ORIGINAL ARTICLE

QT Correction Methods in Infants and Children: Effects of Age and Gender

Abraham Benatar, M.B. Ch.B., Ph.D., F.A.C.C., and Arjen Feenstra, M.D.

From the Department of Pediatric Cardiology, University Hospital UZ Brussel, Free University of Brussels (VUB), Brussels, Belgium

Background: Accurate determination of the QTc interval in children is important especially when using drugs which can prolong cardiac repolarization. Previous work suggests the most appropriate correction formula to be $QTc = QT/RR^{0.38}$. We set out to compute the best population-derived age and gender-related QT correction formula factor in normal children.

Methods: We evaluated a cohort of 1400 healthy children. From a resting 12-lead electrocardiogram, QT and RR intervals were measured. Subjects were divided into four age and gender groups: 0–1 years ($n = 540$); 1–5 years ($n = 281$); 5–10 years ($n = 277$), and >10 years ($n = 302$). QT/RR intervals were plotted and fitted with two regression analyses, linear regression obtaining constant α ($QTc = QT + \alpha \times (1-RR)$), and log-linear analysis deriving constant β ($QTc = QT/RR^\beta$). Furthermore, regression analysis of QTc/RR for the two formulas was performed obtaining slope and R^2 .

Results: Correction constant α decreased steadily with increasing age, genders remained on par until 10 years of age followed by more pronounced decrease in females (range 0.24–0.18). The β constant showed a similar trend however with more pronounced decline (range 0.45–0.31). Regression slopes of QTc/RR plots (all ages and both genders) were close to zero (both formulas).

Conclusion: For the full range of pediatric subjects, the optimum population-based correction factors α and β decreased with increasing age and gender, digressing more so in adolescent girls. More specific correction factors, based on age and gender, are necessary in QT correction.

Ann Noninvasive Electrocardiol 2015;20(2):119–125

QT normal; QTc formula; cardiac repolarization; children; adolescents

In 1920, Bazett corrected the QT interval to make it comparable for different heart rates.¹ In the same year, using a similar strategy Fridericia derived $QTc = QT/RR^{0.33}$.² Since then a number of formulas have been developed, however, worldwide the most common still in use is Bazett's formula, possibly on account of its simplicity.

At higher heart rates these formulas notoriously over- or under-correct the QT interval. With the Bazett formula, at higher heart rates QTc may be erroneously prolonged while with the Fridericia correction, a true prolongation of QT could be masked. In drug development, it is widely acknowledged that QTc Bazett overcorrects at elevated heart rates and its use is therefore not recommended. In this context, the International Conference on

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have updated their recommendations on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs.³

The optimal approach to this correction problem would be a collection of multiple electrocardiograms from an individual and derivation of an individual-specific correction factor. Although ideal, this approach is not always practical. Using a population-specific correction factor is easier and more practical. Previous meta-analysis data from seven clinical trials for attention deficit/hyperactivity disorder⁴ involving 2888 children and adolescents, aged 6 to 17 years, showed that the

Address for correspondence: Abraham Benatar, Department of Pediatric Cardiology, Universitair Ziekenhuis Brussel, 101 Laarbeeklaan, 1090 Brussels, Belgium. Fax: 00322-4775773; E-mail: abraham.benatar@uzbrussel.be

most appropriate formula encountered was $QT_c = QT/RR^{0.38}$.

With this in mind, we set out to compute the best population-specific QT correction from a sample of normal infants, children, and adolescents in our population.

METHODS

We prospectively enrolled a cohort of 1400 healthy children male and female with parental informed consent. Criteria for exclusion of the study included a family history of arrhythmia or sudden death, bundle branch block on ECG, use of medication known to prolong the QT interval or alter the T wave on ECG, metabolic or central nervous system disorder. Bottle-fed infants were receiving infant formulas with adequate calcium, potassium, and sodium content. All children had a normal physical examination. While in a quiet resting state, lying supine, a digital 12-lead electrocardiogram was recorded using a MAC 5500 (Marquette Medical Systems, Milwaukee, WI, USA) at a speed of 50 mm/second. The digital electrocardiograms were stored on a server and subsequently retrieved for analysis. All children were in sinus rhythm and none had a conduction disturbance. The QT and RR intervals were measured digitally from lead II using incorporated on screen calipers and were magnified. The QT was measured from onset of the Q wave to the end of the T wave at the point of return to the isoelectric line from six cycles then averaged. When a separate T and U wave were visible, and the U-wave amplitude was 50% or less of the T-wave amplitude, the initial downslope was extrapolated to the baseline. The RR intervals were measured from the average of 10 cardiac cycles (the same cycles in which the QT intervals were measured). All measurements were performed by a single investigator (AB).

