Comparison of Six Commonly Used QT Correction Formulae And Three Parameter Estimation Methods

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Introduction

QT interval on an electrocardiogram (ECG) trace is an important and widely used surrogate parameter to assess drug safety since prolongation of cardiac repolarisation and QT interval is associated with various serious arrhythmias namely Torsade de Point (TdP) [1].

The duration of QT interval is affected by many factors including age, gender, various medical conditions, and most importantly by heart rate (HR) [1,2]. The QT interval varies with HR: the faster the HR (or the shorter the RR interval [RR=60/HR]), the shorter the QT interval.

This effect is so pronounced that QT measurements have to be corrected for heart rate. These values are referred to as corrected QT interval (QTc). The QTc interval represents the QT interval at a standardised heart rate of 60/minute. The goal of heart rate correction is to provide QTc interval values that are independent of the corresponding RR interval values.

Over the past several decades, many correction formulae have been proposed. However, there is lack of systematic assessment of the sensitivity of formula parameters and validation of the corrected QT intervals.

Aims

The aim of this analysis was to compare six commonly used QT correction methods and three parameter estimating methods.

These methods were applied to four off-drug ECG datasets, a simulated dataset and one on-drug ECG dataset.

Six commonly used QT correction formulae

Deriving a QT correction formula involves two steps:

Step 1: Fitting a model with two regression parameters (β,α) to describe the QT-RR relationship, e.g. $QT=\beta RR^{\alpha}$

Step 2: Using the fitted model to derive a correction formula so that QTc=QT when RR=1, e.g. $QTc=QT/RR^{\alpha}$

Bazzet fitted a parabolic regression model $QT=\beta RR^{\alpha}$ and derived the following correction formula, $QTc=QT/RR^{1/2}$ [3]. Using a similar strategy, Fridericia developed an alternative correction formula, $QTc=QT/RR^{1/3}$ [4]. By fitting a simple linear regression model using the Framingham heart data, Sagie et al suggested a so-called Framingham formula: ($QTc=QT+0.154(1-RR)$) [5].

All the above proposed models for QT-RR relationships are in fact special cases of the following six most commonly used regression models (Table 1). Each regression model has two parameters: α and β. Once they are estimated, they can then be converted to generic heart rate correction formulae (Table 1).

QT-RR relationship	
Regression model	**Generic heart rate correction**
Model 1 (M1): Linear model	
$QT=\beta+\alpha RR$	$QTc=QT+\alpha(1-RR)$
Model 2 (M2): Hyperbolic model	
$QT=\beta+\alpha/RR$	$QTc=QT-\alpha(1/RR-1)$
Model 3 (M3): Parabolic model	
$QT=\beta RR^{\alpha}$	$QTc=QTRR^{\alpha}$
Model 4 (M4): Logarithmic model	
$QT=\beta+\alpha ln(RR)$	$QTc=QT-\alpha ln(RR)$
Model 5 (M5): Shifted logarithmic model	
$QT=ln(\beta+\alpha RR)$	$QTc=ln(e^{QT}+\alpha(1-RR))$
Model 6 (M6): Exponential model	
$QT=\beta+\alpha e^{-RR}$	$QTc=QT-\alpha(e^{-RR}-1/e)$

Table 1: Six most commonly used regression models and generic heart rate correction formulae.

Methods for Estimating the QT Correction Factor

Three computing methods have been proposed to estimate the correction factor for these six correction formulae:

- Golden section interaction procedure
- Ordinary regression model estimated by least square approach
- Mixed model estimated by maximum likelihood approach

Both ordinary regression model and mixed model are regression approaches.

The most popular method for estimating the correction factor has been the ordinary regression model or ordinary least square regression model.

The limitation of the least square approach is that the resulting formula does not guarantee the independence between corrected QT interval and RR.

To measure this independence, the Pearson correlation coefficient (ρ) between QTc and RR is often used. If the correlation between QTc and RR is zero, QTc is essentially considered to be independent of RR.

Mathematically the ρ for a given sample and a correction factor α can be calculated ρ(α). In order to obtain ρ(α) that is close to zero, the golden section iteraction search procedure has been proposed [6].

This method is a technique for finding the minimum (or maximum) unimodal function by successively narrowing the range of values inside which the minimum is known to exist.

Randomised Clinical Trial Data (Example 1)

This example is from 4 thorough QT trials conducted between 2007 and 2008. The ECG databases were derived from the collection of 12-lead surface ECGs performed during the trials.

Mean values of various measurements of QT correction performance from 225 subjects by six selected models with their correction factors estimated by three estimating methods are shown in Table 2.

The absolute values of correlation coefficient and regression slope of QTc-RR were used for calculating their mean values.

