CARDIOVASCULAR MEDICINE

Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval

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Objective: To compare the QT/RR relation in healthy subjects in order to investigate the differences in optimum heart rate correction of the QT interval.
Methods: 50 healthy volunteers (25 women, mean age 33.6 (9.5) years, range 19–59 years) took part. Each subject underwent serial 12 lead electrocardiographic monitoring over 24 hours with a 10 second ECG obtained every two minutes. QT intervals and heart rates were measured automatically. In each subject, the QT/RR relation was modelled using six generic regressions, including a linear model ($QT = \beta + \alpha \times RR$), a hyperbolic model ($QT = \beta + \alpha/RR$), and a parabolic model ($QT = \beta \times RR^{\alpha}$). For each model, the parallelism and identity of the regression lines in separate subjects were statistically tested.
Results: The patterns of the QT/RR relation were very different among subjects. Regardless of the generic form of the regression model, highly significant differences were found not only between the regression lines but also between their slopes. For instance, with the linear model, the individual slope (parameter α) of any subject differed highly significantly ($p < 0.000001$) from the linear slope of no fewer than 21 (median 32) other subjects. The linear regression line of 20 subjects differed significantly ($p < 0.000001$) from the linear regression lines of each other subject. Conversion of the QT/RR regressions to QTc heart rate correction also showed substantial intersubject differences. Optimisation of the formula $QTc = QT/RR^{\alpha}$ led to individual values of α ranging from 0.234 to 0.486.
Conclusion: The QT/RR relation exhibits a very substantial intersubject variability in healthy volunteers. The hypothesis underlying each prospective heart rate correction formula that a "physiological" QT/RR relation exists that can be mathematically described and applied to all people is incorrect. Any general heart rate correction formula can be used only for very approximate clinical assessment of the QTc interval over a narrow window of resting heart rates. For detailed precise studies of the QTc interval (for example, drug induced QT interval prolongation), the individual QT/RR relation has to be taken into account.

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The QT interval adapts to changes in heart rate, which makes it difficult to compare the QT interval recorded at different heart rates. To allow such a comparison, the concept of the heart rate corrected QTc interval was developed and many formulas have been proposed to describe the QT interval heart rate adaptation. Bazett's formula[1] is both the most frequently used and the most criticised.[2–4]

In principle, every heart rate correction formula assumes that a mathematical form exists to describe the physiological QT/RR relation. Such a form may be converted into a formula that normalises a measured QT interval to that which would be associated with a "standard" heart rate, for example, of 60 beats/min. Most studies that have proposed a heart rate correction formula relied on QT and RR interval data obtained from healthy volunteers, different groups of patients, or both. Simple observations or mathematical curve fitting procedures have been used to approximate the QT/RR relation.

Despite the number of studies, the quest for the "optimum" correction formula continues. While various mathematical forms have been used to describe the QT/RR relation, the introduction of any new heart rate correction formula was followed by studies showing the inadequacy of the proposal. This suggests that the QT/RR relation was different in the databases of the various studies. However, the lack of coherence among the studies suggests that the various formulas have been influenced by the individual differences in the QT/RR relation.

Various studies have previously observed interindividual differences in QT/RR patterns, both among healthy subjects and among cardiac patients.[5–7] However, apart from suggestions of comparing the QT intervals at the same heart rate,[8 9] the impact of such differences on heart rate correction has been systematically ignored. Such an impact may be of considerable importance when a very precise heart rate correction of the QT interval is needed and when the "RR bin" method of comparing QT intervals at the same heart rate is not practical (for example, in studies of drug induced QT interval prolongation).

With this in mind, we investigated the impact of individual differences in QT/RR relations among healthy subjects on the optimum heart rate correction.

METHODS

The study investigated 50 healthy volunteers (mean age 33.6 (9.5) years; 25 women aged 31.1 (9.9) years, range 19–59 years; 25 men aged 36.0 (8.6) years, range 26–57 years; age of women *v* men NS). All participants had a normal physical examination, had a normal resting 12 lead ECG, and were free of any history of cardiovascular disease. During the study, the volunteers were asked to refrain from excessive physical exercise, smoking, and alcohol intake and none were on any medication known to affect cardiac repolarisation. The study was approved by the local ethics committee. All participants gave their informed consent.

Electrocardiographic data

All participants were studied using the 12 lead ECG Holter SEER MC recorder from GE Marquette. The recorders were programmed to obtain a 10 second ECG every two minutes and each volunteer was recorded in this regimen for a nominal 24 hours. Thus, thirty 10 second ECGs were obtained each hour (720 ECGs during the full 24 hours).

The ECGs were stored in a digital format with 500 Hz sampling at a 12 bit resolution of the 12 simultaneously recorded leads. A previously described technology was used to construct a median beat from each lead of each ECG[10] and these median beats were used to measure the QT interval in each lead of each ECG using the research version of the QT Guard package by GE Marquette.[11] The determination of whether a QT interval could be reliably measured in a given lead was based on the signal to noise ratio of the isoelectric line between the T and P wave.[11] The measurement software was programmed to determine the end of the T wave using the downslope tangent method calculating the regression tangent from three data samples above and three data samples below the inflex point of the descending limb of the T wave.[12] Visual checks verified the automatic QT interval measurement in selected recordings but the number of ECGs recorded during the study did not allow systematic visual verification and manual adjustments.

Only ECGs with six or more measurable leads were included. The median duration of the QT interval among all measurable leads was used to characterise the representative QT interval.

The ambient heart rate of each ECG was also measured by the QT Guard package and reported in beats/min. This value was converted into mean RR intervals of each recording. Both QT and RR intervals were expressed in seconds.

