

## QT Interval Measurement

### Evaluation of Automatic QTc Measurement and New Simple Method to Calculate and Interpret Corrected QT Interval

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**Background:** Assessment of repolarization duration is often recommended to avoid administration of QT-prolonging drugs in patients with prolonged QTc interval, a frequent situation in the postoperative period. Bazett QT correction inappropriately increases QTc when heart rate is increased, and the use of the Fridericia formula may avoid a falsely prolonged QTc interval. The authors assessed automatic QT interval measurement to detect prolonged QTc interval (women >450 ms; men >440 ms) in the postoperative setting.

**Methods:** Automatic and manual electrocardiograms were performed in 108 patients after anesthesia. Automatic electrocardiographic measurement used the Bazett formula. Manual measurements were made from each electrocardiogram and used as the reference. Agreement between the two methods was analyzed. Bazett and Fridericia QT corrections were compared in this population.

**Results:** Agreement between automatic and manual measurements was low. The Fridericia correction, but not the Bazett correction, was independent from heart rate and allowed adequate QT correction. Sensitivity of automatic measurements to detect prolonged QTc-Bazett interval was 54%. Automatic QTc-Bazett interval less than 430 ms ruled out a manual prolonged QTc interval. When automatic QTc-Bazett was greater than 430 ms, this value was converted according to Fridericia. Automatic QTc-Fridericia greater than 430 ms identified all patients with prolonged manual QTc with a negative predictive error of 0% (95% confidence interval, 0–7%). QTc-Fridericia can be approximated by respectively adding or subtracting 5% to the uncorrected QT for each increase or decrease by 10 beats/min in heart rate from 60 beats/min.

**Conclusions:** Automatic QTc-Bazett measurement, if abnormal, associated with calculation of QTc-Fridericia reliably identifies patients in whom manual QTc measurement must be performed to confirm postoperative prolonged QTc interval.

MEASUREMENT of the duration of ventricular repolarization reflected by the QT interval on the surface electrocardiogram is usually performed to rule out prolonged QT interval.<sup>1–3</sup> Prolongation of QT interval is associated with an increased risk of development of a

potentially lethal cardiac arrhythmia called *torsade de pointes*, a risk that increases with the administration of a QT-prolonging drug.<sup>3</sup> However, a consensus is lacking about many aspects of QT interval monitoring as pointed out by a group of experts from the American Heart Association (Dallas, Texas).<sup>4</sup> Manual measurement is considered in all guidelines the best noninvasive method to assess duration of QT interval,<sup>4</sup> but it is time-consuming and reader dependent.<sup>5</sup> Therefore, automatic QT interval measurement has been developed and integrated into many electrocardiographic devices available for routine use. However, this method is known to be imprecise<sup>6,7</sup> and has never been evaluated in the particular situation of the postoperative period, a situation where a high prevalence of prolonged QT interval has previously been reported.<sup>8</sup>

Because heart rate is the principal determinant of repolarization length, many correction formulae have been developed to calculate a corrected QT interval (QTc) value corresponding to a QT value normalized at a heart rate of 60 beats/min.<sup>9</sup> The most widely used formula, in particular by automatic devices, has been proposed by Bazett but is known to overcorrect the QT interval at high heart rate<sup>9–12</sup> and therefore could lead to a false diagnosis of prolonged QTc interval in patients with increased heart rate, a common feature in the postoperative period.

The aim of this study was to assess automatic QTc interval measurement for the detection of prolonged QT interval in the postoperative setting. From these results, we derived a strategy for the interpretation of QTc interval duration.

## Materials and Methods

This observational study was approved by the ethics committee of Cochin Hospital (Paris, France), and each patient gave consent to participate. Patients admitted to the recovery room with nausea or vomiting were enrolled before any administration of antiemetic drug. Exclusion criteria were cardiac arrhythmias or bundle-branch blocks.

