Effect of physical training on ventricular repolarization in type 1 long QT syndrome: a pilot study in asymptomatic carriers of the G589D KCNQ1 mutation

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Aims High-intensity physical exercise and competitive sports have been traditionally avoided in long QT syndrome. However, endurance training increases vagal activity and thus may improve cardiac electrical stability in healthy subjects. We hypothesized that controlled submaximal endurance training would not adversely affect ventricular repolarization in asymptomatic carriers of a KCNQ1 gene mutation of type 1 long QT syndrome (LQT1).

Methods and results Previously, sedentary carriers of a missense mutation of KCNQ1 gene (LQT1, n = 7) and healthy controls (n = 8) exercised on a bicycle ergometer 3–4 times a week, 30 min a day at 60–75% of maximal heart rate (HR) for a maximum of 3 months. Body surface potential mapping (BSPM) was recorded and QT intervals were determined automatically from 14 channels over the left chest area. Maximal work capacity increased by 4 ± 1% in LQT1 and by 14 ± 2% in controls (both P < 0.05), and left ventricular (LV) mass by 8 ± 1% and 9 ± 1%, respectively (P < 0.05). Resting corrected QT interval shortened by 10 ± 1% (P < 0.05) and QT interval dispersion by 25 ± 9% (P < 0.05) in LQT1, but not significantly in controls. QT intervals at specified HRs during workload and recovery phases were not changed in either group.

Conclusion In this pilot study of asymptomatic carriers of a KCNQ1 gene mutation, submaximal endurance training did not harmfully affect arrhythmia risk markers. Confirmatory studies in a broader spectrum of LQT1 genotypes are needed before any generalization can be made.

KEYWORDS
Arrhythmia; Exercise; Gene mutation; LQTS; QT-interval

Introduction

In the familial long QT syndrome (LQTS), ventricular tachyarhythmias are often connected with intense physical effort or emotional stress, and manifest as syncopal spells or sudden death.1 Thus, LQTS patients have been discouraged from high-intensity physical exercise and competitive sports. Regular physical training modifies HR control in whole or in part through neurocardiac mechanisms in endurance-trained athletes.2 Six weeks of daily exercise after acute myocardial ischaemia decreased the incidence of ventricular fibrillation, markedly in dogs, most likely due to increased cardiac vagal activity.3 Long-term endurance training has been shown to shorten corrected QT interval (QTc) in healthy, elderly women.4 Congenital LQTS originates from sarcolemmal ion channel defects caused by mutations in different genes.5 Mutations of the slow potassium channel gene (KCNQ1) cause the subtype 1 of the LQTS.5,6 In this subtype LQT1, arrhythmias occur particularly during physical effort.7 Often, LQT1 manifests in subjects with normal QTc interval (<440 ms), not necessarily differing from their healthy relatives.8 Swan et al.9 showed that mean QT interval is longer in LQT1 patients with KCNQ1 gene mutation than in healthy subjects at all HRs. Furthermore, LQT1 is associated with exaggerated prolongation of QT interval after exercise.9

We hypothesized that controlled submaximal endurance training would not have adverse effects on ventricular repolarization in LQT1. Therefore, we investigated the effects of...
endurance training on QT interval in previously sedentary, asymptomatic carriers of a KCNQ1 gene mutation.

**Methods**

**Subjects**

Seven asymptomatic carriers of KCNQ1 G589D missense mutation, causing the clinical LQT1 subtype, and eight healthy controls participated in this study. The LQT1 gene mutation carriers were identified through family genetic screening, and they were close, mostly first-degree relatives of the probands with severe symptoms. The age of LQT1 gene carriers ranged from 24 to 55 years (42 ± 2) and of the controls from 24 to 58 years (42 ± 1). Four patients and six controls were female. All were nonsmokers, normotensive, sedentary, and none used any medicine including beta-blockers due to the asymptomatic status. The study complies with the Declaration of Helsinki and was approved by the institutional review board of Helsinki University Hospital. All patients signed a written informed consent.

**Exercise training programme**

To initiate the exercise programme, maximal HR was determined for each subject in a bicycle exercise test, to be used for planning the work level. The first exercise training session was performed under supervision, after which training was performed at home for 3 months using a bicycle ergometer. Exercise started at 60% of maximal HR for 30 min a day three times a week. Thereafter, training intensity increased gradually to 75% of maximal HR for 30 min a day 4 times a week. The subjects used continuous HR display (Polar Electro Inc., Kempele, Finland) to adjust the workload, and reported their mean HRs and exercise duration after each training session.

**Exercise test protocol**

Exercise test on a bicycle ergometer for QT interval analysis was performed before and after 3 months of training. First, a baseline electrocardiographic recording was performed in a resting state for 3 min. Next, the subjects pedalled lightly for 5 min to increase HR to not more than 100 bpm and then rested supine for 10 min. In the following maximal exercise test, the workload was increased stepwise every minute until severe fatigue or dyspnoea. Blood pressure was measured every 3 min during exercise. None had repetitive ventricular arrhythmias. ECG recording was continued throughout the test till 10 min of recovery.

