

Circadian Modulation of QT Rate Dependence in Healthy Volunteers

Gender and Age Differences

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Abstract: QT rate dependence is known to be linked with both circadian variations of the autonomic tone and gender. However, age and heart rate variability (HRV) influences are not well established. The QT/RR relationship was evaluated, separately during the day and at night, on 24-hour electrocardiogram in 60 healthy subjects (30 men) divided into three homogeneous groups (group 1, 20–29; group 2 30–39; group 3, 40–50 years). QT rate dependence was larger during the day in both genders. Women showed stronger QT rate dependence (0.195 during the day vs 0.154 in men $P < .0001$). The circadian modulation decreased with increasing age (day/night slope differences: group 1, 0.038; group 2, 0.031; group 3, 0.001; analysis of variance $P < .05$). In addition, QT rate dependence increased as mean RR decreased ($r = -0.58, P < .0001$) and decreased as HRV parameters increased. Multiple influences on QT rate dependence can be found: not only circadian and gender modulation, but also age, heart rate, and HRV interventions. **Key words:** QT interval, rate dependence, age, autonomic nervous system.

On surface electrocardiogram (ECG), the QT interval is defined as the interval from QRS onset to T wave offset, and it corresponds to both ventricular depolarization and repolarization times. Heart rate (HR) is the main source of QT interval variation (1,2). Following an abrupt change in HR, the QT adaptation is achieved within a 2-minute time frame (1,3). Rate-correction formulae are proposed to allow interindividual comparisons at different

HRs (4–6). However, as they are based on comparison of different individuals with different HRs, these formulae are fundamentally static rather than dynamic. More critically, other physiological sources of ventricular repolarization variations are not considered. QT interval duration not only depends on HR, but is longer in women (6–8) which also have a stronger QT rate dependence (9–12); in addition, modulations by the autonomic nervous system (2,7,13–17) and by electrolyte concentration (18) have been reported. QT interval duration is larger at night than during the day, even when comparisons are made at identical HRs (17), and this phenomenon has been related to the circadian variations of sympathovagal balance (13,14),

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whereas the QT rate dependence is stronger in the awake state (9,10,19). Ventricular repolarization pattern is also dependent on the ventricular myocardium condition as it is prolonged after myocardial infarction and in both dilated and hypertrophic cardiomyopathies (20–22).

It is well established that abnormalities of ventricular repolarization are frequently involved in the genesis of severe ventricular arrhythmias. However, the significance of a prolongation of the HR-adjusted QT interval as a risk factor in postmyocardial infarction (20,22,23), as well as in congenital and acquired long QT syndrome, remains controversial (24). For this reason, alternative features of repolarization that could better identify patients at risk of life-threatening arrhythmias are considered (25–28). In addition to interlead dispersion of the QT interval (the so-called QT dispersion) and to beat-to-beat ECG amplitude oscillation (electrical T-wave alternans), the shortening of the QT interval with increasing HR also characterizes ventricular repolarization. QT rate dependence has been investigated for drug profile determination (29), in coronary artery disease patients (30), and in long QT syndrome (31,32). Although the circadian modulation of QT rate dependence is related to the autonomic nervous system, the relation between heart rate variability (HRV) and ventricular repolarization rate dependence are unknown. Moreover, age effects on QT rate dependence are not yet established.

The aims of this study were (1) to investigate, in healthy volunteers, the trends of the circadian patterns of QT rate dependence, defined as the slope of the regression analysis between QT intervals and corresponding RR intervals, in both genders and with increasing ages, and (2) to evaluate the correlation between the QT rate dependence and both the RR cycle length and the RR variability.

Methods

Population

Sixty healthy volunteers (30 women) aged from 20 to 50 years were recruited after written informed consent. The global population (mean age, 33.9 ± 9.2 years) was divided into three groups of 20 individuals (10 women each): group 1 from 20 to 29 years (mean age, 24.1 ± 2.9 years), group 2 from 30 to 39 years (34.1 ± 2.8 years), and group 3 from 40 to 50 years (44.7 ± 2.8 years). Criteria for enrollment in the study were normal physical examination, including blood pressure, normal resting 12-lead ECG, and normal

echocardiography. For subjects over 40 years, a negative stress test was required.

Resting 12-Lead ECG

All subjects underwent a 12-lead resting ECG immediately before the ambulatory ECG recording. QT and RR intervals were manually evaluated on printouts at a paper speed of 50 mm/sec on lead II. The QT interval was measured from the earliest onset of the QRS complex to the latest end of the T wave, defined as the return to baseline. Values obtained from three consecutive beats were averaged, and Bazett's formula was applied to calculate a corrected QT interval (QTc).

