Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome

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Aims Differences in the sensitivity of the genotype of the congenital long QT syndrome to sympathetic stimulation have been suggested. This study compared the influence of sympathetic stimulation on continuous corrected QT (QTc) intervals between LQT1, LQT2 and LQT3 forms of the congenital long QT syndrome.

Methods and Results We recorded a 12-lead electrocardiogram continuously before and after bolus injection (0·1 µg . kg⁻¹) of epinephrine followed by continuous infusion (0·1 µg . kg⁻¹ . min⁻¹) in 12 LQT1, 10 LQT2, 6 LQT3, and 13 control patients. The QT intervals and previous RR intervals of all beats were measured semi-automatically, and the QTc intervals of all beats were calculated by Bazett’s method. The dynamic response of the RR interval to epinephrine was no different between the four groups. The QTc was prolonged remarkably (477 ± 42 to 631 ± 59 ms; P<0·0005, +24%) at peak of epinephrine in LQT2 patients, but this shortened to baseline levels at steady state (531 ± 25 ms; P=ns vs baseline, +6%). The QTc was much less prolonged at peak of epinephrine in LQT3 (478 ± 44 to 532 ± 41 ms; P<0·05, +11%) and controls (394 ± 21 to 456 ± 18 ms; P<0·0005, +16%) than in LQT1 and LQT2 patients, and shortened to the baseline levels (LQT3; 466 ± 49 ms, −3%, controls; 397 ± 16 ms, +1%; P=ns vs baseline) at steady state.

Conclusion Our data suggest that the dynamic response of ventricular repolarization to sympathetic stimulation differs between LQT1, LQT2 and LQT3 syndromes, and may explain why the trigger of cardiac events differs between the genotypes.

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Key Words: Action potentials, catecholamines, genetics, long-QT syndrome, nervous system, sympathetic.
Introduction

The congenital long QT syndrome is an inherited disease characterized by prolonged ventricular repolarization (QT interval) and life-threatening polymorphic ventricular tachycardia, torsade de points, which may lead to sudden cardiac death[1–3]. Genetic studies have shown that at least five forms of the congenital long QT syndrome are caused by mutations in ion channel genes located on chromosomes 3, 4, 7, 11, and 21[4–6]. Mutations in KCNQ1 and KCNE1 are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_Ks) which underlies the LQT1 and LQT5 syndrome, whereas mutations in HERG and KCNE2 are responsible for defects in the rapidly activating component (I_Kr) underlying LQT2 and LQT6[7]. Mutations in SCN5A alter the function of the sodium channel (I_Na) responsible for LQT3. Recent clinical[7–10] and experimental[11,12] studies have suggested differences in the sensitivity of genotypes of the congenital long QT syndrome to sympathetic stimulation. Exercise-related events dominate the clinical picture in LQT1, while a sudden shock in the form of an auditory stimulus is the predominant trigger of cardiac events in LQT2. Sleep-related episodes are more common in LQT3. Therefore, we hypothesize that the dynamic response of ventricular repolarization (continuous beat-to-beat QT intervals) to sympathetic stimulation differs between genotypes of the congenital long QT syndrome. The purpose of the present study was to compare the influence of epinephrine infusion on continuous corrected QT intervals between LQT1, LQT2 and LQT3 forms of the congenital long QT syndrome.

Methods

Study population

The study population included 12 patients affected with the LQT1 syndrome (KCNQ1 mutations, five unrelated families), 10 patients with the LQT2 syndrome (HERG mutations, five unrelated families), six patients with the LQT3 syndrome (SCN5A mutations, three unrelated families), and 13 healthy volunteers as a control group. The LQT1 group consisted of 10 females and two males, ranging in age from 9 to 68 years (mean, 28 ± 20 years). The LQT2 group included four females and six males from 5 to 61 years (mean, 28 ± 22 years). The LQT3 group included two females and four males from 12 to 65 years (mean, 35 ± 18 years). The control group included eight females and five males from 22 to 48 years old (mean, 29 ± 8 years). Eight patients with LQT1, seven patients with LQT2, and one patient with LQT3 had symptoms (syncope or aborted cardiac arrest).

