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Sympathetic Stimulation Produces a Greater Increase in Both Transmural and Spatial Dispersion of Repolarization in LQT1 Than LQT2 Forms of Congenital Long QT Syndrome

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OBJECTIVES The study compared the influence of sympathetic stimulation on transmural and spatial dispersion of repolarization between LQT1 and LQT2 forms of congenital long QT syndrome (LQTS).

BACKGROUND Cardiac events are more associated with sympathetic stimulation in LQT1 than in LQT2 or LQT3 syndrome. Experimental studies have suggested that the interval between Tpeak and Tend (Tp-e) in the electrocardiogram (ECG) reflects transmural dispersion of repolarization across the ventricular wall.

METHODS We recorded 87-lead body-surface ECGs before and after epinephrine infusion (0.1 μg/kg/min) in 13 LQT1, 6 LQT2, and 7 control patients. The Q-Tend (QT-e), Q-Tpeak (QT-p), and Tp-e were measured automatically from 87-lead ECGs, corrected by Bazett's method (QTc-e, QTc-p, Tcp-e), and averaged among all 87-leads and among 24-leads, which reflect the potential from the left ventricular free wall. As an index of spatial dispersion of repolarization, the dispersion of QTc-e (QTc-eD) and QTc-p (QTc-pD) were obtained among 87-leads and among 24-leads, and were defined as the interval between the maximum and the minimum of the QTc-e and the QTc-p, respectively.

RESULTS Epinephrine significantly increased the mean QTc-e but not the mean QTc-p, resulting in a significant increase in the mean Tcp-e in both LQT1 and LQT2, but not in control patients. The epinephrine-induced increases in the mean QTc-e and Tcp-e were larger in LQT1 than in LQT2, and were more pronounced when the averaged data were obtained from 24-leads than from 87-leads. Epinephrine increased the maximum QTc-e but not the minimum QTc-e, producing a significant increase in the QTc-eD in both LQT1 and LQT2 patients, but not in control patients. The increase in the QTc-eD was larger in LQT1 than in LQT2 patients.

CONCLUSIONS Our data suggest that sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than in LQT2 syndrome, and this may explain why LQT1 patients are more sensitive to sympathetic stimulation. (J Am Coll Cardiol 2001;37:911–9) © 2001 by the American College of Cardiology

The congenital long QT syndrome (LQTS) is a hereditary disorder associated with prolonged ventricular repolarization (QT interval) and life-threatening polymorphic ventricular tachycardia, torsade de pointes (TdP) (1–5). Recent genetic studies have shown that congenital LQTS is a primary electrical disease caused by mutation in specific ion channel genes (6–8). Mutations in *KCNQ1* and *KCNE1* are responsible for defects in the slowly activating component of the delayed rectifier potassium current (I_{Ks}) that underlies the LQT1 and LQT5 forms of the LQTS, whereas mutations in *HERG* and *KCNE2* are responsible for defects in the rapidly activating component of the delayed rectifier potassium current (I_{Kr}) responsible for LQT2 and LQT6. Mutations in *SCN5A* alter the function of the sodium channel (I_{Na}) responsible for LQT3.

Sympathetic stimulation has long been appreciated to play a pivotal role in the genesis of QT prolongation and TdP in some forms of congenital LQTS (4). Among the LQT1, LQT2, and LQT3 forms of LQTS, cardiac events are more likely to be associated with sympathetic stimulation (physical or emotional stress) in the LQT1 than in either LQT2 or LQT3 syndrome. Exercise-related events seem to dominate the clinical picture in LQT1 (9). In

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Abbreviations and Acronyms

APD	= action potential duration
ECG	= electrocardiogram
LQTS	= long QT syndrome
QTc-e	= corrected Q-Tend interval
QTc-p	= corrected Q-Tpeak interval
QTc-eD	= dispersion of QTc-e
QTc-pD	= dispersion of QTc-p
QT-e	= Q-Tend interval
Tcp-e	= corrected interval between Tpeak and Tend
TdP	= torsade de pointes
TDR	= transmural dispersion of repolarization

contrast, a sudden startle in the form of an auditory stimulus (alarm clock) is the predominant trigger of cardiac events in LQT2 (10), whereas cardiac events usually occur at rest or during sleep in LQT3 (9).

Spatial heterogeneity of repolarization represented by QT dispersion has been proposed as a marker of electrical instability under several conditions, including LQTS (11–13). Conversely, a growing number of studies have focused on transmural heterogeneity of repolarization across the ventricular wall (epicardial, mid-myocardial (M), and endocardial cells) and have suggested that an amplified transmural dispersion of repolarization (TDR) was linked to ventricular arrhythmias such as TdP under long QT conditions (14–24). Recent experimental studies using arterially perfused canine left ventricular wedge have suggested that both the peak and the end of the T wave in the electrocardiogram (ECG) are coincident with repolarization of epicardial and maximal M-cell action potentials, respectively, so that the interval between the Tpeak and Tend (Tp-e) reflects TDR (16–21).

In the present study, we recorded 87-lead body-surface mapping before and after infusion of epinephrine, an alpha + beta-adrenergic agonist, in patients with LQT1 and LQT2 syndrome, to compare the influence of sympathetic stimulation on both transmural and spatial dispersion of repolarization between LQT1 and LQT2 syndrome.

