QT Interval: Correction for Heart Rate

Balakrishna Hosmane, PhD[*]
Charles Locke, PhD[†]
David Morris, PhD[‡]

[*]*Division of Statistics, Northern Illinois University, DeKalb, Illinois*
[†]*Department of Experimental Medicine, Abbott Laboratories, Abbott Park, Illinois*
[‡]*Department of Statistics, Abbott Webb Writes, Durham, North Carolina*

ABSTRACT

There are several empirically based proposals in the literature for adjusting QT intervals for heart rate. Two widely used correction formulas are Bazett's and Fridericia's. This study examines the general formulation of heart rate correction of QT intervals, and several of the existing adjustments are used with this approach. Simple correction formulas for both populations and individuals have been derived on the basis that the correlation between corrected QT interval and heart rate should be approximately zero. A Monte-Carlo simulation is used for comparing the performance of Bazett's, Fridericia's, and the proposed corrections. The usefulness of the proposed correction formula is illustrated using data from a clinical trial.

INTRODUCTION

Evaluation of new drugs for unwanted effects on the electrical properties of the heart is receiving heightened attention from pharmaceutical companies and regulatory agencies. This attention arises from recent scientific research that links drug effects in cellular ion channels to changes in electrical characteristics of the electrocardiogram (ECG) that predict clinically important cardiac arrhythmias.[1]

BIOLOGICAL AND HISTORICAL REVIEW

A brief overview of heart function is useful in understanding how disruptions of electrical processes can affect heart rhythm. The heart is divided such that its right side pumps blood though the lungs while the left side pumps blood throughout the remainder of the body. Each half of the heart is further divided into an upper chamber (atrium) and a lower chamber (ventricle). Blood returns from the body into the right atrium that forces blood to fill up the right ventricle. Simultaneously, blood from the lungs is used by the left atrium to fill up the left ventricle. When the ventricles are filled, valves close between the respective atria and ventricles, and the ventricles contract to pump blood.
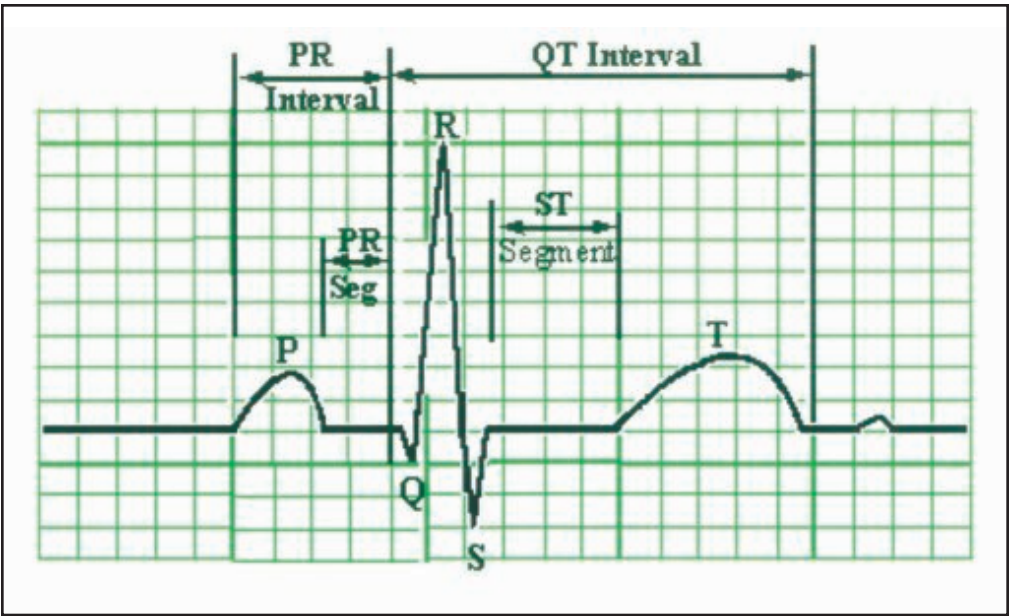
Effective pumping of blood requires

Figure 1. The electrocardiogram: waveform.

continuous electrical coordination of the atria and ventricles. Electrical pacing of the heart begins with an electrical pulse from the specialized tissue of the sinu-atrial (S-A) node near the top of the right atrium. The signal from the S-A node initiates a wave of electrical excitation (depolarization) that spreads throughout the right and left atria and is observed on an ECG as a P wave (Figure 1).