Subjects were divided into four age groups: 0–1 years ($n = 540$); 1–5 years ($n = 281$); 5–10 years ($n = 277$); and > 10 years ($n = 302$). Each age group was further subdivided according to gender, male and female. Intra-observer variability and reproducibility were measured for 10 patients in each age and gender group. The co-investigator randomly assigned electrocardiograms for repeated measurements by the investigator who was blinded to identity.

For each age group and gender subgroup, QT/RR linear regression analyses were performed. Linear regression techniques allow for the estimation of the slope, which can be used for standardizing the data to a normalized heart rate of 60 beats per minute. First, the QT/RR was plotted and fitted with a linear regression for constant α . Second, $\log QT/\log RR$ was plotted and fitted with linear regression analysis for constant β . The first equation we applied assumes a linear relationship between QT and RR intervals deriving the formula $QT_c = QT + \alpha \times (1-RR)$. The second assumes a linear relationship between the logarithms (natural logarithm to the base e) of QT and RR values which derives the formula $QT_c = QT/RR^\beta$. For each of the four age groups and gender subgroups, QTc was calculated from the derived constants α and β , applied to the above-mentioned two formulas. Descriptive statistics were calculated and expressed as the mean, standard deviation, range, and median. The 95% confidence intervals for computed QTc were derived. These data are graphically represented as a bar chart. The data were tested for normal distribution. A paired *t*-test and analysis of variance with post hoc Bonferroni-Dunn and Scheffes F-test at a significance level of 1% were used to compare the calculated age and gender group variables for each of the two formulas. For comparison purposes, QTc Bazett and QTc Fridericia were calculated on the raw data for each group and gender.

In addition, further linear regression analysis was conducted for QTc linear and QTc log against respective RR interval to obtain curve slope and R^2 . A slope and R^2 close to zero were judged to eliminate the effect of heart rate on QT interval. Consequently, linear constant QTc α computed for all the groups was plotted against respective RR interval (Fig. 2A) and log linear constant QTc β was plotted against respective RR interval (Fig. 2B). The level for statistical significance was set at a P value < 0.05 .

The study was approved by the medical ethics committee of the Academic Hospital of the Free University of Brussels (VUB).

RESULTS

The demographic data are presented in Table 1. The age breakdown within groups, median age, gender, and number of subjects are shown in

Table 1. Demographic Data

Age	Mean	Median	Gender	Number
0–1	0.34 ± 0.27	0.29	Male	290
	0.3 ± 0.27	0.25	Female	250
1–5	2.94 ± 1.2	2.97	Male	145
	2.74 ± 1.2	2.6	Female	136
5–10	7.4 ± 1.46	7.4	Male	153
	7.2 ± 1.4	6.96	Female	124
> 10	12.9 ± 1.8	12.8	Male	177
	13.75 ± 2.1	14.2	Female	125

± Standard deviation; age in years.

Table 2. Regression Constants

Age	0–1	1–5	5–10	≥ 10
α				
	Female 0.24	0.24	0.215	0.18
	Male 0.24	0.24	0.215	0.21
β				
	Female 0.45	0.45	0.406	0.31
	Male 0.45	0.45	0.406	0.36

Age in years; α = linear constant; β = log linear constant.

Table 1. There was a slight preponderance of male subjects for the four age groups with a larger number of subjects in the first year age group. In the group beyond age 10 years, there is an overlap of preadolescent and adolescent subjects, with a marginally higher mean and median age in the female gender group. Age did not exceed 16 years.

As expected, heart rate is highest at birth and gradually diminishes with age. Likewise QT interval is shortest at birth and lengthens with age as heart rate diminishes. Small discrepancies in heart rate were observed within each age group among the genders most likely due to the random nature of the sample. Median heart rate was slightly higher in the female gender (Table 3).

