EXPONENTIAL CORRECTION OF QT INTERVAL TO MINIMIZE THE EFFECT OF THE HEART RATE IN CHILDREN

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The exponential correction of the QT interval (eQTc) was studied using 12,543 resting electrocardiograms obtained in children (first and seventh graders) who were screened for heart disease in Kagoshima City.

The values of eQTc to minimize the effect of the RR interval were estimated using following exponential model, $eQTc = (QT \text{ interval}) / (RR \text{ interval})^k$. The parameter $k=0.31$ was found to be the most useful exponent. The distribution of eQTc values showed a hiatus or break at probability points near $p<0.001$ or $p<0.0005$. Tentative criteria for an abnormally long eQTc were selected using these points and the following convenient data: 0.430 and 0.435 for the male and female first graders, and 0.440 and 0.445 for the male and female seventh graders, increased by 0.005, respectively.

Abnormal values must ultimately be selected using data on patients with the long QT syndrome; however, our findings suggest that the exponential correction of the QT interval may be useful in large-scale screening programs for detecting a QT prolongation in young school children.

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THE QT interval of the electrocardiogram (ECG) has been corrected using the square root Bazett's formula (QTc)¹ to minimize the influence of the heart rate. Since then, many other formulas such as the cubic root², logarithmic^{3,4}, linear^{4–7} and exponential⁸ formulas have been proposed to correct the changes induced by heart rate, because there remains the heart rate-induced changes in the QTc. Recent studies have demonstrated that the cubic root Fridericia's

formula⁹ or the exponential formula^{8,10,11} are most useful. Thus the exponential formula is one of the best approaches, because Fridericia's formula is also an exponential formula when 1/3 is used as the exponent.

However, there have been no reports concerning an improved formula using the exponential model and the abnormally long values of the improved formula in pediatric age groups, even though children show rapid heart rates. Thus the application of an improved correction of the QT interval is essential.

Our objectives were to (1) clarify the relationship between the QTc and several

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Fig.1. Relationship between the computer-analysed QTc and the manually measured QTc is shown.

ECG values and body indexes; (2) develop an improved formula to minimize the changes induced by heart rate using the exponential formula, and (3) determine the abnormally prolonged values for the newly established QT correction, using 12,543 resting ECGs of school-aged children who participated in a screening program for heart disease in Kagoshima City, Japan.

SUBJECTS AND METHODS

Subjects

Subjects were 12,543 children: 6,011 first graders (3,062 boys and 2,949 girls) aged 6 years, and 6,532 seventh graders (3,233 boys and 3,299 girls) aged 12 years, whose resting ECGs showed no abnormal findings except for QT prolongation by the computed system for ECG analysis (FCP-1000, Fukuda Denshi, Co. Ltd.). The screening program used at Kagoshima City utilized leads I, aVF, V1, and V6.

ECG values

The following ECG values were analyzed; PR interval, heart rate, mean QRS axis, QT interval, QTc (Bazett's formula), and voltages of Rv1 and Rv6. In the computed system, these values were calculated as follows.

RR interval: After the mean values of all RR intervals for a child were calculated,

the second mean value of selected RR intervals (Within $\pm 25\%$ of the first mean value) was calculated. The second mean value was used as the RR interval for each child.

Heart rate: The heart rate (beats/min) was calculated as $60/(\text{RR interval})$. The second mean value of the RR interval mentioned above was used.

QT interval: The mean value of all QT intervals of all leads for a child was calculated. This value was used as the QT interval for the child.

QTc (Bazett's formula): The QTc was calculated as $(\text{QT interval})/(\text{RR interval})^{1/2}$.

The values of the QT and RR interval mentioned above were used.

Body indexes

Body indexes such as height, weight, chest circumference, and obesity index according to Murata¹² were used for each child determined at each school.

Exponential QT correction (eQTc)

The values of eQTc to minimize the effect of the heart rate were estimated by the following exponential model,

$$eQTc = (\text{QT interval})/(\text{RR interval})^k,$$
 where k is the parameter of the exponent. Staniforth reported that a set of parabolas was produced with minima centering around 0.3, when plots of the residual mean square were made for a range of values of k (0.1–0.7) for each subject in adults.¹¹ Therefore estimates of eQTc were calculated for values from 0.200 to 0.400 at intervals of 0.001. The correlation coefficient between the eQTc and the RR interval was obtained for each parameter k . The best fit of parameter k was defined as that in which the correlation coefficient was closest to 0. The parameter k , in which there was no statistical significance in the correlation coefficient ($p > 0.05$), was selected for the exponential model, and named as the useful range. That is, the eQTc estimated by the above model was not significantly affected by the RR interval.