METHODS

Patient population. The study population included 13 patients afflicted with LQT1 syndrome (*KCNQ1* mutation, 7 unrelated families), 6 patients with LQT2 syndrome (*HERG* mutation, 3 unrelated families) and 7 healthy volunteers as a control group. Seven LQT1 families had seven discrete missense mutations, and three LQT2 families had three discrete mutations. The LQT1 group consisted of 10 females and 3 males, ranging in age from 6 to 54 years (mean, 25 ± 17 years). The LQT2 group included 5 females and 1 male, ranging in age from 19 to 60 years (mean, 31 ± 16 years). The control group included 4 females and 3 males, ranging in age from 13 to 51 years old (mean, 30 ± 12 years).

87-lead body-surface mapping. All protocols were reviewed and approved by our Ethical Review Committee, and informed consent was obtained from all patients. All antiarrhythmic medications were discontinued for at least five drug half-lives. Body-surface potential mapping was recorded with a VCM-3000 (Fukuda Denshi, Tokyo, Japan) (25). Eighty-seven body-surface leads were arranged in a lattice-like pattern (13 × 7 matrix), except for four leads on the midaxillary 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 ECGs 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 recording. These ECG data were scanned with multiplexers and digitized using analog-digital converters with a sampling rate of 1,000 samples/second/channel. The digitized data were stored on a floppy disk and transferred to a personal computer (PC-9821 Xv13, NEC, Tokyo, Japan) with the analysis program developed by our institution.

Measurements. Eighty-seven-lead body-surface ECGs were analyzed using a semiautomated digitizing program. The Q-Tend interval (QT-e) was defined as the time interval between the QRS onset and the point at which the isoelectric line intersected a tangenital line drawn at the maximal downslope of the positive T-wave or at the maximal upslope of the negative T-wave. The Q-Tpeak 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 the T-wave had a biphasic or a notched configuration, the peak of the T-wave was defined as that of the dominant T-wave. The QT-e, the QT-p, and the Tp-e (QT-e minus QT-p) as an index of TDR were measured automatically from all 87-lead ECGs, corrected to heart rate by Bazett's method (QTc-e [corrected Q-Tend interval] QTc-p [corrected Q-Tpeak interval] Tcp-e:

$$\text{QT-e}/\sqrt{\text{RR}},\ \text{QT-p}/\sqrt{\text{RR}},\ \text{Tp-e}/\sqrt{\text{RR}},$$

and averaged among all 87-leads and among 24-leads (rows G–K, columns 2–6), which are thought to reflect the potential from the left ventricular free wall. The Tcp-e/QTc-e ratio was also calculated. Each point determined by the computer was checked visually and edited manually for each lead. The maximum (max) and the minimum (min) of the QTc-e and the QTc-p were also obtained from all 87-leads and among 24-leads. As an index of spatial dispersion of repolarization, dispersion of the QTc-e (QTc-eD) and dispersion of the QTc-p (QTc-pD) were obtained from 87-leads and from 24-leads, and were defined as the interval between the max and the min of the QTc-e and the QTc-p, respectively.

Epinephrine administration. Epinephrine (0.1 μg/kg), an alpha + beta-adrenergic agonist, was injected and was followed by continuous infusion at a constant rate of

