Epinephrine QT Stress Testing in the Evaluation of Congenital Long-QT Syndrome
Diagnostic Accuracy of the Paradoxical QT Response

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Background—A paradoxical increase in the uncorrected QT interval during infusion of low-dose epinephrine appears pathognomonic for type 1 long-QT syndrome (LQT1). We sought to determine the diagnostic accuracy of this response among patients referred for clinical evaluation of congenital long-QT syndrome (LQTS).

Methods and Results—From 1999 to 2002, 147 genotyped patients (125 untreated and 22 undergoing β-blocker therapy) had an epinephrine QT stress test that involved a 25-minute infusion protocol (0.025 to 0.3 μg·kg⁻¹·min⁻¹). A 12-lead ECG was monitored continuously, and repolarization parameters were measured. The sensitivity, specificity, and positive and negative predictive values for the paradoxical QT response (defined as a ≥30-ms increase in QT during infusion of ≤0.1 μg·kg⁻¹·min⁻¹ epinephrine) was determined. The 125 untreated patients (44 genotype negative, 40 LQT1, 30 LQT2, and 11 LQT3) constituted the primary analysis. The median baseline corrected QT intervals (QTc) were 444 ms (gene negative), 456 ms (LQT1), 486 ms (LQT2), and 473 ms (LQT3). The median change in QT interval during low-dose epinephrine infusion was −23 ms in the gene-negative group, 78 ms in LQT1, −4 ms in LQT2, and −58 ms in LQT3. The paradoxical QT response was observed in 37 (92%) of 40 patients with LQT1 compared with 18% (gene-negative), 13% (LQT2), and 0% (LQT3; P<0.0001) of the remaining patients. Overall, the paradoxical QT response had a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for LQT1 status. Secondary analysis of the subset undergoing β-blocker therapy indicated inferior diagnostic utility in this setting.

Conclusions—The epinephrine QT stress test can unmask concealed type 1 LQTS with a high level of accuracy. (Circulation. 2006;113:1385-1392.)

Key Words: long-QT syndrome ■ ion channels ■ epinephrine ■ stress testing ■ electrocardiography

Congenital long-QT syndrome (LQTS) is one of the chief cardiac channelopathies and is characterized by marked genotypic and phenotypic heterogeneity.1 To date, nearly 500 LQTS-associated mutations have been reported in 5 genes encoding essential channel subunits, including KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), KCNE1 (LQT5), and KCNE2 (LQT6).2,3 In addition, a few mutations in ANKB-encoded ankyrin B subserve the pathogenic basis for type 4 LQTS (LQT4).4,5 The LQT1, LQT2, and LQT3 genotypes account for an estimated 70% to 75% of LQTS, and the majority of genotype-phenotype relationships pertain to these 3 LQTS genotypes.6

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Clinically, LQTS affects an estimated 1 in 5000 persons and may lie dormant indefinitely or may present with syncope, seizures, or sudden death at a young age. The mainstays of clinical therapy primarily include β-blocker therapy and device therapy with an implantable cardioverter defibrillator (ICD). The diagnosis of LQTS remains a daunting challenge. The cardinal ECG feature of LQTS, namely, QT prolongation, can be difficult to recognize. In addition, many physicians struggle with independently measuring or confirming the computer-derived rate-corrected QT interval (QTc).7 Furthermore, genetic testing and the phenomenon of incomplete penetrance have revealed that individuals hosting LQTS-causing mutations may nonetheless display resting QTc values that overlap with normal individuals.8–10 In fact, an estimated 25% to 50% of patients with LQT1, LQT2, or LQT3 display a nondiagnostic resting QTc (≤460 ms).

Provocative testing, particularly the epinephrine QT stress test, may aid in unmasking such individuals with concealed LQTS, especially type 1 LQTS (LQT1).11–14 Whether by bolus infusion (Shimizu protocol) or an incremental, escalat-
ing infusion (Mayo protocol), a paradoxical response characterized by QT lengthening rather than expected shortening appears pathognomonic for LQT1. This seemingly gene-specific response to epinephrine is consistent with clinical observations that have shown that exertion is a more common trigger for precipitating cardiac events in LQT1 than in the other LQTS-associated genotypes.

Although genetic testing is now clinically available and has facilitated the correct classification of family members once the family’s disease-causing mutation has been identified, there is the potential for a false-positive genetic test result, with an estimated 3% to 5% of healthy white subjects harboring a rare genetic variant of uncertain clinical significance.

