Ambulatory Electrocardiographic Evidence of Transmural Dispersion of Repolarization in Patients With Long-QT Syndrome Type 1 and 2

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Background—Transmural dispersion of repolarization (TDR) may be related to the genesis of torsade de pointes (TdP) in patients with the long-QT (LQT) syndrome. Experimentally, LQT2 models show increased TDR compared with LQT1, and β-adrenergic stimulation increases TDR in both models. Clinically, LQT1 patients experience symptoms at elevated heart rates, but LQT2 patients do so at lower rates. The interval from T-wave peak to T-wave end (TPE interval) is the clinical counterpart of TDR. We explored the relationship of TPE interval to heart rate and to the presence of symptoms in patients with LQT1 and LQT2.

Methods and Results—We reviewed Holter recordings from 90 genotyped subjects, 31 with LQT1, 28 with LQT2, and 31 from unaffected family members, to record TPE intervals by use of an automated computerized program. The median TPE interval was greater in LQT2 (112±5 ms) than LQT1 (91±2 ms) or unaffected (86±3 ms) patients (P<0.001 for all group comparisons), and the maximal TPE values differed as well. LQT1 patients showed abrupt increases in TPE values at RR intervals from 600 to 900 ms, but LQT2 patients did so at RR intervals from 600 to 1400 ms (longest RR studied). Asymptomatic and symptomatic patients showed similar TDRs.

Conclusions—TDR is greater in LQT2 than in LQT1 patients. LQT1 patients showed a capacity to increase TDR at elevated heart rates, but LQT2 patients did so at a much wider rate range. The magnitude of TDR is not related to a history of TdP. (Circulation. 2002;106:2473-2478.)

Key Words: arrhythmia ■ electrocardiography ■ long-QT syndrome ■ torsade de pointes

Torsade de pointes is the arrhythmia producing syncope and risk of sudden death in patients with the congenital long-QT syndrome (LQTS).1 Torsade de pointes tends to appear during exercise (especially swimming) or psychological stress in LQT1, during stress or startle (particularly auditory stimuli) in LQT2, and during rest in LQT3.2 In experimental LQTS models, transmural dispersion of repolarization (TDR) has been linked to the genesis of torsade de pointes,3 and LQT2 shows increased TDR, determined as the action potential duration difference between midmyocardial and epicardial cells, compared with LQT1 and normal hearts.4 Conversely, β-adrenergic stimulation increases TDR in both LQTS models, transiently in LQT2 and persistently in LQT1.4 In addition, the interval from QRS onset to the T-wave termination and T-wave apex correspond to action potential durations of midmyocardial and epicardial cells, respectively.5 We hypothesized that the T-wave peak to T-wave end (TPE) interval would prolong preferentially with abrupt elevation of heart rates in LQT1 patients, whereas LQT2 patients would show prolonged TPE intervals at a wider range of heart rates. Although earlier studies have shown a weak correlation between the length of the QT interval and symptoms,6,7 we hypothesized that the history of cardiac symptoms may be related to TPE interval rather than the length of the QT interval.

Methods

Study Subjects
We reviewed Holter recordings in 90 individuals either with the LQT1 (31 patients) or LQT2 genotype (28 patients) or unaffected (31 subjects). LQTS patients were from consecutive genotyped series studied at the Helsinki University Central Hospital. The unaffected patients came from the same families and were matched to the patients with respect to age and sex. The patients were categorized as asymptomatic if they had experienced unexplained syncope, documented torsade de pointes, or LQTS-related sudden death. Table 1 shows the clinical characteristics of the study subjects. No subject took β-blockers or any other medication known to influence cardiac
We first determined the maximal TPE values (TPE max ) and the respective RR intervals in each individual. The durations of the TPE max components were considered U waves. Only upright monophasic T components were calculated as T waves; otherwise, the second derivative is also used to detect discontinuities after the peak,9 and the software excludes U waves using the baseline ECG signal, with ≥3 consecutive acceptable TPE measurements.

To analyze the rate dependence of the TPE intervals, we computed the maximal TPE intervals (TPE max ) values against RR intervals in RR steps of 10 ms. We present the TPE max values of all beats during 24 hours against RR intervals with RR steps similarly to TPE med values. We also recorded TPE med intervals at stable heart rates. Heart rates had to be stable for 60 seconds, with RR interval variation ≤10%. The TPE med values were calculated from the averaged ECG signal.

Statistical Analysis

Data are presented as mean±SD. Comparisons between 2 groups were performed by 2-tailed Student’s t test for normally distributed parameters or Mann-Whitney U test for nonnormally distributed parameters or by χ2 test where appropriate. Correlations between continuous variables were determined by Pearson’s correlation coefficients.

Results

Heart Rates

Diurnal heart rates in LQT1, LQT2, and unaffected individuals showed mean rates of 74±9, 74±9, and 76±8, respectively (P=NS). The minimal heart rates ranged from 35 to 81 bpm in LQT1, from 35 to 68 bpm in LQT2, and from 33 to 66 bpm in the unaffected subjects. The maximal rates ranged correspondingly from 93 to 162, from 101 to 175, and from 128 to 188 bpm, respectively. To analyze sufficient data at each specified RR interval, we studied the TPE intervals at heart rates from 43 to 120 bpm (at RR intervals from 1400 to 500 ms).

