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Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings

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Aims There are gender-related differences in the QT interval measured from standard ECG tracings. However, these observations are based on a limited number of beats recorded in resting conditions. Computerized Holter techniques enable ventricular repolarization and its relationship with cardiac cycle length to be analysed long term. Previous studies used only the initial portion of the QT interval to the T wave apex (QTa) to measure ventricular repolarization; however, QTa may underestimate the total QT duration (QTe). The aims of this study were to verify whether QTa and QTe had similar rate-dependence in normal subjects and whether gender-related QTc differences observed in the resting ECG were also present in the long-term QT interval–cycle length relationship.

Methods and results Twenty-four hour Holter recordings were obtained in 40 healthy young subjects, 20 females and 20 males (mean age 28 ± 9 and 26 ± 5 years, respectively ns). Two-channel ECG digitized signals were processed using new automatic QT analysis software (Ela Medical), which converted the 24-h recordings into 2880 30-s templates. It also measured the QT apex (QTa) QT end (QTe) and the RR interval (ms) of each template, and computed the slopes of the linear regressions of QTe and QTa values plotted against the corresponding RR interval (QTe/RR and QTa/RR). Females had a shorter RR interval than males (803 ± 129 vs 877 ± 86 ms, $P=0.037$), with longer mean QTc (420 ± 17 vs 400 ± 200 ms, $P=0.0005$). In both genders, QTa/RR slopes were steeper than QTe/RR slopes ($P=0.0001$). Both QTa/RR and QTe/RR slopes were steeper in females than in males (QTa/RR 0·20 ± 0·04 vs 0·16 ± 0·03, $P=0.001$; QTe/RR 0·16 ± 0·04 vs 0·13 ± 0·03, $P=0.027$). Of note, QTa and QTe at fixed long cycle lengths (1000 ms) were longer in women than in men (QTa_{1000} 330 ± 20 vs 309 ± 18 ms; $P=0.002$; QTe_{1000} 410 ± 17 vs 389 ± 19 ms; $P=0.002$), while they did not differ at fixed short cycle lengths (600 ms).

Conclusions This study demonstrates that both the initial portion of the QT interval (QTa) and the entire QT interval (QTe) are useful since QTa is more prolonged than QTe at increasing cycle lengths, and thus includes most of the heart rate dependency of ventricular repolarization. In normal subjects, both the QTc and the long-term relationship between ventricular repolarization and heart rate are affected by gender. The differences in QTa and QTe duration between males and females are more marked at long cycle lengths and disappear at short cycle lengths. Finally, this study also proves the clinical feasibility of assessing the long-term relationship between ventricular repolarization and heart rate by utilizing the automatic measurement of the QT interval from 24-h Holter recordings.
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Key Words: Long term QT/RR relationship, 24-h Holter monitoring, gender-related differences in QT interval, Automatic QT interval measurement.

Introduction

Clinical and experimental studies demonstrated that prolongation of the QT interval on the baseline surface electrocardiogram (ECG) is associated with increased electrical instability and can favour the development of malignant ventricular arrhythmias[1–3]. A prolonged QT interval may be associated with increased risk for sudden death not only in congenital and acquired long Q-T syndromes[2–4], but also following a myocardial infarction[5,6], and even in healthy adult individuals[7] or during infancy[8].

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Previous studies have shown that there are gender-related differences in the duration of the QT interval measured from standard ECG tracings[9,10]. Women have a longer QTc than men and this difference might be related to different sex hormone levels since it is not present at birth[11] and appears only after puberty[12]. These observations are based on QT interval measurements made in a limited number of beats recorded by brief ECG tracings in resting conditions. However, the duration of the QT interval is modulated by multiple factors, such as heart rate level, circadian rhythm and autonomic nervous system activity[13,14]. Therefore, the QT interval measured on a brief ECG tracing may not reflect the real duration of ventricular repolarization and may underestimate abnormalities of the ventricular repolarization arising in conditions different from baseline.