Twenty-Four-Hour ECG Recordings

All subjects underwent a 24-hour Holter ECG recording (Del Mar 459 recorder, Del Mar Avionics, Irvine, California) with an XYZ-lead configuration. Analog data were digitized and carefully edited with the Marquette Holter system (Marquette Electronics, Inc., Milwaukee, Wisconsin).

ECG data and beat annotations were subsequently transmitted to a personal computer where an analysis based on selective beat averaging was applied. The software for quantitative ECG analysis has been previously described (10,33,34). Briefly from 24-hour data, cardiac QRST complexes of sinus origin were selected according to the preceding HR environment; specifically, only beats preceded by a period of 1-minute HR stability (at 50/min, 60/min, 70/min, and so on) were extracted. To match stability criteria, the RR preceding the target complex and the mean RR interval calculated over the preceding minute had to be identical (± 15 ms). Selected complexes were subsequently averaged. Only templates including at least 50 individual beats were used for quantitative ventricular repolarization analysis.

In order to avoid errors related to different T-wave morphology, only X-lead data were consistently used for each subject, as this lead provided higher signal-to-noise ratios. Intervals between Q onset and T-wave apex (QTm) and between Q onset and T-wave end (QTo) were automatically measured by a dedicated algorithm (34). Briefly, ECG data from averaged templates were first filtered (fourth-order bidirectional Butterworth filter applied recursively), and first and second derivatives are calculated from the filtered data. T-wave apex is estimated by the apex of the interpolated parabola centered around a zero crossing of the first derivative. T-wave offset is subsequently

determined on the basis of first and second derivatives matching specific, amplitude-independent conditions (Fig. 1). Each template is finally edited on a beat-to-beat basis by two senior cardiologists, and, in case of aberrant positions of T-wave apex or T-wave end cursors, the template is manually rejected.

Two different periods of analysis were defined according to subject diaries and mean hourly HR obtained from the 24-hour frequency table: the first period consisted of the 8 consecutive daily hours with fastest HR (diurnal period), and the second of 5 consecutive sleeping hours with lowest HR (nocturnal period). QT dynamics and HRV were evaluated separately for the two periods. Time domain HRV parameters calculated (35) were the mean RR interval (RR), the standard deviation of all sinus RR intervals (SDRR), the proportion of interval differences of successive NN intervals greater than 50 ms (pNN50), and the square root of the mean squared differences of successive NN intervals (rMSSD).

Statistical Analysis

Results are given as mean \pm standard deviation. Numbers in brackets indicate lower and upper limits of the 95% confidence interval [95% CI].

For each individual, and for each circadian period, linear regression analysis between QT intervals obtained in stable HR conditions and corre-

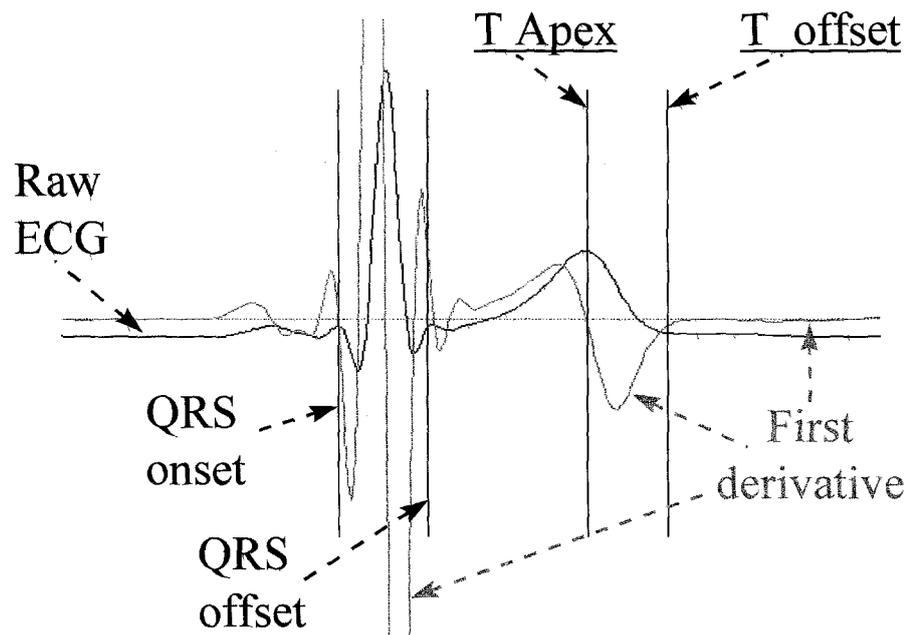
sponding RR intervals was performed (Fig. 2A). In this study, the slope of the regression line was used as an index of QT rate dependence (QT/RR). In addition, all data from each individual were pooled, and a global linear regression analysis was performed on the pooled data (Fig. 2B). Each independent regression analysis (whether on individual or pooled data) was performed by calculating the best linear fit together with the relative 95% CI.