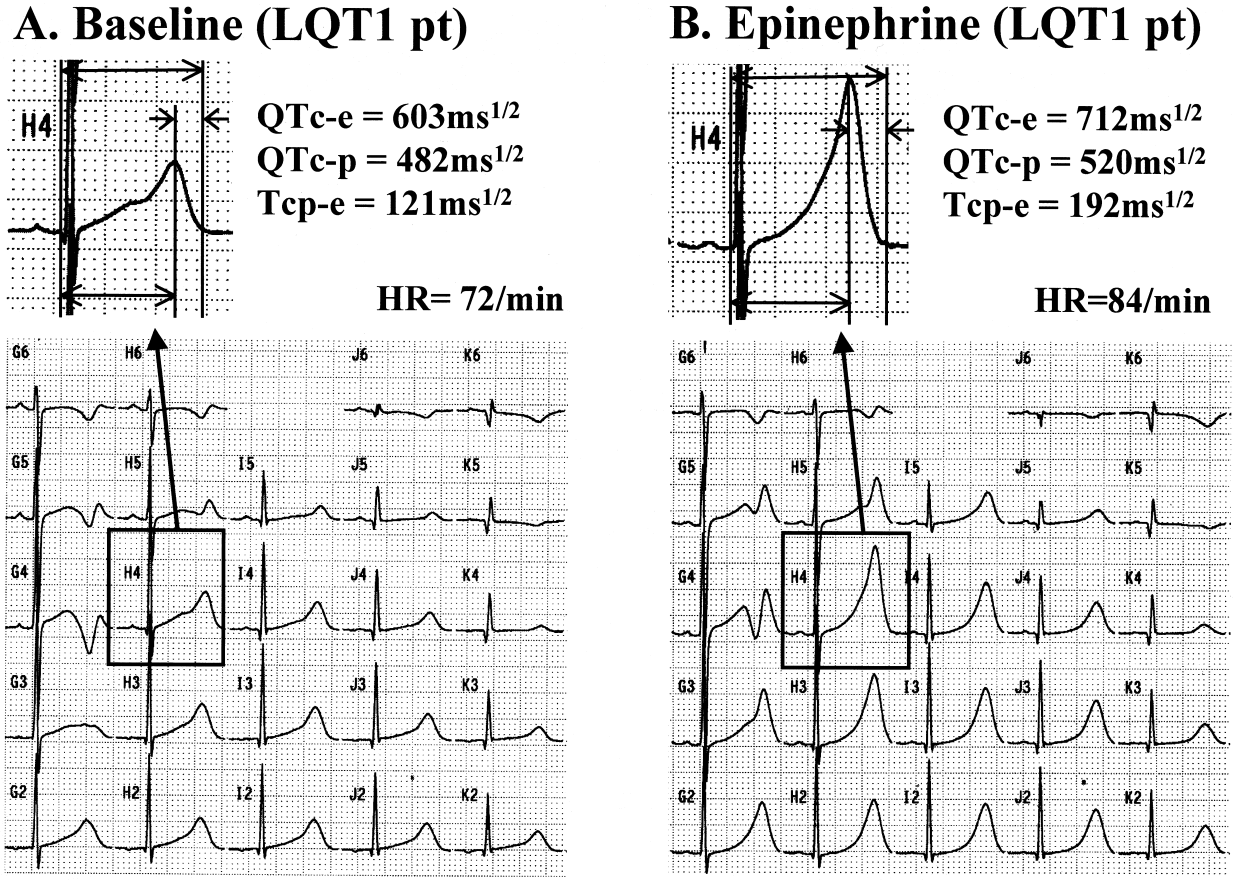

Figure 1. Twenty-four-lead ECGs (G–K: 2–6) that are expected to reflect the potential from the left ventricular free wall under baseline condition **(A)** and during epinephrine infusion **(B)** in a patient (pt) with LQT1 syndrome. A representative ECG (H4) is shown on the upper trace in each panel. The ECGs showed broad-based T waves commonly observed in LQT1 patients. Both the QTc-e and QTc-p were prolonged (603, 482 $ms^{1/2}$) and the Tcp-e was increased (121 $ms^{1/2}$) under the baseline condition **(A)**. Epinephrine produced a prominent prolongation in the QTc-e (712 $ms^{1/2}$), but a mild prolongation in the QTc-p (520 $ms^{1/2}$), resulting in a dramatic increase in the Tcp-e (192 $ms^{1/2}$) **(B)**.

0.1 μg/kg/min in all group patients. Body-surface mapping was recorded during sinus rhythm under baseline conditions and at steady-state conditions of catecholamine (3 to 5 min after epinephrine infusion), in which both the RR and QT intervals reached steady state.

Statistical analysis. Data are reported as the mean ± SD. Two-way repeated-measures ANOVA followed by the Scheffé test was used to compare measurements made before and after epinephrine administration, and to compare each parameter among LQT1, LQT2, and control patients. Differences of each parameter before and after epinephrine were compared among the three groups by using one-way ANOVA followed by the Scheffé test. A value of $p < 0.05$ was regarded as significant.

RESULTS

There were no significant differences in the heart rate among the three groups both before and after epinephrine (before epinephrine: LQT1, 64 ± 7/min; LQT2, 56 ± 12/min; control, 65 ± 9/min; after epinephrine: LQT1, 75 ± 7/min; LQT2, 63 ± 9/min; control, 73 ± 9/min).

Influence of epinephrine on TDR. Figure 1 illustrates 24-lead ECGs (G–K: 2–6), which are expected to reflect the potential from the left ventricular free wall before and after epinephrine in a patient with LQT1 syndrome. A representative ECG (H4 in this case) is shown on the upper trace in each panel. The ECGs showed broad-based T-waves commonly observed in LQT1 patients. Both the QTc-e and the QTc-p were prolonged (603, 482 $ms^{1/2}$) and the Tcp-e was increased (121 $ms^{1/2}$) under the baseline condition. Epinephrine produced a prominent prolongation in the QTc-e (712 $ms^{1/2}$), but a mild prolongation in the QTc-p (520 $ms^{1/2}$), resulting in a dramatic increase in the Tcp-e (192 $ms^{1/2}$). Figure 2 illustrates 24-lead ECGs before and after epinephrine in a patient with LQT2 syndrome. A representative ECG (I4 in this case) is shown on the upper trace in each panel, depicting low-amplitude T wave with notched appearance commonly seen in LQT2 syndrome. As in the LQT1 patient, the QTc-e and the QTc-p were prolonged (518, 414 $ms^{1/2}$) and the Tcp-e was increased (104 $ms^{1/2}$) under the baseline condition. Epinephrine produced a moderate prolongation in the QTc-e (618 $ms^{1/2}$) and the QTc-p (494 $ms^{1/2}$), resulting in a mild increase in the Tcp-e (124 $ms^{1/2}$). Figure 3 illustrates 24-lead ECGs before and after epinephrine in a control patient. A representative ECG (H4 in this case) is shown on