Absolute QT increases with increasing age as heart rate gradually declines and RR interval lengthens.

The derived regression analysis correction factor constants, α and β , are shown in Table 2. The linear constant α (Table 2) progressively declines after the age of 5 years, the descent becoming more pronounced in females beyond age 10 years. The log constant β undergoes a sharper decrease beyond the age of 5 years in both genders with significant disparity between males and females in the group beyond 10 years (Table 2).

For each age group, two sets of QTc were calculated from the optimal constants α and β ,

one for the linear formula and the other for the log formula. The mean, standard deviation, range and median for age group and gender are shown in Table 3. There was no statistically significant difference in QTc linear values between groups and genders. Likewise no difference between groups and genders was observed for log QTc formula values. The 95% confidence intervals for QTc in each age and gender group were calculated and graphically plotted for each formula, linear and log-linear, which are presented in Figures 1A and 1B.

The calculated 95% confidence intervals for the QTc linear constant α formula show no significant statistical difference between age groups and gender. Means are comparable between the genders and across the ages. Likewise, calculated 95% confidence intervals for QTc applying the log constant β formula show no significant statistical difference between age groups and gender. Similarly, means are comparable across the ages and genders.

Linear regression plot for QTc α for all the groups and genders against respective RR intervals derived a slope of 0.0029, R^2 0.0016 (Fig. 2A). Linear regression plot for QTc β for all the groups and genders against respective RR intervals resulted in a slope of 0.0031, R^2 0.0012 (Fig. 2B). For both these formulas, the slopes are close to zero as are R^2 suggesting that they effectively eliminate the effect of heart rate on QT interval.

QTc Bazett shows, as previously observed, an under-correction (prolonged QTc) in the younger with higher basal heart rates. Likewise, QTc Fridericia displays, as previously observed, an overcorrection (shorter QTc) in younger age groups with higher basal heart rates. It is noteworthy that for both these formulas, the mean QTc is significantly longer in girls beyond 10 years of age as compared to boys of similar age groups, $P < 0.05$ (Table 3).

With regard to the intra-observer measurement variability, the maximum difference in measurements did not exceed 15 milliseconds for QT and RR intervals, respectively.

DISCUSSION

We investigated these two linear regression formulas as they are fairly easy to use in clinical practice.

For the formula $QTc = QT + \alpha \times (1-RR)$, we observed a steady α constant from birth to 5 years followed by a slow decline from 5 to 10 years

Table 3. Measured and Calculated Variables in Different Age Groups

Age (years)	0-1	1-5	5-10	≥ 10
Heart Rate				
Female	140 (88-190)[139]	112 (72-147)[111]	88 (54-125)[86]	77 (50-115)[77]
Male	139 (90-190)[136]	107 (73-148)[107]	82 (57-128)[80]	71 (49-110)[72]
QT				
Female	276 ± 21 (220-346) [274]*	305 ± 24 (260-370)[300]*	349 ± 28 (282-438)[346]	379 ± 27 (300-450)[379]
Male	277 ± 21 (220-338)[278]	313 ± 26 (254-370)[312]	360 ± 27 (278-448)[360]	377 ± 28 (302-450)[378]
QTc Linear				
Female	412 ± 12 (383-447)[410]	412 ± 12 (387-442)[411]	412 ± 14 (383-459)[412]	412 ± 16 (380-450)[412]
Male	412 ± 13 (373-444)[411]	412 ± 13 (384-445)[412.5]	412 ± 14 (380-450)[411.5]	412 ± 16 (378-450)[411]
QTc Log				
Female	403.8 ± 18 (363-449)[399]	403.8 ± 16 (370-442) 404]	404 ± 17 (365-448)[403]	404 ± 16 (364-450)[404]*
Male	403.8 ± 18 (350-447)[399]	404 ± 17 (366-446)[403]	404 ± 16 (366-448)[403]	404 ± 17 (365-449)[403]
QTc B				
Female	421 ± 19 (371-473)[417]*	418 ± 16 (380-456)[414]	416 ± 18 (374-469)[416]	423 ± 20 (381-465)[421]
Male	421 ± 20 (359-471)[418]	418 ± 18 (374-458)[413]*	416 ± 18 (377-465)* [413]	413 ± 18 (377-465)[412]
QTc F				
Female	364 ± 17 (320-410)[362]*	374 ± 16 (336-411)[373]*	395 ± 16 (352-444)[393]	406 ± 16 (370-452)[405]
Male	365 ± (313-407)[363]*	375 ± 18 (334-417)[375]*	396 ± 16 (358-450)[396]*	401 ± 17 (363-443)*[399]

Heart rate in beats per minute; age in years; B = Bazett formula; F = Fridericia formula; mean values, ± = standard deviation; brackets represent range; [] represent median values, * P < 0.01 compared to values in other age groups.

followed by a sharper decline more pronounced in the female gender.

