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Relation of Ventricular Repolarization to Cardiac Cycle Length in Normal Subjects, Hypertrophic Cardiomyopathy, and Patients with Myocardial Infarction

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Summary

Background: Prolonged QT interval and QT dispersion have been reported to reflect an increased inhomogeneity of ventricular repolarization, which is believed to be responsible for the development of arrhythmic events in patients with long QT syndrome, coronary heart disease, and myocardial infarction, congestive heart failure, and hypertrophic cardiomyopathy (HC).

Hypothesis: This study was undertaken to determine whether an abnormal QT/RR dynamicity may reflect autonomic imbalance and may contribute to arrhythmogenesis in patients with heart disease.

Methods: The relation between QT, QT_{peak} (QT_p), T_{peak}-T_{end} (T_pT_e) intervals and cardiac cycle length was assessed in 70 normal subjects, 37 patients with HC, and 48 survivors of myocardial infarction (MI). A set of 10 consecutive electrocardiograms was evaluated automatically in each subject using QT Guard software (Marquette Medical Systems, Milwaukee, Wisc.).

Results: In patients with HC, all intervals were significantly prolonged compared with normals ($p < 0.001$ for QT and QT_p; $p < 0.04$ for T_pT_e); in survivors of MI, this was true for the maximum QT and QT_p intervals ($p < 0.05$). A strong linear correlation between QT, QT_p, and RR intervals was observed in normals and in patients with MI and HC ($r = 0.65$–0.59, 0.82–0.77, 0.79–0.74, respectively, $p < 0.0001$). T_pT_e interval only showed a weak correlation with heart rate in normals ($r = 0.24$, $p < 0.05$) and was rate-independent in both patient groups (p = NS). Compared with normals, the slopes of QT/RR and QT_p/RR regression lines were significantly steeper in patients with MI and HC (0.0990–0.0883, 0.1597–0.1551, 0.1653–0.1486, respectively). Regression lines were neither parallel nor identical between normals and patients ($T > 1.96$, $Z > 3.07$). There was no difference in steepness for T_pT_eR/RR lines between groups (0.0110, 0.0076, 0.0163, respectively). T_pT_e/QT_p ratio was similar in normals and in patients with MI and HC (0.30 ± 0.03, 0.31 ± 0.07, 0.30 ± 0.04, respectively), in the absence of any correlation between QT_p and T_pT_e intervals, suggesting disproportional prolongation of both components of QT interval.

Conclusion: Compared with normals, a progressive increase in QT and QT_p intervals at slower heart rates in patients with MI and HC may indicate an enhanced variability of the early ventricular repolarization and may be one of the mechanisms of arrhythmogenesis.

Key words: ventricular repolarization, QT interval, QT/RR dynamicity, hypertrophic cardiomyopathy, myocardial infarction

Introduction

Prolonged QT interval and QT dispersion have been reported to reflect an increased inhomogeneity of ventricular repolarization, which is believed to be responsible for the development of arrhythmic events in patients with long QT syndrome,[1,2] coronary heart disease, and myocardial infarction,[3–5] congestive heart failure,[6] and hypertrophic cardiomy-

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opathy (HC).[7,8] Nevertheless, there is yet no standardized approach to QT interval and QT dispersion assessment. Since conventional measurement of QT interval from the onset of the Q wave to the end of the T wave might be substantially affected by the known difficulty in determining the end of the T wave,[9] several attempts have been reported to substitute QT interval measurement by assessment of the interval from the onset of the Q wave to the maximum amplitude (peak) of the T wave (QT_p).[10,11] However, both approaches depend on heart rate, autonomic tone, and width of the QRS complex[11–13] that may affect reliability of measurement for monitoring purposes. The interval between the peak and the end of the T wave (T_pT_e interval), which is less affected by heart rate and autonomic tone and does not include QRS complex, has been proposed to provide more reliable evaluation of myocardial repolarization.[14–17] Unfortunately, the experience with these possibilities is currently limited.

Thus, the aim of the present study was (1) to assess the ability of QT, QT_p, and T_pT_e intervals measurement based on contemporary computerized techniques to differentiate among normal subjects, patients with HC, and survivors of myocardial infarction (MI); (2) to study the correlation of these parameters with cardiac cycle length; and (3) to investigate the usefulness of the T_pT_e/QT_p ratio to characterize abnormalities of ventricular repolarization.

