Epidemiology and clinical aspects of sudden cardiac death in the young
van der Werf, C.

Citation for published version (APA):
van der Werf, C. (2013). Epidemiology and clinical aspects of sudden cardiac death in the young

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The phenomenon of “QT stunning”: the abnormal QT prolongation provoked by standing persists even as the heart rate returns to normal in patients with long-QT syndrome


Tel Aviv, Israel; Amsterdam, the Netherlands; Lausanne, Switzerland; Melbourne, Australia; Mexico City, Mexico; and Utica, United States

*Heart Rhythm* 2012;9(6):901-8
ABSTRACT

Background
Patients with long-QT syndrome (LQTS) have inadequate shortening of the QT interval in response to the sudden heart rate accelerations provoked by standing - a phenomenon of diagnostic value. We now validate our original observations in a cohort twice as large. We also describe that this abnormal QT interval response persists as the heart rate acceleration returns to baseline.

Objective
To describe a novel observation, termed “QT stunning” and to validate previous observations regarding the “QT stretching” phenomenon in patients with LQTS by using our recently described “standing test.”

Methods
The electrocardiograms of 108 patients with LQTS and 112 healthy subjects were recorded in the supine position. Subjects were then instructed to stand up quickly and remain standing for five minutes during continuous electrocardiographic recording. The corrected QT interval was measured at baseline (QTc_base), when heart rate acceleration without appropriate QT interval shortening leads to maximal QT stretching (QTc_stretch) and upon return of heart rate to baseline (QTc_return).

Results
QTc_stretch lengthened significantly more in patients with LQTS (103±80 ms vs. 66±40 ms in controls; P<0.001) and so did QTc_return (28±48 ms for patients with LQTS vs. -3 ±32 ms for controls; P<0.001). Using a sensitivity cutoff of 90%, the specificity for diagnosing LQTS was 74% for QTc_base, 84% for QTc_return, and 87% for QTc_stretch.

Conclusions
The present study extends our previous findings on the abnormal response of the QT interval in response to standing in patients with LQTS. Our study also shows that this abnormal response persists even after the heart rate slows back to baseline.
INTRODUCTION

Diagnosing congenital long QT syndromes (LQTS) is important but difficult. It is important because highly effective therapy exists for this disease, which is often lethal when left untreated. It can be difficult because (1) arrhythmia-related symptoms almost invariably occur in unmonitored settings, (2) considerable overlap exists between the QT interval of affected and unaffected individuals, and (3) currently available genetic testing still has potential shortcomings in its clinical application.

Consequently, readily-applicable clinical tools to enhance the diagnosis of this dangerous disease are needed. Thus, many patients with suspected LQTS undergo additional diagnostic tests, including Holter recordings, exercise tests, and epinephrine or adenosine challenges.

We recently described that patients with LQTS have an insufficient QT interval shortening in response to the tachycardia provoked by abrupt standing and proposed this phenomenon as an easy bedside test for diagnosing LQTS. The test is based on the fact that as one stands up, the heart rate acceleration is abrupt but the associated QT interval shortening is gradual. As the R-R interval shortens faster than does the QT interval, the QT appears to “stretch” toward the next P wave and the corrected QT interval (QTc) for heart rate actually increases. This phenomenon is universal but is exaggerated in patients with LQTS. Indeed, in our original study, the QTc duration during “maximal QT interval stretching” (when the end of the T wave gets nearest to the subsequent P wave) had the highest discriminative power for diagnosing LQTS.

After the publication of these findings, we noticed that in some patients dramatic changes in the QT interval took place not immediately after standing, but rather after the heart rate returned to baseline. The objectives of the present study were two-fold: (1) to validate the diagnostic accuracy of the test in a much larger cohort of patients with LQTS and controls and (2) to evaluate whether the delayed response of the QT interval, as the accelerated heart rate slows back to baseline, is of additional value for distinguishing patients with LQTS from healthy controls.

METHODS

Population

The LQTS group consisted of 108 patients, including 105 (97%) patients with genetic confirmation and three (3%) patients with an international LQT registry score of ≥4 but unidentified genotype. The control group of 112 healthy individuals consisted of 34 (30%) family members of patients with LQTS not carrying the familial mutation and 78 (70%) unrelated healthy volunteers. This study cohort is double the size of the population included in our original study. Particular emphasis was placed on the diagnostic performance of the test for the patient population without obvious QT prolongation at baseline, defined as men with QTc <470 ms and women with QTc <480 ms.