As suggested by Altman and Gardner (36), comparison between regression lines (eg, day vs night, women vs men) was achieved by calculating the 95% CI of each specific slope difference. Statistical significance was considered when the 95% CI of the slope difference did not include the zero value.

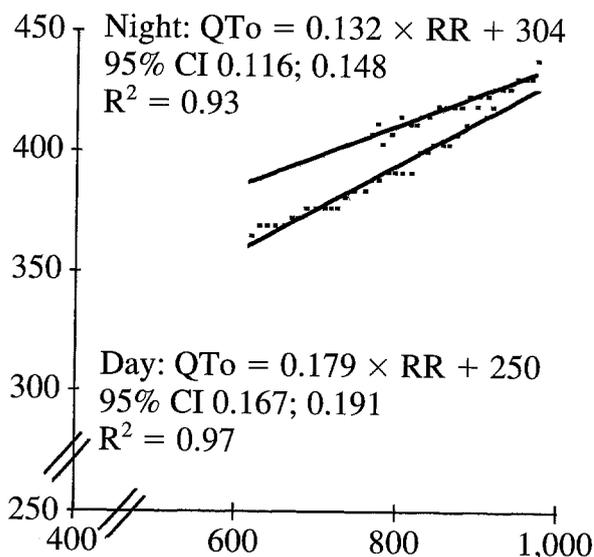
Respective gender and age influences on 12-lead resting ECG data (QTc intervals) were assessed by two-way analysis of variance (ANOVA). Age effect on QT rate dependence was assessed by one-way ANOVA. Single and multiple linear regression analyses were used to investigate relations between individual QT rate dependence and age, gender, mean RR intervals, and HRV parameters considered as independent variables.

Software for statistical analysis was BMDP (BMDP Statistical Software, Inc., Los Angeles, California), and the Altman and Gardner method for comparisons between regression lines was implemented in a personal computer. In all tests, a *P*

Fig. 1. Determination of QRS onset, QRS offset, T apex, and T offset. Representation of filtered and averaged QRST signal and its first derivative from an averaged template (X lead). Vertical bars represent the location of fiducial points. QRS onset is determined on the vector magnitude of the three XYZ recorded leads ($\sqrt{X^2 + Y^2 + Z^2}$). T-wave apex is the apex of the interpolated parabola centered around a zero crossing of the first derivative. T-wave offset is determined on the basis of first and second derivative matching specific amplitude independent conditions.



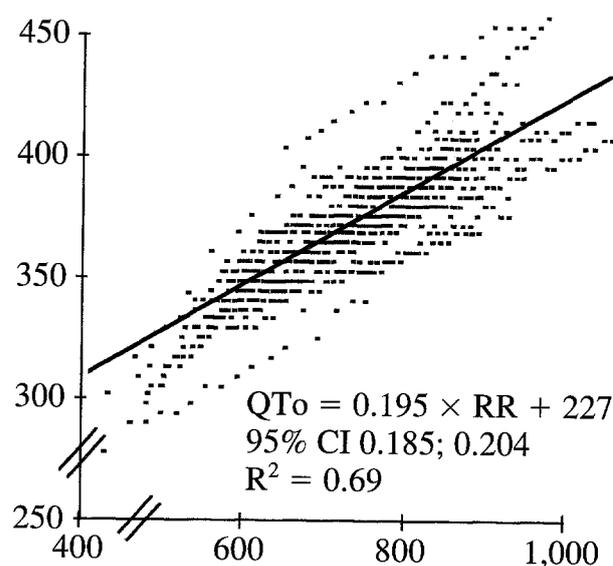
QTo (msec)



A

RR (msec)

QTo (msec)



B

RR (msec)

Fig. 2. Regression analysis between QTo intervals and RR intervals. In these figures, RR intervals are plotted on horizontal axis, and QTo intervals on vertical axis. (A) Example in one 24-year-old woman: Upper line is the linear regression line of QTo/RR at night, lower line is the linear regression line of QTo/RR during the day. Linear regression coefficients are very high. Slope difference is statistically significant (0.047 [0.026;0.067]). Overlapped RR intervals during both circadian periods show longer QT intervals at night than during the day at the same heart rate. (B) Example of the pooling of all QTo/RR pairs obtained in 60 subjects. Linear regression coefficient is still good with a tiny 95% confidence interval. (QTo, QTm: see text for definition.)

value less than .05 was considered statistically significant.

[405;411] ms in groups 1, 2, and 3, respectively (one-way ANOVA NS).