QT/RR relation

To study the QT/RR relation, the data of QT and RR intervals of each subject were studied separately. Different mathematical forms may be used to describe the physiologically observed pattern of the QT/RR relation. Since it is not obvious whether some of these forms are more suited than others, selecting one of such forms arbitrarily may lead to a data processing bias. Therefore, the sequence of QT/RR data points was fitted with six different QT/RR regression models:

- Linear model (model A):
  $QT = \beta + \alpha \times RR$
- Hyperbolic model (model B):
  $QT = \beta + \alpha/RR$
- Parabolic model (model C):
  $QT = \beta \times RR^{\alpha}$
- Logarithmic model (model D):
  $QT = \beta + \alpha \times \ln(RR)$
- Shifted logarithmic model (model E):
  $QT = \ln(\beta + \alpha \times RR)$
- Exponential model (model F):
  $QT = \beta + \alpha \times e^{-RR}$

Note that all six regression models have two parameters that make their closeness of fit easily comparable.

For each model and each recording, the averaged regression residuum was also obtained (that is, the root mean square of the differences between actual and regression projected QT intervals).

Following a visual comparison of the regression parameters, the regression curves using the same model in different participants were compared. The slopes (parameter α) were compared using the regression related *t* statistics test, which investigated whether the regression curves between subjects were parallel. The fit between regression curves was investigated using the regression related *F* statistics test, which investigated whether the regressions of different subjects were identical. These two tests were performed for each pair of different subjects—that is, 2450 ($= 2 \times 50 \times 49/2$) statistical comparisons of the regression lines were performed for each generic regression model. Thus, 14 700 statistical tests were made related to the parallelism and identity of regression lines. Since these tests were not mutually independent (investigating the relation between 50 separate data sets) and the standard corrections of p values for multiple tests were not appropriate, and since the regression tests are rather sensitive, $p < 10^{-6}$ was considered significant in the regression comparisons.

To investigate which of the general regression models fitted the overall data best, the residua of the individual regressions were compared between models using the non-parametric paired Wilcoxon test. Precise p values were provided for these comparisons. For each subject, the regression model from A to F was identified that fitted the QT/RR data best—that is, that led to the lowest averaged residuum.

The subject specific parameters α and β and the residua of individual regression models A to F were compared between women and men using non-parametric Mann-Whitney tests and their relation to age was investigated using Spearman rank correlation coefficients.

Heart rate correction

The formulas of the regression models were converted to generic heart rate correction formulas:

- (A) Linear model:
  $QTc = QT + \alpha \times (1 - RR)$
- (B) Hyperbolic model:
  $QTc = QT + \alpha \times (1 / RR - 1)$
- (C) Parabolic model:
  $QTc = QT/RR^{\alpha}$
- (D) Logarithmic model:
  $QTc = QT - \alpha \times \ln(RR)$
- (E) Shifted logarithmic model:
  $QTc = \ln(e^{QT} + \alpha \times (1 - RR))$
- (F) Exponential model:
  $QTc = QT + \alpha \times (e^{-RR} - 1/e)$

The goal of each heart rate correction formula is to provide QTc interval values that are independent of the corresponding RR interval values. Such independence may, for instance, be tested by computing correlation coefficients. For an "ideal" heart rate correction formula, the correlation between QTc and RR is zero.

Each correction formula from A to F was applied to the QT/RR data of each subject, varying the value of parameter α from 0 to 1 in steps of 0.001. For each correction formula, each value of parameter α, and each subject, the correlation coefficient between the QTc and RR intervals was computed (that is, for instance with the parabolic model C, a correlation coefficient was computed between RR intervals and QT/RR^{α} values). For each subject and for each heart rate correction formula, the value of α was identified by golden section interpolation for which the correlation coefficient between QTc and RR was zero.

Unless specified otherwise, data are presented as mean (SD). Apart from comparisons of parallelism and overlap of QT/RR regression curves, $p < 0.05$ was considered significant.

RESULTS

On average, 671 (58) ECGs were measurable in separate subjects (range 431–741). The difference between the fastest and slowest heart rate recorded during the nominal 24 hours in individual subjects was 65 (6) beats/min.