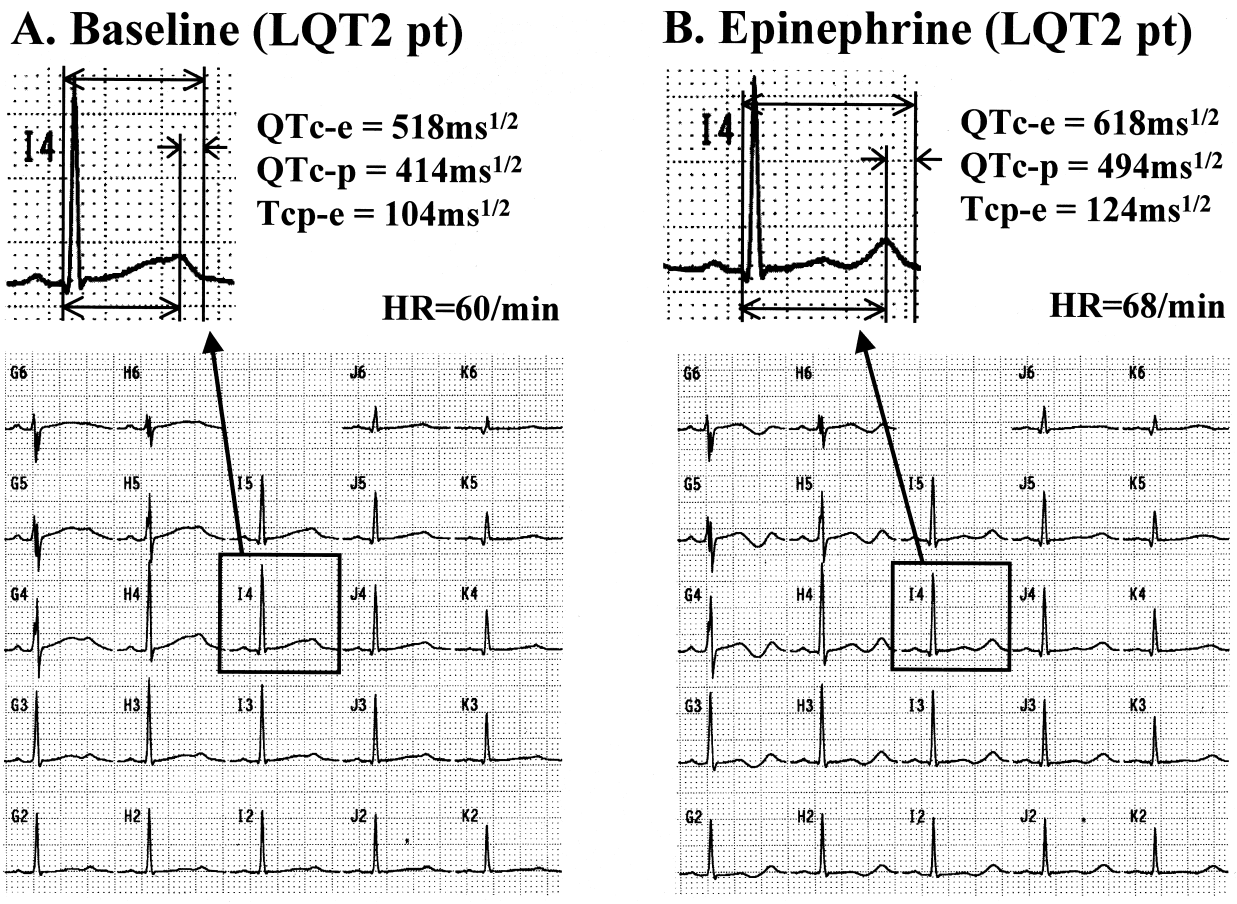

Figure 2. Twenty-four-lead ECGs (G–K: 2–6) under baseline condition **(A)** and during epinephrine infusion **(B)** in a patient (pt) with LQT2 syndrome. A representative ECG (I4) is shown on the upper trace in each panel. The ECGs showed low-amplitude T wave with a notched appearance commonly seen in LQT2 patients. The QTc-e and QTc-p were prolonged (518, 414 $ms^{1/2}$) and the Tcp-e was increased (104 $ms^{1/2}$) under the baseline condition **(A)**. Epinephrine produced a moderate prolongation in the QTc-e (618 $ms^{1/2}$) and the QTc-p (494 $ms^{1/2}$), resulting in a mild increase in the Tcp-e (124 $ms^{1/2}$) **(B)**.

the upper trace in each panel. The QTc-e and the QTc-p were much shorter (396, 314 $ms^{1/2}$) and the Tcp-e was smaller (82 $ms^{1/2}$) than those in the LQT1 and LQT2 patients under the baseline condition. Epinephrine produced no significant changes in the QTc-e (410 $ms^{1/2}$), the QTc-p (325 $ms^{1/2}$), and the Tcp-e (85 $ms^{1/2}$).

Changes in the mean QTc-e, QTc-p, Tcp-e, and Tcp-e/QTc-e ratio, which were averaged among 87-lead ECG before and after epinephrine administration, are summarized in Table 1. The mean QTc-e, QTc-p, Tcp-e, and Tcp-e/QTc-e ratios before epinephrine were larger in LQT1 and LQT2 patients than in control patients ($p < 0.05$). There were no significant differences in these baseline parameters between LQT1 and LQT2 patients. Figure 4 shows composite data of the differences before and after epinephrine in the mean QTc-e, QTc-p, Tcp-e, and Tcp-e/QTc-e ratios, which were averaged among 87-leads, in LQT1, LQT2, and control patients. The changes in the mean QTc-e with epinephrine were largest in LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients, whereas changes in the mean QTc-p were not different among the three groups. As a consequence, changes in the Tcp-e and the Tcp-e/QTc-e ratios were largest in LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients. When the same parameters were averaged among 24-leads, reflecting the potential from the left ventricular wall, the changes in the mean QTc-e, Tcp-e, and Tcp-e/QTc-e ratio in LQT1 and LQT2 patients were more pronounced than those that were averaged among all 87-leads.

