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Frequency-Dependent Electrophysiologic Properties of Ventricular Repolarization in Patients With Congenital Long QT Syndrome

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Objectives. **This study was performed to evaluate the frequency dependency of ventricular repolarization and the effect of epinephrine in patients with congenital long QT syndrome (LQTS).**

Background. **The efficacy of pacemakers in addition to antiadrenergic therapy in the treatment of congenital LQTS has been reported.**

Methods. **Monophasic action potentials were recorded from right and left ventricular endocardium during atrial pacing at heart rates from 70 to 140 beats/min at baseline and from 100 to 140 beats/min during epinephrine infusion (0.1 μg/kg body weight per min) in 11 patients with congenital LQTS and 10 control patients. The response of monophasic action potential duration at 90% repolarization (MAPD90) and the dispersion of MAPD90 were examined.**

Results. **At baseline, both the MAPD90 and the dispersion of MAPD90 were significantly ($p < 0.001$) longer in the congenital LQTS group than the control group. The differences in these variables between the two groups significantly decreased (MAPD90: from 105 to 31 ms; dispersion of MAPD90: from 55 to 13 ms, $p < 0.001$) as heart rate was increased. Epinephrine prolonged the MAPD90 and increased the dispersion of MAPD90 significantly ($p < 0.001$) at all paced heart rates in the congenital LQTS group without frequency dependency but did not change in the control group. Thus, epinephrine increased the differences in these variables between the two groups.**

Conclusions. **The repolarization abnormalities in congenital LQTS were attenuated by increasing the heart rate, which supported the efficacy of pacemaker therapy. However, during sympathetic stimulation, the effects of increased heart rate on these repolarization abnormalities were limited.**

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Congenital long QT syndrome (LQTS) is a hereditary disorder characterized by prolongation of the QT interval and by syncopal episodes and sudden death due to ventricular arrhythmias (1–3). The present treatment of choice is antiadrenergic therapy (e.g., beta-adrenergic blocking agents, left cervicothoracic sympathetic ganglionectomy) because an increase in sympathetic stimulation, such as stress or fright, can precipitate ventricular tachyarrhythmias in the setting of QT prolongation (4,5). In contrast, the efficacy of permanent pacemakers has also been reported (6,7) in the treatment of patients with congenital LQTS who are resistant to beta-blockers and left cervicothoracic sympathetic ganglionectomy.

It has been reported that increases in heart rate due to exercise (8,9) and isoproterenol infusion (9,10) produce a paradoxic prolongation of the QT interval and may precipitate ventricular arrhythmias in patients with congenital LQTS. However, exercise or isoproterenol infusion influences both heart rate and adrenergic activities. The influence of heart rate on ventricular repolarization without adrenergic activities (e.g., pacing) has not been thoroughly evaluated in congenital LQTS.

The purpose of the present study was to evaluate the influence of heart rate on ventricular repolarization in patients with congenital LQTS by using monophasic action potentials and atrial pacing, which has little effect on adrenergic activities, and to assess the effects of epinephrine on these variables.

Methods

Subjects. This study used a patient–control design. Inclusion criteria for patients with congenital LQTS followed the 1993 LQTS diagnostic criteria of Schwartz et al. (11). Eleven patients who met these criteria entered the present study (nine female, two male; 3 to 63 years old, mean [±SD] age 31 ± 19) (Table 1). Seven patients had familial congenital LQTS (Romano-Ward syndrome), and four had idiopathic congenital LQTS. All 11 patients had a history of stress-induced syncope. Polymorphic ventricular tachycardia characteristic of torsade de pointes was documented in seven patients. The mean corrected QT (QTc) interval in the LQTS group was 540 ±

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Abbreviations and Acronyms

ANOVA = analysis of variance
ECG = electrocardiogram, electrocardiographic
LQTS = long QT syndrome
MAPD90 = monophasic action potential duration at 90% repolarization
QTc = corrected QT interval

91 $ms^{1/2}$ (range 450 to 740). All 11 patients had a score of four or more points according to the diagnostic criteria of Schwartz et al. (11), indicating a high probability of congenital LQTS. The criteria for the control group were 1) QTc interval <440 $ms^{1/2}$; and 2) no history of syncope or ventricular arrhythmias. There were 10 control patients, of whom 4 had sick sinus syndrome, and 6 had concealed Wolff-Parkinson-White syndrome (4 women, 6 men; 45 to 74 years old, mean age 59 ± 8). The mean QTc interval in the control group was 405 ± 18 $ms^{1/2}$ (range 370 to 420).

Electrophysiologic studies. The protocol was reviewed and approved by our Ethical Review Committee, and written informed consent was obtained from all participants before the study. Because two patients in the LQTS group were minors, we obtained informed consent from their parents. Electrophysiologic studies were performed in the nonsedated, postabsorbed state in all but two patients in the LQTS group (Patients 8 and 10) who received sodium pentobarbital (3 mg/kg body weight) and diazepam (0.3 mg/kg) as sedation. All antiarrhythmic medications had been discontinued for at least 5 drug half-lives.

