Seasonal Variability of QT Dispersion in Healthy Young Males

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Background: There are few data related to the seasonal influences on the QT dispersion.

Methods: We analyzed the effects of seasons on QT dispersion in a large group of healthy young males. We studied the seasonal variability of QT dispersion in 523 healthy male subjects aged 22 ± 4 years (ranging from 20 to 26). Four seasonal 12-lead resting electrocardiograms (ECGs) recorded at double amplitude were performed at 25 mm/s at intervals of 3 months. Subsequent ECGs were recorded within 1 hour of the reference winter recording. QT dispersion was defined as the difference between the longest and the shortest mean QT intervals.

Results: There was a significant seasonal variation in QT dispersion ($P = 0.001$), with the largest QT dispersion in winter (71 ± 18 ms) and the smallest one in spring (43 ± 19).

Conclusion: There exists a significant seasonal variation in QT dispersion of healthy subjects and such variability should be taken into consideration in the evaluation process of QT dispersion.

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QT interval; QT dispersion; seasonal variation

The prolongation of rate-corrected QT interval with or without drug therapy is considered to be a risk factor for development of malignant ventricular arrhythmias or even sudden cardiac death.^{1–3} QT dispersion (QTd), which is defined as the time interval between the maximum and minimum QT duration, was proposed as an index for the spatial dispersion of ventricular recovery times.⁴ It was proposed that the different ECG leads magnify the ECG signal of different myocardial regions and that, consequently, QTd can be a measure of the heterogeneity of myocardial repolarization. However, QT interval is a dynamic process and recent studies have shown a high degree of daily spontaneous variation in QT, QTc, and QTd.^{5–8}

Not only the time of the day but also seasons might affect QTd.⁹ In this study, we measured the seasonal variability of QTd in a relatively large group of healthy young males.

MATERIALS AND METHODS

Patient Population

The study included 523 healthy volunteers, aged 22 ± 4 years (range 20–26) in military services. History, physical examination, 12-lead ECG, and chest X ray did not reveal any acute or chronic disorder. They were all in sinus rhythm during the period of follow-up. Subjects using drugs, known to affect QT interval, taking alcohol, and smokers were not included.

QT Dispersion Measurements in 12-Lead Resting ECGs

All subjects underwent four seasonal 12-lead resting ECG recordings at intervals of roughly 3 months, between January 2000 and October 2001. Standard 12-lead ECGs were taken using a recorder

(Hewlett Packard, Pagewriter XLi, USA) set at a paper speed of 25 mm/s and an amplitude of 0.5 V/cm, which is double the usual amplitude. The winter ECG was recorded in January (with average temperature of 4 °C), the spring ECG in April (with average temperature of 21 °C), the summer ECG in July (with average temperature of 28 °C), and the fall ECG in October (with average temperature of 15 °C). Because all subjects included in the study were soldiers (military persons), they had to be woken up at 6.30 am. All subjects were asked to refrain from military training during the day of ECG recording and were allowed to rest in sitting position for 20 minutes before ECG. For standardization, ECGs were taken between 10 and 11 am with an interval of 3.5 to 4.5 hours between waking up and recording ECG. To avoid possible circadian variation of QTd, ECGs were recorded within 1 hour of the reference winter recording.⁷

All the measurements of QTd were made blindly by two medically qualified observers. The average values of QT interval and QT dispersion obtained by the two investigators were used for comparison between seasons. QT intervals were measured from the onset of QRS complex to the point of return of the T wave to the isoelectric line. In the presence of the U wave, the QT interval was measured to the nadir between T and U waves. If the end of the T wave in one lead could not be reliably determined, measurements of the QT interval were not made, and these leads were excluded from the analysis in all seasonal ECGs of that subject. A minimum of nine leads was required for the QT interval. In each recording, the intervals of three consecutive complexes in each measurable lead was calculated to get the mean value. QTd was defined as the difference between the maximum and minimum values of the QT interval in any of the 12-lead ECGs in which it could have been measured. We also calculated heart-rate-corrected QT interval and QTd by using Bazett's formula (QT interval in milliseconds divided by the square root of RR interval in seconds).

Blinded inter- and intraobserver reproducibility of QT and QTd measurement were evaluated, and comparison revealed a Spearman's correlation coefficient of 0.93 and 0.94 for QT measurement and 0.91 and 0.92 for QTd duration, respectively ($P < 0.001$). The average absolute values of intraobserver and interobserver variability of QT dispersion measurements were 8 and 11 ms, respectively.

Statistical Analysis

All data are expressed as mean $\pm$ SD. The SPSS for Windows was used for statistical analysis. The seasonal differences of the ECG recording time were analyzed by one-sample *t*-test with the test value being set at zero. Comparisons of the QTd between seasons were made by one-way repeated measures ANOVA. The paired-sample *t*-test was applied to test the significance of the differences between paired measurements. A value of $P < 0.05$ was considered statistically significant.