Influence of epinephrine on spatial dispersion of repolarization. Changes in the max QTc-e, min QTc-e, QTc-eD, max QTc-p, min QTc-p, and QTc-pD, which were obtained from 87-lead ECGs, before and after epinephrine administration, are summarized in Table 2. All parameters except QTc-pD before epinephrine were larger in LQT1 and LQT2 patients than in control patients ($p < 0.05$). There were no significant differences in these baseline parameters between LQT1 and LQT2 patients. Figure 5 shows composite data of the differences before and after epinephrine in the max QTc-e, min QTc-e, QTc-eD, max QTc-p, min QTc-p, and QTc-pD, which were obtained from 87-leads in LQT1, LQT2, and control patients. The changes in the max QTc-e with epinephrine were largest in

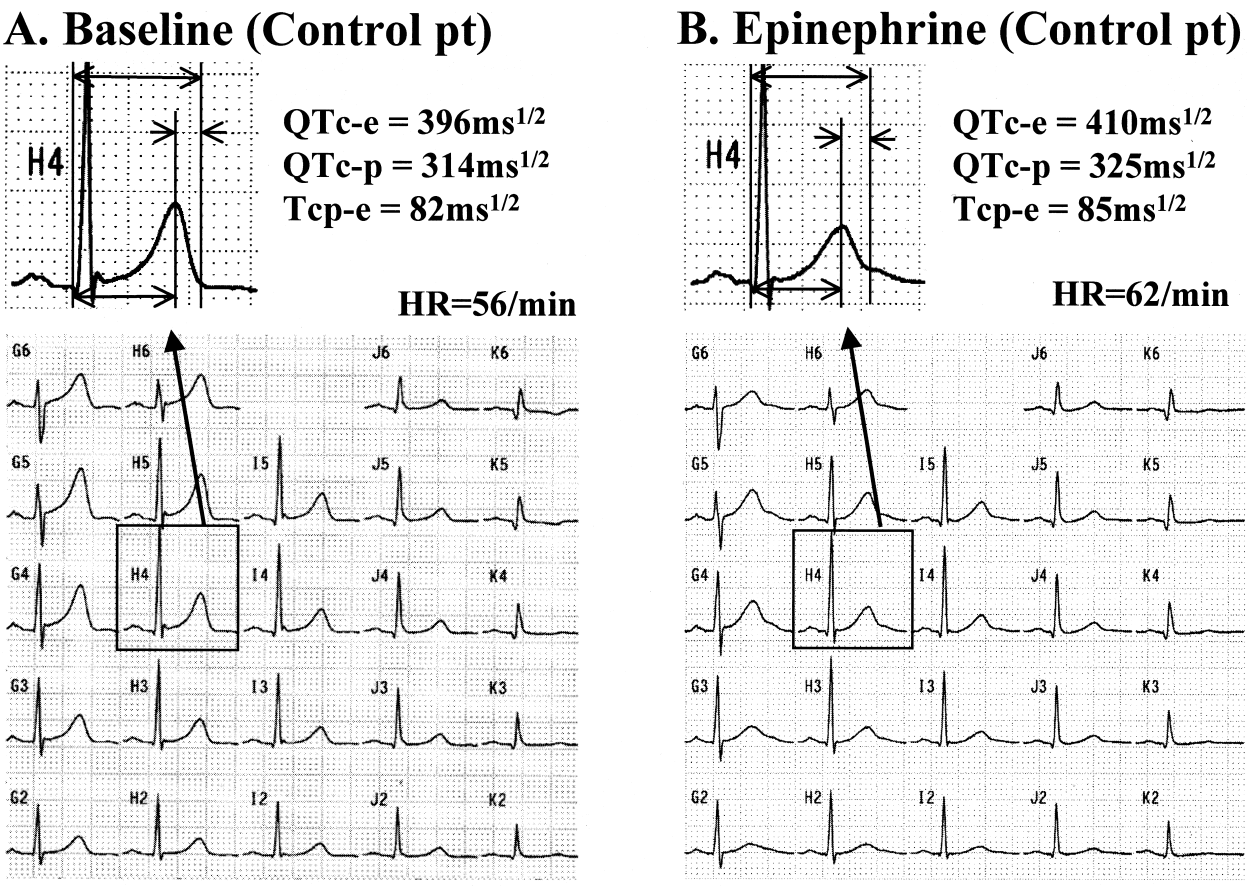

Figure 3. Twenty-four-lead ECGs (G–K: 2–6) under baseline condition **(A)** and during epinephrine infusion **(B)** in a control patient (pt). A representative ECG (H4) is shown on the upper trace in each panel. The QTc-e and QTc-p were much shorter (396, 314 $ms^{1/2}$) and the Tcp-e was smaller (82 $ms^{1/2}$) than those in LQT1 and LQT2 patients under the baseline condition **(A)**. Epinephrine produced no significant changes in the QTc-e (410 $ms^{1/2}$), the QTc-p (325 $ms^{1/2}$), and the Tcp-e (85 $ms^{1/2}$).

LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients, whereas changes in the min QTc-e were not different between LQT1 and LQT2 patients, but significantly larger than those in control patients. As a consequence, the changes in the QTc-eD were larger in LQT1 patients than those in LQT2 and control patients. Conversely, no significant differences were seen in the changes in the max QTc-p, min QTc-p, and QTc-pD among the three groups. When the same parameters were obtained from 24-leads, reflecting the potential from the left ventricular wall, changes in the parameters were similar to those obtained from all 87-leads.