The electrical wave exits the atria near the bottom of the right atrium through the atrioventricular (A-V) node and is propagated via left and right bundles to the respective ventricles. This passage through the A-V node corresponds on the ECG to the interval between the P and R waves, and failure of the electrical wave to complete this passage is known as heart block or left/right bundle branch block. Nearly simultaneous propagation of the electrical wave across the right and left ventricle results in muscle contraction and the pumping of blood from the ventricles. The QRS complex of the ECG corresponds to the initiation of this contrac-

tion. A period of muscle relaxation and repolarization of cellular membranes follows and is generally considered complete at the end of the T wave.

Elucidation of the electrical control of heart function is the culmination of a long interdisciplinary process.[2] Galvani induced contraction of cardiac muscle fibers in frogs with electrical stimulation in 1791. However, this experiment did not show definitively that electricity regulates muscle fiber contraction or heart function in general. Dubois-Reymond described in 1843 small voltage potentials (action potentials) that diminished with muscle contraction, and electrical currents were associated with heartbeats by Koelliker and Muller in 1856. Waller is credited with the first published human ECG in 1887.

In 1895, Einthoven identified the 5 primary topographic features of the ECG tracing (P, Q, R, S, and T waves), and defined in 1912 the current standard ECG leads I, II, and III. Additional standard leads were identified in 1938 (V1 – V6) and in 1942 (aVR, aVL, and aVF). By 1957, Jervell and Lange-Nielsen had

Table 1. QTc Correction Formulas[8]

#	Name	QTc
1	Linear	$QTc = QT + \alpha(1\text{-}RR)\ 1$
2	Hyperbolic	$QTc = QTC + \alpha\,(\frac{1}{RR} - 1)$
3	Parabolic log/log	$QTc = \frac{QT}{RR^{\alpha}}$
4	Logarithmic	$QTc = QT - \alpha Log(RR)$
5	Shifted Logarithmic	$QTc = Ln\{e^{QT} + \alpha(1\text{-}RR)\}$
6	Exponential	$QTc = QT + \alpha(e^{\text{-}RR}\text{-}1/e)$
7	Arcus Tangent	$QTc = QT + \alpha\{arctan(1) - arctan(RR)\}$
8	Hyperbolic Tangent	$QTc = QT - \alpha\left\{\frac{e^2 - 1}{e^2 + 1}\right\} - tgh\,(RR)$
9	Arcus Hyperbolic Sine	$QTc = QT - \alpha\{ln(1 + \sqrt{2}) - arcsin\,h\,(RR)\}$
10	Arcus Hyperbolic Cosine	$QTc = QT - \alpha\{ln(1 + \sqrt{2}) - arccos\,h\,(RR + 1)\}$
11	Square Root	$QTc = QT + \alpha(1\text{-}RR^{1/2})$
12	Cube Root	$QTc = QT + \alpha(1\text{-}RR^{1/3})$

described correlations between hereditary long QT intervals and sudden death. Smirk and Palmer noted in 1960 that ventricular beats (R waves) prematurely occurring during the T wave increase the risk of ventricular arrhythmia. Torsades de pointes, a specific type of ventricular arrhythmia, was first published in 1966 by Dessertenne.

Although some drugs that had been developed as anti-arrhythmic agents also altered ventricular repolarization as evidenced by prolonged QT interval, it was not widely known that noncardiac drugs could also have this property. The use of nonsedating antihistamines, eg, terfenadine and astemizole, from 1985 to 1999 provided an important case study of the public health issues with widespread use of noncardiac drugs that have cardiac effects. Initial reports of cardiac arrhythmias, including torsades de pointes, were predominately associated with high blood concentrations subsequent to overdose.[3] Given the metabolic pathway of these drugs, arrhythmias were eventually reported subsequent to coadministration with drugs that slowed the metabolism of terfenadine and astemizole (also resulting in high blood concentrations). Despite warning letters to physicians and restricted product labeling in 1992, inappropriate medications continued to be coadministered with these drugs.[2] In 1999, both drugs were withdrawn from use in the United States after safer alternatives were developed.[2]