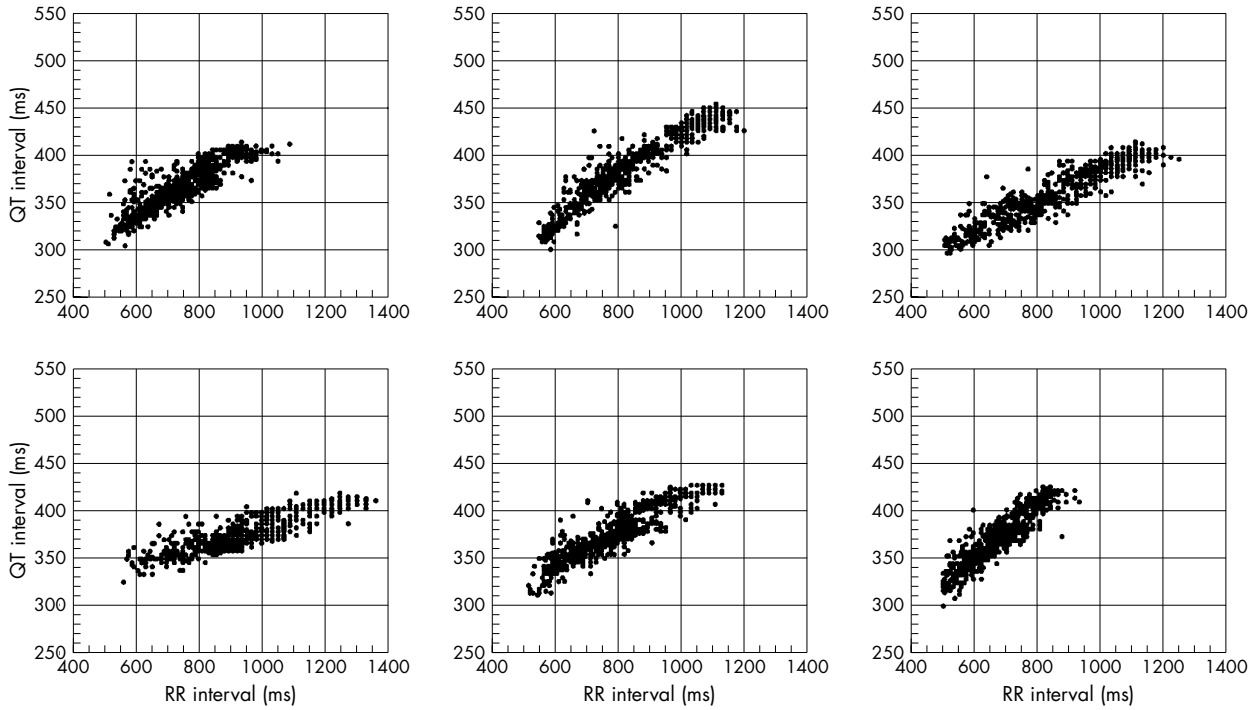

Figure 1 Examples of the QT/RR relation in six subjects in the study. Note the individual differences.

QT/RR relation

Figure 1 illustrates typical patterns of the QT/RR scatter diagrams obtained for separate subjects. Visually, it is obvious that adaptation of the QT interval to the changes in heart rate differed among the study participants. Figure 2 shows scatter diagrams of parameters α and β obtained for the individual regression lines of regression models A to F. The spread of individual regression parameters is obvious.

Figure 3 summarises the results of the statistical comparisons of the slopes (parameter α) of the individual regression models (fig 3A) and of the overlap (parameters α and β together) of the regression lines (fig 3B). For each subject, several other subjects are shown in whom either the slope of the model or the model itself differed significantly. For instance, it can be seen in the panel of linear model A that each subject of the study differed in the slope of the linear

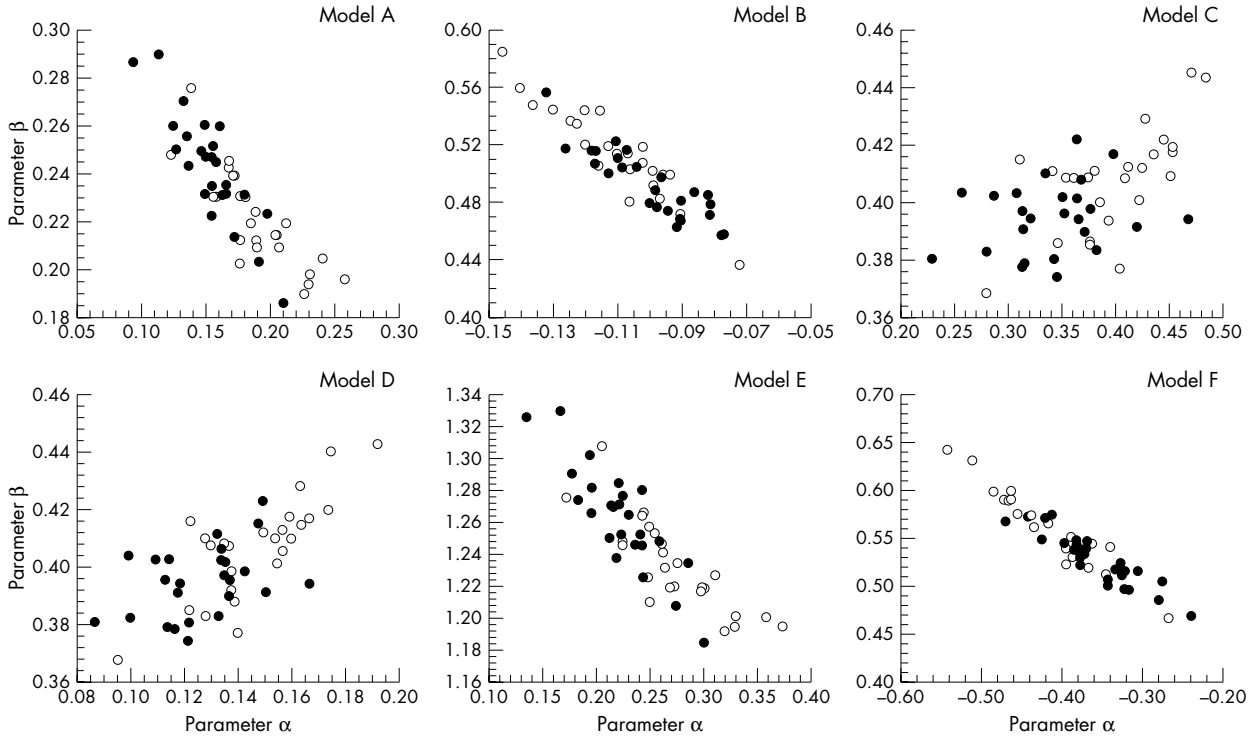

Figure 2 Scatter diagrams of coefficients α and β of the various QT/RR regression models applied to individual participants of the study. Open circles represent women and closed circles represent men.

