Heart Rate Correction of the QT interval

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Since the initial publications by Bazett[1] and Fridericia[2] in 1920 (that were actually preceded by similar considerations by Garrod[3] on mechanical cardiograms in 1870) many attempts have been made to propose a universally applicable formula for heart-rate correction of the QT interval.

Each published heart-rate correction formula (Bazett,[1] Fridericia,[2] Framingham,[4] Hodges,[5] etc.) was the result of fitting a curve to an observed collection of (RR, QT) pairs, and the formulae are different because each investigator drew data from a different population. Based on more recent studies, we now know that the QT/RR relationship varies not only from population to population but also, and more importantly, from individual to individual. The populations studied by Bazett, Fridericia et al., were different accidentally rather than systematically (e.g. by ethnicity or sex). These accidental differences were related to the relatively small sample size of these investigations and the high intersubject variability of the QT/RR relationship.

In other words, the application of any previously published correction formula has to be based on the assumption that the analysed data correspond to the distribution of the QT and RR interval values from which the given formula was previously developed and on which it was previously tested. Since the distribution of the QT/RR interval data in a population of any trial is a result of a combination of individually specific QT/RR patterns (that differ randomly similar to fingerprints), such an assumption is rarely satisfied. Therefore, the application of any arbitrarily selected heart-rate correction formula leads most likely to overcorrection or undercorrection† of the QT interval.

This means that with drugs that change heart rate, the reported values of QTc interval changes are a combination of true QTc changes (if any) and of the drug-related RR interval shifts. In particular, Bazett's formula overcorrects the QT interval in >95% of humans, and it therefore reports false QTc interval prolongation with drugs that accelerate heart rate, and false QTc shortening with drugs that decelerate heart rate.

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† The terms undercorrection and overcorrection of the QT interval are used here in the following sense: Uncorrected QT interval increases with increasing values of RR interval and thus, the correlation between uncorrected QT interval and RR interval is positive as is the slope of the QT/RR regression. The goal of a correction formula is to produce QTc values that are uncorrelated with RR intervals and thus have the slope of QTc/RR regression zero. Hence, in essence, a correction formula should tilt the QT/RR pattern so that the QTc/RR pattern is flat. Those formulae that tilt the QT/RR pattern too much (and thus lead to a negative correlation between QTc and RR and to a negative QTc/RR slope) *overcorrect*, while those formulae that tilt the QT/RR pattern too little (and thus lead to a still positive correlation between QTc and RR and to a positive QTc/RR slope) *undercorrect*.

As an example: In an independent study of 50 healthy volunteers,[14] the individual Pearson correlation coefficients between QTc (Bazett) and RR intervals ranged between –0.877 and –0.089 (ie, Bazett's formula overcorrected in each case) while the individual Pearson correlation coefficients between QTc (Fridericia) and RR intervals ranged between –0.598 and +0.686 with 12 cases of negative correlation (overcorrection) and 38 cases of positive correlation (undercorrection). Only in 11 cases of the 50 subjects was the correlation coefficient between QTc (Fridericia) and RR intervals within the limits of –0.1 and +0.1 which, although still not entirely precise, might be judged as a practically acceptable correction. (There was only 1 such case with Bazett's formula.)

One way to cope with this problem is to generate a trial-population-specific correction formula by fitting a curve to the off-drug data values of the trial in hand. For this purpose, all the drug-free QT and RR interval measurements are pooled from all the individual subjects of the trial, the relationship between the QT and RR intervals is modelled using linear or (more appropriately) non-linear regression analysis, and a heart-rate correction formula is derived from the optimized QT/RR regression model. Such a correction formula ensures that drug-free QTc intervals are independent of RR intervals when considering all the subjects of the trial together. This means that at the level of the data pooled from all trial subjects, the results of the derived heart-rate correction formula are not confounded by drug-related changes in heart rate.

