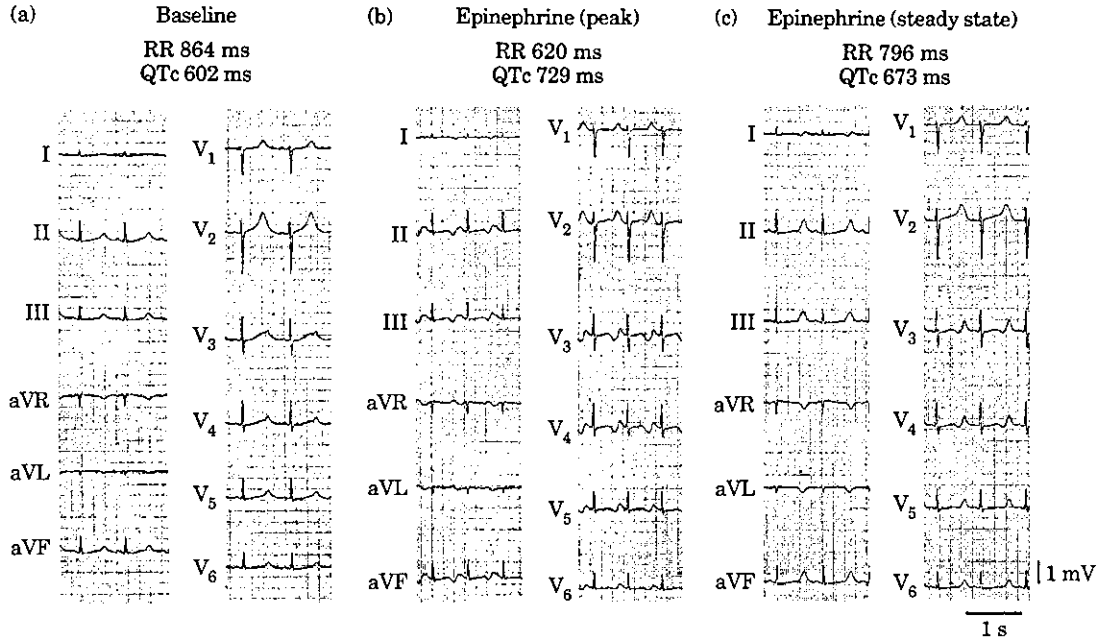

Figure 1 **Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a patient with LQT1 syndrome. The corrected QT (QTc) interval was remarkably prolonged at peak of epinephrine (602 to 729 ms), and remained prolonged at steady state condition (673 ms).**

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 (602 ms) (Fig. 1a). Epinephrine produced a prominent prolongation in the QTc at peak of epinephrine (729 ms) (Fig. 1b), and the QTc remained prolonged at steady state condition (673 ms) (Figs 1c and 5). The electrocardiogram in the LQT2 patient showed low amplitude T waves with a notched configuration commonly seen in LQT2 syndrome[13] and a prolonged QTc (549 ms) under the baseline condition (Fig. 2a). 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 (509 ms) (Figs 3c and 5). The electrocardiogram in the control patient demonstrated normal QTc under the baseline condition (385 ms) (Fig. 4a). The QTc was also 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 groups 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.

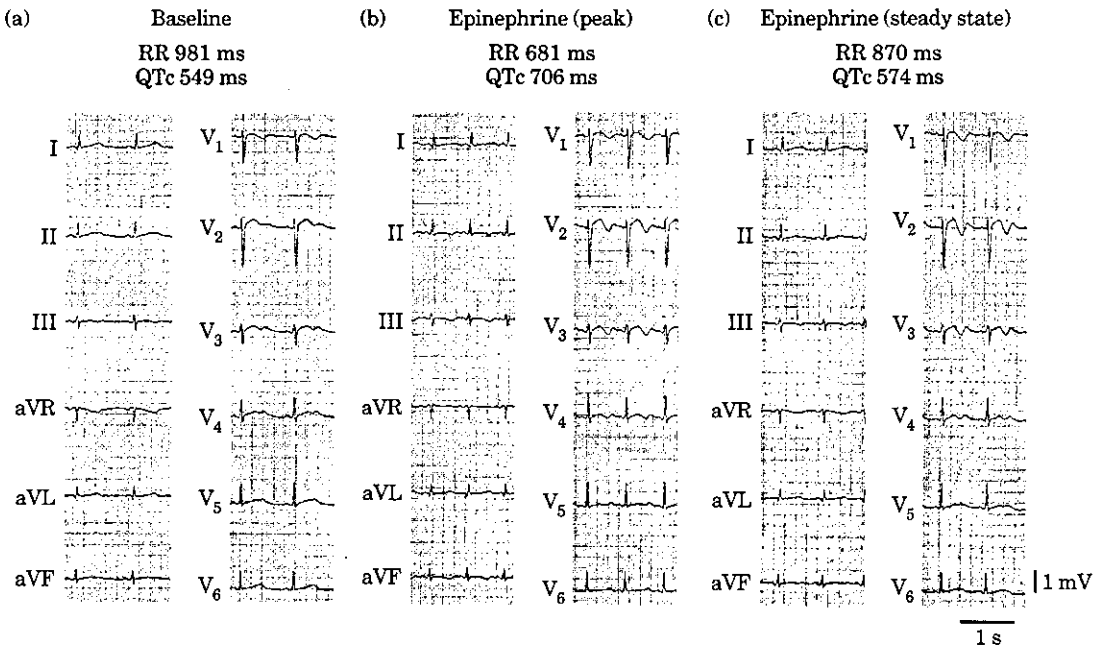

Figure 2 **Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a patient with LQT2 syndrome. The corrected QT (QTc) interval was markedly prolonged at peak of epinephrine (549 to 706 ms) similar to that in the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

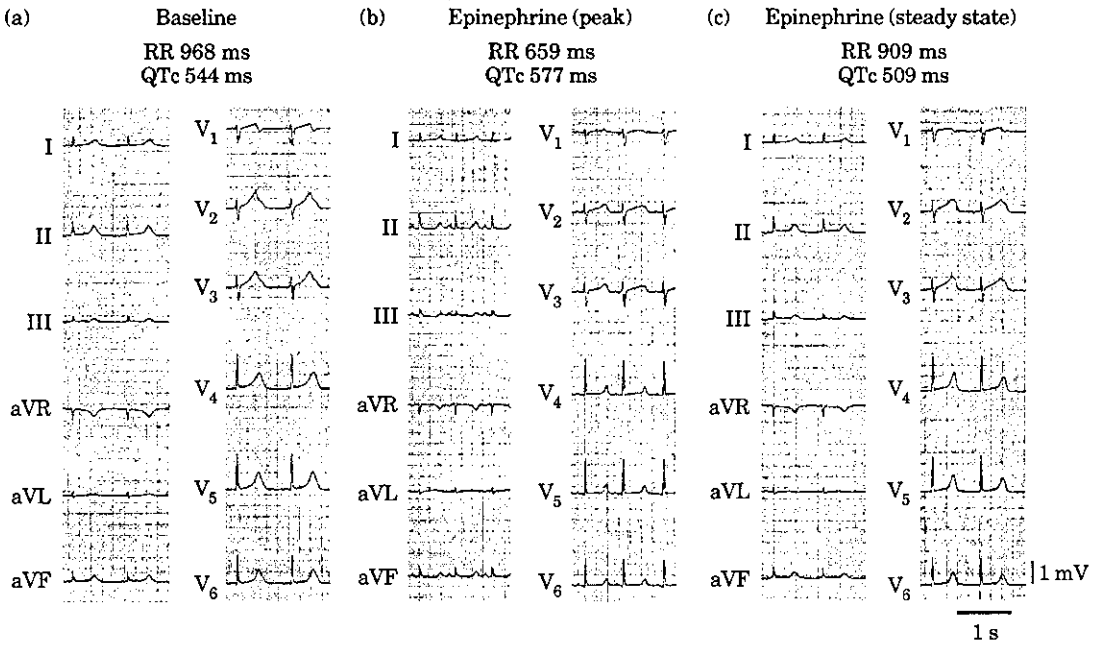

Figure 3 **Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a patient with the LQT3 syndrome. The corrected QT (QTc) interval was slightly prolonged at peak of epinephrine (544 to 577 ms), but much less than 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).**

6B). The QTc was much less prolonged at peak of epinephrine (478 ± 44 to 532 ± 41 ms; $P<0{\cdot}05$, +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

