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Comparison of Formulas for Calculation of the Corrected QT Interval in Infants and Young Children

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Abstract

Objective—To compare four heart rate correction formulas for calculation of the rate corrected QT interval (QTc) among infants and young children.

Study design—R and QT intervals were measured from digital electrocardiograms. QTc were calculated with the Bazett, Fridericia, Hodges, and Framingham formulas. QTc versus RR graphs were plotted, and slopes of the regression lines compared. Slopes of QTc-RR regression lines close to zero indicate consistent QT corrections over the range of heart rates.

Results—We reviewed electrocardiograms from 702 children, with 233 (33%) <1 year of age and 567 (81%) <2 years. The average heart rate was 122 ±20 bpm (median 121 bpm). The slopes of the QTc-RR regression lines for the four correction formulas were: −0.019 (Bazett); 0.1028 (Fridericia); −0.1241 (Hodges); and 0.2748 (Framingham). With the Bazett formula, a QTc >460 ms was 2 standard deviations above the mean, compared with "prolonged" QTc values of 414, 443, and 353 ms for the Fridericia, Hodges, and Framingham formulas, respectively.

Conclusions—The Bazett formula calculated the most consistent QTc; 460 msec is the best threshold for prolonged QTc. The study supports continued use of the Bazett formula for infants and children and differs from the use of the Fridericia correction during clinical trials of new medications.

Keywords

Electrocardiography; Long-QT syndrome; Rate corrected QT; Children

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The authors declare no conflicts of interest.

The congenital long QT syndrome (LQTS) has an estimated prevalence of 1:2000 among infants, and potentially accounts for 10% of sudden infant deaths (1, 2, 3). Early diagnosis of LQTS is important, in order to initiate therapies that prevent arrhythmic events and death (4). One method of establishing a clinical diagnosis of the LQTS is based on the Schwartz score, which assigns points for the presence of electrocardiographic (ECG) findings (i.e., heart rate corrected QT interval [QTc], T wave morphology, bradycardia, torsades de pointes), symptoms (i.e., syncope, congenital deafness), and family history. A total score of 3.5 or higher is taken to indicate a high probability for LQTS (5–8).

In clinical scoring for diagnosis of LQTS, the most crucial determinant among the ECG findings is an accurately measured QTc, which estimates the corresponding QT interval at a heart rate of 60 / minute. Several formulas have been proposed to calculate the QTc, and multiple studies have compared these formulas among adults (9–20). Most pediatric studies have involved adolescents. Few studies have compared the formulas among infants and young children (10, 11, 15–17). As ECG screening for LQTS in newborns is a topic of much debate among physicians and policy makers (21–25), it is useful to examine which QTc correction formula is most appropriate for infants and young children.

Although the Bazett formula is the most widely used correction method in clinical practice, the Fridericia formula is recommended by the U.S. Food and Drug Administration (FDA) for clinical trials on drug safety (26). It is unclear whether the Bazett or the Fridericia formula provides a more consistent QT correction in infants and young children. In addition, there are two other formulas (Hodges and Framingham) which have been proposed for calculation of the QTc. Our goal was to compare four QTc formulas -- to determine which formula provides the most consistent QT interval correction across the wide range of heart rates present in infants and young children.

METHODS

We conducted this study utilizing digital recordings of standard 12-lead ECGs obtained from children ≤6 years old who had sensorineural hearing loss and underwent ECG screening for LQTS (3). The study received approval from the Institutional Review Board at Los Angeles Biomedical Research Institute at the Harbor-UCLA Medical Center.

ECGs were reviewed and analyzed using IQ Manager software v8.3.1 (Midmark Corporation, Versailles, OH). The QT and RR intervals were measured manually, by use of digital calipers at a 4× zoom. Measurements were taken in lead II. If significant artifacts or indiscernible intervals were present in lead II, measurements were instead taken in lead V5, with more distinct waveforms and fewer artifacts. Three consecutive measurements of the QT and preceding RR intervals were taken. In ECGs where the return of the T wave to base line was not easily discernable in either lead II or V5, the end of the T wave was defined as the intersection of a tangent line (drawn along the steepest part of descending portion of the T wave) with the isoelectric line. For each subject, the QT and RR intervals were used to calculate the QTc by use of four different heart rate correction formulas: Bazett

$(\mathrm{QTc}=\mathrm{QT}/\sqrt{RR})$; Fridericia $(\mathrm{QTc}=\mathrm{QT}/\sqrt[3]{RR})$; Hodges [QTc = QT + 1.75 *(HR-60)]; and Framingham [QTc = QT + 0.154*(1-RR)].

