Is the QT Interval an Indicator of Autonomic State?

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SUMMARY

Prolonged QT interval is suggested to indicate an increased risk of sudden cardiac death in certain clinical conditions such as diabetes mellitus. We investigated whether the individual QT interval is an indicator of an autonomic state. An ambulatory 24-hour ECG was recorded in 53 subjects from different clinical backgrounds. Power spectral components of heart rate variability (HRV) and the QT interval were regressively obtained at a heart rate of 60, 70, 80, 90, or 100 beats per minutes (bpm). Log values of the high-frequency component of HRV (HF: 0.15-0.50 Hz, a scale of cardiac parasympathetic tone) failed to show a relationship with the QT interval. In contrast, the QT interval at a heart rate of 90 bpm and 100 bpm showed a significant correlation with the log values of the low-frequency component (LF: 0.04-0.15 Hz) and the log[LF / HF], i.e., a putative scale of sympathetic tone (100 bpm: QT vs logLF: $r = 0.414$, $p < 0.005$, QT vs log[LF / HF]: $r = 0.416$, $p < 0.002$). Also, attenuated rate-dependent QT shortening was associated with greater logLF and log[LF / HF] values at a heart rate of 80, 90, or 100 bpm. These results suggest that the QT interval at a moderate heart rate (approximately 90-100 bpm) and the degree of rate-dependent QT shortening are related to individual sympathetic tone. (Jpn Heart J 2000; 41: 713-721)

Key words: Diabetes mellitus, Coronary artery disease, Ambulatory ECG monitoring, Heart rate variability, Sympathetic nerve, Parasympathetic nerve

Prolonged QT intervals have been shown to be related to an increased risk of sudden cardiac death in apparently healthy subjects$^1$ in addition to patients with coronary artery disease (CAD)$^2$ or diabetes mellitus (DM).$^3$ To clarify the underlying pathogenic mechanism of these clinical observations, it appears important to understand whether the QT interval is associated with a particular cardiac autonomic state or not. However, the response of the QT interval to pharmacological autonomic modifications is often conflicting.$^4$-10 Also, an intricate sympathovagal interaction$^{11}$ blurs the respective contribution of each limb of the autonomic nerve system to the QT interval. Thus, it is not readily predictable how the autonomic state is reflected on the QT interval in conditions without specific
autonomic modifications. In this study, we investigated the relationship between the QT interval and power spectral components of heart rate variability (HRV) in subjects with different clinical conditions. The purpose of this study was to elucidate the autonomic background of individual variation of the QT interval.

**SUBJECTS AND METHODS**

*Study subjects:* Two-channel, 24-hour ambulatory ECG recordings (SM28, Fukuda Denshi, Tokyo, Japan) from 53 subjects were analyzed. These recordings met the following criteria: 1) no medication affecting the autonomic tone or QT interval, 2) maintenance of the sinus rhythm, 3) less than 100 supraventricular or ventricular ectopic beats per 24-hour period, 4) no sinoatrial or atrioventricular block, and 5) no significant deformity of the ST-T segment.

Among these 53 study subjects, routine clinical examinations, two-dimensional echocardiography, and treadmill exercise stress testing revealed no organic heart disease in 23 subjects (18 men and 5 women aged 55 ± 2 [mean ± SEM] years). Angiography confirmed the presence of CAD in 16 patients (12 men and 4 women aged 58 ± 3 years, single vessel affliction in 7 and multiple vessels in 9). All CAD patients were in a stable condition and did not reveal any old myocardial infarction, left ventricular dysfunction, or DM. Fourteen patients (9 men and 5 women aged 58 ± 2 years) with non-insulin-dependent DM but without apparent ischemic heart disease comprised the third group. Their disease duration ranged from 5 to 24 years.

*Measurement of the QT interval:* The ECG lead that recorded the most distinct T waves, usually a modified chest lead V5 (CM5), was used for the analysis. Ten-second ECG recordings were taken at 10-min intervals during the day (10 A.M. to 6 P.M.), and printed at a paper speed of 25 mm/sec (SCM280, Fukuda Denshi). The QT interval was measured from the beginning of the QRS complex to the end of the T wave in sinus beats with a stable isoelectric line. The point at which the tangent drawn to the steepest portion of the falling T wave intersected the isoelectric line was defined as the end of the T wave.12) Six consecutive RR and QT intervals from each tracing were averaged.