Median TPE Intervals

Figure 3 shows the TPE med/RR curves of all beats in the study groups. The average values of TPE med calculated at RR intervals from 500 to 1400 ms, were 91±2 ms in LQT1, 112±5 ms in LQT2, and 86±3 ms in unaffected patients. The TPE med was greater for LQT2 than LQT1 or unaffected individuals (P<0.001), and LQT1 patients showed longer TPE med than unaffected patients (P<0.001). To evaluate possible effects of bifid T waves on the median TPE intervals, we excluded 7 LQT1 and 1 LQT2 patients with prominent humps of the T waves. Among patients with no prominent T-wave humps, the corresponding average TPE med values were 92±2 ms in LQT1 and 113±5 ms in LQT2 patients (P<0.001 between LQT1 and LQT2). Measured at stable heart rates in the whole cohort, TPE med values were 92±3 ms in LQT1, 118±10 ms in LQT2, and 86±3 ms in unaffected patients. At stable heart rates, LQT2 patients showed a tendency to prolong TPE med at RR intervals >1000 ms (data not shown).

Maximal TPE Intervals

Figure 4 shows the maximal TPE values at different RR intervals. The highest TPE max values were 227±73 ms in LQT1, 274±64 ms in LQT2, and 177±32 ms in unaffected

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<tr>
<th>Clinical and ECG Characteristics of Study Subjects</th>
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TABLE 1
Subjects. The TPE max was greater for LQT2 than either LQT1 ($P<0.01$) or unaffected ($P<0.001$) subjects. LQT1 patients exhibited longer TPE max than unaffected patients ($P<0.01$). Among patients with no prominent T-wave humps, the corresponding TPE max values were 211±69 ms in LQT1 and 268±61 ms in LQT2 patients ($P<0.01$ between LQT1 and LQT2). LQT2 patients showed the highest TPE max at longer RR intervals (839±166 ms) than either LQT1 (725±90 ms) ($P<0.01$) or unaffected (646±48 ms) ($P<0.001$) patients. Figures 3 and 4 show that LQT1 patients exhibited the capacity to increase TPE interval at elevated heart rates, whereas LQT2 patients increased their TPE interval at a much wider range of heart rates. Two representative cases are shown in Figure 1. The episodes of the highest TPE max lasted 13±19 seconds in LQT1, 9±5 seconds in LQT2, and 7±4 seconds in unaffected patients ($P=NS$). The highest TPE max correlated with the TPE med values at stable heart rates both in LQT1 ($r=0.63$, $P<0.001$) and in LQT2 ($r=0.80$, $P<0.001$).

The dynamic behavior of the RR intervals at the moment of the highest TPE max values showed an RR shortening in 38% of LQT1 patients, in 41% of LQT2 patients, and in 56% of unaffected subjects, whereas an RR lengthening was present in 62%, 59%, and 44% of patients, respectively. Comparing the behavior of the RR intervals at the moment of the highest TPE max values with the trend of the RR intervals during 30 seconds before the highest TPE max showed an abrupt change.
of the trend (e.g., positive \( \text{dRR}_{\text{TPEmax}} \) and negative mean \( \text{dRR}_{\text{TPEmax}} \); see Figure 2) in 62% of LQT1 and in 71% of LQT2 patients but in only 33% of unaffected subjects.

### Symptomatic Versus Asymptomatic Patients

There were 13 symptomatic and 18 asymptomatic patients in the LQT1 group and 11 symptomatic and 17 asymptomatic patients in the LQT2 group. The baseline Bazett’s QTc (measured from the resting ECGs) or the maximal absolute QT values (measured from 24-hour Holter recordings) did not show significant differences between symptomatic and asymptomatic patients in any group (Table 2). Neither the TPE values in the baseline ECG nor \( \text{TPE}_{\text{med}} \) or \( \text{TPE}_{\text{max}} \) values in the ambulatory ECG were different between patients with or without the history of cardiac events (Table 2). Episode durations as well as the length and the dynamic behavior of the RR intervals at the moment of the highest maximal TPE values were similar in symptomatic and asymptomatic patients (data not shown).

### Discussion

#### Main Findings

The present results show that the TDR, measured as TPE intervals during normal daily activities, is greater in LQT2 than in LQT1 patients. LQT1 patients exhibit abrupt increases in TDR at elevated heart rates, whereas LQT2 patients exhibit increases in TDR at a much wider range of rates. Symptomatic and asymptomatic patients show similar TDR values.

#### TPE Interval as a Measure of TDR

Both in experimental LQTS models and in normal heart preparations, the intervals from QRS onset to the T-wave termination and T-wave apex correspond to action potential durations of midmyocardial cells (the longest action potentials) and epicardial cells (the shortest action potentials), respectively. In addition, experimental studies have shown that the TPE interval in each ECG lead serves as an index of TDR across the ventricle. Therefore, in patients with no myocardial damage, the TPE interval, measured from a precordial lead, appears to be a useful approximation of the TDR. For technical reasons, we determined the highest T-wave peak to be the T-wave apex and excluded flat T waves, as stated in the Methods.

