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Diurnal Pattern of QTc Interval: How Long is Prolonged?

Possible Relation to Circadian Triggers of Cardiovascular Events

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Objectives. **This study sought to evaluate the range and variability of the QT and corrected QT (QTc) intervals over 24 h and to assess their pattern and relation to heart rate variability.**

Background. **Recent Holter monitoring data have revealed a high degree of daily variability in the QTc interval. The pattern of this variability and its relation to heart rate variability remain poorly characterized.**

Methods. **We developed and validated a new method for continuous measurement of QT intervals from three-channel, 24-h Holter recordings. Average RR, QT, QTc and heart rate variability were measured from 5-min segments of data from 21 healthy subjects.**

Results. **Measurement of 6,048 segments showed mean (±SD) RR, QT and QTc intervals of 830 ± 100, 407 ± 23 and 445 ± 16 ms, respectively (mean QTc interval for men 434 ± 12 ms, 457 ± 10 ms for women, $p < 0.0001$). The average maximal QTc interval was 495 ± 21 ms and the average QTc range 95 ± 20 ms. The maximal QTc interval was ≥500 ms in 6 subjects and ≥490 ms in 13. The 95% upper confidence limit for the mean 24-h QTc interval was 452 ms (men 439 ms, women 461 ms). The RR, QT and QTc intervals and the high frequency component of heart rate variability were greater during sleep. Both the QTc interval and the variability between hourly minimal and maximal QTc intervals reached their circadian peak shortly after awakening, before declining to daytime levels.**

Conclusions. **The maximal QTc interval over 24 h in normal subjects is longer than heretofore thought. Both QT and QTc intervals are longer during sleep. The QTc interval and QTc variability reach a peak shortly after awakening, which may reflect increased autonomic instability during early waking hours, and the time of the peak value corresponds in time to the period of reported increased vulnerability to ventricular tachycardia and sudden cardiac death. These findings have implications regarding the definition of QT prolongation and its use in predicting arrhythmias and sudden death.**

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The QT interval on the surface electrocardiogram (ECG) is an indirect measure of the time between ventricular depolarization and repolarization. Its prolongation is thought to be associated with the occurrence of malignant ventricular arrhythmias in patients with the congenital long QT syndrome (1,2), in patients taking antiarrhythmic medications (3), in patients with myocardial ischemia or infarction (4,5) and perhaps even in the general population (5–7).

The definition of QT interval prolongation has been disputed because of uncertainty regarding the true range of the normal QT interval. The problem is confounded by the fact that the normal QT interval varies not only with heart rate (8), but also with gender (8) and, because of circadian variability, with time of day (9,10). To compensate for the dependency of QT on heart rate, a rate-normalized, or corrected, QT (QTc) interval is used to define normal values. Many methods of rate normalization have been developed (11–14). Normal values for the QTc interval have been defined from measurements of single beats on 12-lead ECGs made in large populations of normal subjects at rest during daytime hours (8). These normal values are then applied in a variety of dissimilar clinical situations. Many studies have suggested that the range of values reported as normal for the QTc interval may be too low. Several of these reports have also noted considerable variation over time (15,16) and circadian rhythmicity (9,10) in the QTc interval. By allowing the assessment of the QT interval over a wide range of heart rates, continuous ECG methods like Holter monitoring may allow more accurate assessment of the true nature of QT variation and provide a more accurate reflection of the true range of normal values. Recently, the role of autonomic influences on QT interval duration has been documented, as has the diurnal nature of those influences (17–19).

Thus, our aim was 1) to develop a new method for

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continuous measurement of the QT interval using existing Holter monitor technology, 2) to apply this technique to define the range and variation of the QTc interval, and 3) to assess the role of the autonomic nervous system in the dynamic changes of the QTc interval in normal subjects over 24 h.

Methods

Study subjects. Twenty-one healthy subjects (11 men, 10 women; mean [±SD] age 57 ± 13 years, range 36 to 76) were selected at random from a data base of 508 subjects who had undergone Holter monitoring with analysis of heart rate variability at our institution between 1988 and 1992. All subjects were in sinus rhythm with normal atrioventricular and intraventricular conduction on their surface ECG. All subjects had normal serum electrolyte levels, and none had a history of coronary artery disease, hypertension, diabetes mellitus or supraventricular or ventricular arrhythmias or was taking medications known to affect the QT interval or autonomic tone.