For the formula $QTc = QT/RR^\beta$, we similarly observed a steady β from birth to 5 years, though a much sharper decline from 5 to 10 years and even sharper decline beyond 10 years which was steeper in the female gender. There is a significant disparity between the male and female gender in this latter age group. The study did not however include adolescents beyond 16 years of age.

Any of these two formulas, linear or log linear, when applied in clinical practice would necessitate the use of a different correction constant according to age and gender. A potential limitation in this study is the nonuniform distribution of subject groups' age which were separated in one, four, five, and six year groups (0-1, 1-5, 5-10, and greater than 10 years of age). This was done to obtain an adequate sample size in each group and gender with the intent to improve the statistical power and hence represent a more accurate trend of the constants. Had the sample size been considerably larger in each group, minor variations in the constants, α and β , may have been brought to light.

Another limitation of this study is that we did not test the correction constants on an independent dataset with the same age ranges. We know little how well these correction coefficients would remove the heart rate dependence on the QTc interval when applied in a different population of young healthy subjects.

Using pretreatment electrocardiographic data obtained from a meta-analysis of seven clinical trials for attention deficit/hyperactivity disorder involving 2888 children and adolescents, aged 6 to 17 years, Wernicke et al. found the most appropriate formula to be $QTc = QT/RR^{0.38}$. In their analysis, the optimal correction factor decreased for both males and females from ages 6 to 9 years and then increased from ages 15 to 17 years.⁴ In our study, patients' age did not exceed 16 years and we were therefore unable to validate this finding, which was not the goal of the study.

Published data have demonstrated that the QTc interval changes little over a 24-hour period and is remarkably constant despite significant heart rate changes in healthy children.^{5,11}

Previous studies have shown QT interval to be influenced by gender. Young boys and girls have similar QT interval durations. During puberty, the QT interval in boys shortens, leaving adult women with a longer QT interval than adult men.⁵ Bazett

Figure 1. (A) α linear constant means (circles) and calculated 95% confidence intervals (horizontal bars represent the limits) for age groups and gender. (B) β log constant means (circles) and calculated 95% confidence intervals (horizontal bars represent the limits) for age groups and gender.

Figure 2. (A) QTc α constant all values (pooled) plotted against respective RR interval with regression line displaying slope. (B) QTc β constant all values (pooled) plotted against respective RR interval with regression line displaying slope.

and Fridericia formulas make no adjustment for gender, which appears, when the rate-adjusted QT shortens in boys, possibly as a testosterone effect, but undergoes little change in girls.⁵ Reported gender differences in rate-adjusted QT, in various studies, vary from 12 to 15 milliseconds in younger adults.⁶ In this study, no gender differences in QT were observed from birth to 10 years. In the age group beyond 10 years of age, we observed that girls had a marginally longer QT, in addition to a higher median heart rate. Moreover, the QTc Bazett in this age group was significantly longer in girls.

There is general consensus that normal QTc limits established using upper and lower limits of actual percentile distributions of the rate-adjusted QT are preferable to those as mean QTc $\pm 2 \times$ standard deviation since these distributions are shown to be strongly skewed.⁷

For our data, the 98th percentile QTc computed for the α constant formula was 438 milliseconds for 0–1 year age group, both genders; 440 milliseconds for 1–5 year age group both genders;

442 milliseconds for 5–10 year age group both genders; 441 milliseconds for the 10 years and beyond age group likewise both genders. For the β constant formula, 98th percentile for 0–1 year old girls was 442 milliseconds, 438 milliseconds for boys; 438 milliseconds for 1–5 years age both genders; 440 milliseconds for 5–10 years males and females; 438 milliseconds for girls and 435 milliseconds for boys for ages 10 years and beyond.