The high visibility of the nonsedating antihistamines prompted extensive research into the mechanisms by which drugs cause cardiac arrhythmias. Although many details remain unknown, current research suggests that most drugs with strong arrhythmic potential interfere with a specific potassium channel in cardiac muscle fiber. Partially or completely blocking the potassium channel results in delayed repolarization of the muscle fiber. Delayed repolarization increases the time required to restore the voltage or action potential required for the next muscle contraction. Arrhythmias such as torsades de pointes are possibly triggered by the initiation of

290

Table 2. Estimated η, λ, and P value[6,7]

ρ	Method	η	λ	P Value
−0.1	Bazett	−1/2	2.71703	0.0
	Fridericia	−1/3	1.70281	0.0
	Proposed	−0.0409403	−0.00957	0.49988
−0.2	Bazett	−1/2	2.45421	0.0
	Fridericia	−1/3	1.44484	0.0
	Proposed	−0.0827050	−0.02145	0.49944
−0.3	Bazett	−1/2	2.19125	0.0
	Fridericia	−1/3	1.18674	0.0
	Proposed	−0.1249727	−0.03097	0.49708
−0.5	Bazett	−1/2	1.66491	0.0
	Fridericia	−1/3	0.67012	0.00439
	Proposed	−0.2099809	−0.04909	0.48286
−0.7	Bazett	−1/2	1.13797	0.0
	Fridericia	−1/3	0.15293	0.32639
	Proposed	−0.2972420	−0.05697	0.45515
−0.9	Bazett	−1/2	0.61024	0.00001
	Fridericia	−1/3	−0.36504	0.00528
	Proposed	−0.3884091	−0.04556	0.40585

R waves during the period of delayed repolarization.

Delayed repolarization is manifested on the ECG tracing as an elongated distance from the start of the Q wave to the end of the T wave; this distance is called the QT interval. Drugs that prolong the QT interval presumably increase the risk of cardiac arrhythmias. Unfortunately, the degree of increased risk per unit increase in QT interval is uncertain, and the smallest clinically important increase in QT interval remains undefined. Recent public meetings of regulatory agencies suggest that a 6-millisecond mean increase constitutes a possible threshold for regulatory concern.[1]

Design Implications
Clinical studies to detect QT interval mean increases as small as 5 milliseconds face significant challenges because of the substantial variability in QT inter-vals. Acquisition of the ECG is the first source of variability and bias. Improper placement of the 12 ECG leads contributes noise and/or bias because the leads correspond to vectors over which the heart's electrical field is integrated (ie, summed). Choice of lead(s) for analysis is also important since QT elongations are more frequently detected in some leads rather than others, and no lead uniformly detects all elongations. Each ECG manufacturer can have unique signal processing algorithms within the ECG machine that can produce slightly different values of QT among machine models given the same human input.[1]

Also, the ECG signal can be captured on paper (ECG tracing) or as an electronic digital file (waveform). The choice of media (paper versus digital) for ECG capture is important because QT intervals can be measured more precisely and reproducibly with digital

Table 3. Malik's (α) and Proposed (η) Estimates of the Correction Factor[8]

Function	Mean α (SE)	Mean η (SE)
Linear	0.1668 (0.0364)	0.1635 (0.0402)
Hyperbolic	0.0975 (0.0219)	0.0960 (0.0210)
Parabolic log/log	0.3431 (0.0603)	0.3316 (0.0628)
Logarithmic	0.1278 (0.0235)	0.1240 (0.0227)
Shifted Logarithmic	0.2421 (0.0518)	0.2374 (0.0560)
Exponential	0.3634 (0.0674)	0.3511 (0.0669)
Arcus Tangent	0.2686 (0.0500)	0.2594 (0.0498)
Hyperbolic Tangent	0.2931 (0.0548)	0.2816 (0.0522)
Arcus Hyperbolic Sine	0.2117 (0.0416)	0.2057 (0.0441)
Arcus Hyperbolic Cosine	0.2433 (0.0456)	0.2362 (0.0465)
Square Root	0.2921 (0.0560)	0.2842 (0.0583)
Cube Root	0.4230 (0.0790)	0.4072 (0.0794)

rather than paper-based systems. In addition, recent regulatory initiatives suggest than the determination of points for start of the Q wave and end of the T wave will need to be documented. Identification of the Q and T points is important because expert judgment is often required to choose them appropriately. The use of human experts to measure QT intervals suggests that standardized training and instruction of the experts is prudent in order to reduce inter-rater variability and bias.

