Heart rate correction of QT interval in studies requiring a precise evaluation

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The application of any previously published and ad-hoc selected heart rate correction formula (Bazett, Fridericia, Framingham, Hodges, etc.) is based on the assumption that the data of the analysed study 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 study is a result of a combination of individually specific QT/RR patterns, such an assumption is satisfied extremely rarely and the application of any previously proposed and ad-hoc selected heart rate correction formula leads most likely to overcorrection or undercorrection of the QT interval. This means that with these correction formulae, the reported values of QTc interval changes are a combination of true QTc changes (if any) and of the RR interval shifts. In particular, Bazett's formula belongs to those formulae that systematically overcorrect the QT interval, it therefore leads to artificial QTc interval prolongation in situations of heart rate acceleration, and to artificial QTc shortening with heart rate deceleration. Both false positive and false negative findings may be obtained when relying on such a largely imprecise formula.

The first step to cope with this problem is to reproduce the standard technology that is usually used for the design of heart rate correction formula and to apply it to the baseline data of the study in hand. For this purpose, all the baseline QT and RR interval measurements are pooled from all the individual subjects of the study, the relationship between the QT and RR intervals modelled using linear or (more appropriately) non-linear regression analysis, and a heart rate correction formula derived from the optimised QT/RR regression model. Such a heart rate correction formula ensures that baseline QTc intervals are independent of RR intervals when considering all the subjects of the study together. This means that at the level of the data pooled from all study subjects, the results of the derived heart rate correction formula are not influenced by any changes in heart rate (e.g. when investigation a drug that changes heart rate but does not change the QT beyond of what corresponds to the underlying change in heart rate).

As recently observed, the QT/RR interval patterns are different in different individuals (example in Figure). Thus, the QT/RR interval pattern derived from the pooled data of different study participants is not a good representation of the QT/RR pattern in each participant separately. Consequently, there are two problems with the heart rate correction derived from pooled baseline data of a given study. Firstly, while no systematic undercorrection or overcorrection[†] occurs when considering all the data of the study together, such an undercorrection or overcorrection may occur in individual subjects.

[†] 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 [1], the individual Pearson correlation coefficients between QTc (Bazett) and RR intervals ranged between –0.877 and –0.089 (i.e. 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,

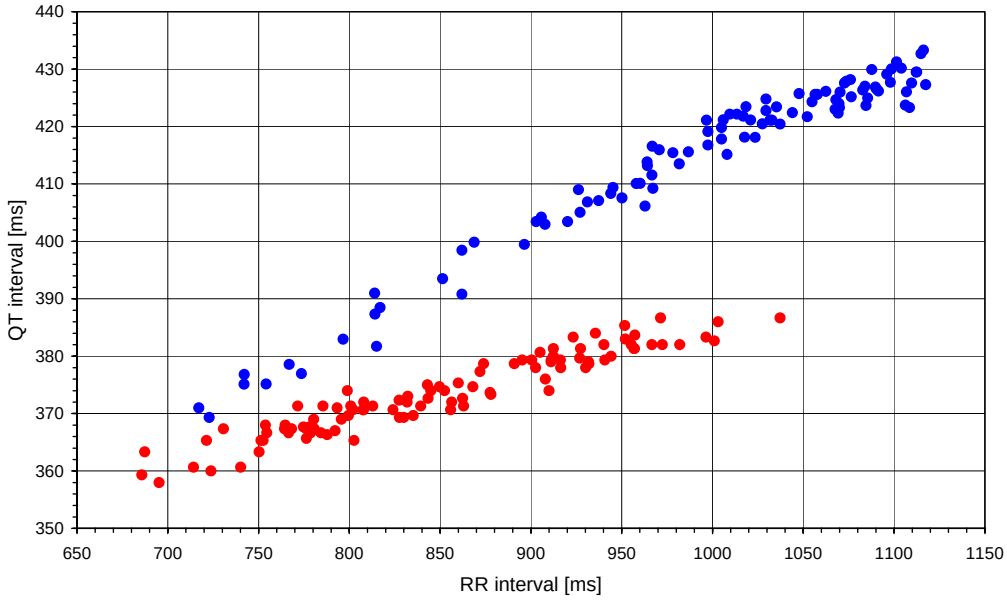

Figure. Example of individual QT/RR patterns seen in a study investigating healthy volunteers [2]. The figure shows QT and RR interval data carefully measured in serial stationary electrocardiograms of 2 healthy male subjects. It is obvious that while in one of them, the QT/RR pattern is rather flat, it is much steeper in the other. Specifically, when the RR interval changes from 750 to 950 ms, the QT interval prolongs in one of these subjects from (approximately) 365 to 385 ms, that is by 20 ms, while in the other subject, it prolongs from (approximately) 375 to 410 ms, that is by 35 ms. Thus, there simply cannot be a common correction formula or a common numerical QT/RR regression model that would fit the data of both these subjects.

Therefore, any outlier analysis based on the pooled correction formula is imprecise and might be substantially misleading. Secondly, and perhaps more importantly, it has been repeatedly observed that the slope of a QT/RR pattern pooled from different individuals is steeper than the mean slope of the individual patterns (because of the distribution of QT/RR distribution within populations of healthy subjects – an independent documentation of this observation is presently in preparation for publication). Therefore, the pooled correction formula is potentially biased by introducing more frequently an individual overcorrection than individual undercorrection of the QT interval. Less frequently, the opposite happens when a pooled formula produces more frequently an individual undercorrection than individual overcorrection [6].

To cope with these problems, the concept of individualised heart rate correction has been developed. The process of developing study specific heart rate correction formula is applied separately to the baseline data of each study participant and subsequently applied to the on-treatment data obtained in the given individual.

The development of the individual heart rate correction formula is influenced by the number of baseline QT/RR interval data points available for each study participant. If this number is not sufficiently large, and if the range of the recorded baseline heart rates is too narrow, not only may extrapolation beyond baseline data occur in the analysis of the electrocardiograms, but also the individual pattern of QT/RR interval distribution might be erroneously approximated. However, if the baseline data available from each study participant are sufficiently numerous and the range of baseline heart rates sufficiently wide, the individual QT/RR pattern is well defined

although still not entirely precise, might be judged as a practically acceptable correction. (There was only one such case with Bazett's formula.)

and can be studied with detailed regression modelling. In such a case, not only the steepness of the pattern and its position along the QT interval axis may be mathematically described, but also the curvature of the QT/RR interval distribution may be studied (for instance, it has been reported in independent data that the QT/RR pattern is more curved in women than it is in men [1,3]). Introducing the curvature of the QT/RR interval pattern into the design of the individual heart rate correction formula leads to a selection of the optimum regression model for each individual. This in turn means that the individual heart rate correction formulae may have a different mathematical form for different subjects. The precision of the heart rate correction is then further improved [4,5].

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