### Electrocardiographic Recording and QT Interval Measurements

For each patient, a standard automatic 12-lead electrocardiogram was obtained (noise filter 0.5–40 Hz), immediately followed by a manual record (noise filter 0.05–

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100 Hz) at a paper speed of 50 mm/s, both using a Pagemaster M1770 (Hewlett Packard, Andover, MA). Corrected QT interval was calculated by the electrocardiograph (automatic QTc) using the Bazett formula ( $QTc_b = QT/\sqrt{RR}$ ).<sup>13</sup>

The manual recording was analyzed by a single investigator (B. C.). Briefly, R-R intervals (*i.e.*, interval between two consecutive R waves) and QT intervals were measured in the chest lead with maximal T-wave amplitude. The end of the T wave was determined as the intersection between the tangent to the steepest down-slope of the T wave and the isoelectric line. Measurements were performed using a digitizing pad (SummaSketch III Professional; Summagraphics, Seymour, CN). Manual QTc<sub>b</sub>, using QT and R-R intervals measured manually, was averaged over three to seven consecutive cardiac beats. Interrater reliability was assessed by re-measuring all manual records by one operator.

Both automatic and manual QTc<sub>f</sub> were also calculated according to the Fridericia formula ( $QTc_f = QT/\sqrt[3]{RR}$ ).<sup>14</sup> For automatic measures, Fridericia values were calculated using the uncorrected QT and heart rate (converted to R-R [s] = 60/heart rate [beats/min]) printed on the automatic electrocardiographic report. Manual QTc<sub>f</sub> was calculated from the same QT and R-R data as those used for the calculation of QTc<sub>b</sub>. Manual QTc measurement was considered in this work as the reference method, whichever correction formula was used.

#### Statistical Analysis

**Agreement Analysis.** Automatic and manual QTc measurements were analyzed according to Bland-Altman for both QT correction formulae.<sup>15</sup> They were also compared using a paired *t* test. Linear regression between the difference and the mean of the two QT measurement methods was assessed, and the slope of the regression line was compared with zero.

Sensitivity and specificity of the automatic method to differentiate normal and prolonged QTc interval were calculated using the manual measure as the reference.

Prolonged QTc interval was defined as QTc greater than 450 ms in women and greater than 440 ms in men.

**Assessment of Heart Rate Correction Formulae.** The correlation coefficient was calculated between R-R and QTc intervals according to either Bazett or Fridericia. These correlation coefficients were taken as measures of the appropriateness to correct QT for heart rate of each formula.<sup>16</sup>

**Approximation of QTc According to Fridericia.** Because automatic QTc determination relies on the Bazett formula, we propose a novel parameter, the approximated QTc<sub>f</sub>, allowing a simple estimation of QTc<sub>f</sub> using the values of uncorrected QT and heart rate routinely printed on the electrocardiographic report. Approximated QTc<sub>f</sub> = uncorrected QT × parameter of correction (see Results section and appendix for details).

The confidence interval of proportion was calculated using the method of Wilson.<sup>17</sup> Data are presented as mean ± SD. Ranges in parentheses indicate lower and upper limits of the 95% confidence interval. Analyses were performed using StatView 6.0 software (SAS Institute, Cary, NC). Statistical significance was considered at *P* < 0.05.

## Results

One hundred eight patients were enrolled. Types of surgical procedures were vascular (14%); neurosurgical (18%); ear, nose, and throat (23%); orthopedic (14%); gynecologic (10%); abdominal (5%); and other surgeries (16%). Ninety-two percent of these procedures were performed during general anesthesia. The mean age of the patients was 45 ± 16 yr, and 57% of the patients were women.