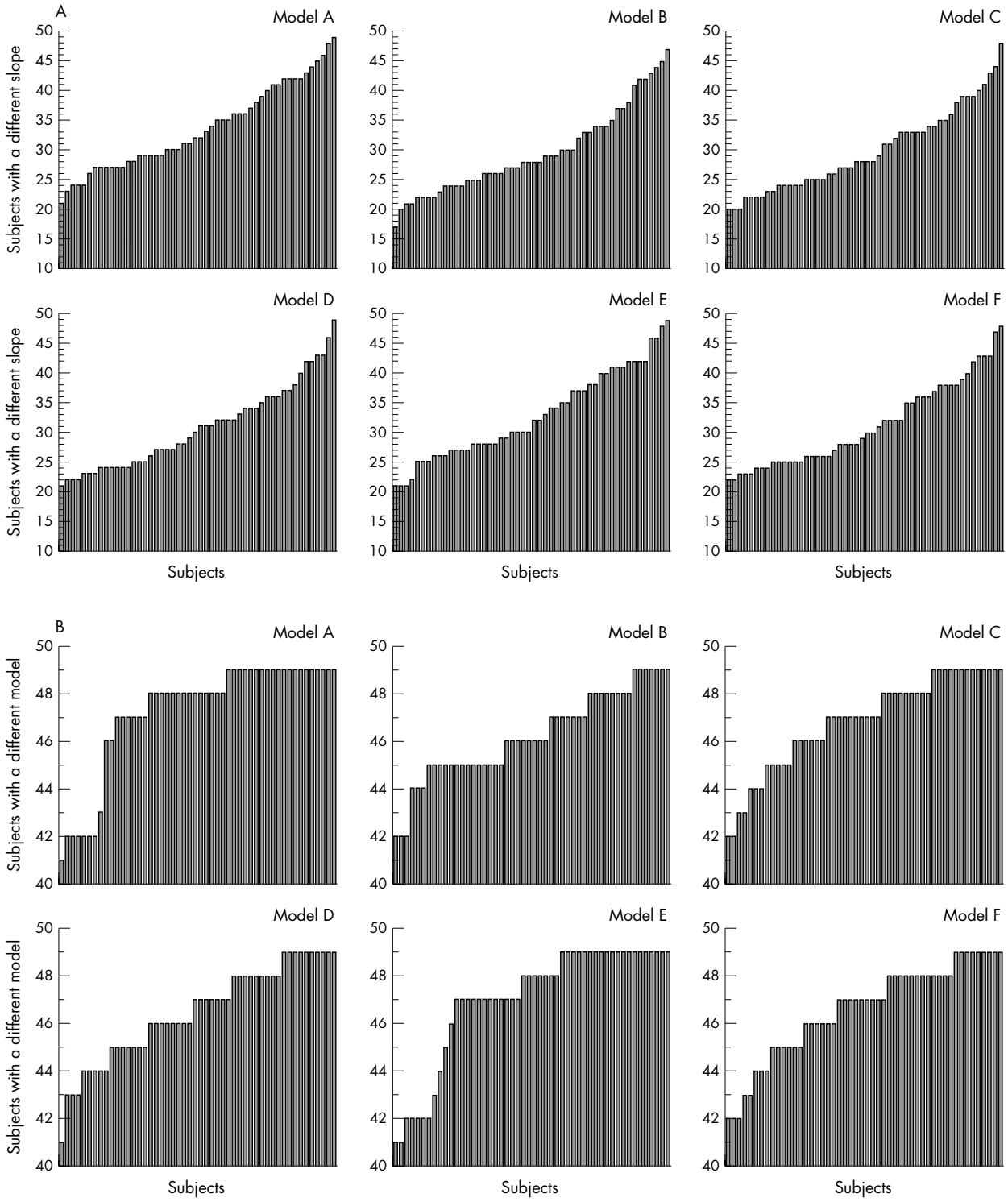

Figure 3 Statistical comparisons of the individual regression models. (A) For each QT/RR regression model and for each subject, the graphs show the number of other subjects for whom the regression parameter α (slope of the regression) was significantly different (with $p < 0.000001$). In each panel, the subjects are sorted according to the results for the given model (that is, the order of subject is not necessarily the same in different panels). (B) The same comparison for the identity of the regression models (parameters α and β tested together).

QT/RR regression model from at least 21 other subjects of the study (the median number of differences was 32), and there was one subject in the whole population whose slope of the linear QT/RR regression differed significantly from the slopes of all other subjects. Figure 3B shows that the lines of the regression models of different subjects fit only very infrequently. For instance, the linear QT/RR regression (model A) of each subject differed significantly from linear models of no fewer than 41 other subjects. Of the 50 subjects in the study, 20 had a unique linear QT/RR regression that was significantly different from the linear regressions of every other subject and the linear regression of 14 other subjects differed significantly from all other subjects but one.

Table 1 compares the QT/RR regression parameters between women and men. Significant differences were noted for both parameters of all regression models. On average, women had

Table 1 Comparison of parameters α and β between women and men (Mann-Whitney test) for each of the QT/RR regression models

	Parameter α			Parameter β		
Regression model	Women	Men	p Value	Women	Men	p Value
(A) Linear	0.19 (0.032)	0.15 (0.026)	4.582×10^{-5}	0.22 (0.02)	0.24 (0.024)	0.00043
(B) Hyperbolic	–0.11 (0.017)	–0.1 (0.016)	0.05	0.51 (0.033)	0.49 (0.024)	0.018
(C) Parabolic	0.4 (0.051)	0.34 (0.051)	0.00022	0.41 (0.018)	0.39 (0.012)	0.0040
(D) Logarithmic	0.15 (0.021)	0.13 (0.018)	0.00043	0.41 (0.018)	0.39 (0.012)	0.0045
(E) Shifted logarithmic	0.27 (0.047)	0.22 (0.037)	3.482×10^{-5}	1.23 (0.028)	1.26 (0.033)	0.00055
(F) Exponential	–0.42 (0.06)	–0.36 (0.052)	0.00040	0.56 (0.038)	0.53 (0.027)	0.00033

steeper and more curved QT/RR regressions than men. However, note in table 1 and fig 2 that the differences between men and women constituted only a minor part of the intersubject differences. The regression parameters were not related to age.

