Interval Representative of Transmural Dispersion of Repolarization in Children and Young Adolescents With Congenital Long QT Syndrome

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Background It has been shown experimentally that the interval from the nadir of the initial negative T wave to the end of the T wave is representative of transmural dispersion of repolarization (TDR) when complex T waves are present. In the clinical setting, however, the interval representative of TDR in patients with long QT syndrome (LQTS) is a controversial subject.

Methods and Results Five symptomatic patients (3 boys, 2 girls; 3 LQT1, 2 LQT2) were evaluated by a face immersion test before and after treatment to compare the configuration of the T wave. When the notch disappeared after treatment, the single peak of the T wave after treatment coincided with the nadir of the notch before treatment. When the notch remained the same after treatment as before treatment and when the QTc decreased, the corrected interval from the nadir of the notch to the end of the T wave was for the most part shortened.

Conclusions The present study showed that the interval representative of the TDR in the clinical surface electrocardiogram can be obtained from the nadir of the notch to the end of the T wave in children and adolescents with LQTS, as was shown in the experimental study. (Circ J 2005; 69: 78–82)

Key Words: Dispersion; Electrocardiography; Long QT syndrome; Syncope; Tests

Long QT syndrome (LQTS) is a rare disorder characterized by prolonged ventricular repolarization and a high risk of cardiac events, including sudden cardiac death1–2. Among the mutations thus far identified in specific ion channel genes causing LQTS3–6, KCNQ1 and KCNH2 have been most commonly identified, and they are known to cause the LQT1 and LQT2 forms, respectively. Recent studies have reported that LQTS-related cardiac events tend to occur under specific circumstances in a gene-specific manner7. In the LQT1 form, exercise and swimming are the most common triggers, whereas in the LQT2 form they are strong emotions, sleep, and rest8.

Results of experimental studies suggest that the interval between the peak and the end of the T wave in a transmural electrocardiogram (ECG) reflects the transmural dispersion of repolarization (TDR) when a normal upright T wave is present, and that TDR is linked to the genesis of torsade de points8–10. When complex (inverted, notched or biphasic, and triphasic) T waves are present, the interval from the nadir of the initial negative T wave to the end of the T wave is representative of the TDR11. However, the definition of the interval representative of TDR on a clinical surface ECG remains a subject of controversy when the T wave shows a notched or a bifid configuration12–16. There has not been a clinical report of the use of the interval from the nadir of the initial negative T wave to the end of the T wave as the definition of the interval representative of TDR when the notched or a bifid T wave is present.

A face immersion test was reported to induce an abnormally prolonged QT interval and notched T waves in children and adolescent with LQTS17, suggesting that the same test would induce a prolongation of the TDR in these young patients. We used the face immersion test to examine the QT intervals and compare the T wave configuration on ECG before and after treatment with the aim of determining whether the interval representative of TDR based on the experimental study can be adapted for use in the clinical setting, assuming that the decrease in the QTc interval after treatment is associated with a decrease in the TDR.

Methods

Study Population

Inclusion criteria for the present study were children and adolescents with LQTS who had been treated and undergone a face immersion test before and after treatment. The 3 boys and 2 girls comprised 3 cases of the LQT1 form (KCNQ1 mutation; 2 families) and 2 of the LQT2 form (KCNH2 mutation, 2 families) (Table 1).

Controls

To determine the normal range of the QT intervals during the face immersion test, 31 control children and adolescents (23 boys, 8 girls; mean age, 12 years; range, 6–17 years) were also examined. Normal ranges were defined as the mean ± 2SD.
Treatment

A β-blocker was prescribed for all patients after they experienced syncope, or after torsade de pointes was recorded by ambulance ECG. If the patient had a past history of syncope at the time of the first visit, the β-blocker was started following the initial face immersion test. Propranolol and mexiletine were initially co-administered to most patients (except for case 3), and mexiletine was recently discontinued in 1 cases after a gene diagnosis of LQT1 was made.