Results

Ventricular Repolarization Duration

Two-way ANOVA (gender, age) of 12-lead resting ECG data showed that the QTc interval was significantly longer in women than in men: 418 ± 18 ms in women versus 406 ± 24 ms in men, $P = .036$. No age effect was detectable: QTc interval duration was 411 ± 21 , 407 ± 21 , and 418 ± 24 ms in groups 1, 2, and 3, respectively, not significant (NS).

QTo/RR relation in steady-state HR conditions from 24-hour ECG data allows to calculate the QTo [95% CI] interval at 60 beats/min (RR = 1,000 msec): This calculated QTo interval was 422 [419; 425] ms in women, 397 [394;399] ms in men ($P < .0001$) and 412 [408;416], 403 [399;407], and 408

QT/RR Regression Lines

Within each subject, the mean number of QT/RR data was 23.5 ± 7 during the day and 17.4 ± 7 at night. Linear correlation coefficients obtained at stable HR were very high: 0.96 ± 0.03 for QTm/RR and 0.95 ± 0.07 for QTo/RR during the day and 0.89 ± 0.12 for QTm/RR and 0.89 ± 0.13 for QTo/RR at night.

Circadian Modulation of QT Rate Dependence

In both genders, regression lines between ventricular repolarization duration and RR intervals were higher during the day than at night for QTm and QTo intervals (Table 1A). For instance, in women, the QTo rate dependence was 0.195

Table 1. Circadian Modulation of QT Rate Dependence, RR Intervals, and HRV Parameters

	Day	Night	Δ Day/Night	[95% CI]
A: QT rate dependence				
QTo/RR men	0.154 [0.146;0.163]	0.133 [0.123;0.143]	0.021	[0.008;0.034]
QTm/RR men	0.142 [0.134;0.150]	0.120 [0.110;0.131]	0.022	[0.008;0.034]
QTo/RR women	0.195 [0.185;0.204]	0.170 [0.159;0.180]	0.025	[0.011;0.039]
QTm/RR women	0.180 [0.174;0.188]	0.125 [0.116;0.135]	0.055	[0.042;0.067]
B: Heart Rate and HRV				
RR (ms)	749 \pm 110	1,002 \pm 141		$P < 10^{-25}$
SDRR (ms)	113 \pm 33	114 \pm 35		NS
rMSSD (ms)	37 \pm 17	61 \pm 33		$P < 10^{-8}$
pNN50 (%)	11 \pm 10	28 \pm 19		$P < 10^{-11}$

Values in brackets are lower and upper limits of 95% confidence interval. Other values are expressed as mean \pm standard deviation. HRV, RR, SDRR, rMSSD, pNN50—see text for definitions. QTo, interval from QRS onset to T offset; QTm, interval from QRS onset to T apex.

[0.185;0.204] during the day and 0.170 [0.159; 0.180] at night. As shown in Table 1B, mean RR intervals and HRV parameters were different between the two circadian periods except for SDRR. Differences observed for pNN50 and rMSSD remained significant after RR interval adjustment.

Gender Differences

In females, with the exception of nocturnal QTm, ventricular repolarization rate dependence was greater in both circadian periods (Table 2A). For instance, the QTo/RR regression line in women during the day reached 0.195 [0.185;0.204], whereas the QTo rate dependence in men was 0.154 [0.146;0.163].

Nocturnal RR intervals were shorter in women (958 \pm 126 ms vs 1,046 \pm 143 ms in men, $P = .013$, Table 2B), but this difference did not reach statistical difference during the day (726 \pm 79 ms

vs 772 \pm 131 ms, respectively, for women and men, $P = .10$). Raw values of SDRR were also shorter in women, but this difference was no more observed during the day after adjustment on RR interval. Raw values of pNN50 and rMSSD were very close between genders (Table 2B).

Age Differences

A circadian modulation of QTm and QTo rate dependence was observed in groups 1 and 2, but it was no longer present in group 3 (Table 3A). During the day, the slopes of QTm and QTo/RR relations decreased with increasing age (ANOVA $P < 10^{-6}$ for QTm and QTo), with a major drop after 30 years. At night, a biphasic trend was apparent, with decreasing slopes between groups 1 and 2, but increasing slopes between groups 2 and

Table 2. QT Rate Dependence, RR Intervals, and HRV Parameters: Gender Differences

