Exercise Test for Patients with Long QT Syndrome

Cheng-Han Chan, Yu-Feng Hu, Pei-Fen Chen, I-Chien Wu and Shih-Ann Chen

Congenital long QT syndrome (LQTS) causes life-threatening cardiac arrhythmias and is the leading cause of sudden cardiac death in young people. Measurements of QT prolongation during exercise or postural change have been recommended to assist in the diagnosis of LQTS, particularly in those with hidden phenotypes. However, most evidence has come from single-center studies without external validation in an independent cohort. Inter-study heterogeneity leads to significant difficulties in interpreting and applying consistent diagnostic criteria for LQTS. A comprehensive systematic review is critically needed to summarize the evidence and validate the diagnostic performance of QT intervals during exercise or postural change across a variety of studies. In this study, we review cross-sectional and cohort studies evaluating the efficacy and feasibility of exercise tests or postural changes in diagnosing LQTS, and propose possible problems resulting from exercise tests.

Key Words: Exercise test • Long QT syndrome • Postural change

INTRODUCTION

Congenital long QT syndrome (LQTS) is usually characterized by a prolongation of the QT interval on electrocardiography (ECG) due to ion channel mutations. Similar to other inherited arrhythmias, it causes life-threatening cardiac arrhythmias and is the leading cause of sudden cardiac death in young people. The LQTS diagnostic criteria are based on the Schwartz criteria. Further, genetic testing is recommended for the detection of pathogenic mutations of relevant ion channels. In the current update of the Schwartz criteria, the diagnostic function of QT prolongation in the recovery process of the exercise stress test was introduced to raise awareness and prevent adverse effects in asymptomatic patients. The 2017 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines also gave class Ila recommendation to use ECG changes after exercise or postural change to diagnose patients with suspected LQTS. Accumulating evidence has been reported on the use of corrected QT interval (QTc) after exercise and postural changes. However, significant variations in study design and populations between different studies and limited patient numbers have led to difficulties in interpreting the data for clinical use. In addition, most evidence has come from single-center studies without external validation in an independent cohort. A comprehensive systematic review is critically needed to summarize the evidence and validate the diagnostic performance of QT intervals during exercise or postural change, and also to highlight the factors which need to be considered when applying these measures. In this review, we assessed the efficacy and feasibility of exercise tests or postural changes in the diagnoses of LQTS.

INCLUSION AND EXCLUSION CRITERIA OF THE STUDIES

PubMed Central was searched from 1999 to 2019
for English language studies using the following keywords: long QT syndrome/diagnosis, exercise test, and electrocardiography. Sixty-three studies were found. All cross-sectional or cohort studies, as well as relevant systematic reviews, guidelines, and cited references were included. The included participants all underwent an exercise test with QT interval measurements, during either postural change or exercise.12 A total of 17 studies were identified and included in our review (Table 1).12-27 LQTS was generally defined as a Schwartz criteria score ≥ 3.5