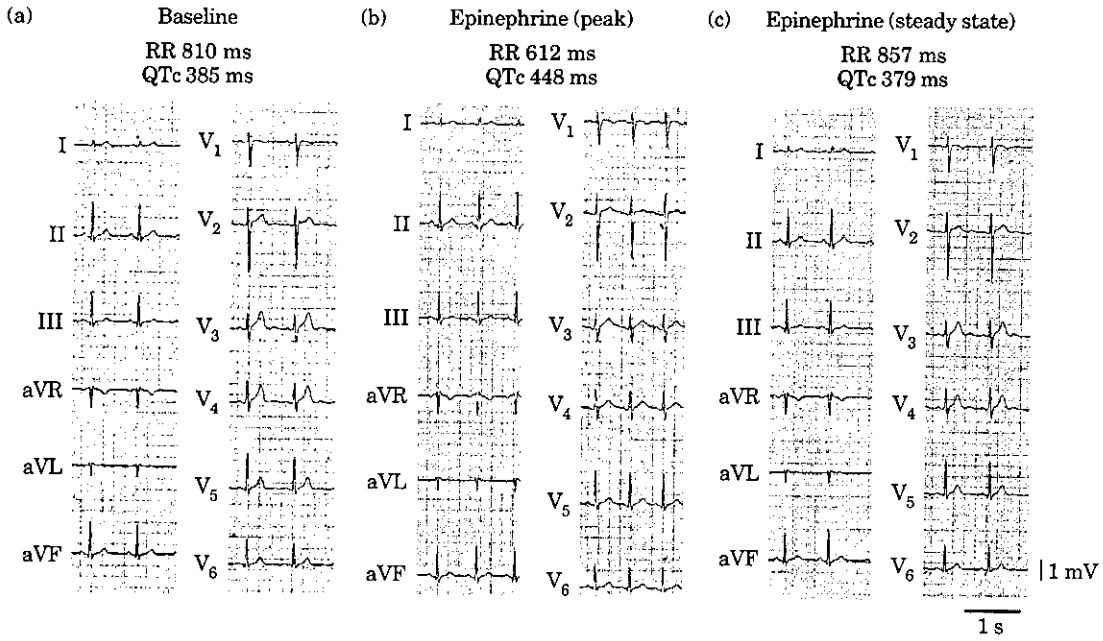

Figure 4 **Twelve-lead electrocardiograms under baseline conditions (a), at peak of epinephrine (b), and at steady state conditions of epinephrine (c) in a control patient. The corrected QT (QTc) interval was slightly prolonged at peak of epinephrine (385 to 448 ms), and was shortened to the baseline level at steady state condition (379 ms).**

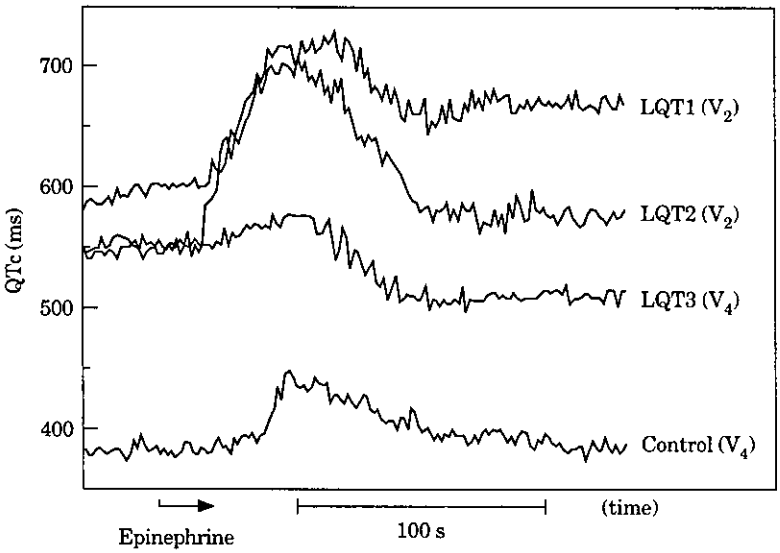

Figure 5 **Line charts of dynamic changes of the corrected QT (QTc) interval in the LQT1, LQT2, LQT3 and control patients shown in Figs 1–4. The QTc interval was prolonged markedly at peak of epinephrine and remained prolonged at steady state condition in the LQT1 patient. The QTc interval was also markedly 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.**

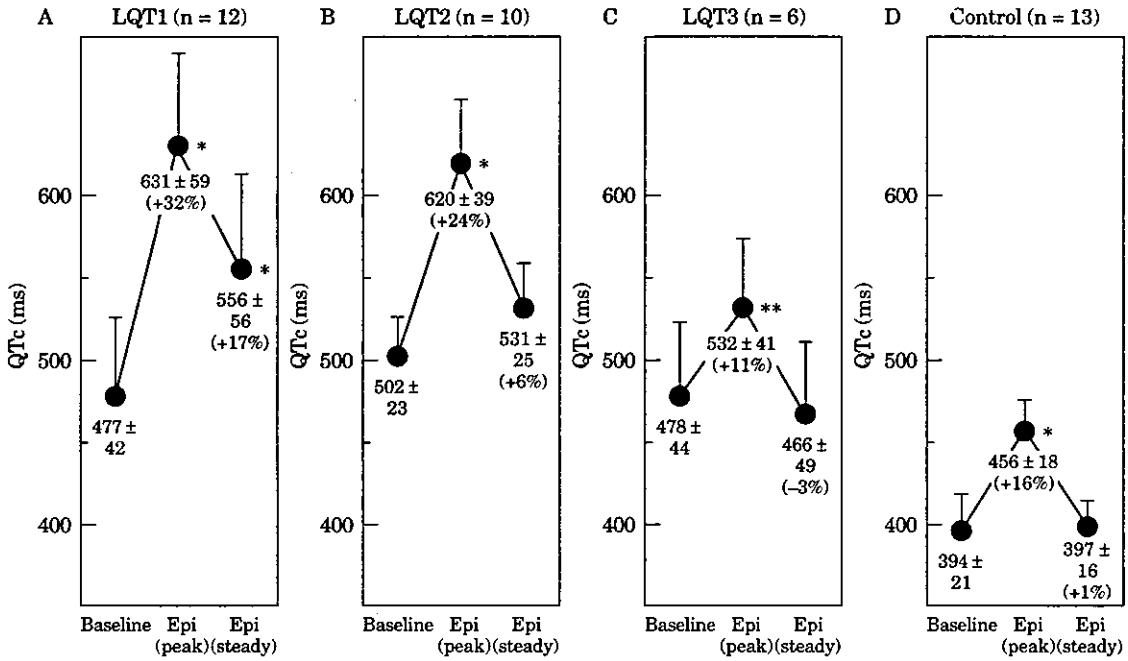

Figure 6 **Composite data of the corrected QT (QTc) intervals under baseline conditions, at peak of epinephrine, and at steady state conditions of epinephrine in the LQT1, LQT2, LQT3 and control groups. A: The QTc intervals were prolonged markedly at peak of epinephrine (477 ± 42 to 631 ± 59 ms), and 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.**

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=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 cathecholamine-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

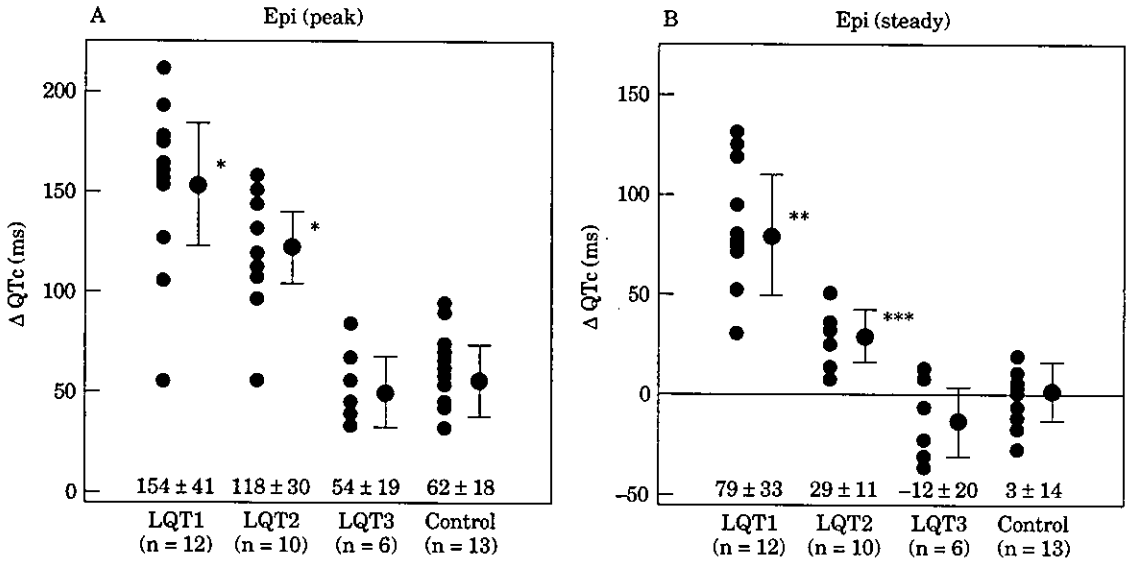

Figure 7 **Comparison of absolute prolongation of the corrected QT (QTc) intervals at peak of epinephrine (A) and at steady state conditions (B) in the LQT1, LQT2, LQT3 and control groups. A: The mean absolute QTc prolongation (*Δ* QTc) at peak of epinephrine was no different between LQT1 and LQT2 groups; both were much more pronounced than in either LQT3 or control patients. B: The mean *Δ* QTc at steady state conditions was significantly larger in the LQT1 group than in the other three groups. Moreover, it was significantly smaller in the LQT3 group than in the LQT2 group ($P<0.05$). *$P<0.0005$ vs LQT3 and Control groups, **$P<0.0005$ vs LQT2, LQT3 and Control groups, ***$P<0.05$ vs LQT3 group.**

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 after-depolarizations in guinea pig myocytes pre-treated with an I_{Kr} 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 (I_{Ks} 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 (I_{Kr} 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 LQT3 model (augmentation of late I_{Na} with ATX-II).