RESULTS

In this study, there was no interseasonal differences in the ECG recording time ($P > 0.05$). Electrocardiographic variables are shown in Table 1. There was a significant seasonal variability in the QTd values ($P < 0.001$) (Fig. 1). They were 71 ± 18 , 43 ± 19 , 50 ± 21 , and 51 ± 17 ms in winter, spring, summer, and fall, respectively. The largest QTd occurred in winter and the smallest one in spring. The seasonal differences in the QTd were significant between winter and spring ($P = 0.0001$), between winter and summer ($P = 0.001$), between winter and fall ($P = 0.001$), between spring and summer ($P = 0.03$), and between spring and fall ($P = 0.02$). There was no significant difference in QTd between summer and fall ($P = 0.87$). Also, there was no significant interseasonal difference in the heart rates ($P = 0.56$).

QT_{min} values did not show interseasonal differences ($P > 0.05$). But there was a seasonal variability in the QT_{max} values ($P < 0.001$). It was 423 ± 24 , 402 ± 18 , 411 ± 23 , and 409 ± 20 ms in winter, spring, summer, and fall, respectively. The seasonal differences in the QT_{max} were significant between winter and spring ($P = 0.01$), between winter and summer ($P = 0.03$), between winter and fall ($P = 0.02$), between spring and summer ($P = 0.004$), and between spring and fall ($P = 0.02$). There was no significant difference in QT_{max} between summer and fall ($P = 0.65$).

DISCUSSION

The major findings of this study are: (1) QTd was found to be maximum in winter and minimum in spring; (2) there was significant interseasonal variability in the QTd and QT_{max} values

Table 1. Electrocardiographic Variables

	Winter	Spring	Summer	Fall
RR interval (ms)	826 ± 99	824 ± 101	825 ± 103	828 ± 98
Mean QT interval (ms)	386 ± 18	382 ± 21	383 ± 19	382 ± 17
QT maximum (ms) ^a	423 ± 24	402 ± 18	411 ± 23	409 ± 20
QT minimum (ms)	354 ± 22	357 ± 20	358 ± 21	356 ± 18
Corrected QT maximum (ms) ^b	464 ± 14	443 ± 16	451 ± 17	450 ± 21
Corrected QT minimum (ms)	389 ± 21	393 ± 24	394 ± 22	391 ± 19
QT dispersion (ms) ^c	71 ± 18	43 ± 19	50 ± 21	51 ± 17
Corrected QT dispersion (ms) ^d	78 ± 16	49 ± 17	55 ± 18	57 ± 14

^a Winter versus spring, $P = 0.01$; winter versus summer, $P = 0.03$; winter versus fall, $P = 0.02$; spring versus summer, $P = 0.04$; spring versus fall, $P = 0.02$; summer versus fall, $P = 0.65$.

^b Winter versus spring, $P = 0.004$; winter versus summer, $P = 0.01$; winter versus fall, $P = 0.02$; spring versus summer, $P = 0.03$; spring versus fall, $P = 0.02$; summer versus fall, $P = 0.82$.

^c Winter versus spring, $P = 0.0001$; winter versus summer, $P = 0.001$; winter versus fall, $P = 0.001$; spring versus summer, $P = 0.003$; spring versus fall, $P = 0.04$; summer versus fall, $P = 0.87$.

^d Winter versus spring, $P = 0.001$; winter versus summer, $P = 0.003$; winter versus fall, $P = 0.02$; spring versus summer, $P = 0.03$; spring versus fall, $P = 0.01$; summer versus fall, $P = 0.61$.

between winter and spring, between winter and summer, between winter and fall, between spring and summer and between spring and fall; and (3) the $QT_{\min}$ values did not show significant variation.

The QTd seemed to reflect the seasonal changes in $QT_{\max}$ values whereas the $QT_{\min}$ values did not change significantly. This is the first study showing that significant changes in QTd are due to the significant seasonal variation in $QT_{\max}$.

QT Dispersion in Normal Subjects and in the General Population

Literature reviews found that the QTd in normal subjects varies mostly between 30 and 60 ms,^{9,10} although average values around 70 ms were also reported. In a total of 8455 healthy sub-

jects of various ages, mean QTd was found to range from 10.5 ± 10.0 ms¹¹ to 71 ± 7 ms.¹² However, most researchers reported a wide overlap of values between normal individuals and different patient groups and this precludes definition of an upper limit of normal in healthy subjects. In our study, the QTd in winter ranged from 53 ms to 88 ms (71 ± 18), which was the season with the maximum QTd.

Compared with healthy controls, increased QTd has been reported in left ventricular hypertrophy,^{12–15} heart failure, and left ventricular dysfunction of various etiologies,^{16,17} hypertension irrespective of the presence or absence of hypertrophy,¹⁸ hypertrophic cardiomyopathy,^{19–21} long QT syndrome,^{22,23} drugs,^{24,25} and many other cardiac and noncardiac disorders known to affect QTd. But our study population included only young healthy subjects without any systemic diseases and medications known to affect QTd.