**Table 1. The clinical studies to diagnose LQTS by exercise tests**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants</th>
<th>Control</th>
<th>LQTS1</th>
<th>LQTS2</th>
<th>Others</th>
<th>Protocol EKG lead measured</th>
<th>QT correction criteria</th>
<th>Usage of β-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sy RW, et al., 2010</td>
<td>25 25 25</td>
<td>25</td>
<td>Burst bicycle Gradual bicycle Bruce</td>
<td>II or lateral precordial NA</td>
<td>Bazett’s</td>
<td>11 (44%) LQTS1; 14 (56%) LQTS2, with β-blockers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obeyesekere MN, et al., 2012</td>
<td>26 LQTS: 26</td>
<td>26</td>
<td>Modified Bruce Gradual bicycle Bruce</td>
<td>V5</td>
<td>Bazett’s</td>
<td>Atenolol 50 mg daily Bisoprolol 5 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong JA, et al., 2010</td>
<td>64 50 45</td>
<td>45</td>
<td>Modified Bruce Gradual bicycle Bruce</td>
<td>V5</td>
<td>Bazett’s</td>
<td>Without any medication that affect the repolarization, including β-blockers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takenaka K, et al., 2003</td>
<td>33 51 47</td>
<td>47</td>
<td>Burst bicycle Gradual bicycle Bruce</td>
<td>V5</td>
<td>Bazett’s</td>
<td>β-blockers were discontinued for 26-30 hours.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adler A, et al., 2012</td>
<td>12 46 47</td>
<td>47</td>
<td>Stand up quickly, then standing still for 5 minutes</td>
<td>NA</td>
<td>Bazett’s</td>
<td>40/82 LQTS1, 28/55 LQTS2, and 3/18 LQTS with β-blockers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andrsova I, et al., 2012</td>
<td>49 50 25</td>
<td>25</td>
<td>Modified Bruce Gradual bicycle Mostly V5</td>
<td>Bazett’s</td>
<td>NA</td>
<td>Some receiving β-blockers at the time of the exercise test 56% β-blockers in LQTS1 and LQTS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horn JM, et al., 2011</td>
<td>88 123 77</td>
<td>77</td>
<td>Modified Bruce Gradual bicycle</td>
<td>II or V5</td>
<td>Bazett’s</td>
<td>No β-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Takenaka K, et al., 2003 circulation</td>
<td>33 51 47</td>
<td>47</td>
<td>Burst bicycle Gradual bicycle Bruce</td>
<td>V5</td>
<td>Bazett’s</td>
<td>β-blockers use in the derivation cohort (33%) validation cohort (30%) Effect of β-blockers was discussed in this article</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sy RW, et al., 2011</td>
<td>86 81</td>
<td>81</td>
<td>Modified Bruce Gradual bicycle</td>
<td>II or V5</td>
<td>Bazett’s</td>
<td>1. Postural QT and QTc measurements were analyzed only in patients who were in a drug-free state.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laksman ZW, et al., 2013</td>
<td>123</td>
<td></td>
<td></td>
<td></td>
<td>Bazett’s</td>
<td>2. Beta blocker use in exercise test: 17 (59%) LQTS1 and 11 (52%) LQTS2 Standing test in 7 children with LQTS was done without β-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aziz PF, et al., 2011</td>
<td>108 29 21</td>
<td>21</td>
<td>Gradual bicycle</td>
<td>II or V5</td>
<td>Bazett’s</td>
<td>LQTS patients taking beta-blockers underwent the test 26 to 30 h after their last dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dionne A, et al., 2018</td>
<td>100</td>
<td>7</td>
<td>Lying supine for 10 minutes, then stand up quickly</td>
<td>II or V5</td>
<td>Bazett’s</td>
<td>Fridericia Framingham Hodge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger WR, et al., 2011</td>
<td>94</td>
<td></td>
<td>Gradual bicycle</td>
<td>Rest: V5 Exercise: II</td>
<td>Bazett’s</td>
<td>Fridericia Hodge Bazett</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viskin S, et al.</td>
<td>82 31 28</td>
<td>28</td>
<td>LQTS: 3 Other: 6</td>
<td>Stand up</td>
<td>NA</td>
<td>LQTS patients taking beta-blockers underwent the test 26 to 30 h after their last dosage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LQTS, long QT syndrome; LQTS1, long QT syndrome type 1; LQTS2, long QT syndrome type 2; LQTS3, long QT syndrome type 3; NA, not available.
or a positive LQTS-related genotype.6,7

MECHANISMS OF QT DYNAMICS DURING EXERCISE

The mechanisms underpinning QT dynamics during exercise are far from clear. Sympathetic pathways are commonly considered to be an important mechanism, as β-blockers decrease QT prolongation.28 Insensitivity to protein kinase A stimulation of IKs (phosphorylation of IK channels) may explain why patients with the KCNQ1 mutation have excessive prolongation of QT intervals during exercise.29 Recently, a genome-wide analysis suggested that QT dynamics during exercise have a heritable component of around 10%, while the recovery markers are less heritable (~6%).30 Most genetic variations associated with QT changes during exercise (peak exercise or recovery) overlapped with those determining resting QT intervals, including KCNQ1, KCNH2, SCN5A-SCN10A, and KCNE1. Hence, this is particularly true for the loci used to assess QTc changes during recovery. All loci for QT dynamics overlapped with resting QT interval loci during recovery. Only five loci (CDKN1A, KIAA1755, KCNQ4, LOC643623, and FOXN3) for QT dynamics during exercise did not overlap with the previously reported loci for resting QT interval. This means that the genetic determinants for QT intervals were similar between the resting and recovery period after exercise. However, the QT intervals at peak exercise were more complex, which may be reflected in the significant variability of QT intervals at peak exercise between studies than those at recovery (see the following section).

