

Q-T Peak Dispersion in Congenital Long QT Syndrome

— Possible Marker of Mutation of *HERG* —

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Congenital long QT syndrome (LQTS) is caused by mutations in various cardiac potassium or sodium channel genes, with 6 different genotypes thus far identified. However, it is unknown whether these genotypes can be differentiated by QT variables. The electrocardiograms obtained from 16 patients with a mutation in *KCNQ1* (LQT1), 7 patients with a mutation in *HERG* (LQT2) and 20 control subjects were analyzed. The corrected QT interval (QTc), Q-T peak interval (QTpc) and dispersion of QTc or QTpc were measured in 6 precordial leads. The corrected interval from T peak to T end (Tpec) was measured in lead V₅. The maximum QTc, QTc dispersion, and Tpec were significantly increased in the LQT1 and LQT2 patients than in the controls. However, there were no significant differences in these indices between the LQT1 and LQT2 patients. In contrast, QTpc dispersion was significantly increased in the LQT2 patients (78±25 ms) compared with the LQT1 patients (29±15 ms) and controls (26±19 ms). These results suggest that increased lag of the peak of the T wave in each precordial lead (QTpc dispersion) may be a possible index to differentiate LQTS patients with *HERG* mutation from those with *KCNQ1* mutation. (Circ J 2003; 67: 495–498)

Key Words: *HERG*; Long QT syndrome; Notched T wave; QT dispersion

Congenital long QT syndrome (LQTS) is associated with life-threatening polymorphic ventricular tachycardia, and is diagnosed by electrocardiogram (ECG), clinical history, family history, and ruling out acquired causes of increased QT interval.¹ Multiple gene abnormalities that result in congenital LQTS have been identified^{2–6} and because several studies have demonstrated differential responses of LQTS patients to interventions targeted to their specific genotype, genotyping may be important for selecting the appropriate treatment.^{7–10} However, genotyping is a complex, time-consuming, expensive process with limited availability, and a mutation may not be found. Genotyping by ECG has been attempted, and it has been suggested that the various genotypes among patients with LQTS are associated with different patterns of the ST-T wave complex. The T wave duration is particularly long in patients with LQT1 who have a mutation in the *KCNQ1* gene, which encodes the slowly activating delayed rectifier potassium channel I_{ks}.^{11,12} Patients with LQT2 have a mutation in the *HERG* gene, which encodes the β -subunit of the channel that underlies the rapidly activating delayed rectifier potassium current I_{kr}, and they usually have low amplitude T and/or notched T waves.^{11,13} T wave onset is unusually prolonged in patients with LQT3, who have a mutation in the *SCN5A* gene which encodes the cardiac sodium channel that is responsible for I_{Na}.^{11,13} In

one study, typical ST-T wave patterns were present in 88% of LQT1 and LQT2 patients.¹⁴ We studied the ECGs of carriers of mutations in the *KCNQ1* or *HERG* gene to determine the differences in QT variables for diagnostic and genotyping purposes.

Methods

Subjects

The study population included 16 patients from 4 families with LQT1, 7 patients from 3 families with LQT2, and 20 control subjects. Among the LQT1 patients, the mutated nucleotides of the 4 *KCNQ1* missense mutations were F193L, S277L, R591H, and D611Y, and among the LQT2 patients, the mutated nucleotides of the 3 *HERG* missense mutations were H492Y, R534C, and E637K. The control subjects did not have LQTS or any cardiac abnormalities. Informed consent was obtained from all subjects in accordance with the guidelines of the Bioethical Committee on Medical Researches, School of Medicine, Kanazawa University.

QT Interval Measurements

All 12-lead ECGs were recorded at 25 mm/s with standard lead positions. All records could be clearly magnified by 200%, and the QT intervals were measured using the ECG obtained from 6 precordial leads (V_{1–6}). The QT interval was defined as the time interval between the onset of QRS and the point at which the T wave crossed the isoelectric line. The Q-T peak interval (QTp) was defined as the time interval between the onset of QRS and the peak of the positive T wave or the nadir of the negative T wave. The T peak-end interval (Tpe) was defined as the time interval between the peak of the T wave and the point at which the T wave crossed the isoelectric line, and was

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Table 1 Clinical Characteristics and T Wave Morphology of LQT Patients and Control Subjects

	LQT1 (n=16)	LQT2 (n=7)	Control (n=20)
Age (years)	29±21	47±26	37±23
Female sex	7/16 (44%)	4/7 (57%)	10/20 (50%)
Prior cardiac events	1/16 (6%)	4/7 (57%)	0/20 (0%)
-blocking therapy	0/16 (0%)	1/7 (14%)	0/20 (0%)
Notched T wave	0/16 (0%)	5/7 (71%)	0/20 (0%)

LQT, Long QT.

