ORIGINAL ARTICLES

Beat-to-Beat QT Dynamics in Healthy Subjects

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Background: Measures of QT dynamics express repolarization abnormalities that carry prognostic information, but the reproducibility of beat-to-beat QT dynamics has never been established. The QT interval is prolonged at night, but how the circadian rhythm and heart rate influence the dynamic QT measurements is still unsettled. The aims of the present study were: (1) to describe the reproducibility of beat-to-beat QT dynamics with respect to intrasubject, between-subject, and between-observer variability and (2) to describe the normal range, circadian variation, and heart rate dependence of QT dynamics.

Methods: Ambulatory Holter recordings were performed three times on 20 healthy volunteers and were analyzed by two experienced cardiologists. Slope and intercept of the QT/RR regression, the variability of QT and R-R intervals expressed as the standard deviation, and the relation between QT and RR variability expressed as a variability ratio were measured among other QT dynamics.

Results: The reproducibility of all QT dynamics was good. All QT dynamics showed circadian variation when calculated on an hourly basis. The day/night variation in slope could be explained by the differences in heart rate, whereas the day/night variation in intercept was heart rate independent.

Conclusion: The present study shows that reliable automatic QT measurements could be performed, encouraging further evaluation of the clinical value of QT dynamics in risk stratification of cardiac patients.

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reproducibility; circadian rhythm; QT dynamics; QT adaptation; healthy subjects; QT/RR slope

QT dynamics are used to measure repolarization abnormalities and have, in retrospective studies, been shown to correlate to outcome in cardiac patients.¹ Several reports now link QT dynamics to malignant ventricular arrhythmias and death^{1–5} indicating the importance of autonomic tone at the ventricular level, similar to the well-known predictive importance of the autonomic tone at the sinus node level.⁶ Before a scientific tool with potential prognostic value can be evaluated in clinical settings it is essential to establish the reproducibility and variation of the methods in a healthy popula-

tion. The variability of a single manual measure of the QT interval within the same subject is about 5%,⁷ but to our knowledge no previous study has investigated the reproducibility of Holter beat-to-beat QT dynamics.

The QT interval is a combination of depolarization and repolarization time. Since depolarization is fairly short and constant, the QT interval mainly reflects repolarization time. Measuring a single QT interval only gives a static picture of the repolarization, which involves a complex interplay between heart rate and the autonomic nervous system.

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Modern 24-hour ambulatory ECG equipment has made it possible to perform automatic measurements of the QT interval in a beat-to-beat fashion allowing estimation of beat-to-beat QT dynamics.⁸

The QT interval exhibits a circadian rhythm. The QT interval is prolonged at nighttime, mostly due to the lower heart rate. However, comparison of QT intervals at identical R-R intervals at day and night has revealed a heart rate independent diurnal variation contributing to the circadian rhythm of QT.^{9,10} The balance in the influence between heart rate dependent and independent factors on the circadian rhythm of QT dynamics has not been investigated.

The aims of the present study were: (1) to describe the reproducibility of beat-to-beat QT dynamics with respect to intrasubject, between-subject, and between-observer variability and (2) to describe the normal range, circadian variation, and heart rate dependence of QT dynamics.

METHODS

Population

Twenty healthy volunteers (11 women and 9 men) aged from 19 to 38 years were examined. The subjects gave informed consent and the local ethical review board approved the study.

Twenty-Four-Hour Holter ECG Recordings

All subjects had three 24-hour Holter recordings made with at least 2 days between the recordings. The recordings were performed using a three-channel digital recorder (Del Mar 483 Digicorder, Delmar Avionics) that recorded the modified chest leads V₂, V₃, and V₅ with a sampling rate of 256 Hz. QT analysis was done on a Model 563 StrataScan (Holter Analysis System, Delmar Avionics) in the lead with the best-defined T wave. The identification of the end of the T wave was done using a modified Laguna's algorithm.¹¹ The QT measurements were performed under continuous visual control with the possibility of manual editing. Editing was done in the beginning of the tape to ensure that the cursor measuring the end of the QT interval was placed correctly in the opinion of the observer; if for some reason the cursor floated, it was readjusted, if this was not successful then the beat was deleted. Each recording was analyzed by two cardiologists blinded to each other's results.

The beat annotation files were moved to a personal computer and ventricular ectopies and artifacts were removed. Supraventricular beats were removed using a modified version of the Ho-Golberger algorithm.¹⁰ Each beat was compared with the local average of the two previous beats and the two subsequent beats. If the beat varied more than 25% from the local average it was excluded. Afterward, to avoid noisy QT intervals, the QT intervals were evaluated the same way, and QT intervals varying more than 25% from the local average were excluded.

