Am J Cardiovasc Dis 2023;13(6):363-371
www.AJCD.us /ISSN:2160-200X/AJCD0147212

Original Article

Differences in circadian variation in QT interval of the ECG in women compared to men

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Received October 24, 2022; Accepted November 13, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Background: Measurement of the QT interval in the ECG (QT interval) is important in evaluating risk for cardiac death and for assessing the impact of drugs on the heart. The objective of this study is to determine whether the time of day affects the QT interval, QT interval variability and whether these relationships are influenced by an individual's sex. Methods: Twenty-four hour ECGs were analyzed in detail on 50 individuals, 49 years of age, without evidence of coronary artery disease, structural heart disease, or significant arrhythmias. Four different QT-heart rate adjustment formulae were calculated and compared. Results: There were significant (P=0.0014) differences between the QT-heart rate relationship during three different time-periods (night 00:00 to 08:00 h, day 08:00 to 14:00 h and evening 14:00 to 24:00 h). Women, compared to men, had a steeper relation of QT to RR interval indicating that when heart rate slows at night, the QT interval is more prolonged which is consistent with a greater susceptibility to fatal arrhythmias. The variability of the QT interval (the SD) was significantly (P<0.01) greater in men than women at night and in the evening but not during the day. There were differences in the ability of different QT heart rate adjustment formulae to blunt the effect of heart rate changes on the QT interval during the day. Conclusion: The time of the day that the QT interval is assessed should be considered. The QT heart rate relationship is different in women than in men especially at night. QT interval variability is greater at night especially in men. There are differences in the ability of QT heart rate adjustment formulae to blunt the effect of heart rate on the QT interval. Differences in the QTc at night might be the basis for the higher prevalence of sudden death in women at night.

Keywords: QT interval in the ECG, day/night values QT variability, men, women, circadian rhythmicity

Introduction

Circadian clocks, endogenous oscillators that control 24-hour physiological processes are composed of transcription-translation-based auto-regulatory feedback loops [1]. The genomic targets of circadian clocks are linked to the regulation of a large number of cellular functions [1]. Normal circadian rhythms are important for health, and disturbances of circadian rhythm have been implicated in the manifestations of cardiovascular diseases [2-4]. One important aspect of cardiac physiology is cardiac electrical repolarization that is assessed by measurement of the QT interval in the ECG (QT interval). Cardiac repolarization is best estimated on the surface electrocardiogram by measuring the duration of the interval from the onset of the Q wave to the end of the T wave. A prolonged QT interval is utilized to diagnose a channelopathy, a defect in cardiac ion channels, or an adverse drug effect on the heart [5, 6]. A prolonged QT interval has considerable prognostic implications as it can identify individuals at risk for subsequent cardiac mortality and sudden cardiac death [5-8]. Whether the QT interval has a circadian rhythm has been subject of debate specifically whether there are any diurnal changes in QT interval after taking into consideration the heart rate changes that occur throughout the day. Some investigators concluded that there are no meaningful changes in QT interval during the day [9-14] while other investigators have concluded that the QT interval shows a definite circadian variation [15-17].

The effect of sex and/or sex hormones on circadian mechanisms have been recently investigated. Disruption of the circadian mechanism factor CLOCK in male mice ($Clock^{\Delta 19/\Delta 19}$) led to the development of an age-dependent cardio-

myopathy that was blunted in female mice especially when receiving ovarian hormones [3]. There is a relative paucity of data on whether there are differences in the circadian rhythmicity of QT interval during the day between men and women, although the absolute value of the QT interval is accepted to be longer in women than in men [5, 18]. Previous investigations of potential differences in QT interval between men and women have not been consistent [19, 20].

The objectives of this study were several folds. First, we sought to test the hypothesis that there are differences in QT interval and the variability of the QT interval throughout the 24-hour day when considering the night, evening and day (8-hour) periods. Second, we sought to examine whether an individual's sex influenced the QT interval and its variability. Third, we sought to determine the extent to which different correction formulae blunt the QTc during the 8-hour time periods of the day.