Abrupt standing test (QT stretching)

The test protocol has been described previously. β-blockers were discontinued for 26 to 30 hours, and any implanted devices were reprogrammed to VVI pacing at 30 beats per minute for the duration of the test. Subjects rested for ten minutes in the supine position as a baseline electrocardiogram (ECG) was recorded. They were then asked to stand up quickly and
remain standing still for five minutes during continuous electrocardiographic recording. QT measurements were performed at four points in time: (1) baseline (QT_{base}), (2) maximal heart rate (QT_{maxHR}), (3) point of maximal “QT stretching” (QT_{stretch}; defined as the time when the end of the T wave gets nearest to the next P wave due to R-R–interval shortening without sufficient QT interval shortening), and (4) upon return of the heart rate to its baseline value (QT_{return}; defined as the first R-R interval within 40 ms of the baseline R-R interval) (Figure 1). At all points, the QT interval was corrected by using the Bazett, Fridericia, and Framingham formulas.

Validation of our previous study
A validation cohort consisting of new subjects not included in our previous study (54 patients with LQTS and 71 healthy volunteers) was used for this purpose. In this cohort, we examined

Figure 1. Standing test demonstrating the point of maximal QT-interval stretching and the return to baseline heart rate in a 23-year-old woman with LQT2. At baseline (left panel), the heart rate is 77 beats/min, the QT-interval is 400 ms, and the corrected QT interval (QTc) is 453 ms. The patient then stands up during continuous electrocardiographic recording (as illustrated in our previous publication13). At the point of maximal QT interval stretching, the heart rate is 120 beats/min, the QT interval is 400 ms, and the QTc is 566 ms (middle panel). At the end of the test, the heart rate returns to baseline but the QT interval remains prolonged, the QTc is 544 ms, and the T wave has abnormal morphology. Note ventricular extrasystole upon return to baseline heart rate (arrow). The QT-related extrasystoles continued to appear as the heart rate returned to baseline.
the discriminative power of QTc_stretch by using a cutoff point of 490 ms. This cutoff value was selected on the basis of its high sensitivity and specificity (88% and 86%, respectively) in the original study population without QT prolongation at baseline.\textsuperscript{13}

Return to baseline

The diagnostic performance of “QT stretching” (i.e., the abnormal QT interval response to standing) was evaluated and compared with that of “QT stunning” (the abnormal persistence of QTc prolongation as the heart rate slows back to baseline) in the entire study population. Excluded from the last analysis were some participants in the first study who went on to perform an exercise test immediately after the standing test and before their heart rate returned to baseline.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number and percentage in each group. Simple comparisons between the two groups of patients were done by using the Student t test for continuous variables and the chi-square test for categorical variables. A two-tailed P<0.05 was considered significant. Values >1.5 times or >3 times the interquartile range are termed as “regular outliers” and “extreme outliers,” respectively. Receiver-operating characteristic (ROC) curve analysis was used to calculate the area under the curve and to evaluate the specificity at the predefined sensitivity of 90%. DeLong and DeLong’s method was used to compare ROC curves of different measurements. The SPSS statistical package was used for all analyses (SSPS, Inc, Chicago, IL).

RESULTS

Baseline characteristics

Among the 108 patients with LQTS, 46 (43%) had type 1 long-QT syndrome (LQT1), 47 (43%) had type 2 long-QT syndrome (LQT2), and 12 (11%) had type 3 long-QT syndrome whereas the genotype remained unidentified for three patients (3%). Baseline characteristics, including age and baseline heart rate, were similar for the LQTS and control groups. Sex was evenly distributed in the control group, but there were more women in the LQTS group. As expected, the baseline QT and corrected QT intervals were longer in the LQTS group (Table 1).

Response to standing

Although the heart rate acceleration in response to standing was similar for the control and LQTS groups (Table 1), their QT interval response was significantly different: While the mean QT interval at the point of maximal QT interval stretching shortened in the control group, it grew longer in the LQTS group (Table 1). Consequently, QTc prolongation at maximal QT interval stretching was significantly more pronounced in the LQTS group (Table 1 and Figure 2). The characteristics of the derivation\textsuperscript{13} and validation cohorts are shown in Table 2. Using a QTc\textsubscript{stretch} cutoff point of 490 ms yielded a sensitivity of 88% and a specificity of 86% in our previous study.\textsuperscript{13} In the present validation cohort without obvious QT prolongation at baseline, using the same cutoff point yielded similar results (sensitivity 89% and specificity 87%).
Table 1. Baseline characteristics and response to standing/return to baseline.