The QTc and RR intervals were then graphed on a scatter plot, with the QTc on the y-axis (in ms) and the RR interval on the x-axis (also in ms). Four different QTc-RR interval scatter plots were generated, one for each QTc formula. The slope of QTc-RR regression line for each QTc formula was determined and used to compare QTc formulas. Regression line slopes close to zero indicate consistency in calculating QTc values across the range of heart rates.

Subjects were also stratified by age, sex, and heart rate, according to the following groups: Ages: ≤ 6, < 2, and < 1 year; Heart rate: ≥ 130 and < 130; and Sex: males and females. QTc-RR scatter plots, means, standard deviations, and ranges were evaluated for each group, as described above.

RESULTS

Our data consisted of ECGs from 702 infants and young children (mean age, 26 ± 19 months; Table I). Almost all ECGs measurements were taken from lead II, with only 10 from lead V5 (1.4%). Correlation coefficients between uncorrected QT intervals and heart rates, between heart rates and age, and between uncorrected QT intervals and age were −0.854, −0.625, and 0.595, respectively. As expected, the QT interval correlated inversely with heart rate, with shorter QT duration at higher heart rates. Heart rate and age were also inversely correlated, with slower rates in older children. Table II (available at www.jpeds.com) summarizes these results among the seven sub-groups.

QTc based on the four heart rate correction formulas for each of the sub-groups and values for each QTc correction formula at which <2.5% (2 standard deviations) of the individuals have greater QTc are shown in Table III. The Fridericia formula gave the narrowest range of QTc values across the different age categories and among males. The Hodges formula gave the narrowest range of QTc values across heart rates (≥130 and <130) and among females. The Bazett formula gave a range of QTc values of 158 ms, with a range of 325 ms to 483 ms. The Framingham gave the lowest overall QTc at 217 ms with a range of 163 ms.

Figure 1 (available at www.jpeds.com) shows the inverse relationship between the uncorrected QT intervals and RR intervals, for all subjects [r = 0.88 (Pearson), $P < 0.001$]. Figures 2 demonstrates the QTc-RR interval scatter plots and regression lines based on the Bazett, Fridericia, Hodges, and Framingham formulas. The Bazett formula gave a regression line with a slope closest to zero (−0.019), indicating the best consistency across heart rates. The slopes of the QTc-RR regression lines for the other correction formulas were Fridericia (+0.1028); Hodges (−0.1241); and Framingham (+0.2748). The Bazett formula was also the most consistent for the variables of sex and age (Table IV; available at www.jpeds.com). The Fridericia formula was second best in five of seven sub-groups, being surpassed by the Hodges formula for HR <130 and among males.

The Bazett and Fridericia methods calculate the corrected QT intervals through different values of an exponent (e) in the correction formula ($\mathrm{QTc} = \mathrm{QT}/\mathrm{RR}^{e}$, where e = 0.5 for the

Bazett correction and 0.33 for Fridericia). Therefore, we computed slopes of QTc-RR regression lines for different values of e (from 0.3 to 0.6). An e value of 0.48 resulted in a regression line with a slope equal to zero (Figure 3; available at www.jpeds.com). Results of these slope calculations further support the conclusion that the Bazett formula provides the greatest consistency in QTc values across heart rates seen in infants and children.

Figure 4 depicts two super-imposed curves of distribution comparing the QTc values computed with data from our subjects by the Bazett and Fridericia formulas, respectively. As can be seen from this graph, using a threshold of 460 ms as definition for "prolonged QT" (>2SD above the mean), calculation of the QTc based on the Fridericia formula will lead to an increased number of false negatives. Likewise using an absolute threshold of 414 ms while calculating QTc based on the Bazett formula will lead to an increased number of false positives. Thus, the definition of "potentially prolonged QT" is dependent on the formula used and needs to be clearly stated.