Methods

Patient selection

The study population consisted of a consecutive series of 50 patients, who were referred to a Cardiology clinic (at Vancouver Hospital during 2020) for palpitations and had no evidence of coronary artery disease or structural heart disease [17]. The data had been retrospectively and prospectively accumulated. It represented a consecutive series of individuals minimizing ascertainment bias. The study group consisted of 50 individuals with an age of 49.4±16.0 years. The sex of the individual was that listed by the individual on the registration to the Clinic. There were 26 women who were 49.6± 13.8 years and 24 men who were 50.3±18.0 years of age. Individuals were not on beta blockers, antihypertensive medications (ACE inhibitors, calcium channel blockers, diuretics, or antiarrhythmic agents). Individuals were excluded if they had, arrhythmias on 24 h ECG (except for ectopics at less than 10 per hour) or incomplete 24 h ECG data specifically missing results on all the ECG variables during at least 2 hours during the 24-h day. The study was approved by our Institution's Committee on Research.

ECG measurements

The 24-hour ECG data were collected and analyzed on a Mortara Hscribe 6 device (Welch Allyn, Inc., Skaneateles Falls, NY, USA). The accuracy of the analysis algorithm had been assessed in accordance with the EC38 and EC57 standards published by the American National Standards Institute and the Association for the Advancement of Medical Instrumentation, as well as the IEC 60601-2-47 [21]. Noise and artifacts had been removed or lessen by signal processing resulting in a reported '99.9% QRS detection accuracy' [21].

QT segment analysis was performed using an algorithm that determined the interval between the earliest ventricular depolarization activity and the end-of-T point on each single complex. The QT duration of normal QRS complexes was calculated from a series of 30-second windows. Heart rate was calculated for every beat based on the RR intervals in a series of 7.5-second windows in the defined profile period (one hour) to determine the mean heart rate [21]. The mean heart rate (RR) interval for each hour was used to correct the mean QT interval for each hour because the mean values cover the whole period for each hour. There was no correction for the effect of hysteresis as it was not possible to obtain the kind of data necessary to analyze this factor for every sampling time.

The heart rate dependency of the QT interval was adjusted using four different heart rate correction formulae (QTc). The QT intervals were corrected for heart rate with the Fridericia approach (QTcFRD) [$QT/RR^{1/3}$, where RR is the RR interval] [22], the Hodges formula (QTcHDG) [QT + 0.00175 (60/RR) - 60] [23], Framingham formula (QTcFRM) [QT + 0.154 * (1 - RR)] [24] and the Rabkin-spline formula (QTcRBK). The linear model of QTcRBK includes seven orthogonal b-spline basis functions, B1(x), ..., B7(x), taking heart rate (HR) as their argument and allowing for a non-linear regression relationship to be fit between HR and QT. QTc=533.52 - 77.57B1(HR) - 102.51B2(HR) - 131.96B3(HR) - 146.35B4(HR) - 197.89B5(HR) - 233.70B6(HR) - 247.20B7(HR) + 9.61 female (with a dummy variable (female) that was 1 if the subject was female and 0 if not) [18]. It was developed based on ECGs from part of the 13,600 indi-