The QT intervals at heart rates of 60, 70, 80, 90, and 100 beats per minute (bpm) were calculated by fitting the raw data into the formula \( QT = A + Bx (RR)^{1/2} \), where A and B are the regression parameters.13,14) *Power spectral analysis of HRV:* After the recordings were scanned by computer (SCM280, Fukuda Denshi), digitized RR intervals were transferred to a personal computer using commercially available Holter data-process-
ing software (Version 1.033, Fukuda Denshi). Consecutive series of RR intervals obtained during the day were subjected to a "coarse-graining" spectral analysis\(^{15}\) which allows elimination of the \(1/f\) component\(^{16,17}\) from the HRV autopower spectra while leaving the harmonic component intact.

In principle, a 5-min interval was cut out to represent each 10 minutes of data. A series of RR intervals with poor signal quality were excluded from the analysis. The power and frequency of each spectral component were calculated by fast Fourier transformation together with the mean RR interval.\(^{15}\) The low-frequency (LF) component (0.04-0.15 Hz: msec\(^2\)) and the high-frequency (HF) component (0.15-0.5 Hz: msec\(^2\)) of the spectrum were then determined.\(^{18-21}\) Because the spectral power values were skewed towards larger values, the log value of the HF component was used in scaling parasympathetic tone. Log values of the LF / HF ratio were used in scaling the sympathetic tone.\(^{18,19,21}\) The logLF, logHF, and log [LF / HF] values at heart rates of 60, 70, 80, 90, and 100 bpm were calculated by linear regression analysis.

Analysis and statistics: In addition to the QT intervals, its rate-adaptation (rate-dependent QT shortening) was also included in the analysis. The degree of rate-dependent QT shortening was represented by the percentage change between 60 bpm and 100 bpm (\(\Delta QT = [QT\text{ interval at 100 bpm} - QT\text{ interval at 60 bpm}] / QT\text{ interval at 60 bpm} \times 100\)).

Data are expressed as the mean ± SEM. Comparisons between the three subject groups were made by one-way analysis of variance. When a significant F value was obtained, further comparison between the two groups was performed using the Bonferroni method. The significance of correlations between the HRV components and the QT interval or \(\Delta QT\) was assessed by simple linear regression analysis. A value of \(p < 0.05\) was considered significant.

RESULTS

QT interval and HRV in the three groups: The QT interval in DM patients was shorter than in normal or CAD subjects at a heart rate of 90 or 100 bpm (Figure 1). LogLF, logHF, and log [LF / HF] values over the range of heart rate from 60 to 100 bpm are compared in Figure 2. Inter-group differences in logLF were significant at heart rates of 80 bpm (\(p < 0.001\)), 90 bpm (\(p < 0.0002\)), and 100 bpm (\(p < 0.0005\)). Log [LF / HF] also showed significant inter-group variation at heart rates of 90 bpm (\(p < 0.02\)) and 100 bpm (\(p < 0.02\)). In contrast, there were no significant differences
in logHF between the three groups over the range of heart rates.

**Relationship between QT interval and HRV:** The correlation between the QT interval and logLF was seen to be significant at heart rates of 90 bpm ($r = 0.320$, $p < 0.02$) and 100 bpm ($r = 0.414$, $p < 0.005$ [Figure 3A]). Although logHF showed no apparent relationship to the QT interval over the range of heart rates, a correlation was found to exist between log [LF / HF] and the QT interval at a heart rate of 90 bpm ($r = 0.323$, $p < 0.02$) and 100 bpm ($r = 0.416$, $p < 0.002$ [Figure 4A]).

A positive relationship was found between $\Delta$QT and logLF at a heart rate of 80 bpm ($r = 0.352$, $p < 0.01$), 90 bpm ($r = 0.443$, $p < 0.001$), and 100 bpm ($r = 0.463$, $p < 0.0005$), and similarly between $\Delta$QT and log [LF / HF] (80 bpm: $r = 0.440$, $p < 0.001$, 90 bpm: $r = 0.480$, $p < 0.0005$, 100 bpm: $r = 0.459$, $p < 0.001$). LogHF did not show a significant relationship with $\Delta$QT.

