Correction for Heart Rate Is Not Necessary for QT Dispersion in Individuals without Structural Heart Disease and Patients with Ventricular Tachycardia

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Background: It remains controversial whether QT dispersion should be corrected for heart rate, especially when the limitations of rate correction formulae are considered. We investigated whether incremental atrial pacing affects QT dispersion and the rate-corrected values according to Bazett's formula in individuals without structural heart disease and in patients with history of sustained ventricular tachycardia.

Methods: We studied 32 individuals without structural heart disease (group A), and 16 patients with a history of sustained ventricular tachycardia (group B). QT dispersion and corrected for heart rate QT dispersion using Bazett's formula (QTc dispersion) were calculated in sinus rhythm, and during continuous right atrial pacing for one minute at 100 and 120 beats/min.

Results: Interobserver variability was not significant ($P \geq 0.10$). QT dispersion did not differ at rest between groups A and B and did not change significantly from baseline at any heart rate in both groups. However, QTc dispersion increased significantly with atrial pacing in a similar manner in group A and group B (42 ± 19 ms at rest vs 53 ± 23 ms at 120 beats/min, $P < 0.001$ for group A, 39 ± 16 ms at rest vs 60 ± 19 ms at 120 beats/min, $P < 0.001$ for group B).

Conclusions: We conclude that QT dispersion remains unchanged during atrial pacing at heart rates up to 120 beats/min in both individuals without structural heart disease and in patients with a history of sustained ventricular tachycardia. Correction by Bazett's formula results in prolongation of QTc dispersion, yielding values which may be misleading.

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QT dispersion; atrial pacing; ventricular tachycardia; Bazett's formula

QT interval dispersion (QTD) is a noninvasive index of arrhythmogenicity, considered to reflect the inhomogeneity of refractoriness of the ventricular myocardium. It has been shown to be predictive of ventricular arrhythmias in patients with various arrhythmogenic substrates such as long QT syndrome,¹ ischemic heart disease,² myocardial hypertrophy,^{3,4} or dilated cardiomyopathy.⁵ QTD can be easily calculated from the surface 12-lead

ECG by subtracting the minimum from the maximum QT interval.

In most published studies QTD is corrected for heart rate (QTcD). This value is calculated by subtracting the minimum QT interval corrected for heart rate (QTc min) from the maximum corrected for heart rate QT interval (QTc max). Bazett's formula⁶ is almost always used for the correction of the QT interval, since it is simple to calculate.

Table 1. Characteristics of Normal Individuals (Group A) and Patients with a History of Sustained Ventricular Tachycardia (Group B)

	Group A	Group B	P Value
Patients	32	16	NS
Age (years $\pm$ SD)	38.7 $\pm$ 13.5	53 $\pm$ 14.6	NS
Male	24	14	NS
RR interval (ms $\pm$ SD)	832 $\pm$ 180	842 $\pm$ 127	NS
LVEF (mean $\pm$ SD)	52 $\pm$ 3	48 $\pm$ 14	NS

LVEF = left ventricular ejection fraction; SD = standard deviation.

From previous studies it is clear that Bazett's formula is subject to many limitations and other formulae have been proposed for this purpose,⁷ but their clinical use is restricted because of their calculation complexity. The error for correction of heart rate is minimal for rates between 50 and 80 beats/min,⁸ but above these limits, QTc values may appear abnormally prolonged, leading to wrong conclusions, especially during dynamic conditions where heart rate is expected to rise.

There is no consensus of whether QTD should be corrected for heart rate, especially when the limitations of rate correction are considered. In this study we investigated whether incremental programmed heart rate changes affect QTD and its rate-corrected values in individuals without structural heart disease and in patients with a history of sustained ventricular tachycardia.

