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Postema, P.G.

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The response of the QT-interval to the brief tachycardia provoked by standing

A bedside test for diagnosing Long-QT syndrome

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S. Viskin
P.G. Postema
Z.A. Bhuiyan
R. Rosso
J.M. Kalman
J.K. Vohra
M.E. Guevara-Valdivia
M.F. Marquez
E. Kogan
B. Belhassen
M. Glikson
B. Strasberg
C. Antzelevitch
A.A.M. Wilde

Tel Aviv, Shavi and Rabin Medical Centers, Tel Aviv, Israel
Academic Medical Center, Amsterdam, The Netherlands
Royal Melbourne Hospital, Melbourne, Australia
UMAE Hospital Dr. Antonio Fraga-Mouret CMN La-Raza IMSS and Instituto Nacional de Cardiologia, Mexico City, Mexico
Masonic Medical Research Laboratory, Utica, New York, USA
ABSTRACT

OBJECTIVES
This study was undertaken to determine if the short-lived sinus tachycardia that occurs during standing will expose changes in the QT-interval of diagnostic value.

BACKGROUND
The QT shortens during heart rate acceleration but this response is not instantaneous. We tested whether the transient, sudden sinus tachycardia that occurs during standing would expose abnormal QT prolongation in patients with long QT syndrome (LQTS).

METHODS
Patients (68 LQTS [LQT1: 46%, LQT2: 41%, LQT3: 4%, not genotyped: 9%] and 82 controls) underwent a baseline electrocardiogram (ECG) while resting in the supine position and were then asked to get up quickly and stand still during continuous ECG recording. The QT-interval was studied at baseline and during maximal sinus tachycardia, maximal QT prolongation and maximal “QT-stretching.”

RESULTS
In response to brisk standing, patients and controls responded with similar heart rate acceleration of 28±10 beats/min (p=0.261). However, the response of the QT-interval to this tachycardia differed. On average the QT-interval of controls shortened by 21±19ms while the QT-interval of LQTS-patients increased by 4±34ms (p<0.001). Since the RR-interval shortened more than the QT, during maximal tachycardia the QTc increased by 50±30ms in the control-group and by 89±47ms in the LQTS-group (p<0.001). Receiver operator curves showed that the test adds diagnostic value. The response of the QT-interval to brisk standing was particularly impaired in patients with LQT2.

CONCLUSIONS
Evaluation of the response of the QT-interval to the brisk tachycardia induced by standing provides important information that aids in the diagnosis of LQTS.
INTRODUCTION

The diagnosis of the long QT syndrome (LQTS) is straightforward when torsade de pointes is documented in a patient with obvious QT prolongation.\textsuperscript{1,2} Often, however, diagnosing LQTS is problematic for several reasons: first, arrhythmic symptoms occur infrequently, making it difficult to document torsade de pointes. Second, overlap in the duration of the QT-interval exists between carriers of LQTS-mutations and healthy controls.\textsuperscript{3} Third, failing to identify a mutation does not exclude the diagnosis of LQTS and misinterpreting innocent genetic changes as “mutations” may occur.\textsuperscript{4} Thus, diagnosing LQTS remains a challenge.\textsuperscript{5}

The QT-interval shortens during tachycardia but adaptation of the QT-interval to sudden heart rate acceleration is not instantaneous.\textsuperscript{6,7} Moreover, patients with LQTS often display abnormal responses to heart rate changes.\textsuperscript{8,9} We therefore aimed to take advantage of the abrupt sinus tachycardia that normally occurs during standing to evaluate whether maladaptation of the QT-interval to heart rate acceleration would expose pathologic QT-changes in LQTS-patients.

METHODS.

Patient groups.
The LQTS-Group consisted of patients with high-probability for LQTS (International LQTS-Registry Score ≥4 points\textsuperscript{10}) or definite LQTS (documented torsade de pointes and/or LQTS mutation). The control group consisted of healthy volunteers (92%) and asymptomatic relatives of LQTS-patients who are non-carriers of the familial mutation (8%) that take no medications. The study was approved by our Institutional Review Committee.

Interventions.
LQTS-patients taking beta-blockers underwent the test 26 to 30 hours after their last dosage. For the test, participants rested supine for 10 minutes. They then got-up quickly and remained standing for 5 minutes during continued ECG recording. Implanted devices were programmed to single-chamber ventricular pacing at 35 beats/min for the duration of the test.