**Figure 1.** QT intervals (with SEM bars) of the three groups. The QT interval was regressedively obtained from the formula QT=A+Bx(RR)^1/2. * $p < 0.005$ vs CAD, ** $p < 0.02$ vs normal and $p < 0.0005$ vs CAD.
Figure 2. A: Mean logLF with SEM bars shown. * $p < 0.005$ vs normal and $p < 0.001$ vs CAD, ** $p < 0.02$ vs normal and $p < 0.001$ vs CAD. B: Mean logHF. No significant inter-group differences were found to exist over the range of heart rates. C: Mean log[LF/HF]. * $p < 0.02$ vs CAD, ** $p < 0.05$ vs CAD.
DISCUSSION

The major findings of the present study are as follows: 1) QT intervals at a heart rate of 90 and 100 bpm were correlated with logLF and log [LF / HF] values, 2) a significant relationship was also found between ΔQT and logLF values and between ΔQT and log [LF / HF] values at heart rates of 80,
90, and 100 bpm, 3) logHF values showed no relationship with the QT interval or ∆QT.

**Earlier studies associated with autonomic regulation of the QT interval:** Although a number of earlier studies using autonomic agonists and antagonists have suggested predominant parasympathetic modulation of the QT interval, others have emphasized the sympathetic regulation of this interval.

Browne, et al. reported a shortening of the corrected QT interval during treatment with propranolol. Viitasalo, et al. found that orally administered atenolol reduced the QT interval at a heart rate of 60 bpm but prolonged it at a heart rate of 90 bpm or higher. Conflicting reports also exist where, with heart rate kept constant by atrial pacing, isoproterenol infusion reduced QT interval in one report, but in another report, isoproterenol showed a marked prolongation of the QT interval even if the heart rate is taken into consideration. Consequently, the difference in sympathovagal regulation between the sinus node and ventricular repolarization, variation in the parasympathetic modification of the sympathetic tone at different heart rates, and the rate-dependent feature of the QT interval contribute to the difficulties in defining the autonomic background of the prolonged QT interval.

**Interpretation of the present results:** The relationship between heart rate and LogHF was distinct with negligible inter-group differences (Figure 2B). This observation was consistent with the view that the sinus node is regulated predominantly by parasympathetic activity when the triggering rate is relatively low. In contrast, logLF and log [LF / HF] at 90 and 100 bpm were not uniform between the three groups (Figure 2A,C), suggesting considerable diversity in sympathetic activity.

The QT interval at relatively slower heart rates (60 bpm and 70 bpm) failed to show a distinct association with HRV components. Low-toned sympathetic activity and the lack of a primary effect from parasympathetic activity on the duration of ventricular action potential may explain this observation. Alternatively, small inter-individual variation of both autonomic components at this range of heart rate may be another explanation. In contrast, a significant relationship between the QT interval and logLF or log [LF / HF] suggests that a relatively longer QT interval at 90 or 100 bpm may imply enhanced sympathetic tone. A pronounced correlation between ∆QT and logLF or log [LF / HF] indicated that an enhanced sympathetic tone was also linked to a diminished rate-dependent shortening of the QT interval.

**Discussion of the methods and limitations:** Extrapolation of the results was restricted by the limitations inherent to HRV analysis. An earlier study
warranted the dissociation between HRV analysis and cardiac norepinephrine spillover.24) The proportion and density of sympathovagal innervation vary between the sinus node and ventricles should be taken into consideration.22) The electrochemical coupling, receptor functions, postsynaptic signal transduction, or neural reflex of diseased hearts may also differ from those of normal hearts.24) In spite of these limitations, we found a probable linkage between the QT interval and the sympathetic tone. Because HRV and the QT interval are essentially independent parameters, except for their dependency on autonomic nerve activity, the present result conversely supports the quantitative significance of both the QT interval and HRV relative to individual variation of the autonomic state.

CONCLUSIONS

In the absence of electrolyte abnormalities, treatment with antiarhythmic agents, or any other factors that affect the duration of ventricular action potential, the QT interval measured at moderate heart rates and the degree of rate-dependent QT shortening are markers of sympathetic tone. The present observation may offer an insight into why the QT interval has a prognostic significance.

REFERENCES