Thus, in addition to its role in exposing concealed LQTS, epinephrine provocation may provide an in vivo functional assay for individuals who host a novel, reportedly LQT1-associated mutation.

In this study, we sought to determine the diagnostic accuracy of this epinephrine-induced paradoxical QT response among patients referred for evaluation of LQTS.

Methods

Study Design and Population

The results from the epinephrine QT stress test were analyzed in this institutional review board–approved retrospective study. Between 1999 and 2002, 147 individuals (92 females) had an epinephrine QT stress test conducted as part of the referred evaluation for LQTS in Mayo Clinic’s Long QT Syndrome Clinic. Independently, comprehensive genotyping of the known LQTS-associated channel genes was performed. In addition to the 37 genotype-positive subjects from the original study, the present study cohort included a prospective enrollment of 110 patients referred for LQTS evaluation, comprising 44 additional patients with genotyped LQTS, 44 patients referred for LQTS evaluation who were subsequently deemed genotype negative, and 22 patients who were evaluated while undergoing β-blocker therapy.

The primary analysis was performed on the subset of patients (n=125) who were not taking any β-blocker medication at the time of their evaluation. This subset included 40 patients (24 female) with LQT1 (median age 26 years, range 12 to 49 years), 30 (18 female) with LQT2 (median age 27 years, range 10 to 55 years), 11 (5 female) with LQT3 (median age 26 years, range 12 to 47 years), and 44 (30 female) patients referred for LQTS evaluation who were subsequently found to have a negative LQTS genetic test, hereafter designated as genotype negative (median age 16 years, range 8 to 59 years). A secondary analysis was performed on the subset of patients (n=25, 15 females) who were taking β-blocker medications at the time of the study.

Epinephrine QT Stress Test

The epinephrine QT stress test was performed in the clinical electrophysiology laboratory at the Mayo Clinic in Rochester, Minn. A physician and/or nurse was present throughout every study. A 12-lead ECG monitor, cardiorespiratory monitor, and continuous blood pressure monitor were connected to each patient. Defibrillator pads were placed on each patient, and a portable cardioverter-defibrillator was tested and kept available in the room. A peripheral intravenous line was placed and secured. The patient was then placed supine and the room quieted and darkened to allow the patient to relax.

After 10 minutes of rest, baseline parameters were obtained, including the heart rate, blood pressure, and repolarization measurements (QT and RR). These were measured with digital calipers on the Cardiolab 7000 System (GE Medical Systems, Milwaukee, Wis) as outlined previously.11 In brief, the recording speed was set at 50 mm/s and the gain at 5000 to obtain clear visualization of the QRS–T and U waves. In general, at least 4 measurements from lead II were obtained to generate an average QT and QTc at each stage. If the T-wave offset was poorly visualized in lead II, then precordial lead V1 generally provided the best lead for calculation. The QTc was calculated by the Bazett formula (QT divided by the square root of the RR interval).

An infusion of epinephrine was then initiated at 0.025 µg·kg⁻¹·min⁻¹. After 10 minutes of the infusion, the measurements were repeated. The epinephrine infusion was then increased sequentially to 0.05, 0.1, and 0.2 µg·kg⁻¹·min⁻¹, and the measurements were repeated 5 minutes after each dose increase. The epinephrine infusion was then discontinued, and measurements were obtained 5 and 10 minutes afterward. Originally, the infusion was initiated at 0.05 µg·kg⁻¹·min⁻¹ and escalated to a maximum dose of 0.3 µg·kg⁻¹·min⁻¹.11 After reporting our initial observations of a gene-specific response at a low dose and patient side effects (nausea, headache) at the highest dose, we subsequently changed to the current escalation protocol.12 The total duration of epinephrine infusion was 25 minutes. The change in the uncorrected QT interval (ΔQT) and the change in QTc (ΔQTc) were calculated by the difference between the maximal and minimal QT and QTc, respectively, at any time during the epinephrine infusion at a dose of ≥0.1 µg·kg⁻¹·min⁻¹. Established stopping criteria included systolic blood pressure ≥200 mm Hg, nonsustained ventricular tachycardia or polymorphic ventricular tachycardia, >10 premature ventricular contractions per minute, T-wave alternans, or patient intolerance.