DISCUSSION

Several formulas have been proposed for heart rate corrections of QT intervals, each with limitations. For example, the Bazett formula has been reported to over-correct the QT interval at faster heart rates and under-correct at slower rates (12, 15, 18, 27–29). Conversely, the Fridericia formula has been shown to do the opposite -- under-correct at faster and over-correct at slower rates (12,13,15). Our data are consistent with these limitations, as indicated by negative and positive values of the slopes of regression lines for the Bazett and Fridericia QTc-RR plots, respectively. However, almost all of these studies are limited to adolescents or adults in resting states with an upper limit of heart rates of 100 bpm (12, 15, 18, 27, 29). Furthermore, use of the terms *overcorrection* and *undercorrection* in the absence of an accepted absolute correction factor, may be questioned.

Because of these limitations, many studies across a range of age groups have been done, to identify new heart rate correction formulas or validate established methods (12, 14, 15, 27,29–31). However, new formulas may lack the simplicity needed for routine clinical use (31). Moreover, most studies have been done on adults, and of the pediatric studies, most represent the adolescent age group, with less attention on infants and young children (10, 11, 15–17).

Previous work comparing various heart rate correction formulas have produced conflicting results. One study examined 24-hour Holter monitors from adults (36–76 years of age) and found no significant differences among five formulas (9). Another study on individuals <20 years of age showed that the Bazett formula yields the most consistent results across heart rates and ages (10). A study on children and adolescents 6–17 years of age found the best heart rate correction QT formula to be $QTc = QT/RR^{0.38}$, which is close to the Fridericia formula ($QTc = QT/RR^{0.33}$) (11). Given these inconsistencies, some investigators have suggested that separate rate correction formulas may be appropriate for different heart rate ranges, creating a "bin-method" for analysis of the QTc (32).

We found the Bazett formula not only provides the most consistent correction across a wide range of high heart rates, it is consistent with clinical practice of 460 ms as threshold for identifying infants and children at risk for LQTS. In a study of ECGs obtained at 3 or 4 days of age in over 30,000 infants, the Bazett formula demonstrated consistent correlation of the QT and RR intervals and correctly defined infants with a QTc > 440 ms as 2 SD above the mean and at significant risk for sudden death (4). Furthermore, in another large study of ECG screening of newborns 15–25 days of age, Schwartz and co-workers again used the Bazett formula to identify potential cases of LQTS based on a QTc >460 ms with subsequent genetic confirmation (1). Our findings provides further evidence for the continued use of the Bazett formula in light of increasing debate on newborn ECG screening.

A strength of our study is the large sample size (n=702) and population-based recruitment of subjects which reflects the general demographics of the newborn and infant population in the state of California (3). Furthermore, to our knowledge, it is one of the few studies to compare four commonly used QTc formulas among infants and young children. Additionally, this study was performed with digital electrocardiography with amplification of the initial ECG data to allow more precise measurements than previously possible with standard ECG recordings. Although the original study was designed to identify individuals with sensorineural hearing loss and possible LQTS, very few potentially affected children were found. Therefore, we are unable to evaluate the various formulas for use in LQTS diagnosis. We recognize that there are several limitations to precise measurement of QT intervals on the ECG which are inherent to the basic technology. These include QT variance or dispersion among various leads, where leads V2–V3 may have longer QT duration due to onset of the QRS 20 ms earlier than limb leads. Another limitation inherent to QT measurement occurs when the T and U wave are superimposed or cannot be separated, or when the T and P waves are superimposed. Use of the tangent method was required in a small number of cases in this study, with recognition that this method may shorten the QT interval in patients with a delayed return of the T wave to the baseline, as in patients with LQTS type 1. However, the analyses performed in this study were performed in accordance with current Recommendations for the Standardization and Interpretation of the ECG (32).

Our study population was predominantly Hispanic (59%). However, this is similar to the demographics of births in California (51% Hispanics, according to 2009 vital statistics).