For each valid beat the QT interval and the R-R interval were available and the corrected QT interval was calculated using Bazett's formula: $QT_c = \frac{QT}{\sqrt{RR}}$.

QT, QTc, and RR

QT, QTc, and RR were defined as the average of all valid QT intervals, QTc intervals, and R-R intervals in the 24-hour recording, respectively.

SDNN

Variability in the R-R interval was expressed as the standard deviation of all normal-to-normal R-R intervals.

SDQT and SDQTc

Variability in the QT interval was expressed as the standard deviation of all QT intervals (SDQT) and of all corrected QT intervals (SDQTc), respectively.

Variability Ratio (VR)

A new measure of QT dynamics indexing QT variability to heart rate variability called variability ratio (VR) is introduced. In healthy subjects, variations in the QT interval follow variations in the R-R interval, although the magnitude of the variations is smaller in the QT interval than in the R-R intervals. Changes in the VR indicate a disturbed regulation of the repolarization: $VR = SDQT/SDNN$.

Slope and Intercept

The relation between ventricular repolarization and heart rate was expressed as the slope and intercept of the linear regression line when the QT interval of each beat was plotted against the

corresponding R-R interval. Since diurnal variation is reported^{9,10,13} three time periods were examined: from 9 AM–12 AM (Slope_{day}, Intercept_{day}), 6 PM–9 PM (Slope_{evening}, Intercept_{evening}), and 2 AM–5 AM (Slope_{night}, Intercept_{night}) as well as the whole 24-hour time period (Slope_{24hour}, Intercept_{24hour}).

To describe the circadian rhythm, all parameters defined above were calculated on an hourly basis through the entire 24-hour period.

Heart Rate Dependence

To avoid the influence of heart rate on day/night variations in the QT interval, the data were further examined for R-R intervals between 700 and 1000 ms only. This insures that the regression line was calculated on a similar distribution of R-R intervals both at day and at night.

Statistical Analysis

Results are given as mean $\pm$ SE unless otherwise stated. Statistical calculation was done using Statistica® (Statsoft, Tulsa, OK). A two-way analysis of variance (ANOVA) with repeated measurements was used to calculate interobserver standard deviation (SD_{bo}), within-subject standard deviation (SD_{ws}), and between-subject standard deviations (SD_{bs}). Reproducibility was furthermore expressed as the coefficient of variance (CV) defined as standard deviation divided by the mean. Student's *t*-test and Wilcoxon matched-pairs test were used for comparison when appropriate. Correlations were expressed as Pearson's correlation coefficient. A *P* value lower than 0.05 was considered significant.

RESULTS

Figure 1 shows an example of the relationship between QT intervals and R-R intervals for 24 hours and at day and night, respectively. As shown in this example, the QT/RR relation has a curvilinear appearance; therefore, a logarithmic, a square root, and a reciprocal fit were performed and compared to the linear fit for all subjects. The linear fit performed better than the nonlinear fits when the entire 24-hour period was examined, whereas the logarithmic and square root functions were slightly better than the linear fit for day and night periods. The modest improvement in fit (0.5–1.1%) at day and night did not justify the use of nonlinear fits to describe the general QT/RR relation.

Table 1 shows the reproducibility and average of the investigated parameters. The reproducibility was calculated using ANOVA and expressed as the standard deviation between observer, SD_{bo}; the standard deviation within subjects, SD_{ws}; and the standard deviation between subjects SD_{bs}. The averages of all 120 measurements for each of the examined parameters are shown too. The coefficient of variance for between-observer and within-subject was for all parameters except slope, SDQT, and SDQTc below 10, whereas slope calculated on 3-hour periods had the highest values, around 25. ANOVA provided a test for whether the mean values between observers, the mean value between days, and the mean values between subjects were significantly different as shown.

There was an observer bias in determining the end of the T wave (12 ms for both QT and QTc). This bias was seen in the intercepts of the linear regressions for the different time periods too (bias from 9 to 15 ms). There was no bias in detecting the variability of the QT interval or the length of the R-R interval as seen in Table 1.

Linear regression lines were similar during day and evening, whereas night regression lines had reduced slope and increased intercept compared to day. The slope of the regression line for the entire 24-hour period was larger than any of the investigated 3-hour period slope and the 24-hour intercept was significantly smaller (see Table 1). The correlation coefficients for the linear regression of QT versus RR were similar for day, evening, and night, 0.61 ± 0.04 , 0.61 ± 0.04 , and 0.65 ± 0.01 , respectively (*P* = 0.22), whereas it was significantly better for the whole 24-hour period (0.84 ± 0.02) (*P* < 10^{-8}).