PROTOCOLS OF EXERCISE TEST

Four exercise test protocols were used in the included studies: the Bruce protocol, modified Bruce protocol, gradual bicycle protocol, and burst bicycle protocol (Table 1). Physiological responses to exercise and maximum oxygen uptake on a cycle ergometer vary from those obtained on a treadmill. Although the Bruce protocol, modified Bruce protocol, and gradual bicycle protocol are all recommended in exercise test guidelines,11 it remains uncertain whether different protocols are associated with variable sensitivity of QTc changes following exercise. Moreover, most of the studies used a single protocol. Therefore, it was also difficult to compare the effect of different protocols on QTc intervals. A rapid or gradual increase in workload was contrasted with burst and gradual bicycle exercise protocols in patients with LQTS1 and LQTS2. While equivalent results from burst or gradual exercise could discriminate patients with LQTS1 or LQTS2 from controls, QT adaptation tended to be more prevalent in burst than gradual bicycle exercise protocols.12,14,21 Similar cutoff values could be used for upright burst and gradual bicycle exercise protocols.21,22 Some disparity between the treadmill test and bicycle protocols (burst or gradual) was observed.14 The changes in QTc intervals at peak exercise were minimal in LQTS2 patients by the treadmill test, while changes in QTc intervals of more than 20 ms were observed in both bicycle protocols. Similarly, no distinction in burst and gradual bicycle protocol was observed. A gradual supine bicycle protocol was recommended to minimize signal artifacts from upper body motion during exercise.14

MEASUREMENT OF QTc INTERVALS AT EXERCISE TEST

The measurement of QT intervals during exercise was typically performed on lead II or V5, as these leads had the largest T-wave amplitude12 or the longest interval among the 12 leads.14 Generally, the end of the T-wave was determined as the intersection point between the isoelectric baseline and the tangent line, indicating the maximal downward or upward slope of the T-wave in all studies (Figure 1).31 Manual measurements were applied in all 17 studies, which was important to visually validate the QTc interval prolongation reported by a computer algorithm.32 Generally, when the T-wave had a biphasic, bifid, or notch configuration, the tangent was often applied after the latter crest (Figure 1).15,18,21 It was difficult to distinguish the U-wave from the T-wave terminal notch, particularly when the larger U-waves merged with the T-wave. Some studies suggested that small U-waves should be omitted from the measured QT interval, and that large U-waves should be merged into T-waves. Therefore, during QT interval measurements,
U-waves were included in two studies. Changes in the U-wave during exercise are poorly understood, and this may lead to variable measurements of QT intervals, particularly during exercise, which would likely result in diagnostic inconsistency.

The AHA/ACCF/HRS guidelines recommend that linear regression functions rather than Bazett’s formula should be used for QT rate correction, because Bazett’s formula does not produce a linear relationship between RR and QTc intervals at fast heart rates. However, Bazett’s formula was used in all stress studies. Other uncommon formulas were also used, including the Fridericia formula, Framingham formula, and Hodge formula. Rate correction of QT intervals by Bazett’s formula is not recommended if the variability of the RR interval is high, e.g., atrial fibrillation, or if the identification of the end of the T-wave is not accurate. In general, this information was not provided in the included studies. It is very difficult to identify the end of the T-wave, especially during high heart rate with baseline artifacts, which are not uncommon in exercise tests. These greatly complicate the measurements of QT intervals.