**ECG recording**

In order to record unipolar potentials from the chest area, Body Surface Potential Mapping (BSPM) was used. The BSPM system uses 123 Ag/AgCl electrodes attached to 18 flexible plastic strips, each with a vertical inter-electrode distance of 5 cm, and horizontal distance according to the anatomical dimensions of the thorax, with highest density over the left anterior chest area. In the present study, QT data were analysed from 14 electrodes covering the precordial area, corresponding to the general area of the chest leads in a 12-lead ECG (Figure 1). Signals were band-pass filtered at 0.16–300 Hz, digitized with a sampling frequency of 1 kHz, and stored on a computer disk. Data were baseline corrected and signal averaged, excluding signals judged invalid by visual inspection.

**QT interval measurement**

QT intervals were determined as an average of the whole resting period (3 or 10 min), and as an average of 10–20 consecutive beats during the exercise test. During mild exercise, QT interval was analysed at HRs of 80 and 90 bpm. During maximal exercise, test analyses were performed at HRs of ~90, 100, 110, 120, 130, and 140 bpm during workload and recovery.
carriers, and 405 ± 13 ms in controls. All LQT1 gene carriers had QTc within normal limits (Table 1).

### Effect of training on physiological variables

The results are shown in Table 1. LQT1 gene carriers had lower maximal HR than controls ($P < 0.05$). Physical training did not affect resting and maximal HRs in either group. Maximal workload increased by $4 ± 1\%$ and $14 ± 2\%$ in patients and controls, respectively ($P < 0.05$ for both). The LV mass increased by $8 ± 1\%$ in LQT1 and $9 ± 1\%$ in controls ($P < 0.05$ in both groups).

### Effect of training on electrocardiographic variables at rest

Physical training shortened resting QTc by $10 ± 1\%$ ($P < 0.05$) in LQT1, whereas no shortening occurred in controls. The change in QTpeak and QT end was not statistically significant (Table 1). QT interval dispersion at rest decreased by $25 ± 9\%$ ($P < 0.05$) in LQT1 after training, whereas no significant changes occurred in controls (Table 1).

### Effect of training on QT interval during exercise and recovery

The QTc at 5 min after mild exercise was shortened by $6 ± 2\%$ ($P < 0.05$) in LQT1 patients after training. No significant change occurred in controls (Figure 2).

The changes observed in QT and QTpeak intervals were not statistically significant at any measured HR level during the workload or recovery of the exercise test. The adaptation of QT interval to HR, described as QT interval/HR slope, was not significantly affected by training (Figures 3 and 4).

### QT interval duration

QT interval within normal limits is not unusual in carriers of LQT1 gene mutation, and does not necessarily protect from arrhythmias, even in symptomatic subjects. In the present study, the LQT1 gene carriers, who were not taking any medications, including beta-blockers, had QTc shorter than the upper normal limit, but had QTc longer than the healthy controls. Moreover, in spite of only mildly affected QT intervals, maximal HR during stress test was blunted in the LQT1 patients, which is in accordance with earlier studies, demonstrating that the KCNQ1 mutation causes diminished chronotropic response also in asymptomatic carriers.

### Effects on ventricular repolarization

Patients with the KCNQ1 mutation have exaggerated QT interval prolongation after exercise during recovery. In our study, endurance training did not adversely modify the QT interval responses to workload and recovery phases of the exercise test. Even more, QTc during recovery after mild exercise was shortened in LQT1 by training. The duration of the end part of the T-wave, thought to represent transmural dispersion of repolarization, showed no change, and the QT interval dispersion decreased. Favourable influence on these markers of ventricular electrical stability might be related to an improvement in autonomic nervous system control by regular exercise training, observed previously in healthy subjects.

### LV structural changes

In our study, moderate endurance training increased LV mass, both in LQT1 gene carriers and controls, which was evident even after only 3 months of moderate endurance training. This is in accordance with earlier endurance training studies. It is noteworthy that this physiological increase in ventricular mass is not associated with any
lengthening of QT interval or any increase in inhomogeneity of repolarization, that are known to occur in pathological increase of LV mass in hypertension. The presumed increase in cardiac mass, by enlargement of cardiac myocytes, could possibly have a stabilizing effect on the electrical events in the myocardium.

Limitations
To perform the exercise programme at home required exclusion of symptomatic LQTS patients and supervised initiation of training. The small number of subjects and inclusion of only a single KCNQ1 mutation limit the generalization of the conclusions. Although the used surrogates, QT interval duration, and dispersion are associated with arrhythmia risk, their decreases do not necessarily indicate diminished risk. There remains a need to investigate asymptomatic KCNQ1 mutation carriers who have longer QTc intervals.

Implications
While family screening reveals increasing numbers of asymptomatic carriers of mutations causing LQT1 subtype, it becomes important to decide whether counselling should include limitation of exercise, which is otherwise considered to promote health. Although the present study is insufficient to assure patients due to a small number of subjects, it suggests that moderate endurance training might not increase arrhythmia risk in asymptomatic patients who carry KCNQ1 gene mutations. If similar observations are confirmed in more representative patient cohorts, moderate endurance training might not be discouraged in asymptomatic KCNQ1 gene carriers.
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References