Usefulness of Epinephrine Test in the Congenital Long QT Syndrome

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CASE PRESENTATION

A 14-year old Japanese boy was successfully resuscitated from cardiac arrest (near drowning) during swimming and referred to the National Cardiovascular Center for evaluating his diagnosis and treating him. He had had no previous history of syncope. Physical examination and laboratory data were normal on admission. None of chest radiographs and echocardiograms detected abnormal findings. His baseline 12-leads ECG showed borderline prolonged corrected QT (QTc) interval (442 ms) (Figure 1A).¹ Family study including his parents and two younger sisters showed neither history of syncope or cardiac arrest nor QT prolongation in their baseline 12-leads ECG.

Epinephrine test using our own protocol (bolus injection of 0.1 µg/kg followed by continuous infusion 0.1 µg/kg/min) was conducted. Epinephrine prolonged the QTc remarkably (585 ms), and induced spontaneously terminating torsade de pointes (TdP) (Figure 1B),¹ suggesting that he may be affected with congenital form of long QT syndrome (LQTS), especially LQT1 syndrome, which is most sensitive to sympathetic stimulation among several forms of LQTS. Molecular screening for LQT1 gene, KCNQ1, was first performed, and we could confirm successfully his molecular diagnosis as LQT1 syndrome. Oral β-blocker therapy (propranolol 1mg/kg) was started, and he has been symptom free for 7 years.
DISCUSSION

Low Penetrance in Congenital LQTS

Congenital LQTS is a hereditary disorder characterized by prolonged QT interval in the 12-leads electrocardiogram (ECG) and a polymorphic ventricular tachycardia, TdP. The clinical diagnosis of LQTS is based on the baseline QTc interval, cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death, and a family history of apparent LQTS. However, the hypothesis that electrocardiographic diagnosis could miss patients affected by LQTS had already been proposed before the genetic bases of the disease were known. These initial observations were based on the evidence that syncopal events could occur among family members with a "normal" QT interval. Vincent et al. reported that 5 (6 %) of 82 mutation carriers from 3 LQT1 families had a normal QT interval. Priori and co-workers have reported a very low penetrance (38 %, 9/24) in 9 families with only 1 clinically affected individual of LQTS. They recently conducted a large study of genotyped LQTS, demonstrating that penetrance was significantly lower in the LQT1 (64%) than in the LQT2 (81%) or the LQT3 (90%) syndromes. These findings strongly suggest the need for novel tools to unveil concealed mutation carriers of LQTS, especially those with LQT1 syndrome. The identification of patients with concealed LQTS enables the physicians to initiate potentially life-saving pharmacotherapies and healthstyle modifications.

The Epinephrine Test in Congenital LQTS

Provocative tests using catecholamine or exercise testing have long been considered to unmask some forms of congenital LQTS. Treadmill or ergometer exercise testing has been used to confirm the clinical diagnosis in patients with latent LQTS. However, it is often difficult to measure the QT interval precisely because of motion artifacts in the ECG recordings during exercise. As a catecholamine challenge test, isoproterenol has been used as a provocative testing. However, the recent major insights have been gleaned from using epinephrine.

The two major protocols developed for epinephrine test include the bolus injection followed by brief continuous infusion developed by our group, and the escalating-dose protocol by Ackerman's group (the Mayo protocol). Both protocols are extremely useful and safe, and overall are well tolerated. Each protocol has some advantages and disadvantages with respect to the other.

1. Bolus Protocol (Bolus Injection Followed by Brief Continuous Infusion)

We used bolus protocol (bolus injection of epinephrine 0.1µg/kg followed by continuous infusion of epinephrine 0.1µg/kg/min) (Figure 2) and suggested that epinephrine test produced genotype-specific responses of the QTc interval in patients with LQT1, LQT2 and LQT3. Epinephrine
remarkably prolonged the QTc interval at peak effect when the heart rate was maximally increased (1 – 2 minutes after the bolus injection), and the QTc remained prolonged during steady-state epinephrine effect (3 – 5 minutes) in patients with LQT1 (Figure 3).\textsuperscript{1,12} The paradoxical QT response, i.e. the longer absolute QT interval even though the shorter preceding RR interval during epinephrine infusion, was often observed in patients with LQT1 syndrome (Figure 3).\textsuperscript{12} In patients with LQT2, the QTc was also prolonged at peak epinephrine effect (during bolus), but returned to close to the baseline levels at steady state epinephrine effect (Figure 3).\textsuperscript{12} On the other hand, the QTc was less prolonged at peak epinephrine effect in the LQT3 patients than in the LQT1 or LQT2 patients, and was abbreviated below the baseline levels at steady state epinephrine effect (Figure 3).\textsuperscript{12} The differential responses of the QTc interval to our bolus protocol explain why the LQT1, LQT2, and LQT3 patients exhibit genotype-specific triggers for cardiac events.\textsuperscript{17}