**ANALYSES BETWEEN EXERCISE PHASES**

There are four phases of exercise with each protocol: resting, postural change, peak exercise, and recovery. Even in the same treadmill protocol, it is not surprising that different LQTS strategies and measurements were used between laboratories. Most of the studies did not present comprehensive data for all four phases, and so comparisons between these studies were difficult. At the pre-exercise resting phase, the participants could be in the supine position or sitting without movement. The peak exercise phase, described as maximum heart rate exercise in most studies and QTc interval, was measured at maximum heart rate. In some studies, maximum QT intervals during the exercise phase were used instead of the QTc interval at maximum heart rate. One study used the QT measurement when the heart rate accelerated to 130 bpm after exercise. During the recovery phase, QTc measurements could be analyzed from the time right after peak exercise to 7 minutes. Although 4 minutes into the recovery phase is used for the Schwartz score and widely accepted for the diagnosis of LQTS, its diagnostic performance remains controversial at different time points (peak exercise into recovery).
Walker et al. used the longest QTc prolongation during the exercise test instead of the QT interval for a fixed time of recovery. An arbitrary cutoff value of 85 ms prolongation resulted in a sensitivity of 77% and a specificity of 90% for the diagnosis of LQTS. Sy et al. reported that a QTc interval > 445 ms at 4 minutes in the recovery phase could be used to diagnose LQTS, and that a QTc interval > 460 ms at 1 minute in the recovery phase favored LQTS1. In comparison, Rejane et al. used a QTc of 410 ms at 3 minutes in the recovery phase, which had a sensitivity of 75% and a specificity of 76.5%. Aziz et al. reported a threshold value of QTc > 460 ms during the late recovery phase (7 minutes) when distinguishing LQTS and concealed LQTS children from normal patients.

POSTURAL CHANGES OF QTc INTERVALS FOR THE DIAGNOSIS OF LQTS

During postural changes from supine to standing, heart rate acceleration followed by changes in QT intervals were observed. The patients were typically required to stay in the supine position for 5-10 minutes. The postural change led to artifacts within 10 seconds after standing, and thus the measurement of QT change was usually taken 30 seconds or 1 minute after standing abruptly. The QT intervals after postural change were also measured at the maximal QT interval during continuous ECG recording after postural change. Some protocols were not defined clearly. In normal controls, the QT interval either did not change or became shorter. Due to heart rate acceleration, the QTc interval increased by 48 ± 42 ms in normal adult controls and 63.3 ± 32.8 ms in pediatric controls immediately after standing. Dionne et al. reported a substantial increase in QTc while standing at the upper limit of normal at the 95th percentile of 563 ms in healthy children. No major differences in QTc response with respect to sex and age (children vs. adolescents) were observed. In LQTS patients, prolongation of the QTc interval from 30 to 80 ms in LQTS1 or 45 to 126 ms in LQTS2 were observed, followed by diminished T-wave voltage. Changes in QTc interval were significantly higher in LQTS patients than in controls. QTC interval > 487 ms during postural change had a sensitivity of 90% and specificity of 86% to diagnose LQTS. LQTS2 was associated with more QT prolongation than LQTS1, either during maximum tachycardia after standing or at slowdown back to baseline heart rate. Therefore, the diagnostic efficiency of postural change was better in LQTS2 than LQTS1. However, postural change in the QTc interval between LQTS patients and controls was not observed in children, and it is currently not included in the Schwartz criteria.