Computerized analysis of 24-h Holter recordings can now provide long-term evaluation of the QT interval duration and of its relationship with heart rate. Previous studies measured ventricular repolarization using only the initial portion of the QT interval to the T wave apex (QTa)[15]. However, QTa may underestimate total QT duration (QTe). Therefore, we studied the relationship between heart rate and both the early portion of the QT interval (QTa) and the entire QT interval (QTe) using a new dedicated program. This measured QTe and QTa from robust QRST templates, and computed the slopes of the linear regressions of QTe and QTa values plotted against the corresponding RR interval (QTe/RR and QTa/RR) over the entire 24-h recording.

The aims of this study were two-fold. Firstly we evaluated whether QTa and QTe had a similar relationship with cycle length in normal subjects and if they provide different information on the rate-dependency of ventricular repolarization. Second, we assessed whether the gender-related differences in QT intervals observed in the resting ECG were also present in the long-term relationship between ventricular repolarization and heart rate. Preliminary data were recently reported[16].

Methods

Study population

Twenty-four hour Holter recordings were obtained in a group of 40 non-hospitalized healthy young subjects, 20 females and 20 males of similar age (mean age, respectively, 28 ± 9 and 26 ± 5 years, ns), free of any known cardiac or non-cardiac medical condition, and with a normal baseline 12-lead ECG.

Automatic analysis of Holter recordings

All recordings were obtained using portable battery-operated 2-channel Holter recorders (Ela Medical recorder model 2448 in 29 cases, and Marquette Electronics Inc, Milwaukee, WI, U.S.A., recorder model 8500 in 11 cases). All tapes were analysed by an automatic analysis system, performing a 200 Hertz A/D conversion with an 8 bit resolution. The digitized two-channel ECG signals were processed by ELATEC Holter analysis software (Ela Medical, Mountrouge, France), which classified all beats as sinusal, ventricular or artifacts, and allowed manual verification of the automatic classification by a trained operator (E.H.L., M.S.B. or A.M.). The verified digitized data were then processed using dedicated QT analysis software newly developed by Ela Medical, which converted the 24-h recording into 2880 templates obtained at 30 s intervals. To improve the signal-to-noise ratio, one median complex was computed every 6 s from the consecutive sinus beats, then the five median beats within each 30-s template were averaged in order to obtain a single representative PQRST complex for each of the 2880 templates. For each template, the algorithm automatically measured the mean and standard deviation of the QT apex (QTa), the QT end (QTe), and the RR interval (in ms). The T-wave apex was determined by fitting a parabola through the peak of the T wave as described by Merri *et al.*[15], whereas the T-wave end was determined by the intersection of the tangent to the downslope of the T wave with the isoelectric baseline. In each template, the QTa measurement was performed only if the amplitude of the T wave was greater than 0·15 mV. Samples of the automatic plots of the PQRST complex with QTe and QTa measurements are illustrated in Fig. 1. For each template, the mean QTe and QTa values were then plotted against the mean cycle length of the 30 s interval. The program automatically computed both linear regressions (QTe/RR and QTa/RR) for the entire 24 h and provided the slope, the intersect, and the correlation coefficient of the linear regressions automatically (Fig. 2). The program also provides the values of QTa and QTe at fixed cycle lengths (25 ms stepwise), and the 24-h mean and standard deviation of RR intervals and of QTe corrected for heart rate according to the Bazett's formula (QTc).

Statistical analysis

All data are expressed as mean ± standard deviation. Differences between QTa/RR and QTe/RR slopes were analysed by the Wilcoxon signed-rank test. Differences between males and females were analysed by the Mann–Whitney test. A P value lower than 0·05 was considered significant.