#### TDR in Experimental LQT1 and LQT2 Models

In experimental LQT1 models, \( I_{\text{Ks}} \) block prolongs action potential durations homogeneously across the ventricular wall at any rate, and thus, TDR does not change significantly. \( \beta \)-Adrenergic stimulation with isoproterenol increases TDR in LQT1. This may be explained by a larger augmentation of \( I_{\text{Ks}} \), by isoproterenol in epicardial and endocardial cells than in M cells, in which \( I_{\text{Ks}} \) is weaker. The result is abbreviation of epicardial but not of midmyocardial action potential durations, giving rise to increased TDR and a prolonged TPE interval. In LQT2 models, conversely, \( I_{\text{Kr}} \) block has a relatively greater effect on M cells, increasing TDR and prolonging TPE interval in a rate-dependent manner. In this model, rapid pacing abbreviated TDR to nearly control values. \( \beta \)-Adrenergic stimulation with isoproterenol...
increased TDR in LQT2 models also, because isoproterenol transiently prolongs action potential durations in M cells, possibly because of a more rapid increase of inward $I_{Na-Ca}$ current than of outward $I_{Ks}$ current.14

**TPE Interval in LQT1 and LQT2**

We found that LQT2 patients showed greater TPE intervals than LQT1 patients or unaffected subjects. In fact, the TPE interval can be used as a diagnostic criterion in differentiation between LQT2 and LQT1 patients.15 Although bifid T waves are more common in LQT2 than in LQT1 patients16 and this morphological T-wave difference between the genotypes might contribute to determining the TPE intervals, excluding the cases with bifid T waves did not eliminate the difference between the genotypes. Although LQT1 patients and unaffected subjects had stable TPE levels independent of heart rates, LQT2 patients showed a trend to decrease TPE intervals at high heart rates and to increase TPE durations at low heart rates. These findings are in accordance with previous experimental studies by Shimizu and Antzelevitch.13,14 In addition, our data show that LQT1 patients also have longer TPE intervals than unaffected subjects at RR intervals from 500 to 1400 ms.

We observed abrupt increases of TPE interval in both LQT1 and LQT2 patients and unaffected subjects. This finding confirms the concept that abrupt changes in TDR occur.17 LQT1 patients showed long TPE intervals at elevated heart rates, whereas LQT2 patients exhibited the highest TPE values at wide heart rate ranges. In both LQT1 and LQT2 patients, the longest TPE intervals were associated with sudden change in the heart rate trend. Similar rate changes were not always associated with predictable increases in TPE interval. According to the sympathetic stimulation tests both with isoproterenol in experimental LQT1 and LQT2 models4 and with epinephrine in LQT1 and LQT2 patients,18 the present findings show the capacity of both LQT1 and LQT2 patients to transiently and dramatically increase the TDR.

**TPE Interval as a Risk Factor in LQT1 and LQT2**

Torsade de pointes is the feared clinical arrhythmia in both the congenital LQTS and acquired abnormal QT prolongation. Prolonged QT interval is not a sufficient factor to provoke torsade de pointes, however, and the concept of early afterdepolarizations and nonuniform prolonged repolarization has been proposed.19 Changes of the TPE interval are expected to show the dynamicity of the TDR in clinical settings in LQTS patients. The present results showed that the magnitude of TPE interval did not differ between asymptomatic and symptomatic patients in either LQT1 or LQT2. Conversely, symptomatic LQT2 patients exhibited a trend toward longer QT intervals than asymptomatic patients. Previously, Zareba et al20 reported that each 10-ms increase in QTc increases the risk of cardiac events by 6% in both LQT1 and LQT2. Increased TPE interval may show the electrophysiological substrate for torsade de pointes, and the observed capacity to increase TPE interval seems to be a property of both $I_{Kr}$ and $I_{Ks}$ defects. In LQT1 as well as in LQT2, sudden changes of heart rate, presumably caused by fluctuation in autonomic nervous activity, appear to enhance TPE interval. Our findings in both LQT1 and LQT2 patients are in accordance with previous clinical observations of the importance of autonomic impacts on the occurrence of symptoms.2

**Study Limitations**

We excluded U waves as defined in the Methods. This may have removed some terminal parts of T waves, especially in LQT2 patients. We used this definition because U-wave inclusion presents more difficulty in excluding physiological U waves in unaffected subjects, especially in women. As the second recording channel, we used traditional modified V1 showing negative, biphasic, or bifid T waves very often and with a low amplitude; thus, the comparison of the TPE interval behavior between different ECG leads remains an issue for further studies. Our method of recording RR interval differences and their trends gives only an approximation to evaluate the impacts of autonomic fluctuations on the TPE intervals. We cannot rule out the possibility that the absence of an association between TPE interval and a history of cardiac events in the study population might be a power issue related to the small number of patients and events. Different KvLQT1 mutations in LQT1 and HERG mutations in LQT2 may cause differences in TPE interval.

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