Methods

Subjects

Seventy healthy volunteers (35 men, mean age 38 ± 12 years, range 13–59); 37 patients with documented HC (24 men, mean age 39 ± 14 years, range 14–64); and 48 survivors of acute MI (37 men, mean age 65 ± 12, range 35–87) constituted the study population. None of the healthy subjects presented with a history of cardiovascular disease and all had normal physical examination and electrocardiograms (ECG). Idiopathic HC was diagnosed according to World Health Organization criteria.[18] In all patients, two-dimensional echocardiography showed left ventricular wall hypertrophy ≥ 15 mm in the absence of any cardiac or systemic cause. The diagnosis of MI was based on the presence of typical chest pain lasting 30 min without relief by nitrates and/or ST segment elevation in the 12-lead ECG of 0.1 mV in two of the concordant limb leads or 0.2 mV in two of the precordial leads, and at least 1.5-fold increase in creatine phosphokinase. Q-wave MI was diagnosed in 31 (65%) patients; 22 patients had anterior MI, 26 patients had inferior MI. Patients with MI were not age matched to normal subjects and patients with HC ($p < 0.01$), whereas no difference in age was observed between normal subjects and patients with HC. At the time of the recording, 25 patients with MI and 4 patients with HC received beta-blocking therapy; 3 patients with HC were receiving amiodarone. No subject received other antiarrhythmic agents or other drugs that were likely to influence cardiac repolarization.

Electrocardiogram Recordings and QT Interval Measurement

All subjects were in sinus rhythm during ECG recordings. For QT analysis in the HC group, ECGs were recorded on the day of the first visit of patients for routine examination. In patients with MI, ECG recordings made on the Day 5 after the onset of symptoms were analyzed. In each subject, 10 consecutive ECG recordings were obtained in supine position using a MAC-VU electrocardiograph (Marquette Medical Systems, Milwaukee, Wisc.). Automatic measurements were performed using a research version of the QT Guard software package (Marquette Medical Systems). Algorithm of computerized QT interval measurement was described elsewhere.[19] Briefly, a least-square curve fitting method was applied to locate the end of the T wave, which was detected at the intersection of the least-square-fit line around the tangent to the downslope of the T wave with isoelectric baseline. For determination of the peak of the T wave, a regional centering method was applied. The T_pT_e interval was calculated as the difference between the QT and QT_p intervals. To avoid operator bias, the automatic measurements were not manually modified. A technical default feature of the QT Guard package excludes measurement of QT interval in lead V_1 based on a high incidence of the flat T waves which may affect accuracy of the T_p and T_e detection; although this feature can be switched off, it was applied to the data of this study.

Statistical Analysis

In each subject, the QT, QT_p, and T_pT_e intervals were computed in each ECG lead. The mean, minimum, and maximum values of QT, QT_p and T_pT_e intervals were determined in each of the 10 consecutive ECG recordings and subsequently averaged to obtain "representative" values for each subject. In a similar way, the mean, minimum, and maximum T_pT_e/QT_p ratio was obtained for each subject. Data are presented as mean ± standard deviation. Continuous variables derived from the individual recordings were compared using unpaired Student's *t*-test. Regression lines were constructed and the values of slopes were calculated for presenting data on correlation between QT intervals and RR interval according to equation: $[QT] = a \times [RR] + b$, where a is a slope and b is an intercept. Individual regression lines among groups were compared by the test of parallelism and identity using criteria $T < 1.96$ and $Z < 3.15$, respectively. A p value of < 0.05 was considered to be statistically significant.

Results

QT, QT_p, and T_pT_e Intervals

No difference was observed in mean RR interval among normal subjects, patients with HC, and patients with MI (911 ± 133, 937 ± 171, and 874 ± 176 ms, respectively; p = NS).

TABLE I QT, QT_{peak}, and T_{peak}-T_{end} intervals in normal subjects and patients with hypertrophic cardiomyopathy and myocardial infarction

Parameter (mean ± SD)	Normal subjects	HC patients	MI patients
QT maximum (ms)	384 ± 21	431 ± 41[a]	404 ± 40[c]
QT minimum (ms)	364 ± 23	391 ± 39[a]	368 ± 41
QT mean (ms)	378 ± 20	421 ± 35[a]	390 ± 40
QT_p maximum (ms)	304 ± 20	340 ± 40[a]	317 ± 40[c]
QT_p minimum (ms)	271 ± 22	296 ± 39[a]	274 ± 40
QT_p mean (ms)	290 ± 20	323 ± 33[a]	296 ± 39
T_pT_e maximum (ms)	103 ± 8	111 ± 16[a]	102 ± 13
T_pT_e minimum (ms)	74 ± 8	79 ± 12[b]	76 ± 9
T_pT_e mean (ms)	88 ± 6	96 ± 10[a]	90 ± 10
T_pT_e/QT_p maximum	0.38 ± 0.05	0.37 ± 0.07	0.37 ± 0.07
T_pT_e/QT_p minimum	0.25 ± 0.03	0.24 ± 0.04	0.25 ± 0.04
T_pT_e/QT_p mean	0.30 ± 0.03	0.30 ± 0.04	0.31 ± 0.05