Table 2 QT Variables in the LQT1, LQT2 and Control Groups

	LQT1 (n=16)	LQT2 (n=7)	Control (n=20)
Maximum QTc (ms)	463±47 [§]	493±23 [§]	407±22
Minimum QTc (ms)	432±42 [†]	454±29 [§]	389±27
QTc dispersion (ms)	31±18*	39±29*	18±14
Maximum QTpc (ms)	363±41 [†]	392±20 [§]	321±27
Minimum QTpc (ms)	334±42*	314±31	295±25
QTpc dispersion (ms)	29±15	78±25 [¶]	26±19
Tpec (ms)	92±18*	102±51*	75±16

QTc, corrected QT interval; QTpc, corrected interval from the onset of QRS to the peak of the T wave; Tpec, corrected interval from the peak to the end of the T wave. * $p < 0.05$ vs Control, [†] $p < 0.001$ vs Control, [§] $p < 0.0001$ vs Control, [¶] $p < 0.0001$ vs LQT1 and Control.

measured from lead V5. When the T wave had a biphasic or a notched configuration, the peak of the T wave was defined as that which had the higher voltage. T waves with a voltage less than 0.1 mV or biphasic T waves with a difference between each voltage less than 0.1 mV were excluded, and this study did not include patients whose T wave was excluded in more than 2 leads. The QT interval, QTp and Tpe were corrected to the heart rate by Bazett's method (QTc: QT/RR^{1/2}, QTpc: QTp/RR^{1/2}, and Tpec: Tpe/RR^{1/2}, respectively). The dispersion of QTc or QTpc was defined as the interval between the maximum and the minimum values of QTc or QTpc, respectively.

Detection of Notched T Wave

The ECGs of all subjects were examined for notched T wave, which we defined as a T wave with a perceptible or distinct protuberance just beyond the apex or on the descending limb of an upright T wave, as previously reported.¹⁵

Statistical Analyses

Results are expressed as the mean ± SD. The significance of differences of the values among the 3 groups was analyzed by one-way ANOVA followed by Bonferroni/Dunn analysis. Categorical data were compared using chi-square analysis. Logistic regression analysis was performed using StatView 5.0 (Abacus Concepts, Inc, Berkeley, CA). A $p < 0.05$ was considered to be statistically significant.

Results

Clinical Data and T Wave Morphology

The clinical characteristics of the subjects are summarized in Table 1. There was no significant difference in age among the 3 groups. The proportion of females did not differ significantly among the 3 groups. Notched T wave was

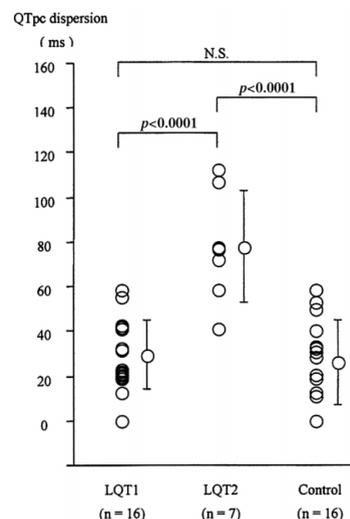


Fig 1. Comparison of the QTpc dispersion in the ECGs of the LQT1, LQT2, and control subjects. The QTpc dispersion was significantly higher in the LQT2 group than in the LQT1 and control groups. NS, not significant.

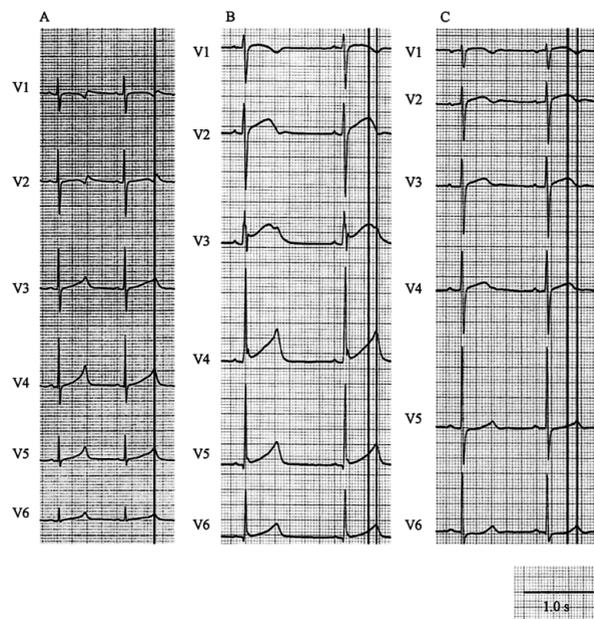


Fig 2. Precordial ECGs in representative patients with long QT syndrome. (A) ECG of a patient with LQT1 shows prolonged QT interval, but a lag of the peak of the T wave is not apparent. (B) ECG of a LQT2 patient with notched T wave shows prolonged QT interval and a lag of the peak of the T wave is apparent. (C) ECG of a LQT2 patient without notched T wave shows prolonged QT interval and a lag of the peak of the T wave is apparent.

found in 5 of the 7 patients with LQT2, in contrast to none of the LQT1 patients or control subjects.

