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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} ($T_{p\text{-}e}$), 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} [$cT_{p\text{-}e}$]). 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 $cT_{p\text{-}e}$ 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 $cT_{p\text{-}e}$ 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

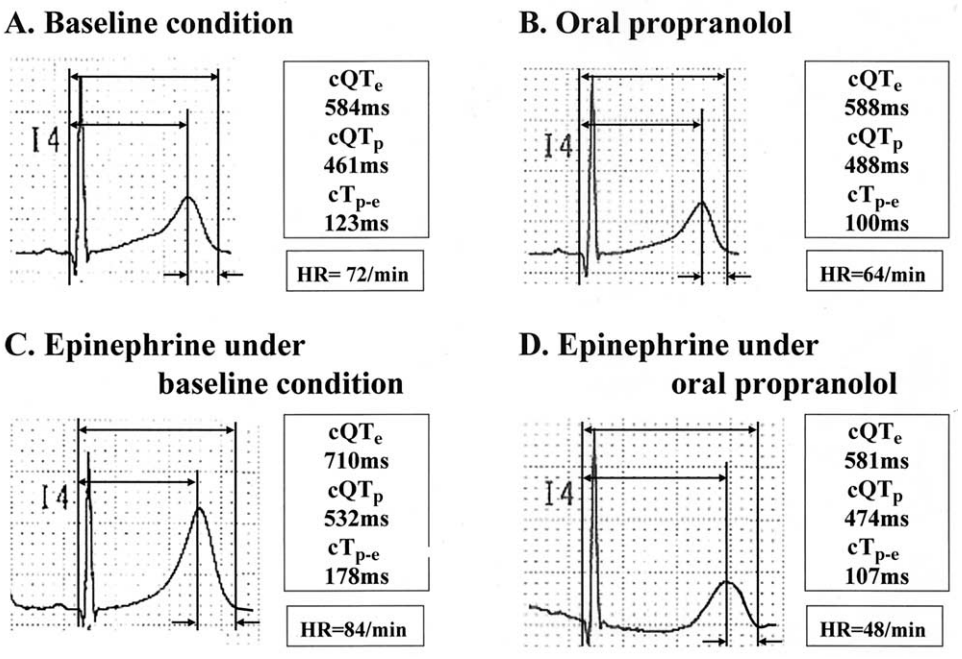

Figure 1. Electrocardiographic lead I4 of the body-surface map, which corresponds to lead V_6 of the standard 12-lead electrocardiogram, at the baseline condition **(A)**, with oral propranolol **(B)**, during epinephrine infusion at baseline **(C)** and during epinephrine infusion with oral propranolol **(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.

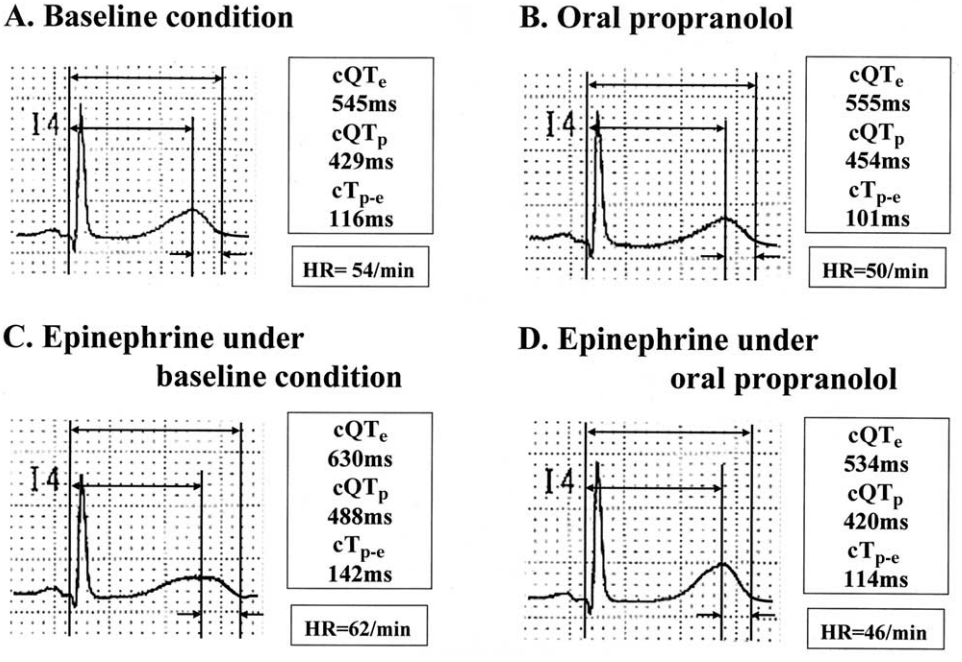

Figure 2. Electrocardiographic lead I4 of the body-surface map, at the baseline condition **(A)**, with oral propranolol **(B)**, during epinephrine infusion at baseline **(C)** and during epinephrine infusion with oral propranolol **(D)** in a patient with LQT2 syndrome. Both cQT_e and cQT_p were prolonged (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 $cT_{p\text{-}e}$ 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 $cT_{p\text{-}e}$ (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 $cT_{p\text{-}e}$ (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 $cT_{p\text{-}e}$ value. The differences in the mean cQT_p and mean $cT_{p\text{-}e}$ 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 $T_{p\text{-}e}$ 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 $cT_{p\text{-}e}$, Maximum cQT_e, Minimum cQT_e and cQT_e-D in the LQT1 and LQT2 Groups

	Mean cQT_e		Mean cQT_p		Mean $cT_{p\text{-}e}$		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; $cT_{p\text{-}e}$ = corrected $T_{peak}\text{–}T_{end}$ interval.