#### Agreement between Automatic and Manual QTc Interval

**QTc Interval Using the Bazett Correction Formula.** Manual QTc<sub>b</sub> was 438 ± 32 ms, significantly greater than the automatic QTc<sub>b</sub> value (433 ± 28 ms; *P* < 0.02), with a mean difference in QTc<sub>b</sub> of 6 ms (1–10 ms). Limits of agreement between automatic and manual

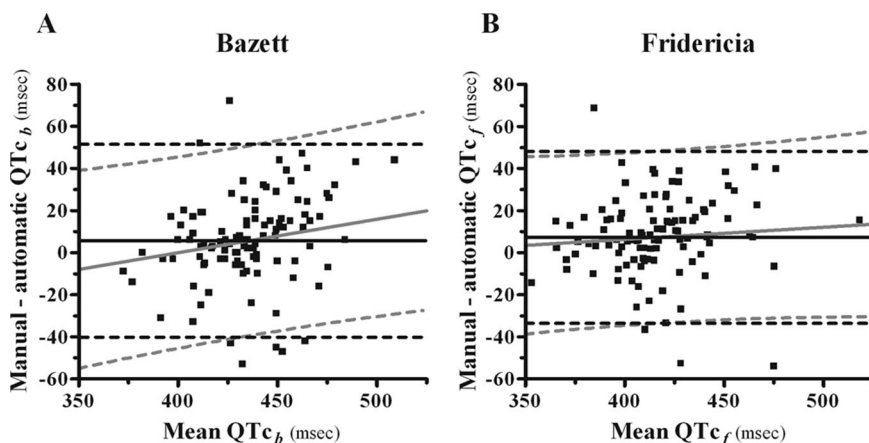


Fig. 1. Bland-Altman plots for the automatic versus manual measurement of QTc. Plots are shown for the Bazett heart rate correction formula (A) and for the Fridericia correction (B). Solid lines represent the mean of difference between manual and automatic QTc measurements; dashed solid lines represent the 95% confidence interval of the mean. Light solid lines represent linear regression between difference and mean of the two QTc measurement methods, and light dashed lines represent the 95% prediction band of these regression lines. Slope of the linear regression was significantly different from zero only with the Bazett correction (*P* < 0.05).

QTc<sub>b</sub> interval at the level of 95% were -39 and 51 ms (fig. 1A). The slope of linear regression was  $0.16 \pm 0.08$ , significantly different from zero ( $P < 0.05$ ). This indicates that automatic QTc<sub>b</sub> underestimates manual QTc<sub>b</sub> as QTc<sub>b</sub> increases.

**QTc Interval Using the Fridericia Correction Formula.** Manual QTc<sub>f</sub> was  $420 \pm 29$  ms, significantly lower than manual QTc<sub>b</sub> values ( $438 \pm 32$  ms;  $P < 0.001$ ). The mean difference between manual QTc<sub>f</sub> and automatic QTc<sub>f</sub> measures ( $413 \pm 28$  ms) was 7 ms (3-11 ms) ( $P < 0.001$ ). Lower and upper limits of the 95% confidence interval of the mean difference were -33 and 47 ms, respectively (fig. 1B).

**Interrater Reliability.** The intraclass correlation coefficient between pairs of QTc interval measurements from manual records was 0.998, and the coefficient of variation was 0.47%.

*Diagnosis of Prolonged QTc Interval Using Automatic Measures*

**Using the Bazett Correction Formula.** Manual QTc<sub>b</sub> was found to be prolonged in 36% (27-46%) of patients. The sensitivity of the automatic method to differentiate normal and prolonged manual QTc<sub>b</sub> interval was 54% (37-70%), and the specificity was 90% (80-95%). The positive and negative predictive values were 75% (55-89%) and 77% (66-86%), respectively.