Apart from the problems of signal acquisition and measurement, QT intervals are characterized by substantial inter- and intrasubject variability. Sources of intersubject variability can include genetic predisposition to long QT intervals, electrolyte concentrations, autonomic activity, age, and sex.[4] Given that drug effects are presumably related to interstitial concentrations at cardiac muscle fibers, it is difficult to predict for populations or individuals when the concentrations are maximized. Intrasubject variability is strongly influenced by circadian rhythms that influence autonomic tone and heart rate.[5]

The above challenges probably prevent a single clinical study from definitively characterizing a new drug's ability to alter the QT interval. However, it is useful to consider the design of clinical trials that assess specific aspects of QT interval elongation. Consider a study of healthy volunteers to assess dose response with QT interval. Which doses are selected? In general, a target dose will hypothetically possess the target efficacy profile and another dose will be placebo (the zero dose). There should also be a maximal dose that corresponds to the largest tolerated dose. If the maximal dose is much larger than the target dose and there is some prior evidence that the drug may affect QT interval, an intermediate dose may be selected between the target and maximal doses. The intermediate dose could be used to establish the highest dose not associated with QT effects. One should also consider adding an active control drug with QT effects consistent with the lowest threshold for regulatory/scientific concern. Without an active control demonstrating QT effects during the study, there will always be some uncertainty in interpreting lack of QT effects in the experimental drug.

Table 4. Study Design

Group	Period 1	Period 2
I	1 mg bid (n = 8)	1 mg tid (n = 8)
	placebo (n = 4)	placebo (n = 4)
II	2 mg bid (n = 8)	1.5 mg tid (n = 8)
	placebo (n = 4)	placebo (n = 4)
III	3 mg bid (n = 8)	2 mg tid (n = 8)
	placebo (n = 4)	placebo (n = 4)

Duration of dosing must also be considered for drugs that will be administered more than once per treatment course. For drugs that are not completely excreted from the body between doses, study duration may need to extend until accumulation of drug plateaus in the body (ie, drug concentrations achieve steady state) for all doses. ECG assessments may be planned for the first day of dosing in addition to the steady-state period. Scheduling of ECG assessments must be customized to sample QT at times most relevant to the absorption and excretion of the drug. Obviously, the ECG schedule should be consistent across treatment groups and days in order to control for circadian rhythms.

The study design should standardize activity levels across treatments and ensure that no imbalances among treatment occur for important covariates such as age and sex. Electrolyte levels may be monitored during the studies, especially if the new drug has some effect on them. Subjects with a genetic predisposition to long QT intervals are typically excluded from these studies. Given the number of important inter-subject covariates, the proposed treatments are often presented in a crossover study so that treatment differences are taken within each subject. This approach can present logistical problems if the study consists of placebo, 3 doses of drug, and an active control with each treatment being administered for a week. In these situations, researchers must balance the sample size efficiency of the crossover study against its ability to answer a sufficient number of research questions in an appropriate time period.

As mentioned earlier, a single-dose response study in healthy volunteers will probably not provide sufficient evidence to fully characterize the ECG profile of a drug. Drug effects could differ in patients with the target disease, in patients with other illnesses in addition to the target disease, or in patients who are taking other medications at the same time. Combinations of factors could also synergistically increase any effects of the drug. These issues may be addressed in dedicated studies or incorporated into the efficacy/safety studies conducted in later phases of development. However dose selection, duration of dosing, timing of ECG measurements, and control of variability will need to be addressed in any study design to evaluate QT interval.

Heart Rate Corrections
Regardless of study design, the statistician will need to adjust QT interval for the influence of heart rate because heart rate is negatively correlated with QT interval; ie, slower heart rates tend to be associated with longer QT intervals. Exercise regimens that maintain pre-specified heart rates are impractical because exercise affects autonomic tone, and QT changes lag several minutes behind heart rate changes. The proposals for corrected QT (QTc) intervals are

Table 5. Estimated η, λ, and *P* Value (Population Correction)[6,7]

Period #	Method	η	λ	*P* Value
1	Bazett	−1/2	1.34852293	0.0001
	Fridericia	−1/3	0.30325439	0.0079
	Proposed	−0.26235	−0.13832480	0.2237
2	Bazett	−1/2	1.22166795	0.0001
	Fridericia	−1/3	0.19145713	0.0474
	Proposed	−0.28602	−0.09705817	0.3142

generally based on the RR interval from which heart rate is calculated (heart rate = 60/RR). The ideal QTc interval, would be uncorrelated with RR interval. Two commonly used correction formulae were proposed in 1920 by Bazett and Fridericia.[6,7] Unfortunately, each formula can lead to bias for some clinically relevant values of RR.