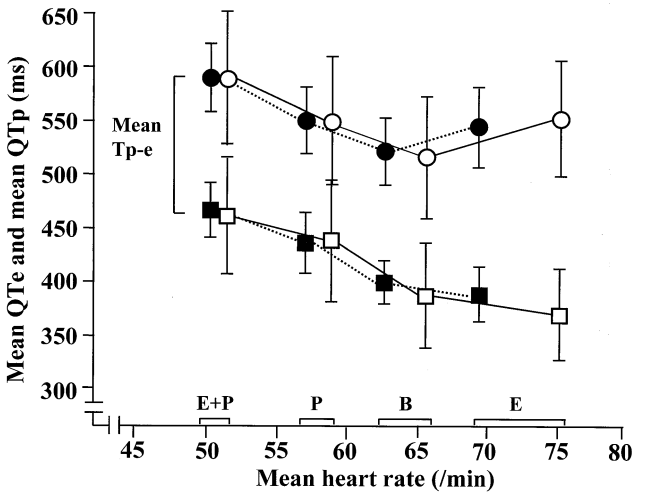

Figure 3. Plots of the mean QT_e and mean QT_p values against the mean heart rate in 11 patients with LQT1 **(open circles and squares)** and 11 patients with LQT2 **(solid circles and squares)**. In both groups of patients, the mean $T_{p\text{-}e}$ value (mean QT_e − mean QT_p) after propranolol administration **(P)** was smaller than that at the baseline condition **(B)**, even if the mean heart rate was slower after propranolol. The mean $T_{p\text{-}e}$ 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 $T_{p\text{-}e}$ 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 $cT_{p\text{-}e}$ (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 $cT_{p\text{-}e}$ 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 $cT_{p\text{-}e}$, 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 $T_{p\text{-}e}$ values were not corrected by the heart rate (Fig. 3). In both groups, the mean $T_{p\text{-}e}$ 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 $T_{p\text{-}e}$ 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 $cT_{p\text{-}e}$, Maximum cQT_e, Minimum QT_e and cQT_e-D in the LQT1 and LQT2 Groups

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

*$p < 0.05$ 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.

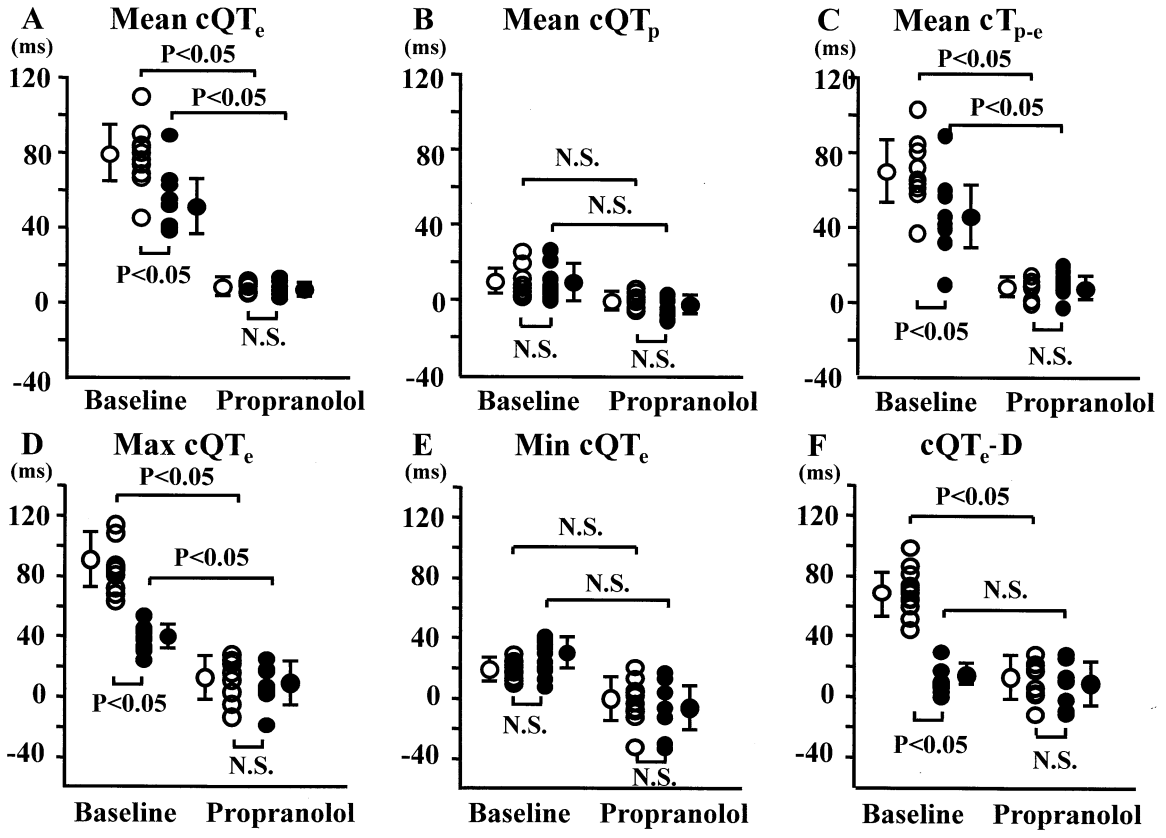

Figure 4. Differences before and after epinephrine at the baseline condition and with oral propranolol in the mean cQT_e **(A)**, mean cQT_p **(B)**, mean cT_{p-e} (**C**), maximum cQT_e **(D)**, minimum cQT_e **(E)** and cQT_e-D **(F)** in 11 LQT1 patients **(open circles)** and 11 LQT2 patients **(solid 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

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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