Table 2 shows the averaged residua of the generic models as well as the results of their statistical comparison. Of the six models, linear model A, parabolic model C, and shifted logarithmic model E performed best in leading to the lowest averaged residua. Hyperbolic model B (the linear relation between QT interval and heart rate) was the worst model, fitting the individual QT/RR data least well. On average, shifted logarithmic model E fitted the individual data marginally better than linear model A and parabolic model C. The distribution of the types of optimum models differed between women and men ($p = 0.0088$, χ^2 test).

The regression residua did not differ between men and women but, as shown in table 3, they decreased significantly with increasing age. This relation was due mainly to the observation in men. In women, the decrease of residua with increasing age was much weaker and did not reach significance.

Heart rate correction

Figure 4 compares subject specific heart rate corrections of the individual regression models. Very substantial differences in the individually optimum heart rate corrections are seen. Table 4 compares the optimum settings of the individual formulas in separate subjects. For instance, when the parabolic heart rate correction $QTc = QT/RR^{\alpha}$ was individually optimised, the individual values of parameter α ranged from 0.233 to 0.485 (average 0.371 (0.058)). When the heart rate correction $QTc = QT/RR^{0.371}$, corresponding to the averaged value of individually optimised parameters α, was used, the individual correlation coefficients between the QTc and RR intervals ranged from –0.712 to 0.578 (that is, the formula based on the population mean parameter α was substantially overcorrecting in some subjects while substantially undercorrecting in others).

Table 2 Residua and statistical comparison of the residua of regression models

Regression model	Regression residuum (ms)	Optimum cases (all/women/men)
(A) Linear	11.08 (1.98)	20 / 8 / 12
(B) Hyperbolic	11.96 (2.15)	0 / 0 / 0
(C) Parabolic	11.14 (1.99)	5 / 4 / 1
(D) Logarithmic	11.27 (2.01)	6 / 3 / 3
(E) Shifted logarithmic	11.07 (1.98)	12 / 5 / 7
(F) Exponential	11.18 (2.00)	7 / 5 / 2

Model	A	B	C	D	E
B	8.58×10^{-9}				
C	0.0848	1.48×10^{-9}			
D	0.000312	7.65×10^{-10}	1.82×10^{-7}		
E	0.382	5.11×10^{-9}	0.0104	3.12×10^{-5}	
F	0.0160	8.632×10^{-10}	0.000157	1.51×10^{-8}	0.00232

The top part of the table shows the mean regression residua obtained with the QT/RR regression models, each individually optimised for each subject. For each regression model, the top part also shows the number of subjects for whom the particular model was the optimum among all regression models considered (that is, leading the lowest residuum in the given subject). The bottom part of the table shows p values of the paired comparisons (Wilcoxon test) of the regression residua summarised in the top part of the table.

Table 3 Spearman rank correlation coefficients between age and the residua of individual QT/RR regressions for each of the QT/RR regression models

	All (n=50)		Men (n=25)		Women (n=25)	
Regression model	R	p Value	R	p Value	R	p Value
(A) Linear	–0.396	0.0044	–0.492	0.012	–0.248	0.23
(B) Hyperbolic	–0.342	0.015	–0.366	0.072	–0.273	0.18
(C) Parabolic	–0.404	0.0036	–0.515	0.0084	–0.267	0.19
(D) Logarithmic	–0.391	0.0049	–0.442	0.027	–0.293	0.15
(E) Shifted logarithmic	–0.403	0.0037	–0.499	0.011	–0.25	0.23
(F) Exponential	–0.399	0.0041	–0.485	0.014	–0.293	0.16