Statistical Analysis

All continuous variables were reported as median and range because of the nonparametric nature of the data. ANOVA was performed by the Kruskal-Wallis rank sum test to determine the differences between the 4 groups with respect to age, baseline heart rates, peak heart rates, change in heart rates, baseline QT and QTc, and QT and QTc during epinephrine provocation. A P<0.05 was considered statistically significant. The Bonferroni correction (P × number of groups being compared) was made to the probability value for comparison of any 2 of the 4 groups.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Table 1 summarizes the baseline demographics of the primary study cohort, which consisted of 125 untreated patients. The age and sex distributions and resting heart rates were not significantly different between the 4 genotypes; however, there was a significant difference in the chronotropic response to epinephrine infusion. The peak heart rate achieved was significantly lower in the LQT3 group: median peak heart rate of 80 bpm (range 56 to 100 bpm) versus 92.5 bpm (range 55 to 130 bpm) in the gene-negative, 88 bpm (range 63 to 124 bpm) in the LQT1 group, and 96.5 bpm (range 62 to 119 bpm) in the LQT2 group (P<0.005). The change in heart rate approached but did not achieve statistical significance (P=0.08). This was likely due to the fact that the LQT3 group tended to have lower baseline heart rates as well.

The median baseline QTc was significantly longer in patients with LQT2 (486 ms, range 388 to 644 ms) and LQT3 (median 473 ms, range 424 to 532 ms) than in patients with LQT1 and the gene-negative subset. Importantly, among those with LQT1, the median baseline QTc was only 456 ms (range 397 to 517 ms), and 23 (58%) of 40 had baseline QTc ≤460 ms, which indicates that a significant proportion of LQT1 is concealed at rest. The median baseline QTc in the gene-negative group was 444 ms (range 394 to 677 ms). Just over half (54%) of all patients referred for an LQTS evalua-
tion and an epinephrine QT stress test had a QTc <460 ms at rest.

Effect of Epinephrine on the Uncorrected QT Interval

With epinephrine infusion, at a dose of ≤0.1 μg · kg⁻¹ · min⁻¹, the median QT interval increased from 440 to 530 ms in patients with LQT1 (median ΔQT 78 ms) while decreasing marginally from 458 to 455 ms in LQT2 (median ΔQT ~4 ms) and from 460 to 427 ms in LQT3 (median ΔQT ~58 ms), consistent with observations from our initial pilot study (Figures 1 and 2). Similar to our early observations involving healthy volunteers, genotype-negative patients referred for epinephrine QT stress testing also displayed QT interval shortening (420 to 402 ms, ΔQT 23 ms).

In the original pilot study involving 19 patients with LQT1 and 27 healthy volunteers, a ΔQT threshold between 25 and 60 ms to denote a positive paradoxical response was defined post hoc as the “paradoxical QT response” pathognomonic for LQT1. Accordingly, in the present study, 37 (92%) of 40 patients with LQT1, 4 (13%) of 30 with LQT2, 0 (0%) of 11 with LQT3, and 8 (18%) of 44 genotype-negative patients displayed this paradoxical QT response (P<0.0001). Table 2 summarizes the diagnostic accuracy of the paradoxical response (sensitivity 91%, specificity 83%, positive predictive value 72%, and negative predictive value 95%) were nearly identical to those with manifest QT prolongation at rest.

Subset Analysis of Patients With Concealed LQTS

Subset analysis of patients with concealed LQTS as defined by baseline QTc of ≥460 ms was also performed. Seventy (56%) of 125 study patients met this criteria, including 23 (58%) of 40 LQT1 patients, 8 (27%) of 30 LQT2 patients, 5 (45%) of 11 LQT3 patients, and 34 (77%) of 44 genotype-negative patients. In this subset analysis, the performance characteristics of the paradoxical response were nearly identical to those with manifest QT prolongation at rest.

Analysis of Changes in QTc With Epinephrine

With epinephrine infusion, the median ΔQTc changed from 444 ms (range 394 to 677 ms) to 485 ms (398 to 631 ms) in the genotype-negative group. In patients with LQT1, the median ΔQTc changed from 456 ms (range 397 to 517 ms) to 597 ms (492 to 685 ms). In patients with LQT2, the median ΔQTc changed from 486 ms (range 388 to 644 ms) to 545 ms (410 to 652 ms), and in patients with LQT3, the median ΔQTc changed from 473 ms (range 424 to 532 ms) to 476 ms (424 to 532 ms).
to 518 ms; Figure 3A). The median change in QTc among the
groups was 28 ms (range −53 to 195 ms) in the gene-negative
group, 138 ms (range 36 to 220 ms) in LQT1, 47 ms (range
−93 to 172 ms) in LQT2, and −6 ms (range −39 to 58 ms)
in LQT3 (Figure 3B).