Computer-assisted QT measurements. All subjects underwent 24-h three-channel Holter monitoring (Marquette 8000T Laser Holter). The computer's identification of beats was reviewed and mislabeled beats or inaccurate fiduciary points corrected. Beats of ectopic origin and those exhibiting aberrant conduction were excluded from further analysis. Holter analysis algorithms were modified for the purpose of this study (PRMDK and QRSDK algorithms, Marquette Electronics, Inc). The 24-h recording for each patient was divided into 288 five-minute segments by PRMDK software, and templates representing the average QRST interval for each 5-min segment were generated. Each template was displayed at fourfold enlargement, and electronic cursors with 2-ms resolution were positioned to the visually determined onset and offset of the QT interval. Because the QT interval varies considerably as a function of ECG lead, we used for analysis a single channel, representing a modified V_5 lead (positive electrode at 5th intercostal space, left anterior axillary line; negative electrode beneath the right clavicle, just lateral to the sternum). Templates with artifacts that precluded reliable determination of the QT interval were rejected. Such intervals constituted <2.1% of the total intervals analyzed. For each 5-min segment, the average RR intervals were calculated using the QRSDK software. The data were transferred to a NeXT computer system for further analysis. Using the average RR and QT data obtained in this manner, the QTc interval for each 5-min segment was calculated using the linear (Framingham) correction formula $QTc = QT + a(1 - RR)$ (20,21). The regression variable a was individually determined for each subject by plotting values for QT intervals for each 5-min segment as a function of RR interval. This plot was then fitted with least-square multiple regression analysis using the formula $QT = a \times RR + b$. (This "fitting" form of the linear formula yields the "correction" form because when RR = 1, QT = a + b. Solving for a + b yields the correction formula.) We selected the linear rather than the more commonly used Bazett formula because it has been reported to provide more reliable correction (20,21).

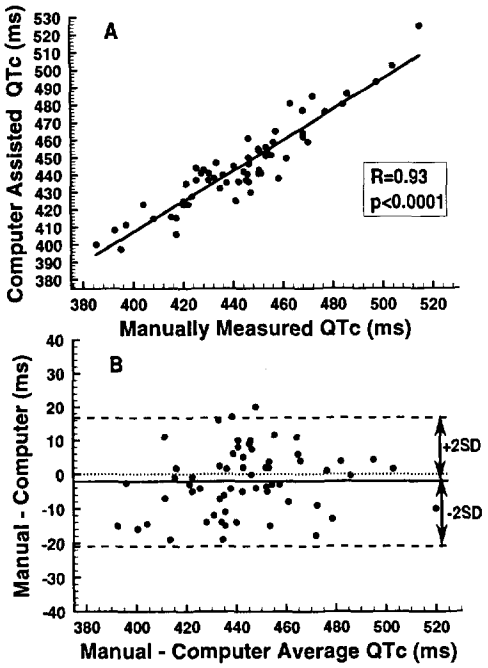

Figure 1. Linear regression (**A**) and Bland-Altman (22) analysis (**B**) of the relation between computer-assisted and manually determined QTc measurements. In **B,** the **ordinate** shows the difference between manual and computer-assisted QTc intervals as a function of the mean values of the two measurements: (manual + computer-assisted QTc interval)/2. **Solid line** = mean difference between the two measurements (−2.0 ± 9.4 ms).

Validation of method. To validate the technique, we compared the computer-assisted QTc values to manually measured QTc values in 21 healthy subjects. The ECG printouts were made at a paper speed of 25 mm/s from electronically recorded Holter data at maximal, minimal and average heart rates for each patient, so as to analyze the method over a wide range of heart rates. For each printout, five consecutive RR and QT intervals were measured using a Hipad Digitizer. The QTc interval was calculated for each beat using the linear formula, and the mean QTc interval was calculated for each of the 61 samples (2 of the original 63 samples were rejected for technical reasons).

Figure 1A shows the relation between the manually determined and computer-assisted QTc intervals from the same Holter segments. The manually determined and computer-assisted measurements correlate closely ($R = 0.93$, $p < 0.0001$ by linear regression analysis). The slope of the regression line is 1. The regression line closely approximates the line of identity. Figure 1B shows the difference between manually determined and computer-assisted QTc measurements, assessed by the method of Bland and Altman (22). The average difference between manually determined and computer-assisted QTc intervals was −2.0 ± 9.4 ms.

Reproducibility of measurements. The QT interval onset and offset were determined by a single investigator (J.M.) for

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all subjects. To examine for interobserver variability, independent, duplicate determinations were made by a second investigator (F.A.E.) on a subgroup of 288 QRST templates. The standard deviation of the differences between pairs of readings (δ), computed as suggested by Rose et al. (23), was 5.4 ms. The coefficient of variability (δ/mean QT interval) (12,13) was 1.2%. We also tested for the presence of intraobserver variability by randomly inserting 30 duplicate segments into a series of 300 assessed by a single observer. These duplicate segments had a standard deviation of 6.51 ms (coefficient of variability 1.6%).