Table 2 shows a comparison of measurements in women and men. R-R and QTc intervals were similar at day and evening, but during night women had shorter R-R and longer QTc intervals. No gender difference was found in either slope or intercept, although there was a trend for a higher slope among women at night. In the 24-hour period, SDNN was lower among women whereas VR was lower among men.

The correlations between the QT dynamics, RR, and SDNN are summarized in Table 3. For simplicity, only slope and intercept at night and 24 hours are shown. It must be noted though that slope and intercept were highly correlated within the same time period, but the correlation between the three time periods was weak.

Figure 1. QT/RR relation: An example of the QT/RR relation for the 24-hour period. The dark gray and light gray area represents RR QT pairs during the awake period, and the medium gray and light gray RR QT pairs during sleep. The light gray area represents RR QT pairs in the overlap between the awake and sleep period (upper panel). The QT/RR relation for the defined day-period from 9 AM to noon in the same subject (lower left panel). The QT/RR relation for the defined night-period from 2 AM to 5 AM in the same subject (lower right panel).

Circadian Rhythm and Heart Rate Dependence

Figure 2 shows the circadian distribution of QT, QTc, SDQT, RR, SDNN, slope, intercept, and

VR. VR showed stable higher values during daytime than in nighttime. SDQT and slope showed the same trend but a more pronounced peak in the awakening hour. SDNN showed a pronounced peak in the awakening hour too, but all other hourly

Table 1. Reproducibility Expressed as the Standard Deviation Between Observer, Within Subjects, and Between Subjects, the Average and the Significance of the Variation Between Observer, Within Subjects, and Between Subjects, Respectively

Parameters	SD _{bo}	SD _{ws}	SD _{bs}	Mean
RR (ms)	34	35 ^d	80 ^e	847
QT (ms)	13 ^c	11	18 ^e	375
QTc (ms)	12 ^c	10	14 ^e	412
SDNN (ms)	15	16 ^d	37 ^e	176
SDQT (ms)	3	3	5 ^e	27.6
SDQTc (ms)	3	3	4 ^e	24.4
VR	0.012	0.012 ^d	0.026 ^e	0.160
Slope _{day}	0.02	0.02	0.03 ^e	0.079
Slope _{evening}	0.02	0.02	0.03 ^e	0.083
Slope _{night}	0.017	0.018	0.020 ^e	0.059 ^a
Slope _{24hour}	0.018	0.019	0.026 ^e	0.134 ^b
Intercept _{day} (ms)	23 ^c	22	29 ^e	299
Intercept _{evening} (ms)	23 ^c	22	26 ^e	299
Intercept _{night} (ms)	21 ^c	21	31 ^e	345 ^a
Intercept _{24hour} (ms)	21 ^c	20	24 ^e	263 ^b

SD_{bo} = SD between observer; SD_{ws} = SD within subjects; SD_{bs} = SD between subjects. P < 0.05. Mean = the average of all 120 measures of each parameters; RR = mean R-R interval; QT = mean QT interval; QTc = mean corrected QT interval by Bazett; SDNN = standard variation of all R-R intervals; SDQT and SDQTc = standard deviation of all QT and QTc intervals, respectively; VR = variability ratio.

^aNight values significant different from day and evening values (P < 0.0001).

^bTwenty-four-hour values significantly different from all 3-hour periods (P < 0.0001).

^cSignificantly different mean values between observer (P < 0.05).

^dSignificantly different mean between days (P < 0.05).

^eSignificantly different mean values between subjects (P < 0.05).

SDNN values were similar. Intercept reflected an inverse image of slope with higher values during night and a significant dip in the awakening hour.

Table 4 shows the slope and intercept for R-R intervals between 700 and 1000 ms only. Figure 3 shows an example of a linear regression for

beats between 700 and 1000 ms for day and night, respectively.