Two or three 6F or 7F monophasic action potential catheters (monophasic action potential-pacing combination catheter, EP Technologies Inc.) were introduced through a femoral vein and advanced into the right ventricle under fluoroscopic guidance to record the right ventricular monophasic action potentials. Another 6F or 7F catheter was introduced through a femoral artery and advanced into the left ventricle to record the left ventricular monophasic action potential. A standard 6F bipolar electrode catheter with 10-mm interelectrode spacing (USCI Inc.) was positioned in the right atrial appendage for atrial pacing.

Monophasic action potential recordings. Monophasic action potentials were recorded simultaneously from two or three sites at the right or left ventricular endocardium, or both, in each patient by the contact electrode technique, as described previously (9,12–16). A total of 33 sites were recorded in 11 patients in the LQTS group and 26 in 10 control patients. In the right ventricle, monophasic action potential recordings were obtained from two sites in all patients with congenital long QT syndrome and all control patients. In the left ventricle, those were obtained in all patients in the LQTS group syndrome but in only six control patients. Readings of monophasic action potentials, six surface electrocardiographic leads and arterial pressure through a radial artery were displayed simultaneously on a strip-chart recorder (Siemens-Elema, 16-

Table 1. Clinical Characteristics of 11 Patients With Congenital Long QT Syndrome and 10 Control Patients

Pt No.	Age (yr)/Gender	Diagnosis	Syncope With Stress	Torsade de Pointes	SCL (ms)	QT (ms)	QTc (ms)
LQTS group							
1	30/F	Romano-Ward	+	+	710	400	480
2	29/F	Idiopathic	+	+	600	390	500
3	27/F	Romano-Ward	+	+	780	490	550
4	33/F	Romano-Ward	+	−	780	400	450
5	45/F	Romano-Ward	+	−	890	450	480
6	23/F	Romano-Ward	+	+	1,180	710	650
7	18/F	Idiopathic	+	−	940	560	580
8	3/M	Romano-Ward	+	+	740	640	740
9	58/M	Idiopathic	+	−	960	450	460
10	9/F	Romano-Ward	+	+	850	440	480
11	63/F	Idiopathic	+	+	960	480	490
Control group							
1	61/M	SSS	−	−	1,360	430	370
2	45/F	SSS	−	−	820	380	420
3	55/M	Con WPW	−	−	1,020	420	420
4	67/M	SSS	−	−	970	410	420
5	56/F	SSS	−	−	1,280	430	380
6	59/M	Con WPW	−	−	850	370	400
7	52/F	Con WPW	−	−	980	410	410
8	74/M	Con WPW	−	−	930	385	400
9	57/M	Con WPW	−	−	1,000	410	410
10	62/F	Con WPW	−	−	860	390	420

Con WPW = concealed Wolff-Parkinson-White syndrome; F = female; LQTS = congenital long QT syndrome; M = male; Pt = patient; QTc = corrected QT interval; SCL = sinus cycle length; SSS = sick sinus syndrome.

channel Mingograf) at a paper speed of 100 mm/s. Signals of monophasic action potentials were amplified and filtered at a frequency of 0.05 to 500 Hz, and those of ventricular electrograms were amplified and filtered at a frequency of 50 to 500 Hz. Monophasic action potentials were obtained after placement of the catheter electrode in a position providing continuous recordings of stable amplitude, smooth configuration and isopotential diastolic baselines (phase 4) from a single endocardial site during both sinus rhythm and constant atrial pacing. Once the contact catheter was stabilized, monophasic action potentials could be recorded continuously from the same endocardial site for long periods without additional manipulation of the catheter.

The duration of monophasic action potential was determined at 90% repolarization (MAPD90), which included early afterdepolarization-like activity if present. The dispersion of MAPD90 was defined as the difference between the longest MAPD90 and the shortest MAPD90 in each patient. The QT interval was measured in all 12 leads, and the longest QT interval was used for analysis. The QT(U) interval was defined as the time between QRS onset and the point at which the line of maximal downslope of the T wave [or the late component of the T(U) complex, if present] crossed the baseline before the isoelectric UP interval. The QTc interval was calculated according to Bazett's formula ($QTc = QT/\sqrt{RR}$). QRS duration was determined by measuring the QRS duration in lead II from beginning to end.

Protocol. The following protocol was used to investigate the response of MAPD90, dispersion of MAPD90, QT interval and QRS duration for various heart rates at steady state for comparison between the LQTS and control groups. Constant right atrial pacing was performed with 2-ms rectangular stimuli at twice diastolic threshold delivered from a programmable stimulator (Nihon Kohden Inc., model SEL-3120) in both groups. Right atrial pacing at 70, 80, 100, 120 and 140 beats/min was performed. Monophasic action potential recordings were obtained during constant atrial pacing for at least 3 min at each heart rate until monophasic action potential duration had reached a new steady state (12,13). Each pacing run was followed by a recovery period of at least 3 min. The mean MAPD90 and QT intervals of at least 4 consecutive beats during constant atrial pacing were used for analysis.