<table>
<thead>
<tr>
<th></th>
<th>LQTS group (N=108)</th>
<th>Control group (N=112)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>30 ± 16</td>
<td>33 ± 12</td>
<td>0.128</td>
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<tr>
<td>Females</td>
<td>67 (62%)</td>
<td>53 (47%)</td>
<td>0.043</td>
</tr>
<tr>
<td>Baseline HR, beats per min</td>
<td>70 ± 12</td>
<td>72 ± 11</td>
<td>0.115</td>
</tr>
<tr>
<td>Baseline QTc, ms</td>
<td>469 ± 40</td>
<td>416 ± 30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to maximal tachycardia, sec</td>
<td>10 ± 4</td>
<td>10 ± 4</td>
<td>0.43</td>
</tr>
<tr>
<td>Time to maximal QT-stretching, sec</td>
<td>10 ± 4</td>
<td>12 ± 6</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to return to baseline HR, sec</td>
<td>33 ± 44</td>
<td>32 ± 66</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Response to standing and return to baseline heart rate *

<table>
<thead>
<tr>
<th></th>
<th>LQTS group (N=108)</th>
<th>Control group (N=112)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHR during maximal tachycardia, beats/min</td>
<td>25 ± 10</td>
<td>26 ± 10</td>
<td>0.431</td>
</tr>
<tr>
<td>ΔQT during maximal HR, ms</td>
<td>-2 ± 37</td>
<td>-19 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQTc during maximal HR, ms</td>
<td>92 ± 48</td>
<td>62 ± 39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQT during maximal QT stretching, ms</td>
<td>8 ± 51</td>
<td>-14 ± 35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQTc during maximal QT stretching, ms</td>
<td>103 ± 80</td>
<td>66 ± 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQT upon return to baseline HR, ms</td>
<td>22 ± 42</td>
<td>-5 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQTc upon return to baseline HR, ms</td>
<td>28 ± 48</td>
<td>-3 ± 32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, except for sex, for which data are presented as mean and percentage.

HR indicates heart rate; LQTS, long QT syndrome; QTc, corrected QT interval.

*Delta values are in relation to baseline: ΔHR denotes heart rate change from baseline; QTc, corrected QT interval; ΔQT and ΔQTc denote changes in QT and QTc from baseline, respectively.

Return to baseline heart rate

The heart rate returned to baseline within one minute of standing in almost all patients, and there was no significant difference between the groups in their heart rate response (Table 1). In contrast, the QT interval response to this heart rate slowing differed significantly between the groups: As the heart rate slowed down to baseline values, QT<sub>return</sub> in the control group shortened by 5±28 ms in comparison with QT<sub>base</sub> while it lengthened by 22±42 ms in the LQTS group. Since, by study design, the heart rate was almost identical at baseline and upon return to baseline, the change in the QTc was very similar to the change in the QT interval (Table 1 and Figure 2). Importantly, while in 74% of the subjects in the LQTS group QTc<sub>return</sub> was longer than QTc<sub>base</sub> (Figure 3) only 44% of the controls demonstrated such a response. Furthermore, in 30 patients with LQTS (28%), QTc<sub>return</sub> was longer than QTc<sub>base</sub> by 50 ms or more (Figure 4), whereas only two controls (2%) had the QTc prolongation of this magnitude.

Diagnostic value of tests in the entire cohort

ROC curve analysis revealed that - at a cutoff point of 90% sensitivity - the specificity for the identification of LQTS increased from 73% at the baseline QTc to 87% for the QTc during maximal QT interval stretching and 84% for the QTc upon return of the heart rate to baseline (Table 3). The use of Fridericia<sup>15</sup> and Framingham<sup>16</sup> formulas for correction of the QT interval at these time points yielded similar results (not shown).
Figure 2. Box plots of the results obtained in patients with long QT syndrome and controls. Dark boxes represent the interquartile range, that is, the range between the 25th and the 75th percentile; the thick black line in the box is the 50th percentile, and the bars represent the range of results excluding outliers. Black dots are “outliers,” and asterisks are “extreme outliers.” The top and bottom rows show results for the uncorrected QT interval and for the corrected QT interval (QTc) (using the Bazett formula). Note that the uncorrected QT interval of controls hardly changes (on average) as the tachycardia accelerates during standing and as it slows back to normal. Note also that although there is a statistically significant difference between the QTc of patients and controls already at baseline, the magnitude of the difference increases and the overlapping between the groups decreases during the two stages of the test.