DISCUSSION

The present study is the first to show that modern Holter technology allows QT dynamics parameters

Table 2. Gender Differences

	Women	Men	P Value
RR _{night} (ms)	999 ± 33	1120 ± 32	<0.001
QTc _{night} (ms)	405 ± 3	392 ± 4	<0.001
SDNN (ms)	160 ± 8	199 ± 11	<0.001
VR	0.170 ± 0.008	0.147 ± 0.004	<0.05
Slope _{day}	0.084 ± 0.010	0.080 ± 0.008	NS
Slope _{evening}	0.084 ± 0.008	0.082 ± 0.005	NS
Slope _{night}	0.063 ± 0.004	0.054 ± 0.003	0.08
Slope _{24hour}	0.139 ± 0.011	0.128 ± 0.005	NS
Intercept _{day} (ms)	291 ± 10	292 ± 6	NS
Intercept _{evening} (ms)	257 ± 9	260 ± 4	NS
Intercept _{night} (ms)	340 ± 7	352 ± 7	NS
Intercept _{24hour} (ms)	257 ± 9	260 ± 4	NS

RR_{night} = mean R-R interval at night; QTc_{night} = mean corrected QT interval by Bazett at night; SDNN = standard variation of all R-R intervals; VR = variability ratio.

Table 3. Correlation Coefficients (r)

	SDNN	VR	RR	QTc	Slope _{night}	Intercept _{night}	Slope _{24hour}	Intercept _{24hour}
SDQT	0.69*	0.30*	0.16	0.28*	−0.01	0.44*	0.41*	−0.43*
SDNN		−0.48*	0.65*	−0.14	−0.33*	0.59*	−0.24	0.26*
VR			−0.69*	0.52*	0.45*	−0.28*	0.90*	−0.76*
RR				−0.31*	−0.41*	0.58*	−0.57*	0.62*
QTc					0.25	0.20	0.45*	−0.090
Slope _{night}						−0.78*	0.41*	0.43*
Intercept _{night}							−0.16	0.38*
Slope _{24hour}								−0.89*

RR = mean R-R interval; QTc = mean corrected QT interval by Bazett; SDNN = standard deviation of all R-R intervals; SDQT = standard deviation of all QT intervals; VR = variability ratio.

*P < 0.05.

to be calculated automatically and reproducibly on a beat-to-beat basis. Good reproducibility encourages further evaluation of the potential value of 24-hour QT analysis in risk stratification in cardiac patients.

Reproducibility

The reproducibility of mean QT, mean QTc, mean RR, VR, intercept, and SDNN was excellent with a coefficient of variance of 10% or less both between observer and within subject. The reproducibility of SDQT, SDQTc and Slope_{24hour}, was acceptable with CV between 10% and 14%. All 3-hour-period slopes had only moderate, between-observer and within-subject, reproducibility.

Arildsen et al.¹⁴ have published the only other study regarding reproducibility of QT dynamics from Holter recordings. They found a reproducibility of slope that was comparable to the one in the present study. However, their study was performed on manually selected periods with stable heart rate and manually measured QT intervals, whereas the present study shows that the reproducibility is similar with automatic QT interval calculation.

Interobserver Reproducibility

This study is the first to show that interobserver reproducibility of the QT dynamics is good even though manually editing was allowed, but as expected the determination of the end of the T wave is subjective.

Slope and Intercept

The results of slope found in the present study are in accordance with previous reported results us-

ing all evaluable beats (beat-to-beat). Studies with beat selection, which only use QT interval in periods with stable R-R intervals to exclude influence from QT lag and hysteresis, report higher values, about 0.15 for Slope_{day},^{9,10,15} and about 0.15–0.21 for slope_{24hour}.^{16,17} The lower values for the slopes with beat-to-beat calculation are due to the lag in the QT interval with sudden changes in the R-R interval. Sudden tachycardia initially had long QT intervals and sudden bradycardia initially had short QT intervals, both of which tend to reduce slope compared with the beat selection method. Since the present study shows that the beat-to-beat method is reproducible, the lack of selection bias and the inclusion of all dynamic information make beat-to-beat evaluation preferable.

Several authors have reported larger values for slope in women compared to men,^{9,16} although Coumel was not able to reproduce this observation.¹³ In our study, the heart rate was similar for women and men at day, but slightly higher in women at night. It can be noted that the standard deviation of the slope estimates was higher in women compared to men. It could be explained by the fact that women had larger between-subject variation in heart rate, and it is known that slope correlates to heart rate.¹⁰

Some of the studies reporting gender differences in slope have also reported higher heart rates in women, and the nonsignificant trend in our study for a higher slope at night in women, could simply be explained by the higher heart rate.

It has been generally accepted that slope is lower at night than during daytime.^{9,10,13} The present study shows that when one compares QT/RR linear regressions for similar heart rates no differences in slope can be seen between day and night, but the

Figure 2. Circadian variation: The hourly mean and standard error of mean. RR, mean R-R interval; QT, mean QT interval; QT_c, mean corrected QT interval by Bazett; SDNN, standard deviation of all R-R intervals; SDQT and SDQT_c, standard deviation of all QT and QT_c intervals, respectively; VR, variability ratio.