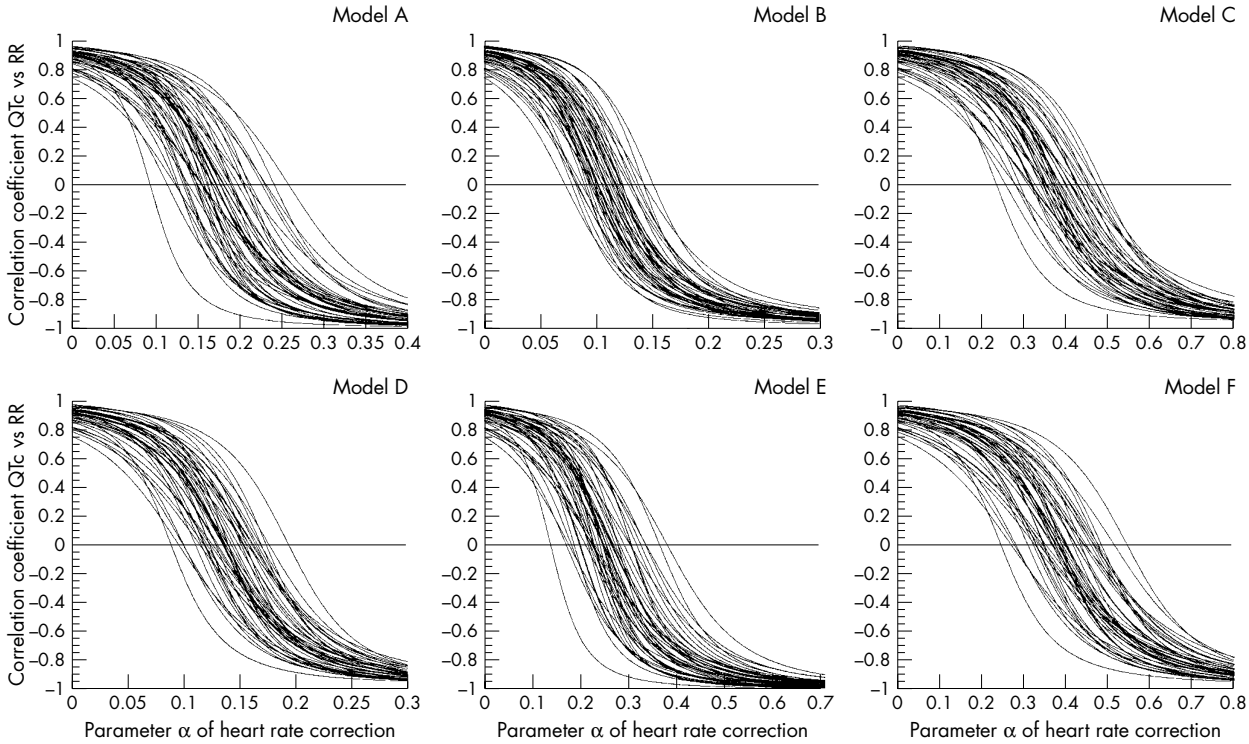

Figure 4 For each QT/RR regression model, the corresponding heart rate correction formula was tested for each subject. Parameter α of the correction formula was varied between 0 and 1 and for each setting of α the correlation coefficient between the QTc and RR intervals was calculated. The graphs show the dependencies of these correlation coefficients on α for individual subjects.

DISCUSSION

Because of the substantial intersubject variability of the QT/RR interval relation, no mathematical formula can be found to describe the QT/RR relation correctly in every person. A mathematical description of the QT/RR relation that is valid in one healthy subject is not necessarily valid in another. Consequently, a heart rate correction formula that performs well in one subject may substantially overcorrect or undercorrect the QT interval in another subject. Hence, there is no optimum heart rate correction formula that would permit accurate comparisons of QTc intervals. For instance, when correcting a QT interval of 360 ms recorded at 75 beats/min (RR interval of 800 ms), the range of exponent α of 0.233–0.485 noted in this study leads to a range in $QTc = QT/RR^{\alpha}$ of 379–401 ms. At 85 and 95 beats/min, this difference increases to 390–426 ms and 401–450 ms, respectively (fig 5).

In addition, our study suggests that even the shape of the QT/RR relation is different in different people. While the liner model was the optimum in 40% of subjects in this study (32% of women and 48% of men), the pattern of other subjects was non-linear (see table 1 and some of the images in fig 1). Surprisingly, in none of the subjects did we observe a linear relation between QT interval and heart rate, which has also been frequently proposed to model the QT/RR relation.

From a physiological point of view, it is not obvious why the QT/RR relation should exhibit this substantial degree of intersubject variability. Our study was not designed to characterise the electrophysiological details of repolarisation processes among the participants. We can therefore only speculate that the QT/RR adaptation is likely to be dependent on the complex interplay of the individual ionic channels that maintain the action potential of ventricular myocytes.[13–15] The subclinical

Table 4 Evaluation of individual heart rate correction formulas

	Optimum parameter α		Individual correlation coefficients QTc (correction with mean α) v RR						
				p Value (numbers of subjects)					
Model	Mean (SD)	Range	*Range*	10^{-2}–10^{-3}	10^{-3}–10^{-4}	10^{-4}–10^{-5}	10^{-5}–10^{-6}	10^{-6}–10^{-7}	< 10^{-7}
(A) Linear	0.1713 (0.1764)	0.0928 to 0.2577	–0.8469 to 0.6485	3	2	1	2	4	38
(B) Hyperbolic	0.1090 (0.1266)	0.0721 to 0.1507	–0.5216 to 0.6239	2	8	6	0	6	28
(C) Parabolic	0.3715 (0.3830)	0.2336 to 0.4856	–0.7130 to 0.5765	2	4	2	1	8	33
(D) Logarithmic	0.1378 (0.1663)	0.0884 to 0.1929	–0.6936 to 0.6518	6	2	0	3	3	36
(E) Shifted logarithmic	0.2485 (0.2623)	0.1356 to 0.3741	–0.8442 to 0.6755	3	1	1	3	4	38
(F) Exponential	0.3878 (0.4035)	0.2439 to 0.5427	–0.7157 to 0.6529	3	1	2	1	6	37

For each generic heart rate correction formula, the table summarises the values of correction parameters α optimised in individual subjects (that is, parameters that lead to the correlation between QTc and RR intervals being zero) as well as the performance of heart rate correction based on the mean value of parameter α among all subjects. For example, in the third line of the table, when a parabolic heart rate correction $QTc = QT/RR^{\alpha}$ was optimised for individual subjects, the individually optimum parameters α ranged from 0.2336 to 0.4856 and their mean was 0.3715. When the heart rate correction $QTc = QT/RR^{0.3715}$, corresponding to the mean optimum parameter α, was applied to individual subjects, the individual correlation coefficients between QTc and RR intervals ranged from –0.7130 to 0.5765. These correlation coefficients were different from 0 in two subjects with a p value between 10^{-2} and 10^{-3} and in four subjects with a p value between 10^{-3} and 10^{-4}, etc, and in 33 subjects with p value < 10^{-7}.