Recording of standard 12-lead electrocardiograms

All protocols were reviewed and approved by our Ethical Review Committee, and informed consent was obtained from all patients. A standard 12-lead electrocardiogram was recorded with an FDX6521 (Fukuda Denshi Co., Tokyo, Japan) in the supine position. All antiarrhythmic drugs including beta-blockers were discontinued for at least five drug half-lives. These electrocardiographic data were digitized using analog-digital converters with a sampling rate of 1000 samples/second/channel. The digitized data were stored and analysed by using a personal computer and a program developed by our institution. The QT interval was defined as the time interval between the QRS onset and the point at which the isoelectric line intersected a tangential line drawn at the minimum dV/dt point of the positive T wave or at the maximum dV/dt point of the negative T wave (so-called tangential methods). When a bifurcated or secondary T wave (pathological U wave) appeared, it was included as part of the measurement of the QT interval, but the normal U wave, which was apparently separated from a T wave, was not included. This process was semi-automatically performed against a continuous beat-to-beat 5-averaged QRS complex using a computerized protocol. The longest QT interval that could be measured continuously was used for analysis. The QT interval was measured in the same lead before and during epinephrine infusion in each patient. A dynamic change in the corrected QT interval, as demonstrated by Bazett’s method (QTc: QT/√RR), in all beats was compared between the four groups.

Epinephrine administration

A bolus injection of epinephrine (0.1 μg·kg⁻¹), an α+β-adrenergic agonist, was followed immediately by continuous infusion (0.1 μg·kg⁻¹·min⁻¹) in all group patients. The electrocardiogram was continuously recorded during sinus rhythm under baseline conditions and usually for 5 min under epinephrine infusion. The effect of epinephrine on both RR and QT intervals reached steady state conditions usually 2–3 min after the start of epinephrine. The QTc data, as representing the peak effect of epinephrine, was collected 1–2 min after the start of epinephrine when the RR interval was at its shortest, while the QTc data, as representing steady state conditions of epinephrine, was collected 3–5 min after the start of epinephrine.

Statistical analysis

Data are reported as the mean±SD. Repeated-measures two-way ANOVA followed by Scheffé’s test was used to compare measurements made before and after epinephrine administration, and to compare differences between LQT1, LQT2, LQT3 and control patients. Repeated-measures one-way ANOVA followed by Scheffé’s test was used to compare changes of the measurements with epinephrine between the four groups. A value of P<0.05 was regarded as significant.
Results

Influence of epinephrine on RR intervals

There were no significant differences in the dynamic changes of the RR interval before and after epinephrine between the four groups (baseline conditions: LQT1, 863 ± 122 ms; LQT2, 982 ± 183 ms; LQT3, 834 ± 125 ms; control, 903 ± 164 ms; at peak of epinephrine: LQT1, 630 ± 89 ms; LQT2, 698 ± 112 ms; LQT3, 610 ± 66 ms; control, 634 ± 90 ms; at steady state conditions of epinephrine: LQT1, 793 ± 89 ms; LQT2, 884 ± 173 ms; LQT3, 772 ± 106 ms; control, 820 ± 139 ms).