Recent work suggests that population-based correction formulae, such as Bazett, perform poorly because each person has a unique QT-RR relationship.[8] Thus, empirical methods were developed for each proposed functional relationship to find the subject-specific parameter values that produce zero correlation between QT and RR for that subject. A best formula is then chosen from among all considered models. Although this approach is clinically appealing, the statistical shortcomings are obvious.

Some of the well-known methods of adjusting QT intervals (QTc) for heart rate (HR) are provided below.

(i) Bazett[6]: QTc = QT{HR/60}$^{1/2}$

(ii) Fridericia[7]: QTc = QT{HR/60}$^{1/3}$

(iii) Framingham[9]: QTc = QT + 0.154{1 − (60/HR)}

(iv) Van de Water[10]: QTc = QT − 0.087{(60/HR) − 1}

(v) Regression[11]: QTc = QT{HR/HR$_m$}$^{-\beta}$, where HR$_m$ is the reference heart rate and β is the estimated slope parameter in a regression model Log(QT)= α + βLog(HR) + Error

There are several other regression type correction formulas in the literature, some of which are given in Table 1, and they all seem to work well for a specific data set, but not so well across all data sets.[8,12]

In this study, a general linear model framework to derive formulas for heart rate QTc intervals using first-order Taylor series approximation was used.[13] Most of the models used in the literature for heart rate adjustment of QT intervals are particular cases of the model used in this study. The proposed correction formula not only provides that the correlation of a function of QTc, which is usually an identity or a log function, and HR is approximately zero, but also minimizes the approximate variance of the function of QTc. This latter feature means that QTc itself will have a relatively small variance, which is desirable in clinical trials in which drugs are evaluated or compared with respect to effect on QTc interval. A small-scale Monte-Carlo simulation study was conducted to compare the correction formulas. In addition, the exact correction formula proposed by Malik[8] was compared to this study's proposed approximate estimate. To illustrate the usefulness of the formulas, they are used

Table 6. Estimated λ and *P* value (Individual Correction)

Period #	Method	λ	*P* Value
1	Proposed	−0.16924566	0.1505
2	Proposed	−0.12210764	0.2413

with data from a clinical trial.

DERIVATION OF THE CORRECTION FORMULA

For the general framework in which the methodology of this study is developed, it is assumed that QTc is related to QT interval (QT) and heart rate (HR) as follows:

$$h(QTc) = f(QT) - \eta \cdot g(HR),$$

where *f* and *g* are some smooth functions and *h* is a monotone function. Most of the models considered in the literature may be put in this framework. For example, let

$$H(QTc) = Log(QTc), f(QT) = Log(QT) \text{ and } g(HR) = Log(HR/60).$$

These choices of *f, g,* and *h* would yield

$$QTc = QT\{HR/60\}^{-n}.$$

For $\eta = -1/2$ and $\eta = -1/3$ Bazett's and Fridericia's correction formulas were obtained, respectively. For the following choice,

$$f(QT) = QT, g(HR) = 1-(60/HR),$$

and $h(QTc) = QTc$.

Van de Water's and the Framingham formulas were obtained with $\eta = 0.087$ and $\eta = 0.154$, respectively.[9,10]

Now, the main results for both population and individual heart rate corrections for QT intervals are presented; the proof of which are provided in the Appendix.

Study Wide (Population) Correction

First consider the case when each subject has only 1 ECG. Assume that (QT, HR) has a bivariate distribution with means (μ, ν) and variances (σ^2, τ^2) and correlation ρ. Then,

(i)   the correlation between $h(QTc)$

and *HR* is approximately 0 for

$$\eta = \rho \frac{CV_{QT}}{CV_{HR}} \left(\frac{\mu \cdot f'(\mu)}{\nu \cdot g'(\nu)} \right)$$

where $CV_{QT} = \dfrac{\sigma}{\mu}$, $CV_{HR} = \dfrac{\tau}{\nu}$ and

f', g' are the first derivatives of *f* and *g*, respectively,

(ii) the approximate variance of $h(QTc)$ is minimized for the value of *η* given in (i).