Results

All Holter recordings had a low level of artifacts, with an adequate number of QRST templates automatically computed by the algorithm. In all recordings, the incidence of supraventricular beats was less than 0·5% and the number of ventricular beats was less than 10 per

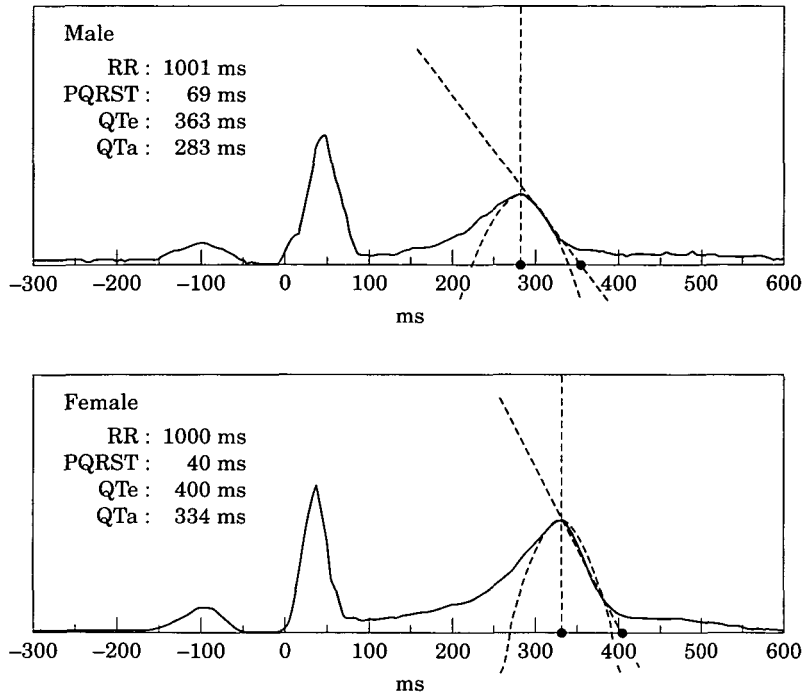

Figure 1 **Example of two templates obtained in two subjects. The T-wave apex was determined by fitting a parabola through the peak of the T wave, whereas the T-wave end was determined by the intersection of the tangent to the downslope of the T wave with the isoelectric baseline. In each template, the QTa measurement was performed only if the amplitude of the T wave was greater than 0·15 mV. Note that the female subject (bottom) shows longer QTa and QTe than the male subject (top) at the same RR interval (1000 ms).**

24 h. All 24 h linear regressions (both QTe/RR and QTa/RR) had a correlation coefficient greater than 0·70).

Gender effects

The mean 24 h RR interval was shorter in females than in males (803 ± 129 vs 877 ± 86 ms, $P=0·037$) while the mean 24 h QTc was longer (420 ± 17 vs 400 ± 20 ms; $P=0·0005$; Table 1). In both genders, QTa/RR slopes were steeper than QTe/RR slopes ($P=0·0001$), indicating that QTa is prolonged more than QTe when the cycle length increases. Both 24 h linear regression slopes were significantly steeper in females than in males (QTa/RR 0·20 ± 0·04 vs 0·16 ± 0·03; $P=0·001$; QTe/RR 0·16 ± 0·04 vs 0·13 ± 0·03, $P=0·027$; Table 1). This indicates that the gender differences in both QTa and QTe were more marked at long cycle lengths. Examples of QTa/RR and QTe/RR regression lines in males and females are illustrated in Fig. 2.

Table 1 ***Patient characteristics***

	RR interval	QTc	QTa/RR	QTe/RR
Males (n=20)	877 ± 86	400 ± 20	0·16 ± 0·03	0·13 ± 0·03
Females (n=20)	803 ± 129	420 ± 17	0·20 ± 0·04	0·16 ± 0·04
P	0·037	0·0001	0·001	0·027

When we analysed the absolute values of the QT interval at fixed cycle lengths, we found that the differences in both QTa and QTe between males and females were present at long but not at short cycle lengths. When the RR interval was 1000 ms, QTa was 330 ± 20 ms in females and 309 ± 18 ms in males ($P=0·002$) and QTe was 410 ± 17 ms in females and 389 ± 19 ms in males ($P=0·002$). When the RR interval was 600 ms, QTa was 253 ± 20 ms in females and 244 ± 23 ms in males (ns) and QTe was 343 ± 24 ms in females and 343 ± 23 ms in males (ns). Examples of templates at RR interval of 1000 ms in a male and in a female subject are illustrated in Fig. 1.