[a] = $p < 0.001$.
[b] = $p < 0.04$ with HC and MI patients.
[c] $p < 0.05$ with normal subjects.
Abbreviations: HC = hypertrophic cardiomyopathy, MI = myocardial infarction, QT = interval between the Q wave onset and the end of the T wave, QT_p = interval between the Q wave onset and the peak of the T wave, T_pT_e = interval between the peak and the end of the T wave, T_pT_e/QT_p = ratio between T_{peak}-T_{end} and QT_{peak} intervals.

Table I shows the absolute values of QT, QT_p, and T_pT_e intervals in the three groups. In patients with HC, the mean, minimum, and maximum QT, QT_p, and T_pT_e intervals were significantly longer than in normal subjects ($p < 0.001$ for QT and QT_p and < 0.04 for T_pT_e intervals). Although all intervals were prolonged in patients with MI compared with normal subjects, a significant difference between both groups was only observed for the maximum QT and QT_p intervals ($p < 0.05$). In patients with HC, QT, QT_p, and T_pT_e intervals were also significantly longer than in patients with MI ($p < 0.01$).

T_pT_e/QT_p Ratio and Correlation between T_pT_e and QT_p Intervals

The T_pT_e/QT_p ratio was similar in normal subjects and in patients with HC and MI (0.30 ± 0.03, 0.30 ± 0.04 and 0.31 ± 0.07, respectively). No difference was observed in the T_pT_e/QT_p ratio among normal subjects and patient groups in most individual leads. There was no association between QT_p and T_pT_e intervals in all groups.

Correlation between QT, QT_p, T_pT_e, and RR Intervals

Figure 1 presents correlation between the mean values of QT, QT_p, T_pT_e intervals and RR interval in normal subjects and in patients with HC and MI. In all subjects, a strong linear correlation between QT and RR intervals (coefficient of correlation r = 0.65–0.82) and QT_p and RR intervals (r = 0.59–0.77) was observed ($p < 0.0001$). T_pT_e interval showed only a weak association with heart rate in normal subjects (r = 0.24, $p < 0.05$). In both patient groups, T_pT_e interval was rate-independent (p = NS).

The slopes of regression between the mean, minimum and maximum QT, QT_p, T_pT_e intervals and RR interval in normal subjects and in patients with HC and MI are listed in Table II. Compared with normal subjects, both patient groups had significantly steeper slopes for QT/RR and QT_p/RR ($p < 0.05$).

The values of criteria of parallelism and identity of regression curves are shown in Table III. In patients with HC and MI the regression lines for the mean and maximum QT/RR and QT_p/RR were parallel but did not overlap. No difference was observed among normal subjects and patient groups in steepness of T_pT_e/RR slopes. The regression lines for T_pT_e/RR were parallel in all the three groups and identical in normal subjects and patients with MI.

Discussion

In our study we used modern computerized methods to assess QT interval and its components in normal subjects and cardiac patients. Previously, we showed that the automatic algorithm used in the QT Guard software package provided more stable and reproducible QT interval measurement compared with traditional manual methods in both the normal subjects and patients with HC.[20] Acceptable reliability and agreement of automatic QT interval assessment with manual measurement have been shown in patients with long QT syndrome[10] and patients post MI.[21]

QT, QT_p, T_pT_e Intervals in Normal Subjects and Cardiac Patients

In normal subjects, the mean values of QT, QT_p, and T_pT_e intervals observed in our study are similar to those reported previously.[14, 15] Like other investigators,[7, 22] we noted significantly higher values of all intervals in patients with HC. In patients with MI, only the maximum values of QT interval differed significantly from those in normal subjects, which agrees with previous results observed in survivors of MI.[5, 23] A significant prolongation of T_pT_e interval was previously found only in patients with MI who died suddenly, compared with those who had a favorable outcome.[17] In patients with HC, all intervals were significantly prolonged compared with patients with MI. One possible explanation for this discrepancy is that patients with HC are likely to have more extensive myocardial involvement than patients with MI, thus providing more pronounced repolarization abnormalities.