Influence of epinephrine on QTc intervals

Figures 1–4 illustrate 12-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a representative LQT1, LQT2, LQT3 and control patient, respectively. Figure 5 illustrates the line charts of dynamic changes of the QTc interval in the four patients. In the LQT1 patient, the electrocardiogram under the baseline condition showed a prolonged QTc interval (602 ms), which was remarkably prolonged at peak of epinephrine (729 ms) and remained prolonged at steady state condition (673 ms). Epinephrine also prolonged the QTc dramatically at peak of epinephrine (706 ms) (Fig. 2b), but shortened it above the baseline levels at steady state condition (574 ms) unlike in the LQT1 patient (Figs. 2c and 5). Although the QTc under the baseline condition was prolonged (544 ms) in the LQT3 patient (Fig. 3a), the QTc was much less prolonged at peak of epinephrine (577 ms) than in the LQT1 or LQT2 patients (Fig. 3b), and shortened below the baseline level at steady state condition (379 ms) (Figs. 4c and 5). The electrocardiogram in the control patient demonstrated normal QTc under the baseline condition (385 ms) (Fig. 4a). The QTc was prolonged slightly at peak of epinephrine (448 ms) (Fig. 4b), and shortened to the baseline level at steady state condition (379 ms) (Figs. 4c and 5). Composite data of the QTc interval under baseline conditions, at peak of epinephrine, and at steady state conditions of epinephrine in the four patients are shown in Fig. 6. Once again, the QTc was prolonged markedly at peak of epinephrine (477 ± 42 to 631 ± 59 ms; P<0.0005), and remained prolonged at steady state conditions (556 ± 56 ms; P<0.0005 vs baseline condition) in the LQT1 patients (Fig. 6A). Percent delta prolongation of the QTc intervals with epinephrine, which was defined as a percentage of [QTc (epinephrine) – QTc (baseline)/QTc (baseline)], was +32% at peak of epinephrine and +17% at steady state conditions. The QTc was also prolonged dramatically at peak of epinephrine (502 ± 23 to 620 ± 39 ms; P<0.0005, +24%) in the LQT2 patients, but returned to the baseline levels at steady state conditions (531±25 ms; P=ns vs baseline condition, +6%) (Fig. 6B).
The QTc was much less prolonged at peak of epinephrine (478±44 ms; \(P<0.05, +11\%\)) in the LQT3 than in the LQT1 and LQT2 patients, and was abbreviated to the baseline levels at steady state conditions (466±49 ms; \(P= ns\) vs baseline condition, −3\%) (Fig. 6C). In the control patients, the QTc was slightly

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Figure 2 Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a patient with LQT2 syndrome. The corrected QT (QTc) interval was markedly prolonged at peak of epinephrine (549 to 706 ms) similar to that in the LQT1 patient shown in Fig. 1, but was shortened above the baseline level at steady state condition (574 ms).

Figure 3 Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a patient with the LQT3 syndrome. The corrected QT (QTc) interval was slightly prolonged at peak of epinephrine (544 to 577 ms), but much less than in the LQT1 and LQT2 patients shown in Figs 1 and 2, and was shortened below the baseline level at steady state condition (509 ms).
Figure 4  Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a control patient. The corrected QT (QTc) interval was slightly prolonged at peak of epinephrine (385 to 448 ms), and was shortened to the baseline level at steady state condition (379 ms).

Figure 5  Line charts of dynamic changes of the corrected QT (QTc) interval in the LQT1, LQT2, LQT3 and control patients shown in Figs 1–4. The QTc interval was prolonged markedly at peak of epinephrine and remained prolonged at steady state condition in the LQT1 patient. The QTc interval was also markedly prolonged at peak of epinephrine, but was shortened above the baseline level at steady state condition in the LQT2 patient. The QTc interval was much less prolonged at peak of epinephrine in the LQT3 patient than in either the LQT1 or LQT2 patient, and was shortened below the baseline level at steady state condition. The QTc interval was also slightly prolonged at peak of epinephrine, and was shortened to the baseline level at steady state conditions in the control patient.
prolonged at peak of epinephrine (394 ± 21 to 456 ± 18 ms; \( P < 0.0005, +16\% \)), and shortened to the baseline levels at steady state conditions (397 ± 16 ms; \( P = \text{ns} \ vs \ baseline \) condition, +1\%) (Fig. 6D). Figure 7 illustrates absolute prolongation of the QTc interval at peak of epinephrine and at steady state conditions in the four groups. The absolute QTc prolongation at peak of epinephrine was no different between LQT1 and LQT2 patients; both were much more pronounced than in LQT3 or control patients (\( P < 0.0005 \)) (Fig. 7A). The absolute change in the QTc at steady state conditions was significantly larger in the LQT1 patients than in the other three groups (\( P < 0.0005 \)). Moreover, it was significantly smaller in the LQT3 patients than in the LQT2 patient (\( P < 0.05 \)) (Fig. 7B). There were no significant differences in the response of the QTc interval between symptomatic and asymptomatic patients in any genotypes of the long QT syndrome.

**Induction of arrhythmias by epinephrine**

No arrhythmias were induced by epinephrine in any patient with the LQT1, LQT2 and LQT3 syndromes. This was probably due to avoidance of prolonged infusion of epinephrine (<5 min) in our study protocol.