Discussion

This is the first study to compare the linear relationship of the RR interval with both the initial portion (QTa) and the entire QT interval (QTe). We have demonstrated that QTa and QTe are not redundant since QTa is more

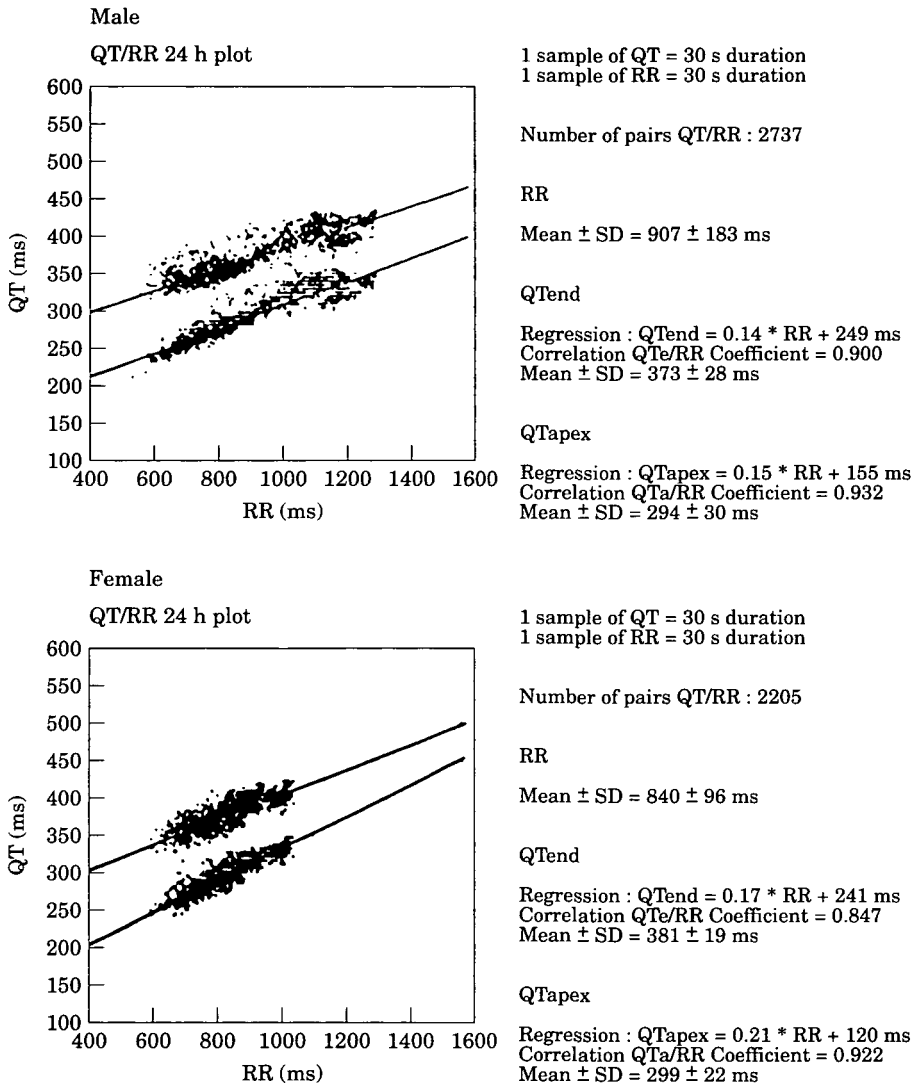

Figure 2 **Example of the 24 h relationship between QT and RR intervals in two subjects. Each dot represents the value of QTa or QTe measured for each template plotted against the corresponding RR interval. The program computed both linear regressions (QTe/RR and QTa/RR) for the entire 24 h automatically and provided their slope, intersect and correlation coefficient. Also, the mean values and the standard deviation of QTe, QTa and RR intervals of the entire 24 h are calculated. Note that the female subject (bottom) has steeper slopes than the male subject, indicating that it prolongs the QT interval further when the cycle length increases.**