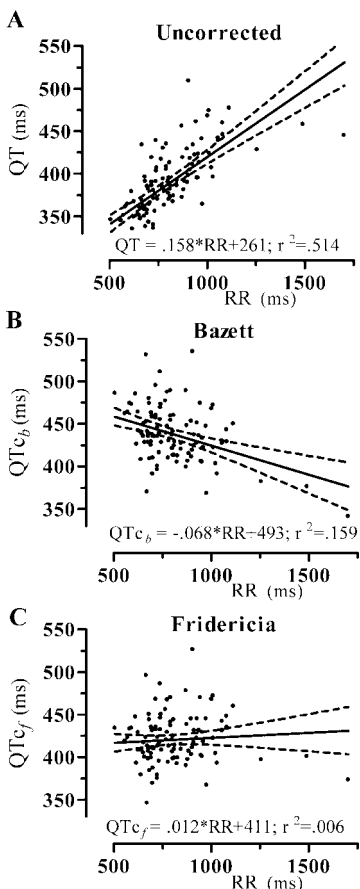
**Using the Fridericia Correction Formula.** Manual QTc<sub>f</sub> was prolonged in 15% (9-23%) of patients. Sensitivity and specificity of the automatic measurement were 44% (21-69%) and 96% (89-99%), respectively. The positive and negative predictive values were 63% (32-88%) and 91% (83-95%), respectively. The negative predictive value of automatic QTc measurement was greater when using the Fridericia formula than when using the Bazett formula ( $z = 2.43$ ,  $P < 0.02$ ).

*Comparison of QT Interval Correction Formulae*

The mean R-R interval was  $798 \pm 188$  ms (equal to heart rate of  $79 \pm 17$  beats/min). As expected, the linear regression between uncorrected QT interval duration and R-R interval had a significant positive slope (fig. 2A), *i.e.*, repolarization lengthens as heart rate decreases. A significant correlation was found between QTc<sub>b</sub> and R-R intervals ( $r = -0.398$ ;  $-0.546$  to  $-0.226$ ;  $P < 0.001$ ; fig. 2B). Corrected QT interval according to the Fridericia formula was not significantly influenced by heart rate ( $r = 0.076$ ;  $-0.115$  to  $0.261$ ;  $P = 0.4$ ; fig. 2C). Therefore, the Fridericia formula appropriately corrected QT for heart rate in the study population. Hence, manual QTc<sub>f</sub> will be considered below as the reference value.

*Threshold Definition of Prolonged QTc Interval Using Automatic Measurements*

The analysis of various thresholds of automatic QTc<sub>b</sub> to identify prolonged manual QTc<sub>f</sub> using a receiver opera-



**Fig. 2.** Uncorrected QT versus R-R interval relation (A) and heart rate-corrected QTc versus R-R interval relation using Bazett (B) and Fridericia (C) formulas. Solid lines represent linear regressions of these relations; dashed lines represent the 95% confidence band of the regression lines.

tor characteristic curve permits identification of the value of 430 ms where sensitivity was 100% (81-100%) and specificity was 53% (43-63%).

*Approximation of the Fridericia Correction Formula*

Values of the parameter of correction to calculate “approximated QTc<sub>f</sub>” are presented in table 1 for heart rates between 40 and 125 beats/min. In our patients, approximation of QTc<sub>f</sub> was not significantly different from automatic QTc<sub>f</sub> (mean difference, 1.8 ms;  $P = 0.6$ ).

**Table 1.** Approximation of QTc<sub>f</sub> Interval for Various Heart Rates

Heart Rate, beats/min	Parameter of Correction	Approximation of QTc <sub>f</sub>
Around 40 (40-44)	0.90	90% of uncorrected QT
Around 50 (45-54)	0.95	95% of uncorrected QT
Around 60 (55-64)	1.00	100% of uncorrected QT
Around 70 (65-74)	1.05	105% of uncorrected QT
Around 80 (75-84)	1.10	110% of uncorrected QT
Around 90 (85-94)	1.15	115% of uncorrected QT
Around 100 (95-104)	1.20	120% of uncorrected QT
Around 110 (105-114)	1.25	125% of uncorrected QT
Around 120 (115-124)	1.30	130% of uncorrected QT