STUDY POPULATION

We prospectively studied 48 patients, including 32 individuals without structural heart disease (age 38.7 $\pm$ 13.5 years, range 10-67, 24 male, group A), who underwent electrophysiologic study for evaluation of supraventricular tachycardias or syncope, and 16 patients with a history of sustained ventricular tachycardia (VT), (age 53 $\pm$ 14.6 years, range 20-76, 14 male, group B) evaluated for risk stratification of ventricular tachycardia with electrophysiological study. Patient characteristics are summarized in Table 1. All patients in group A had a normal resting 12-lead ECG, and patients with conduction abnormalities were excluded in group B. No patient was receiving antiarrhythmic drugs at the time of the study for a period of at least five drug half-lives. All patients in group A had a nor-

mal left ventricular ejection fraction and the mean ejection fraction in group B was 48 $\pm$ 14% (range 25-60%). Nine group B patients had a history of coronary artery disease and previous myocardial infarction, three had a history of cardiomyopathy, and four had no structural heart disease. Patients with coronary artery disease did not have any evidence of active ischemia by thallium exercise scintigraphy.

STUDY DESIGN

All patients had agreed to participate in the study by signing an informed written consent form. A 6 Fr quadripolar electrode (Josephson curve, CR Bard Electrophysiology, Billerica, MA, USA) was inserted percutaneously through the right femoral vein and was placed at the right atrium in order to sense and pace the atrium. Constant atrial pacing was performed for 1 minute at 100 and 120 beats/min with a pacing output at twice the diastolic threshold. There was a 5-minute resting period between pacing sequences. A surface 12-lead ECG was recorded simultaneously at 50 mm/sec paper speed using the Bard EP System.

QT AND QTD MEASUREMENT

The QT intervals were measured manually with a custom-made computer software after the 12-lead ECG was digitized with the AVEC E3 color scanner by two different observers. QT intervals were measured from the onset of QRS complex to the end of the T wave. The end of the T wave was defined as the point of return to the isoelectric line. When a U wave was present, the QT interval was measured to the nadir of the curve between the T and U wave.⁹ The measurements were carried out from the last three consecutive beats prior to the termination of pacing.

The QTD was defined as the difference between the maximum and minimum QT intervals, respectively, on the simultaneously recorded 12-lead ECG. QT interval was corrected for heart rate using Bazett's formula $QTc = QT/\sqrt{(R-R)}$ for all leads. Subsequently, QTcD was calculated as the difference between the maximum and minimum QTc. We elected to test the Bazett's formula because it is the most well known and widely used. The mean QT interval (QTM) was defined as the ratio of the summation of the QT intervals to the number of the ECG leads used for measurement.

Table 2. Interobserver Variability for QTD, QTcD for Groups A and B

	Sinus Rhythm		100 beats/min		120 beats/min	
	QTD	QTcD	QTD	QTcD	QTD	QTcD
Group A	0.8 ± 7.8	0.9 ± 8.9	0.5 ± 6.6	0.6 ± 8.5	1.8 ± 5.3	3.2 ± 9.2
Group B	2.6 ± 5.9	2.9 ± 6.7	0.3 ± 6.1	0.4 ± 8	1 ± 7.9	1.4 ± 11.4

Numbers refer to the absolute mean value of the measurement errors.
All values are expressed in ms ± SD.

ECGs where the T wave end was difficult to determine in more than two leads, and therefore the QT interval was impossible to measure, were excluded from the study.

Intervals including QTD, QTcD, and QTM were calculated in sinus rhythm at basal conditions and during continuous right atrial pacing for one minute at 100 and 120 beats/min.

STATISTICAL ANALYSIS

All variables are expressed as mean ± standard deviation (SD), unless otherwise indicated. Repeated measures analysis of variance was used to assess differences in QTD and QTcD (at baseline, paced 100 beats/min and 120 beats/min). Also the influence of the patient group (normals vs VT patients) in the changes of QTD and QTcD was tested with repeated measures analysis of variance with between factor the patient group. Interobserver variability was tested with the paired *t*-test. A *P* value < 0.05 was considered statistically significant. The SPSS version 10.0 for Windows, (Chicago, IL, USA) statistical package was used for analysis.

RESULTS

Patient Characteristics

Patient characteristics are provided in Table 1. The group of patients with VT due to coronary

artery disease tended to be older than the no VT group, but this was not statistically significant.

Interobserver Variability

The difference in measurements between the two observers for QTD and QTcD using the paired *t*-test was not significant for both groups, Table 2.

QT Measurements

By means of repeated measures QTD at baseline, paced at 100 beats/min and 120 beats/min did not differ, Table 3. The patient group (normal vs VT group) did not influence the values of QTD.