Power spectral analysis of heart rate variability. We used software developed and validated in our laboratory for power spectral analysis of heart rate variability (24). Power was calculated in the following frequency ranges: 0.0167 to 0.05, 0.05 to 0.15, 0.15 to 0.35 and 0.35 to 0.5 Hz for very low, low, high and very high frequencies, respectively. High frequency power, which reflects the respiratory component of sinus arrhythmia, is thought to be an index of vagal activity, whereas the low frequency/high frequency ratio may be an index of sympathovagal balance (25,26). Reliable estimation of pure sympathetic tone in ambulating subjects is not yet possible.

Data analysis. Results are presented as mean value ± SD. Comparisons by gender between QTc values were made using the pooled *t* test. The QTc values during wakefulness and sleep were compared using analysis of variance followed by the Tukey-Kramer procedure. To test for the presence of chronobiologic patterns, mean data were fitted by the SASSYSNLIN procedure to a cosinor function by ordinary least-squares analysis. The standard variables of amplitude, period (τ), acrophase (time to crest) and mesor (rhythm-adjusted mean value) were estimated (27–29). A p value < 0.05 indicated statistical significance.

Results

Patient data. A total of 6,048 five-minute segments were analyzed from the Holter recordings of 21 subjects. The results are summarized in Table 1. Although we used the linear correction formula, the data would have been similar had we used the Bazett formula. To allow comparison with previously published data, the QTc values obtained using the Bazett correction formula are shown in parentheses. Women had a significantly shorter mean RR interval and longer QT and QTc intervals than men. In women, the maximal QTc interval, as well as the average of each subject's QTc range, was significantly greater than that in men.

Our data suggest that when QT and QTc intervals are measured over 24 h, the maximal values exceed generally accepted values for the upper limits of normal. Thus, six subjects, all women, had QTc intervals >500 ms at some time during the recordings, and the mean maximal QTc interval was 495 ± 21 ms. Figure 2 shows an analysis of the percent of QTc values within each subject that exceeded the threshold values shown on the abscissa. For each subject, the percent of QTc intervals >500 ms was low (~1% overall, women 2%, men 0).

Table 1. Results of Measurements in 21 Normal Subjects

	All Subjects (n = 21)	Women (n = 10)	Men (n = 11)	p Value
Age (yr)	57 ± 13	57 ± 15	57 ± 12	NS
RR interval (ms)	830 ± 100	790 ± 80	870 ± 100	0.0001
QT interval (ms)	407 ± 23	404 ± 26	410 ± 13	0.05
QTc interval (ms)	445 ± 16	457 ± 10	434 ± 12	0.0001
	(443 ± 15)	(451 ± 13)	(435 ± 13)	(0.0001)
dQTc (ms)	95 ± 20	102 ± 22	88 ± 14	0.0002
	(117 ± 28)	(121 ± 28)	(113 ± 28)	(0.001)
Max QTc interval (ms)	495 ± 21	511 ± 16	479 ± 12	0.05
	(505 ± 21)	(515 ± 21)	(497 ± 17)	(0.05)
95% UCL	452	461	439	
	(450)	(459)	(443)	

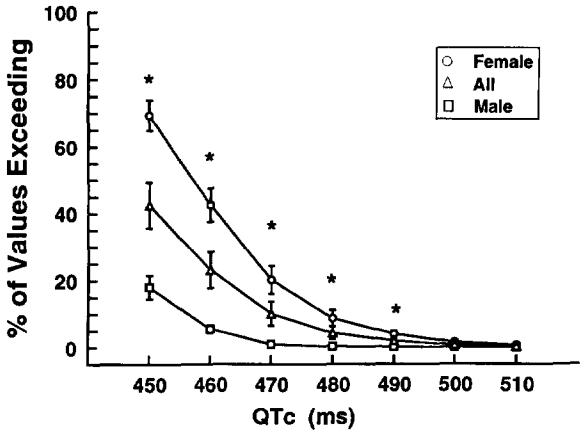
Data presented are mean value ± SD, unless otherwise indicated. dQTc = intrasubject range of heart-rate corrected QT interval (QTc); Max = maximal; QTc = QTc interval obtained using Framingham (Bazett) formula; UCL = upper 95% confidence limit for QTc intervals.

However, the percent >450 ms was substantial (42 ± 31%, women 69 ± 21%, men 18 ± 16%). The gender differences for these data were statistically significant, from 450 to 490 ms.

The mean intrasubject QTc interval range was large (95 ± 20 ms) and was significantly larger in women (102 ± 22 ms) than in men (88 ± 14 ms, $p < 0.001$).

Circadian variations in RR and QT intervals over 24 h. Figure 3 shows the hourly mean values and standard deviations of the RR, QT and QTc intervals, as well as the 95% confidence intervals for QTc intervals. The bottom panel shows the percent of subjects who slept during each hour, as determined from their diaries. The RR, QT and QTc intervals were significantly cosinusoidal and had a period τ ranging from 26 to 32 h. As expected, the RR interval was longer during hours of sleep than during wakefulness, presenting a circadian periodicity, with a rapid decrease in the early morning hours. The variation in the mean QT interval closely reflected the circadian variation in the RR interval. Mean hourly QTc intervals had a similar but greatly blunted circadian pattern, with an average difference between day (10 AM to 4 PM) and

Figure 2. Mean percent of intrasubject QTc values that exceeded values shown on the **abscissa**. *p < 0.05, men versus women.