As mentioned above and demonstrated in Figure 1, the QT/RR interval patterns are different in different individuals. Thus, the QT/RR interval pattern derived from the pooled data of different trial participants is not a good representation of the QT/RR pattern in each participant separately. Consequently, there are 2 problems with the heart-rate correction derived from pooled drug-free data of a given trial. First, while no systematic undercorrection or overcorrection occurs when considering all the data of the trial together, undercorrections and overcorrections do occur in individual subjects, so any outlier analysis based on the pooled correction formula can be misleading. In graphical terms, a correction formula based on the 2-person population of Figure 1 would reflect a normalized QT/RR relationship that lay between the 2 groups of points there. At low heart rates, all of the QT intervals normally seen in these 2 individuals would be judged by the population-based model to be abnormally prolonged (in the subject represented with open red symbols) or abnormally shortened (in the subject represented with solid blue symbols).

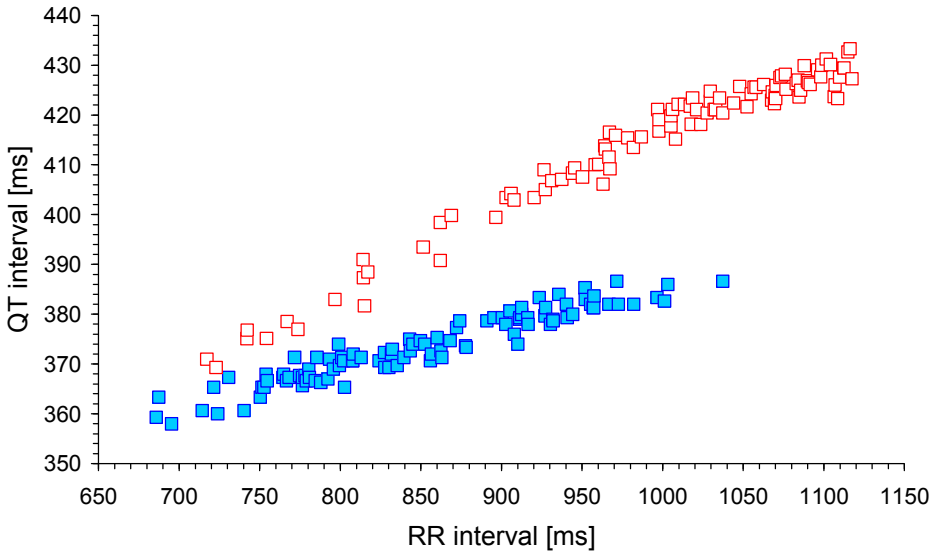

Figure 1: Scatter diagrams of QT and RR intervals measured in serial stable 12-lead electrocardiograms obtained during day-time hours in two male subjects.[7] A total of 100 data-points were obtained in each of the 2 subjects and are distinguished by different marks. The QT/RR pattern is much steeper in 1 subject than in the other. Specifically, when the RR interval changes from 750 to 950ms, the QT interval prolongs in 1 of these subjects by approximately 20ms, while in the other subject it prolongs by approximately 35ms. Thus, there cannot be a common correction formula or a common numerical QT/RR regression model that would fit the data of both these subjects. More subtly, the QT/

RR pattern of 1 subject (solid blue symbols) is more nearly linear than that of the other subject (open red symbols).

Secondly, and perhaps more importantly, the slope of a QT/RR pattern pooled from different individuals is usually steeper than the mean slope of the individual patterns (because of the distribution of QT/RR relationships within populations of healthy subjects).[8] Therefore, the pooled correction formula is potentially biased: It will lead to individual overcorrection more frequently than individual undercorrection.

To improve upon the trial-specific heart-rate correction formula, one can compute a separate correction formula for each study participant, using drug-free data from only that individual.[9-11]

Development of an individual heart-rate correction formula requires a large number of drug-free QT/RR data points, including a reasonably large range of heart rates. If such data are available, the individual QT/RR pattern is well defined, and detailed regression modelling can be used to define the pattern's position, slope, and curvature (for instance, it has been reported in independent data that the QT/RR pattern is more curved in women than it is in men[6,10]). The optimum regression model for each individual can then be derived, and the individual heart rate correction formulae may have not only different parameters, but even different mathematical forms for different subjects.[8]

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