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

Matti Viitasalo, MD; Lasse Oikarinen, MD; Heikki Swan, MD; Heikki Väänänen, MSc; Kathy Glatter, MD; Päivi J. Laitinen, MSc; Kimmo Kontula, MD; Hal V. Barron, MD, PhD; Lauri Toivonen, MD; Melvin M. Scheinman, MD

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...
TABLE 1. Clinical and ECG Characteristics of Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31±1</td>
<td>32±1</td>
<td>35±13</td>
</tr>
<tr>
<td>Men/women</td>
<td>16/15</td>
<td>17/11</td>
<td>17/14</td>
</tr>
<tr>
<td>Symptomatic/asymptomatic</td>
<td>13/18</td>
<td>11/17</td>
<td>...</td>
</tr>
<tr>
<td>No. of different mutations</td>
<td>5</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Baseline ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc, ms</td>
<td>477±44</td>
<td>476±47</td>
<td>415±26*</td>
</tr>
<tr>
<td>TPE interval in lead V5, ms</td>
<td>77±9†</td>
<td>95±24</td>
<td>77±8¶</td>
</tr>
<tr>
<td>TPEmax interval in any lead, ms</td>
<td>94±18†</td>
<td>118±35</td>
<td>89±14‡</td>
</tr>
</tbody>
</table>

*P<0.001 vs LQT1 and LQT2; †P<0.01 vs LQT2; ‡P<0.001 vs LQT2.

repolarization during the Holter recording. All subjects were in sinus rhythm and did not show bundle-branch block. Normal daily activities were allowed during the recordings. The Ethical Review Committees of the institutes approved the study, and informed consent was obtained from all participants. Recordings and analyses were done without the investigator knowing the genotypes or symptom histories.

Holter Recordings and Analyses
All study subjects underwent a 2-channel 24-hour ECG recording (model 8501; Marquette Electronics Inc). The tapes were initially analyzed with a Marquette 8000 Holter Analysis system (version 5.8 software) to label the QRS complexes and were classified with respect to normal, ventricular extrasystoles, or aberrant complexes. The ECG data were then transferred to a personal computer for further analysis of the TPE intervals.

Measurement of the TPE Intervals
The ECG signal was preprocessed by oversampling, subtracting the fitted third-order spline baseline, and retriggering. Before determination of the median TPE values (defined later), signal-to-noise ratio was also improved by continuously averaging 5 successive QRST complexes. By use of an algorithm based on a method originally presented by Simson for QRS onset identification and a previously validated algorithm for determination of T-wave fiducial points, the software first determines the QRS onset as the time instant at which the steepest increase or decrease of TPE interval lengthening back to the shorter stable level of TPE interval. For analyzing the decreasing or increasing behaviors of the RR intervals, we calculated an approximation of the RR slope (ΔRR, dRR) by resampling and using the second-order smoothing filter. We determined the dRR value (expressed in ms)/s at the time of TPEmed (dRR TPEmed). In addition, we determined whether the mean of the dRR during 30 seconds before TPEmed (mean dRR TPEmed) was negative (denoting predominantly increasing heart rate) or positive (denoting predominantly decreasing heart rate) (Figure 2). We also recorded maximal TPE intervals at different RR intervals with RR steps of 50 ms (from 500 to 700 ms) or with RR steps of 100 ms (from 700 to 1400 ms). All the maximal TPE intervals were determined and checked visually by use of the unaveraged ECG signal, with ≥3 consecutive acceptable TPE measurements.

To analyze the rate dependence of the TPE intervals, we computed the median TPE interval (TPEmed) values against RR intervals in RR steps of 10 ms. We present the TPEmed values of all beats during 24 hours against RR intervals with RR steps similarly to TPEmed values. We also recorded TPEmed intervals at stable heart rates. Heart rates had to be stable for 60 seconds, with RR interval variation ≤10%. The TPEmed 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 TPEmed/RR curves of all beats in the study groups. The average values of TPEmed 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 TPEmed was greater for LQT2 than LQT1 or unaffected individuals (P<0.001), and LQT1 patients showed longer TPEmed than unaffected patients (P<0.001). To evaluate possible effects of bifid T waves on the median TPE intervals, we excluded 7 LQT1 and 11 LQT2 patients with prominent humps of the T waves. Among patients with no prominent T-wave humps, the corresponding average TPEmed 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, TPEmed 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 TPEmed at RR intervals >1000 ms (data not shown).

Maximal TPE Intervals
Figure 4 shows the maximal TPE values at different RR intervals. The highest TPEmed values were 227±73 ms in LQT1, 274±64 ms in LQT2, and 177±32 ms in unaffected
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 $211\pm 69$ ms in LQT1 and $268\pm 61$ ms in LQT2 patients ($P<0.01$ between LQT1 and LQT2). LQT2 patients showed the highest TPE max at longer RR intervals ($839\pm 166$ ms) than either LQT1 ($725\pm 90$ ms) ($P<0.01$) or unaffected ($646\pm 48$ 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 $13\pm 19$ seconds in LQT1, $9\pm 5$ seconds in LQT2, and $7\pm 4$ 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 59% 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.

**Figure 1.** TPE intervals plotted against the respective preceding RR intervals (solid circles) in a LQT1 patient (top left) and a LQT2 patient (top right). The longest TPE intervals at specified RR intervals are given by open circles, and respective ECG signals compared with the shortest TPE interval at similar RR intervals are shown under the plots.
of the trend (eg, positive dRR_{TPE\text{max}} and negative mean dRR_{TPE\text{max}}; 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 TPE_{med} or TPE_{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, \( I_{\text{Ks}} \) 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
Torsade de pointes is the feared clinical arrhythmia in both congenital LQTS and acquired abnormal QT prolongation. Prolonged QT interval is not a sufficient factor to evaluate the impacts of autonomic fluctuations on the TPE intervals. 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.

Acknowledgments
This study was supported by grants from the Aarne Koskelo Foundation, Finland; the Finnish Foundation for Cardiovascular

TABLE 2. QT and TPE Intervals in Symptomatic and Asymptomatic LQT1 and LQT2 Patients

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Baseline ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc, ms</td>
<td>480±41</td>
<td>475±47</td>
</tr>
<tr>
<td>TPE interval in lead V6, ms</td>
<td>77±9</td>
<td>78±9</td>
</tr>
<tr>
<td>TPE_{max} interval in any lead, ms</td>
<td>88±14</td>
<td>98±20</td>
</tr>
<tr>
<td>Ambulatory ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal QT, ms</td>
<td>567±49</td>
<td>551±56</td>
</tr>
<tr>
<td>TPE_{med} interval, ms</td>
<td>91±2</td>
<td>91±2</td>
</tr>
<tr>
<td>TPE_{max} interval, ms</td>
<td>221±83</td>
<td>231±67</td>
</tr>
</tbody>
</table>
Research, Finland; the Paavo Nurmi Foundation, Finland; and the Mc Eowen Foundation, San Francisco, Calif.

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

_Circulation_. 2002;106:2473-2478
doi: 10.1161/01.CIR.0000036369.16112.7D
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/19/2473

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/