Cut-Offs for Screening Prolonged QT Intervals From Fridericia’s Formula in Children and Adolescents
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Background: The corrected QT interval (QTc) according to Bazett's formula (QTc = QT/RR^{1/2}) has been used in clinical practice. Bazett's formula, however, overcorrects the QT interval at fast heart rates and undercorrects it at low heart rates. Guidelines and some investigators have recommended using Fridericia's formula (QTc = QT/RR^{1/3}) in these cases, especially in tachycardic subjects. The aim of the present study was to determine cut-offs for QTc suitable for screening pediatric subjects with prolonged QT intervals, based on manually measured values corrected by Fridericia's formula in a large number of subjects.

Methods and Results: Three consecutive QT and RR intervals were measured in 4,655, 4,655, and 5,273 1st, 7th, and 10th graders, aged 6, 12, and 15 years, respectively. Each QT interval was corrected by Fridericia's formula, and mean values were calculated. Determination of the cut-offs for screening was based on the prevalence of abnormal electrocardiographic phenotypes of 1:1,164 and on the upper 0.025 percentile in the QTc distribution derived from previous studies. The tentative cut-offs suitable for screening subjects with prolonged QT intervals were 430 ms for 1st graders, 445 ms for 7th graders, and 440 and 455 ms for 10th grade boys and girls, respectively.

Conclusions: These tentative cut-offs can be used to screen subjects with prolonged QT intervals in the clinical setting. Further studies are needed to confirm their validity. (Circ J 2010; 74: 1663–1669)

Key Words: Cut-off; Fridericia's formula; QT interval; Screening

Long QT syndrome (LQTS) is a rare disease characterized by prolonged ventricular repolarization and increased propensity to syncope and sudden cardiac death. Because the QT interval is inversely related to heart rate, measured QT intervals are generally corrected for heart rate to identify prolongation. Among many formulae investigated, the corrected QT interval (QTc) according to Bazett’s formula (QTc = QT/RR^{1/2}) has been used in clinical practice and in the medical literature. Bazett’s correction, however, overcorrects the QT interval at fast heart rates and undercorrects it at low heart rates. Published diagnostic criteria using the QTc from Bazett’s formula recommend additional diagnostic caution when scaling with tachycardic patients. Under these circumstances, the guidelines of the International Conference of Harmonization, as well as some authors, recommend using Fridericia’s correction (QTc = QT/RR^{1/3}). Cut-offs used to screen children and adolescents with prolonged QT intervals, corrected according to Fridericia’s formula, have previously been reported using automatically measured data for QT and RR intervals (QT/RR data). The accuracy of automatic QTc measurements, however, is questionable in many cases, and should be supplemented by manual readings.

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The estimated prevalence of symptomatic patients with LQTS is around 1 in 5,000 subjects. The prevalence of abnormal electrocardiographic (ECG) phenotypes, namely that of abnormally prolonged QT intervals irrespective of the presence or absence of symptoms and/or family history, was estimated to be 1 in 1,164 among 7th graders aged 12 years.
No criteria have been proposed for the pediatric population using Fridericia’s correction with manually measured data, although subjects in this age group are frequently tachycardic.

Methods

Subjects
Subjects were 1st, 7th, and 10th graders, aged 6, 12, and 15 years, respectively, in Kagoshima, Japan. Of these, the 1st and 7th graders were the same cohort. ECGs of 4,655 subjects (2,368 boys and 2,287 girls) were recorded when they were in the 1st grade in 1994 and again when they were in the 7th grade in 2000. The same 1st and 7th graders were the subjects of a previous report. ECGs from 10th graders were obtained 3 years later, in 2003; only 2,735 subjects (1,312 boys and 1,423 girls) from this cohort re-entered the present study, either because they moved out of Kagoshima or because they entered private high schools. Children and adolescents in public schools participated only in the Kagoshima City Medical Association programs during the study period. In 2003, 2,538 new 10th graders were included, giving a total of 5,273 15-year-old subjects (2,598 boys and 2,675 girls). None of the subjects had any abnormal findings including arrhythmias with wide QRS, except for QT intervals. Information on the subjects (name, sex, and ECGs) was collected from the Screening Program for Heart Diseases in Kagoshima, operated by the Kagoshima City Medical Association. We obtained permission from the ethics committee of the National Hospital Organization Kagoshima Medical Center to use and analyze these data, on the condition that the confidentiality of all personal data would be maintained.