Beta-adrenergic stimulation with isoproterenol is known to augment a number of currents, including Ca^{2+}-activated I_{Ks}, Ca^{2+}-activated chloride current, L-type Ca^{2+} current, and Na^+/Ca^{2+} 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 I_{Ks} and Ca^{2+}-activated chloride current vs L-type Ca^{2+} current and Na^+/Ca^{2+} 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 I_{Ks} 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.*[15] and Shimizu *et al.*[12], sympathetic stimulation transiently prolongs the QT interval and the action potential duration possibly due to a more rapid increase of L-type Ca^{2+} current and Na^+/Ca^{2+} exchange current than of I_{Ks} 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 I_{Ks}. 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 I_{Ks} as well as a reduction in the electrogenic Na^+/Ca^{2+} exchange current as a result of an increase in I_{Na} (gain of function) at the action potential plateau[19,20]. Our results, as well as the experimental data by Priori *et al.*[15] and Shimizu *et al.*[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[7,21,22].

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.*[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 (β-adrenergic) stimulation and of augmented late I_{Na} 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.

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.

We are indebted to Drs Yasuko Tanabe and Takeshi Aiba for collecting data and helpful discussion.

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Differential Effects of Beta-Blockade on Dispersion of Repolarization in the Absence and Presence of Sympathetic Stimulation Between the LQT1 and LQT2 Forms of Congenital Long QT Syndrome

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OBJECTIVES This study compared the effects of beta-blockade on transmural and spatial dispersion of repolarization (TDR and SDR, respectively) between the LQT1 and LQT2 forms of congenital long QT syndrome (LQTS).

BACKGROUND The LQT1 form is more sensitive to sympathetic stimulation and more responsive to beta-blockers than either the LQT2 or LQT3 forms.

METHODS Eighty-seven-lead, body-surface electrocardiograms (ECGs) were recorded before and after epinephrine infusion (0.1 μg/kg body weight per min) in the absence and presence of oral propranolol (0.5–2.0 mg/kg per day) in 11 LQT1 patients and 11 LQT2 patients. The Q-T_{end} interval, the Q-T_{peak} interval and the interval between T_{peak} and T_{end} (T_{p-e}), representing TDR, were measured and averaged from 87-lead ECGs and corrected by Bazett's method (corrected Q-T_{end} interval [cQT_e], corrected Q-T_{peak} interval [cQT_p] and corrected interval between T_{peak} and T_{end} [cT_{p-e}]). The dispersion of cQT_e (cQT_e-D) was obtained among 87 leads and was defined as the interval between the maximum and minimum values of cQT_e.

RESULTS Propranolol in the absence of epinephrine significantly prolonged the mean cQT_p value but not the mean cQT_e value, thus decreasing the mean cT_{p-e} value in both LQT1 and LQT2 patients; the differences with propranolol were significantly larger in LQT1 than in LQT2 ($p < 0.05$). The maximum cQT_e, minimum cQT_e and cQT_e-D were not changed with propranolol. Propranolol completely suppressed the influence of epinephrine in prolonging the mean cQT_e, maximum cQT_e and minimum cQT_e values, as well as increasing the mean cT_{p-e} and cQT_e-D values in both groups.

CONCLUSIONS Beta-blockade under normal sympathetic tone produces a greater decrease in TDR in the LQT1 form than in the LQT2 form, explaining the superior effectiveness of beta-blockers in LQT1 versus LQT2. Beta-blockers also suppress the influence of sympathetic stimulation in increasing TDR and SDR equally in LQT1 and LQT2 syndrome. (J Am Coll Cardiol 2002;39:1984–91) © 2002 by the American College of Cardiology Foundation

Genetic studies have shown that congenital long QT syndrome (LQTS), a hereditary disorder characterized by a prolonged QT interval and torsade de pointes (1–3), is primarily an electrical disease caused by a mutation in specific ion channel genes (4–6). Mutations in *KCNQ1* and *KCNE1* are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) underlying the LQT1 and LQT5 forms of LQTS, whereas mutations in *KCNH2* and *KCNE2* result in defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for the LQT2 and LQT6 (6). Mutations in *SCN5A* decrease the function of the late sodium channel (I_{Na}) responsible for LQT3. Recent clinical and experimental studies have suggested that patients with LQT1 syndrome are more sensitive to sympathetic stimulation (physical or emotional stress) than are those with either LQT2 or LQT3 syndrome (7–11). We recently used 87-lead, body-surface electrocardiography and reported that epinephrine produced a greater increase in both transmural and spatial dispersion of repolarization (TDR and SDR, respectively), as well as the QT interval, in patients with LQT1 than in those with LQT2 , which may explain why those with LQT1 are more sensitive to sympathetic stimulation (12). In contrast, beta-blockers have been reported to

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Abbreviations and Acronyms

APD = action potential duration
ECG = electrocardiogram
LQTS = long QT syndrome
cQT_e = (corrected) Q-T_{end} interval
cQT_p = (corrected) Q-T_{peak} interval
cQT_e-D = (corrected) dispersion of QT_e
SDR = spatial dispersion of repolarization
cT_{p-e} = (corrected) interval between T_{peak} and T_{end}
TDR = transmural dispersion of repolarization

be most effective in suppressing cardiac events, such as syncope or sudden cardiac death, in patients with LQT1 (7). However, the mechanism responsible for the differential effectiveness of beta-blockers between the LQT1 and LQT2 syndromes is unclear. The peak and end of the T-wave on the electrocardiogram (ECG) are reported to be coincident with repolarization of epicardial and the longest M-cell action potentials, respectively, so that the interval between the T_{peak} and T_{end} is expected to reflect TDR (10,11,13–15). In this study, we recorded 87-lead, body-surface mapping before and after epinephrine infusion in the absence and presence of oral propranolol, a beta-blocker, in patients with LQT1 or LQT2 syndrome, and we compared the effects, in both the LQT1 and the LQT2 syndromes, of beta-blockade on TDR and SDR as well as the QT interval, under normal sympathetic tone or during sympathetic stimulation.

METHODS

Patient group. The study group included 11 patients with LQT1 syndrome (*KCNQ1* mutation; 6 unrelated families) and 11 patients with LQT2 syndrome (*KCNH2* mutation; 5 unrelated families). Six LQT1 families had six discrete missense mutations, and 5 LQT2 families had five discrete mutations. The LQT1 group consisted of eight females and three males, ranging in age from 6 to 54 years (mean 30 ± 16). The LQT2 group included seven females and four males, ranging in age from 17 to 61 years (mean 32 ± 17 years).

87-lead, body-surface mapping. All protocols were reviewed and approved by our Ethical Review Committee, and an informed consent was obtained from all patients. All anti-arrhythmic medications, except oral propranolol, were discontinued for at least five drug half-lives. Body-surface potential mapping was recorded with the VCM-3000 (Fukuda Denshi Co., Tokyo, Japan) (16). Eighty-seven body-surface leads were arranged in a lattice-like pattern (13 × 7 matrix), except for four leads on the mid-axillary lines, which covered the entire thoracic surface; 59 leads were located on the anterior chest (rows A–I) and 28 leads on the back (rows J–M). These 87 unipolar electrograms, with Wilson's central terminal as a reference, the standard 12-lead ECG and the Frank X, Y and Z scalar leads were simultaneously recorded during sinus rhythm. All subjects remained relaxed in the supine position during the recording. The ECG data were scanned with multiplexers and digitized using analog-to-digital converters with a sampling rate of 1,000 samples/s per channel. The digitized data were stored on a floppy disk and transferred to a personal computer (PC-9821 Xv13 NEC, Tokyo, Japan); the analysis program was developed at our institution.

