Bias of QT Dispersion

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Background: Prolonged QT dispersion (QTD) is associated with an increased risk of arrhythmic death but its accuracy varies substantially between otherwise similar studies. This study describes a new type of bias that can explain some of these differences.

Material: One dataset (DiaSet) consisted of 356 subjects: 169 with diabetes, 187 nondiabetic control persons. Another dataset (ArrSet) consisted of 110 subjects with remote myocardial infarction: 55 with no history of arrhythmia and 55 with a recent history of ventricular tachycardia or fibrillation.

Methods: 12-lead surface ECGs were recorded with an amplification of 10 mm/mV at a paper speed of 50 mm/s. The QT interval was measured manually by the tangent-method. The bias depends on the magnitude of the measurement errors and the measurable part of the bias increases with the number of the repeated measurements of QT.

Results: The measurable bias was significant for both datasets and decreased for increasing QTD in the DiaSet ($P < 0.001$) and in the ArrSet ($P = 0.11$). The bias was 2.5 ms and 1.9 ms at QTD = 38 ms and 68 ms, respectively, in the ArrSet, and 7.5 ms and 2.8 ms at QTD = 19 ms and 55 ms, respectively, in the DiaSet.

Conclusions: This study shows that random measurement errors of QT introduces a type of bias in QTD that decreases as the dispersion increases, thus reducing the separation between patients with low versus high dispersion. The bias can also explain some of the differences in the mean QTD between studies of healthy populations. Averaging QT over three successive beats reduces the bias efficiently.

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The presence of heterogeneity in the recovery of ventricular refractory periods is an important factor in the development of ventricular arrhythmia. The QT dispersion (QTD) is a measure of this heterogeneity and is defined as the difference between the maximum and minimum QT interval ($QT_{\max} - QT_{\min}$) in the 12-lead surface ECG (ECG12). High values of QTD are present in individuals with a variety of heart diseases, including hypertrophic cardiomyopathy, heart failure, myocardial infarction, and angina.¹⁻⁷ Its clinical value is however

limited due to methodological problems.^{8,9} Biphasic T waves, the gradual transition from mono to biphasic waves, and T waves of low amplitude all contribute to varying "standards" for the rejection of leads and a low reproducibility of QTD. The standard deviations (SD) for the intra- and interobserver reproducibilities are about 12 ms and 16 ms, respectively.^{1,10,11}

Furthermore, the QTD formula is far more complicated than a first glance would suggest. Notice that QTD is always positive or zero because $QT_{\max}$

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Figure 1. Influence of measurement errors on QTD. The figures show the QT interval measures in ten leads in two different ECGs. The QT intervals were subsequently sorted according to the size of the true QT intervals. The theoretical true QT intervals are free of measurement errors and are shown as vertical lines surrounded by a hatched interval representing the reproducibility SD = 6 ms. The measured QT values are shown as black dots. (Left): The true QTD is zero but repeated measurements show that (mean, SD) of the measured QTD is (18, 5) ms. (An analytical equation for the result of the repeated measurements {40} does not exist so the result was obtained by simulating the repeated measurements one million times in Matlab version 4.2c.1. from Matworks Inc., USA, Internet: www.mathworks.com.) The reason for the large difference between the true and measured QTD is that the location of QT_{min} and QT_{max} (lead d and h) are entirely determined by the random measurement errors of QT changing from one measurement of the beat to the next. (Right): The true QTD is 135 ms and repeated measurements showed that (mean, SD) of the measured QTD is (135.8) ms. The true QTD and the measured QTD are identical because the location of QT_{min} and QT_{max} is entirely determined by the true QT values being the same from one measurement of the beat to the next. In other words, the differences between the true QT values exceed the reproducibility's SD so much that the measurement errors of QT do not interfere with the location of QT_{min} and QT_{max} .