α Estimating Method	Measurement	M1	M2	M3	M4	M5	M6
Golden Section							
	α	0.1407	0.1452	0.3525	0.1426	0.2108	0.3915
	ρ	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Slope	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean of QTc	403.08	402.56	402.88	402.82	403.05	402.78
	RMSE	NA	NA	NA	NA	NA	NA
	SD of QTc	7.0471	7.1180	6.9538	7.0278	7.0777	7.0224
	Minimum of QTc	385.07	384.82	385.49	385.10	384.90	385.08
	Maximum of QTc	423.26	423.89	423.40	423.31	423.27	423.26
	Range of QTc	38.195	39.073	37.915	38.210	38.375	38.177
Regression							
	α	0.1407	0.1440	0.3527	0.1425	0.2108	0.3914
	ρ	0.0000	0.0221	0.0078	0.0081	0.0007	0.0081
	Slope	0.0000	0.0017	0.0006	0.0006	0.0001	0.0006
	RMSE	7.0213	7.0882	6.9968	7.0016	7.0118	6.9962
	Mean of QTc	403.08	402.57	402.87	402.81	403.05	402.78
	SD of QTc	7.0471	7.1143	6.9532	7.0274	7.0777	7.0219
	Minimum of QTc	385.07	384.86	385.49	385.10	384.89	385.08
	Maximum of QTc	423.26	423.68	423.38	423.27	423.27	423.22
	Range of QTc	38.195	38.823	37.895	38.175	38.376	38.145
Mixed Model							
	α	0.1409	0.1418	0.3733	0.1508	0.2113	0.3936
	ρ	0.2691	0.3085	0.3701	0.3688	0.2588	0.2857
	Slope	0.0230	0.0284	0.0369	0.0370	0.0220	0.0248
	RMSE	7.4857	7.7542	10.271	10.279	7.4403	7.5243
	Mean of QTc	401.19	404.58	401.99	402.18	401.42	402.92
	SD of QTc	7.5089	7.7769	7.9639	8.0447	7.5178	7.5464
	Minimum of QTc	382.23	385.68	382.10	381.94	382.39	384.10
	Maximum of QTc	422.17	427.08	425.65	425.74	422.37	424.00
	Range of QTc	39.943	41.399	43.545	43.798	39.978	39.895

Table 2: Mean values of various measurements of QT corrections for 225 subjects (38467 ECGs) from 4 thorough QT studies

- **Golden section approach** - mean absolute correlation coefficient and mean absolute regression slope of QTc-RR was zero for all six QT correction formulae.
- **Regression approach** - although the mean values for correct factor α were close to those from golden section approach for all six QT correction formulae, the mean absolute correlation coefficients and the mean absolute regression slopes of QTc-RR were not equal to zero for all five non-linear regression models (Models 2-6).
- **Mixed model approach** - performed worst in terms of all five performance indices: the QTc-RR correlation, the absolute regression slope of QTc-RR, RMSE, standard deviation and range of QTc. These values were statistically significantly different from 0 (P<0.001) - therefore the mixed model fails to make QTc values independent of RR values.

Simulation Study (Example 2)

In this example, a dataset was simulated for individual QT-RR patterns according to a proposed strategy [7]. The aim of the simulation was to get a wide range of possible QT-RR patterns.

The simulation results were generally in agreement with those observed for Example 1 (Table 2).

Two observations are particularly worth commenting on.

The golden section procedure generated QTc values that were totally uncorrelated to RR for all six formulae (mean values of the estimated absolute individual correlation coefficients and regression slopes were always equal to zero).

The parabolic QT correction formula produced QT intervals with the smallest mean variation when QTc intervals were uncorrelated to RR intervals.

4-way Crossover Study (Example 3)

This example is different from Example 1 in that it contains off-drug ECGs and on-drug ECGs, enabling evaluation of various QT correction methods under the real-life scenario of a thorough QT study.

The results were consistent with those observed from Example 1 and 2. However, there was a marked difference in the mean absolute correlation coefficients between the golden section approach and two regression approaches.

The mean values of ρ generated by the golden section approach were zero for all six correction formulae but the mean values of ρ generated by the least square regression model and mixed model were statistically significantly different from zero (P<0.001) for all six correction formulae.

Discussion

The results from 225 individual off-drug QT-RR profiles from the 4 clinical trials (Example 1) demonstrated that the golden section approach always provides the best correction factor for all six correction formulae in terms of QTc-RR relationship.

The mean absolute values of correlation coefficients and slopes for the 225 subjects were equal to zero meaning that the golden section approach generated QTc values that were invariant of the heart rate regardless of correction formulae.

The results from the simulated ECG data (Example 2) confirmed the above observation. Even for the on-drug ECG dataset (Example 3), the golden section approach also yielded zero correlation coefficient and near zero slope for all six correction formulae.

The parabolic model (Model 3) produces QTc intervals which were independent of RR and with the smallest variation in terms of standard deviation and range - smallest mean range of QTc from the golden section (37.915 msec), largest mean range of QTc for the hyperbolic model (39.073 msec).

Conclusions

- In conclusion, the golden section procedure always finds the correction factor that makes the QTc totally independent of RR for all six correction formulae.
- In particular the parabolic correction formula ($QTc=QT/RR^{\alpha}$) also generates QTc values with the smallest variation for both off-drug and on-drug ECGs.
- It is therefore recommended that parabolic correction formula should be used to correct QT for heart rate in clinical studies and that its correction factor (α) should be estimated using the golden section approach.
- In contrast, least square regression model and mixed model may use a correction formula that fails to make the QTc independent of RR and should be avoided when deriving the best correction factor.

References

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