Measurements. Eighty-seven-lead, body-surface ECGs were analyzed using a semi-automated digital program. The Q-T_{end} interval (QT_e) 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 first derivative (dV/dt) point of the positive T-wave or at the maximum dV/dt point of the negative T-wave. When a bifurcated or secondary T-wave (pathologic U-wave) appeared, it was included as part of the measurement of the QT interval, but a normal U-wave, which was apparently separated from the T-wave, was not included. The Q-T_{peak} interval (QT_p) was defined as the time interval between the QRS onset and the point at the peak of the positive T-wave or the nadir of the negative T-wave. When a T-wave had a biphasic or notched configuration, the peak of the T-wave was defined as that of the dominant T-wave deflection. The QT_e, QT_p and interval between the T_{peak} and T_{end} (T_{p-e}) ($QT_e - QT_p$), as an index of TDR, were measured automatically from all 87-lead ECGs, corrected to the heart rate by Bazett's method (corrected Q-T_{end} interval [cQT_e], corrected Q-T_{peak} interval [cQT_p] and corrected interval between T_{peak} and T_{end} [cT_{p-e}]: $QT_e/\sqrt{RR}$, $QT_p/\sqrt{RR}$ and $T_{p-e}/\sqrt{RR}$) and averaged among all 87 leads. Each point determined by the computer was checked visually and edited manually for each lead. The maximum and minimum values of cQT_e were also obtained from all 87 leads. As an index of SDR, dispersion of the cQT_e (cQT_e-D) was obtained from 87 leads and defined as the interval between the maximum and minimum values of the cQT_e.

Epinephrine administration. A bolus injection of epinephrine (0.1 μg/kg body weight), an alpha- and beta-adrenergic agonist, was immediately followed by continuous infusion of epinephrine (0.1 μg/kg per min), in the absence and presence of oral propranolol administration (0.5–2.0 mg/kg per day, for at least 5 days or more) in both groups of patients. Body-surface mapping was recorded during sinus rhythm under baseline conditions and at steady-state conditions of epinephrine (3–5 min after epinephrine infusion), in which both the RR and QT intervals reached steady state.

Statistical analysis. Data are reported as the mean value ± SD. Two-way repeated-measures analysis of variance (ANOVA), followed by the Scheffé F test, was used to compare measurements made before and after drug administration and to compare each variable between the LQT1 and LQT2 groups. Differences in each variable before and after drug administration were compared between the two groups by using one-way ANOVA, followed by the Scheffé F test. Differences in each variable before and after epinephrine were also compared between the absence and

JACC Vol. 39, No. 12, 2002
June 19, 2002:1984–91

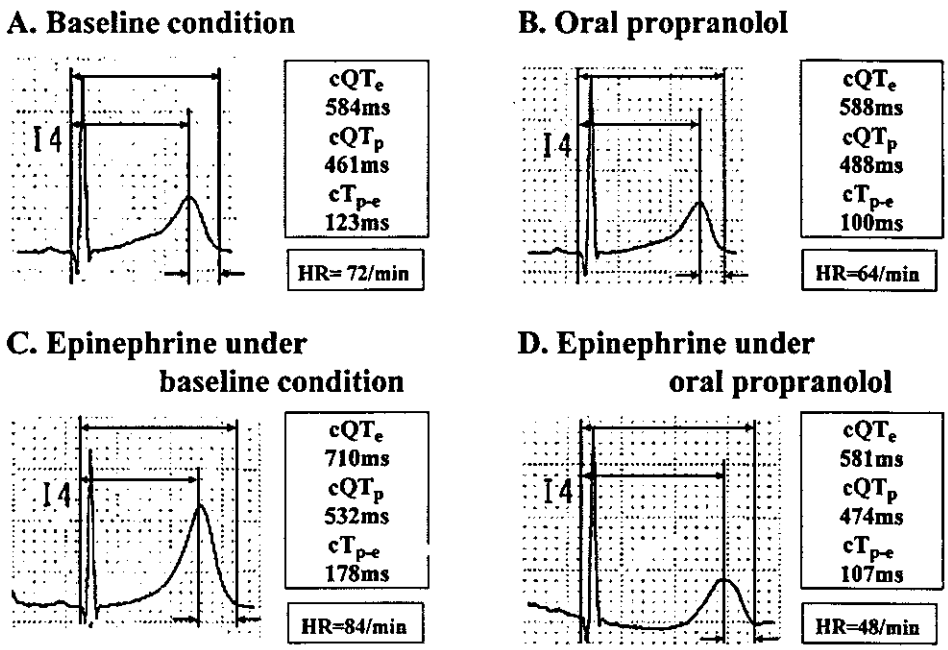

Figure 1. Electrocardiographic lead I4 of the body-surface map, which corresponds to lead V_6 of the standard 12-lead electrocardiogram, at the baseline condition **(A)**, with oral propranolol **(B)**, during epinephrine infusion at baseline **(C)** and during epinephrine infusion with oral propranolol **(D)** in a patient with LQT1 syndrome. Both cQT_e and cQT_p were prolonged (584 and 461 ms, respectievly) and cT_{p-e} was increased (123 ms) at the baseline condition. Propranolol produced no significant change in cQT_e (588 ms), but prolonged cQT_p (488 ms), resulting in a decrease in cT_{p-e} (100 ms). Epinephrine produced a remarkable prolongation in cQT_e (710 ms), but a mild prolongation in cQT_p (532 ms), resulting in an increase in cT_{p-e} (178 ms), and this was completely suppressed by oral propranolol. HR = heart rate.

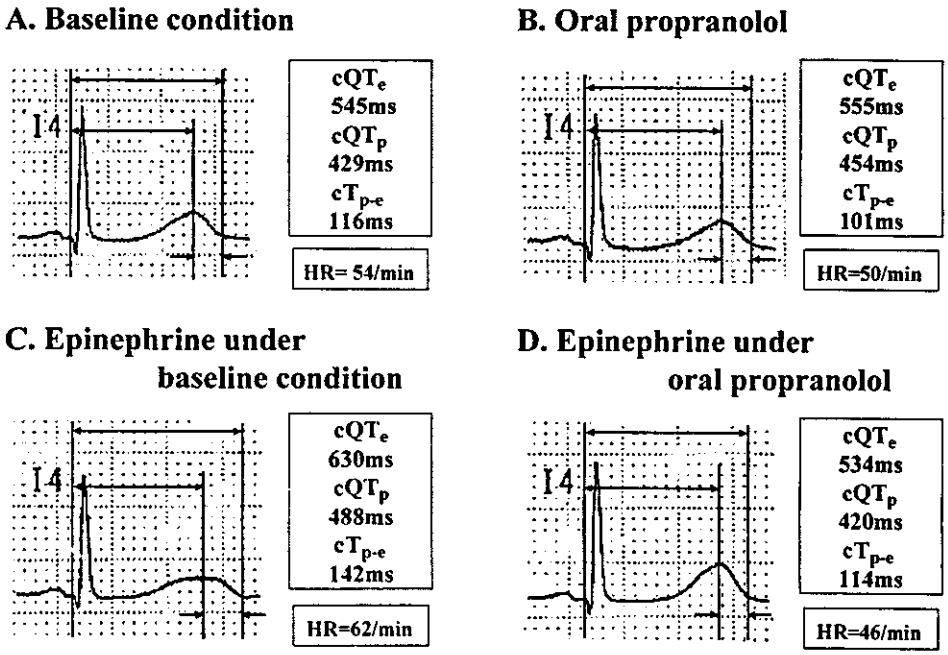

Figure 2. Electrocardiographic lead I4 of the body-surface map, at the baseline condition **(A)**, with oral propranolol **(B)**, during epinephrine infusion at baseline **(C)** and during epinephrine infusion with oral propranolol **(D)** in a patient with LQT2 syndrome. Both cQT_e and cQT_p were prolonged (545 and 429 ms, respectively) and cT_{p-e} was increased (116 ms) at the baseline condition. Propranolol produced no significant change in cQT_e (555 ms), but prolonged cQT_p (454 ms), resulting in a decrease in cT_{p-e} (101 ms). Epinephrine produced a prolongation in cQT_e (630 ms), but a mild prolongation in cQT_p (488 ms), resulting in an increase in cT_{p-e} (142 ms), and this was completely suppressed by oral propranolol. HR = heart rate.

presence of propranolol by using one-way ANOVA, followed by the Scheffé's F test. A value of $p < 0.05$ was regarded as significant.

RESULTS

There were no significant differences in the heart rate between the two groups before and after epinephrine in the absence and presence of propranolol (epinephrine/propranolol = −/−: 66 ± 7 beats/min for LQT1 and 62 ± 5 beats/min for LQT2; −/+: 58 ± 5 beats/min for LQT1 and 56 ± 4 beats/min for LQT2; +/−: 76 ± 6 beats/min for LQT1 and 70 ± 6 beats/min for LQT2; +/+: 50 ± 5 beats/min for LQT1 and 50 ± 4 beats/min for LQT2).