There was significantly greater overlap of ΔQTc values
among the groups, which made it difficult to use this
parameter to distinguish between genotypes. Prior studies
have suggested using the ΔQTc (%) to distinguish between
groups. This is defined as percentage of [QTc (epineph-
rine) − QTc (baseline)] / QTc (baseline)]. We found that
overall, 5 (11%) of 44 subjects in the gene-negative group, 16
(40%) of 40 in the LQT1 group, 2 (7%) of 30 in the LQT2
and 0 (0%) of 11 in the LQT3 group demonstrated a
ΔQTc (%) of ≥32%. This yielded a sensitivity of 40%,
specificity of 92%, positive predictive value of 70%, and
negative predictive value of 76% for the correct prediction of
LQT1 status (data not shown).

Analysis of False-Positive Paradoxical
QT Responses

Because the typical response of healthy individuals, LQT2,
and LQT3 patients is to shorten their QT interval with
epinephrine, we investigated further the apparent positive
response obtained from the 12 LQT1-negative individuals
who nevertheless exhibited a ΔQT ≥30 ms at or before
infusion of 0.1 μg · kg⁻¹ · min⁻¹ epinephrine. The phenotype
of these so-called false-positives is summarized in Table 3.
The original data were reexamined in all 12 cases. In 5
patients (3 genotype-negative and 2 LQT2 patients), the
recorded paradoxical response appears erroneous owing to
exclusion of a low-amplitude U wave at baseline but the
subsequent inclusion of this U wave at higher doses, when the
U wave became more prominent or fused with the T wave.
In all 5 of these individuals, the QTU interval actually decreased
during epinephrine compared with the baseline QTU interval.

In 6 other cases (5 gene-negative and 1 LQT2), the test was
technically positive but the dynamicity of the QT response
was quite distinct from the LQT1 profile. Each patient
displayed a pattern of initial QT prolongation followed by a
subsequent decrease in the QT interval (typically at 0.1 to 0.2
μg · kg⁻¹ · min⁻¹ epinephrine). Thus, by the prespecified
criterion of the absolute increase in the QT interval during
low-dose infusion, these individuals were labeled as paradox-
ical response positive. However, careful analysis at higher
doses demonstrated a subsequent attenuation of the QT
interval rather than persistent paradoxical prolongation
throughout the epinephrine infusion, which is more charac-
teristic of LQT1.

The only patient in whom this pattern of subsequent QT
shortening at higher doses was not documented was a patient
with LQT2 in whom the study was terminated at 0.05 μg ·
kg⁻¹ · min⁻¹ epinephrine owing to the development
of ventricular bigeminy. Thus, we do not know how this patient
might have responded to higher doses of epinephrine.

Analysis of the False-Negative Responses

Next, we scrutinized the epinephrine QT stress test for the 3
LQT1-positive individuals who failed to display the paradox-
oical response (ie, false-negatives; Table 4). Patient 1
(W379R-LQT1) was a 48-year-old female with a baseline
QTc of 483 ms (ΔQT 10 ms). Although she had been
completely asymptomatic all her life, she had a 17-year-old
dughter who had died suddenly and had another daughter
with recurrent syncope (who is also LQT1 positive, with a
positive epinephrine QT stress test and ΔQT 51 ms). Patient
2 (Q530X-LQT1) was a 40-year-old male with a baseline

## Table 2. Validity of the Test at a ΔQT ≥30 ms

<table>
<thead>
<tr>
<th>ΔQT</th>
<th>LQT1</th>
<th>Non-LQT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 ms</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>&lt;30 ms</td>
<td>3</td>
<td>73</td>
</tr>
</tbody>
</table>

Sensitivity = 92.5%, Specificity = 86%, n = 125
QTc of 456 ms (ΔQT 28 ms). He was asymptomatic, although he had some family members who did have recurrent syncope (although there were no sudden deaths). LQT1 was in fact suspected on the basis of his epinephrine QT stress test, although he technically missed the specified cutoff value by 2 ms. Patient 3 (L191fs/90-LQT1) was a 25-year-old male with a baseline QTc of 445 ms (ΔQT 20 ms). He had been asymptomatic and had several family members who were LQT1 positive but similarly asymptomatic.