	Women (n = 30)	Men (n = 30)	Δ Gender	[95% CI]
A: QT rate dependence				
QTo/RR day	0.195 [0.185;0.204]	0.154 [0.146;0.163]	0.041	[0.028;0.053]
QTm/RR day	0.180 [0.174;0.188]	0.142 [0.134;0.150]	0.038	[0.025;0.049]
QTo/RR night	0.170 [0.159;0.180]	0.133 [0.123;0.143]	0.037	[0.022;0.051]
QTm/RR night	0.125 [0.116;0.135]	0.120 [0.110;0.131]	0.005	[-0.009;0.019]
B: Heart rate and HRV				
RR day (ms)	726 \pm 79	772 \pm 132		$P = .106$
RR night (ms)	958 \pm 127	1,047 \pm 143		$P = .013$
SDRR day (ms)	104 \pm 24	122 \pm 39		$P = .040$
SDRR night (ms)	101 \pm 30	126 \pm 37		$P = .008$
rMSSD day (ms)	36 \pm 15	38 \pm 19		NS
rMSSD night (ms)	61 \pm 35	62 \pm 30		NS
pNN50 day (%)	11 \pm 8	12 \pm 13		NS
pNN50 night (%)	28 \pm 22	28 \pm 17		NS

Values in brackets are lower and upper limits of 95% confidence interval [95% CI]. Other values are expressed as mean \pm standard deviation. HRV, RR, SDRR, rMSSD, pNN50—see text for definitions. QTo, interval from QRS onset to T offset; QTm, interval from QRS onset to T apex.

3 (ANOVA $P < .01$ for QTo/RR, NS for QTm/RR). The circadian modulation (day/night slope difference) decreased with increasing age for both QTm (ANOVA $P < .001$) and QTo (ANOVA $P < .05$).

A significant negative linear regression between age and mean RR intervals ($r = -0.31$, $P = .017$) was obtained at night but not during the day ($r = 0.03$, NS). Similarly, negative correlations between HRV parameters and age were found. For instance, rMSSD decreased at night when age increased ($r = -0.59$, $P = .0001$).

Heart Rate and Heart Rate Variability

Mean RR intervals of the corresponding circadian period were consistently correlated with QT rate dependence (for QTm/RR, QTo/RR in both circadian periods). For instance, diurnal QTo rate dependence decreased with increasing mean diurnal RR interval ($r = -0.58$, $R^2 = 0.34$, $P < .0001$, Fig. 3). Similarly, HRV parameters (SDRR, pNN50, rMSSD) showed a significant negative correlation with QT rate dependence. For instance, diurnal QTo rate dependence decreased when diurnal pNN50 increased ($r = -0.49$, $P < .0001$).

Using multiple linear regression analysis, mean RR of the period considered was the only factor significantly correlated with the diurnal QTo/RR and nocturnal QT/RR relations ($P < .0001$). However, the diurnal QTm/RR relation was significantly correlated with diurnal mean RR ($P = .0004$), diurnal SDRR ($P = .033$) and sex ($P = .04$).

Then, mean RR of the circadian period considered might explain (R^2) 32 to 43% of QT rate dependence.

Discussion

This study, based on a homogeneous healthy population, confirms that the ventricular repolarization is characterized by a circadian pattern with a greater daytime rate dependence. Although QT rate dependence is stronger in females both during the day and at night, the circadian modulation is present in both genders. Our study is the first to demonstrate that the relation between ventricular repolarization and HR changes with aging. This attenuation is more pronounced during the day, resulting in a parallel decrease of QT/RR circadian modulation. Using multiple linear regression analysis, mean RR interval of the circadian period considered is consistently correlated with the rate dependence of ventricular repolarization.

ECG Processing and Statistical Analysis

In this study, determination of RR interval and ventricular repolarization measurements were fully automatic. Aberrant values were deliberately rejected but not manually modified. Thus, results are not jeopardized by a poor reproducibility of the technique, which on the contrary approaches 100%. The beat averaging approach reported here selects cardiac complexes with a preceding RR interval varying by no more than a few milliseconds. Exclusion of sudden short-term changes in RR interval yields significantly different QT rate dependence (32,33). For instance, evaluation of the QT/RR regression on a beat-to-beat basis consistently provides a lesser magnitude of QT shortening when compared to selec-

Table 3. Circadian Modulation of QT Rate Dependence and Heart Rate: Age Differences

	Day	Night	Δ Day/Night	[95% CI]
A: QT Rate Dependence				
QTo/RR Gr 1 (n = 20)	0.195 [0.183;0.208]	0.157 [0.142;0.172]	0.038	[0.019;0.057]
QTo/RR Gr 2 (n = 20)	0.151 [0.142;0.160]	0.120 [0.109;0.132]	0.031	[0.016;0.045]
QTo/RR Gr 3 (n = 20)	0.145 [0.132;0.159]	0.144 [0.124;0.164]	0.001	[-0.021;0.024]
QTm/RR Gr 1 (n = 20)	0.182 [0.168;0.196]	0.122 [0.107;0.137]	0.060	[0.040;0.080]
QTm/RR Gr 2 (n = 20)	0.141 [0.132;0.150]	0.109 [0.098;0.121]	0.032	[0.017;0.046]
QTm/RR Gr 3 (n = 20)	0.116 [0.102;0.129]	0.114 [0.095;0.133]	0.002	[-0.020;0.024]
B: Heart Rate				
RR Group 1 (ms)	741 \pm 77	1,048 \pm 118		$P < 10^{-12}$
RR Group 2 (ms)	741 \pm 136	970 \pm 152		$P < 10^{-4}$
RR Group 3 (ms)	763 \pm 119	980 \pm 147		$P < 10^{-5}$