Effect of propranolol in the absence of epinephrine. Figures 1A and 1B, illustrates ECG lead I4 of body-surface mapping, which corresponds to lead V_6 of the standard 12-lead ECG before and after propranolol in a patient with LQT1 syndrome. Both the cQT_e and cQT_p were prolonged (584 and 461 ms, respectively) and the cT_{p-e} was increased (123 ms) under the baseline condition. Propranolol produced no significant change in the cQT_e (588 ms), but it did prolong the cQT_p (488 ms), resulting in a decrease in the cT_{p-e} (100 ms). Figures 2A and 2B, illustrates ECG lead I4 before and after propranolol in a patient with LQT2 syndrome. Propranolol also had no effect on the cQT_e (545 → 555 ms), but it did prolong the cQT_p (429 → 454 ms), thus decreasing the cT_{p-e} (116 → 101 ms). Changes in all repolarization variable before and after propranolol in 11 LQT1 patients and 11 LQT2 patients are shown in Table 1. There were no significant differences in any baseline variables between the LQT1 and LQT2 groups. In both groups of patients, propranolol produced no significant change in the mean cQT_e value, but it did cause a significant prolongation of the mean cQT_p value, resulting in a significant decrease in the mean cT_{p-e} value. The differences in the mean cQT_p and mean cT_{p-e} values with propranolol were significantly larger in the LQT1 group than in the LQT2 group ($p < 0.05$) (Table 1). These findings were true even though the repolarization variables were not corrected by the heart rate. Figure 3 plots the mean QT_e and mean QT_p values against the mean heart rate in the LQT1 and LQT2 groups. In both groups, the mean T_{p-e} value (mean QT_e − mean QT_p) after propranolol was smaller than that under the baseline condition, even if the mean heart rate was slower after propranolol. In contrast, no significant changes were observed with propranolol in the maximum cQT_e, minimum cQT_e and cQT_e-D values in both groups of patients (Table 1).

Effect of propranolol in the presence of epinephrine. Figure 1C and Figure 2C illustrate ECG lead I4 of body-surface mapping during epinephrine alone in patients with LQT1 and LQT2 syndrome, respectively. In both patient groups, epinephrine produced a prolongation of the cQT_e (710 and 630 ms in LQT1 and LQT2, respectively), but a mild prolongation in the cQT_p (532 and 488 ms,

Table 1. Propranolol-Induced Changes in the Mean cQT_e, Mean cQT_p, Mean cT_{p-e}, Maximum cQT_e, Minimum cQT_e and cQT_e-D in the LQT1 and LQT2 Groups

	Mean cQT_e		Mean cQT_p		Mean cT_{p-e}		Maximum cQT_e		Minimum cQT_e		cQT_e-D	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
LQT1 group (n = 11)	547 ± 56	550 ± 61 (2 ± 5)	410 ± 45	439 ± 57* (29 ± 16)†	137 ± 20	110 ± 10* (−27 ± 13)†	590 ± 55	597 ± 62 (6 ± 12)	494 ± 55	491 ± 59 (−2 ± 11)	96 ± 10	105 ± 10 (8 ± 13)
LQT2 group (n = 11)	539 ± 31	541 ± 31 (2 ± 8)	414 ± 22	430 ± 25* (15 ± 6)	124 ± 12	111 ± 15* (−13 ± 10)	597 ± 33	606 ± 33 (9 ± 6)	496 ± 24	505 ± 22 (10 ± 10)	101 ± 20	100 ± 16 (−1 ± 13)

*$p < 0.05$ vs. before. †$p < 0.05$ vs. LQT2. The mean value ± SD in parentheses indicates the difference between before and after epinephrine administration. All data are presented as the mean value ± SD in ms.
LQT1 and LQT2 = long QT syndrome types 1 and 2, respectively; cQT_e = corrected $Q\text{-}T_{end}$ interval; cQT_e-D = dispersion of cQT_e; cQT_p = corrected $Q\text{-}T_{peak}$ interval; cT_{p-e} = corrected $T_{peak}\text{-}T_{end}$ interval.

JACC Vol. 39, No. 12, 2002
June 19, 2002:1984–91

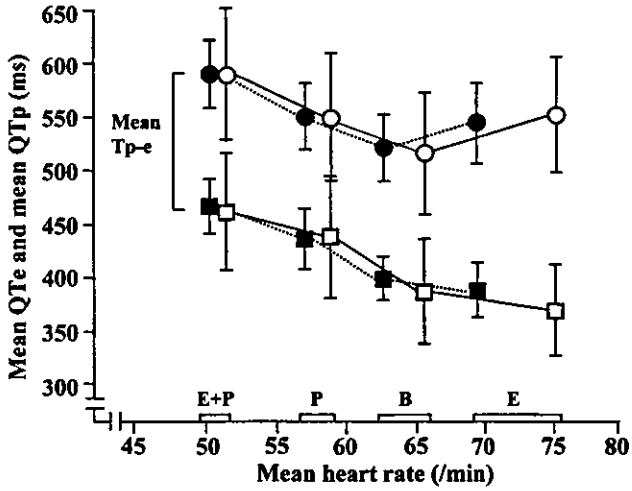

Figure 3. Plots of the mean QT_e and mean QT_p values against the mean heart rate in 11 patients with LQT1 **(open circles and squares)** and 11 patients with LQT2 **(solid circles and squares)**. In both groups of patients, the mean T_{p-e} value (mean QT_e − mean QT_p) after propranolol administration **(P)** was smaller than that at the baseline condition **(B)**, even if the mean heart rate was slower after propranolol. The mean T_{p-e} value after epinephrine administration **(E)** was much greater than that at the baseline condition, even if the mean heart rate was faster after epinephrine in both groups. Moreover, the mean T_{p-e} value after epinephrine was larger in the LQT1 group than in the LQT2 group, even if the mean heart rate was faster in the LQT1 group.

respectively), resulting in an increase in the cT_{p-e} (178 and 142 ms, respectively). Changes in all repolarization variables before and after epinephrine under the baseline condition in 11 LQT1 and 11 LQT2 patients are summarized in Table 2 and Figure 4. In both groups, epinephrine produced a significant prolongation in the mean cQT_e value, but not in the mean cQT_p value, resulting in a significant increase in the mean cT_{p-e} value. Moreover, epinephrine produced a larger prolongation in the maximum cQT_e than in the minimum cQT_e, resulting in a significant increase in the cQT_e-D in both groups. The differences in the mean cQT_e, mean cT_{p-e}, maximum cQT_e and cQT_e-D values with epinephrine were significantly larger in the LQT1 group than in the LQT2 group ($p < 0.05$) (Table 2, Figs. 4A, 4C, 4D and 4F). Once again, these findings were true even though the mean QT_e, mean QT_p and mean T_{p-e} values were not corrected by the heart rate (Fig. 3). In both groups, the mean T_{p-e} value after epinephrine administration was much greater than that under the baseline condition, even if the mean heart rate was faster after epinephrine. Moreover, the mean T_{p-e} value after epinephrine administration was larger in the LQT1 group than in the LQT2 group, even if the mean heart rate was faster in the LQT1 group.

Figures 1D and 2D illustrate ECG lead I4 of body-surface mapping during epinephrine with oral propranolol in patients with LQT1 and LQT2 syndrome, respectively. Changes in all repolarization variables before and after epinephrine with oral propranolol in 10 LQT1 and 9 LQT2 patients are summarized in Table 3 and Figure 4. In both groups of patients, propranolol completely suppressed the

Table 2. Epinephrine-Induced Changes at the Baseline Condition in the Mean cQT_e, Mean cQT_p, Mean cT_{p-e}, Maximum cQT_e, Minimum QT_e and cQT_e-D in the LQT1 and LQT2 Groups

	Mean cQT_e		Mean cQT_p		Mean cT_{p-e}		Maximum cQT_e		Minimum cQT_e		cQT_e-D	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
LQT1 group (n = 11)	547 ± 56	627 ± 51*† (80 ± 16)†	410 ± 45	421 ± 41 (11 ± 7)	137 ± 20	206 ± 21*† (69 ± 17)†	590 ± 55	681 ± 51*† (91 ± 17)†	494 ± 55	513 ± 51* (20 ± 6)	96 ± 10	168 ± 24*† (72 ± 15)†
LQT2 group (n = 11)	539 ± 31	593 ± 35* (54 ± 14)	414 ± 22	424 ± 27 (10 ± 9)	124 ± 12	168 ± 17* (44 ± 18)	597 ± 33	638 ± 28* (40 ± 8)	496 ± 24	523 ± 16* (27 ± 11)	101 ± 20	114 ± 16* (14 ± 7)

*$p < 0.05$ vs. before. †$p < 0.05$ vs. LQT2. The mean value ± SD in parentheses indicates the difference between before and after epinephrine administration. All data are presented as the mean value ± SD in ms.
Abbreviations as in Table 1.