Validity of the Test in Patients Taking β-Blockers
By their inherent antagonism to epinephrine, β-blockers may affect the test results in patients who are taking these agents. Subgroup analysis of the 22 patients taking β-blocker medications demonstrated that the sensitivity of the test was only 60% and the specificity 59%. The positive predictive value was 30%, whereas the negative predictive value was 83%, which indicates that test performance deteriorated significantly when patients were studied while β-blocked.

Safety of the Epinephrine QT Stress Test
The epinephrine QT stress test is extremely safe. Some patients did note palpitations, especially at the high doses of epinephrine (≥ 0.2 μg · kg⁻¹ · min⁻¹). Isolated premature ventricular extrasystoles occurred in 3 (7%) of 44 gene-negative patients, 4 (10%) of 40 LQT1 patients, 5 (17%) of 30 LQT2 patients and 0 (0%) of 11 LQT3 patients. Ventricular bigeminy occurred in 1 (2%) of 44 of gene-negative patients, none of the LQT1 patients, 3 (10%) of 30 LQT2 patients and 1 (9%) of 11 LQT3 patients. Nonsustained ventricular tachycardia was observed in 2% of the cohort (1 gene-negative, 1 LQT1, and 1 LQT3 patient). There was a single patient (LQT1) who developed macroscopic T-wave alternans. No patient developed sustained ventricular tachycardia.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Genotype</th>
<th>Baseline QTc, ms</th>
<th>ΔQT, ms</th>
<th>Symptoms</th>
<th>Family History</th>
<th>Late Shortening of QT at Higher Epinephrine Doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/F</td>
<td>Gene negative</td>
<td>506</td>
<td>55</td>
<td>Syncope</td>
<td>None</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>2</td>
<td>16/F</td>
<td>Gene negative</td>
<td>414</td>
<td>96</td>
<td>Exercise-induced syncope</td>
<td>None</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>3</td>
<td>16/F</td>
<td>Gene negative</td>
<td>427</td>
<td>80</td>
<td>Spells</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>4</td>
<td>16/F</td>
<td>Gene negative</td>
<td>436</td>
<td>82</td>
<td>Presyncope</td>
<td>+</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>5</td>
<td>8/F</td>
<td>Gene negative</td>
<td>451</td>
<td>84</td>
<td>Asymptomatic</td>
<td>+</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>6</td>
<td>13/F</td>
<td>Gene negative</td>
<td>428</td>
<td>75</td>
<td>Asymptomatic (abnormal QTc on screening ECG)</td>
<td>None</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>7</td>
<td>30/M</td>
<td>Gene negative</td>
<td>412</td>
<td>140</td>
<td>Asymptomatic</td>
<td>Abnormal QTc in incidental ECG in child</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>8</td>
<td>23/F</td>
<td>Gene negative</td>
<td>448</td>
<td>100</td>
<td>Epinephrine-induced NSVT</td>
<td>None</td>
<td>Yes (at 0.2)</td>
</tr>
<tr>
<td>9</td>
<td>42/F</td>
<td>LQT2</td>
<td>505</td>
<td>76</td>
<td>Syncope</td>
<td>+</td>
<td>Absent, but test terminated at 0.05 due to ventricular bigeminy</td>
</tr>
<tr>
<td>10</td>
<td>34/F</td>
<td>LQT2</td>
<td>506</td>
<td>72</td>
<td>Syncope</td>
<td>+</td>
<td>Yes (at 0.1)</td>
</tr>
<tr>
<td>11</td>
<td>33/M</td>
<td>LQT2</td>
<td>454</td>
<td>53</td>
<td>Clearly vasovagal syncope, otherwise negative</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
<tr>
<td>12</td>
<td>24/M</td>
<td>LQT2</td>
<td>490</td>
<td>30</td>
<td>Asymptomatic</td>
<td>+</td>
<td>Error of measurement—U-wave included</td>
</tr>
</tbody>
</table>

F indicates female; M, male; and NSVT, nonsustained ventricular tachycardia.

*Dosages of epinephrine (shown in parentheses) are in micrograms per kilogram per minute.