Our findings may have implications for the pharmaceutical industry and clinical trials. The FDA currently recommends use of the Fridericia formula, due to the under-correction of the Bazett formula at slower heart rates. The Fridericia correction may work well for adults, in whom average heart rates tend to be 60–90 bpm. However, children, especially infants, tend to have average heart rates well above 100 bpm. Therefore, the Bazett correction may be more appropriate for drug safety trials and clinical studies involving infants and young children. When the Fridericia formula is used in evaluation of new drugs, a QTc of 414 ms should be viewed as the threshold for significant QTc prolongation. On the other hand, a QTc of 460 ms appears to be an appropriate threshold for potentially significant QTc prolongation when the Bazett formula is used. Consistent use of the Bazett formula by clinicians as well as the FDA may be needed to avoid confusion as to what value constitutes

a prolonged QTc in a young child. This is an important topic which will require further study and validation. Regardless, definition of “potentially prolonged QT” is dependent on the formula used for calculation of this value and needs to be clearly stated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ECG	Electrocardiogram
LQTS	Long QT Syndrome
QTc	Corrected QT

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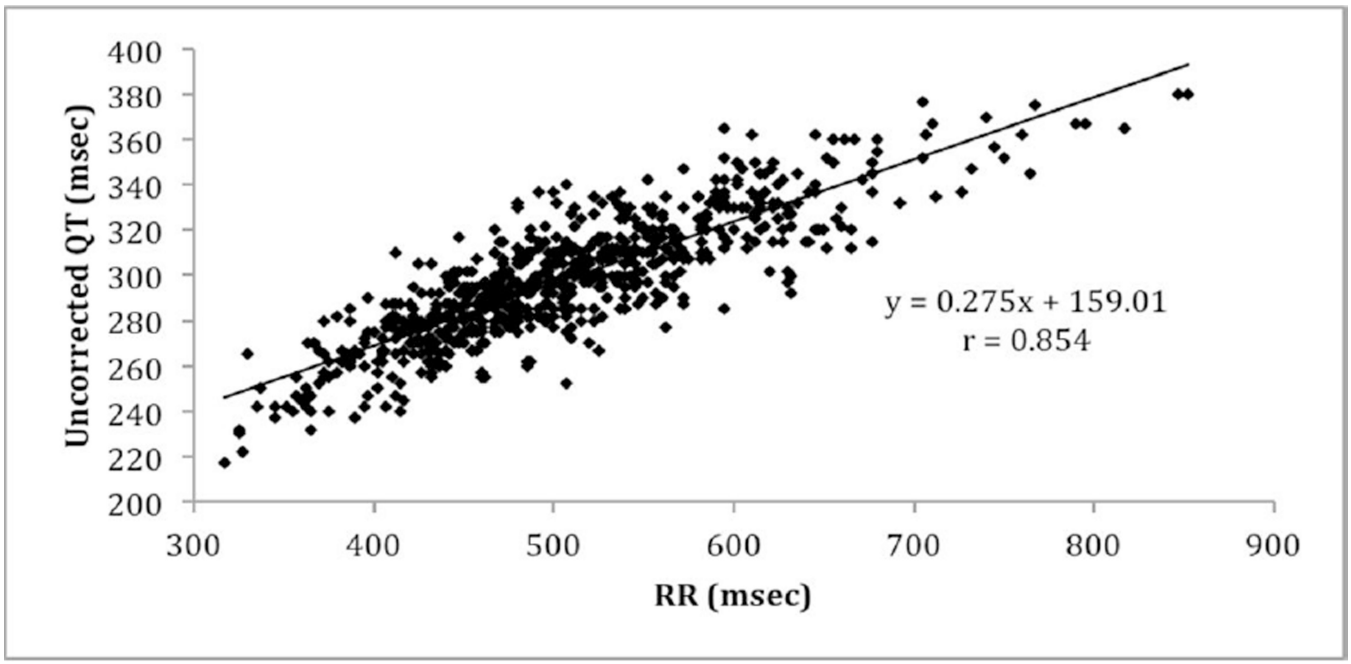

Figure 1.
Uncorrected QT-RR Scatter Plot of all subjects.