The choice of $f(QT) = Log(QT)$, $g(HR) = Log(HR/60)$ and $h(QTc) = Log(QTc)$ will lead to $QTc-QT\{HR/60\}^{-\eta}$

and

$$\eta = \rho \frac{CV_{QT}}{CV_{HR}}.$$

The case in which there is more than 1 predose ECG per subject, the *η* given in (i) above will be estimated for each subject using only the individual predose ECG data. The average of estimated *η* across all subjects will be used as the population correction.

Individual Correction

If there are several ECGs per subject, use the following adjustment procedure to determine the correction factor for each individual QT interval for heart rate. Assume that for subject *j*, $(QT_i, HR_i), i=1,\ldots,T$ is a stationary bivariate time series[14] with means (μ_i, ν_i), variances (σ_i^2, τ_i^2) and cross-correlation function $\rho(k)$ = correlation between QT_i and $HR_{(i+k)}$. Then,

(i)   the correlation between $h(QTc_i)$

and HR_i is approximately 0 for

$$\eta = \rho(0) * \frac{CV_{QT_i}}{CV_{HR_i}} \left(\frac{\mu_i * f'(\mu_i)}{v_i * g'(v_i)} \right)$$

where $\rho(0)$ is the cross-correlation

between QT_i and HR_i, $CV_{QT} = \dfrac{\sigma_i}{\mu_i}$,

and , $CV_{HRi} = \dfrac{\tau_i}{v_i}$,

(ii) the approximate variance of $h(QTc_i)$ is minimized for the value of η given in (i).

PROCEDURE FOR COMPUTING QTC WITH CLINICAL DATA

A brief description of the estimation procedure to compute both population and individually QTc intervals follows:

Population Correction

If there is a single predose ECG per subject, then use predose ECGs from all subjects to compute the proposed population correction factor η given in (i) of Study Wide (Population) Correction section.

If there is more than 1 predose ECG per subject, then use predose ECGs to compute the correction factor η given in (i) of Study Wide (Population) Correction section for each subject using only that individual's data and the average of these η's across all subjects will be used as the population proposed correction factor.

Individual Correction

The proposed individual correction factor η as given in (i) of Individual Correction, Correction Formulation Section is computed using only each individual predose ECG data. Assume that the ratio of means of QT and HR remain constant across all time points. These correction factors are used to

compute postdose QTcs.

SIMULATION RESULTS

Independent random samples (N=100) were generated from bivariate normal random vector (QT, HR) with mean vector (400, 75), standard deviations (25, 10), and correlation ρ taking values –0.1, –0.2, –0.3, –0.5, –0.7, and –0.9. For the method proposed in this study, η was estimated, treating these samples as the predose samples with 1 ECG per subject. Two more samples (N=100) were generated (one for placebo and the second for treated groups) each from bivariate normal distribution for (QT, HR) with mean vectors (400, 75), (350, 60) and corresponding standard deviation (SD) vectors (25, 10), (20, 8), respectively. The value of the correlation coefficient ρ varied from –0.1 to –0.9 as used in the generation of predose sample. The QTc intervals were computed using Bazett's, Fridericia's, as well as this study's proposed method for a specific choice of functions
$f(QT)=Log(QT), g(HR)=Log(HR/60)$
with

$$QTc=QT\{HR/60\}^{-\eta} \text{ where } \eta = \rho \frac{CV_{QT}}{CV_{HR}} .$$

To assess the performance of the 4 correction methods, a simple linear regression model was fitted

QTc = ø + λ* HR + TRT + Error, where TRT takes a value 0 for placebo and 1 for the treated group. It was assessed that the method works if the estimated value of λ is close to zero (a larger *P* value for testing the null hypothesis $H_0 : \lambda=0$ should indicate a better performance). The estimates of η, λ, and *P* values were averaged more than 1000 replicates (simulation size). The results are given in Table 2. These results clearly indicate that the proposed correction method outperforms Bazett's and Fridericia's methods. Bazett's method performs very poorly compared

with all other methods considered in the simulation.