Manual measurements of QTc from the Electrocardiograms

To compare the values between the computer-analyzed QTc and that measured

TABLE I STATISTICAL DATA OF THE QTc VALUES IN 12,543 SCHOOL-AGED CHILDREN

	Group A#	Group B	Group C	Group D
Total no.	3,062	2,949	3,233	3,299
Mean	0.397	0.398	0.394	0.406
S.D.	0.018	0.019	0.021	0.022
Minimum	0.340	0.332	0.323	0.334
Maximum	0.462	0.468	0.475	0.487
QTc $\geq$ 0.45 ^s	9	19	24	78
(%)	(0.29%)	(0.64%)	(0.74%)	(2.36%)

#; Groups A, B, C, and D refer to first-grade males, first-grade females, 7th-grade males, and 7th-grade females, respectively.

^s; Number of children who showed QTc equal to or greater than 0.45, and the incidence in each group.

TABLE II CORRELATION BETWEEN QTc AND OTHER INDEXES

Groups	height	weight	PR ^s	QRS	RR	Rv1	Rv6
A#			0.051**	0.081*****	-0.488*****		-0.067*****
B				0.085*****	-0.478*****	-0.064***	-0.112*****
C	-0.085*****	-0.065*****	0.049**	0.063***	-0.502*****	0.039*	-0.095*****
D			0.090*****	0.074*****	-0.537*****		-0.096*****

Each line shows the correlation coefficients between the QTc and each index, and the probabilities (*; $p < 0.05$, **; $p < 0.01$, ***; $p < 0.001$, ****; $p < 0.0005$, *****; $p < 0.0001$).

#; Group A, B, C, and D refer to first-grade males, first-grade females, 7th-grade males, and 7th-grade females, respectively.

^s; The words PR, QRS, RR, Rv1, and Rv6 refer to mean PR interval, duration of QRS complexes, RR interval, voltage of Rv1, and that of Rv6, respectively.

manually, we measured the QT and RR intervals in lead I of ECGs of 101 seventh graders selected at random. The ECGs were recorded at 25 mm/sec, the same as the computer analysis. Measurements were done manually by one of the authors (M.Y.) from the beginning of the QRS complex to the end of T waves. The mean values of 5 consecutive QRST complexes were used as the manually measured QTc.

Statistical method

Analyses of correlation and a stepwise-multiple regression model were carried out on the IBM 3081K computer system of the Kagoshima University, using a statistical program package of SAS. Student's t-test was used to evaluate the means, and the chi-square test was used for the association.

RESULTS

Differences between the computer-analyzed QTc and the manually measured QTc

The relationship between the computer-analyzed QTc and the manually measured QTc is shown in Fig. 1. The correlation coefficient was 0.936 ($p < 0.001$, $y = 0.0237 + 0.947x$, where y is the computer-analyzed QTc, while x is the manually measured QTc).

Statistical analyses of the relationships between QTc and other indexes

The first and seventh graders were each divided into 2 groups according to sex, and designated as follows; group A, first-grade boys; group B, first-grade girls; group C, 7th-grade boys, and group D, 7th-grade girls. The mean values and the incidence of

Fig.2. Relationship between the QT interval and the RR interval in group D.

Fig.3. Relationship between the QTc (Bazett's formula) and the RR interval in group D.

TABLE III BEST FITS OF THE EQUATIONA AND USEFUL RANGES IN EACH GROUP

Groups	Best fit	Useful ranges [#]
A ^s	0.309	0.297–0.321
B	0.305	0.293–0.317
C	0.319	0.309–0.329
D	0.308	0.298–0.318

[#]; Refer to the text.

^s; Groups A, B, C, and D refer to first-grade males, first-grade females, 7th-grade males, and 7th-grade females, respectively.

QTc equal to or longer than 0.45 in each group appear in Table I. Group D showed a significantly longer mean QTc than the

other 3 groups ($p < 0.001$), and group C showed longer QTc than groups A and B ($p < 0.001$). An incidence of the QTc equal to or longer than 0.45 was significantly higher in group D than in the other groups ($p < 0.0005$).

The correlation coefficient between QTc and the other ECG values or body indexes is shown in Table II. The highest level of significance was found in the relationship between QTc and the RR interval. Other relatively high statistical significances were shown in the duration of QRS complexes and the voltage of Rv6.

Best fit of the equation

Figs. 2 and 3 show the relationships between the RR interval and QT interval, and

Fig.4. Relationship between the eQTc (new formula) and the RR interval in group D.

those between the RR interval and the QTc, in group D. Fig. 3 clearly shows that the QTc failed to minimize the heart rate-induced changes.

Next, an exponential formula for correcting the QT interval was examined to minimize the effect of the heart rate. The best fits of the exponent and the useful range in each group appear in Table III. The best fit of the exponent was 0.31, except in group C, which showed the best fit at 0.32. Fig. 4 shows no relationship between the RR interval and the eQTc in group D when 0.31 was used as the exponent.