prolonged than QTe at increasing cycle lengths, thus including most of the heart rate dependency of ventricular repolarization. Despite the limitation due to the small population size, the present study suggests that in normal subjects gender affects not only QTc measured from short ECG tracings, but also the long-term relationship between ventricular repolarization and 24 h heart rate. The differences in QTa and QTe duration between males and females are more marked at long cycle lengths and disappear at short cycle lengths. Finally, in a manner similar to that reported by Merri *et al.*[15], we have demonstrated the ability to assess the long-term relationship between ventricular repolarization and heart rate by utilizing the automatic measurement of the QT interval from 24-h Holter recordings.

Methodological considerations

The automatic measurement of the QT interval by Holter techniques may raise methodological concerns, due to the relatively low sampling rate, the shifting of the isoelectric baseline, and the known difficulties in

determining the end of the T wave. To overcome such difficulties, Merri *et al.* proposed measuring the initial portion of the QT interval, from Q wave onset to T wave apex (QTa) automatically[15]. Nonetheless, the QTa cannot be assumed to be equivalent to the entire QT interval (QTe), particularly in long QT syndromes, where the entire ventricular repolarization and, especially the latter portions of the T wave, may be variously altered, depending on the ionic mechanism underlying the QT interval prolongation. Indeed, the different genetic mutations that cause three forms of the long QT syndrome are associated with three different T wave morphologies on standard ECG[17] and produce different degrees of QT shortening when heart rate increases[18]. Specifically, the duration of the QT interval to the peak of the T wave (QTa) differs between patients with different genotypes, with a greater QTa/QTe ratio in LQT3 patients, those with a mutation involving SCN5A, the cardiac sodium channel[19]. The present study shows that even in individuals with a normal QT interval, QTa does not reflect the entire duration of ventricular repolarization. Thus, the possibility of measuring both QTa and QTe during the 24 h allows a better assessment of the behaviour of ventricular repolarization. As a consequence, caution should be used when data obtained from the measurement of the QTa are applied to the entire duration of the QT interval.

The algorithm utilized in the present study determined the end of the T wave by measuring the intersection of the tangent to the downslope of the T wave with the isoelectric baseline. This method, proposed by Browne *et al.*[20] has the limitation of underestimating the QT interval duration, by excluding the final portion of the T wave, particularly when there is a second component or a notch. On the other hand it has the advantage of a more accurate measurement of the QT interval at high heart rates, i.e. during exercise or in infants, where the following P wave may be superimposed on the last portion of the T wave.

The QT interval has been automatically measured from each of 2880 templates obtained by averaging sinus beats on a 30 s basis. This robust technique is less exposed to the limitations inherent in the measurement of several single QT intervals during the 24 h, but it does not allow a beat-to-beat analysis of the dynamic adaptation of the QT interval to changes in heart rate. Moreover, measuring the QT interval in segments of 30 s may be more appropriate for studying the long-term relationship between ventricular repolarization and cycle length since it partly overcomes the necessity of a stationary signal. However, the possibility of an incorrect automatic measurement of the QT interval has to be taken into account. The program allows the visualization of all templates and it is possible to eliminate those with an error in the measurement. In the majority of recordings, no template has been discarded, and in a few of them only two or three templates have been eliminated.