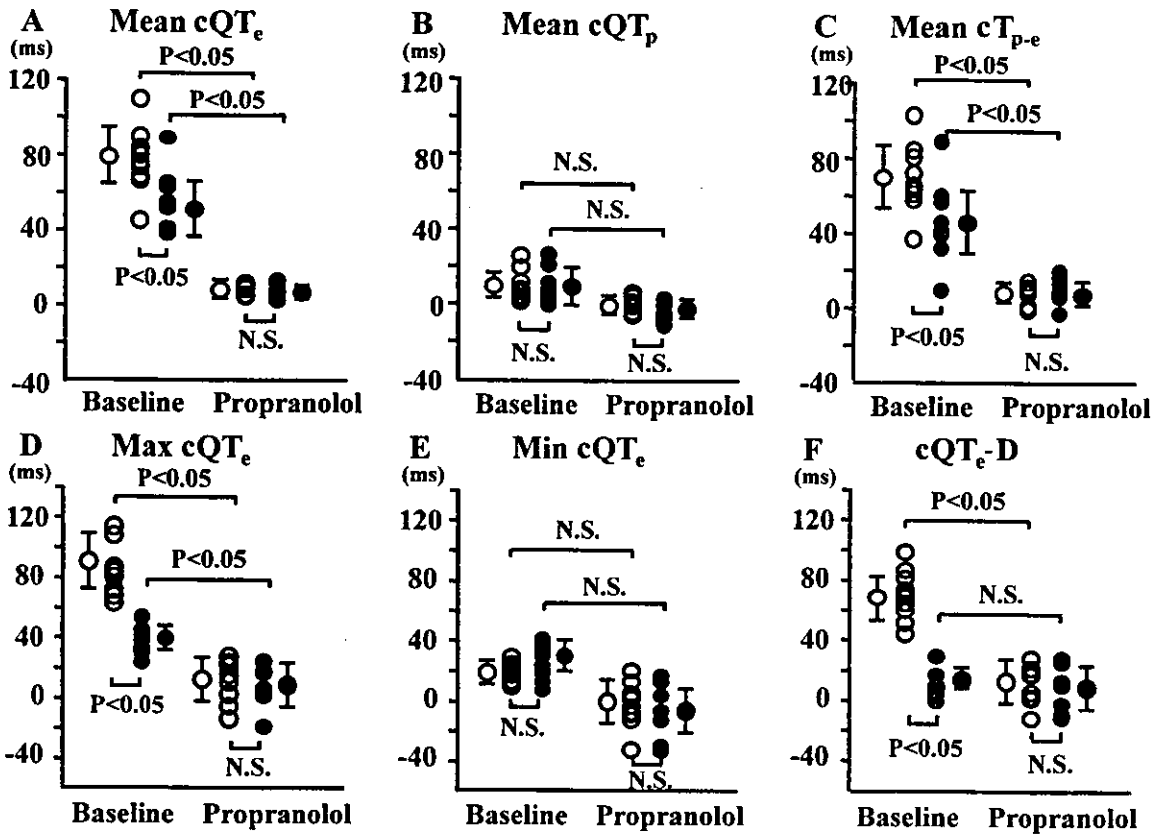

Figure 4. Differences before and after epinephrine at the baseline condition and with oral propranolol in the mean cQT_e **(A)**, mean cQT_p **(B)**, mean cT_{p-e} **(C)**, maximum cQT_e **(D)**, minimum cQT_e **(E)** and cQT_e-D **(F)** in 11 LQT1 patients **(open circles)** and 11 LQT2 patients **(solid circles)**. The differences in the mean cQT_e, mean cT_{p-e}, maximum cQT_e and cQT_e-D values with epinephrine at the baseline condition were significantly greater in the LQT1 group than in the LQT2 group. In both groups, propranolol completely suppressed the influence of epinephrine, and the differences in all variables with epinephrine plus oral propranolol were not significantly different between the two groups.

influence of epinephrine in prolonging the mean cQT_e, maximum cQT_e and minimum cQT_e values, as well as in increasing the mean cT_{p-e} and cQT_e-D values. The differences in all variables with epinephrine with oral propranolol were not significantly different between the two groups.

DISCUSSION

The major findings of this study were: 1) propranolol under normal sympathetic tone produces a greater decrease in TDR in LQT1 than in LQT2 syndrome but does not change the SDR in either the LQT1 or LQT2 syndrome; and 2) propranolol completely suppresses the influence of sympathetic stimulation in increasing TDR and SDR and prolonging the QT interval in both the LQT1 and LQT2 syndromes.

Effects of beta-blockade when sympathetic tone is normal. Although beta-blockers have been shown to be effective in preventing cardiac events in patients with LQTS, especially the LQT1 form (7,17), Linker et al. (18) reported that beta-blockade modified neither the corrected QT (cQT) interval nor cQT dispersion on the 12-lead ECG. Priori et al. (19) have reported that patients with LQTS who responded to beta-blockers showed less cQT dispersion than did non-responders. To the best of our knowledge, this is the first study to compare the effect of beta-blockade on both TDR and SDR between the LQT1 and LQT2 syndromes. The data suggest that beta-blockade under normal sympathetic tone decreases the mean cT_{p-e} value, as an index of TDR, more in LQT1 than in LQT2 syndrome, which likely explains the superior effectiveness of beta-blockers in LQT1 versus LQT2 syndrome. Experimental studies using arterially perfused wedge preparations have demonstrated that therapeutic concentrations of propranolol had little or no effect on the $Q\text{-}T_{end}$ interval, action potential duration (APD) of the three cell types or TDR (10,11), in contrast to the clinical data of the present study. In the clinic, patients with either LQT1 or LQT2 were exposed to considerable sympathetic tone even under baseline conditions, which is expected to shorten the APD more in epicardial cells (larger I_{Ks}) than in M cells (weaker I_{Ks}), resulting in an increase in TDR, especially in the LQT1 group. Therefore, beta-blockers reverse the influence of normal sympathetic tone and are expected to prolong the epicardial APD and to decrease TDR, especially in the LQT1 patients.

The cQT_e-D, as an index of SDR, was not changed with beta-blockade alone in both the LQT1 and LQT2 syndromes, even though 87-lead ECGs were simultaneously

JACC Vol. 39, No. 12, 2002
June 19, 2002:1984–91

Table 3. Epinephrine-Induced Changes With Oral Propranolol in the Mean cQT_e, Mean cQT_p, Mean cT_{p-e}, Maximum cQT_e, Minimum cQT_e and cQT_e-D in the LQT1 and LQT2 Groups

	Mean cQT_e		Mean cQT_p		Mean cT_{p-e}		Maximum cQT_e		Minimum cQT_e		cQT_e-D	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
LQT1 group (n = 10)	538 ± 62	550 ± 60 (11 ± 3)	429 ± 58	431 ± 57 (2 ± 3)	110 ± 9	118 ± 8 (8 ± 5)	590 ± 62	605 ± 51 (14 ± 15)	486 ± 58	486 ± 52 (1 ± 14)	104 ± 10	119 ± 11 (14 ± 12)
LQT2 group (n = 9)	541 ± 31	551 ± 32 (9 ± 2)	435 ± 24	434 ± 23 (−1 ± 4)	111 ± 15	117 ± 17 (6 ± 7)	604 ± 35	615 ± 36 (10 ± 13)	502 ± 23	497 ± 34 (−5 ± 17)	106 ± 13	117 ± 11 (11 ± 14)

The mean value ± SD in parentheses indicates the difference between before and after epinephrine administration. All data are presented as the mean value ± SD in ms.
Abbreviations as in Table 1.

recorded. Our data are consistent with the results of Linker et al. (18); however, they may be explained by a recent, elegant study using computer simulation, conducted by Burnes et al. (20), who suggested that regional heterogeneity of repolarization was not reflected in QT dispersion recorded from the body-surface, 12- or 64-lead ECG.