DISCUSSION

Transmural and spatial dispersion of repolarization in LQT1 and LQT2 syndrome. The congenital LQTS is characterized by a prolonged QT interval and TdP, which often cause severe symptoms such as syncope or sudden cardiac death (1–5). In addition to prolonged QT interval, QT dispersion, measured as interlead variability of the QT

Table 1. Epinephrine-Induced Changes in the Mean QTc-e, the Mean QTc-p, the Mean Tcp-e, and the Mean Tcp-e/QTc-e Ratio, Which Are Averaged Among All 87-Leads, in LQT1, LQT2, and Control Patients

	Mean QTc-e		Mean QTc-p		Mean Tcp-e		Mean Tcp-e/QTc-e ratio	
	Before	After	Before	After	Before	After	Before	After
LQT1 pts (n = 13)	543 ± 64‡	618 ± 63*†	406 ± 49‡	419 ± 48‡	136 ± 29‡	198 ± 33*†	0.25 ± 0.04‡	0.32 ± 0.04*†
LQT2 pts (n = 6)	532 ± 33‡	580 ± 24*‡	400 ± 16‡	406 ± 18‡	131 ± 21‡	173 ± 13*‡	0.25 ± 0.03‡	0.30 ± 0.2*‡
Control pts (n = 7)	400 ± 19	397 ± 18	321 ± 19	314 ± 15	78 ± 7	82 ± 6	0.19 ± 0.02	0.20 ± 0.01

*$p < 0.05$ vs. before. †$p < 0.05$ vs. LQT2 pts. $p < 0.005$ vs. Control pts. ‡$p < 0.05$ vs. Control pts.
pts = patients; QTc-e = corrected Q-Tend interval; QTc-p = corrected Q-Tpeak interval; Tpc-e = corrected Tpeak-Tend interval.

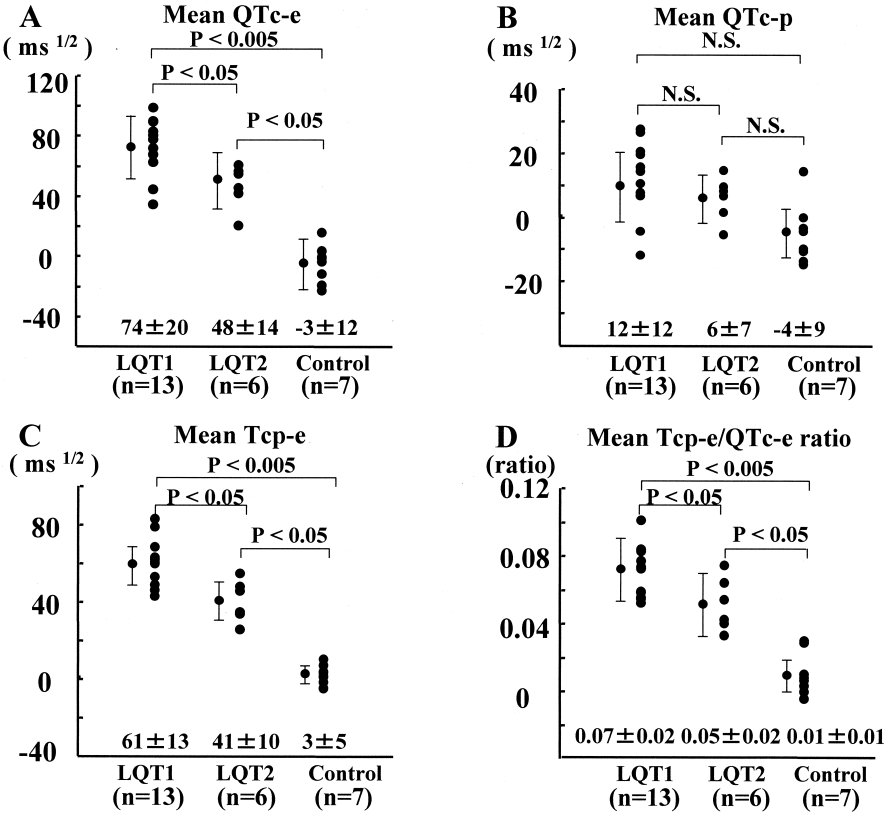

Figure 4. Comparison of the differences before and after epinephrine in the mean QTc-e **(A)**, QTc-p **(B)**, Tcp-e **(C)**, and Tcp-e/QTc-e ratio **(D)**, which were averaged among 87-leads, in LQT1, LQT2, and control groups. The changes in the mean QTc-e with epinephrine were largest in LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients **(A)**, whereas changes in the mean QTc-p were not different among the three groups **(B)**. As a consequence, the changes in the Tcp-e **(C)** and Tcp-e/QTc-e ratio **(D)** were largest in LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients.

interval, is believed to be a marker of spatially heterogeneous ventricular repolarization and electrical instability. Although several clinical studies have reported an increased QT dispersion in the congenital LQTS (11–13), recent experimental studies have suggested an important role of transmural electrical heterogeneity—that is, TDR across the ventricular wall in the generation of TdP under long QT conditions (15–24). Experimental studies have suggested that the Tp-e in each ECG lead serves as an index of TDR across the ventricle of which the ECG lead reflects the potential (16–21). In contrast, the QT dispersion is thought to provide an index of interventricular differences in the repolarization of M regions throughout the ventricle (spatial dispersion of repolarization) (26).