Measurements.
As subjects stand up, there are movement related artifacts that preclude QT measurements for ≤5 s followed by transient sinus tachycardia. One investigator, blinded to the patients’ grouping, performed the measurements specified below at 4 points in time: 1) Baseline: during the maximal sinus bradycardia recorded as the patient rested supine; 2) Maximal Tachycardia: during the fastest sinus rate achieved in response to standing; 3) Maximal QT: at the time of maximal prolongation (if any) of the QT-interval during the first 30 s after standing and 4)
Maximal QT-Stretching: time where (due to R-R shortening without QT-shortening) the end of the T-wave gets nearest to the next P-wave. At all these stages the QTc was corrected for the heart rate using Bazett’s formula. We then repeated our analysis with the Fridericia and Framingham formulas.

**Statistics.**

To examine the hypothesis that rapid standing influences QT parameters of LQTS-patients and controls differently, analysis of variance (ANOVA) for repeated measures was performed with the RR, QT and QTc as dependent variables and with stage (i.e., baseline, maximal tachycardia, etc.) and subject’s status (LQTS or control) as between-subject variable. Contrast analysis was then performed to compare QT-parameters in relation to baseline for both patient groups. We excluded from this analysis all patients with obviously long and obviously normal QT-intervals at baseline because additional tests are superfluous for them. Accordingly, we limited this analysis to males with baseline QTc 390-450ms and to females with QTc 400-480ms. DeLong and DeLong’s method (nonparametric comparison of areas under multiple correlated ROC curves) was used to compared ROC curves before and after standing. Discriminant analysis was performed to examine the best separation between the two groups. For this purpose, 70% of the total sample was randomly selected and a discriminant U-function was applied in a stepwise method. Simple comparisons between the two groups of patients were done using student’s t-test for continuous variables and Chi-square for categorical variables. Two tailed p-value ≤0.05 was considered significant. Values >1.5 times or >3 times the inter-quartile range are termed regular outliers and extreme outliers, respectively. The SPSS statistical package was used for all statistical evaluation (SSPS Inc. Chicago, IL, USA).

**RESULTS**

The study cohort consisted of 68 LQTS-patients and 82 controls subjects. Among LQTS-patients, 31(46%) have LQT1, 28(41%) LQT2 and 3(4%) LQT3 and 6(9%) have unsuccessfully genotyped LQTS. Patients and controls were of similar age. We recruited a similar number of healthy males and females for the control group whereas female gender predominated in the LQTS group. (Table 1, Figure 1A).

**Normal response of the QT-interval to standing**

In response to standing, the sinus rate increased within 10 s to 95±14 beats/min (Table 1). Males and females had similar heart rate acceleration (p=0.7) and the response of their QT-interval to this heart rate speeding was similar (the QT shortened by 21±19ms in both genders, p=0.8). Since the QT decreased less than the RR-interval during standing-induced tachycardia, the QTc of controls increased (by 50±28ms [12±7%] in males and by 50±32ms
Response of patients with LQTS

The LQTS-patients and controls had similar heart rate acceleration in response to standing (Table 1). However, the response of their QT-interval to this sudden change in heart rate was different (Figures 2, 3 and 4). During maximal sinus tachycardia, the QT of controls shortened by ≥20ms in 59%, remained unchanged (varied by <20ms) in 39% and increased by ≥20ms in only 2%. In contrast, among LQTS-patients, the QT shortened in only 24%, remained unchanged in 43% and actually increased in 34% (p<0.001). Thus, while the averaged QT of controls shortened by 21±19ms, the QT of LQTS-patients hardly changed (it lengthened by 4±34ms, p<0.001, Figure 1E). Consequently, during maximal tachycardia the QTc of controls increased by only 50±30ms (13±8% from baseline), whereas the QTc of LQTS-patients increased by 89±47ms (20±11% from baseline, p<0.001, Figure 1F).

We then identified the complex with longest uncorrected QT-interval during standing-induced tachycardia. Despite a similar heart rate at this point, only the QT of LQTS-patients had increased in comparison to baseline [by 37±44ms (p=0.001)].
At the point of maximal QT-stretching the QTc increased by 54±38ms in controls and by 94±49ms in LQTS-patients, p<0.001 (figure 1D). Ventricular extrasystoles representing early-afterdepolarizations or T-wave alternans were observed during maximal QT-stretching in 4 LQTS-patients (Figure 4).