Values in brackets are lower and upper limits of 95% confidence interval [95% CI]. Other values are expressed as mean \pm standard deviation. Group 1: 20–29 years; group 2: 30–39 years; group 3: 40–50 years. QTo, interval from QRS onset to T offset; QTm, interval from QRS onset to T apex.

QTo/RR (Day)

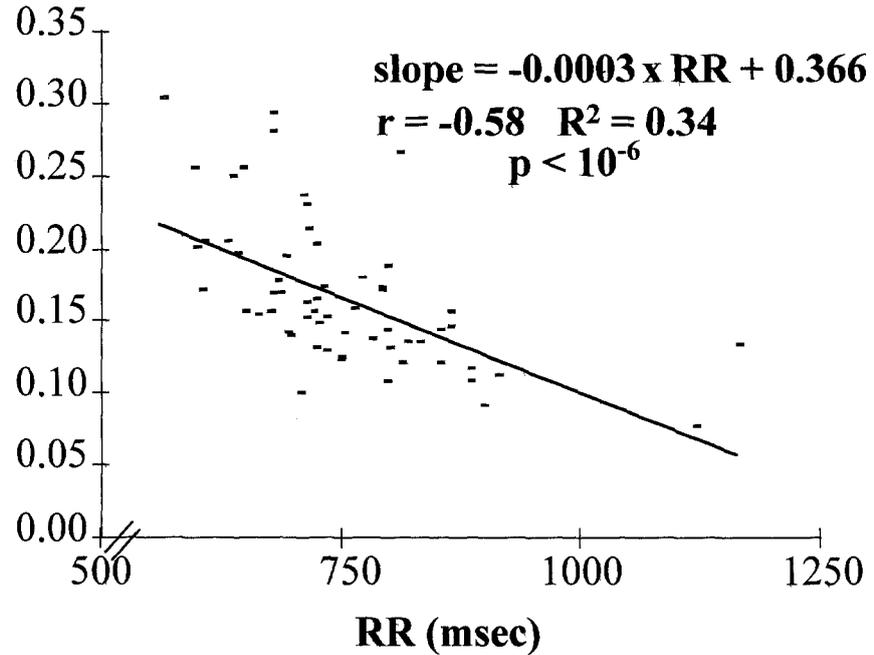


Fig. 3. Regression analysis between individual mean RR interval and individual slope of the QTo/RR relation. RR intervals are plotted on horizontal axis, and QTo/RR slopes on vertical axis. There is a good negative linear correlation with $P < .0001$. In this example, RR interval may explain about 34% (R^2) of the diurnal QTo/RR slope.

tion of stable HR segment (32). The relationship between QT and HR is often described as mono-exponential (29) in particular when the exercise test is used, even though, at steady state, a linear trend is definitely demonstrated (1). Kligfield et al. also explored the QT dynamicity pattern from treadmill exercise tests, but with a modified protocol providing stable HR segments at the end of each stage they found a linear QT/RR relation (11).

A second innovative feature of this study is that ventricular repolarization rate dependence is analyzed using a validated statistical approach (36).

Most published data are based on averaged regression lines, and the CI of the relationship between QT and HR is either ignored or not considered. Table 4 shows the respective values of QT rate dependence obtained by averaging individual slopes or by calculating a global linear regression from pooled individual data. Both methods provided relatively close results, but in 25% of cases, the mean of individual slopes fell outside the 95% CI of the global linear regression. Consequently, the statistical meaning of a crude averaging of individual regression lines is questionable.

Table 4. QT Rate Dependence: Global Regression Versus Averaging of Individual Slopes

	Pooling [95% CI]	Mean ± SD	Range 3-97%
Men			
QTo/RR day	0.154 [0.146;0.163]	0.152 ± 0.05	0.091-0.212
QTm/RR day	0.142 [0.134;0.150]	0.144 ± 0.03	0.095-0.222
QTo/RR night	0.133 [0.123;0.143]	0.124 ± 0.05	0.059-0.194
QTm/RR night	0.120 [0.110;0.131]	0.116 ± 0.05	0.057-0.182
Women			
QTo/RR day	0.195 [0.185;0.204]	0.181 ± 0.05*	0.111-0.264
QTm/RR day	0.180 [0.174;0.188]	0.178 ± 0.05	0.106-0.250
QTo/RR night	0.170 [0.159;0.180]	0.161 ± 0.05	0.098-0.251
QTm/RR night	0.125 [0.116;0.135]	0.147 ± 0.05*	0.089-0.254

QTo, interval from QRS onset to T offset; QTm, interval from QRS onset to T apex; SD, standard deviation.