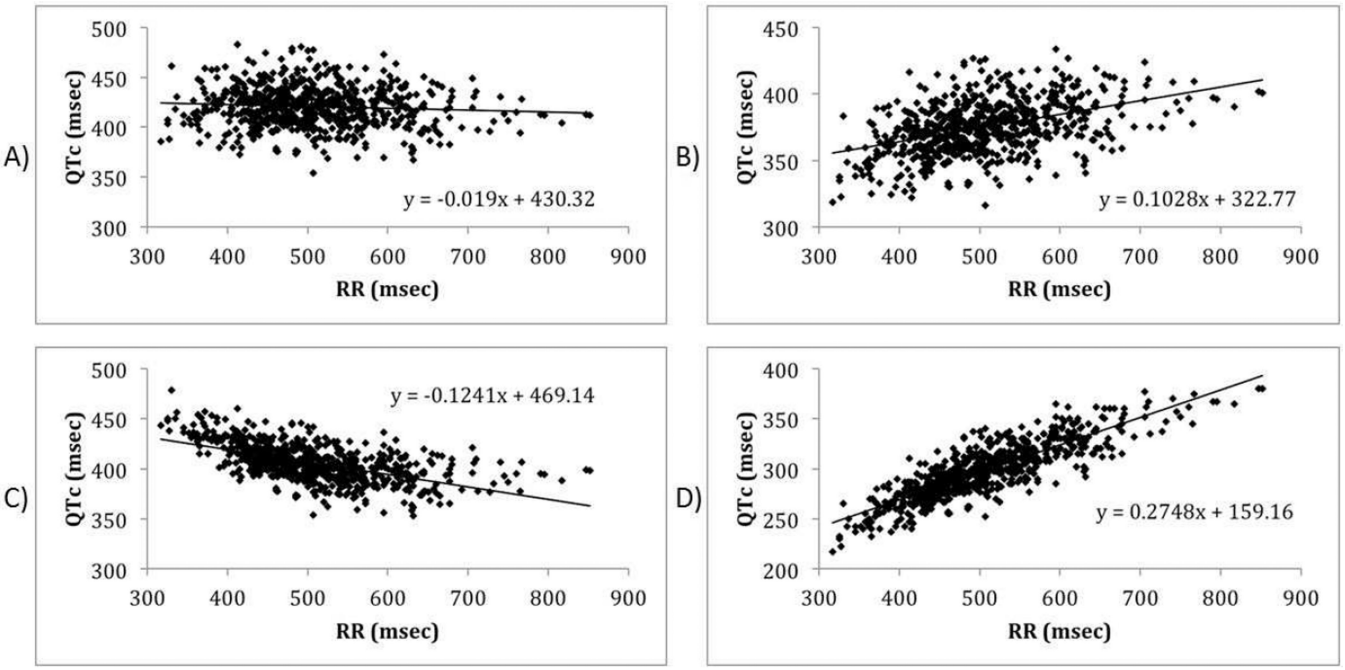

Figure 2.

QTc-RR Scatter Plot of all subjects: (a) Bazett, (b) Fridericia, (c) Hodges, (d) Framingham formulas. A linear regression slope closer to zero indicates better QT correction across different heart rates (RR intervals).