Effects of beta-blockade during sympathetic stimulation. Physical exercise and strong emotion have long been known to precipitate syncope and sudden cardiac death in patients with congenital LQTS (1–3). Among three forms of congenital LQTS, the LQT1 form has proved to be more sensitive to sympathetic stimulation, compared with either LQT2 or LQT3, both clinically (7–9,21) and experimentally (10,11). In the clinic, QT dispersion has been reported by Sun et al. (22) to be markedly increased with epinephrine in patients with LQTS. In our present study and previous studies using 87-lead, body-surface ECG, augmentation of sympathetic stimulation with epinephrine infusion produced a greater increase in both TDR (mean cT_{p-e}) and SDR (cQT_e-D) in LQT1 versus LQT2 syndrome (12), supporting the fact that the LQT1 patients are more at risk when they are under strong sympathetic stimulation. In the present study, oral propranolol completely suppressed epinephrine's influence on increasing TDR and SDR in both the LQT1 and LQT2 syndromes. This finding was consistent with the effects of propranolol in experimental models of the LQT1 and LQT2 syndromes (10,11). Increases in both TDR and SDR are thought to provide a substrate for reentrant arrhythmias, such as torsade de pointes in congenital LQTS (10,11,13–15,23–25). Therefore, our data suggest that beta-blockers at least prevent the substrate for reentry from being arrhythmogenic during augmentation of sympathetic stimulation, equally in the LQT1 and LQT2 syndromes. Schwartz et al. (7) have recently demonstrated that beta-blockers were more effective in suppressing the recurrence of cardiac events in LQT1 versus LQT2 syndrome (81% vs. 59%). Taken together with our data, other predisposing factors such as hypokalemia or bradycardia, as well as triggering factors such as early afterdepolarization-mediated extrasystole, in addition to augmented sympathetic stimulation, may play a more significant role in the development of torsade de pointes in patients with LQT2 syndrome.

Study limitations. Although recent experimental studies using arterially perfused wedge preparations have shown that the transmural voltage gradient across the ventricular wall has an important contribution to the cellular basis of normal and abnormal T-waves (10,11,13–15), there is not enough evidence to claim that this observation can be transferred to the clinical ECG. Therefore, great caution must be taken in interpreting the data of the present study.

Because 87-lead, body-surface mapping is not widely available, we measured repolarization variables by using six precordial leads. As shown in the Figures 1 and 2, the results were basically similar to those obtained from 87 leads (data not shown).

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IMAGES IN CARDIOLOGY

Visualisation of activation and repolarisation in congenital long QT syndrome

A three dimensional electroanatomic mapping system (CARTO, Biosense Webster) can visualise the activation sequence during normal or abnormal rhythm, and has recently been used as a guide for catheter ablation for some tachyarrhythmias. Activation time at each site is measured from a bipolar (or a unipolar) electrogram and is determined as the interval between the QRS onset and the time minimum of the first derivative (V_{min}) of the QRS deflection. On the other hand, the time maximum of the first derivative (V_{max}) of the T wave, which is measured from a unipolar electrogram, is shown to be coincident with repolarisation at each site.

We report on a 16 year old Japanese male with congenital long QT syndrome who had episodes of syncope and a prolonged corrected QT interval (589 ms) with a notched configuration (below left). During the electrophysiological study, after obtaining informed consent, endocardial mapping of unipolar recording in the right and left ventricle was performed during constant atrial pacing (80 beats/min). We constructed maps of both activation time (panels A (right anterior oblique (RAO) 30°) and B (left anterior oblique (LAO) 45°)) and repolarisation time, which was defined as the interval between the QRS onset and the V_{max} of the T wave (panels C (RAO 30°) and D (LAO 45°)). Each colour bar of the maps is relative to the QRS onset of surface ECG lead V1, ranging from 4 ms (orange) to 84 ms (purple) in the activation time map, and from 263 ms (orange) to 494 ms (purple) in the repolarisation time map, respectively. Endocardial activation started at the inferoseptum and the anteroseptum of the left ventricle (LV) simultaneously and spread to the right ventricle (RV) and the rest of the LV. The free wall of the right ventricular outflow tract was activated last. In contrast, the repolarisation sequence was considerably opposite to the activation sequence. The left and right ventricular outflow tract repolarised first and the apex of the RV and the LV repolarised last. The dispersion of the repolarisation time was increased (231 ms) in this case compared with the averaged dispersion of the repolarisation time in three normal controls (172 (10) ms), which may be arrhythmogenic in this syndrome.

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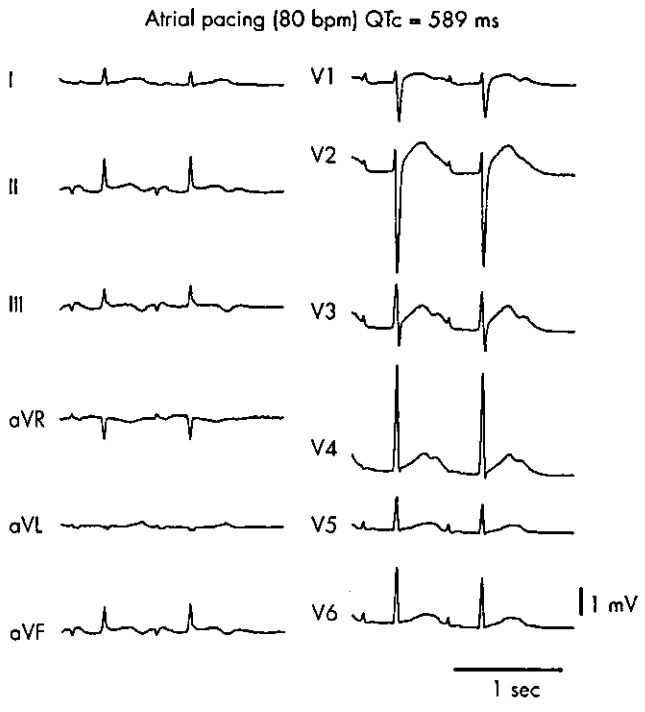

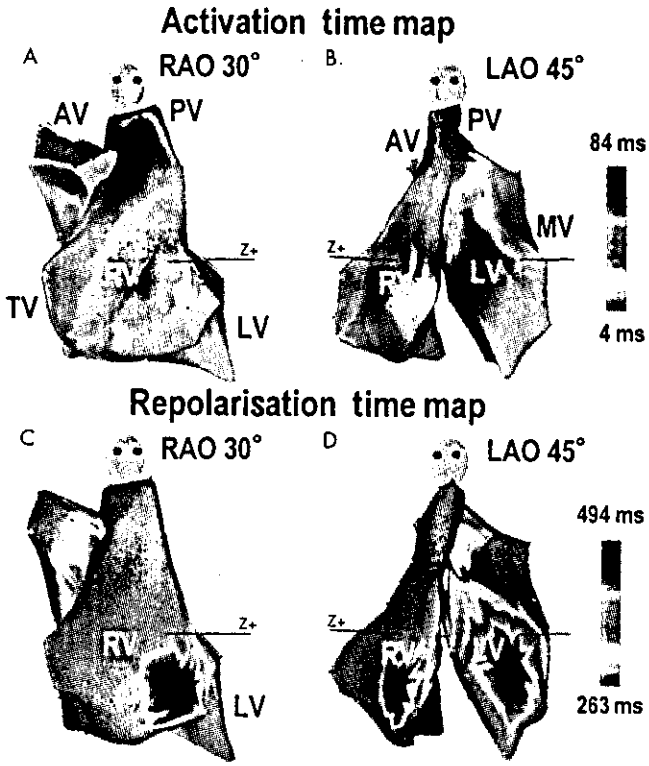

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Detection of spatial repolarization abnormalities in patients with LQT1 and LQT2 forms of congenital long-QT syndrome

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Abstract

The aim of this study is to detect the spatial current dispersion that appears in the T-wave of patients with congenital long-QT syndrome (LQTS). To observe this dispersion, magnetocardiograms (MCGs)—which have a high spatial resolution—of LQT1 patients ($n = 7$), LQT2 patients ($n = 9$) and a control group ($n = 33$) were recorded. The dispersion was evaluated by plotting current-arrow maps (CAMs) calculated from the MCG signals. In the case of LQT1, abnormal current arrows in the CAMs appeared above the inferior part of the heart in two LQT1 patients with a long corrected QT interval (QTc) (>0.6), and the current direction was from the left (origin side) to the right ventricular muscle (110°). In six out of nine LQT2 patients, abnormal current arrows with angles below 20° were observed above the right inferior part or lower septum; the current direction was from the right (origin side) to the left ventricular muscle. However, in the case of the LQT2 patients, the QTc values did not correlate with the abnormal current. These findings suggest that the origin of abnormal repolarization in LQT1 is the left ventricular muscle and the origin of that in LQT2 is the right ventricular muscle or lower septum. The estimation of the origin in LQTS patients can provide important information such as the risk factor of sudden death.