* Indicates values not included in the 95% confidence interval [95% CI].

Circadian Modulation of QT Rate Dependence

It has been reported that sleep prolongs the QT interval with a magnitude of about 25 ms (2,13,14,17). The rate-corrected QT interval (Bazett) also exhibits a circadian pattern variation indicating that the ventricular repolarization duration is influenced by factors other than the cycle length, such as the autonomic nervous system (7).

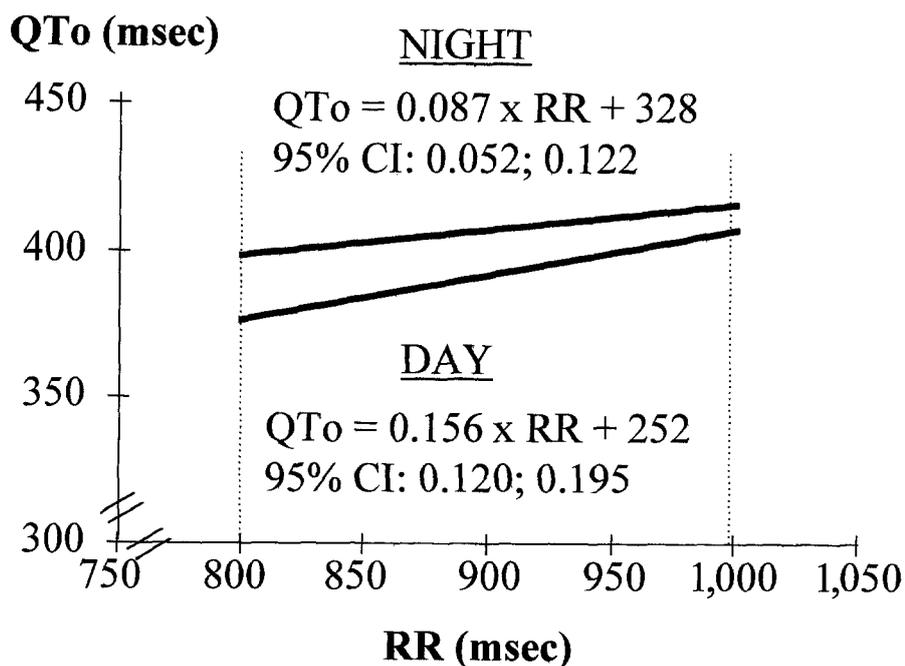
Since the original work of Browne, it is well established that the slope of the regression line between QT and RR intervals is steeper during the day than at night (17). Despite important differences in ECG processing, the values reported in this study are in accordance with our previously published data using a commercially available Holter system (9). Comparisons given in Table 1 are not obtained with a full overlap of the day and night RR interval values. To eliminate a possible confounding effect due to extreme (nonoverlapped) RR intervals, the QT/RR relation at common HR values (practically, between 800 and 1,000 ms RR intervals) was calculated. As shown in Figure 4, the diurnal slope value was still stronger during the day (0.156 vs 0.087 for day and night, respectively). Consequently, the day/night behavior reflects a double QT rate dependence and not two quasilinear portions of a single monoexponential relation.

Gender Influences

Although consistently reported (6,8,11,12,24,37), the magnitude of the QTc gender-related difference has been given different interpretations. Macfarlane found that a 10-ms difference is within the error measurement limits and considered it questionable (8). Due to the difference of HR also present in both genders, comparison of QT interval needs to be performed only after rate correction. However, the (mostly used) Bazett formula risks to introduce further biases, as it is well known to undercorrect at slow HR and overcorrect at fast HR (6,37).

These discrepancies suggest that it might be more appropriate to describe the repolarization behavior by the unadjusted QT HR relation. From the cohort of the Framingham study, Sagie provided a correction formula that applies to both men and women (6). However, the adequacy of using resting ECG from a large sample of subjects to evaluate dynamicity of the QT interval within a single subject is questionable. When evaluated from exercise test or ambulatory Holter data, a difference in QT rate dependence between males and females is observed (11,12). The slopes of QT dynamicity reported by Kligfield (11) were higher than those obtained in our study (for QT₀ interval: 0.237 ± 0.071 in men and 0.333 ± 0.127 in women), but the autonomic and neurohumoral responses between exercise test and ambulatory recording are not comparable. The slope values for QT₀ interval reported by Stramba-

Fig. 4. Day (lower line) and night (upper line) slopes of QT₀/RR fitted on pooled data (60 subjects) of overlapped RR intervals (800 to 1,000 ms). RR intervals are plotted on horizontal axis, and QT intervals on vertical axis. Slope difference equals 0.069 [0.017;0.121]. Despite the relationship between QT/RR slope and RR interval, the two circadian slopes are still different when the same heart rates are considered.