Under the baseline condition in the present study, the max QTc-e, min QTc-e, QTc-eD, max QTc-p, min QTc-p, and QTc-pD were larger in LQT1 and LQT2 patients than in control patients, consistent with previous clinical studies (11–13). It is noteworthy that both QTc-eD and QTc-pD were comparable between LQT1 and LQT2 patients in the setting of similar values of the QTc-e and the QTc-p in our study population. To our best knowledge, our study is the first one to compare the QTc-eD and QTc-pD between LQT1 and LQT2 syndrome. With regard to TDR, the Tcp-e as well as Tcp-e/QTc-e ratio were larger in LQT1 and LQT2 patients than in control patients. Once again, no significant differences existed in the Tcp-e between LQT1 and LQT2 patients. These data suggest that both transmural and spatial dispersion of repolarization are increased in patients with congenital LQTS, but that no significant differences were observed between LQT1 and LQT2 syndrome under baseline conditions without strong sympathetic stimulation.

Influence of sympathetic stimulation on transmural and spatial dispersion of repolarization in LQT1 and LQT2 syndrome. Physical exercise and strong emotion are known to precipitate syncope and sudden cardiac death in patients with congenital LQTS (3–5). Several experimental models of LQTS (27) and clinical studies (4,28) have suggested that catechoalmine-enhanced early after depolarizations and triggered activity both play a pivotal role in the genesis of QT prolongation and TdP. However, conditions that give rise to early after depolarizations and triggered activity also produce a marked dispersion of ventricular repolarization in this syndrome (5).

Among three forms of congenital LQTS, the LQT1 syndrome is reported clinically as well as experimentally to be more sensitive to sympathetic stimulation and more responsive to beta-blockers than either LQT2 or LQT3 syndrome (9,17,20). Sympathetic (beta-adrenergic) stimu-

Table 2. Epinephrine-Induced Changes in the max QTc-e, the min QTc-e, the QTc-eD, the max QTc-p, the min QTc-p, and the QTc-pD, Which Are Obtained From all 87-Leads, in the LQT1, LQT2, and Control Patients

	Max QTc-e		Min QTc-e		QTc-eD		Max QTc-p		Min QTc-p		QTc-pD	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
LQT1 pts (n = 13)	585 ± 68‡	675 ± 64*†	491 ± 63‡	512 ± 68‡	93 ± 26‡	162 ± 34*†	439 ± 49‡	447 ± 57‡	356 ± 50‡	360 ± 57‡	82 ± 9	87 ± 17
LQT2 pts (n = 6)	597 ± 31‡	636 ± 32*‡	495 ± 29‡	521 ± 30‡	102 ± 16‡	116 ± 9*‡	450 ± 18‡	452 ± 24‡	358 ± 21‡	359 ± 18‡	92 ± 16	93 ± 12
Control pts (n = 7)	422 ± 21	425 ± 16	368 ± 22	364 ± 17	53 ± 7	61 ± 13	350 ± 18	352 ± 16	285 ± 17	279 ± 17	65 ± 10	73 ± 6

*$p < 0.05$ vs. before. †$p < 0.05$ vs. LQT2 pts. $p < 0.05$ vs. Control pts. ‡$p < 0.05$ vs. Control pts.
Max = maximum; Min = minimum; pts = patients; QTc-eD = dispersion of corrected Q-Tend interval; QTc-pD = dispersion of corrected Q-Tpeak interval.

lation is known to augment a number of currents, including Ca^{2+}-activated I_{Ks}, Ca^{2+}-activated chloride current ($I_{Cl(Ca)}$), and Na^+/Ca^{2+} exchange current ($I_{Na\text{-}Ca}$). An increase in net outward repolarizing current, due to a relatively large increase of I_{Ks} and $I_{Cl(Ca)}$ versus $I_{Na\text{-}Ca}$, is thought to be responsible for the abbreviation of action potential duration (APD) and QT interval in response to beta-adrenergic stimulation under normal conditions (5). A defect in I_{Ks} (especially in the M region) could offset this balance and account for failure of beta-adrenergic stimulation to abbreviate APD and QT interval in LQT1 syndrome (17). A recent experimental study by Shimizu and Antzelevitch (20) has elucidated the cellular basis for differential effects of beta-adrenergic stimulation in the LQT1, LQT2, and LQT3 models of the congenital LQTS. In the LQT1 model produced by an I_{Ks} blocker, chromanol 293B, beta-adrenergic stimulation with isoproterenol has been shown to prolong the QT interval and the APD of the M cell in which I_{Ks} is intrinsically small, but to abbreviate that of the epicardial and the endocardial cells, resulting in a persistent increase in TDR and in a widening of the T wave, as commonly seen in LQT1 patients (29). In contrast, isoproterenol initially prolonged and then abbreviated the QT interval and the APD of the M cell just above the control level, whereas the APD of the epicardial and the endocardial cells was constantly abbreviated, resulting in a transient increase in TDR. In the clinic, Sun and coworkers (30) recently reported that epinephrine markedly increased the QT-eD (dispersion of Q-Tend interval) as an index of spatial dispersion of repolarization in patients with LQTS. Commensurate with this, Priori et al. (13) have shown that the QT-eD was significantly reduced by left cardiac sympathetic denervation in LQTS patients who did not respond to beta-blockers.