Malik indicated how one can compute the correction factor a using iterative procedure so that the correlation between QT interval and heart rate is exactly zero for a choice of a functional relationship between QT interval and heart rate. Since there is no mechanistic model to describe the relationship between QT interval and heart rate, Malik[8] lists some of the most common choices for these functions in Table 1. Table 3 presents the mean and the standard error (SE) for both α and η obtained using simulated data. The results indicate that η and α are quite similar.

AN EXAMPLE

To illustrate the methodology discussed above, this paper used a phase I, randomized, double-blind, placebo-controlled, escalating multiple-dose study of DRUG in healthy subjects. A total of 36 subjects were assigned to 3 groups of 12 subjects each. Within each treatment group, subjects were randomized in a double-blind fashion such that 8 subjects received 2 doses of DRUG (1 in each period) and 4 were assigned to receive placebo in each period. Table 4 outlines the study design.

Subjects were administered study drug twice a day for 4 days during period 1, and 3 times a day for 4 days during period 2. Serial ECG measurements were obtained on day –1 and on the last day of each dosing regimen. ECGs were measured for each subject at times 0 (predose) and 2, 3, 4, 5, 7, 10, 12, 13.25, 14.5, 17.5, and 24 hours after the morning dose during period 1, and 2 additional times (8 and 9 hours) were used during period 2. These measurements were obtained using Marquette equivalent in the 12-lead format at 50 mm/sec and calibrated at 2 cm/mV. The machine was configured to provide QT, PR, QRS intervals and heart rate.

The association between QT intervals and heart rate were explored with the predose data, and it was concluded that the relationship is linear in log scale, ie, choice of functions are

$$f(QT)=Log(QT), g(HR)=Log(HR/60)$$
with
QTc = QT$\{HR/60\}^{-\eta}$ where

$$\eta = \rho\, \frac{CV_{QT}}{CV_{HR}}\,.$$

For the individual correction, the adjustment of QT interval for heart rate was computed using η obtained from each subject. In the population approach, the QTc interval was computed using the average values of η from all subjects.

To compare the adjustment methods, a regression model was fitted
QTc = ϕ + λ*HR + Error,
using repeated measure methodology and tested to see whether λ=0, ie, there is no significant heart rate effect on QTc. The results are provided in Table 5, and they indicate that the proposed method seems to work very well for correcting QT interval for heart rate.

For the individual QT interval correction, the results are given in Table 6 and are similar to the results obtained using population method.

DISCUSSION

Evaluation of new drugs for unwanted effects on the heart is receiving heightened attention because of research that has identified drugs that prolong the QT interval as risk factors for cardiac arrhythmia. The degree of increased risk per unit increase in QT interval is uncertain, and the smallest clinically important increase in QT interval remains undefined. Recent public meetings of regulatory agencies suggest that a 5-millisecond mean increase constitutes a possible threshold for regulatory concern.[1]

Clinical studies to detect QT interval mean increases as small as 5 milliseconds face significant challenges because of the substantial variability in QT intervals. The first source of variability is the process of acquiring and measuring the QT interval. Placement of ECG leads, choice of lead(s) to be measured, standardization of ECG machines, choice of media (paper versus digital), and variability in expert measurement of the QT interval comprise critical components of the process.

QT intervals are characterized by substantial inter- and intrasubject variability apart from that engendered by acquisition and measurement. Sources of intersubject variability can include genetic predisposition to long QT intervals, electrolyte concentrations, autonomic activity, age, and sex. Intrasubject variability is strongly influenced by circadian rhythms that influence autonomic tone and heart rate.[2]

A single study will probably not provide sufficient evidence to fully characterize the ECG profile of a drug. However, dose selection, duration of dosing, timing of ECG measurements, patient population, and control of variability will need to be addressed in any study design to evaluate QT interval.

The proposed correction factor closely approximates the empirical method of Malik, but also provides a framework from which the statistical properties of the correction factor can be derived. Although this approach appears to provide adequate estimation of correction factors on average, it may fail to correct appropriately for a subject with an unusual QT-RR relationship. Thus, one should investigate further when extreme QTc values are observed.

Further research is warranted to elucidate the correlation structure between QT and RR over time within a subject. Defining these structures could improve the mixed models used to obtain correction factor estimates and associated SEs. However, extensive monitoring with Holter recorders will be needed to obtain a sufficiently dense data set.

