Screening for QT Prolongation Using a New Exponential Formula

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We prospectively screened 14,227 school-aged children for evidence of QT prolongation using a exponential formula \( (e\text{QTc} = \text{QT interval}/(\text{RR interval})^{0.31}) \) and criteria (ie: abnormal eQTc was defined as being equal to or greater than 0.430 and 0.435 for male and female first-graders, respectively, and 0.440 and 0.445 for male and female seventh-graders, respectively). We previously reported that this new exponential correction of the QT interval may be useful for eliminating the effect of heart rate in school-aged children. Computer analyses detected 13 children with abnormally prolonged eQTc. All of the children who had abnormal QTc values by conventional QTc criteria also had abnormal eQTc values using the new criteria. Nine of these 13 children were ultimately confirmed to have a prolonged QT interval. Six cases of QT prolongation were detected that would not have been found if conventional screening criteria were used, since these cases had heart rates greater than 75 beats/min. One child had parents who were deaf. This case would not have been detected if only conventional screening were used. These results suggest that exponential correction of the QT interval (eQTc) is useful for prospectively screening large populations for evidence of QT prolongation. (Jpn Circ J 1995; 59: 185—189)

The QT interval of the electrocardiogram (ECG) is usually corrected using Bazett’s formula \( (\text{QTc} = \text{QT}/\text{RR}^{1/2}) \). We also have previously used QTc to screen children for evidence of QT prolongation as part of a screening program for heart disease in Kagoshima City, Japan. The criteria used included a QTc of equal to or greater than 0.46 and a heart rate of equal to or less than 75 beats/min.

However, QTc does not always adequately correct for alterations due to heart rate. Thus, different formulas have been proposed to minimize the effect of heart rate in adults. These include the cubic root formula proposed by Fridericia; Ashman’s logarithmic formula; the linear formula; Kovacs’ inverse formula; and Sarma’s exponential formula. Recent studies have demonstrated that the cubic root and the exponential formulas are the most useful for determining QT prolongation.

We previously reported that QTc fails to adequately correct for the effect of heart rate, and that a new exponential correction of the QT interval may be useful for eliminating the effect of heart rate in children.

In our previous study, we used statistical methods to determine criteria for abnormality with a new exponential formula (ie: \( e\text{QTc} = \text{QT}/\text{RR}^{0.31} \)). However, we realized that a prospective study would be needed to verify its validity.

Key words:
- Long QT syndrome
- School-aged children
- Prospective study

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In this report, we describe our results using the new formula and criteria in a prospective study in Kagoshima City in 1992.

**MATERIALS AND METHODS**

**Subjects**

A screening program for heart disease is conducted once a year for all of the first-graders (at their entrance into elementary school) and seventh-graders (at their entrance into junior high school) in Kagoshima City. Our new exponential formula and tentative criteria were used in this screening system.

The study population included 14,227 children. Of these, 6,524 were first-graders (3,306 boys and 3,218 girls) approximately 6 years of age, and 7,703 were seventh-graders (3,913 boys and 3,790 girls) approximately 12 years of age.

A medical history was taken and a physical examination, chest roentgenogram, resting supine 12-lead ECG, and treadmill exercise testing were performed for all children who had abnormally prolonged eQTc by computer analyses.

**ECG Values**

The screening program used at Kagoshima City used leads I, aVF, V₁, and V₆. The following ECG values were analyzed: RR interval, heart rate, QT interval, QTc (Bazett's formula), and eQTc (new exponential formula). These values were calculated using a computer system (FCP-1000, Fukuda Denshi, Co., Ltd.) that has been described previously. The sampling interval was 4 msec, and the recording time was 8 sec. eQTc was calculated as (QT interval)/(RR interval). The values of the QT and RR intervals have been noted in a previous study. The criteria for an abnormally prolonged eQTc was defined as being equal to or greater than 0.430 and 0.435 for male and female first-graders, respectively, and 0.440 and 0.445 for male and female seventh-graders, respectively.

**RESULTS**

Computer analyses identified 13 children as having abnormally prolonged eQTc (Table I). Nine of these 13 children were finally diagnosed as having a prolonged QT. Six of these 9 children had heart rates greater than 75 beats/min by computer analyses, therefore, these 6 cases would not have been identified if only conventional screening criteria had been used. One of these children had deaf parents (Table I, Case No. 6). Her father had congenital deafness and her mother has been deaf since infancy. The etiology for their deafness is
We have previously reported that QTc fails to adequately correct for the effect of heart rate, and that new exponential corrections of the QT interval may be useful for eliminating the effect of heart rate in children.\textsuperscript{14}

\textbf{Conventional QTc Criteria}

It is well known that the QT interval is negatively correlated with the heart rate, therefore, Bazett introduced the square root formula\textsuperscript{1}: \(\text{QTc} = \frac{(\text{QT interval})}{(\text{RR interval})^{1/2}}\). However, QTc is positively correlated with the heart rate, and false-positive cases may appear at higher heart rate. Therefore, a cut-off value is established for the heart rate in conventional QTc criteria; i.e., lower than 80 beats/min in the Minnesota-Code, and 75 beats/min in our screening program.