Analysis of our results after excluding LQTS-patients with very long baseline QT or with unknown genotype, or with the use of Fridericia's or Framingham formulas, also showed that the difference in QTc between LQTS-patients and controls at all stages of the test was statistically significant.

**Comparison of LQT1 and LQT2**

Patients with LQT1 and LQT2 had similar baseline QT/QTc intervals and developed similar heart rate acceleration upon standing (Table 2). However, the groups had discordant
responses of the QT-interval: The QT of LQT1-patients shortened by 8±32ms while it lengthened by 21±28ms among LQT2-patients. Consequently, LQT2-patients displayed the maximal QTc prolongation (Table 2, Figures 1G-1H).

**Diagnostic value of the test**

The QTc of LQTS-patients and controls was different already at baseline but the difference increased during standing (Figure 1A-1D). ROC-curves demonstrate incremental diagnostic value (Table 3). For example, for the population with QTc 390–480ms at baseline, the baseline-QTc that identified LQTS with 90% sensitivity had only 61% specificity. In contrast,
during maximal QT-stretching, the QTc value identifying LQTS with 90% sensitivity also had 86% specificity. With DeLong and DeLong analysis, the ROC curves of QT and QTc at maximal heart rate were significantly better than the ROC for baseline QT ($p=0.008$) and QTc ($p=0.026$).

**DISCUSSION**

Accurate diagnosis of the LQTS is crucial because this is a potentially lethal disorder for which effective therapy exists. We report that just observing the response of the QT-interval to the sudden heart rate acceleration provoked by quick standing provides diagnostic information.

**THE NORMAL RESPONSE OF THE QT-INTERVAL TO BRISK STANDING.**

The fact that the QT-shortening in response to sudden heart rate acceleration is not instantaneous has been known for almost a century.\(^{11}\) Already in 1920, Bazett emphasized...
that “with exercise, the heart rate increases promptly but the QT shortens more slowly”.

Animal and clinical studies show that following an abrupt increase in ventricular pacing-rate it takes up to 2 minutes until the ventricular refractory period and the QT-interval shorten (accommodate) to a new steady state. Beat-to-beat analysis of the human action potential show that during a sudden increase in pacing rate, the action potential shortens abruptly at the first fast heart beat but then requires several hundred beats to finally shorten to a new steady state.

In our study, maximal heart rate acceleration occurred within 15 s of standing and such timing is too short for QT-accommodation. Thus, the insufficient QT-shortening of our healthy controls is actually expected. The fact that during standing-induced sinus tachycardia the QT shortened in 59% of controls while it remained unchanged in the rest is consistent with observations from Holter recordings in healthy volunteers. Such studies show that the speed of response of the QT-interval to sudden changes in heart rate is highly individual and independent of the basic QTc.
Chapter 03

### Table 2. Baseline Characteristics and Response to Standing, LQT1 versus LQT2

<table>
<thead>
<tr>
<th></th>
<th>LQT1 (n=31)</th>
<th>LQT2 (n=28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33±15</td>
<td>30±13</td>
<td>0.400</td>
</tr>
<tr>
<td>Female gender</td>
<td>21(68)</td>
<td>23(82)</td>
<td>0.243</td>
</tr>
<tr>
<td>Baseline heart rate (beats/min)</td>
<td>67±11</td>
<td>62±9</td>
<td>0.051</td>
</tr>
<tr>
<td>Baseline QT (ms)</td>
<td>445±42</td>
<td>455±45</td>
<td>0.375</td>
</tr>
<tr>
<td>Baseline QTc (ms)</td>
<td>468±39</td>
<td>460±39</td>
<td>0.445</td>
</tr>
<tr>
<td><strong>Response to standing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increment in heart rate (beats/min)</td>
<td>24±10</td>
<td>26±11</td>
<td>0.474</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>95±14</td>
<td>91±13</td>
<td>0.053</td>
</tr>
<tr>
<td>ΔQT during maximal tachycardia (ms)</td>
<td>-8±32</td>
<td>21±28</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔQTc during maximal tachycardia (ms)</td>
<td>67±41</td>
<td>114±42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔQTc during longest QT (ms)</td>
<td>80±50</td>
<td>126±49</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔQTc during maximal QT-stretching (ms)</td>
<td>73±43</td>
<td>119±48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD or n(%). ΔQT, QT interval change from baseline; ΔQTc, corrected QT interval change from baseline; QTc, corrected QT.