TABLE 4. Analysis of False-Negative Responses Among the LQT1 Group

<table>
<thead>
<tr>
<th>No.</th>
<th>Age and Sex</th>
<th>Baseline QTc, ms</th>
<th>ΔQT, ms</th>
<th>Clinical Symptoms</th>
<th>Family History</th>
<th>Epinephrine Stress Test in Family Members</th>
<th>LQT1 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/F</td>
<td>483</td>
<td>10</td>
<td>None</td>
<td>(1) Sudden death in daughter (age 17 y)</td>
<td>Positive (ΔQT 51 ms in surviving daughter)</td>
<td>W379R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) Another daughter with 1 syncopal episode, who carries the same mutation and had a positive epinephrine test</td>
<td>Not done in other family members</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td>456</td>
<td>28</td>
<td>None</td>
<td>(1) No sudden death</td>
<td></td>
<td>Q530X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) Syncope in twin daughters of his sister</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3) Sister is asymptomatic mutation carrier</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4) Patient’s 11-year-old son carries the mutation and is asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25/M</td>
<td>445</td>
<td>-20</td>
<td>None</td>
<td>(1) 7 other mutation carriers in family, all asymptomatic</td>
<td>(1) Patient’s father: ΔQT 35 ms</td>
<td>L191fs/90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) Index case was nephew with ALTE (age 7 weeks). Currently well. ALTE likely unrelated to LQTS.</td>
<td>(2) Patient’s sister: ΔQT 62 ms</td>
<td></td>
</tr>
</tbody>
</table>

F indicates female; M, male; and ALTE, apparent life-threatening event.
torsade de pointes, ventricular fibrillation, or cardiac arrest. Although defibrillator patches were placed at the start of every study, no patients required defibrillation. There were no deaths during the study.

Discussion
The high incidence of concealed LQTS (resting QTc ≤460 ms) has prompted the need for highly sensitive and specific provocative testing to unmask this entity. Furthermore, with the advent of genotype analysis as a commercially available diagnostic test for LQTS, there is a small but significant number (<5%) of the population who may host a rare, novel “mutation” in the gene, KCNQ1, that is responsible for LQT1.20 The dilemma faced by the clinician then is whether the genetic test has indeed elucidated an LQT1-causing mutation or whether the genetic variant itself could be simply background genetic noise and a false-positive result. An accurate provocative test for LQT1 would prove invaluable in such a situation. The present study was designed to validate prior works on the relationship between the paradoxical QT response and LQT1 and determine the performance characteristics of the epinephrine QT stress test in the clinical evaluation of LQTS.

Physiological Basis of the Paradoxical QT Response
In the normal heart, epinephrine increases both inotropy and chronotropy. This is achieved in part by G-protein/cAMP/protein kinase A–mediated phosphorylation of IKs (slowly activating delayed rectifier potassium channel) and the Ca2+-activated Cl− channel.19 IKs is one of the dominant potassium channels responsible for repolarization (particularly phase 3), which allows potassium ions to exit the cell. When phosphorylated, IKs is enhanced, which causes the overall action potential duration (and thus the QT interval) to shorten.20−22 This explains the observed attenuation of the QT interval that occurs with epinephrine infusion in normal subjects. On the other hand, individuals with KCNQ1 mutations (LQT1) have compromised IKs channels that are not as responsive to sympathetic stimulation, and phase 3 repolarization in these individuals is retarded. Consequently, during epinephrine infusion, there are relatively more unopposed depolarizing forces via the L-type calcium channel and the sodium–calcium exchanger that prolong the action potential duration and hence the QT interval.23−27 Those individuals with KCNH2 mutations (LQT2) have dysfunctional rapidly activating delayed rectifier potassium (IKr) channels. These channels represent a smaller fraction of the potassium channels responsible for phase 3 repolarization and are not as sympathetically responsive as IKs channels. Therefore, in patients with LQT2, there may be a transient prolongation of the action potential duration during epinephrine infusion, followed by an abbreviation of the action potential duration and the absolute QT interval due to the presence of unimpaired IKr channels. This transient prolongation of the QT interval followed by shortening is a characteristic feature of the LQT2 phenotype.23−27 The LQT3 phenotype is characterized by a constant reduction of the action potential duration with epinephrine due to stimulation of the intact IKr channel and augmentation of a late inward Na current.23 Thus, the epinephrine QT stress test provides an in vivo physiological assessment of the integrity of the IKs pathway.