Epinephrine infusion. After baseline study, epinephrine was infused at a constant rate of 0.1 μg/kg body weight per min in both groups. After a steady state was achieved, the previously described protocol was repeated. Because sinus heart rate increased >90 beats/min after epinephrine infusion in almost all patients, right atrial pacing was performed only at 100, 120, and 140 beats/min during epinephrine infusion.

Data analysis. Data were evaluated as differences in MAPD90, dispersion of MAPD90, QT interval, and QRS duration between the groups (LQTS group vs. control group) or within the groups (control state vs. epinephrine) at each heart rate. Results are expressed as mean value ± SD. The differences in each measurement (MAPD90, dispersion of MAPD90, QT interval and QRS duration) between the groups in relation to heart rate during the control state and epinephrine infusion were tested using multiple regression analysis with dummy variables. We used $Y = c + b^1 \cdot D + b^2 \cdot HR + b^3 \cdot D \cdot HR$ as regression model, where Y = the measured variable (MAPD90, dispersion of MAPD90, QT interval and QRS duration); c, b^1, b^2 and b^3 = estimated regression coefficients; HR = heart rate; and D = a dummy variable for the group (control group = 0, LQTS group = 1). The changes in each measurement before and after epinephrine infusion within the groups as a function of heart rate were determined using repeated measures analysis of variance (ANOVA) with the Greenhouse-Geisser correction for within-subject correlations (17). Differences within groups (control state vs. epinephrine) or between groups (LQTS group vs. control group) at each heart rate were also analyzed by the Student *t* test (paired or unpaired). Values of $p < 0.05$ were considered statistically significant.

Results

Clinical characteristics. Clinical characteristics of the 11 LQTS group patients and the 10 control group patients are shown in Table 1. All 11 LQTS group patients had a prolonged QTc interval. The mean QTc interval during sinus rhythm before epinephrine infusion was 540 ± 91 $ms^{1/2}$ (range 450 to 740 $ms^{1/2}$) in the LQTS group and 405 ± 18 $ms^{1/2}$ (range 370 to 420 $ms^{1/2}$) in the control group. Epinephrine significantly shortened the sinus cycle length in both groups (LQTS group: from 914 ± 102 to 620 ± 50 ms, $p < 0.0005$; control group: from 1,013 ± 180 to 740 ± 120 ms, $p < 0.005$).

Response of MAPD90 to heart rate (Table 2). During the control state, at paced heart rates of 70, 80, 100, 120, and 140 beats/min, the mean MAPD90 was, respectively, 395 ± 60, 345 ± 52, 310 ± 42, 275 ± 28 and 239 ± 16 ms in the LQTS group (n = 33 sites: 22 in the right ventricle, 11 in the left ventricle) (Fig. 1, upper panel) and 290 ± 26, 272 ± 20, 248 ± 19, 232 ± 17 and 208 ± 10 msec in the control group (n = 26 sites: 20 in the right ventricle, 6 in the left ventricle) (Fig. 2, upper panel) and was significantly ($p < 0.001$) longer in the LQTS group than in the control group at all heart rates tested. Although the mean MAPD90 decreased with increasing heart rate in both groups, the differences in mean MAPD90 between the LQTS and control groups were 105, 73, 62, 43 and 31 ms, respectively, at each paced heart rate, indicating attenuation of difference of the MAPD90 between the two groups at faster heart rates. Moreover, the MAPD90, which was examined over the range of paced heart rates, was significantly longer at slower than at faster paced heart rates ($p < 0.001$) in the LQTS group.

During epinephrine infusion, the MAPD90 was prolonged significantly ($p < 0.001$ by ANOVA) to 339 ± 59, 310 ± 57 and 278 ± 52 ms, respectively, in the LQTS group at all paced heart rates of 100, 120, and 140 beats/min tested (Fig. 1, lower panel). The degrees of prolongation of mean MAPD90 compared with the control state were 29 ms (9%), 35 ms (13%), and 39 ms (16%), respectively, at paced heart rates of 100, 120

Table 2. MAPD90 and Dispersion of MAPD90 in Relation to Paced Heart Rate and Effect of Epinephrine on MAPD90 and Dispersion of MAPD90 in 11 Patients With Congenital Long QT Syndrome and 10 Control Patients