**Discussion**

**Differential response of the QTc interval to sympathetic stimulation between LQT1, LQT2 and LQT3 syndromes**

Sympathetic stimulation such as physical exercise and strong emotion has long been known to precipitate syncope and sudden cardiac death in some forms of the congenital long QT syndrome\[1,2\]. Several experimental\[14,15\] and clinical\[16,17\] studies have suggested that catecholamine-enhanced early afterdepolarizations and triggered activity as well as an increased dispersion of ventricular repolarization provide a substrate for torsade de pointes, often leading to cardiac events. Recent evidence has demonstrated a differential response of the genotype of the long QT syndrome to sympathetic stimulation and beta-blockers\[7-10\]. Schwartz and co-workers reported that cardiac events

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**Figure 6** Composite data of the corrected QT (QTc) intervals under baseline conditions, at peak of epinephrine, and at steady state conditions of epinephrine in the LQT1, LQT2, LQT3 and control groups. A: The QTc intervals were prolonged markedly at peak of epinephrine (477 ± 42 to 631 ± 59 ms), and remained prolonged at steady state conditions (556 ± 56 ms) in the LQT1 group. B: The QTc intervals were also prolonged dramatically at peak of epinephrine (502 ± 23 to 620 ± 39 ms) in the LQT2 group, but returned to the baseline levels at steady state conditions (531 ± 25 ms). C: The QTc intervals were slightly but significantly prolonged at peak of epinephrine (478 ± 44 to 532 ± 41 ms) in the LQT3 group, and were shortened to the baseline levels at steady state conditions (466 ± 49 ms). D: The QTc intervals were slightly but significantly prolonged at peak of epinephrine (394 ± 21 to 456 ± 18 ms), and were shortened to the baseline levels at steady state conditions (397 ± 16 ms) in the control group. The numbers in parentheses indicate percent delta prolongation of the QTc interval with epinephrine. *\( P < 0.0005 \) vs baseline condition, **\( P < 0.05 \) vs baseline condition.

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are much more associated with sympathetic stimulation in the LQT1 genotype than in either LQT2 or LQT3\[7\]. Wilde et al. demonstrated that a sudden shock in the form of an auditory stimulus (alarm clock, telephone bell or ambulance siren, etc.) is the predominant trigger of cardiac events in the LQT2 syndrome[9]. Cardiac events usually occur at rest or during sleep in LQT3 [7], although relatively little is known about the influence of sympathetic stimulation on torsade de pointes. Experimentally, Priori and co-workers have suggested differences in the effect of isoproterenol, a beta-adrenergic agonist on action potential duration in pharmacological models of the LQT2 and LQT3[15]. They demonstrated that isoproterenol transiently prolonged action potential duration and induced early afterdepolarizations in guinea pig myocytes pre-treated with an IKr blocker, dofetilide (in the LQT2 model) but not in the LQT3 model (anthopleurin A). More recently, Shimizu and Antzelevitch examined the cellular mechanism of beta-adrenergic stimuli under conditions mimicking the LQT1, LQT2 and LQT3 syndromes[11,12]. In the LQT1 model (IKr block with chromanol 293B), isoproterenol persistently prolonged the QT and the action potential duration of M (mid-myocardial) cells, resulting in a development of torsade de pointes only in the presence of isoproterenol. In the LQT2 model (IKr block with d-sotalol), isoproterenol initially prolonged, then abbreviated the QT and the M cell action potential duration, thus transiently increasing the incidence of torsade de pointes. In contrast, isoproterenol constantly abbreviated the QT and the M cell action potential duration, causing a suppression of torsade de pointes in the LQT1 model (augmentation of late INa with ATX-II).

Beta-adrenergic stimulation with isoproterenol is known to augment a number of currents, including Ca2+-activated IKs, Ca2+-activated chloride current, L-type Ca2+ current, and Na+/Ca2+ exchange current. The response of action potential duration and of the QT to beta-adrenergic stimulation largely depends on the balance of these currents. An increase in net outward repolarizing current, due to a relatively large increase of IKs and Ca2+-activated chloride current vs Ca2+-type Ca2+ current and Na+/Ca2+ exchange current, is thought to be responsible for the abbreviation of action potential duration and the QT interval in response to beta-adrenergic stimulation under normal conditions. A defect in IKs could account for failure of beta-adrenergic stimulation to abbreviate action potential duration and the QT interval, resulting in persistent QT prolongation under sympathetic stimulation in the LQT1 genotype[4,16–18]. Our data, showing a persistent prolongation in the QTc interval at steady state conditions of epinephrine in the LQT1 patients, are consistent with the experimental study by Shimizu et al.[11,12] as well as clinical studies which demonstrated cardiac events associated with exercise[7,8].