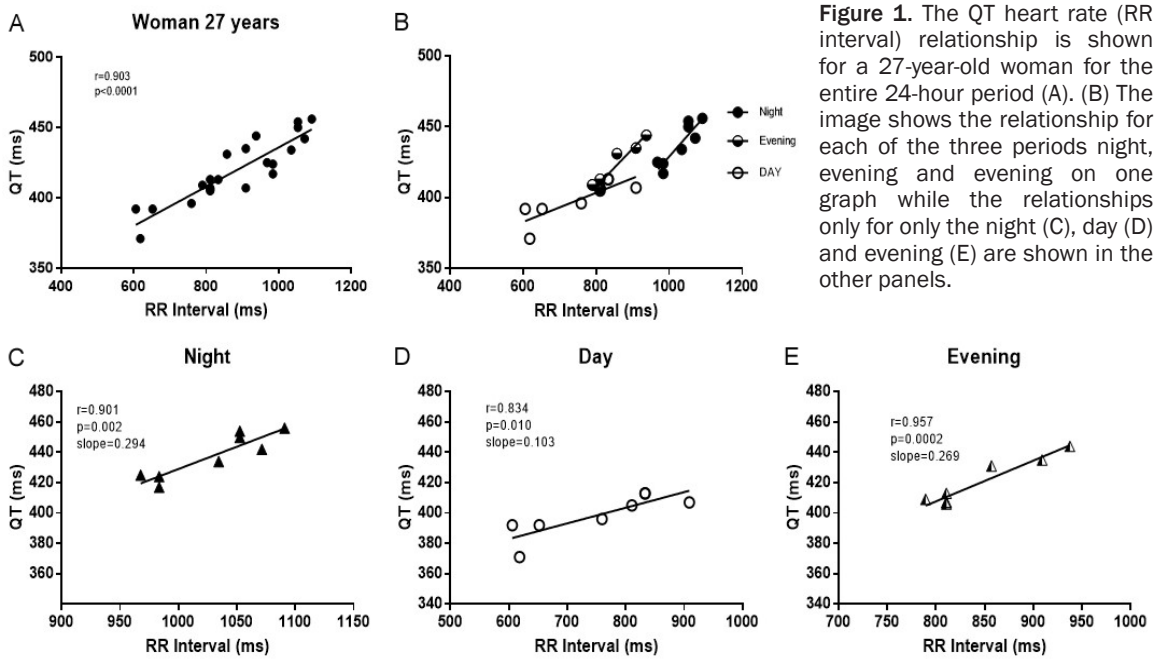

Figure 1. The QT heart rate (RR interval) relationship is shown for a 27-year-old woman for the entire 24-hour period (A). (B) The image shows the relationship for each of the three periods night, evening and evening on one graph while the relationships only for only the night (C), day (D) and evening (E) are shown in the other panels.

viduals in the NHANES US population study, tested in another portion of the NHANES data base, and was found not only to be relatively independent of heart rate but also superior to other QTc formulae in its ability to adjust for the impact of heart rate on the QT interval [18]. The Bazett formula was not used because it is the one which least adjusts for heart rate [18] and fails to reflect the circadian rhythm of QT interval, while other formulae are consistent with this pattern [17]. We used the nomenclature for QTc abbreviations which specified the first three consonants of the first authors' names with the exception of the Framingham formula [25].

Data analysis

The data were analyzed in three different time periods 00:00 to 08:00 h (referred to as night), 08:00 to 16:00 h (referred to as day) and 16:00 to 24:00 h (referred to as evening). The relationship between the QT interval and heart rate was examined by both a linear regression and non-linear [log (QT) linear (heart rate)] relationship. Comparison of the slopes of the QT-time of day relationships used T-test for two data sets or ANOVA for more than two data sets. Data analysis used GraphPad Prism Version 7.0 (San Diego, CA, USA).

Results

Example of obfuscation of different QTc intervals during a 24-hour period

The QT-heart rate relationship over a 24-hour time frame can mask diurnal variations. A case exemplifies this from an individual in whom there was a significant (r=0.903) linear relationship between QT and heart rate over the 24-hour period (**Figure 1A**). However, if one considered the time when each QT-heart rate was determined, there appeared to be three different relationships, with different intercepts and the slopes, that were not similar (F=8.37, P=0.003) (**Figure 1B**). Indeed, focusing on each of the three eight-hour time periods (**Figure 1C-E**) displayed three different relationships. The slope of the relationship was markedly different during the day compared to the evening or night. While the slope of the relationship was similar between the evening and the night, the intercepts were markedly different between the evening and night periods.

Relationship of QT interval to heart rate during three 8-hour time periods

Considering the entire group of 50 individuals, and each 8-hour time-period, the well-known relationship between the QT interval and RR