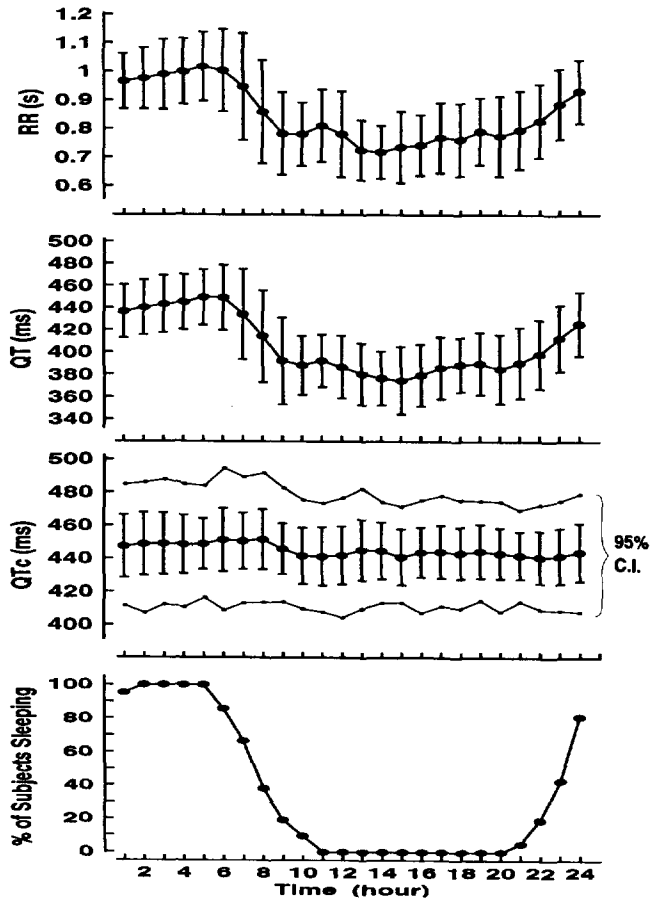


Figure 3. RR, QT and QTc intervals and percent of subjects asleep as a function of time of day, as determined from Holter tape timing tracks. Each **data point** represents mean data for the hour preceding it. C.I. = confidence interval.

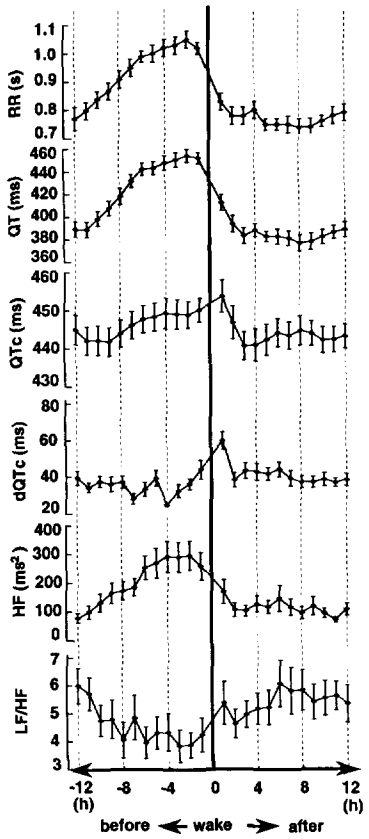


Figure 4. RR, QT and QTc intervals and heart rate variability data normalized to the time of subjects' awakening (0 on **abscissa**). Each **data point** represents mean data for the hour preceding it. dQTc = average range for intrasubject Holter recording, between hourly minimal and maximal QTc interval; HF (LF) = high (low) frequency component of heart rate variability.

night (12 AM to 6 AM) that was small (6 ms) but statistically significant, and with a somewhat longer period (τ = 32 h).

There was considerable variability in the time that subjects went to sleep and awakened, as shown in the bottom panel of Figure 3, which may have clouded the pattern of circadian QTc variation. Figure 4 shows the data normalized to the hour of awakening (labeled 0 on the abscissa), as indicated by the subjects' diaries. As expected, this normalization slightly reduced the period τ of RR, QT and QTc intervals to 20 to 22 h. Like the uncorrected QT interval, the mean QTc interval decreased during hours of wakefulness, but the difference in values between sleep and wakefulness was much smaller. Unlike the uncorrected QT interval, there was a distinct, though transient, increase in the QTc interval during the first hour after awakening, when the longest hourly mean QTc interval occurred.