Malik et al. studied the subject specific QT/RR patterns from numerous ECG recordings in 352 adults (176 male and 176 female) and applied 12 different regression models.⁸ None of the regression models investigated fitted the QT/RR data well. The linear QT/RR regression model was found to be the optimum fit, while the log-linear model rarely provided an optimum fit. Their study was performed with four separate 14-hour daytime 12-lead Holter recordings with Mason-Likar electrode positions.

Differences in QT interval between standard electrocardiograms and ambulatory ECGs have been previously described in adults.⁹ More recently, longer maximum QTc intervals on Holter ECGs than in routine ECGs in children with Turner syndrome were reported.¹⁰ Krasemann et al. studied the QTc interval as measured by the 24-hour recording in 282 healthy children and found the average corrected QT interval over 24 hours to be significantly longer than in the routine ECG and in any of the channels.¹¹ The differences may be accounted for by the lead positions which are different in the ambulatory ECG as compared to the routine ECG.¹¹ The Mason-Likar electrode positions are comparable to positions used for the routine ECG, although placement of 12 leads in a child for 24 hours would not be an easy task, and the yield of adequate low noise signals would not be optimal. Obtaining subject-specific normative QT data from 24-hour recordings with the use of either 5 wire, or 7 wire electrodes, and bipolar–unipolar combinations are likely to lead to erroneously prolonged QTc intervals.

The creation of a QT knowledge management system in children as that developed by Tornøe et al. may allow testing methods on a subject level.¹²

CONCLUSION

The work presented here, based on electrocardiographic data of 1400 children, indicates

that overall, there is no single appropriate QT correction formula. Ranges for linear and log-linear correction constants for males and females for different ages are reported. Ages extended from birth to teenage years exhibiting a wide range of heart rates. For the full range of pediatric subjects studied, the optimum population-based correction factors α and β decreased with increasing age and gender, digressing more so in adolescent girls. More specific correction factors, based on age and gender, are necessary in QT correction. Both formulas performed well in correcting the effect of RR interval on QT interval, even in infants. They exhibit superior dissociation of the QTc interval from RR interval (least slope and lowest R^2) as compared to the Bazett and Fridericia formulas.

REFERENCES

1. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–370.
2. Fridericia L. Die systolendauer im Elektrokardiogramm bei normalen menschen und bei herzkranken. *Acta Med Scand* 1920;53:469–486.
3. ICH E14 guideline: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Questions and answers (R2). 2014 (21 March) <http://www.raps.org/regulatoryDetail.aspx?id=6753>
4. Wernicke JF, Faries D, Breitung R, et al. QT correction methods in children and adolescents. *J Cardiovasc Electrophysiol* 2005;16(1):76–81.
5. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol* 1992;8:690–695.
6. Rautaharju PM, Surawicz B, Gettes LS, Recommendations for the Standardization and Interpretation of the Electrocardiogram Part IV: The ST Segment, T and U Waves, and the QT Interval: A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: Endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2009;119:e241–e250.
7. Rautaharju PM, Zhang ZM. Linearly scaled, rate-invariant normal limits for QT interval: Eight decades of incorrect application of power functions. *J Cardiovasc Electrophysiol* 2002;13(12):1211–1218.
8. Malik M, Hnatkova K, Kowalski D, et al. Importance of subject-specific QT/RR curvatures in the design of individual heart rate corrections of the QT interval. *J Electrocardiol* 2012;45(6):571–581.
9. Rasmussen V, Jensen G, Hansen JF. QT interval in 24-hour ambulatory ECG recordings from 60 healthy adult subjects. *J Electrocardiol* 1991;24(1):91–95.
10. Dalla Pozza R, Bechtold S, Urschel S, et al. QTc interval prolongation in children with Turner syndrome: The results of exercise testing and 24-h ECG. *Eur J Pediatr* 2009;168(1):59–64.
11. Krasemann T, Strompen C, Blumenberg J, et al. Changes of the corrected QT interval in healthy boys and girls over day and night. *Eur Heart J* 2009;30(2):202–208.
12. Tornøe CW, Garnett CE, Wang Y, et al. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol* 2011;5(7):1035–1042.