Table 2. Baseline characteristics of derivation* and validation cohorts.

<table>
<thead>
<tr>
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<th>Derivation cohort (N=150)</th>
<th>Validation cohort (N=125)</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>34 ± 12</td>
<td>30 ± 15</td>
</tr>
<tr>
<td>Female gender</td>
<td>88 (59%)</td>
<td>63 (51%)</td>
</tr>
<tr>
<td>LQT1</td>
<td>31 (21%)</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>LQT2</td>
<td>28 (19%)</td>
<td>25 (20%)</td>
</tr>
<tr>
<td>LQT3</td>
<td>3 (2%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>82 (54%)</td>
<td>71 (57%)</td>
</tr>
</tbody>
</table>

Data are presented as number and percentage, except for age, for which data are presented as mean ± standard deviation.
LQT1 indicates type 1 long QT syndrome; LQT2, type 2 long QT syndrome; LQT3, type 3 long QT syndrome.
*Derivation cohort based on our previous study.13
Subpopulation analysis

Several subgroup analyses were performed in an attempt to find a specific group for which this test is most or least adequate. These subpopulation analysis included division based on sex, change in heart rate from baseline to maximal tachycardia, and the baseline QTc. In all these subgroups, both phases of the test (i.e., “abrupt standing” and “return to baseline”) added diagnostic accuracy and in the LQT1 group “QT stunning” (upon return to baseline heart rate) performed better than “QT stretching” (rapid standing) (Table 4). Of the patients with LQTS, 26% had symptoms believed to be of arrhythmic origin. As expected, the baseline QTc of patients with symptomatic LQTS was longer than the baseline QTc of patients with asymptomatic LQTS (QTc of 483±33 ms vs. 465±41 ms; P=0.039). This difference increased in magnitude at the point of maximal QT interval stretching (571±44 ms vs. 544±47 ms; P=0.013) but became nonsignificant once the heart rate returned to baseline (514±54 ms vs. 493±58 ms; P=0.110).

LQT1 versus LQT2

Baseline characteristics of the two groups were similar except for a slightly larger increase in the heart rate in the LQT2 group (Table 4). However, the response of their QT interval to heart rate acceleration was different. In accordance with our original observation in a cohort half the size of the current study group,13 QTc prolongation from baseline to maximal stretching was significantly longer in patients with LQT2 than in patients with LQT1 (112±53 ms vs. 76±43 ms; P<0.001), whereas QTc return was similar in patients with LQT1 and patients with LQT2 (Table 4).
DISCUSSION

The normal response to brisk standing is a sudden acceleration of heart rate with only gradual shortening of the QT interval. As the R-R interval shortens more than the QT interval, the QTc lengthens transiently even in healthy individuals. However, in patients with LQTS, the absolute QT interval may entirely fail to shorten and may even get longer during this short-lasting tachycardia. Consequently, the QT interval "stretches" all the way to the next P wave and the QTc markedly increases in patients with LQTS. In our original study, the QTc after standing was better than the baseline QTc for distinguishing patients with LQTS from healthy controls.

In the present study, we used a new cohort of patients and controls to validate our original observations. A QTc\textsubscript{stretch} cutoff point of 490 ms (derived from our previous study) yielded similarly high sensitivity and specificity values (89% and 87%, respectively) in the present analysis with a cohort twice as large. These results confirm our previous conclusions concerning the discriminatory power of the “stretched” QTc interval in differentiating between individuals with and without LQTS. In addition, we focused on the response of the QT interval as the heart rate slows back to baseline and found that QTc\textsubscript{return} differentiates between patients and controls as reliably as does QTc\textsubscript{stretch}. In fact, QTc\textsubscript{return} provided superior predictive characteristics than did QTc\textsubscript{stretch} in patients with LQT1.

The normal QT interval response to heart rate acceleration and deceleration

The “cleanest” way to study the effects that sudden changes in heart rate have on the QT interval, isolating as much as possible the effects of heart rate change from the effects of adrenergic stimulation, is by pacing the ventricle at a steady rate and then abruptly increasing (or decreasing) the pacing rate. Such studies\textsuperscript{19–21} show that when the heart rate is abruptly increased, there is a sudden QT interval shortening that is only partial\textsuperscript{21} and is eventually followed by a gradual and progressive QT interval shortening until a new steady state is reached.\textsuperscript{21} A

Table 4. Characteristics of LQT1 and LQT2 groups.