Face Immersion Test

A face immersion test was repeated once or twice yearly before and after treatment. The shortest QTc intervals during the tests were used as the data after treatment. Propranolol and mexiletine were initially co-administered to most patients (except for case 3), and mexiletine was recently discontinued in 1 cases after a gene diagnosis of LQT1 was made.

Table 1 Characteristics of the Subjects With Long QT Syndrome

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>LQTS form</th>
<th>Gene analysis</th>
<th>Age at clinical diagnosis</th>
<th>Age of first syncope</th>
<th>No. of syncopal episodes</th>
<th>Triggers</th>
<th>Dose of propranolol* (mg/kg per day)</th>
<th>Dose of mexiletine* (mg/day)</th>
<th>Interval from starting Rx§ (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>F</td>
<td>LQT1</td>
<td>C677T (A226V)</td>
<td>13</td>
<td>6</td>
<td>5</td>
<td>Exercise, swimming, noise</td>
<td>1.1</td>
<td>300</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>M</td>
<td>LQT1</td>
<td>G760A (V254M)</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>Exercise, swimming</td>
<td>1.6</td>
<td>150</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>M</td>
<td>LQT1</td>
<td>G760A (V254M)</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>Exercise</td>
<td>1</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>F</td>
<td>LQT2</td>
<td>Deletion (2637-2638)</td>
<td>13</td>
<td>19</td>
<td>1</td>
<td>Sleep</td>
<td>0.2†</td>
<td>200</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>F</td>
<td>LQT2</td>
<td>G157A (G53R)</td>
<td>12</td>
<td>19</td>
<td>3</td>
<td>Defecation, rest, standing up</td>
<td>0.2†</td>
<td>200</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Dose of each drug at the time of the post-treatment test. Mexiletine was discontinued if a genetic diagnosis of LQT1 was made.
†Torsade de pointes was recorded on an ambulance ECG during sleep.
‡Carvedilol (8 mg/day, 0.3 mg/kg per day) was prescribed.
§Interval between starting treatment and the time of the post-treatment test.
¶Patients 4 and 5 (LQT2 form) could not tolerate propranolol at a dose of 0.6–1.2 mg/kg per day, so mexiletine and a very small dose of propranolol were prescribed.

QT Measurements

The QT interval in lead V5 was used because face immersion induces a notched T wave in that lead. It was manually measured from the onset of the QRS complex to the end of the T wave by one of authors (MY). The inter-leader coefficient of variability was 1.9% of the mean QT interval. The end of the T wave was defined as the isoelectric line intersecting a tangential line drawn at the maximal downslope of the positive T wave. The mean corrected values of the QT and the interval from the nadir of the notch to the end of the T wave (Tnadir–Tend) were obtained after the 3 successive QT and Tnadir–Tend were corrected to the heart rate, according to Bazett’s formula.

Comparison of the Configuration of the T Wave Before and After Treatment

To identify the interval representative of TDR, we compared the configuration of the T wave of the same patient before and after treatment, assuming that the decrease in the QTc interval after treatment was associated with the decrease in the TDR, as based on data from previous experimental studies. The representative T wave was chosen from each ECG when the preceding RR interval was identical both before and after treatment (Figs 2–4).
Genetic Analysis

Genomic DNA was isolated from anticoagulated blood samples after all participants gave informed consent. Exons encoding the complete sequence of the KCNQ1 and KCNH2 genes were amplified using polymerase chain reaction (PCR) analysis (PC707–02 ASTEC-Japan, thermal cycler). Subsequently, amplicons were analyzed by single-strand conformational polymorphism analysis. Gels were run at room temperature, and then silver-stained (Nippon Bio-Rad) and air-dried. DNA fragments showing aberrant bands were purified (Qiagen, PCR purification kit), sequenced by a BigDye cycle sequencing kit (Applied Biosystems, Perkin-Elmer), and analyzed on an ABI-310 automatic sequencer (Applied Biosystems, Perkin-Elmer) according to the supplier’s instructions. The genetic analyses revealed 2 missense mutations in the 2 LQT1 families and 1 missense mutation in 1 LQT2 patient. One deletion was found in 1 LQT2 patient (Table 1).