Although the variation in mean hourly QTc intervals was small, individual QTc measurements demonstrated a large degree of variability for each subject. The average daily range between each subject's minimal and maximal QTc interval was 95 ± 20 ms. The hourly mean QTc range was 38 ± 6 ms, and, as Figure 4 shows (dQTc), was lower at night than during the daytime. It fit a circadian pattern with τ = 19.6 ± 2.1 h. There was a marked increase in QTc range, to its highest value, immediately after awakening.

Correlation with heart rate variability. Figure 4 also shows the hourly mean high frequency and low frequency/high frequency ratios. Like the RR, QT and QTc intervals, the high frequency component of heart rate variability was higher during hours of sleep than during wakefulness, with a rapid decrease on awakening. The low frequency/high frequency ratio increased after awakening and was higher during daytime than nighttime hours. Both of these variables were cosinusoidal, with τ = 22 to 23 h, similar to that of RR and QT data. Both the higher high frequency and the lower low frequency/high frequency ratio during sleep suggest a relatively increased parasympathetic tone during sleep, with parasympathetic withdrawal on awakening.

Discussion

We describe a new computer-assisted method for continuous assessment of the QT and QTc intervals. We found that the QTc interval, when assessed over 24 h, is much longer than

heretofore reported. The QTc intervals demonstrated a pattern of circadian variation that was parallel to that of the RR interval and the high frequency component of heart rate variability. A notable exception to this pattern was that QTc intervals lengthened shortly after subjects awoke, a time when the high frequency component of heart rate variability and cardiac cycle length were both declining.

Diurnal variation in QTc interval and heart rate variability over 24 h. The QT interval varied with a circadian pattern, largely reflecting the variation in the RR interval. As expected, both of them were longer at night than during the day and were well correlated with power in the high frequency band of the spectrally analyzed heart rate variability measurements, which is thought to reflect relative parasympathetic tone (25,26). This finding is in keeping with the generally observed relative increase in parasympathetic tone during sleep. The QTc intervals varied in a similar pattern, although the range was smaller (but statistically significant). This finding is in agreement with observations reported in previous studies (9,10,17–19). The small range of the QTc interval between day and night is consistent with the relative insensitivity of that measure to vagal activity that has recently been reported by Sarma et al. (9). Thus, because the QTc interval is influenced by multiple factors, one of which is vagal activity, these data do not imply that one can extrapolate heart rate variability data from the QTc interval, or vice versa.

Paradoxic prolongation of QTc interval in the morning and after awakening. In view of the increased relative sympathetic tone that has been reported to occur during the early morning hours (26), we expected that the QTc interval during those hours would decrease relative to the values obtained during sleep. Instead, we found that the mean QTc interval slightly lengthened and, in fact, reached its peak value during the first hour after awakening despite a rapid decrease in QT and RR intervals and an increase in the low frequency/high frequency ratio (supporting the presence of an increased relative sympathetic to parasympathetic tone). This finding suggests the presence of hysteresis between the rate of change of heart rate and QT interval as they adapt to waking conditions. That is, the decline in the RR interval occurs over a relatively shorter period of time than the decline in the QT interval, thereby resulting in an increase in QTc interval.

The intrasubject difference between hourly minimal and maximal QTc intervals also demonstrated a circadian pattern: Hourly average QTc variation was lower at night than during the day, perhaps reflecting the greater uniformity in activity during sleep. The average difference between subjects' hourly minimal and maximal QTc values reached its peak during the first hour of wakefulness. Such a peak in QTc variation would be expected if the first hour of wakefulness included portions during which each subject was both sleeping and awake. However, we were careful to select the "cutoff" between sleep and wakefulness for each subject such that measurements after that "cutoff" did not include "sleep time." Moreover, the postawakening peak in QTc variation is the culmination of a slower but steady early morning increase that begins >3 h before the time of awakening. Thus, the morning increase and postawakening peaks in QT and QTc variation are not likely to represent an artifact resulting from sloppy identification of time of awakening.

To some extent, the dependency of the QTc interval on heart rate is independent of autonomic tone (30). However, factors such as autonomic tone may modify this dependency (17,18,31): Vagal stimulation and acetylcholine cause a rate-independent prolongation (32,33), whereas atropine (30) and exercise-induced increases in tone cause a rate-independent shortening of the QT interval (34). Thus, autonomic tone influences the QT interval indirectly by modulating heart rate and directly by affecting action potential duration and conduction velocity (32,33). The circadian variation in QTc interval probably reflects both the underlying heart rate and autonomic tone. It has been shown (17) to be present but blunted in transplanted hearts, pronounced in innervated heart and absent in diabetic autonomic neuropathy.