		Paced Heart Rate									
		70 beats/min		80 beats/min		100 beats/min		120 beats/min		140 beats/min	
Group	No. of Sites Sampled	MAPD90 (ms)	Dispersion of MAPD90 (ms)	MAPD90 (ms)	Dispersion of MAPD90 (ms)	MAPD90 (ms)	Dispersion of MAPD90 (ms)	MAPD90 (ms)	Dispersion of MAPD90 (ms)	MAPD90 (ms)	Dispersion of MAPD90 (ms)
Control state											
LQTS group	33	395 ± 60*	78 ± 17*	345 ± 52*	54 ± 23*	310 ± 42*	38 ± 17*	275 ± 28*	27 ± 14	239 ± 16*	27 ± 10
Control group	26	290 ± 26	23 ± 10	272 ± 20	22 ± 11	248 ± 19	16 ± 9	232 ± 17	18 ± 8	208 ± 10	14 ± 7
Δ		105	55	73	32	62	22	43	9	31	13
Epinephrine											
LQTS group	33					339 ± 59†‡	62 ± 33§‖	310 ± 57†‡	52 ± 36§‖	278 ± 52†‡	35 ± 15§‖
Control group	26					260 ± 24	19 ± 11	236 ± 15	16 ± 10	213 ± 13	18 ± 4
Δ						79	43	74	36	65	17

*$p < 0.001$ versus Control group (Control state). †$p < 0.001$ versus congenital long QT syndrome (LQTS) group (Control state). ‡$p < 0.001$ versus Control group (Epinephrine). §$p < 0.05$ versus LQTS group (Control state). ‖$p < 0.05$ versus Control group (Epinephrine). Data are expressed as mean value ± SD or difference (Δ) between mean value in LQTS group and that in Control group at each heart rate. MAPD90 = monophasic action potential duration at 90% repolarization.

and 140 beats/min. Epinephrine-induced changes in the MAPD90 in the LQTS group were not frequency dependent. In the control group, there was a tendency to prolongation of the MAPD90 to 260 ± 24, 236 ± 15 and 213 ± 13 ms at all heart rates tested, but there were no significant differences (Fig. 2, lower panel). Therefore, the differences in the mean MAPD90 between the two groups increased to 79, 74 and 65 ms at the respective paced heart rates of 100, 120 and 140 beats/min during epinephrine infusion. When the MAPD90 was examined over the range of paced heart rates during epinephrine infusion, there was no significant frequency-dependent relation between the two groups, indicating that increasing the heart rate by atrial pacing did not shorten the MAPD90 significantly during epinephrine infusion (Fig. 3A).

Response of dispersion of MAPD90 to heart rate (Table 2). The dispersion of MAPD90 was calculated from two sites in the right ventricular and one site in the left ventricular endocardium in all patients with LQTS and six control patients. In four control patients, dispersion of MAPD90 was calculated from only two sites in the right ventricular endocardium.

During the control state, at paced heart rates of 70, 80, 100, 120 and 140 beats/min, the mean dispersion of MAPD90 was, respectively, 78 ± 17, 54 ± 23, 38 ± 17, 27 ± 14 and 27 ±

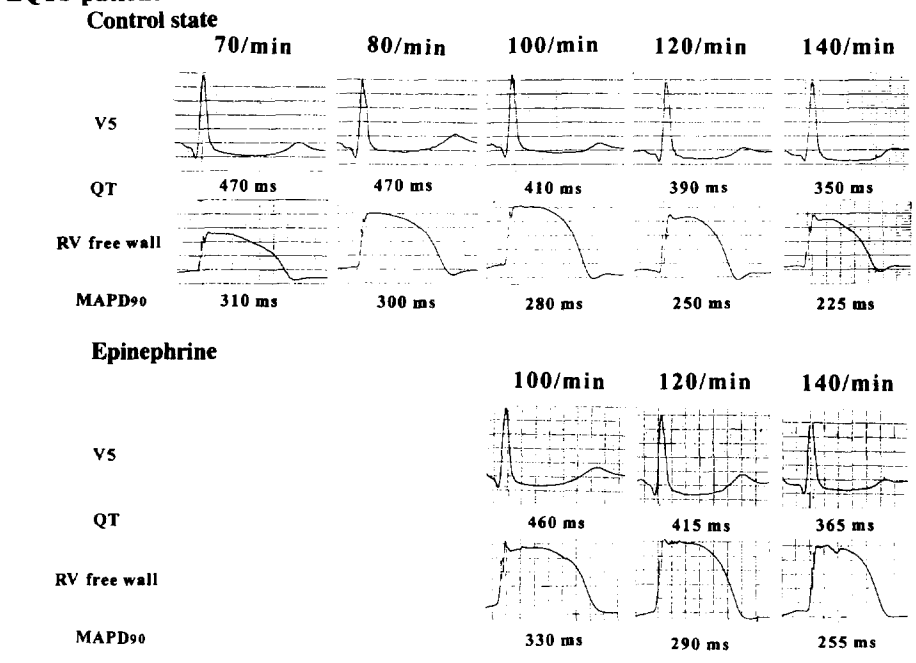

Figure 1. Recordings of the monophasic action potential at each paced heart rate from 70 to 140 beats/min before epinephrine infusion (Control state, **upper panel**) and from 100 to 140 beats/min during epinephrine infusion (Epinephrine, **lower panel**) in a patient with congenital LQTS (Patient 5). Simultaneous recordings of surface ECG lead V_5 monophasic action potential from the right ventricular (RV) free wall. The measurements below each recording are the QT interval and the MAPD90 at each heart rate. As heart rate was increased by constant atrial pacing, both the QT interval and the MAPD90 were shortened. Epinephrine prolonged both QT interval and MAPD90 at all paced heart rates of 100, 120 and 140 beats/min.