Relationship between QT interval and cycle length

The QT interval has been traditionally measured from short ECG tracings in the resting state. Although several formulae have been proposed for the correction of QT intervals for heart rate[21], the Bazett's formula still remains the most widely accepted. However, if this method represents a reasonable approximation in resting condition, its use during exercise or in the long-term analysis of ventricular repolarization has been questioned[22]. To overcome the limitations of Bazett's formula, particularly at the shorter and longer cycle lengths reached throughout the 24 h, different approaches have been proposed. One possibility is represented by expressing the relationship between a wide range of QT and RR intervals through a linear regression analysis. This approach has been criticized with the argument that the relationship between QT interval and cardiac cycle length is not linear, but exponential[23]. This is true when the short-term dynamic adaptation of ventricular repolarization duration to changes in heart rate is evaluated during exercise or cardiac pacing[23,24]. In the long-term, a polynomial equation is probably the one that better describes the relationship between QT and RR intervals. The observation in the present study that the correlation coefficients of the linear regression are, in most cases, above 0·90 and never below 0·70 suggests that this approximation may be considered acceptable for the study of the QT/RR relationship from Holter recordings.

Merri *et al.*[15] computed the linear relationship between the initial portion of the QT interval (QTa) and the cycle length in normal subjects. The rationale of the use of QTa was not only due to technical reasons, but it was based on previous studies suggesting that the rate-dependency of the QT interval is largely confined in the initial portion[9]. Since in the present study we were able to measure both the initial portion (QTa) and the entire QT interval (QTe), we compared for the first time the two linear relationships with the RR interval. The slope of the QTa/RR relationship was always steeper than that of the QTe/RR relation, indicating that QTa is more prolonged than QTe at increasing cycle lengths, including most of the heart rate dependency of ventricular repolarization.

Gender effects

Previous studies have shown that there are gender-related differences in QTc measured from short ECG tracings. In a large population of healthy individuals Merri *et al.*[9] showed that women have a longer QTc when compared to men and this finding was subsequently confirmed in an even larger population by the analysis of the data coming from the Framingham Heart Study[10]. These observations contributed to an update of the diagnostic criteria for the idiopathic long QT

syndrome[25]. Recently, we analysed 9734 electrocardiograms recorded in neonates and found that the gender-related differences in QTc observed in the adult population are not present at birth[11]. Studies in which the QT interval was measured in groups of children at different ages[12,26] have shown that the gender-related differences appear only after puberty. This suggests that sex steroid hormones may have differential influences on ventricular repolarization[27].

In the present study we have also shown that the mean QTc of the 24 h Holter recording is longer in females than in males. More importantly, the slopes of the linear relationship between absolute values of QT and RR intervals were steeper in women than in men. This was true for both QTa/RR and QTe/RR slopes, indicating that females prolong QT interval more than males when heart rate decreases. In the studies performed in the adult population, a longer QTc among women[9,10] is the result of a similar absolute value of the QT interval in the presence of a shorter cycle length. One can argue that the different QT/RR relationship between women and men might simply reflect the presence of a different range of RR intervals, since women showed higher heart rates throughout the 24-h. However, when we analysed the absolute values of the QT interval at fixed cycle lengths, we found results that parallel those obtained by analysing the QT/RR slopes. The difference in both QTa and QTe between males and females were more pronounced at long cycle lengths and disappeared at short cycle lengths.

Our observation that in normal subjects the gender-related differences in QT interval are accentuated when heart rate is low, may have implications for the understanding of the female prevalence among patients who develop torsade de pointes in association with drugs that prolong ventricular repolarization[28]. Experimental and clinical studies have suggested that the genesis of drug-induced torsade de pointes is favoured by long cycle lengths[29,30]. Also, an increased propensity of women to develop torsade de pointes has been recently reported during complete heart block[31].

The mechanisms underlying the gender-related differences in the relationship between ventricular repolarization and cardiac cycle length during the 24 h remains to be elucidated. It has to be noted that our findings have been obtained in a population of normal subjects and we cannot exclude that a different behaviour might be observed among patients with prolonged ventricular repolarization.

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