What, then, is the explanation for the paradoxically increased QTc interval and for the increased QTc variation during the first hour after awakening? It may lie in the fact that the relation of QT interval duration to factors such as heart rate and autonomic tone is complex. Several areas of complexity have been identified: 1) The effects of autonomic stimulation may be dependent on its duration. Thus, a short period of sympathetic nerve stimulation or catecholamine injection resulted in prolongation, whereas a long period resulted in reduction of the QT interval in the dog (31). 2) QT duration may reflect complex interactions between catecholamine levels or between catecholamine levels and heart rate. For example, Lecocq et al. (35) found that during isoproterenol-induced tachycardia in humans, the QT interval either did not change or increased and no longer adapted to changes in heart rate. Other investigators (32) found that the prolongation in action potential duration by acetylcholine is accentuated in the presence of isoproterenol, suggesting that modulation of action potential duration (and therefore QT interval) may not wholly parallel modulation of heart rate. Thus, because the regulation of the QT interval is complex and may depend on factors other than heart rate, it is not surprising that at a time when both heart rate and autonomic tone are changing, the decrease in the QT interval and the increase in heart rate might be "out of step," with the QT interval lagging behind heart rate, thereby resulting in a transient prolongation of QTc interval. Instability between the response by heart rate and QT interval to changing autonomic conditions also explains our observation that the temporal dispersion between longest and shortest QT interval is greatest during the first hour after awakening (Fig. 4). This dispersion diminishes when the new steady state conditions associated with wakefulness are achieved. Nonetheless, QTc variation remains somewhat higher during daytime waking hours than during sleep, perhaps reflecting the greater variations in autonomic tone and range of heart rates expected during wakefulness.

These observations suggest that the period that immediately follows awakening is one in which action potential

duration is longer or conduction velocity is lower in relation to heart rate than at other times. Moreover, observations by Litovsky and Antzelevitch (32) suggest that the response of action potential duration to agents such as acetylcholine and iosproterenol may be more pronounced in epicardial than endocardial canine myocytes. Because spacial and temporal dispersion of action potential characteristics, especially when they involve alterations in refractoriness and conduction velocity, may influence the propensity of the heart to develop arrhythmias, it is possible that our observations regarding the prolongation of QTc interval, and its instability during early wakefulness, may be related to the observed increased incidence during this period of ventricular tachycardia and sudden cardiac death (36).

Computer-assisted QT measurements: technical considerations. In contrast to other, more fully automated methods (9,37), our method requires operator intervention in that the fiduciary points for each 5-min segment must be manually identified. The operator has the option of eliminating technically uninterpretable segments from the analysis, which may provide an advantage over more fully automated systems that frequently misidentify fiduciary points, especially termination of the T wave. In a recently published study (10), 10% to 40% of automatically measured QT intervals required manual correction. The requirement for operator intervention in our system may have the advantage of a high level of consistency and reliability, particularly for use of the QT interval in research, which is supported by the low intraobserver and interobserver error of our technique.

Another advantage of our technique is that it relies on the measurement of 5-min average templates and corresponding average RR intervals. In contrast to beat-to-beat measurement, this technique eliminates the error arising from the hysteresis in QT-RR relation, when the heart rate rapidly changes (38), while preserving QTc alterations that arise from more sustained alterations in the relation between heart rate and QT interval, such as those previously reported.

We selected the termination point of the T wave visually. It has been suggested (39) that this point be defined as the intersection between a line drawn to the tangent of the terminal limb of the T wave and the baseline. However, this method may underestimate or overestimate the QT interval (39), particularly when the slope of the terminal T wave is not constant.

The QT intervals measured on a Holter monitor may be different from those measured on a standard 12-lead ECG because of differences in lead position or in frequency response (40). Nonetheless, because we used the same ECG leads and Holter equipment in all subjects, the data are likely to be comparable and thus adequate for assessment of QT and QTc intervals over 24 h.

We selected the linear formula over the more commonly used Bazett formula because it has been reported (21) to provide more reliable QT correction. Like many of the formulas that have been proposed to avoid the well known deficiencies in the Bazett formula (12,41,42), the linear formula takes individual variations in the QT/heart rate relation into account by incorporating one or more regression variables that must be individually determined for each subject. These formulas have provided better QT correction than formulas that do not have a provision for such "customization" (12,41–43). In a preliminary study (44) in which we compared the performance of five correction formulas on Holter monitor tapes, four that invoke individually calculated regression variables all performed equally, much better than the simple Bazett formula (44).

The applicability of our findings to clinical or research situations in which the Bazett formula is used might be questioned. However, the differences between values obtained using the linear and the Bazett correction formulas were minimal (Table 1). When we performed our statistical analyses on Bazett-corrected data, we found only minor quantitative but no qualitative differences from those shown, suggesting that our results are also meaningful when the Bazett formula is used.