The experimental studies employing arterially-perfused canine left ventricular wedge preparations also showed a differential responses of action potential duration (APD) and QT interval to sympathetic stimulation with isoproterenol between the LQT1, LQT2 and LQT3 models, suggesting the cellular basis for genotype-specific triggers for cardiac events.\textsuperscript{18} The LQT1 model using a specific $\text{IK}_S$ blocker, chromanol 193B, showed a persistent prolongation of APD and QT interval at steady state conditions of isoproterenol infusion. Under baseline conditions, $\beta$-adrenergic stimulation is expected to increase net outward repolarizing current, due to larger increase of outward currents, including $\text{IK}_S$ and $\text{Ca}^{2+}$-activated chloride current ($\text{ICl(Ca)}$), than that of an inward current, $\text{Na}^+$/Ca$^{2+}$ exchange current ($\text{INa-Ca}$), resulting in an abbreviation of APD and QT interval. A defect in $\text{IK}_S$ as seen in LQT1 could account for failure of $\beta$-adrenergic stimulation to abbreviate APD and QT interval, resulting in a persistent and paradoxical QT prolongation under sympathetic stimulation. In the LQT2 model using an $\text{IK}_F$ blocker, d-sotalol, isoproterenol infusion initially prolonged but then abbreviated APD and QT interval probably due to an initial augmentation of $\text{INa-Ca}$ and a subsequent stimulation of $\text{IK}_S$. In the LQT3 model using ATX-II, an agent that slows the inactivation of the sodium channel, isoproterenol infusion constantly abbreviated APD and QT interval as a result of a stimulation of $\text{IK}_S$, because an inward late $\text{INa}$ was augmented in this genotype.
**Figure 2**

_Provocative test (Epinephrine)_

**Protocols**

Epinephrine (Epi)
- bolus injection (0.1 μg/kg)
- + continuous infusion (0.1 μg/kg/min)

**Measurements**

Corrected QT interval (QTc) (Bazett’s methods)
- Baseline condition
- Peak Epi effect (1 – 2 min)
- Steady-state Epi effect (3 – 5 min)

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**Figure 3**

_Differential Response of Dynamic QT Interval to Sympathetic Stimulation with Epinephrine_

LQT1 | LQT2 | LQT3 | Control
--- | --- | --- | ---
Baseline
- V4: QTc = 576ms QTc = 592ms QTc = 560ms QTc = 389ms

Epinephrine (Peak)
- V4: QTc = 711ms QTc = 684ms QTc = 582ms QTc = 450ms

Epinephrine (Steady-State)
- V4: QTc = 696ms QTc = 611ms QTc = 532ms QTc = 409ms

(Shinoda W et al. Heart Rhythm 2004; 1: 176-283)
Based on the clinical and experimental data mentioned above, the epinephrine test in patients with congenital LQTS is expected to presumptively diagnose the LQT1, LQT2, and LQT3 genotype by monitoring the temporal course of the QTc to epinephrine at peak effect following bolus injection and at steady-state effect during continuous infusion, (Figure 4).\textsuperscript{12} as well as to unmask concealed patients with LQTS.

The clinical ECG diagnosis (sensitivity) was improved by using the steady state epinephrine effect from 68% to 87% in the 31 LQT1 patients, from 83% to 91% in the 23 LQT2 patients, but not in the 6 LQT3 patients from 83% to 83% (Figure 5) in our cohort.\textsuperscript{12} The bolus protocol of epinephrine effectively predicts the underlying genotype of the LQT1, LQT2 and LQT3.\textsuperscript{12} The prolongation of QTc $\geq$ 35 ms at steady state epinephrine effect could differentiate LQT1 from LQT2, LQT3 or control patients with a predictive accuracy $\geq$ 90% (Figure 6). The prolongation of QTc $\geq$ 80 ms at peak epinephrine effect could differentiate LQT2 from LQT3 or control patients with predictive accuracy of 100% (Figure 7). A flow chart to predict LQT1, LQT2, LQT3 and control patients with the epinephrine test is illustrated in the Figure 8.
**Figure 5**  
**Accuracy of ECG Diagnosis Before and After Epinephrine**

<table>
<thead>
<tr>
<th>LQT1</th>
<th>Baseline</th>
<th>Epinephrine (Steady state)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>ECG criteria*</td>
<td>21/31 (68)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>Score ≥ 4**</td>
<td>21/31 (68)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>LQT2</td>
<td>Baseline</td>
<td>Epinephrine (Steady state)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>ECG criteria*</td>
<td>19/23 (83)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>Score ≥ 4**</td>
<td>19/23 (83)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>LQT3</td>
<td>Baseline</td>
<td>Epinephrine (Steady state)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>ECG criteria*</td>
<td>5/6 (83)</td>
<td>30/30 (100)</td>
</tr>
<tr>
<td>Score ≥ 4**</td>
<td>3/6 (50)</td>
<td>30/30 (100)</td>
</tr>
</tbody>
</table>

*Δ QTc > 470 ms in asymptomatic individuals and a QTc > 440 ms for males and > 400 ms for female associated with ≥1 of the following: 1) stress-related syncope, 2) documented TdP, or 3) family history of early sudden cardiac death.