CHANGES IN QTc INTERVALS DURING EXERCISE IN THE CONTROLS

When we went through the studies to distinguish LQTS patients from normal controls by certain cutoff points of QTc intervals, inter-study variability was observed which increased the difficulty in establishing consistent criteria to diagnose LQTS. This could be explained by the heterogeneous characteristics of the controls or LQTS patients due to the variable inclusion criteria. In analysis of control groups (Table 2), three different sources were observed. First, patients with a low risk of LQTS due to clinical diagnosis or a negative genotype were used as controls in the same hospital where LQTS patients were recruited (hospital-based). Second, the genotype-negative family members of LQTS patients were used as controls (family-based). Third, healthy volunteers from the community were used as controls. Generally, the underlying comorbidities were not well defined. The mean age ranged from 9.7 to 38 years, and the mean values of the QTc intervals before exercise ranged from 402 to 437 ms. The biggest variability in mean QTc intervals was observed during peak exercise (406-482 ms). The QTc intervals at peak exercise were longer in family-based controls and shorter in hospital-based controls. During the recovery phase, the time points for calculating the QTc interval were different as mentioned above. The mean QTc intervals during the recovery phase were 396-441 ms with lower variability than those during peak exercise. In the recovery phase, the QTc intervals were either minimally increased or decreased relative to those at rest. Only one study, which recruited healthy volunteers, showed an increase in QTc interval by 17 ms from rest to recovery.
The updated Schwartz criteria for the diagnosis of concealed LQTS uses a 480 ms cutoff value at 4-minute recovery. According to the report by Sy et al., this cutoff (4-minute recovery > 480 ms) had 100% specificity to identify the patients who almost definitely had LQTS.22 QT prolongation during recovery (3-4 minutes after exercise) was generally recommended to predict LQTS.22 This was relatively easy to record and measure as a result of minimal patient movement and stable heart rate. Aziz et al. stated that a threshold value of QTc > 460 ms during the late recovery phase (7 minutes) was useful in distinguishing concealed LQTS children from normal patients.26 KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) are the most common LQTS genes, accounting for ≈ 90% of all genotype-positive cases.2 These criteria were not applicable to everyone with LQTS, as these patients had variable genotypes and phenotypes that clearly responded differently to exercise.

In the absence of functional I\textsubscript{Ks} from the KCNQ1 mutation, QT fails to adapt with increased heart rate.29 The LQT1 patients had a lower repolarization reserve during exercise as evidenced by a progressive or persistent pattern of QTc prolongation at higher heart rates, manifested as QTc prolongation during the peak exercise phase.12,14,15,23,27 In LQT1 patients, the prolongation of QTc intervals was maximal at peak exercise, followed by those at postural change and during the recovery phase (Table 3) (Figure 2). Horner et al. reported a QTc prolongation > 30 ms at 3 minutes of recovery may provide a 75% pregenetic test probability for LQT1.18 The standard deviation of QTc intervals in LQT1 patients ranged from 21 ms to 90 ms at peak exercise, indicating significant inter-study variance (Table 3). The QTc intervals during peak exercise and early to mid-recovery phase (3-4 minutes) could help to identify LQT1.
Maximum QTc prolongation occurred at sub-maximum heart rates with a subsequent fall toward baseline values at higher heart rates in the patients with LQTS2. LQTS1 patients showed a QTc that decreased gradually during recovery, while LQTS2 patients had QTc intervals that increased as the recovery period progressed. In LQTS2 patients, prolongation of the QTc intervals was maximal at postural change (Table 4). However, there was no significant QTc prolongation during peak exercise and recovery phase (Figure 2). Several studies reported that QTc intervals increased in the late recovery phase (more than 4 minutes) in LQTS2 patients. Aziz et al. reported that interval changes in QTc intervals from 1 minute to 7 minutes of recovery (> 30 ms) favored the diagnosis of LQTS2 and were useful in distinguishing between LQTS1 and LQTS2 in children. This illustrates the disparity in repolarization between the late and early recovery phases between LQTS1 and LQTS2. However, major differences were observed between studies, and thus it is difficult to decide whether the QT intervals in the late recovery phase are the optimal criterion for the identification of LQTS2.

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Most of the studies that performed exercise selected the patients using the Schwartz score, and discrepancies between the controls and LQTS patients were present before exercise. The unmet clinical need to perform exercise tests should focus on identifying concealed LQTS patients either with/without genetic tests. Either an absolute QTc > 460 ms during the recovery phase or ΔQTc (QTc recovery to QTc baseline) ≥ 30 ms distinguished patients with either manifest or concealed LQTS1.