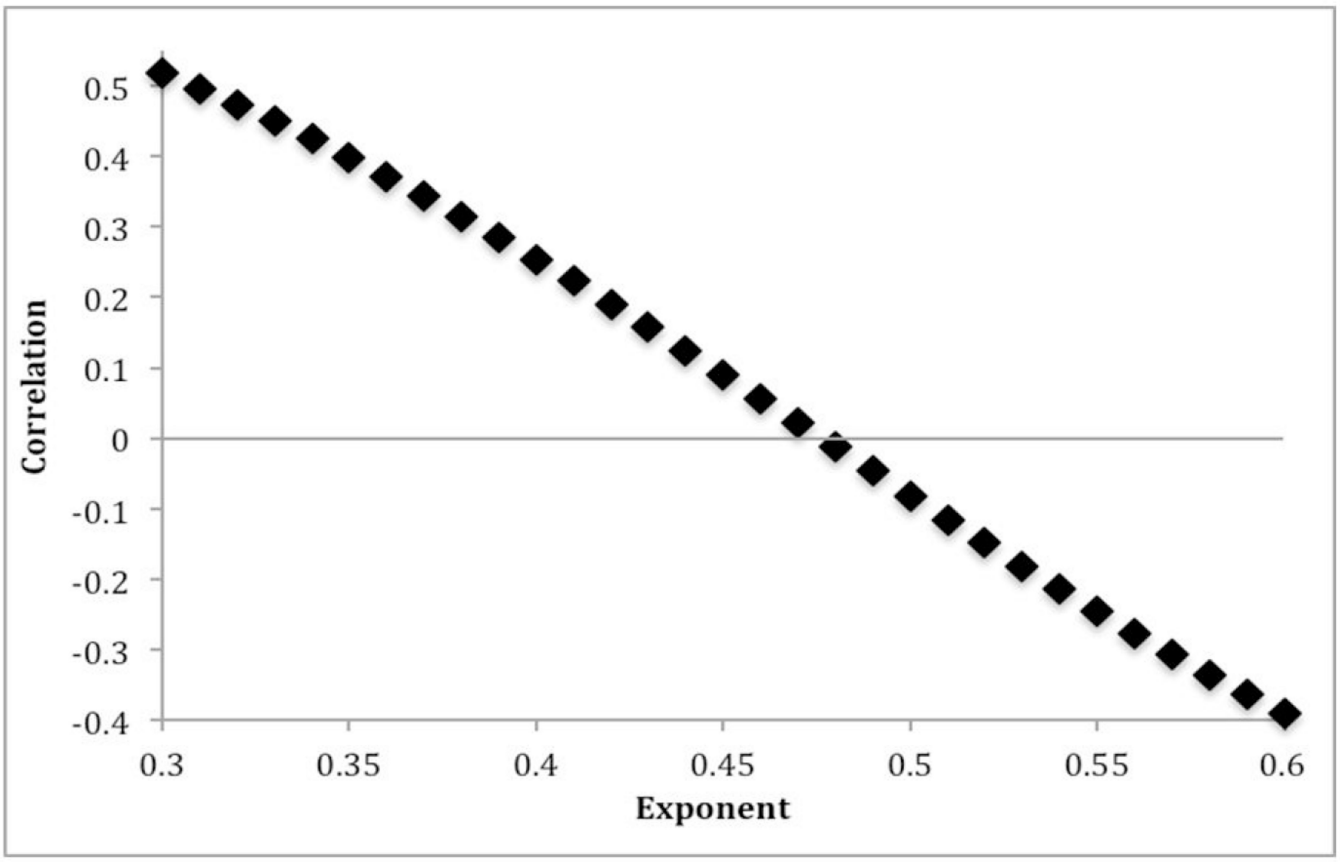

Figure 3.

Correlation coefficient between QTc and RR with various correction factor exponents.

The correction factor exponent e in the formula $QTc = QT/RR^{e}$ is varied across the values of 0.3 – 0.6.