Measurement and Correction of QT Intervals
All resting ECGs were recorded at a speed of 25 mm/s at each school, by medical technologists from the Screening Program for Heart Diseases in Kagoshima. The QT interval of 3 consecutive beats was measured from the onset of the Q wave to the end of the T wave in lead V5. 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. Bifid T waves, but not U waves, were included in the QT measurement. When the notch was present in more than 3 leads and the notch appeared at the same timing, the T wave was defined as the bifid T wave. The QT/RR data from the 1st and 7th grade subjects in the previous report were used in the present study. The data in the previous study were measured by 2 authors (T.F. and M.Y.); the intra-reader coefficient of variability for mean QT interval for the 2 authors was 1.7%, and the interreader coefficient of variability was 1.9%. The QT/RR data for the 10th grade subjects were measured by 1 author (M.Y.) in the present study. The QT/RR data for each of 3 consecutive beats were corrected using Fridericia’s formula (QTc=QT/RR1/3) and the mean values for the 3 consecutive QTc were used.

Comparison of Bazett’s Formula With Fridericia’s Formula for QTc
To assess the effectiveness of the present study, association between the RR intervals and the uncorrected QT intervals, QTc from Bazett’s and from Fridericia’s formulas were determined using data of 7th grade girls.

Cut-Offs for Screening Subjects With Prolonged QT Intervals
In the previous study using the same cohort, the prevalence of abnormal ECG phenotypes was 4 in 4,655 subjects (1 in 1,164) in the 7th grade and 0 in 4,655 in the 1st grade. In another study using automatically measured data corrected using Fridericia’s formula, a long hiatus was identified at the statistical point of the upper 0.025 percentile in the distribution of QTc intervals in both genders in all groups (1st, 7th, and 10th graders). The hiatus was defined as the absence of subjects between neighboring QTc in the distribution of the
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QTc. Cut-offs for screening were then determined by grade and gender, using 2 different methods. First, cut-offs were determined based on the long hiatus in the distribution of the QTc intervals near the statistical point of the upper 0.025 percentile (mean QTc +3.480756×SD). Second, cut-offs were determined to screen the 7th graders, at least at a rate of 1 in 1,164. Because the incidence of subjects with abnormal ECG phenotypes and/or symptomatic patients may increase with age, the cut-offs should screen more than 1 in 1,164 for 10th graders. The cut-offs for 1st graders could be based only on the statistical distribution, because none of the cohort had abnormal ECG phenotypes in the 1st grade in the previous study.10

Statistical Analysis
Difference in the mean QTc between genders was examined using unpaired Student’s t-tests. P<0.05 was considered statistically significant.

Results
Comparison of QTc From Bazett’s and Fridericia’s Formulas
Association between RR intervals and the uncorrected QT intervals, QTc from Bazett’s and Fridericia’s formulas were determined using the data of 7th grade girls. Because the QT intervals are affected by the RR intervals, namely by heart rates (Figure 1), the QT intervals are corrected by the RR intervals to minimize the effect of heart rates usually with Bazett’s formula, but the QTc intervals from Bazett’s formula were still affected by the RR intervals (r=-0.464, P<0.0001; Figure 2). Bazett’s correction overcorrects at high heart rate (at short RR intervals) and undercorrects at low heart rate (at long RR intervals).

Figure 2. RR interval vs corrected QT interval (QTc) from Bazett’s formula in 7th grade girls.

Figure 3. RR interval vs corrected QT intervals (QTc) from Fridericia’s formula in 7th grade girls.
Table. Number of Subjects vs Manually Measured QT/RR Intervals

<table>
<thead>
<tr>
<th></th>
<th>1st graders</th>
<th></th>
<th>7th graders</th>
<th></th>
<th>10th graders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
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<tr>
<td></td>
<td>(n=2,368)</td>
<td>(n=2,287)</td>
<td>(n=2,368)</td>
<td>(n=2,287)</td>
<td>(n=2,598)</td>
<td>(n=2,675)</td>
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<tr>
<td>RR interval (ms)</td>
<td>764±108</td>
<td>733±106</td>
<td>805±132</td>
<td>765±122</td>
<td>949±185</td>
<td>873±154</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>332±23</td>
<td>327±22</td>
<td>353±25</td>
<td>350±25</td>
<td>360±29</td>
<td>358±27</td>
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<tr>
<td>HR (beats/min)</td>
<td>82±12</td>
<td>84±12</td>
<td>77±12</td>
<td>81±13</td>
<td>66±13</td>
<td>71±13</td>
</tr>
<tr>
<td>Mean QTc (ms)</td>
<td>367±18</td>
<td>364±18</td>
<td>380±18</td>
<td>384±18</td>
<td>368±20</td>
<td>376±20</td>
</tr>
<tr>
<td>0.025 percentile (ms)</td>
<td>430</td>
<td>427</td>
<td>443</td>
<td>447</td>
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<td>446</td>
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</tbody>
</table>

Data are expressed as mean±SD.
HR, heart rate; QTc, corrected QT interval.