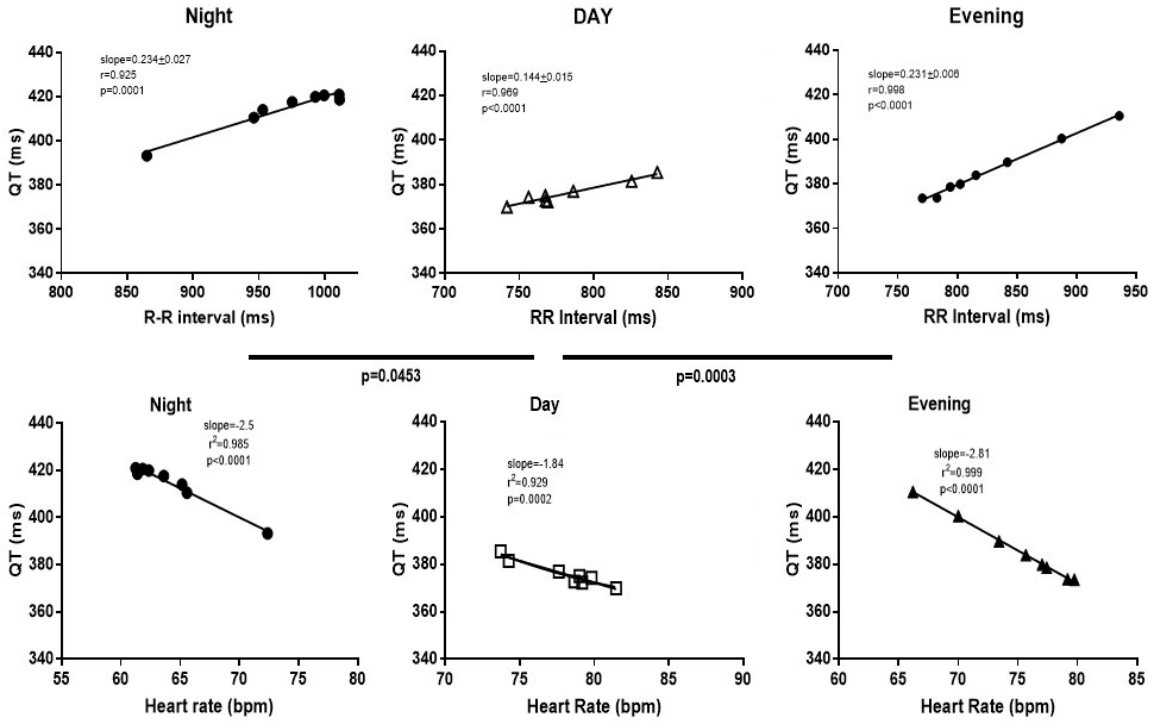

Figure 2. The image shows the QT/RR interval relationship for the entire group during the three 8-hour periods of the day specifically night, day and evening in the upper three panels and for the QT heart rate relationship for the three 8-hour periods in the bottom three panels.

interval (or heart rate) specifically shorter QT interval at shorter RR intervals (faster heart rates) compared to longer R-R intervals (slower heart rates) was evident in each of the three 8-hour time periods (**Figure 2**). The correlations were highly significant (P<0.01) in each time-period. Within each 8-hour period, there were no differences in the QT/RR relationship when a linear or log linear correlation was considered for night-time (r=0.925 vs r=0.984; linear vs log-linear), day-time (r=0.969 vs r=0.960; linear vs log-linear), or evening (r=0.998 vs r=0.999; linear vs log-linear). The slope of the QT-heart rate relationship was significantly larger at night compared to the day-time or evening compared to day-time. It was evident that the slopes of the relationship, were not equal (F=9.628, P=0.0014), and were steeper in the evening and night and less steep during the day.

Male - female differences in QT interval and its variability during three 8-hour time periods

To determine whether there were any differences between men and women in the 8-hour time periods, the QT interval-heart rate relationship was examined separately for men and women (**Figure 3**). The QT interval was greater for women compared to men at equivalent heart rates during each of the 8-hour time periods. Both men and women showed the same overall relationship with a smaller slope of the relationship during the day compared to the night or the evening. The slope of the QT interval-heart rate relationship was significantly different between men and women at night (P=0.009) and in the evening (P=0.03) but not during the day-time. The QT interval was consistently longer at equivalent heart rates for women compared to men during the night, day, or evening time periods.

The standard deviation around the estimate of the QT interval was significantly (P<0.01) greater in men than in women at night and in the evening but not during the day (**Figure 4**). During the day, there was no significant difference in the standard deviation of the slopes of the QT interval-heart rate variability for men or women. During the evening, SD gradually becomes larger and becomes even larger at night.