T_pT_e/QT_p Ratio

Previously, computation of ratio between QT interval and its parts or rate-corrected QT interval has been used to differ-

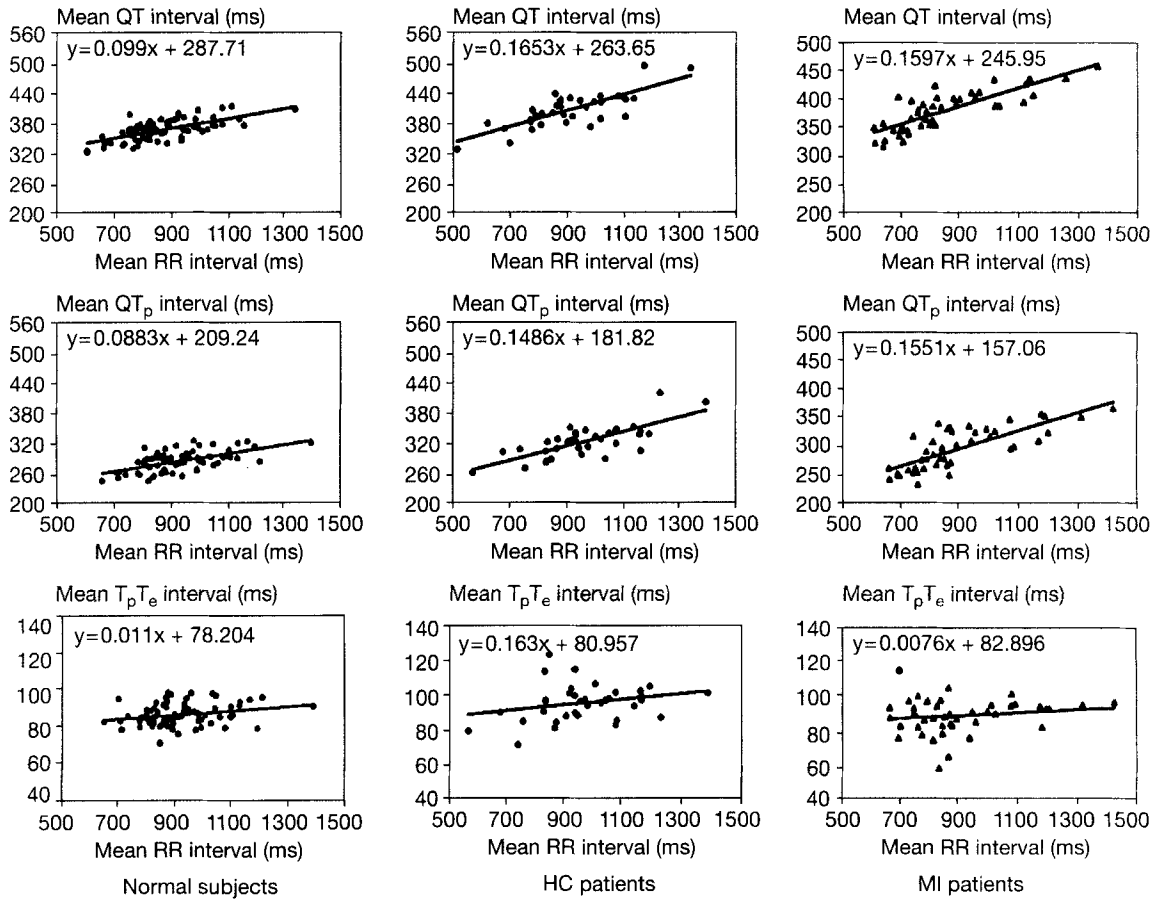

FIG. 1 Regression lines for QT/RR, QT_p/RR, and T_pT_e/RR in normal subjects and in patients with hypertrophic cardiomyopathy (HC) and myocardial infarction (MI). The steepness of the lines is significantly higher in both patient groups than in normal subjects. Abbreviations as in Table I.

entiate patients with heart disease,[14, 15, 24] but results appeared to be inconsistent. We compared the T_pT_e/QT_p ratio in normal subjects and in patients with HC and MI and found it similar in all groups. However, we observed no correlation between QT_p and T_pT_e interval in any of the three groups, suggesting disproportional prolongation of both components of QT interval. The consistency of T_pT_e/QT_p ratio in the absence of correlation between QT_p and T_pT_e intervals may be associated with specific shapes of the T wave in the three groups.