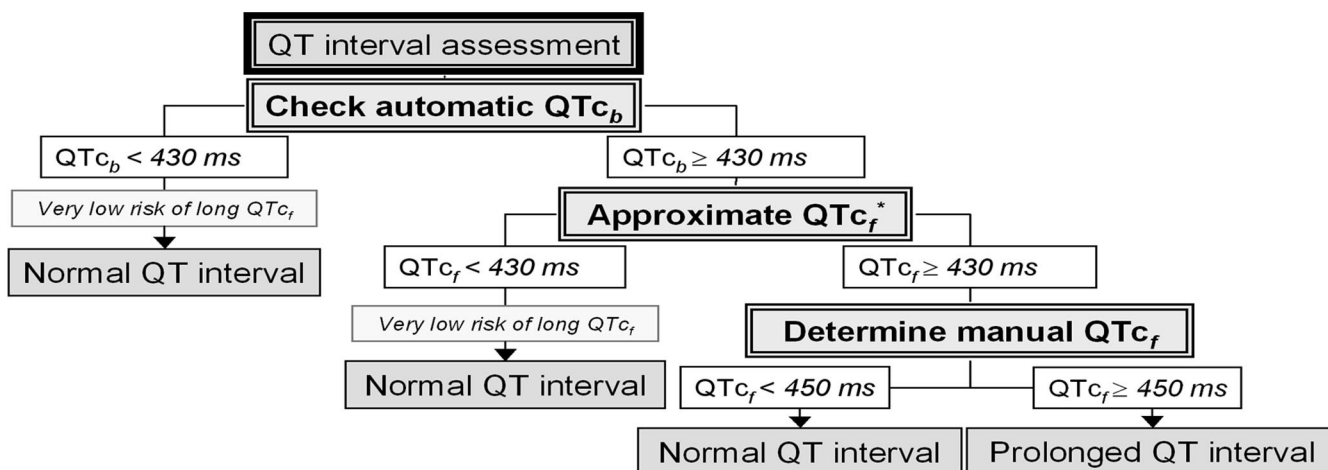


Fig. 3. Multiple-step diagnosis of prolonged QT interval. \* Approximate QTc for heart rates between 40 and 125 beats/min.

Ninety percent of our patients had a heart rate between 50 and 100 beats/min; in this range, the maximal error between approximated  $QTc_f$  and actual  $QTc_f$  was 11 ms.

#### Multiple-step Approach to Diagnose Prolonged QTc Interval

To comply with threshold value used in the E14 guideline,<sup>11</sup> prolonged QTc interval will be defined below as a manual  $QTc_f$  of 450 ms or greater, irrespective of sex. Automatic  $QTc_b$  was 430 ms or greater in 58 patients. Approximated  $QTc_f$  was calculated in these patients (fig. 3). In 31 of them (53%), approximated  $QTc_f$  was below 430 ms, confirmed by a normal manual  $QTc_f$  in all of them. Twenty-seven patients (25%) had both  $QTc_b$  and approximated  $QTc_f$  of 430 ms or greater. Among these 27 patients, manual assessment of  $QTc_f$  was normal ( $< 450$  ms) in 15 patients (55%) and above 450 ms in 12 patients (45%).

## Discussion

We found that electrocardiographic device-generated QTc interval measurement, which uses the Bazett formula by default, is inappropriate to identify all patients with prolonged QTc interval in part because of inadequate QT interval correction. However, automatic uncorrected QT and R-R measurements can be used to generate QTc according to the Fridericia formula.

#### Difficulties in Diagnosing Prolonged QT Interval

**Definition of Prolonged QT Interval.** Ideally, the threshold between normal and prolonged QT interval should be based on an assessment of the arrhythmic risk

related to QT/QTc interval duration.<sup>5</sup> To date, these studies requiring a very large number of patients are lacking in the field of anesthesiology. However, given the high prevalence of prolonged QT interval in our patients, using standard definitions, and the extremely low incidence of arrhythmic events, the standard threshold might be defective in postanesthesia patients.<sup>18,19</sup>