Range of QTc interval in normal subjects: Should the upper limit of the QTc interval be revised upward? Recent studies have suggested that upper limits reported in "standard" ECG textbooks, such as 440 ms (45), may be too low, and should be increased to, for example, 460 ms (46). Recently published data (9,10,15,16) obtained by Holter monitoring have demonstrated a high degree of daily spontaneous variability in the QTc interval. Morganroth et al. (15), using three ECG samples/h from Holter recordings, found that the average range of the QTc interval was 76 ± 19 ms (35 to 108 ms) in 20 normal subjects over 24 h. Fifty-five percent of subjects had a QTc interval >440 ms, and one had a QTc interval >500 ms.

Our continuous measurement of QTc intervals over 24 h in healthy subjects shows that the range of values may be even larger: The average maximal QTc interval was 495 ± 21 ms. The average range between the minimal and maximal QTc interval was 95 ± 20 ms. We also found that the upper limit of the diurnally varying QTc interval was higher than heretofore reported: The 95% upper confidence limit was 452 ms (men 439 ms, women 461 ms). However, individual QTc measurements were highly variable, and, as shown in Figure 2, any arbitrarily chosen "cutoff" value for the upper limit of normal defines as abnormal a substantial proportion of intervals in normal subjects. For example, even if one selects as the upper limit a value as long as 460 ms, 23% of QTc values exceed that limit (6% in men, 42% in women). QTc intervals >500 ms were not uncommon. Although this may, to some extent, reflect QTc prolongation during sleep, the mean corrected QT interval was only slightly longer at night.

Women consistently had longer QTc intervals than men and also had a wider range between their minimal and maximal QTc intervals. The observation that women have a longer QTc interval was described as early as 1920 by Bazett (11). It has been proposed (47) that this gender difference reflects a shortening of the QTc interval in adolescent boys. Our observation (Fig. 2) that exceedingly large QTc values were more common in women is consistent with a recent report by

Rautaharju et al. (48) that QT prolongation was more than three times as likely in elderly women than in elderly men, after adjustment of other factors associated with QT prolongation.

Conclusions. Our study suggests that caution should be exercised when categorizing a single clinically measured QTc interval as prolonged. The occurrence of long QT intervals in normal subjects underlines the importance of assessing the QT interval within the clinical context. Further studies in larger groups of subjects may confirm the need to increase the upper limit of normal. Alternatively, assessment of repolarization may be enhanced by considering ECG waveform characteristics other than just the duration of the QT interval (49). Studies on the normal circadian QT pattern and on deviations from that pattern induced by disease and medications may yield new information pertinent to the autonomic regulation of the heart and may be useful in refining the use of the QT interval as a marker for abnormalities.