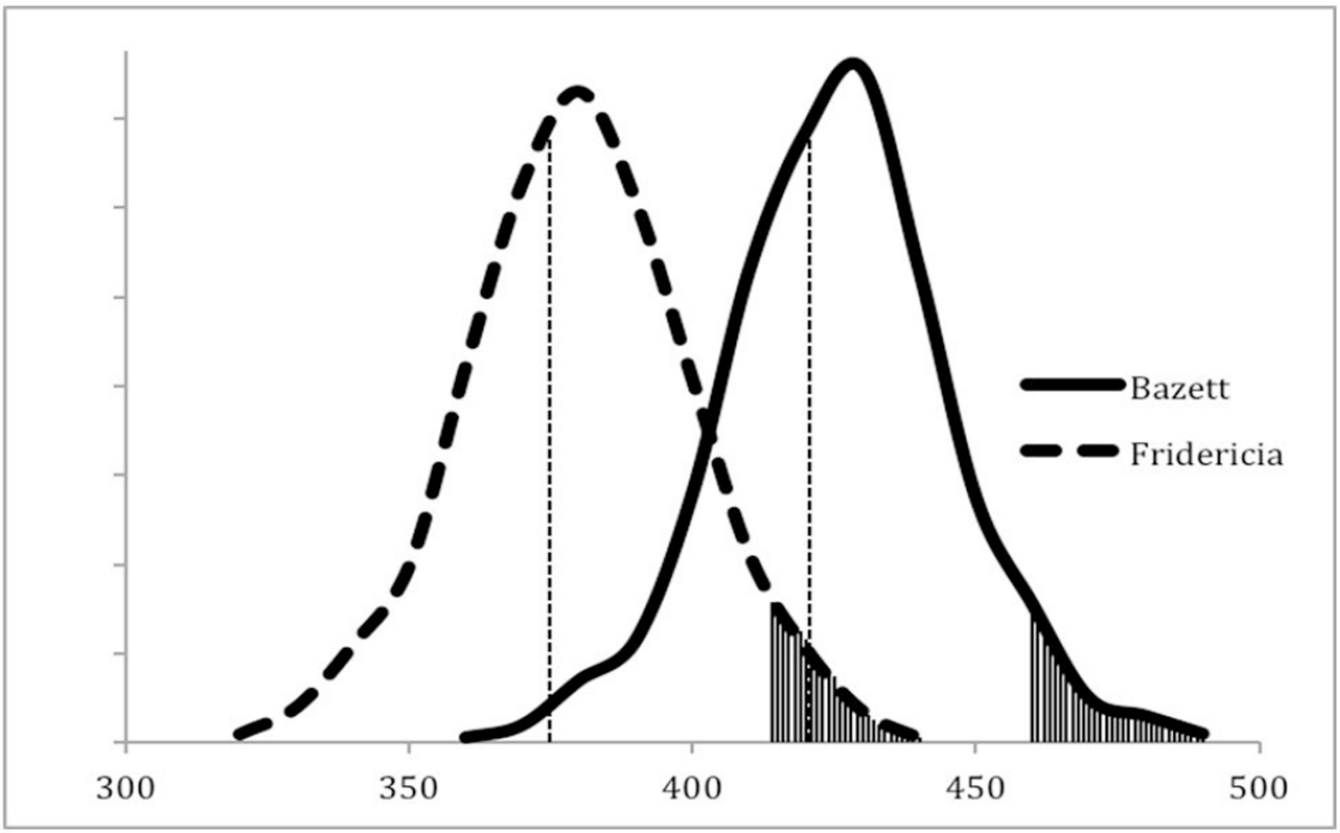

Figure 4.

Two superimposed distribution curves comparing the QTc values computed by the Bazett vs Fridericia formulas. The X-axis denotes QTc values in msec. The vertical line represents the mean for each formula, and the shaded area under the curve represents values > 2SD, for each respective formula.

Table 1

Demographics of Sample Cohort

Characteristic	Value
Number of subjects	702
Average Age	26 ± 19.8 months
Age Range	1–72 months
Male (%)	382 (54%)
Female (%)	320 (46%)
Race/Ethnicity	
Caucasian (%)	147 (21%)
African-American (%)	28 (4%)
Hispanic (%)	414 (59%)
Asian (%)	56 (8%)
Other (%)	57 (8%)

Table 3

Calculated QTc (msec) values for All Sub-Groups

Formula	Age ≤6 yo	Age < 2 yo	Age < 1yo	HR ≥ 130	HR < 130	Male	Female
Bazett QTc							
Mean	421	420	422	422	420	420	421
Std Dev	20	21	21	20	20	21	19
Min-Max	354–483	354–483	354–483	373–483	354–479	354–479	374–483
Range	129	129	129	110	125	125	109
2 SD threshold	460	461	464	461	460	462	459
Fridericia QTc							
Mean	375	368	368	365	380	375	374
Std Dev	20	19	20	18	19	21	18
Min-Max	316–434	316–427	316–421	318–427	316–434	316–434	318–427
Range	**118**	**111**	**105**	109	118	**118**	109
2 SD threshold	414	407	408	402	417	417	411
Hodges QTc							
Mean	406	411	415	419	400	406	407
Std Dev	18	19	20	17	16	18	18
Min-Max	353–478	354–478	354–478	371–478	353–446	353–478	359–460
Range	125	124	124	**107**	**93**	125	**101**
2 SD threshold	443	449	455	452	431	442	444
Framingham QTc							
Mean	298	284	281	275	311	299	297
Std Dev	27	23	22	18	23	28	26
Min-Max	217–380	217–362	217–350	217–337	273–380	222–380	217–375
Range	163	145	133	120	133	158	158
2 SD threshold	353	330	326	311	356	356	349