Figure 4. Corrected QT intervals (QTc) using Fridericia’s formula in (A,B) 7th grade boys and (C,D) girls. (A) Total boys and (C) total girls; (B) 51 boys and (D) 74 girls with the longest QTc.
heart rate (at long RR intervals). In contrast, the QTc intervals with Fridericia’s formula were not affected by the RR intervals (Figure 3).

**Cut-Offs for Screening Subjects With Prolonged QT Intervals**

The mean QT intervals increased in duration with age (Table). The mean heart rates of 10th grade boys were lower than those of 10th grade girls, and 7th grade boys and girls. Thus, the mean QTc for 10th grade boys was lower than that for 10th grade girls, and 7th grade boys and girls. There were gender differences in mean QTc in all grades (P<0.0001 for all groups). The upper 0.025 percentile cut-offs were around 430 ms for 1st graders, around 445 ms for 7th graders, and 0.440 and 0.445 ms for 10th grade boys and girls, respectively (Table).

The distribution of QTc in 7th graders contained the 1st long hiatus between 438 and 448 ms in boys, and between 436 and 446 ms in girls (Figure 4). Supposing a cut-off for QTc of 445 ms for 7th graders, this point is included in this hiatus, and the cut-off would identify 4 out of 2,369 boys (1 in 592) and 3 out of 2,286 girls (1 in 762). The 1st long hiatus in the distribution of QTc in 10th graders (Figure 5) occurred between 437 and 442 ms in boys and between 455 and 504 ms; tentative cut-offs could therefore be 440 and 455 for boys and girls, respectively, if the long hiatus is thought to be important. These cut-offs identified 5 out of 2,598 boys (1 in 520) and 4 out of 2,675 (1 in 669) girls, indicating a slightly higher incidence in 10th graders compared with 7th graders. Because there were no 1st graders with abnormal ECG phenotypes in the previous study,10 430 ms, near to the start of the upper 0.025 percentile, was tentatively used as a cut-off for 1st graders (Figure 6). The tentative cut-offs suitable for screening subjects with prolonged QT intervals are 430 ms for 1st graders, 445 ms for 7th graders, and 440 and 455 ms for 10th grade boys and girls, respectively.

**Discussion**

The present study identified tentative cut-off QTc for screening children and adolescents with prolonged QT intervals in the 1st, 7th, and 10th grades. These cut-offs were measured manually and corrected with Fridericia’s formula for children and adolescents and can be used in the clinical setting to screen subjects with prolonged QT intervals, even those with high heart rates.

Bazett’s formula remains the standard for clinical use worldwide, although it may over- or undercorrect when the heart rate is fast or slow, respectively. Fridericia’s formula
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suffers from the same limitations at slow heart rate, but could provide a more accurate correction factor in subjects with tachycardia. Figure 2 clearly shows that Bazett’s formula over- or undercorrects when the heart rate is fast or slow, respectively. Figure 3 shows that Fridericia’s formula overcorrects a little at low heart rate (at long RR intervals), because the correlation coefficient was slightly positive (r = 0.035), but the association was not significant. The former and the present data suggest that we may recommend using Fridericia’s formula.

Clinically applicable pediatric cut-offs for QTc intervals for Fridericia’s formula are needed. Aihoshi et al determined cut-offs for QTc corrected with Fridericia’s formula to screen children and adolescents with prolonged QT interval, and these criteria have been used clinically in the Screening Program for Heart Diseases in some areas in Japan. These values, however, were based on automatically measured data, and criteria using manually measured data are lacking. One of the reasons why Fridericia’s formula has not been used nationwide may be the lack of clinically applicable pediatric cut-offs. To our knowledge, the present study is the first to derive cut-offs using manually measured data corrected with Fridericia’s formula.

The cut-off for 10th grade boys was lower than that for 7th grade boys. This may be because the mean heart rate in 10th graders was significantly lower than that in 7th graders, although the mean QT interval was longer in 10th graders than that in 7th graders.

There were limitations to the present study. We produced only tentative cut-offs based on data for 1st, 7th, and 10th graders, aged 6, 12, and 15 years, respectively. Subjects in the 1st, 7th, and 10th grades are required to participate in the Screening Program for Heart Diseases in Japan, and ECG data are therefore available for children in these grades, provided that we obtain permission from the ethics committees to use and analyze these data. It would be more difficult to obtain a large sample of good ECG data from children in other grades, although cut-offs should be prepared for all ages in the future. Another limitation is that the tentative cut-offs in the present study have not been applied clinically to the Screening Program for Heart Diseases in Japan. We should determine whether these cut-offs are appropriate to screen all children who are genetically or clinically diagnosed with long QT syndrome.

In conclusion, these cut-offs can be used to screen pediatric subjects with prolonged QT intervals in a clinical setting, and further studies should be conducted to confirm the validity of these results.

Figure 6. Corrected QT intervals (QTc) with Fridericia’s formula in 1st graders: (A) 238 boys and (B) 181 girls with the longest QTc.
References