Correlation between QT, QT_p, T_pT_e Intervals and Cardiac Cycle Length

A significant association between QT and QT_p and cardiac cycle length was observed in all three groups, with higher correlation in patients groups than in normal subjects. A strong linear correlation between QT and QT_p and RR interval was found by other investigators.[10, 17, 25–27] T_pT_e interval showed only a weak association with heart rate in normal subjects and

TABLE II The slopes of regression between the mean, minimum, and maximum QT, QT_{peak}, T_{peak}-T_{end} intervals and RR interval in normal subjects and patients with hypertrophic cardiomyopathy and myocardial infarction

	Normal subjects			HC patients			MI patients		
	QT/RR	QT_p/RR	T_pT_e/RR	QT/RR	QT_p/RR	T_pT_e/RR	QT/RR	QT_p/RR	T_pT_e/RR
Mean	0.0990	0.0883	0.0110	0.1653	0.1486	0.0163	0.1597	0.1551	0.0076
Minimum	0.0931	0.0784	0.0155	0.1563	0.1512	0.0103	0.1414	0.1369	0.0008
Maximum	0.0998	0.0851	0.0057	0.1740	0.1561	0.0161	0.1541	0.1538	0.0243

Abbreviations as in Table I.

TABLE III Comparison of parallelism and identity of the mean and maximum slopes of QT/RR, QT_p/RR, and T_pT_e/RR regression lines in normal subjects and in patients with hypertrophic cardiomyopathy and myocardial infarction

	T	Z
Normal subjects vs. HC patients		
QT mean	2.682	53.788
QT maximum	3.076	88.099
QT_p mean	2.377	30.546
QT_p maximum	2.602	39.432
T_pT_e mean	0.514	12.086
T_pT_e maximum	0.690	6.575
Normal subjects vs. MI patients		
QT mean	3.073	12.722
QT maximum	2.565	20.659
QT_p mean	2.832	6.483
QT_p maximum	2.967	10.834
T_pT_e mean	0.245	0.907
T_pT_e maximum	1.481	1.214
HC patients vs. MI patients		
QT mean	0.206	11.767
QT maximum	0.712	13.014
QT_p mean	0.045	6.890
QT_p maximum	0.178	6.639
T_pT_e mean	0.261	3.296
T_pT_e maximum	0.367	3.859

The criteria for parallelism and identity of regression lines are $T < 1.96$ and $Z < 3.15$, respectively. Abbreviations as in Table I.

was rate-independent in patients with HC and MI. These data are in agreement with the results of previous studies[10, 14, 15] that showed relative constancy of T_pT_e interval at different heart rates during exercise in normal subjects, whereas significant changes in QT and QT_p interval duration were observed at higher heart rates. It may be suggested that prolongation of QT interval at slow heart rate is mainly due to prolongation of QT_p interval rather than changes in the terminal part of the T wave. Rate correction is necessary for QT_p interval when it is used for assessment of repolarization abnormalities.

In our study, QT/RR and QT_p/RR slopes were significantly steeper in both patient groups than in normal subjects. Our results are comparable with previous observations made in patients with long QT syndrome,[26] coronary artery disease, MI,[27, 28] and HC.[29] No difference was observed in steepness of regression curves for T_pT_e/RR between the three groups, which confirmed the dominant role of QT_p interval changes in QT interval variability. Such a rapid and enhanced response of QT interval duration to heart rate changes may indicate pronounced inhomogeneity of ventricular repolarization in cardiac patients. It has been proposed that a progressive increase in ventricular repolarization at slower heart rates may be associated with a higher risk of arrhythmogenesis.[10, 30] Autonomic imbalance may augment vulnerability to ventricular arrhythmias. Absence of identity of regression lines in patients with HC and MI specifies rate-dependent changes in myocardial repolarization with regard to underlying heart disease. Thus, evaluation of the relationship between QT interval and cardiac cycle length may provide additional information on myocardial repolarization abnormalities.

Practical Implication

The present study showed a strong correlation between QT and QT_p and RR intervals in normal subjects and patients with HC and MI, whereas T_pT_e interval was rate-independent, indicating that prolongation of QT interval at slow heart rate was mainly due to an increase in QT_p interval rather than changes in the terminal part of the T wave. Like QT interval, QT_p interval should be corrected for heart rate when used for assessment of ventricular repolarization. Similar T_pT_e/QT_p ratio in the absence of correlation between QT_p and T_pT_e interval in all subjects confirms disproportional prolongation of both components of QT interval. An increased steepness of QT/RR and QT_p/RR slopes in both patient groups compared with normal subjects may reflect an enhanced variability of QT interval duration in response to heart rate changes, which may contribute to arrhythmogenesis in patients with heart disease. Absence of identity even of parallel regression lines in all groups indicates specific responses of QT, QT_p, and T_pT_e intervals to cycle length changes in different groups. Moreover, the difference in steepness of the slopes seems potentially to be more pronounced in patients with unfavorable prognosis, which warrants further investigation. The present study purports that data on QT interval dynamicity available in one clinical setting cannot be applied directly to others. The pattern of QT interval variability may have more clinical potential than QT interval itself.

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