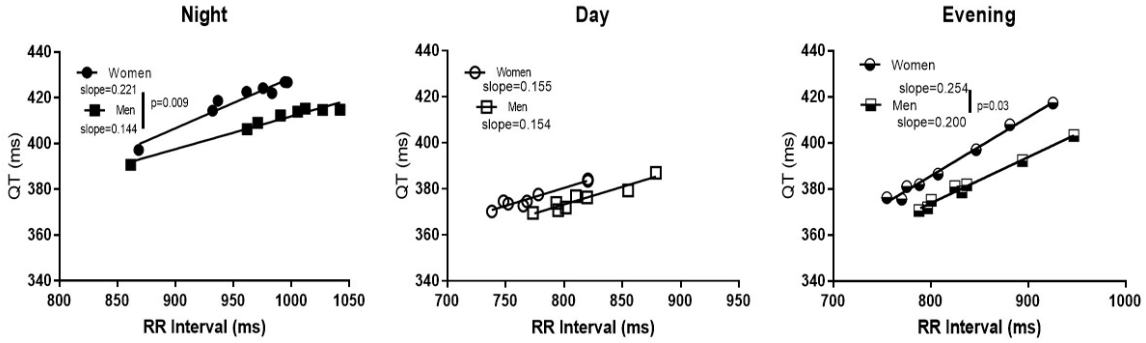

Figure 3. The image shows the QT/RR interval relationship for the three 8-hour periods of the day specifically night, day and evening for women and men separately.

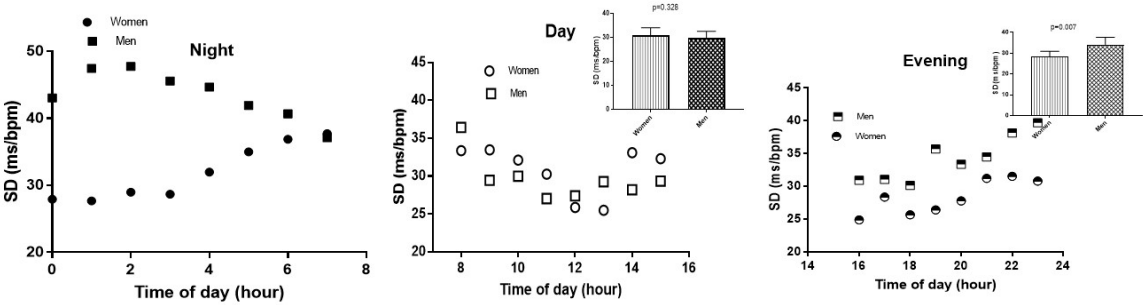

Figure 4. The image shows the Standard deviation of the QT interval at each hour of the day, for the three 8-hour periods of the day specifically night, day and evening. The inset shows the mean standard deviation during each of those 8-hour periods.

Comparative effect of different heart rate correction factors during the day

Utilizing four different heart rate correction formulae to adjust for the QT dependency on heart rate showed that there were different patterns of QTc in each of the three time periods (**Figure 5**). The positive slope of QTc in the evening reflects the slowing of the heart rate from the early hours of evening until midnight. QTcFRD had significant (F=22.5, P<0.0001) different slopes between men and women in each of the three time periods. The same was the case for QTcFRM (F=22.31, P<0.0001) and QTcHGD (F=19.5, P<0.00001) but not for QTcRBK (F= 1.7, P=0.16). The finding with QTcRBK may reflect its better ability correct for the effect of heart rate on the QT interval [18]. Overall, the slopes of the QTc were different between men and women mainly in the evening, occasionally at night and not usually during the day.

Discussion

This study demonstrates the impact of the time of day and an individual's sex on the QT interval-heart rate relationship. Specifically, we identified that the time of the day that the ECG is taken influences the QT interval, the relationship between the QT interval and heart rate, as well as the variability in the QT interval. Importantly, the relationship between QT interval and heart rate is similar in the evening and night and both are significantly different from the relationship during the day. This has practical implications when ECGs are done during the day or in the evening, assuming that individuals infrequently have ECGs done at night. It also has practical consideration for in-hospital ECG monitoring during the night. It suggests that at the same heart rate, the QT interval will be longer in the evening or night than during the day. It also identified differences between women and men for three of the QT interval-heart rate correction formulae.