CONCLUSION

The importance of adjusting QT interval for heart rate is evidenced by numerous publications on this topic. Most of these adjustment procedures have been empirically based. In this study, a unified approach was presented with simple closed forms for population and individual correction formulas that show that the correlation of adjusted QT interval and heart rate is approximately zero. The estimate of the correction factor proposed by Malik[8] obtained using iterative procedure is similar to the proposed estimator used in this study. The simulation and the example from a clinical trial provide an empirical validation of the proposed method.

REFERENCES

1. *ICH Harmonised Tripartite Guideline*: The Clinical Evaluation of QT/QT$_c$ Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, *E14*, Step 4, 12 May 2005

2. ECG timeline—history of the electrocardiogram. Available at: http://www.ecglibrary.com/ecghist.html. Accessed November 14, 2006.

3. Scheife RT, Cramer WR. Sedative and cardiovascular profile of newer antihistamines. *Consult Pharm*. 1996;11:1037-1053. Available at: http://www.ascp.com/publications/tcp/1996/oct/clinical.html. Accessed April 25, 2006.

4. Morganroth J, Brown AM, Critz S, Crumb WJ, Kunze DL, Lacerda AE, Lopez H. Variability of the QTc interval: impact on defining drug effect and low-frequency cardiac event. *Am J Cardiol*. 1993;72(6):26B-31B.

5. Ong JJ, Sarma JS, Venkataraman K, Levin SR, Singh BN. Circadian rhythmicity of heart rate and QTc interval in diabetic autonomic neuropathy: implications for the mechanism of sudden death. *Am Heart J*. 1993;125:744-752.

6. Bazett HC. An analysis of the time relations of electrocardiograms. *Heart.* 1920;7:355-370.

7. Fridericia LS. Die sytolendauer in elektrokardiogramm bei normalen menschen und bei herzkranken. *Acta Med Scand.* 1920;53:469-486.

8. Malik M. Problems of heart rate correction in the assessment of drug-induced QT interval prolongation. *J Cardiovasc Electrophysiol.* 2001;12:411-420.

9. Sagie A, Larson MG, Goldberg RJ, et al. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). *Am J Cardiol.* 1992;70:797-801.

10. Van de Water A, Verheyeu J, Xhoneux R, Reneman R. An improved method to correct the QT interval of the electrocardiogram for changes in heart rate. *J Pharmacol Methods.* 1989;22:207-217.

11. Spence S, Soper K, Hoe C, Coleman J. The heart rate-corrected QT interval of conscious beagle dogs: a formula based on analysis of covariance. *Toxicol Sci.* 1998;45:247-258.

12. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol.* 1993;72:23B-25B.

13. Casella G, Berger R. *Statistical Inference.* Pacific Grove, CA: Wadsworth; 1990.

14. Diggle P. *Time Series: A Biostatistical Introduction.* Oxford: Clarendon Press; 1990.

APPENDIX

The proofs of the results given in Derivation of the Correction Formula section follow.

Consider the assumed relationship among QTc, QT, and HR given by

$$h(QTc) = f(QT) - \eta * g(HR),$$

where *f* and *g* are some smooth functions and *h* is a monotone function. The first-order approximation using Taylor series approximation around (μ, ν) is given by

$$h(QTc) = f(QT) - \eta * g(HR) \approx (QT - \mu)f'(\mu) - \eta(HR - \nu)g'(\nu).$$

Then,

$$COV(h(QTc), HR) \approx f'(\mu)COV(QT, HR) - \eta g'(\nu)\tau^2.$$

The value of η that makes $COV(h(QTc), HR)$ approximately zero is given by

$$\eta = \left[\frac{COV(QT, HR)}{\tau^2}\right] \frac{f'(\mu)}{g'(\nu)} = \rho \frac{CV_{QT}}{CV_{HR}} \left(\frac{\mu * f'(\mu)}{\nu * g'(\nu)}\right)$$

Also note that

$$\mathrm{Var}(h(QTc)) \approx [f'(\mu)]^2\sigma^2 + \eta * [g'(\nu)]^2\tau^2 - 2\eta * f'(\mu) * g'(\nu) * COV(QT, HR).$$

Then $Min_\eta\{Var(hQTc)\}$ is attained at $\eta = \rho \dfrac{CV_{QT}}{CV_{HR}} \left(\dfrac{\mu * f'(\mu)}{\nu * g'(\nu)}\right).$