In the present study, epinephrine increased the Tcp-e as an index of TDR in LQT1 patients much more than that in LQT2 patients; both were more pronounced than that in control patients. This was mainly due to much more prolongation of the mean QTc-e than that of the mean QTc-p in LQT1 patients, and was very compatible with the experimental data by Shimizu et al. (17,20). Our result showing significant increase in the QTc-eD with epinephrine in both LQT1 and LQT2 patients is consistent with the findings by Sun et al. (30). Furthermore, the changes in the QTc-eD with epinephrine in LQT1 patients were larger than those in LQT2 patients. These data suggest that strong sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than in LQT2 patients, and this may support the fact that LQT1 patients are much more at risk under strong sympathetic stimulation.

Comparison between 87-lead and 24-lead body-surface mapping recordings. The mean Tcp-e before and after epinephrine averaged among 24-leads, which are thought to reflect the potential from the left ventricular free wall, was greater than that averaged among all 87-leads in both

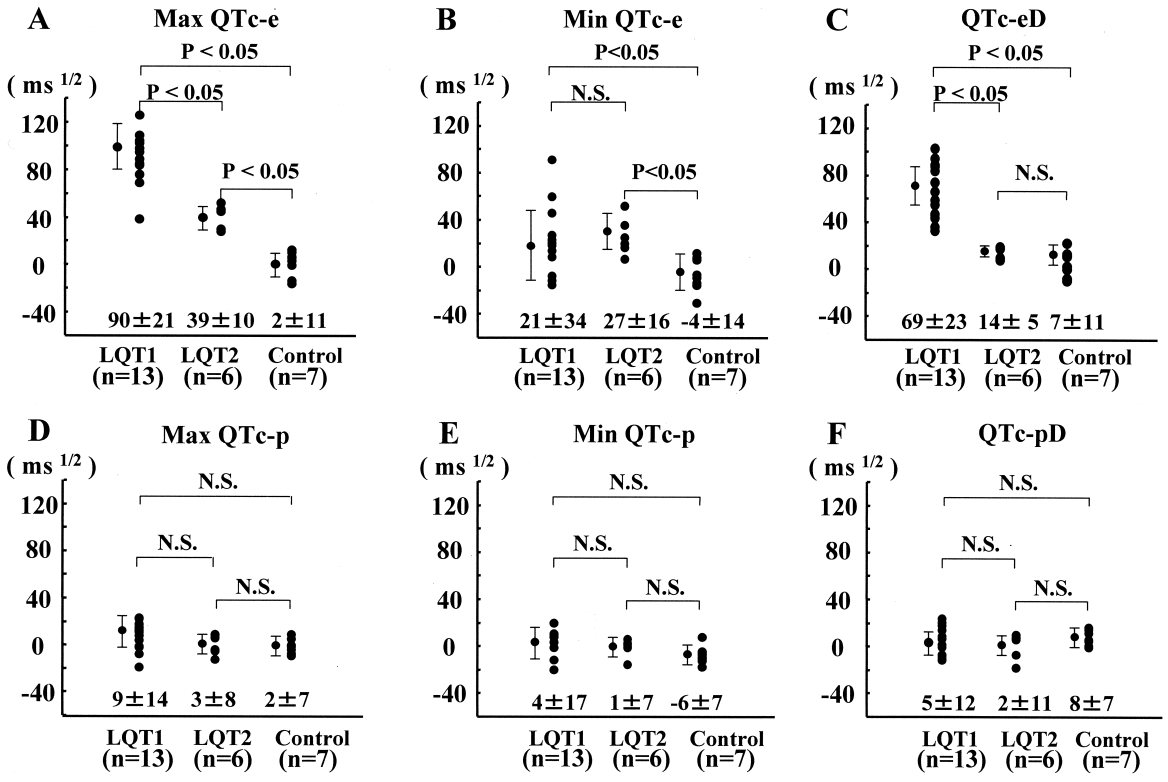

Figure 5. Comparison of the differences before and after epinephrine in the max QTc-e **(A)**, min QTc-e **(B)**, QTc-eD **(C)**, max QTc-p **(D)**, minQTc-p **(E)**, and QTc-pD **(F)**, which were obtained from 87-leads, in LQT1, LQT2, and control groups. Changes in the max QTc-e with epinephrine were largest in LQT1 patients, intermediate in LQT2 patients, and were not significant in control patients **(A)**, whereas changes in the min QTc-e were not different between LQT1 and LQT2 patients, but were significantly larger than those in control patients **(B)**. As a consequence, changes in the QTc-eD were larger in LQT1 patients than those in LQT2 and control patients **(C)**. In contrast, no significant differences were seen in the changes in the max QTc-p **(D)**, min QTc-p **(E)**, and QTc-pD **(F)** among the three groups.

LQT1 and LQT2 patients. In addition, the QTc-eD, which was defined as the difference between the max QTc-e and the min QTc-e, was comparable, when it was calculated from 24-leads and from 87-leads. Difficulties of the measurement of QT dispersion at the body surface are well-known problems of body-surface mapping, including the effects of distance from the heart and a summation of currents from various regions at any electrical site. For all that, our data indicate that both transmural and spatial dispersion of repolarization in the left ventricular free wall and probably ventricular septum are more pronounced, and this may be more important in the arrhythmogeneity in patients with LQT1 and LQT2 syndrome.

Conclusions. The present data suggest that sympathetic stimulation produces a significant increase in both transmural and spatial dispersion of repolarization in LQT1 and LQT2 syndrome but not in control patients. Moreover, the increase in the transmural and spatial dispersion of repolarization with epinephrine is greater in LQT1 than in LQT2 syndrome, providing further support of the fact why LQT1 patients are more sensitive to sympathetic stimulation.

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