Women had higher QT interval values than men at equivalent heart rates. This finding has been reported in a number of population samples [18-20, 26]. The longer QT interval in women compared to men has been attributed to the ability of estrogens to prolong cardiac repolar-

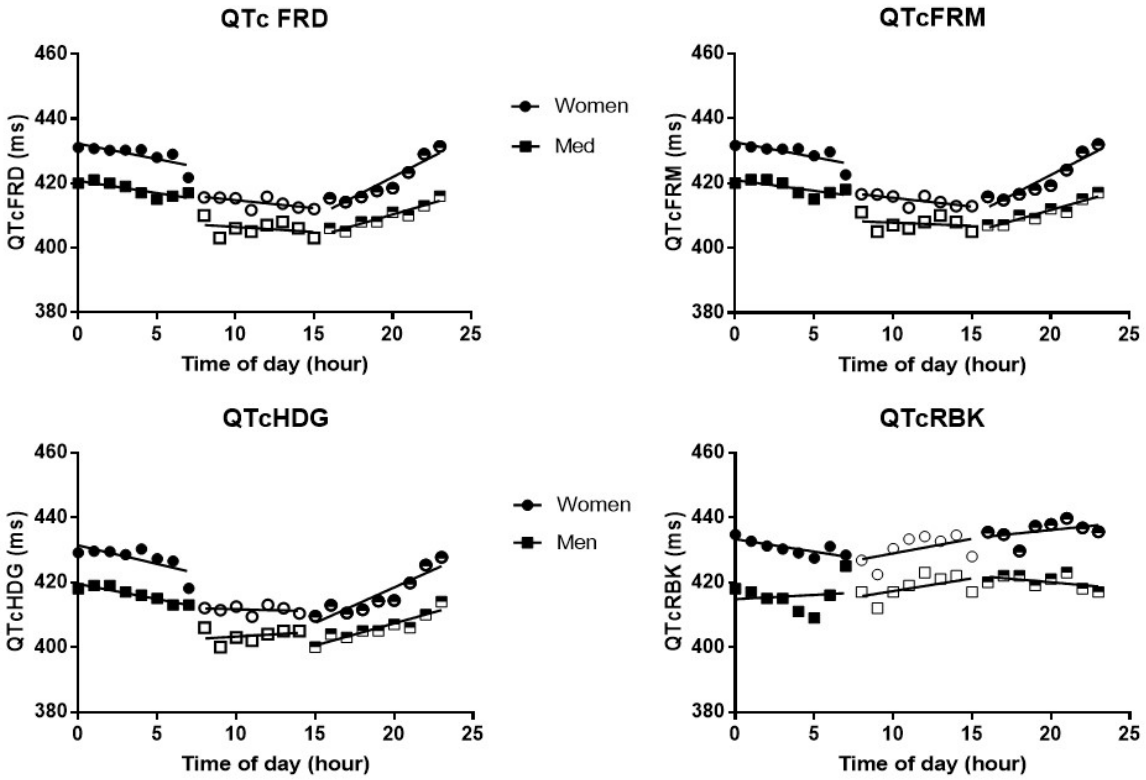

Figure 5. The image shows the QT interval during the 24-hour day, after heart rate correction, for women and men, using four different formulae specifically the Fridericia approach (QTcFRD) [22], the Hodges formula (QTcHDG) [23], the Framingham formula (QTcFRM) [24] and the new spline formula (QTcRBK) [18].

ization and male sex hormones to shorter QT interval [27-30]. The relationship is more complex because it is also influenced by the progesterone/estradiol ratio as well as by other steroid sex hormones such as follicle-stimulating hormone [29] and androstenedione [30].

We found differences in the slope of the relationship between QT interval and RR interval between men and women. Specifically, there was a steeper slope of the QT/RR relationship in women than men but only in the evening and at night and not during the day. Previous investigations of potential differences have not been consistent. Stramba-Badiale *et al* reported on 20 young men and 20 young women and found that QT interval-RR slopes were steeper in females than in males but did not consider the time of day of the relationship [19]. Sredniawa *et al* reported a steeper slope of the QT interval-RR interval relationship but mainly during daytime [20]. Our finding of a steeper QT interval-RR interval relationship in women at night, means that when heart rate slows at night, the QT interval is more prolonged in women than men. Potential mechanisms or explanations for this observation include genomic and non-genomic effects of sex and sex hormones on cardiac membrane ion channels [30]. Several sex hormones regulate the expression of the delayed rectifier current HK2 which alters the repolarization phase of the cardiac action potential [31]. In addition, hormones directly affecting cardiac ion channels producing changes in the QT interval on the surface ECG [32].