In contrast the QTcD measurements demonstrate a progressive prolongation of the values (*P* < 0.001) with the increasing pacing rate, Table 4. The patient group also did not influence the values of QTD.

As expected, QTM was shortened gradually in both groups with atrial pacing (*P* < 0.001). The patient group did not influence the values of QTM, Table 5.

DISCUSSION

Our study demonstrated that QTD is not influenced by heart rate and that correction for rates faster than 100 beats/min may result in pathologic values in both normal individuals and patients

Table 3. QTD Changes in Normal Individuals (Group A) and in Patients with Sustained Ventricular Tachycardia (Group B) during Atrial Pacing

	QT Dispersion			P Value within Subjects
	Sinus Rhythm	100 beats/min	120 beats/min	
Group A	38 ± 17	37 ± 15	37 ± 16	0.29
Group B	35 ± 14	36 ± 9	42 ± 13	0.29
P value between subjects	0.89	0.89	0.89	

All values are expressed in ms ± SD.

Table 4. QTcD Changes in Normal Individuals (Group A) and in Patients with Sustained Ventricular Tachycardia (Group B) during Atrial Pacing

Corrected QT Dispersion				
	Sinus Rhythm	100 beats/min	120 beats/min	P Value within Subjects
Group A	42 ± 19	48 ± 20	53 ± 23	<0.001
Group B	39 ± 16	47 ± 12	60 ± 19	<0.001
P value between subjects	0.88	0.88	0.88	

All values are expressed in ms ± SD.

with a history of VT. Since 1990, when QTD was proposed as a simple, noninvasive index of arrhythmogenicity in patients with organic heart disease, there has been some controversy concerning its clinical utility. In various studies it has been reported that QTD is an independent risk factor for increased mortality in elderly patients¹⁰ and increased arrhythmogenicity in patients with a history of previous myocardial infarction and ventricular tachycardia,¹¹ and long QT syndrome,^{1,12} but other investigators failed to confirm these findings.^{13, 14} One of the problems in clinical practice is the observed overlap of QTD values between individuals with and without history of ventricular arrhythmias,¹⁵ and the large margin of error in its measurement, and therefore the clinical benefit of this index remains low when applied on an individual basis.

QTD Correction for Heart Rate in Sinus Rhythm

Although QT interval is rate related and several formulae have been proposed for correction for heart rate, it is not known if QTD needs to be corrected for heart rate. Our study demonstrates that there is no difference in the original and cor-

rected for heart rate QTD values during the normal range of sinus rhythm in both normal controls and in patients with a clinical history of sustained ventricular tachycardia. This is in accordance with published series where there are no substantial differences between the original and the corrected for heart rate values.^{2, 16} This is probably because in most studies heart rate varies between 50 and 80 beats/min, the difference in correction with Bazett's formula being negligible for this range of rates.⁸ Therefore it seems from these data that heart rate correction of QTD in sinus rhythm is not necessary.

QTD Correction for Heart Rate during Atrial Pacing

The question remains if QTD should be corrected for faster heart rates, especially during loading conditions which affect heart rate. In our study QTD remained unchanged throughout the increased heart rates in both patients without structural heart disease and in patients with history of sustained ventricular tachycardia, despite the proportional decrease of QTM. On the other hand QTcD increased as a result of applying Bazett's formula for heart rate correction. The limitations of

Table 5. QTM Changes in Normal Individuals (Group A) and in Patients with Sustained Ventricular Tachycardia (Group B) during Atrial Pacing

Mean QT Interval				
	Sinus Rhythm	100 beats/min	120 beats/min	P Value within Subjects
Group A	355 ± 18	340 ± 23	324 ± 23	<0.001
Group B	374 ± 38	354 ± 30	340 ± 22	<0.001
P value between subjects	0.10	0.10	0.10	

All values are expressed in ms ± SD.

Bazett's formula, which is the most widely used formula for rate correction, should be taken into account. Over the years it has been recognized that this formula is inferior to other more complicated mathematical models of the QT/RR or QT/heart rate relationship, especially when one or both the extremes of heart rate were considered.⁸ Despite these limitations, Bazett's formula is still widely used because it is easy to calculate. In our study the increase of QTcD can be explained by looking into the mathematics of Bazett's formula. The formula is $QTcD = QT \max/\sqrt{RR} - QT \min/\sqrt{RR}$, i.e., $QTcD = QTD/\sqrt{RR}$. It is obvious that in higher heart rates (lower RR interval values in seconds) the square root of the RR interval is a smaller number, compared to lower heart rates where the value is larger. Provided that the numerator QTD does not change in heart rates up to 120 beats/min (0.5 s), as it has been proven in our study, when it is divided by a smaller number, the QTcD value is expected to increase.