$\geq QT_{min}$. This has major statistical and practical implications as illustrated in Figure 1. If the operator tries to measure QT in an ECG where the true (free of measurement error) QTD is zero, then the measured QTD will rarely be exactly zero due to errors in the measurement of QT. For the same reason, the location of the leads with the maximum and minimum QT values will change randomly from one repeated measurement to the next. However, if the true QTD is long (e.g., 120 ms), the differences between the true QT values will exceed the measurement errors of the QT values, thus the minimum and maximum QT value will be located in the same leads from one repeated measurement to the next. Calculations show that if, for example, the reproducibility of QT is SD = 6 ms, then the bias varies from 19 to 0 ms for a variation of the true dispersion from 0 to 120 ms. Numerical simulations were used for this example because the interaction between the range of the true QT intervals, and the measurement errors constitute a non-trivial statistical problem for which there does not yet exist an analytical equation.¹²

These examples indicate that the measurement errors of QT result in a measured QTD value that is too long when the true QTD is short. The purpose of this article is to describe this systematic error, which has not been reported before.

MATERIALS

All measurements were based on ECG12 printed at a paper speed of 50 mm/s with an amplification of 10 mm/mV. The leads were recorded in two groups of six leads: I, II, III, aVF, aVR, aVL and V1-V6. Patients who did not satisfy the requirements for all analyses were excluded so that all statistics refer to the same group of patients. The exclusion criteria were (1) QT could not be measured in the required number of beats; (2) QT was measured in less than three leads in the precordial or the frontal leads; (3) QT's reproducibility had a SD in one or more leads that exceeded four times the reproducibility's SD for the whole dataset. Leads were rejected if the amplitude of the T wave

was too low, if the baseline was too unstable, or if the start of QRS was not well defined.

The diabetes dataset (DiaSet) consisted of 356 subjects: 169 with diabetes, and 187 nondiabetic control persons. QT was measured in three successive beats. Leads were rejected according to the above criteria or if the T wave was biphasic. There was 307 patients satisfying the requirements for this study, 126 with diabetes, and 162 nondiabetic control persons. The age was mean $\pm$ SD = 54 ± 9 years.

The arrhythmia dataset (ArrSet) as previously published³ included 110 subjects with a remote myocardial infarction in a case-control design: 55 had no history of arrhythmia, and 55 had a recent history of ventricular tachycardia (VT) or ventricular fibrillation (VF), or had been resuscitated from cardiac arrest (RCA). QT was measured in two successive beats. There were 89 patients satisfying the requirements for this study: 44 with no history of arrhythmia, and 45 with RCA or documented episodes of VT/VF. The age was mean $\pm$ SD = 62 ± 7 years.

METHOD

The term cardiac plane is used to designate either the frontal or the precordial leads. The end of the T wave was measured manually by the tangent-method defined as the intersection between the steepest tangent of the terminal part of the T wave and the baseline going from the current to the following PQ interval. The start of QRS was defined individually for each lead.

Statistical Analysis and Terms

The F-test is used to compare two variances. Trends in variances are analyzed by Bartlett's test and by observing whether the variances increase or decrease with the stratifying variable. Probabilities are abbreviated to the symbol P and $P \leq 0.05$ is considered statistically significant. The reproducibility of QTD is calculated as the standard deviation (SD) of repeated measurements of QTD.

True QT and QTD

The true QT values and the true QTD value refer to the hypothetical QT and QTD values that would be obtained if the errors of measuring QT were zero.

Figure 2. The relation between QTD_{biased}, QTD_{unbiased}, the true QTD and the measurable bias.

The Bias of QTD

QTD_{unbiased} is calculated after averaging QT over two to three successive beats, whereas QTD_{biased} is the average of QTD in successive beats. Figure 2 shows that the two parameters are identical if only a single beat is measured. Both measures are longer than the true QTD and are therefore biased. They do, however, react differently to averaging of repeated measurements of QT. QTD_{unbiased} converge towards the true QTD as the measurement errors of QT are reduced due to averaging. QTD_{biased} converge towards the mean of QTD as the measurement error of QTD is reduced due to the averaging. The existence of the bias can therefore be proved indirectly, by analyzing the difference: QTD_{biased} - QTD_{unbiased}. We call this difference the bias although it only represents a fraction of the total bias. This fraction can be estimated to 30%-40% of the total bias if one assumes that the bias of QTD_{unbiased} is proportional to $1/\sqrt{n}$ where "n" is the number of repeated measurements.