The differences in the QT duration and the QT interval-RR interval relationship between women compared to men, likely have adverse consequences. We believe that our finding might explain in part the observation that cardiac sudden death occurs more commonly in women than in men [33, 34]. Women are more likely than men to develop potentially fatal polymorphic ventricular tachycardia and torsades de pointes, during administration of cardiovascular drugs that prolong cardiac repolarization

[35]. Women are more likely than men to have a longer QT interval on the same dose of oral d,l-sotalol, normalized for body weight [36]. Because drug-induced polymorphic ventricular tachycardia is facilitated by longer cycle lengths, the longer QT interval in women is a potential explanation for the greater prevalence of this potentially fatal cardiac arrhythmias in women than in men [20]. The steeper QT interval-RR interval relationship at night may explain the higher prevalence of cardiac sudden death at night in women compared to men [34].

We found that the QT was considerably longer during the evening and night than during the day and the slope of the QT interval-heart rate relationship was steeper in the evening and night compared to the day-time. These data support a circadian rhythmicity for the QT interval. While there has been some controversy, the evidence supports a circadian rhythm for the QT interval (for review see [17]). Most of the studies, however, did not examine specific time periods to compare directly different times during the 24-hour day [10-12, 15, 16, 37]. Some investigators contend that there is no true difference and suggest that the day/night variation in slope could be explained by the differences in heart rate between the day and night [38]. Jensen *et al* reported no differences in the slope of the QT interval-RR interval, after considering heart rate between day and night, but they only evaluated 3 hours of the day (09:00 to 12:00 h) and three hours of the night (02:00 to 05:00 h) [38]. Other investigators contend that the slope of the QT interval/heart rate relationship is steepest in the morning, less steep during the day and flat at night although the precise times labelled as day and night were not defined [20]. We found differences in QT interval between the day and evening or night. This finding can only partially be explained by more physical activity during the day time because prolongation of the QT interval during sleep reflects not only inactivity but also withdrawal of sympathetic tone at night [39].

Difference in the QT interval-heart rate relationship during the day compared to the night is consistent with a circadian variation in the QT interval which is governed by the brain-hierarchical clock system controlling cardiac function, as well as the intrinsic rhythmicity at the myocardial subcellular level, guided by clock genes in the heart that rhythmically alter protein output and function [40]. Our clinical data support the concepts arising from mathematical modelling of the cardiac action potential which led to several equations that support the contention that the QT interval is controlled by a circadian clock [41]. Expression of the potassium channel interacting protein-2 (KChIP2), a regulator of the heart transient outward potassium current, modulates the duration of cardiac repolarization [41]. The clock-dependent oscillator, kruppel-like factor 15 (Klf15) transcriptionally controls changes in expression of KChIP2 throughout the day [42].

The standard deviation around the estimate of the QT is an index of variability [43]. The SD was significantly greater in men than women at night and in the evening but not during the day. During the evening, SD gradually becomes larger and becomes even larger at night. These data indicate there is less variability in assessing the QT interval in women than in men at night.

Study limitations

There are several limitations of the study that warant discussion. First, the QT interval was calculated with a computer alogrithm. All computer alogithms have the challenges to assess the T wave in the detail required to accurately calculate the QT interval. Calculation of thousands of QRS complexes per hour in each 24-hour recording, however, cannot be reasonably done manually so that a computer alogarithm is necessary. Second, the steepness of the slope of the QT interval-RR interval relationship implies a further prolongation of the QT interval at longer cycle lengths. Third, when comparing QT interval/heart rate correction formulae, it is important to reemphasize the lack of a 'gold standard' for the clinical assessment of the QT interval and cardiac repolarization.

Conclusion

The time of the day that the QT interval is being evaluated should be a consideration for QT interval evaluation. QT-heart rate correction formulae differ in their ability to adjust for the effects of heart rate changes during the 24-hour day. The QT-heart rate relationship is different in women than men. QT interval variability is greater in men than in women especially at night. Differences in the QTc at night might be the basis for the higher prevalence of sudden death in women at night.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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