**HETEROGENEITY BETWEEN STUDIES**

Absolute values of the QTc intervals in the controls...
and LQTS patients had significant differences, suggesting variability between studies. There are several possible reasons for this heterogeneity. First, the genetic background. Some studies did not specify the subgroups by the types of LQTS, and even among the same LQTS type, different mutation locations in the KCNQ1 and KCNH2 genes might induce different phenotypes and cardiac events.\textsuperscript{23,37,38} Second, medications during exercise test were different, especially β-blockers which would change and shorten the QTc intervals in LQTS patients during exercise.\textsuperscript{14} However, there were no clear guidelines for the use of β-blockers between studies (Table 1), which may then have contributed to the variation in QTc intervals. Third, different exercise protocols can lead to variable stress conditions. In addition, measurements of the QTc intervals differed significantly. The time point for calculating the QT intervals during exercise and definition of the QT endpoint (including the U-wave or not) were also dependent on heterogeneity. Interestingly, when comparing the interval changes in the QTc intervals between rest and peak exercise, the most prominent heterogeneity was in the control groups rather than in the LQTS patients. This suggests that variability of the “standards”

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number</th>
<th>Age</th>
<th>Remarks</th>
<th>QTc intervals (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sy RW, et al., 2010\textsuperscript{12}</td>
<td>25</td>
<td>33 ± 16</td>
<td>Non β-blocker use, n = 37</td>
<td>Rest: NA</td>
</tr>
<tr>
<td>Wong IA, et al., 2010\textsuperscript{14}</td>
<td>45</td>
<td>34.5 ± 21</td>
<td>β-blocker use, n = 30</td>
<td>Postural change: 482 ± 39, Peak exercise: 527 ± 67, Recovery 3 or 4 minutes: 491 ± 36</td>
</tr>
<tr>
<td>Takenaka K, et al., 2003\textsuperscript{15}</td>
<td>31</td>
<td>31 ± 18</td>
<td></td>
<td>470 ± 25</td>
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<tr>
<td>Adler A, et al., 2012\textsuperscript{16}</td>
<td>47</td>
<td>28 ± 16</td>
<td></td>
<td>520 ± 61</td>
</tr>
<tr>
<td>Androsova I, et al., 2012\textsuperscript{17}</td>
<td>5</td>
<td>39 ± 16</td>
<td>Asymptomatic\textsuperscript{*}</td>
<td>470 ± 42</td>
</tr>
<tr>
<td>Horner JM, et al., 2011\textsuperscript{18}</td>
<td>10</td>
<td>25 ± 14</td>
<td>Concealed\textsuperscript{a}</td>
<td>501 ± 72</td>
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<tr>
<td>Chattha IS, et al., 2010\textsuperscript{21}</td>
<td>25</td>
<td>33 ± 16</td>
<td></td>
<td>459 ± 32</td>
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<tr>
<td>Swan H, et al., 1999\textsuperscript{17}</td>
<td>81</td>
<td>28 ± 14</td>
<td></td>
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<tr>
<td>Sy RW, et al., 2012\textsuperscript{22}</td>
<td>22</td>
<td>25 ± 14</td>
<td></td>
<td>405 ± 25</td>
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<tr>
<td>Aziz PF, et al., 2011\textsuperscript{26}</td>
<td>21</td>
<td>11.4 ± 4.7</td>
<td></td>
<td>475 ± 5 ± 35</td>
</tr>
<tr>
<td>Viskin S, et al.\textsuperscript{35}</td>
<td>28</td>
<td>30 ± 13</td>
<td></td>
<td>460 ± 39</td>
</tr>
</tbody>
</table>

NA, not available, data presented by the chart of the article.

\textsuperscript{*} Asymptomatic LQTS2: low to mediate probability of diagnosis according to clinical signs, Schwartz score ≤ 3. \textsuperscript{a} Concealed LQTS2: normal to borderline QTc measurement at rest. \textsuperscript{1} Exercise, recovery, record QTc at HR 130 bpm. \textsuperscript{1} Average of QTc interval were calculated when mean and standard deviation were all presented.
CONCLUSIONS

Although exercise tests are recommended to diagnose patients with LQTS, they should ideally be reserved for patients with LQT1 and LQT2; however, the cutoff point for the diagnosis of LQTS is not consistent. Moreover, QTc changes during postural change may be applicable to LQT2. More data with consistent recruitment criteria, precise diagnosis, and genetic background are needed to establish the criteria for the diagnosis of LQTS.

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DECLARATION OF CONFLICT OF INTERESTS

All authors declare no conflict of interest.

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