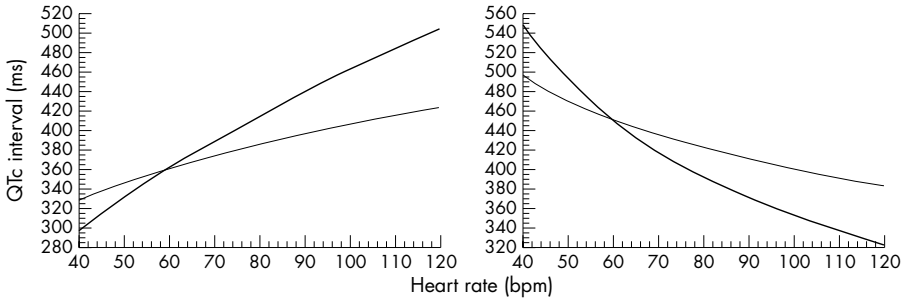

Figure 5 Illustration of the differences between individually optimised heart rate correction formulas found in the study: In the mathematical "family" of correction formulas QTc = QT/RR$^{\alpha}$, the study found the coefficient α ranging from 0.233–0.485. The figure shows the differences between the correction formulas QTc = QT/RR$^{0.233}$ (grey lines) and QTc = QT/RR$^{0.485}$ (black lines). For both formulas, the left panel shows the QTc values corresponding to a QT interval of 360 ms measured at different heart rates. The right panel shows "normality limits"—that is, QT interval durations that, when measured at different heart rates, correspond to QTc = 450 ms.

variability of the genes responsible for some of these channels has been described.[16 17] Thus, a similar variability may also exist for the other channels and all of these subtle subclinical variabilities are integrated in to the QT/RR relation. In this way, the ionic complexity of the repolarisation process may lead to substantial differences between otherwise healthy normal hearts.

Relation to previous studies: heart rate correction

In addition to reports already cited,[5–7] Molnar and colleagues[18] reported linear regressions between the QT and RR interval to be (visually) different in a group of 21 healthy subjects. Our observations are in good agreement with the known differences in QT interval behaviour among subjects. Our findings also agree with the discordant results reported by many previous studies investigating the general QT/RR relation and heart rate correction.

The optimisation of the formula QTc = QT/RR$^{\alpha}$ is a good example of discordant results. The original study by Bazett[1] involved ECGs of 12 normal children aged 1 day to 11 years, 50 ECGs of 37 normal boys to men aged 38 years, 32 ECGs of 20 normal women aged 20–53 years, and 16 ECGs in three normal men subjected to exercise. The suggestion that $\alpha = 0.5$ was based purely on observation and a more detailed analysis of the data[19] shows that $\alpha = 0.4$ was nearer to the optimum in the data of Bazett's original study. Fridericia's study[20] evaluated 50 ECGs of 28 men and boys and 22 women and girls and concluded that the optimum parameter $\alpha = 0.3558$ for this data set may be approximated by $\alpha = 1/3$. In a study of 200 "quite healthy" Japanese subjects (135 men) aged 18–64 years, Mayeda[21] found that $\alpha = 0.604$ and in 12 543 ECGs of Japanese children and adolescents, Yoshinaga and colleagues[22] found $\alpha = 0.31$ ranging from 0.305 in 6 year old girls to 0.319 in 12 year old boys. Simonson and associates[23] investigated ECGs of 649 men and 311 women and concluded that $\alpha = 0.32$ in addition to an age correction factor (increase of QT by about 3 ms every 10 years). In a study of nine healthy adult men involving heart rate changes by atrial pacing, atropine, isoproterenol, exercise, and recovery, Kawataki and colleagues[24] concluded that $\alpha = 0.25$. Boudolas and associates[25] found that $\alpha = 0.398$ in men and 0.384 in women. Hodges[26] reported that $\alpha = 0.38$.

Similar discrepancies exist with other types of heart rate correction. For the formula QTc = QT + α × (1 – RR), Schlamowitz[27] reported that $\alpha = 0.205$ (in 650 healthy soldiers aged 18–44 years), Simonson and colleagues[23] found $\alpha = 0.14$, and Larsen and Skulason[28] reported $\alpha = 0.125$. In cases of QT prolongation caused by hypocalcaemia, Ljung[29] found $\alpha = 0.2$, and in the data of the Framingham study (2239 men and 2779 women) Sagie and colleagues[30] found $\alpha = 0.154$ applicable to both sexes. Despite the size of the Framingham study population, the report by Sagie and colleagues was almost immediately criticised by Karjalainen and associates,[31] who proposed a nomogram based correction based on data from 324 young (18–28 years) and 396 middle aged (40–55 years) men.

Many other formulas for QTc computation have been proposed, for example, with a formula mathematically equivalent to our hyperbolic model, QTc = QT + α × (HR – 60), where HR is heart rate in beats/min and QTc is measured in milliseconds, values of parameter α ranging from 1.23 to 1.87 were reported.[32 33] Other suggestions have involved much more complicated mathematical forms[34–36] but none of the suggestions appears to have solved the problem of a universally applicable accurate QTc computation.

The intrasubject variability of the QT/RR relation that was observed in our investigation fully explains the discordant results of previous studies. QT/RR data collection taken from different subjects not only depends on the specific population but also fails to represent the individual QT/RR relation.