All the subjects in this study were male. Regarding the effect of gender on QTd, published reports show either no statistically significant difference in QT dispersion between the genders^{26,27} or marginally greater values in men.²⁸

Age is one of the parameters that can affect QTd. Savelieva et al.²⁹ found a statistically significant difference in QTd between the age groups 17–29 years and 50–80 years with QTd values of 29.1 ± 17.8 and 21.7 ± 13.3 ms, respectively. However, in another large study, Mac Farlane et al.²⁶ found no significant age differences (QTd was 23.6 ± 7.7 ms, 24.7 ± 8.2 ms, 24.7 ± 8.5 ms, and 25.4 ± 8.5 ms in the

Figure 1. Seasonal QT dispersion values.

age groups <30, 30–40, 40–50, and >50 years, respectively). In our study, the average age of the subjects was 22 ± 4 years, ranging from 22 to 26.

Seasonal Variability and QT Dispersion

Voon et al.⁸ studied the seasonal variability of QTd in 25 healthy subjects (12 women and 13 men) aged 36 ± 5 years (range 25–46) and reported similar results with a significant seasonal variability ($P = 0.001$), with the largest QTd occurring in winter (66 ± 21 ms) and the smallest in spring (48 ± 18 ms). In our study with 523 healthy subjects, we have found similar seasonal changes but the QTd in winter was much more pronounced compared to Voon's study.

The underlying mechanism of seasonal variability of QTd is still unknown. In healthy subjects, QTd shows circadian variation with greater values at night (0–6 am) than in the daytime (10 am to 4 pm).⁷ In this study, the subsequent ECGs were recorded within 1 hour of the reference winter recording session and there was no significant interseasonal differences in the ECG recording time. Therefore, the circadian variation could not explain the seasonal variability in the QTd in this study. The circadian changes were thought to occur due to the effects of autonomic nervous system and sympathetic nervous system stimulation in the early morning hours, which induce regional changes in the dispersion of ventricular repolarization.⁷ The morning peak in QTd corresponds to the time of increased vulnerability to ventricular tachycardia and sudden cardiac death.³⁰

QTd was found to be maximum in the winter season in Voon's and our studies. Review of the studies about the effect of cold on human nervous system has shown that plasma levels and urinary excretion of norepinephrine and epinephrine increases both in experimental studies^{31–33} and in the winter season.^{34–36} A larger QTd in winter in healthy subjects may arise partially from the stimulation of sympathetic nervous system that in turn induces regional changes in dispersion of ventricular repolarization. In Voon's study, the average temperature in the winter season was 19°C , which is quite different from our average temperature (4°C) in the winter season. The difference in temperature may reflect itself with greater QTd values in our study compared to Voon's study (71 ± 18 vs 66 ± 21 ms, respectively).

Clinical Implications

In the Rotterdam study, QTd was found to be a predictor of cardiac and all causes of mortality in a general population of 5182 adults aged 55 years or older followed for a mean of 4 years.³⁷ Moreover, Okin et al. reported that increased QTd was a significant predictor of all-cause and cardiovascular mortality in American Indians.³⁸ Recently, Perkiomaki et al. showed that increased QTc dispersion predicted stroke mortality in the elderly.³⁹ There are a number of studies that have reported greater QTd in patients with sudden arrhythmic death than in a comparable group without arrhythmias in chronic heart failure,⁴⁰ hypertrophic cardiomyopathy,⁴¹ long QT syndrome,²² and coronary artery disease.⁴² Increased heterogeneity of ventricular repolarization favors the development of malignant ventricular arrhythmias,⁴³ and QT prolongation may reflect this heterogeneity. However, increased dispersion of ventricular repolarization may exist with a normal QT interval.⁴⁴ In human studies, QTd was shown to be correlated with increased dispersion of action potential duration using simultaneously recorded epicardial monophasic action potential mapping and 12-lead ECG.⁴⁵ Thus, QTd may represent the inhomogeneity better and be a more sensitive marker for high-risk patients.

In this study, we have demonstrated a significant seasonal variation of QTd with its maximum values during the winter season, which may cause vulnerability to malignant ventricular arrhythmias and sudden cardiac death. Studies examining the seasonal variation of sudden cardiac death have found more frequent events in the winter season.^{46,47}

Study Limitations

The study population included only healthy subjects and seasonal variability was not compared with a group of patients. Sometimes, the precise measurement of the QT interval is difficult because it is difficult to determine a discrete termination of the T wave. This is particularly problematic in the context of rapid heart rates, prominent U waves, and other repolarization abnormalities. Current measurement of QT dispersion involves manual measurement of the QT interval with a standard ECG recorded at 25 mm/s. There is considerable inter- and intraobserver variability reported in the manual measurement of QT dispersion. We attempted to minimize this error by having all

measurements performed by two operators using the same standardized technique.

CONCLUSION

The major result of this study is the significant seasonal variability of QT dispersion with the maximum in winter and minimum in spring. Besides circadian variation, seasonal variation of QTd should be considered in risk assessment. Our data seem to support the possible role of cold in the winter season and sympathetic nervous system activation in the generation of heterogeneous ventricular repolarization

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