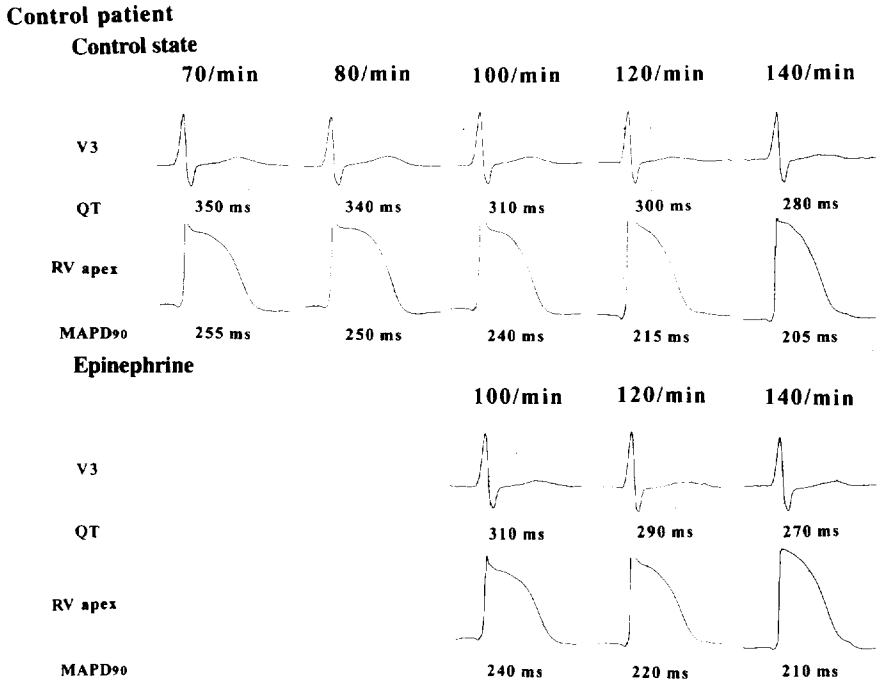

Figure 2. Recordings of monophasic action potential at each paced heart rate from 70 to 140 beats/min before epinephrine infusion (Control state, **upper panel**) and from 100 to 140 beats/min during epinephrine infusion (Epinephrine, **lower panel**) in a control patient (Patient 8). Simultaneous recordings of surface ECG lead V_3 monophasic action potential from the right ventricular (RV) apex. The measurements below each recording are the QT interval and the MAPD90 at each heart rate. As heart rate was increased by constant atrial pacing, both the QT interval and the MAPD90 were shortened. Epinephrine did not change markedly both the QT interval or the MAPD90 at any heart rate.

10 ms in the LQTS group (n = 11) and 23 ± 10, 22 ± 11, 16 ± 9, 18 ± 8 and 14 ± 7 ms in the control group (n = 10) and was significantly ($p < 0.001$) greater in the LQTS group than in the control group at paced heart rates of 70, 80 and 100 beats/min. The mean dispersion of MAPD90 decreased with increasing heart rate in the LQTS group, whereas it was almost constant in the control group. Therefore, the differences in mean dispersion of MAPD90 between the two groups were 55, 32, 22, 9 and 13 ms at each paced heart rate, indicating attenuation of difference in the dispersion of MAPD90 between the two groups at faster heart rates. Moreover, the dispersion of MAPD90, which was examined over the range of paced heart rates, was significantly greater at slower than at faster paced heart rates in the LQTS group ($p < 0.001$).

During epinephrine infusion, the dispersion of MAPD90 increased significantly ($p < 0.05$ by ANOVA) to 62 ± 33, 52 ± 36 and 35 ± 15 ms at paced heart rates of 100, 120 and 140 beats/min, respectively, in the LQTS group. The degree of increase in mean dispersion of MAPD90 compared with that in the control state was 24 ms (63%), 25 ms (93%) and 8 ms