**Measurement of the QT Interval.** QT interval monitoring is difficult because neither manual nor automatic measurements ideally reflect the duration of ventricular repolarization. In our study, we chose manual high-precision measurement performed by a trained reader as the reference method in accordance with guidelines<sup>11</sup> and consensus on the subject.<sup>5</sup> Compared with this method, automatic measures did not detect prolonged QT interval in almost 50% of patients. Because electrocardiograph manufacturers use a similar algorithm for waveform measurements, it is unlikely that our results were significantly influenced by the chosen device. However, it would be impractical and time-consuming to assess  $QTc_f$  interval manually in all patients. Furthermore, Viskin *et al.*<sup>1</sup> recently found that less than 40% of physicians, even among cardiologists, reliably recognize QT prolongation on a standard electrocardiogram. Automatic measurements may be useful to identify patients in whom manual measurement is justified to confirm prolonged QT interval.

#### QT Interval Correction

No consensus exists on the way to correct QT interval to account for heart rate changes.<sup>9</sup> Using more than 10,000 electrocardiograms, Luo *et al.*<sup>12</sup> demonstrated that the threshold for normal QT interval is greatly influenced by the correction formula used. We found significant correlation between  $QTc_b$  and R-R values, indicating that the Bazett formula does not satisfactorily correct QT interval duration in our patients.<sup>16</sup> Moreover, as shown in figure 2, the Bazett formula overcorrects QT at high heart rates, *i.e.*,  $QTc_b$  is falsely prolonged as heart

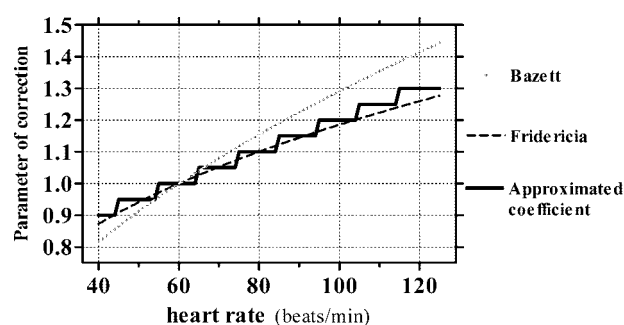
<sup>11</sup> E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (Geneva, Switzerland). Available at: <http://www.ich.org>. Accessed October 10, 2005.

rate increases above 60 beats/min. This probably accounted in part for the high prevalence of prolonged QT interval in our patients. To the best of our knowledge, this is the first time that the Bazett correction has been evaluated in the postoperative period. The choice of the postoperative period when heart rate tends to be high may, however, have disadvantaged the Bazett correction. Nevertheless, it is now clearly demonstrated that the Fridericia formula, although still imperfect, corrects QT interval better than does the Bazett formula as heart rate diverges from 60 beats/min.<sup>9,10,16</sup> Therefore, the Fridericia formula seems to be a proper QT interval correction in the postoperative setting.

### Simple Multiple-step Approach for the Diagnosis of Prolonged QT Interval

Our results indicate that it is not possible to rely solely on automatic QTc<sub>b</sub> interval to identify all patients with prolonged QTc interval, because automatic QTc<sub>b</sub> has a low sensitivity. To help clinicians identify patients with prolonged QT interval in the postoperative setting, we built a multiple-step approach using a combination of automatic and manual QT interval determination (fig. 3). However, we cannot exclude that the effect of anesthesia on cardiac repolarization in particular by changes in plasma electrolytes or residual volatile anesthetics effects may have affected our results.<sup>20</sup>

The value of QTc<sub>b</sub> automatically calculated by the electrocardiographic device was first considered. Patients with automatic QTc<sub>b</sub> of less than 430 ms were at very low risk of having a prolonged QT interval. The false-negative rate was at most 7% in the studied population (upper limit of the 95% confidence interval of the negative predictive error). No further investigation seems to be justified in these patients. Patients with automatic QTc<sub>b</sub> greater than 430 ms may have either normal or prolonged manual QTc<sub>f</sub>. In these patients, calculation of QTc<sub>f</sub> should be determined to reduce the number of falsely prolonged QT intervals. We propose a