RESULTS

Reproducibility of QTD

The reproducibility and the bias of QTD are based on a stratified analysis. The stratification layers were defined such that, as far as possible, there were the same number of subjects in each layer.

Table 1 shows that when QTD increases, the bias decreases, and the SD increases. The bias decreased by 0.6 and 3.6 ms from the shortest to the

Table 1. Stratification of QTD's Reproducibility with Respect to QTD

QTD (ms)		QTD (ms)	
From-to	Mean	Bias	SD
ArrSet ($N_s = 89$, $N_{repeat} = 2$)			
0-55	38	2.5	8.9
55-95	68	1.9	10.5
95-215	124	1.9	12.9
Pooled	80	2.1	11.0
P			0.17
DiaSet ($N_s = 307$, $N_{repeat} = 3$)			
0-25	19	7.5	8.7
25-40	31	4.5	10.6
40-170	55	2.8	13.2
Pooled	35	4.9	11.0
P			<0.001

The first two columns describe the strata as the minimum, maximum, and mean of QTD in the strata. The last two describe the bias and the reproducibility of QTD in the strata. N_s = number of subjects; N_{repeat} = number of repeated measurements.

longest stratification layer in DiaSet and ArrSet, respectively. Linear regression of the bias versus QTD shows that its offset is significant for both the ArrSet and the DiaSet $P = 0.02$ and < 0.0001 , respectively. The decreases of the bias with increasing QTD is insignificant ($P = 0.11$) for the ArrSet and significant ($P < 0.001$) for the DiaSet. The increase of SD is insignificant for the ArrSet ($P = 0.17$) and significant for the DiaSet ($P < 0.001$). The reproducibility of QTD is SD = 11 ms for ArrSet with a mean QTD = 80 ms, and 11 ms for the DiaSet with a mean QTD = 35 ms.

DISCUSSION AND CONCLUSION

Bias in connection with measurement errors of QTD is usually understood to be the difference in mean QTD measured by two different observers and is accordingly independent of random measurement errors. This study shows that random measurement errors of QT introduces another type of a bias in QTD that decreases as the dispersion increases, thus reducing the separation between patients with low versus high dispersion.

The reproducibility of QT was previously found to have an SD of 9 and 8 ms for the ArrSet and the DiaSet, respectively.¹³ Only a part of the bias could be measured with the two to three repeated measurements available in our data, but the results

confirmed the theoretical model in the introduction. The results indicate that if the reproducibility of QTD has an SD = 8 ms, then the total bias varies from about 8 ms to 0 ms for QTD = 20 and 120 ms, respectively. The number of repeated measurements and the noise level vary widely between studies, so the bias will vary between studies resulting in different mean values for the QTD dispersion in otherwise identical populations. We have estimated that the bias can explain a difference of about 3-5 ms in mean QTD between studies in healthy populations and that it can reduce the difference between a healthy population and a high risk population with elevated QTD with about 3-5 ms.

Averaging QT over successive beats has been recommended¹⁴ because it reduces the measurement errors of the mean QT interval with the square root of the number of repeated measurements. (It is better to measure QT in successive beats than to make repeated measurements of the same beat, because the former will also reduce reproducibility errors due to eventual asynchronous recording of the leads.) Averaging does not reduce bias between observers, but the type of bias in this study is directly related to the measurement error of the averaged QT interval and is therefore reduced by averaging.

It is often argued that signal processing of digitized ECGs makes reproducibility studies and especially studies of manual QT measurements obsolete, because the computer's reproducibility is perfect. However, the reality is that most interventional trials using death as endpoint have used and will for the foreseeable future use paper ECGs. These trials provide the raw material we must use to analyze whether the QT dispersion can predict death. Current computer algorithms mimic manual measurements of QT and are as prone as manual measurements to biological variability and variability in the placement of the leads on the body. This kind of variability resembles the manual measurement errors and will most likely affect the accuracy of QTD in the same way.

The main limitation of the study is that the reproducibility of QT was estimated from measurement of successive beats. It will therefore include QT's physiological beat-to-beat variations that have a cyclic period of about five beats and an SD of about five ms.^{15, 16}

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