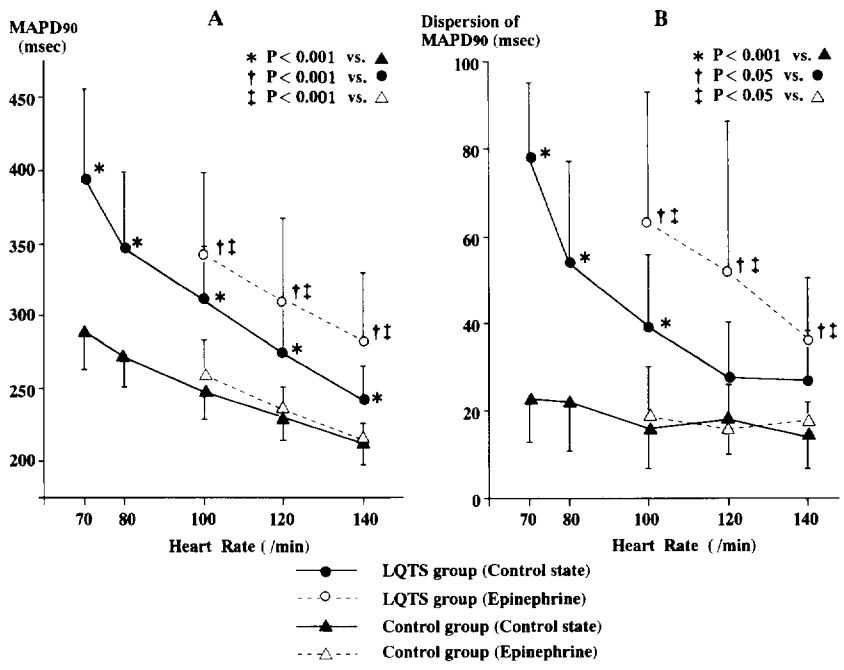

Figure 3. Changes in MAPD90 (**A**) and dispersion of MAPD90 (**B**) in relation to paced heart rate and effect of epinephrine infusion (0.1 μg/kg per min) on MAPD90 and dispersion of MAPD90 in 11 patients with congenital LQTS and 10 control patients.

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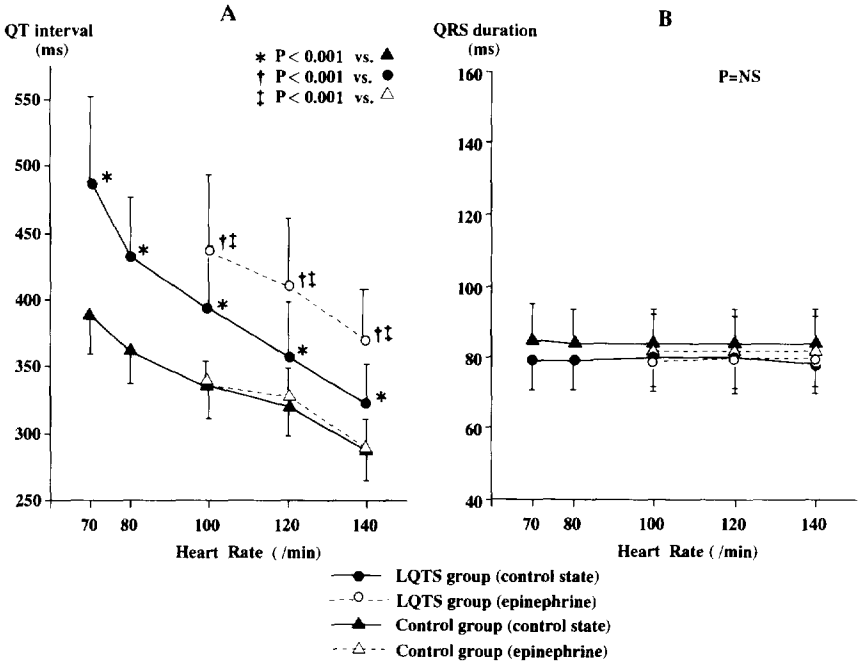

Figure 4. Changes in the QT interval **(A)** and the QRS duration **(B)** in relation to paced heart rate and effect of epinephrine infusion (0.1 μg/kg per min) on QT interval and QRS duration in 11 patients with LQTS and 10 control patients.

(30%), respectively, at paced heart rates of 100, 120 and 140 beats/min. Epinephrine-induced changes in the dispersion of MAPD90 in the LQTS group were not frequency dependent. In the control group, there were no significant changes in mean dispersion of MAPD90 (19 ± 11, 16 ± 10 and 18 ± 4 ms) at any paced heart rate during epinephrine infusion. Hence, the differences in the mean dispersion of MAPD90 between the two groups increased to 43, 36 and 17 ms at paced heart rates of 100, 120, and 140 beats/min, respectively, during epinephrine infusion. Although there was also an attenuation in the differences of the mean dispersion of MAPD90 between the two groups by increasing heart rate even during epinephrine infusion, the dispersion of MAPD90 was significantly ($p < 0.05$) much greater in the LQTS group than in the control group at heart rates of 100, 120 and 140 beats/min. These findings indicate that increasing the heart rate by atrial pacing did not decrease the dispersion of MAPD90 significantly during epinephrine infusion (Fig. 3B).

Response of QT interval to heart rate (Table 3). During the control state, at paced heart rates of 70, 80, 100, 120 and 140 beats/min, respectively, the mean QT interval was 490 ± 63, 429 ± 46, 396 ± 49, 360 ± 39 and 324 ± 31 ms in the LQTS group ($n = 11$) (Fig. 1, upper panel) and 391 ± 31, 363 ± 25, 336 ± 25, 321 ± 23 and 285 ± 22 ms in the control group ($n = 10$) (Fig. 2, upper panel) and was also significantly ($p < 0.001$) longer in the LQTS group than in the control group at all heart rates tested, as with the MAPD90. Although the mean QT interval decreased with increasing heart rate in both groups, the differences in mean QT interval between the LQTS and control groups were 99, 66, 60, 39 and 39 ms at each paced heart rate, indicating attenuation of differences in the QT interval between the two groups at faster heart rates. Moreover, the QT interval, which was examined over the range of paced heart rates, was significantly longer at slower than at faster paced heart rates in the LQTS group ($p < 0.005$).