QT Variables

The QT variables in each group are summarized in Table 2. Both the maximum QTc and maximum QTpc of the LQT1 and LQT2 groups were significantly increased in comparison with those in the control group. However, there were no significant differences in these parameters between the LQT1 and LQT2 groups. QTc dispersion and Tpec were

also increased in the LQT1 and LQT2 patients compared with the control subjects, but they did not significantly differ between the LQT1 and LQT2 patients. In contrast, QTpc dispersion was significantly increased in the LQT2 group compared with the LQT1 and control groups (Fig 1).

The ECG of a LQT1 patient showed an increased maximum QTc (546 ms) (Fig 2A), but because the dispersion of QTpc (32 ms) was not increased, a lag of the peak of the T wave was not apparent. The ECG of a LQT2 patient with a distinct notched T wave (Fig 2B) showed increased maximum QTc (480 ms) and QTpc dispersion (77 ms). The ECG of a LQT2 patient without a notched T wave (Fig 2C) also presented increased maximum QTc (468 ms) and QTpc dispersion (112 ms). Because both of these LQT2 patients had increased QTpc dispersion, a lag of the peak of the T wave was apparent.

Discussion

Our results showed that the maximum QTc, QTc dispersion and Tpec were significantly increased in both the LQT1 and LQT2 patients compared with the normal controls. However, none of these indices significantly differed between the LQT1 and LQT2 patients. In contrast, QTpc dispersion was significantly increased in the LQT2 patients compared with the LQT1 patients and normal controls.

QTpc Dispersion in LQT2

In the arterially perfused wedge model of the canine left ventricle, it has been shown that the peak of the T wave coincides with the end of the action potential in epicardial cells!⁶ There are transepical gradients in the ion channel expression and characteristics of action potentials. The action potential duration was significantly longer in cells isolated from the left ventricular apex than in cells isolated from the base, and the largest component of I_{K_r} in apical myocytes was I_{K_r} whereas it was I_{K_s} in basal myocytes!¹⁷ Similar results have been reported for isolated human myocytes!¹⁸ These results suggest that epicardial cells in the apex express a higher level of *HERG*, compared with those in the base!⁹ and for this reason, the action potential duration in LQT2 patients is more prolonged in epicardial cells in the apex than in cells in the base, leading to an increase in QTpc dispersion. This hypothesis is supported by the results of the present study; that is, in the majority of the patients with LQT2, the maximum QTpc was recorded in V₅ or V₆ and the minimum QTpc was recorded in V₂ or V₃. QT variables with 87-lead body-surface ECGs in 13 LQT1 patients, 6 LQT2 patients and 7 controls have been analyzed!²⁰ and the values of QTpc dispersion of the LQT2 patients were similar to those of our LQT2 patients; however, the values of QTpc dispersion of their LQT1 patients and normal controls were higher than those in our subjects, such that they found no significant difference in the QTpc dispersion among the 3 groups!²⁰ The location and number of leads may affect the value of QTpc dispersion because of differences in the distribution of each type of potassium channel. QT variables measured from the 6 precordial leads may underestimate the true inter-ventricular repolarization. However, QTpc dispersion can be fully detected from only the 6 precordial leads, and may be a simple and useful index to differentiate patients with LQT2 from those with LQT1. With regard to this question, further investigations are necessary.

Notched T Wave in LQT2

Notched T wave was found in 5 of the 7 LQT2 patients in contrast to none of the LQT1 patients or control subjects. Notched T wave has been reported as a specific marker of mutation of *HERG*!^{21,22} Three types of cells with different electrophysiological characteristics exist in the ventricular wall!¹⁶ in the presence of an I_{K_r} blocker, used to mimic defects in *HERG*, the action potential duration of the cells in the epicardium, M-region, and endocardium became prolonged. However, the rate of prolongation in the 3 regions differs and leads to separation of their repolarization times. Separation of epicardial and endocardial repolarization times creates a notch in the descending limb of the T wave!⁶ In contrast, chromanol 293B, a specific I_{K_s} blocker used to mimic defects in *KCNQ1*, prolongs the action potential duration homogeneously with a broad-based T wave characteristic!¹² In our study, notched T wave was recognized only among patients with LQT2, which is in agreement with previous reports!^{21,22}

In LQT2 patients, notched T wave with a distinct protuberance is not always detected on 12-lead ECG; therefore, Holter recording analysis is superior for detecting notched T wave!^{22,23} Certain clinical conditions, including sympathovagal imbalance and glucose-induced insulin secretion, induce notched T wave!^{24,25} Because the LQT2 patients who did not show a distinct notched T wave had increased dispersion of QTpc, increased dispersion of QTpc may be more useful than detection of notched T wave on one-point ECG analysis.

Study Limitations

We measured the QT interval and the Q-T peak interval manually because we lacked an automated measurement system for these variables. However, because the intra-observer variability was small, it is presumed that the effect of manual measurements was none or very small. The number of patients and detected mutations in each group were both very small, so additional studies of larger samples are necessary to confirm and clarify our results.

Conclusions

Increased lag of the peak of the T wave in each precordial lead (QTpc dispersion) is a possible index for differentiating LQTS patients with a mutation in *HERG* from those with a mutation in *KCNQ1*.

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