<table>
<thead>
<tr>
<th></th>
<th>LQT1 group (N=46)</th>
<th>LQT2 group (N= 47)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>32 ± 16</td>
<td>28 ± 16</td>
<td>0.240</td>
</tr>
<tr>
<td>Female</td>
<td>29 (63%)</td>
<td>29 (63%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline HR, beats/min</td>
<td>71 ± 11</td>
<td>70 ± 13</td>
<td>0.592</td>
</tr>
<tr>
<td>Baseline QTc, msec</td>
<td>470 ± 42</td>
<td>470 ± 42</td>
<td>0.978</td>
</tr>
<tr>
<td>Response to standing &amp; return to baseline HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔHR during maximal tachycardia, beats/min</td>
<td>22 ± 11</td>
<td>28 ± 9</td>
<td>0.017</td>
</tr>
<tr>
<td>QTc during maximal QT stretching, msec</td>
<td>537 ± 54</td>
<td>568 ± 40</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔQTc during maximal QT stretching, msec</td>
<td>76 ± 43</td>
<td>131 ± 104</td>
<td>0.002</td>
</tr>
<tr>
<td>QTc upon return to baseline HR, msec</td>
<td>499 ± 66</td>
<td>500 ± 50</td>
<td>0.913</td>
</tr>
<tr>
<td>ΔQTc upon return to baseline HR, msec</td>
<td>28 ± 48</td>
<td>28 ± 47</td>
<td>0.996</td>
</tr>
</tbody>
</table>

Data, except for female gender, are mean ± standard deviation. HR indicates heart rate; ΔHR, HR change from baseline; QTc, corrected QT interval; ΔQT and ΔQTc, changes from baseline in QT and in QTc, respectively.
similar sequence of events takes place when the pacing rate is suddenly decreased: a partial immediate QT interval lengthening is followed by additional gradual QT interval lengthening. However, it takes longer for the QT to accommodate to the new heart rate when the heart rate slows down than when it speeds up. For example, in one study it took up to two minutes for the QT interval to reach a new steady state once the pacing rate was suddenly increased, but as long as three minutes in response to a sudden decrease in pacing rate of similar magnitude. Sympathetic stimulation increases the magnitude of the immediate QT interval response; however, to reach a new steady state the QT continues to change gradually. Explanations for the “immediate-transient” and the “gradual-progressive” components of QT accommodation in response to heart rate changes can be found elsewhere.

During our standing test, the heart rate accelerates to its peak and slows back to normal within an average of 20 and 40 seconds, respectively, not leaving enough time for QT accommodation. This rapid sequence of events probably explains why the absolute QT interval (not corrected for heart rate) of healthy controls hardly changed as the heart rate peaked and then returned to baseline during standing.

The phenomenon of “QT stretching”

The duration of the action potential is largely dependent on the duration of the preceding diastolic interval. The action potential duration is represented in the ECG by the QT interval, whereas the diastolic interval is represented better by the TQ interval (from the end of the T wave to the onset of the next QRS complex) than by the R-R interval. As the heart rate accelerates suddenly, the TQ interval shortens disproportionately more in patients with LQTS, leaving a considerably shorter diastolic interval for the next beat, which will then exhibit slower repolarization (longer QT interval). This probably explains why even the absolute QT interval lengthens (on average) instead of shortening despite the standing-induced tachycardia. R-R–interval shortening without QT interval shortening results in a very long QTc, which stretches all the way to the next P wave. Acceleration induced early afterdepolarizations and increased dispersion of repolarization, as seen in the tissue models of LQTS, probably explain the LQT-related arrhythmias seen in some of our patients during the test.

The phenomenon of “QT stunning”

As patients with LQTS remain standing still and their accelerated heart rate returns to baseline, their absolute QT intervals (not corrected for the heart rate) are significantly longer than the QT intervals they had at comparable heart rates just before standing. Moreover, their T-wave morphology (even if normal at baseline) often becomes grossly abnormal (Figures 3 and 4). The fact that heart rate deceleration occurred while the QT interval had not yet shortened in response to a faster rate assumedly led to increased dispersion of repolarization, occasionally leading to deceleration-induced LQTS-related arrhythmias (Figure 1).