**Fig. 4.** Parameter of correction for calculation of corrected QT interval using the Fridericia formula ( $1/\sqrt[3]{60/\text{heart rate}}$ , heavy dashed line) and the Bazett formula ( $1/\sqrt{60/\text{heart rate}}$ , light dashed line) are displayed for heart rates between 40 and 125 beats/min. The approximated parameter of the Fridericia correction (approximated QTc<sub>f</sub>) is displayed by the solid line (appendix and table 1).

new way to calculate QTc<sub>f</sub> that is both easily memorizable and calculable. The heart rate for which no correction is needed is, by definition, 60 beats/min. For each increase of 10 beats/min from 60 beats/min, the correction factor increases by one multiple of 5%, *i.e.*,  $1 \times 5 = 5\%$ ,  $2 \times 5 = 10\%$ ,  $3 \times 5 = 15\%$ , and so forth, and inversely when heart rate is below 60 (fig. 4). Finally, the QTc<sub>f</sub> is easily calculated by adding or subtracting a multiple of 5% of uncorrected QT interval (easily calculable as QT divided by 10 and then by 2). Without any manual QT interval measurement, calculation of approximated QTc<sub>f</sub> would have identified more than one half (54%) of falsely prolonged automatic QTc<sub>b</sub> intervals. In patients with both abnormal automatic QTc<sub>b</sub> and approximated QTc<sub>f</sub>, a manual determination of QTc<sub>f</sub> is necessary to identify actual QT interval prolongation.

In conclusion, automatic Bazett QTc calculation unreliably identifies patients with prolonged QTc interval. The proposed three-step strategy permits one to limit misinterpretation linked either to the use of Bazett or to automatic measurement.

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## Appendix

### *Approximation of the Fridericia Correction*

#### *Formula*

We propose an approximation of the Fridericia correction formula by use of a simple calculation that can be performed by clinicians without a scientific calculator, *i.e.*, without calculating the cubic root of the R-R interval in the Fridericia formula. The Fridericia formula ( $QT_{c_f} = QT / \sqrt[3]{RR}$ ) can be simply decomposed into two parts: QT, the

uncorrected QT interval in ms, and  $1/\sqrt[3]{RR}$ , the parameter of correction of this equation. Because  $R-R = 60/\text{heart rate}$ , the parameter  $1/\sqrt[3]{RR}$  is equal to  $1/\sqrt[3]{60/\text{heart rate}}$ . First, it was calculated for heart rates ranging from 40 to 130 beats/min by increments of 1 beat/min. Second, this parameter was represented in the figure 4. Graphically, we observed that this parameter increases by approximately 5% for each increase of heart rate of 10 beats/min. The proposed approximation is shown in table 1. Approximated QT<sub>c</sub> is calculated by multiplying the uncorrected QT and the parameter of correction related to the measured heart rate. Finally, the approximated parameter was compared to Fridericia, resulting in a slight mean overestimation of  $1.1 \pm 2.0\%$  ( $P < 0.0001$ ).

### *Example of Approximated QT<sub>c</sub> Calculation*

Given an uncorrected QT of 380 ms and a heart rate of 93 beats/min, 5% of 380 is first calculated (mentally by dividing by 10, *i.e.*, suppressing the unity = 38, and then by dividing again by 2 =  $38/2 = 19$ ). For a heart rate of 93 beats/min, table 1 indicates 115% of uncorrected QT; thus the result is  $QT_c = QT + 10\% \text{ of } QT + 5\% \text{ of } QT$ ;  $QT_c = 380 + 38 + 19 = 437$  ms. For this example, the  $QT_{c_f}$  calculated from automatically measured raw QT and R-R intervals was 439 ms, and  $QT_{c_b}$  reported by the device was 473 ms.