Badiale are close to those of this study (0.16 ± 0.04 in females and 0.13 ± 0.03 in males), but, strikingly, this investigator did not look at the circadian modulation of QT dynamicity and only calculated a global 24-hour QT/RR relation (12).

Studies in which the QT interval was measured at different ages, including newborns and children, demonstrated that the gender differences appear only after puberty and seem to disappear above 50 years (37,38). Recent findings of Drici (39) suggest that sex differences observed in QTc duration are related to sex hormones, which modulate potassium channel proteins. Since potassium channels are involved in the repolarization rate dependence, these effects could also explain the sex differences in QT rate dependence.

The higher risk for women to develop drug-induced Torsade de pointes (TdP) is well recognized (40–43). Heart rate slowing also enhances the risk of TdP. Our observation that the QT interval shows a greater rate dependence in women implies that the ventricular repolarization is further prolonged in women when the HR is low. Thus, the behavior of the QT rate dependence may provide complementary information to that of resting ECG. Thus, this method may help to identify patients prone to develop drug-induced Torsade de pointes.

Age Differences

Ventricular repolarization duration was similar between groups 1, 2, and 3. To the best of our knowledge, this study is the first to describe a decrease of the circadian modulation of QT rate-dependence with increasing age. This trend seems to derive from an attenuated diurnal QT/RR relation in group 3 (Table 3). In a population of normal subjects with a mean age of 48 ± 5 years (corresponding to our group 3), Tavernier et al. did not observe different slopes between the two circadian periods (44). Regarding aging, QT dynamicity also provides deeper physiological information than the conventional static approach. The mechanisms underlying the age-related differences in QT rate dependence are unknown. However, at the atrial level, the decrease of HRV with increasing age is well established (45). One can hypothesize that the decrease of the circadian modulation of QT rate dependence with aging reflects the diminution of autonomic nervous system influences on the ventricles.

Heart Rate Influences

Within a single subject, the mean HR of the circadian period is consistently correlated with the corresponding individual QT rate dependence. This phenomenon was first described by Karjalainen et al. from the resting ECG in a healthy young male population (46). These authors showed a stronger QT rate dependence in subjects with faster resting HR. However, Karjalainen also assessed the QT/RR relationship using a single QT/RR pair for each subject. This cannot be considered as an equivalent of the intrasubject evaluation of QT dynamicity obtained from 24-hour ECG recordings.

HR influences match well with both the circadian modulation and the gender differences of QT rate dependence. Indeed, the stronger adaptation found during the day and in women is associated with faster HR. The direct role of sex hormones on ventricular repolarization is now established even if other gender-related influences are not ruled out. The shorter RR interval in females appears to be associated with a gender difference in exercise capacity rather than gender-related differences in autonomic tone (47).

The respective behaviors of QT rate dependence and of HR with aging seem less concordant, and there are circadian-related differences. During the day, HR remains stable throughout groups 1 to 3, whereas QT rate dependence shows a clear decrease (Table 3). Conversely, at night, QT rate dependence remains relatively stable throughout groups 1 to 3, but RR interval decreases significantly. Because we found a significant negative correlation between the diurnal QTm rate dependence and SDRR after multiple linear analysis, we cannot exclude that the decrease of QT dynamicity from group 1 to group 3 should rather follow beat-to-beat cycle length variability than the values of mean HRs, at least during the day.

Study Limitations

The population enrolled is relatively small, and mean slopes must be taken cautiously. Moreover, groups of subjects at extreme ages (<20 and >50 years old) were not included. Resting ECG data have shown that these two populations have specific repolarization patterns, at least regarding gender influences, when compared to the population during reproductive years. In addition, physiological data from normal older subjects are crucial since it concerns the vast majority of patients with underlying heart disease.

Finally, this investigation was limited to a single aspect of QT dynamicity, that is, the global duration of the ventricular repolarization in stable HR environment.

Conclusion

Not only circadian period and gender, but also age, HR, and HRV must be considered for ventricular repolarization rate dependence evaluation. The correlation between QT rate dependence and HR should probably be interpreted as an effect of the autonomic nervous system on the ventricle and the sinus node, respectively. However, QT rate dependence provides additional information, which may improve the full understanding of ventricular repolarization behavior. Therefore, QT rate dependence evaluation may be clinically relevant for assessment of the risk of ventricular arrhythmia.

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