Types of Epinephrine QT Stress Tests
Catecholamine challenge has been studied utilizing different methodology, including exercise testing and epinephrine infusion. Although they may appear similar at the outset, there are significant differences between these provocative studies. It has been shown that for a given increase in heart rate, QT shortening in normal individuals is greater with catecholamine infusion than with exercise.28 Hence, observations from catecholamine infusion studies may not necessarily be applicable to exercise stress testing. Also, exercise may induce hyperkalemia, whereas epinephrine infusion at higher levels (≥0.2 μg · kg−1 · min−1) may induce hypokalemia due to intracellular shift of K+ ions. This discrepancy can affect repolarization parameters significantly. Although we continue to perform both exercise and epinephrine QT stress tests in all patients seen at the Mayo Clinic LQTS clinic, we have found the epinephrine QT stress test to be easier to standardize and interpret because it is independent of patient effort and free of movement artifacts.

The 2 major protocols developed for epinephrine infusion include the bolus and brief infusion developed by Shimizu13,14 and the escalating-dose protocol (Mayo protocol).11,12 Although both protocols are extremely useful, it is important to recognize that the responses to epinephrine derived from the Mayo graded-infusion protocol do not necessarily transfer to the bolus protocol. Among the advantages of the gradually escalating-dose protocol are better patient tolerance and a lower incidence of false-positive responses. On the other hand, one of the distinct advantages of the Shimizu protocol is the ability to monitor the temporal course of the epinephrine response at peak dose (during the bolus) and during steady state (during the infusion). This is particularly important in individuals with LQT2 in whom there may be transient prolongation of the uncorrected QT interval followed by subsequent shortening. In fact, our analysis of the 12 false-positive results revealed 3 LQT2 individuals who behaved precisely in this manner but whose low-dose QT response was ≥30 ms. We would therefore suggest using caution in interpreting the test as being positive for LQT1 in those individuals with an initial positive paradoxical response followed by QT attenuation. In addition, careful scrutiny of the U-wave morphology can decrease false-positive assignments further. In those individuals whose QTU complexes are difficult to separate, baseline QTU measurements (not QT) must be compared with peak epinephrine QTU measurements to minimize errors. Recognizing these important caveats, the presence of a paradoxical QT response that commences with low-dose epinephrine and persists should be viewed as presumptive clinical evidence of LQT1 pending confirmation by genetic testing.

Response of the QTc to Epinephrine
As mentioned previously, the uncorrected QT interval is a direct reflection of the change in the repolarization that
occurs during epinephrine infusion. The QTc (as calculated by the Bazett formula), on the other hand, is a derived variable that is affected by the heart rate (and thus the RR interval). In the presence of a brisk chronotropic response, the QTc may be prolonged significantly due to a decreased RR interval despite a shortening of the absolute QT interval.

Although prior research by Noda et al. showed that individuals with LQT1 had a ΔQTc (%) of 32%, we found this response to have unacceptable diagnostic utility. At least with this Mayo protocol of escalating epinephrine infusion, effects on QTc with epinephrine should not be used to make an LQTS diagnosis. We previously observed epinephrine QTc values as high as 600 ms and a ΔQTc exceeding 140 ms in our healthy volunteers.

Safety of the Epinephrine QT Stress Test
Both the Shimizu and Mayo protocol epinephrine QT stress tests are extremely safe. Overall, the test is well tolerated, with a low incidence of adverse events (primarily simple, self-limited arrhythmias) during the study. Since discontinuing the 0.3 μg · kg⁻¹ · min⁻¹ infusion level, we have not had to terminate any study due to patient intolerance. To date, we have never had to defibrillate a patient. Nonetheless, it remains a theoretical possibility that the epinephrine could precipitate torsades de pointes or ventricular fibrillation. Patients and families need to be counseled appropriately about this heretofore theoretical risk. Despite the absence of any significant cardiac events to date, we continue to recommend that the epinephrine QT stress test be performed in electrophysiological laboratories with appropriate resuscitation equipment (including a portable defibrillator) readily available.