Statistical Analysis

Wilcoxon’s rank test and Fisher’s exact probability test were used. A probability value of <0.05 was considered significant.
Results

Changes in QTc Values During the Test

The QTc value of all patients was already prolonged at maximum heart rate during the face immersion test performed before treatment. Moreover, at the minimum heart rate, the QTc value was prolonged, except in 1 patient (Fig 1a). The mean QTc value, amplified by the face immersion test before treatment (0.504±0.039 s1/2), significantly decreased to 0.428±0.031 s1/2 after treatment (p=0.0431), even at the minimal heart rate (Fig 1b). One of the 5 children showed a normal QTc value after treatment.

Comparison of the Configuration of the T Wave During the Test Before and After Treatment

The notch in the T wave in Case 1 (LQT1 form) disappeared after treatment (Fig 2a). The single peak of the T wave after treatment coincided with the nadir of the notch of the T wave before treatment. The notch in the T wave in Case 2 (LQT1 form) was not as prominent as that in Case 1 before treatment (Fig 2b). The T wave after treatment showed a single peak, which coincided with the minor notch in the ascending limb of the T wave before treatment. Case 3 (LQT1 form) showed a T wave with a single peak both before and after treatment, with a decrease in the QTc value of 70 ms1/2 and a decrease in the corrected Tpeak – Tend value of 32 ms1/2 at the minimum heart rate (Fig 3). The notch in the T waves in Cases 4 and 5 (LQT2 form) remained the same after treatment, although the QTc value decreased (Fig 4a,b). The interval between the onset of the QRS complex and the nadir of the notch both before and after treatment was the same, and the interval from the nadir of the notch to the end of the T wave was for the most part shortened.

Fig 5 shows the significant positive relationship (p<0.0001) between the decrease in the QTc and the decrease in the corrected interval representative of TDR in each patient when the interval was defined as that from the nadir to the end of the notched T wave, except for the case 3.

Discussion

The present study demonstrated that the interval representative of TDR on the surface ECG can be obtained from the nadir of the notch to the end of the T wave in children and adolescents with congenital LQTS. An experimental study had shown that the interval from the nadir of the initial negative T wave to the end of the T wave is representative of the TDR, when complex (inverted, notched or biphasic, and triphasic) T waves are present!1 but whether that definition applied to the clinical setting when the T wave shows a notched or bifid configuration is still a subject of controversy.12 – 15 In the present study the single peak of the T wave before treatment coincided with the nadir of the T wave before treatment (Fig 2) and furthermore, that interval was for the most part shortened (Fig 4). A significant positive relationship was obtained between the decrease in the QTc value and the decrease in the interval representative of TDR when the interval was defined as that from the nadir to the end of the T wave (Fig 5). Further investigation is needed to determine whether the same method can be adapted in adult patients, as the QT interval and QT dispersion responses to drug therapy differ among pediatric and adult patients.20

Another point to be considered is that β-blockers do not substantially influence QT interval duration. The available epidemiological evidence shows that the QT interval on the resting ECG of patients taking β-blockers is only slightly shortened when the QTc value is considered.21 In the present study, both the QTc interval and the corrected interval representative of TDR shortened during face immersion after therapy. One of the reasons for a reduction in the QTc value may be the effect of mexiletine, because Iκs block may be induced by face immersion and because the sodium channel block by mexiletine reduces transmural dispersion of repolarization in the LQT2 form (Iκs block).22 Further investigations with more patients to show the difference in the QTc values between treatment groups are needed.

A limitation of the present study was a small number of patients used for the analysis, but to the best of our knowledge, this is the first investigation to focus on the interval representative of TDR when complex T waves are present. Clinically, it would be very useful to show the difference in TDR between genotype, gender, age and treatment groups. A prospective, controlled study would indicate the usefulness of a decreased TDR as a surrogate marker for positive clinical outcomes.

Conclusion

The present study showed that the interval representative of the TDR can be obtained from the clinical surface ECG in children and adolescents with LQTS, when it is defined as being from the nadir to the end of the T wave.

References

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