In an experimental study Zabel et al.¹⁷ investigated the changes in the duration and the dispersion of the monophasic action potential recorded from multiple sites from the endocardium and epicardium of both ventricles in 18 isolated Langendorff-perfused rabbit hearts throughout the range of paced steady-state cycle lengths from 1200 - 300 ms. The duration of the action potential decreased significantly at shorter cycle lengths, but in contrast the dispersion of the action potential did not change. Assuming that the rate-dependent behavior of action potential duration is similar between the rabbit and human heart, they proposed that rate-correction of parameters of dispersion of repolarization is probably not necessary.

The same group recently confirmed these findings in humans. They studied 35 patients with a history of VT with atrial pacing and exercise testing and demonstrated that dispersion of QT interval and other ECG variables of dispersion of ventricular repolarization are independent of heart rate.¹⁸ Subramanian et al.¹⁹ compared the changes in QTD and QTcD with the changes in the monophasic action potential recorded from the right ventricular apex during atrial pacing over a wide range of cardiac cycles (750-350 ms) in 18 patients, and found that QT interval and monophasic action potential decreased proportionally as expected. QTD was not altered, but QTcD increased significantly at shorter cycle lengths, which is consistent with our findings. Sporton et al.²⁰ studied the QTD and

QTcD changes in patients with myocardial ischemia induced by continuous atrial pacing at a pacing rate up to 120 beats/min. Ischemia caused by the increase in heart rate resulted in an increase in both QTD and QTcD in patients with coronary artery disease. The absence of active ischemia in our patients in group B may explain the lack of QTD prolongation in these patients, in contrast to the coronary patients of Sporton et al.²⁰

QTD Correction for Heart Rate in Patients with Sustained Ventricular Tachycardia

Our study demonstrated that QTD correction for heart rate is not only unnecessary in patients with sustained ventricular tachycardia in sinus rhythm and during higher heart rates with atrial pacing, but could also be misleading. In our study, if we had relied on this type of correction and had not included a control group, we would have inaccurately concluded that QT dispersion was abnormal in the patients with ventricular tachycardia. However QTcD increased similarly with atrial pacing in normal individuals. Thus in the absence of a control group we could have drawn wrong conclusions, considering that atrial pacing increases QTcD sensitivity, being normal at baseline and rendered abnormal with atrial pacing at 120 beats/min.

Resting QTD values did not differ from normal individuals. Some studies have shown increased values of QTD in patients with ischemic heart disease and a history of sustained ventricular tachycardia,¹¹ although other investigators failed to confirm this finding in patients with dilated cardiomyopathy or ischemic heart disease.^{5,14} The relatively small number of patients with ventricular tachycardia and the inclusion of patients with substrates for sustained ventricular tachycardia other than coronary artery disease in our study may also explain the similar to the normal subjects QTD values.

QTD may increase if ischemia is present.²⁰ Exercise-induced ischemia was absent in our patients with coronary artery disease, proven by thallium scintigraphy and the absence of ECG changes during atrial pacing.

Study Limitation

It has been reported that the QTD measurements are subjective and variable between observers. We

carefully examined this issue by evaluating the results between two observers blinded to each other's results. The measurements did not demonstrate significant differences between the two readers.

CONCLUSIONS

Our study shows that QTD remains unchanged during atrial pacing at heart rates up to 120 beats/min in both individuals without structural heart disease and in patients with a history of sustained ventricular tachycardia who do not demonstrate active myocardial ischemia, despite the observed decrease of QTM interval in both groups. In contrast the corrected for heart rate parameters using Bazett's formula yielded increased values, which may be considered abnormal in both groups, in a similar manner. Therefore the use of QTcD according to Bazett's formula in studies which involve dynamic changes of the heart rate in various populations with heart disease may lead to artefactually prolonged QTD values, and thus we propose the use of the noncorrected form of QTD.

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