QT behavior after brisk standing and during exercise

Recently, we and others demonstrated that a prolonged QTc during the recovery phase of an exercise test is highly accurate in distinguishing patients with LQTS (in particular LQT1) from controls. In both studies, prolonged QT intervals after exercise were found to be very accurate.
Figure 3. QT stunning in a 19-year-old woman with type 1 long QT syndrome. At baseline, the QT interval is 440 ms and the corrected QT interval (QTc) is only slightly prolonged (QTc 480 ms). The heart rate acceleration induced by standing is not shown. By the time the heart rate slows down to baseline, the QT interval is frankly abnormal in terms of both duration and morphology. Note that despite very similar heart rates before and after standing (left and right panels, respectively), the QTc lengthened from 480 to 508 ms.

Why do patients with LQT1 and LQT2 respond differently to the standing test?

Previous studies have shown that patients with LQT1 and LQT2 behave differently during exercise.\textsuperscript{6,24–26} In patients with LQT1 the QTc intervals are longer during peak exercise and during the recovery phase,\textsuperscript{6,24–26} whereas in patients with LQT2 the QT interval during recovery from exercise is shorter than that measured at similar heart rates while exercising.\textsuperscript{18} In contrast, we found that patients with LQT2 develop more QT prolongation than do patients with LQT1, both at the time of maximal tachycardia induced by standing and when the heart rate slowed.
Figure 4. QT stunning in asymptomatic long QT syndrome carriers. Top panel: Standing test in a 42-year-old asymptomatic man with LQT2 evaluated as part of family screening. During baseline, the QT interval is strictly normal and there is only minimal and nondiagnostic T-wave notching in the anterolateral leads. The standing-induced tachycardia is not shown. By the time the heart rate returns to normal, the QT is grossly abnormal. Genetic testing confirmed LQT2-carrier status. Lower panel: Brief sample recordings of lead I from a patient with type 1 long QT syndrome are shown. The trace before standing is shown on top of the trace, demonstrating the return of the heart rate to baseline to demonstrate that despite a very similar heart rate (last two complexes) the QT interval is much longer after standing.
back to baseline. It is known that changes in action potential duration in response to heart rate acceleration differ significantly in response to sudden versus gradual changes. It is known that changes in action potential duration in response to heart rate acceleration differ significantly in response to sudden versus gradual changes. Differences in heart rate acceleration patterns during abrupt standing compared with gradual exercise could explain the differences between our observations and previous studies. The Ontario group of Krahn et al. report, in contrast to our findings, that patients with LQT1 have more QTc prolongation than do patients with LQT2 in response to standing. Differences in the methodology of the respective studies are worth noting: In Ontario, the standing ECG is recorded once (sometime after standing) whereas we perform continuous electrocardiographic recording and perform our measurements at the time of maximal QT interval stretching.

Study limitations
(1) Although the QT and R-R intervals were measured by a single blinded investigator, in some cases the length of the QT interval and morphology of the T wave made the diagnosis of LQTS evident. Thus, the possibility of bias cannot be excluded. (2) The ratio of patients to controls (nearly 1:1) in our case-control series is not representative of the expected 1:2500 ratio in the general population. Since the pretest probability and performance of any tests is influenced by the prevalence of the disease tested for, caution should be exercised when interpreting the results of the standing test during the screening of ostensibly healthy population (such as athletes).

Clinical implications
(1) Our test is simple and can be performed as a stand-alone bedside test or just prior to commonly performed diagnostic investigations, such as exercise testing. (2) Determining where the T wave ends during tachycardia is often difficult, whether this is performed during the standing test or the exercise test. Also, the formulas used for correcting the QT interval for heart rate, especially the Bazett formula, do not work well during tachycardia. Assessing the QTc upon return of the heart rate to baseline is advantageous in both regard. (3) The QT stunning phenomenon is a universal phenomenon that so far has remained unrecognized. Recognition of this phenomenon is important because in centers performing exercise tests, patients generally wait in the sitting position in anticipation for the test and then stand up, as the “baseline” ECG for the exercise test is performed, to begin exercising shortly thereafter. It is therefore possible to provoke QT stretching during the baseline ECG of the exercise test and it is also possible to begin exercising while the QT is still “stunned.” The effects that such phenomena will have on the response of the QT interval to exercise have not been determined. Caution should be taken when using the exercise test to diagnose LQTS.

ACKNOWLEDGEMENTS
We thank Louise R. Olde Nordkamp, MD, and Sebastién P. Krul, MD, from the Academic Medical Center in Amsterdam and Hila Zohar from the Tel Aviv Medical Center for their invaluable help in collecting ECGs for this study.
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