During epinephrine infusion, the QT interval was prolonged significantly ($p < 0.001$ by ANOVA) to 437 ± 57, 411 ± 50 and 368 ± 36 ms, respectively, in the LQTS group at paced heart rates of 100, 120 and 140 beats/min (Fig. 1, lower panel). The degree of prolongation of the QT interval compared with that in the control state was 41 ms (10%), 51 ms (14%) and 44 ms (14%) at paced heart rates of 100, 120 and 140 beats/min, respectively. Epinephrine-induced changes in the QT interval in the LQTS group were not frequency dependent. In the control group, there were no significant changes in QT interval (335 ± 19, 328 ± 21 and 285 ± 21 ms) at each paced heart rate (Fig. 2, lower panel). Therefore, the differences in the mean QT interval between the two groups increased to 102, 83 and 83 ms at paced heart rates of 100, 120 and 140 beats/min, respectively, during epinephrine infusion. When the QT interval was examined over the range of paced heart rates, there was no significant frequency-dependent relation between the two groups during epinephrine infusion, indicating that increasing heart rate by atrial pacing did not shorten the QT interval significantly during epinephrine infusion (Fig. 4A).

Response of QRS duration to heart rate (Table 3). The QRS duration was nearly constant at all paced heart rates, and there was no frequency-dependent effect in either group. There were no significant differences between the two groups at any of the paced heart rates tested. Epinephrine did not change the QRS duration significantly in either group (Fig. 4B).

Table 3. QT Interval and QRS Duration in Relation to Paced Heart Rate and Effect of Epinephrine on QT Interval and QRS Duration in 11 Patients With Congenital Long QT Syndrome and 10 Control Patients

		Paced Heart Rate									
		70 beats/min		80 beats/min		100 beats/min		120 beats/min		140 beats/min	
Group	No. of Sites Sampled	QT Interval (ms)	QRS Duration (ms)	QT Interval (ms)	QRS Duration (ms)	QT Interval (ms)	QRS Duration (ms)	QT Interval (ms)	QRS Duration (ms)	QT Interval (ms)	QRS Duration (ms)
Control state											
LQTS group	11	490 ± 63*	79 ± 8	429 ± 46*	79 ± 8	396 ± 49*	80 ± 10	360 ± 39*	80 ± 9	324 ± 31*	78 ± 6
Control group	10	391 ± 26	85 ± 10	363 ± 25	84 ± 10	336 ± 25	84 ± 10	321 ± 23	84 ± 10	285 ± 22	84 ± 10
Δ		99	6	66	5	60	4	39	4	39	6
Epinephrine											
LQTS group	11					437 ± 57†‡	79 ± 7	411 ± 50†‡	80 ± 10	368 ± 36†‡	80 ± 10
Control group	10					335 ± 19	82 ± 10	328 ± 21	82 ± 10	285 ± 21	82 ± 10
Δ						102	3	83	2	83	2

*$p < 0.001$ versus Control group (Control state). †$p < 0.001$ versus congenital long QT syndrome (LQTS) group (Control state). ‡$p < 0.001$ versus Control group (Epinephrine). Data are expressed as mean ± SD or difference (Δ) between mean value in LQTS group and that in Control group for each heart rate.

Discussion

There were two major new findings of the present study: 1) Increasing heart rate by atrial pacing shortened the prolonged monophasic action potential duration and QT interval and decreased the increased dispersion of monophasic action potential duration in patients in the LQTS group in the absence of sympathetic (epinephrine) stimulation; and 2) epinephrine blunted the effects of increased heart rate by atrial pacing on these repolarization abnormalities.

Response of MAPD90 and QT interval to heart rate in congenital LQTS. It was previously reported (8–10) that increasing the heart rate with exercise or isoproterenol infusion produces a paradoxic prolongation of the QT interval and may precipitate ventricular arrhythmias in patients with congenital LQTS. When the heart rate was increased by exercise and isoproterenol infusion, sympathetic activity increased concomitantly. It is well known that sympathetic stimulation plays an important role in ventricular repolarization abnormalities in congenital LQTS (9,14–16,18). Bhandari et al. (19) reported the response of the QT interval to atrial pacing in control subjects and patients with congenital LQTS. They demonstrated that atrial pacing, which has little effect on sympathetic activity, significantly shortened QT interval, and the degree of percent change in QT interval shortening was similar in the two groups. Our results were compatible with their finding with respect to shortening QT interval by atrial pacing in patients with congenital LQTS. In our study the degree of shortening in repolarization variables (MAPD90, dispersion of MAPD90 and QT interval) by increasing the heart rate was much greater in patients with congenital LQTS than in control patients. These bradycardia-dependent repolarization abnormalities have been recognized as characteristic of patients with acquired LQTS, and tachycardia-dependent repolarization abnormalities have been suggested (20) in patients with congenital LQTS. However, Jackman et al. (20) suggested that both congenital and acquired LQTS have a similar membrane defect with diminished repolarizing currents.