### The Response of LQTS-patients to Brisk Standing

Adaptation of the QT-interval to gradual changes in heart rate is impaired in the LQTS and we show that this maladaptation worsens when the changes in heart rate are sudden. The sympathetic stimulation that occur while standing affects the QT-interval independently of the concomitant tachycardia; such adrenergic stimulation would be expected to exert different effects on patients with normal versus abnormal QT.

The LQT2-patients developed maximal QTc prolongation in response to standing. This observation was unexpected because during epinephrine-infusion tests, the largest QT-changes occur in LQT1. However, predominant prolongation of the M-cell action potential – leading to increased transmural dispersion of repolarization and early-afterdepolarization

### Table 3. ROC Curve Analysis of Variables

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>90% sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QT interval</td>
<td>0.836</td>
<td>0.759–0.914*</td>
<td>395</td>
</tr>
<tr>
<td>Baseline QTc interval</td>
<td>0.850</td>
<td>0.775–0.925*</td>
<td>423</td>
</tr>
<tr>
<td>QT interval at maximal heart rate</td>
<td>0.900</td>
<td>0.840–0.960*</td>
<td>375</td>
</tr>
<tr>
<td>QTc interval at maximal heart rate</td>
<td>0.933</td>
<td>0.889–0.978*</td>
<td>474</td>
</tr>
<tr>
<td>QT interval during maximal QT stretching</td>
<td>0.923</td>
<td>0.874–0.973*</td>
<td>487</td>
</tr>
</tbody>
</table>

*p <0.001 for all receiver-operating characteristic (ROC) curves. AUC, area under the curve; CI, confidence interval; QTc, corrected QT.
activity – is a well recognized response to sudden heart rate acceleration in models of LQT2. Interestingly, clinical arrhythmias in LQT2 are characteristically triggered by situations involving sudden (as opposed to gradual) heart rate acceleration, like sudden startling by noise.

**Limitations**

Although all QT measurements were performed by a blinded investigator, the QT-duration and T-wave morphology would often reveal the patients’ identity. Thus, potential for biased measurements exists. However, a small study comparing the effects of standing on 16 patients with LQT2 and 27 controls also showed significantly larger increments in the QTc of LQT2-patients.

**Conclusions**

**Diagnostic implications** Our test is easy to perform and should be used in addition to more accepted tests when necessary. Conversely, it is important to avoid over-diagnosis of LQTS based on QTc estimations performed when the patient stands. We have patients referred for evaluation following the incidental finding of a long QT interval in a single ECG but with strictly normal QT intervals in subsequent recordings. In these cases, the culprit ECG was the baseline ECG of an exercise test. Rather than representing a truly resting ECG, these were traces demonstrating the normal QTc prolongation in response to brisk standing immediately prior to exercise. Similarly, inadvertent QT-stretching during Holter recordings may lead to over-diagnosis of LQTS.

**Clinical implications** The onset of QT-interval related ventricular ectopy observed in a few LQTS-patients upon standing suggests that untreated patients are at risk for more serious arrhythmias every time they stand up. This is important because physicians are likely to misinterpret syncope as vasovagal if this occurred upon standing. Interestingly, standing is reported as trigger for syncope by one third of symptomatic LQTS-patients. We did not evaluate the effects of therapy but Walker reported that beta-blocker therapy attenuates the QT-stretching effects of standing.

**Research implications** An intriguing aspect of this study relates to the outliers in the control group. A few controls demonstrated exaggerated QT-stretching during standing that was of the magnitude observed in the LQTS-group (Figure 1C-1D). Rather than simply representing false positives, it is possible that these are individuals with normal QT but impaired repolarization reserve. Larger studies should be conducted to determine if these outliers share genotypic characteristics or demonstrate exaggerated QT prolongation in response to drugs or other insults.
Acknowledgments
Ori Rogowski performed the statistical analysis. Hila Zohar and Ilana Meir provided invaluable technical help. In addition, we thank the patients for their cooperation.

REFERENCES