Role of Epinephrine QT Stress Testing in the Clinical Evaluation of LQTS
At the Mayo Clinic’s Long QT Syndrome Clinic, the epinephrine QT stress test is recommended to all ungenotyped patients (usually ≥12 years of age) who present for a first or second opinion evaluation of LQTS, regardless of resting QTc. As seen here, most patients have not yet started β-blocker therapy when they come for evaluation. For those who are taking β-blockers already, we recommend a period of β-blocker washout (2 to 3 days) given the confounding effect of β-blockers on the test. Depending on the index of suspicion, this should generally be done by inpatient monitoring. However, if the patient is taking atenolol, the test is usually interpretable by having the patient skip the pretest morning dose (data not shown).

For these ungenotyped patients, the presence of a paradoxical QT response that manifests during low-dose infusion and persists is sufficient for the presumptive clinical diagnosis of LQT1 given its demonstrated 75% positive predictive value. Because no LQT3 patient has shown this paradoxical response to date, β-blocker therapy can be initiated safely while awaiting definitive confirmation of LQT1 status by genetic testing, which can take 4 to 6 weeks.

Besides its role in the evaluation of ungenotyped patients, we recommend epinephrine QT stress testing for patients who have newly received a genetic diagnosis of LQT1, particularly if the patient’s resting ECG is unremarkable (ie, concealed) and if the LQT1-associated KCNQ1 mutation is novel. Recognizing that an estimated 5% of healthy normal subjects host rare variants in KCNQ1 of uncertain functional significance and given the near universality of the paradoxical QT response in LQT1, this provocation study provides an in vivo physiological confirmation and corroboration of the pathogenetic status assigned to the novel mutation. In addition, this test is performed on patients who host concealed LQT2 to determine whether or not T-wave notching can be induced with low-dose epinephrine. At this time, an epinephrine QT stress test is not recommended for patients with clinically and genetically established type 3 LQTS (LQT3).

Conclusions
The epinephrine QT stress test has become a standard part of the clinical evaluation at Mayo Clinic’s Long QT Syndrome Clinic. The test provides a safe and reliable way of unmasking LQT1. A positive epinephrine QT stress test (paradoxical QT response of ≥30 ms during low-dose epinephrine infusion) provides a presumptive clinical diagnosis of LQT1, with a positive predictive value of 75%. This is extremely useful, particularly in the setting of a normal resting QTc, where correctly diagnosing LQTS is a daunting challenge and prediction of genotype by T-wave morphology assessment is virtually impossible. The proper inclusion/exclusion of U waves and identification of patients who manifest a persistent paradoxical QT prolongation that begins at a low dose further enhances the diagnostic accuracy of the test. In addition, given that LQT1 subjects almost always display this paradoxical QT response, the epinephrine QT stress test can also be used as an in vivo functional assessment of the integrity of the KCNQ1-encoded I₆,K pathway to corroborate the genetic assignment of LQT1. Finally, the epinephrine QT stress test fails to accurately predict the genotype in patients who are taking β-blockers.

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References


CLINICAL PERSPECTIVE

Congenital long-QT syndrome (LQTS) is one of the most common, potentially lethal heritable arrhythmia syndromes or cardiac channelopathies. Nearly 50% of LQTS, particularly type 1 LQTS (LQT1), lies concealed with a normal or equivocal resting ECG. Catecholamine provocation testing may help unmask concealed LQTS. Whether by the Shimizu (bolus) protocol or the Mayo (escalating infusion) protocol, patients with LQT1 manifest a paradoxical lengthening of the absolute QT interval during infusion of epinephrine. In this prospective study involving one of the largest cohorts of patients evaluated by the epinephrine QT stress test, we examined the clinical utility of the paradoxical QT response. A prolongation of the absolute QT interval by ≥30 ms during infusion of low-dose epinephrine was associated with a positive predictive value of 76% for LQT1 even if the resting ECG was normal. The diagnostic sensitivity eroded if the patient was demonstrably β-blocked. Furthermore, nearly every patient (96%) with an established LQT1-associated channel mutation displayed this paradoxical response. By providing an in vivo functional assessment of the integrity of the patient’s KCNQ1-encoded I Ks potassium channel, the epinephrine QT stress test may also assist in distinguishing background genetic noise from pathogenic, LQT1-conferring mutations. Thus, the epinephrine QT stress test plays an important role in the clinical evaluation of LQTS by (1) enabling a pregenetic determination of probable LQT1, especially when the baseline QT interval is normal, and (2) functionally confirming the veracity of a positive LQT1 genetic test result.
Epinephrine QT Stress Testing in the Evaluation of Congenital Long-QT Syndrome: Diagnostic Accuracy of the Paradoxical QT Response
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