Recently, linkage studies (21,22) have demonstrated three separate loci for this inherited disorder (i.e., on chromosomes 3, 7 and 11), and three forms of LQTS have been shown (23–25) to result from mutations in ionic channel genes on chromosomes 3, 7 and 11. Mutations in the chromosome 3 gene SCN5A, a sodium ion channel gene, were linked to LQT3 syndrome, whereas those in the chromosome 7 gene HERG, a rapid-activating delayed rectifier potassium ion current (I_{Kr}) gene (26), were related to LQT2 syndrome. Recently, mutations in the chromosome 11 gene KVLQT1, a potassium ion channel gene, were found to be responsible for LQT1 syndrome (25). Mutations in the gene SCN5A are responsible for the inactivation of the sodium ion current, and mutations in gene HERG and KVLQT1 are likely to impair expression of potassium ion current. In the present study, genotypes of the 11 patients with congenital LQTS were not investigated. Moss et al. (27) reported that the three genes responsible for LQTS were associated with a different T wave pattern on the ECG. In most patients within our study, congenital LQTS may be associated with chromosome 7 or 11 or other unknown genes rather than chromosome 3 on the basis of their T wave pattern (data not shown). If most of our patients have mutations in the chromosome 7 gene HERG, action potential duration may shorten to a greater extent with faster than with slower pacing rate because of reverse-use dependency caused by depressed delayed rectifier potassium ion current (28). Schwartz et al. (29) reported that patients with congenital LQTS linked to chromosome 3 had a shortened QT interval in response to increases in heart rate. Even if LQTS in some of our patients is linked to chromosome 3, action potential duration may shorten similarly with rapid pacing.

Response of dispersion of MAPD90 to heart rate in congenital LQTS. Recent experimental and clinical studies using monophasic action potentials have demonstrated (14–16,20) that early afterdepolarizations and prolonged action potential duration play an important role in ventricular arrhythmias in congenital LQTS. However, it is hypothesized

that an electrophysiologic substrate of ventricular arrhythmias may be created by an increased dispersion of repolarization (30–32). Kuo et al. (31) assumed that when the increase in dispersion of repolarization reached a critical level, propagation of premature impulses originating from the area with a short action potential duration encountered a block in the area with a long action potential duration and created conditions favorable for reentry. This concept has been further investigated by several clinical methods. Linker et al. (33) and Priori et al. (34) demonstrated the presence of an increased QT interval dispersion in patients with congenital LQTS using the surface 12-lead ECG. Shimizu et al. (35) also reported an increased QT interval dispersion and recovery time by recording 87-lead body surface mapping. In the present study using monophasic action potential, the dispersion of MAPD90 was greater in the LQTS group than in the control group at all paced heart rates and decreased with increasing heart rate in patients with congenital LQTS. These findings support the efficacy of permanent pacemaker therapy in congenital LQTS because increasing the heart rate without sympathetic activity may improve the electrophysiologic substrate of ventricular arrhythmias.

Effect of epinephrine on relation between ventricular repolarization and heart rate. We previously reported (14–16) that isoproterenol or epinephrine prolonged the MAPD90 and the QT interval, increased the dispersion of MAPD90 and induced early afterdepolarization in patients with congenital LQTS. The present study further evaluated the effect of epinephrine on the relation between ventricular repolarization and heart rate. Epinephrine significantly prolonged the MAPD90 and the QT interval and increased the dispersion of MAPD90 at paced heart rates of 100, 120 and 140 beats/min in patients with congenital LQTS. The degree of prolongation of MAPD90 and the QT interval by epinephrine compared with the control state was relatively constant, and rate-dependent changes in these repolarization variables were attenuated by epinephrine. These results indicate that permanent pacemaker therapy may not be sufficient to prevent ventricular arrhythmias during sympathetic stimulation in congenital LQTS.

Study limitations. There are several limitations to the present study. Monophasic action potential recordings were obtained from only two or three endocardial sites in each patient. Especially for the left ventricle, monophasic action potential recordings were obtained in all patients with congenital LQTS but in only six control patients. This nonuniformity of recording sites limits the calculations of dispersion of monophasic action potential durations across both ventricles. More detailed mapping of monophasic action potential recordings is necessary to define dispersion more precisely. Furthermore, we could only evaluate the rate-dependent effects of epinephrine on repolarization variables for narrow range of heart rates (100, 120 and 140 beats/min). It remains for other studies to examine a wider range of heart rates to evaluate more completely the rate-dependent effects of epinephrine on repolarization variables.

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