**Diagnostic criteria by Schwartz et al.**

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**Figure 6**

**Prediction of Genotype with Epinephrine Test (Δ QTc)**

<table>
<thead>
<tr>
<th></th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tr>
<td>LQT1 vs. LQT2</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Δ QTc ≥ 35 ms</td>
<td>97%</td>
<td>96%</td>
<td>97%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>(Steady – Baseline)</td>
<td>(90%)</td>
<td>(83%)</td>
<td>(88%)</td>
<td>(86%)</td>
<td>(87%)</td>
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<tr>
<td>LQT1 vs. LQT3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Δ QTc ≥ 35 ms</td>
<td>94%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>(Steady – Baseline)</td>
<td>(90%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(67%)</td>
<td>(92%)</td>
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<td>LQT1 vs. Control</td>
<td></td>
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<tr>
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<td>100%</td>
<td>97%</td>
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<tr>
<td>(Steady – Baseline)</td>
<td>(90%)</td>
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<td>(97%)</td>
<td>(91%)</td>
<td>(93%)</td>
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</tbody>
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NPV, negative predictive value. PPV, positive predictive value. Se, sensitivity. Sp, specificity. Percentages in parenthesis indicate those calculated by data measured simply from lead V5.

(Schwartz W et al. Heart Rhythm 2006; 3: 279-283)
**Figure 7**

*Prediction of Genotype with Epinephrine Test (Δ QTc) (Continued)*

<table>
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<tr>
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<th>PPV</th>
<th>NPV</th>
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<tr>
<td>Δ QTc ≥ 80 ms</td>
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<td>(100%)</td>
<td>(100%)</td>
<td>(75%)</td>
<td>(93%)</td>
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<tr>
<td>(Peak – Baseline)</td>
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<tr>
<td>LQT2 vs. Control</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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</tr>
<tr>
<td>Δ QTc ≥ 80 ms</td>
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<td>(88%)</td>
<td>(93%)</td>
<td>(91%)</td>
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<tr>
<td>(Peak – Baseline)</td>
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</tr>
</tbody>
</table>

NPV, negative predictive value. PPV, positive predictive value. Se, sensitivity. Sp, specificity. Percentages in parenthesis indicate those calculated by data measured simply from lead V5.


**Figure 8**

*Epinephrine Test*

Δ QTc ≥ 35 ms  
(Steady state – Baseline)

YES  NO

LQT1  LQT2  Control (or LQT3)

Δ QTc ≥ 80 ms  
(Peak – Baseline)

YES  NO

2. Mayo Protocol (Incremental, Escalating Epinephrine Infusion)

Ackerman et al. have used the Mayo protocol (incremental, escalating infusion protocol for 25-minute, 0.025 to 0.3 µg/kg/min) in the LQT1, LQT2, LQT3 patients and genotyped-negative patients. The median change of the QT interval was 78 ms in LQT1, -4 ms in LQT2, -58 ms in LQT3, and -23 ms in the genotype-negative patients by epinephrine infusion at low-dose of ≤ 0.1 µg/kg/min. A paradoxical QT prolongation, defined as a 30-ms increase in the QT (not QTc) interval during low-dose epinephrine infusion, was specifically observed in the LQT1 patients (92%), but not in the LQT2 (13%), the LQT3 (0%), and the genotype-negative patients (18%).

Molecular diagnosis is still unavailable to many institutes and requires high costs and is time-consuming. The presumptive, pre-genetic diagnosis of either LQT1, LQT2, or LQT3 based upon the response to epinephrine would facilitate molecular screening by targeting suspected genes. Moreover, a clinical diagnosis of concealed LQTS by the epinephrine test enables to limit exposure of the individuals to potentially dangerous conditions such as participation into competitive sport and use of drugs known to prolong repolarization, thus reducing the risk of life threatening cardiac arrhythmias. Furthermore, the identification of the QT or QTc response to epinephrine test like that in LQT1, LQT2, or LQT3 patients can guide gene-specific treatment strategies, even though the individuals can not be genetically diagnosed.

It is noteworthy that the induction of TdP or ventricular fibrillation (VF) should be always taken into account during the epinephrine test. Therefore, it goes without saying that epinephrine test should only be done by cardiologists under enough preparation of intravenous β-blockers as well as direct cardioverter for unintentionally induced VF. However, the induction of TdP or VF is extremely uncommon. In over 400 studies conducted using the Mayo protocol and our bolus protocol...
respectively, only two episodes of TdP (10 beats and 20 beats) and one episode of macroscopic T wave alternans have been observed (Figure 1B).¹

REFERENCES


