterogeneity.

### Table 3 Comparison of total QT intervals (ms) during exercise and recovery at specified heart rates in Long QT syndrome and control groups

| Heart rate | Patients | | | | | | | | Controls | | | | | |
|------------|---------|------------|---------|------------|---------|---------|-------------------------------------------------|-------------------------|-------------------------|-------------------------------------------------|-------------------------|-------------------------------------------------|---------|
|            | Exercise | Recovery   | P value* | Exercise | Recovery   | P Value* | | | | | | | | |
| 90         | 323 ± 38 | 311 ± 38   | ns       | 245 ± 12 | 239 ± 30   | ns       | | | | | | | | |
| 100        | 291 ± 28 | 289 ± 47   | ns       | 240 ± 21 | 228 ± 21   | ns       | | | | | | | | |
| 110        | 269 ± 33 | 271 ± 40   | ns       | 230 ± 16 | 206 ± 15   | 0·004    | | | | | | | | |
| 120        | 255 ± 32 | 253 ± 38   | ns       | 221 ± 12 | 194 ± 11   | <0·0001  | | | | | | | | |
| 130        | 249 ± 38 | 241 ± 37   | ns       | 206 ± 13 | 184 ± 6    | <0·0001  | | | | | | | | |
| 140        | 241 ± 37 | 219 ± 25   | 0·007    | 194 ± 21 | 179 ± 7    | 0·04     | | | | | | | | |
| 150        | 228 ± 36 | 211 ± 33   | 0·01     |           |           |          | | | | | | | | |

*Intra-individual difference; paired samples.

### References