However, many children have heart rates higher than these cut-off values. Many false-positive cases will appear if the cut-off value is not used, and false-negative cases will appear if the cut-off value is used. Therefore, QTc appears to be unsuitable for correcting the QT interval in children, since they have higher heart rates than adults.

\textbf{Selectivity and Sensitivity of the New Criteria}

All of the children who had abnormal QTc values by conventional criteria also had abnormal eQTc values when the new criteria were used. Therefore, it should be acceptable to use eQTc instead of QTc for screening and detection of QT prolongation.

A child who had deaf parents was screened using the new criteria. However, her condition would not have been identified if only conventional screening criteria were used. Although neither of her parents was diagnosed as having prolonged QT, deafness and the long QT syndrome are closely related.\textsuperscript{15-17} Therefore, it is significant that this case was detected only when the new criteria were used.

Another important point has led us to use the eQTc value instead of the QTc value. An 11-year-old girl drowned in a swimming pool on June 22th 1992. She was finally diagnosed as a case of long QT syndrome, due to QT prolongation in her resting ECG and the appearance of torsades de pointes and ventricular tachycardia following stimulation by isoproterenol and epinephrine. A resting 4-lead ECG was obtained from her in

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The 4-lead resting supine electrocardiogram of a child who drowned in a swimming pool on June 22th 1992, taken in 1987.}
\end{figure}

\textbf{DISCUSSION}

\textbf{Principal Findings}

The principal finding of this study is the usefulness of the new exponential formula; \(\text{eQTc} = \frac{(\text{QT interval})}{(\text{RR interval})^{0.31}}\) and the tentative abnormal values of eQTc for prospective screening of a large population for evidence of QT prolongation.

\textbf{Previous Investigations}

Several investigators have studied the relationship between the QT interval and the RR interval using different formulas.\textsuperscript{1,5-10}

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the screening program for heart disease in 1987, when she was 6 years old (Fig. 1). The QTc value of this ECG was 0.51, but she was not identified as having prolonged QT by the conventional screening criteria, since her heart rate was greater than 75 beats/min. In contrast, the eQTc value in this ECG is 0.473 which indicates that she would have been identified as having prolonged QT if the new criteria were used.

There is not yet any golden standard for judging the long QT syndrome, since QTc is inadequate for correcting the QT interval in children, and a genetic diagnosis for the long QT syndrome has not yet been established. Therefore, it is difficult to evaluate the sensitivity of the new criteria.

Differences between the QT Interval Measured in 4-Lead ECG and That Measured in 12-Lead ECG

The QT interval is usually measured in standard 12-lead ECG. However, the screening program in this study used 4-lead ECG. Therefore, we compared the QT interval in 4-lead ECG to that in 12-lead ECG. We used the ECG values of 251 first-grade boys, 259 first-grade girls, 253 seventh-grade boys, and 251 seventh-grade girls from the screening program for heart disease in Kagoshima City in 1994. There were no significant differences between the QT interval in 4-lead ECG to that in 12-lead ECG.

Limitations

Four children were identified as having abnormal eQTc values by computer analyses, but were ultimately found to be normal. The eQTc values in these four cases were normal by manual measurement. One possible explanation for this result is that the computer system may have failed to read either the beginning of the QRS-complex or the end of the T-wave due to baseline tremor in these false-positive cases.

We investigated the methods used to screen for QT prolongation in a previous report[14] and in this prospective study. The former cases with long QT syndrome should be examined further using the new formula and criteria.

Similarity with Fridericia’s Correction

The authors used 0.31 as the exponential parameter in this prospective study. Our previous report[14] was the first to show tentative criteria for screening of QT prolongation using an exponential formula in children. To date, there has been no study of the criteria for Fridericia’s correction in children. The exponential parameter used to calculate eQTc (0.31) is similar to that in Fridericia’s formula (0.33). Therefore, it is likely that the same cases would have been detected if Fridericia’s formula had been used.

We are now comparing the present exponential formula with Fridericia’s formula, and investigating abnormal values from Fridericia’s formula in children, using data from the screening program for heart disease in Kagoshima City in 1992 and 1993.

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