Keywords: long-QT syndrome, magnetocardiogram, current-arrow map

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1. Introduction

Long-QT syndrome (LQTS) is characterized by a prolonged QT interval in an electrocardiogram (ECG). Moreover, it causes an atypical polymorphic ventricular tachycardia known as *Torsade de Pointes* (TdP) (Schwartz *et al* 1975, Moss *et al* 1985, Zipes 1991, Shimizu *et al* 1991, Shimizu and Antzelevitch 1997, Vos *et al* 2000, Fujiki *et al* 2001). To clarify the mechanism that produces TdP, monophasic action potentials (MAPs) in the right and left ventricular endocardium of LQTS patients have been recorded (Shimizu *et al* 1994, 1995, 1998). These examinations suggested that early afterdepolarizations (EADs) could be associated with TdP, which causes sudden death, because premature ventricular contraction occurs after the appearance of the EAD peak and initiates the TdP. Furthermore, their findings suggest that the EADs play an important role in the exaggeration of long QT intervals.

Furthermore, to clarify the regional and transmural differences in the electrophysiology of a ventricular cell, LQTS models based on an arterially perfused wedge of a canine left ventricle (LV) have been investigated (Shimizu and Antzelevitch 1997, 1998, 1999, 2000, Yan and Antzelevitch 1998, Shimizu *et al* 1999). Using the wedge LQT1 model, these studies found that action potential duration (APD) during transmembrane activity in M cells is prolonged and transmural dispersion of repolarization (TDR) increases. It was suggested that the LQT1 waveform has a broad-based T-wave because of the increased TDR (Shimizu and Antzelevitch 1998). The LQT2 model suggested that APDs during transmembrane activity of all epicardials, M cells, and endocardials are prolonged. So TDR does not increase; therefore, the LQT2 waveform has a notched low-amplitude T-wave shape (Shimizu and Antzelevitch 1997).

In addition, three forms of the congenital LQTS (LQT1, LQT2 and LQT3) have been identified by genetic-linkage analysis (Wang *et al* 1995, 1996, Curran *et al* 1995). The causes of these forms are mutations in ion-channel genes located on chromosomes 3 (*SCN5A*), 7 (*HERG*) and 11 (*KvLQT1*).

Although the above-mentioned animal and MAPs examinations are very useful for investigating the regional and transmural mechanism of the T-wave of LQTS models, the two-dimensional spatial mechanism in the whole heart of LQTS patients is still unclear.

A magnetocardiogram (MCG) can visualize a pseudo current distribution in the heart, because tangential components of the magnetic field (or a tangential vector calculated from the normal component of a magnetic field) show a pattern of peaks immediately above an electrically activated region (Hosaka and Cohen 1976, Tsukada *et al* 1998, 1999, Miyashita *et al* 1998, Horigome *et al* 1999). Therefore, we have applied foetus (Kandori *et al* 1999a, 1999b, 2001c, 2002) and adult MCGs to diagnose heart diseases (Kandori *et al* 2001a, 2001b, Tsukada *et al* 2000a, 200b). In particular, with the aim of preventing sudden death in the uterus, MCGs of foetuses with LQTS can be measured (Kandori *et al* 2001c). On the other hand, although MCG signals of adult LQTS patients have been analysed by the one-dipole model (Schmitz *et al* 1998), the cause of repolarization abnormality is still unclear. To clarify the spatial mechanism of T-wave abnormality in genetically identified LQT1 and LQT2 syndromes, we recorded MCG signals from LQT1 and LQT2 patients and analysed them by using a current-arrow map (CAM), which is an empirical method that creates a two-dimensional map of pseudo currents.

Table 1. Electrophysiological characteristics of control group and patients with long-QT syndrome.

Patient	Age (years)	Sex	RR (ms)	QT (ms)	QTc (ms)	Abnormality
			LQT1 group			
1	37	F	1100	678	646	+
2	30	F	1100	428	408	–
3	9	F	800	612	684	+
4	34	F	1020	523	518	–
5	19	F	1050	466	455	–
6	16	F	930	458	475	–
7	54	F	1150	521	486	–
Mean ± SD	28 ± 15	M/F = 0/7	1021 ± 121	527 ± 90	525 ± 102	
			LQT2 group			
8	61	F	1400	635	537	+
9	27	M	1050	524	511	+
10	33	F	1100	606	578	–
11	25	F	1100	615	586	–
12	22	F	1200	514	469	+
13	33	F	920	566	590	+
14	32	M	809	453	504	+
15	21	F	1208	652	593	–
16	19	M	996	561	562	+
Mean ± SD	30 ± 13	M/F = 3/6	1087 ± 173	570 ± 65	548 ± 45	
			Control group			
Mean ± SD	32 ± 7	M/F = 16/17	959 ± 156	400 ± 30	411 ± 24	

2. Materials and methods

2.1. Subjects

Electrocardiographic data of the LQT1 and LQT2 patients and normal control volunteers are listed in table 1. There were seven LQT1 patients (all females, 9–54 years old) and nine LQT2 patients (six females and three males, 19–61 years old). Thirty-three healthy volunteers (17 females and 16 males, 22–48 years old) with no history of cardiac disease were included as a control. In table 1, the ages of the volunteers and patients with LQT1 and LQT2 match well, the average RR interval of the LQT1 and LQT2 patients is longer than that of the controls, and the average QT interval and the average corrected QT interval (QTc) are longer than those of the control group. QTc was calculated from Bazett's formula ($QTc = QT/\sqrt{RR}$). The characteristics of individual LQT patients are also listed in table 1. Note that all data in table 1 were obtained from MCG signals.

2.2. Magnetocardiographic study

MCG signals over a period of 30 min were recorded by using a SQUID (superconducting quantum interference device) system (MC-6400, Hitachi, Ltd) with a 64-coaxial gradiometer (Tsukada *et al* 1998, Kandori *et al* 2001a, 2001b). This system was installed in a magnetically shielded room with a double Mumetal layer. Figure 1 shows the measurement plane in a subject's chest. The sensor array is an 8 × 8 matrix on a flat plane with a pitch of 25 mm. Each sensor incorporates a first-order gradiometer comprising an 18 mm diameter bobbin with a 50 mm long baseline.

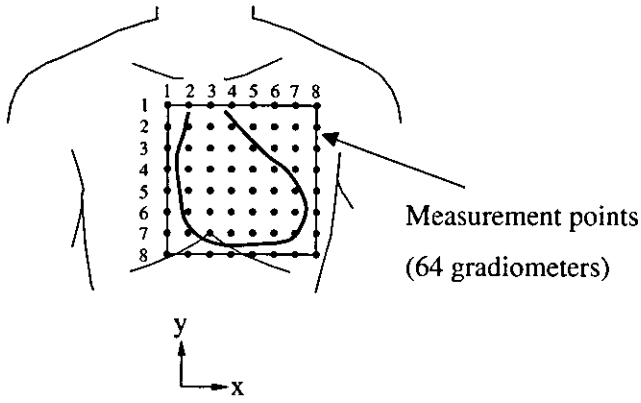

Figure 1. MCG measurement area (8 × 8 matrix) above the heart. The position of the sensor (line 7, row 3) is set above the xiphoidstumum.

The MCG waveforms of each patient and volunteer were averaged 20–30 times by using an R-wave peak as a trigger. The averaged overlapped waveforms (as shown in figure 2(b)) were used to manually determine a Q onset and a T end, from which the QT intervals listed in table 1 were calculated.

Our MCG system (MC-6400) can produce a CAM, which visualizes a pseudo current pattern in a heart, from the derivatives of the normal component (B_z) of the MCG signals (Miyashita *et al* 1998, Kandori *et al* 2001a, 2001b) as

$$I_x = \mathrm{d}B_z/\mathrm{d}y \tag{1}$$

and

$$I_y = -\mathrm{d}B_z/\mathrm{d}x. \tag{2}$$

The magnitude of the current arrows $\left(I = \left(I_x^2 + I_y^2\right)^{1/2}\right)$ is plotted as a contour map. Although the CAM maps cannot depict actual-current flow and localize activity in the heart, they have the clinical utility to diagnose the heart disease or investigate its mechanism.

Repolarization abnormalities of LQTS patients were determined by producing the CAM of a T-wave. Namely, the abnormalities were justified visually when a current arrow with an abnormal direction was visible. To evaluate the angle as a number, the direction of the current arrow corresponding to the maximum T-wave was detected. The angle of the current arrow (see figure 5) is expressed as an electrical axis, which is commonly used in ECG study.

3. Results

3.1. CAM pattern of the normal control group

In the case of the normal control group, 64 waveforms in a two-dimensional plane were obtained as shown in figure 2(a). In this figure, waveforms of the QRS complex and the T-wave have two characteristics: the left lower part of the plane contains negative waveforms, and the right upper part of the plane contains positive waveforms of the QRS complex and T-wave. The overlapped waveforms of the 64 positions in figure 2(b) appear positive and negative. From the overlapped waveforms, the activation period of the T-wave can be confirmed. In figure 2(b), five lines are shown to indicate the times at which the five images shown in