Table 4. Comparison of Separate QT/RR Regression for R-R Intervals Overlap (700–1000 ms) at Day and Night

Parameters	Mean $\pm$ SD
Slope _{dayoverlap}	0.071 $\pm$ 0.022
Slope _{nightoverlap}	0.066 $\pm$ 0.019
Intercept _{dayoverlap}	300 $\pm$ 18*
Intercept _{nightoverlap}	338 $\pm$ 25*

*Day and night values being significantly different ($P < 0.0001$).

intercept is significantly higher at night compared to day. The earlier finding that slope is larger at day is explained by different RR distribution at day and night period.

Correlations

The well-known correlation between QTc and mean RR is found in our study too, showing that Bazett's correction of the QT interval is far from perfect. The negative correlation between intercept and slope has not been reported before but is not surprising. The QT/RR regression line passes through its point of gravity (mean QT, mean RR), therefore an increased slope will lead to a lower intercept. Since SDQT resembles the span of the QT intervals and SDNN resembles the span of the R-R intervals of the QT/RR regression plot, VR is correlated to slope and thereby intercept. The correlation between RR and SDNN, respectively, QT

Figure 3. Linear regression for the R-R interval overlap in the same subject. Linear regression performed on beats with R-R intervals from 700 to 1000 ms at nighttime (dashed line) and daytime (full line). The lines have similar slopes but higher intercept at night.

and SDQT explain the correlation between VR, RR, and QTc.

Circadian Variation

The circadian rhythm of RR, QT, QTc, and slope are practically identical to what have been shown by Yi et al.^{5,18} This study is the first to show the circadian rhythm of VR, SDQT, and intercept. All parameters show circadian variations. The circadian variation of SDQT and SDNN reveals that the variability of the QT interval is larger at daytime as compared to nighttime, whereas the variability of the R-R interval is similar at daytime and nighttime. These findings are reflected in VR. The pronounced peaks of SDQT, SDNN, slope and the dip in intercept in the awakening hour occur because the awakening hour consists of slow beats, while the subject is sleeping and fast beats when rising. The standard deviation of the QT and R-R intervals will then increase compared to an hour consisting of either slow or fast beats. Since the QT interval exhibits a heart rate independent prolongation during sleep,¹⁹ the long R-R intervals before awakening will have relatively long QT intervals giving rise to an increased slope and a decreased intercept.

Alternative Fits

We investigated the QT/RR relation further since the QT/RR relation has a curvilinear appearance. Nonlinear fits can describe the relation statistically significantly better, but the improvement in the quality of the fit was minimal, and the use of the generally accepted simple linear model is therefore justified.

Variability Ratio

VR is a method of quantifying the adaptation of the QT interval to changes in R-R intervals in a simple manner. We have found that VR is changed in nonsurviving myocardial patients, and VR seemed in that study a better risk marker than slope.²⁰ The reproducibility of VR was excellent in healthy subjects and a normal range of 0.16 [0.11–0.21] (mean [95% confidence interval]) was established.

Beat Selection

It is well known that when the R-R interval changes, the adaptation of the QT interval is delayed (QT lag).²¹ In addition, the adaptation is different whether the R-R interval is accelerated

or decelerated (QT hysteresis).^{22,23} It is uncertain whether all beat (beat-to-beat analysis) or selected beats only (beat-selection analysis) should be included in the QT/RR analysis.

The advantage of selecting QT intervals during stable heart rate only is a better linear QT/RR fit.¹⁰ However, this can lead to a selection bias where subjects with a more stable heart rate (decreased HRV) have more beats included in the analysis. The definition of a stable heart rate is not clear, and papers are using different selection methods leading to results that are difficult to compare.

The present study had chosen to use beat-to-beat analysis in the determination of the QT/RR relationship, which preserves all physiological information including QT lag and hysteresis. This had been shown to contain prognostic information in MI patients.^{24,25} Future studies have to show whether beat-to-beat analysis or beat-selection analysis are superior.

CONCLUSION

In conclusion, the present study shows that reliable automatic QT measurements could be performed, encouraging further evaluation of the clinical value in risk stratification. All parameters showed circadian variation. Intercept exhibits a nonheart-rate-dependent prolongation during night, whereas the day/night difference in slope (often referred to as different QT rate adaptation) can, in healthy subjects, be explained by the differences in heart rate.

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