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References

1. Moss AJ. Measurement of the QT interval and the risk associated with QTc prolongation: a review. Am J Cardiol 1993;72:23B–5B.
2. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. Am Heart J 1975;89:378–90.
3. Selzer A, Wray W. Quinidine syncope: paroxysmal ventricular fibrillation occurring during treatment of chronic atrial fibrillation. Circulation 1964;30: 17–26.
4. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. Circulation 1978;57:1074–7.
5. Algra A, Tijssen JGP, Roelandt JRTC, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83:1888–94.
6. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991;84:1516–23.
7. Goldberg RJ, Bengston J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (the Framingham Heart Study experience). Am J Cardiol 1991;67: 55–8.
8. Lepeschkin E. Modern Electrocardiography. Vol. 1. Baltimore: Williams & Wilkins, 1951:180–8.
9. Sarma JSM, Venkataraman K, Nicod P, et al. Circadian rhythmicity of rate-normalized QT interval in hypothyroidism and its significance for development of class III antiarrhythmic agents. Am J Cardiol 1990;66:959–63.
10. Ong JJ, Sarma JS, Venkataraman K, Levin SR, Singh BN. Circadian rhythmicity of heart rate and QTc interval in diabetic autonomic neuropathy: implication for the mechanism of sudden death. Am Heart J 1993;125:744–52.
11. Bazett HC. An analysis of time-relations of the electrocardiogram. Heart 1920;7:353–70.
12. Puddu PE, Jouve R, Mariotti S, et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic root Fridericia's equation. J Electrocardiol 1988;21:219–29.
13. Rautaharju PM, Zhou SH, Wong S, Prineas R, Berenson GS. Functional characteristics of QT prediction formulas. The concepts of QTmax and QT rate sensitivity. Comput Biomed Res 1993;26:188–204.
14. Ahnve S. Correction of the QT interval for heart rate: review of different formulas and the use of Bazett's formula in myocardial infarction. Am Heart J 1985;109:568–74.
15. Morganroth J, Brozovich FV, McDonald JT, Jacobs RA. Variability of the QT measurement in healthy men, with implications for selections of an abnormal QT value to predict drug toxicity and proarrhythmia. Am J Cardiol 1991;67:774–6.
16. Marti V, Guindo J, Homs E, Vinoles X, Bayes de Luna A. Peaks of QTc lengthening measured in Holter recordings as a marker of life-threatening arrhythmias in postmyocardial infarction patients. Am Heart J 1992;124: 234–5.
17. Bexton RS, Vallin HO, Camm AJ. Diurnal variation of the QT interval—influence of the autonomic nervous system. Br Heart J 1986;55:253–8.
18. Murakawa Y, Inoue H, Nozaki A, Sugimoto T. Role of sympathovagal interaction in diurnal variation of QT interval. Am J Cardiol 1992;69:339–43.
19. Browne KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP. Prolongation of the Q-T interval in man during sleep. Am J Cardiol 1983;52:55–9.
20. Adams W. The normal duration of the electrocardiographic ventricular complex. J Clin Invest 1936;15:335–42.
21. Sagie A, Larson MG, Goldberg RJ, Bengston JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797–801.
22. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
23. Rose G, Blackburn H, Gillum R, Prineas R. Cardiovascular Survey Methods. 2nd ed. Geneva: World Health Organization, 1982:145.
24. Myers G, Martin G, Magid N, et al. Power spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. IEEE Trans Biomed Eng 1986;33:1149–56.
25. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482–92.
26. Pagani M, Malfatto G, Pierini S, et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv Syst 1988;23:143–53.
27. Minors DS, Waterhouse JM. Analysis of biological time series. In: Arendt J, Minors DS, Waterhouse JM, editors. Biological Rhythms in Clinical Medicine. London: Wright, 1989:272–93.
28. Reinberg A, Smolensky MH, editors. Biological Rhythms and Medicine. New York: Springer, 1983:23–46.
29. SAS Institute I. SYSNLIN procedure. In: SAS/ETS User's Guide. Version 5. Cary, NC: SAS Institute, 1984:505–50.
30. Ahnve S, Vallin H. Influence of heart rate and inhibition of autonomic tone of the QT interval. Circulation 1982;65:435–9.
31. Abildskov JA. Adrenergic effects on the QT interval of the electrocardiogram. Am Heart J 1976;92:210–6.
32. Litovsky SH, Antzelevitch C. Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. Circ Res 1990;67:615–27.
33. Amlie JP, Refsum H. Vagus-induced changes in ventricular electrophysiology of the dog heart with and without β-blockade. J Cardiovasc Pharmacol 1981;3:1203–10.
34. Fananapazir L, Bennett DH, Faragher EB. Contribution of heart rate to QT interval shortening during exercise. Eur Heart J 1983;4:265–71.
35. Lecocq B, Lecocq V, Jaillon P. Physiologic relation between cardiac cycle and QT duration in healthy volunteers. Am J Cardiol 1989;64:481–6.
36. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–43.
37. Laguna P, Thakor NV, Caminal P, et al. New algorithm for QT interval analysis in 24-hour Holter ECG: performance and applications. Med Biol Eng Comput 1990;28:67–73.
38. Yamada A, Hayano J, Horie K, et al. Regulation of QT interval during postural transitory changes in heart rate in normal subjects. Am J Cardiol 1993;71:996–8.
39. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation 1952;6:378–88.
40. Garson A. How to measure the QT interval—what is normal? Am J Cardiol 1993;72:14B–6B.
41. Hegglin R, Holtzmann M. Die Klinische Bedeutung des Verlangerter-Distanz (Systolendauer) in Electrokardiogram. Z Klin Med 1937;132:1–32.
42. Kovacs S. The duration of the QT interval as a function of heart rate: a

derivation based on physical principles and a comparison to measured values. Am Heart J 1985;110:872–8.

43. Funck-Bretano C, Jaillon P. Rate-corrected QT interval: techniques and limitations. Am J Cardiol 1993;72:17B–22B.
44. Molnar J, Zhang F, Weiss JS, Rosenthal J. Why not Bazett's? Evaluation of 5 QT correction formulas using a new software assisted method of continuous QT measurement from 24-hour Holter recordings [abstract]. PACE 1995;18:852.
45. Goldman MJ. Principles of Clinical Electrocardiography. 8th ed. Los Altos, CA: Lange Medical, 1973:24–8.
46. MacFarlane PW, Lawrie TDV, editors. Comprehensive Electrocardiography: Theory and Practice in Health and Disease. Vol. 3. Oxford: Pergamon Press, 1988:1531–2.
47. Rautaharju PM, Zhou SH, Wong S, et al. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8: 690–5.
48. Rautaharju PM, Manolio TA, Psaty BM, Borhani NO, Furberg CD. Correlates of QT prolongation in older adults (the cardiovascular health study). Am J Cardiol 1994;73:999–1002.
49. Merri M, Albert M, Benhorin J, Hall JW, Locati E, Moss AJ. Electrocardiographic quantitation of ventricular repolarization. Circulation 1989;80: 1301–8.