Although epinephrine prolonged the QTc interval dramatically at peak of epinephrine in our LQT2 patients, it shortened the QTc to the baseline levels at steady state conditions. The dynamic responses of the QTc interval in the LQT2 patients were clearly different.
from that in the LQT1 patients. Taken together with the experimental studies by Priori et al.\textsuperscript{[15]} and Shimizu et al.\textsuperscript{[12]}, sympathetic stimulation transiently prolongs the QT interval and the action potential duration possibly due to a more rapid increase of L-type $\text{Ca}^{2+}$ current and $\text{Na}^{+}/\text{Ca}^{2+}$ exchange current than of $\text{IK}_s$ so that inward current predominates. Continuous sympathetic stimulation finally reverses the QT and the action potential duration to the baseline levels due to subsequent stimulation of $\text{IK}_s$. The transient prolongation of the QT interval, and possibly induction of early afterdepolarization-mediated extrasystoles following a sudden increase in sympathetic activity, may explain why cardiac events generally occur following a shock, especially from a sleep state (alarm clock, etc.) in patients with the LQT2 syndrome.

In the LQT3 patients in this study, the absolute QTc prolongation at peak of epinephrine was much less than in the LQT1 and LQT2 patients. Moreover, the QTc was shortened to or below the baseline levels at steady state conditions. The dynamic change in the QTc interval in the LQT3 patients is probably due to an increase in $\text{IK}_s$ as well as a reduction in the electrogenic $\text{Na}^{+}/\text{Ca}^{2+}$ exchange current as a result of an increase in $\text{INa}$ (gain of function) at the action potential plateau\textsuperscript{[19,20]}. Our results, as well as the experimental data by Priori et al.\textsuperscript{[15]} and Shimizu et al.\textsuperscript{[12]}, are concordant with clinical findings that LQT3 patients often have cardiac events at rest or during sleep when sympathetic tone is expected to be low\textsuperscript{[7,21,22]}.

\section*{Limitations of the study}

First, the number of the patients in this study, especially with LQT3, was relatively small for ascertaining the effect of sympathetic stimulation. However, the response of the QTc interval was specific and clearly different between the LQT1, LQT2 and LQT3 patients.

Second, we measured the dynamic change of the QTc interval before and after epinephrine infusion. It is inappropriate to use the Bazett’s formula for rate correction at peak of epinephrine when the RR interval was close to 600 ms. This may contribute to slight but significant prolongation of the QTc as the RR reached its shortest (at peak of epinephrine) even in the LQT3 and the control patients, which was in contrast to the experimental data by Shimizu et al.\textsuperscript{[12]}, demonstrating a constant abbreviation of the QT and action potential duration in the LQT3 model. We used Fridericia’s formula for rate correction of QT at peak of epinephrine, and found less and insignificant prolongation of QTc (Fridericia) in both LQT3 and control groups (data not shown). Moreover, the discrepancy of the QTc (QT) response between the LQT3 patients and the experimental LQT3 model can be explained by the different levels of sympathetic ($\beta$-adrenergic) stimulation and of augmented late $\text{INa}$ between patients and the experimental model.

Third, five of the 12 LQT1, three of the 10 LQT2 and one of the six LQT3 patients, but none of control patients are children (<15 years old). However, even though we left children out of the analysis in the long QT syndrome groups, there were no significant differences in the QTc data between patient groups with and without children.

\section*{Conclusion}

The dynamic response of ventricular repolarization (QTc interval) to sympathetic stimulation differs between LQT1, LQT2 and LQT3 forms of the congenital long QT syndrome, and this may explain why the trigger of cardiac events differs between genotypes of the congenital long QT syndrome.

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