Investigation of methods to assess the individual relationship between the RR and QT interval of the ECG

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Background
The attribute of certain drugs to alter the characteristics of cardiac repolarisation has been recognized as an important safety aspect. The QT interval is the key parameter to assess the risk of such changes. However, this interval depends on the actual heart rate (determined as the RR interval) and might be affected by systematic changes.

Introduction
In the analysis of the QT interval, the absolute value as measured from the ECG has to be corrected in relation to the heart rate, which is subject to circadian variability and various external factors. Particularly in "Thorough QT studies", this QTc value is of interest. An abundance of different correction methods has been proposed and applied, in terms of the underlying dependence between RR and QT length as well as regarding the proceeding of estimating the necessary parameters and the level on which these parameters are valid (mainly, study population and individual subject) [1-3].

Data and Methods
The data were taken from a "Thorough QT Study", consisting of the ECG profiles at four baseline days with up to 12 measurement time points. At each time point, triple ECGs have been recorded and four wave forms per ECG have been measured. This study was performed in 56 healthy subjects of both gender.
The relationship between QT interval and RR interval was analysed applying linear mixed models [4], using the hierarchical structure of the data set, in detail, "subject", "day" and "time" as well as interactions. Several statistical models have been tested and compared using model selection criteria (e.g. AIC) if appropriate. Different model restrictions are applied on the random effects on several levels and the nested structure is used to explore the correlation structure of the measured values. The time-dependent correlation of intra-subject repeated measurements is taken into account, comparing the appropriateness of Gaussian, exponential and power structure with parametric forms to adjust for daily seasonality [5].
These comparisons are performed for the following mathematical dependence assumptions:
a) Parabolic: $QTc = QT / RR^{\alpha}$, using logarithmic RR ad QT values in a linear model
b) Linear: $QTc = QT + \beta\,(1\text{-}RR)$
c) Log-linear scale for obtaining $QTc = QT + \gamma \ln RR$
Another objective of this investigation is the difference arising from using the RR and QT values of single wave forms on the one hand, and aggregations of them on the other. The effect of using randomized subsamples, taking one observation per time point, contrasting the analysis of mean values per time point, is explored.

Results
According to likelihood ratio, it is useful to include not only individual effects per subject, but also effects per day nested within each subject. Restricting the effects per subject to intercept or slope is not useful.
No model a)-c) for the RR-QT relationship was found to be clearly superior to the others.
There is a meaningful correlation between the measurements taken within short periods. Considering longer periods (up to a whole treatment day), the correlation analysis is clearly superposed by circadian variation in the ECG scheme [6]. For parabolic dependence, this correlation is fit best by an exponential structure. However, there is no generally best covariance structure to model it for all dependence assumptions a)-c). In more general repeated measurement analysis, it seems useful to treat the intervals of one ECG or all ECGs of one time point as one block of measurements.
The results vary more between the wave-by wave and mean analysis than between the full data and subsample calculation.

Discussion
No univocal recommendation for the choice of dependence model results from this analysis. However, the individual correction per subject [1] could be improved by random effects for different treatment periods to adjust the model. The relevant discrepancies between single ECG and mean value analysis should be considered in more comprehensive investigations.

References

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