Relation to previous studies: sex differences

While the uncorrected QT intervals were reported to be rather similar in men and women,[37–39] female subjects of all ages have a slightly faster mean heart rate.[37–39] Hence, when the same heart rate correction formula is applied, a prolonged QTc interval is found in women.[37 38] Previous studies of 24 hour recordings suggested that the QTc interval tends to be more prolonged in women at slower heart rates.[40] This is in good agreement with our observation that women have a steeper QT/RR pattern. The QTc interval has also been observed to be more prolonged in women than in men in response to pharmacological provocation.[41]

Our observation of decreasing QT/RR residua with increasing age is probably partly related to the known age related decrease in short heart rate variability.[42] However, since we have observed this phenomenon to be expressed more in men, direct hormonal changes of cardiac repolarisation are also likely to be involved, as already documented in animal experiments.[43]

Limitations of the study

The design and execution of our study have several limitations. Most important, we used an automatic measurement of the QT interval and the precision of the measurement was checked in only a small subsample of all the ECGs. While the technical performance of the QT Guard system combined with taking the median measurement among measurable leads is certainly superior to the automatic readings of the QT interval reported by standard commercial electrocardiographs, there remains a small possibility of inaccuracies in our data. The QT Guard system also does not measure the averaged RR interval and our conversion of rounded heart rate values to the RR intervals resulted in a discrete scale of RR

interval values. While these technical limitations of the analysis have to be considered, the differences between the QT/RR relations of different subjects were so substantial that they could not have been caused by technical errors.

There are several possible "expressions" of the QT interval measured in all 12 leads of a standard ECG. Because of superior measurement stability, we used only the median duration of all measurable leads in this study and did not try to investigate other possibilities, such as the maximum duration, the so-called quasiorthogonal QT interval (measured from the earliest Q onset to the latest T offset in leads I, aVF, and V2), etc. However, experience shows that the difference between median and maximum QT interval (caused by projections of the T wave loop as well as measurement imprecision) is < 10 ms in most normal ECGs. The results were therefore hardly influenced by this choice of QT expression.

The circadian pattern of QTc intervals has only been reported using general heart rate correction formulas (mainly Bazett correction)[44] and observations of the circadian QTc pattern were probably related mostly to the known circadian changes in heart rate, which translate to circadian changes of QTc (Bazett) because of overcorrection or undercorrection. However, the possibility of a true circadian rhythm of the QT/RR relation cannot be excluded and the existence of such a pattern was not considered in our analysis. Thus, the individual QT/RR regression could be made up of a series of more precise patterns—for example, those of day and night. However, this detail could not have caused the substantial intersubject differences.

The QT/RR relation also exhibits substantial hysteresis. Previously, it was described that 90% of QT interval adaptation to an abrupt change in heart rate takes approximately two minutes.[45] Since our ECG data were restricted to 10 second serial recordings, we have not been able to account for such hysteresis and in some of the ECGs of this study, the measured QT and RR interval values may not represent the true QT/RR relation in the given subject.

Finally, we have investigated the QT/RR relation under general conditions of a "normal" day of the participants, rather than under tightly specified conditions or provocations leading to heart rate change. Since heart rate is not the only determinant of the QT interval, it is reasonable to expect that other conditions that achieve heart rate change by different autonomic mechanisms would have different, heart rate independent influences on QT interval duration. Thus, extrapolations of individual QT/RR relation should not go beyond the conditions under which the QT/RR pattern has been assessed.

Implications of the study

From a practical point of view, our observations mean that in clinical practice when assessing the QT interval of a particular patient, general heart rate correction formulas (for example, Fridericia's) can only be used for an approximate clinical assessment over a narrow band of resting heart rates (for example, between 50 and 70 beats/min). If the resting heart rate is outside these limits, application of a general correction formula may lead to potentially misleading results.

The use of any general heart rate correction formula for a detailed analysis of QTc interval, such as for multivariate risk prediction, assessment of drug induced QT interval changes, etc, is inappropriate and likely to lead to non-reproducible results. When a precise determination of QTc interval is needed, the heart rate correction should be optimised for the given person. Such an optimisation does not require as many data points as were used in this study. Several tens of ECGs over a range of heart rates seem to be sufficient.[46] In an independent set of data, we have recently observed that the QT/RR relation not only differs from person to person but also is stable within each person over time.[47] Thus, individually optimised heart rate correction should be more sensitive than any "universal" correction formula to detect minor changes in QTc interval, particularly if the QT/RR pattern has been assessed under conditions similar to those surrounding the analysed data (for instance, off and on drug ECG recordings should be recorded under fairly similar conditions to avoid bias caused by heart rate independent factors influencing myocardial repolarisation).

This need for individualised correction should always be considered when comparison of the QT interval at the same heart rate is not possible or is impractical to organise (for example, supine ECGs off and on treatment with a drug that changes heart rate).

Further studies aimed at finding the "correct" description of the normal QT/RR relation common to all healthy subjects and the "correct" heart rate correction formula are likely to be counterproductive. Substantial intrasubject variability precludes the success of the quest for a universal heart rate correction.

Finally, the correction parameter $\alpha = 0.5$ of Bazett formula is outside the extremes of the individual QT/RR patterns observed in this study. We can therefore confirm all the previous criticism of Bazett's formula. Although we have not directly disproved Bazett's correction applied strictly to basal resting conditions in a healthy population, the fact that the formula is outside the extremes found in this study as well as of similarly analysed independent populations[46] cannot be dismissed lightly. It therefore seems safe to deduce that blind application of Bazett's correction should be discouraged regardless of the circumstances.

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