It would have been best to use a different value for group C, but this was not clinically practical. If the value 0.31 as the exponent for group C was within the useful range, it might be applied to all four groups. Table IV shows the statistical data on the eQTc in each group using 0.31 as the exponent. This table also shows the probability values of $p < 0.05$, $p < 0.01$, $p < 0.005$, $p < 0.001$ and $p < 0.0005$ from the normal distribution. For example, the probability point of $p < 0.05$ refers the value of $(\text{mean}) + 1.960 \times (\text{standard deviation})$.

Abnormal value for the eQTc in each group

Figs. 5-a to 5-d show the distribution of the values of the eQTc in every 0.001 of the last 100 children of group A, 60 of group B, 140 of group C, and 111 of group D. Each Figure also shows the probability points of $p < 0.001$ and $p < 0.0005$ from the normal distribution.

All groups showed a large hiatus, or "break", in the consecutive distribution of the eQTc values near the probability points of $p < 0.001$ or $p < 0.0005$. The precise abnormal value should be determined after the clinical measurement of ECGs of patients with the long QT syndrome. However, these breaks were thought to be useful as screening values for abnormally prolonged eQTcs. The tentative criteria for an abnormally long eQTc value for groups A, B, C, and D might be 0.430, 0.435, 0.440, and 0.445 (increasing by 0.005), respectively.

DISCUSSION

Various formulas to correct the heart rate-induced changes have been established for use in adults, with the cubic root Fridericia's formula⁹ or the exponential formula^{8,10,11} being thought of as the most useful statistically according to the Akaike Information Criterion^{8,9} or the mean-squared residual (MSR) values^{8,9,11}. Thus, the exponential formula is one of the best, in that Fridericia's formula is also exponential when 1/3 is used as the exponent. Staniforth also focused that the minimum MSR centered around 0.3 as the exponent¹¹.

However, there are no reports concerning an improved formula using the exponential format and abnormally long values for pediatric age groups, even though infants and children show high heart rates. Thus an improved formula with criteria for abnormally long values is desirable.

Fig. 5-a

Fig. 5-c

Fig. 5-b

Fig. 5-d

Fig. 5. a-d distribution in order of eQTc by 0.001 of children sampled in group A (n=100) (5-a), group B (n=) (5-b), group C (n=140) (5-c), and group D (n=111) (5-d).

TABLE IV STATISTICAL DATA ON eQTc VALUES IN SCHOOL-AGED CHILDREN

	group A [#]	group B	group C	group D
Total no.	3,062	2,949	3,233	3,299
Mean	0.375	0.376	0.378	0.386
S.D.	0.015	0.016	0.017	0.017
Minimum	0.326	0.318	0.322	0.336
Maximum	0.440	0.452	0.442	0.459
Probability points				
p < 0.05	0.404	0.407	0.411	0.419
p < 0.01	0.414	0.417	0.422	0.430
p < 0.005	0.417	0.421	0.426	0.434
p < 0.001	0.424	0.429	0.434	0.442
p < 0.0005	0.430	0.434	0.440	0.448

[#]; Group A, B, C, and D refer first-grade males, first-grade females, 7th-grade males, and 7th-grade females, respectively.

^{\$}; Refer to the text.

In this report, we used the computer-analyzed QT and RR intervals. Since the correlation coefficient between the computer-analyzed QTc and manually measured QTc showed a significantly positive correlation, we applied the computer-oriented data. Also, since the computer-analyzed data collected in screening programs for

heart disease are frequently used among the Japanese pediatric cardiologists, we have to determine the statistical values of the computer-analyzed QTc or the eQTc.

The data presented showed that the best fit in the exponential formula was 0.31 for the first graders, both boys and girls (groups A and B) and the seventh-grade females

(group D). While 0.31 was not the best fit for the seventh-grade males (group C), this value is within the useful range. Since it is convenient to use one formula, 0.31 can be used for all groups.

The abnormal value must be finally selected using the data on patients with the long QT syndrome. We decided tentative criteria statistically. An interesting finding was that the distribution of the eQTc in all groups showed a hiatus or break at the probability points of around $p < 0.001$ or $p < 0.0005$. This was most apparent in group D. Tentative criteria were selected using the probability points near $p < 0.001$ or $p < 0.0005$, and the convenient data: 0.430 for group A, 0.435 for group B, 0.440 for group C, and 0.445 for group D, increasing by 0.005. Table IV also shows that the differences between the nearest groups at the probability points of $p < 0.001$ and $p < 0.0005$ are around 0.005.

These findings suggest that the exponential correction of the QT interval is useful in pediatric age groups as has been shown in adults, and that eQTc can be used in screening for the QT prolongation in children.

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