Weighing the QT Intervals with the Slope or the Amplitude of the T Wave

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Objective: The reproducibility of QT interval measurements is low, even for the mean QT interval based on the standard ECG. In this study we analyzed whether the reproducibility of the mean weighed QT interval was better than the simple mean QT interval. The weighing was based on the amplitude of the T wave or the slope of the steepest tangent on the terminal part of the T wave.

Material and methods: 12-lead ECGs of 130 postmyocardial infarction patients were obtained. The QT intervals were measured by the tangent-method on two occasions by the same observer Mismatch QT intervals were defined as QT intervals that were measured at only one occasion. Sixteen ECGs were rejected. The data were split into 34 and 80 ECGs for optimization and validation of the weighing, respectively. The weighed QT dispersion was calculated as the weighed mean of the three longest minus the weighed mean of the three shortest QT intervals.

Results: Weighing with the slope increased the reproducibility by 41% ($P = 3\ 10^{-6}$), but weighing with the amplitude reduced it by 20% ($P = 0.02$). However, if measurements with errors above 75 ms were rejected, weighing with the slope or the amplitude increased the reproducibility with 26% and 20% ($P = 0.02$), respectively. Weighing did not change the reproducibility of the weighed QT dispersion.

Conclusion: Weighing with the slope improved the reproducibility of the mean weighed QT interval. However, if measurements with errors above 75 ms were rejected, weighing with the amplitude also increased the reproducibility. Weighing did not change the reproducibility of the weighed QT dispersion. Weighing is particularly efficient at reducing the negative impact of mismatch QT intervals on the reproducibility.

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Prolonged QT intervals and prolonged QT dispersions are associated with higher risk of arrhythmic death.[1-13] Drugs influence both measures.[14-17] A study of QT interval changes has become a standard requirement during evaluation of new drugs.[18] The QT interval is, however, notoriously difficult to measure. The standard deviation (SD) of the inter- and intraobserver measurement errors is 10-15 ms for the QT interval in a single lead of the standard 12-lead ECG. The mean of the QT intervals in the twelve leads is about a factor three more reproducible and is therefore used frequently.[1] Weighing the QT intervals proportionally to their reproducibility can further improve the reproducibility of the mean QT interval. This possibility has never been tested, probably due to the lack of methods to predict the reproducibility of individual QT intervals.

We have previously shown that the longest and the shortest QT intervals are the least reproducible and that they tend to be measured on the T waves with the smallest amplitudes and slopes.[19,20] The amplitude or the slope of the T wave might therefore be used to estimate the reproducibility of the individual QT interval.

Weighing might also improve the reproducibility of a new QT dispersion (QTD3) measure that we proposed recently.[21] QTD3 is the mean of the three

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longest minus the mean of the three shortest QT intervals.

The purpose of this study is to analyze how much weighing with the amplitude and the slope of the T wave can improve the reproducibility of the mean QT interval and QTD3.

MATERIAL AND METHODS

Materials

ECGs of 100 men and 30 women with myocardial infarction were recorded on paper at 25 mm/s and an amplification of 10 mm/mV one week after the acute phase and treatment with either percutaneous transluminal coronary angioplasty or thrombolysis. The age was: mean ± SD = 66 ± 13 years.

The ECGs were scanned into a computer for evaluation in a dedicated program "Cardio" (contact Kaspar Lund e-mail: kasparlund@bigfoot.com), where the user is able to display the ECG at about eight times normal size. The baseline was defined by setting points in the P-QRS segment in two succeeding beats. The start of QRS was defined by one sample. The segment from the J point to past the end of the T wave was sampled by setting points so that a line passing through those points defined the shape of the T wave. The operator clicked with the mouse on the last part of the T wave and the program proposed a tangent calculated by the least squares method. The operator could then adjust the tangent in the rare cases where it was necessary. The endpoint of the T wave was located at the intersection between the tangent and the baseline. The QT interval, the amplitude of the apex preceding the end of the T wave, and the slope of the tangent were measured and averaged over three successive beats for each lead.

The QT intervals were measured twice at 6-week intervals. Sixteen ECGs were discarded when the baseline or the rhythm was too unstable or if the QT interval was measured in less than six leads. The 114 remaining ECGs were divided into two groups: (1) The "Training Data" including 34 ECGS, and (2) The "Validation Data" including 80 ECGs.

QT Interval

The calculation of the weighed mean QT interval is shown in equation. The classical mean QT interval (QTM) is calculated using equation 1 and setting all weights to one ($w_I = 1$).

Equation 1: Calculation of the mean QT interval with and without weighing.

$$\mathrm{QTMw} = \frac{\sum_{i=1}^{N} \mathrm{QT}_i w_i}{\sum_{i=1}^{N} w_i} \text{ and } \mathrm{QTM} = \mathrm{QTMw}$$

$$\text{for } w_i = 1$$

QTM and QTMw are the mean and weighed mean QT interval; $w_{i:}$ is the weight of the QT interval in lead "i"; N is the number of measured leads in the ECG.

QT Dispersion Measures

The weighed QTD3 (QTD3w) is calculated as the weighed mean value of the three longest QT intervals minus the weighed mean value of the three shortest QT intervals (see equation 2). The "nonweighed" QTD3 is calculated using Equation 2 and setting all weights to one ($w_I = 1$).

Equation 2: Calculation of QTD3 and QTD3w.

$$\mathrm{QTD3w} = \frac{\mathrm{QT}_{L1}w_{L1} + \mathrm{QT}_{L2}w_{L2} + \mathrm{QT}_{L3}w_{L3}}{w_{L1} + w_{L2} + w_{L3}} - \frac{\mathrm{QT}_{s1}w_{s1} + \mathrm{QT}_{s2}w_{s2} + \mathrm{QT}_{s3}w_{s3}}{w_{s1} + w_{s2} + w_{s3}}$$

$$\mathrm{QTD3} = \mathrm{QTD3w} \text{ for } w_i = 1$$

Symbols: QT_{L1}, QT_{s1}, w_{L1}, w_{s1} are the QT intervals and the weights of the longest and the shortest QT intervals; QT_{L2}, QT_{s2}, w_{L2}, w_{s2} are the QT intervals and the weights of the second longest and the second shortest QT intervals etc.

Weights

The tangent of the terminal part of the T wave is defined by the line $y = ax + b$, where a is the slope of the tangent and b the offset for $x = 0$. The interception ($x = Te$) with the baseline ($y = 0$) is $Te = \frac{-b}{a}$. Measurement errors of the amplitude (∂b) and the slope (∂a) translate into measurements errors of Te (∂Te) as shown in the equation $\partial Te = \frac{-1}{a}\partial b + \frac{b}{a^2}\partial a$. However, because the amplitude and the slope are so strongly correlated we estimate the reproducibility of the QT interval from only the amplitude or only the slope.

The measurement errors of the QT interval are equal to 2Te plus a constant term representing the measurement errors of Q. We tried out various power-law relations between the measurement errors and the slope or the amplitude with and without a constant to model the reproducibility of Q. We finally chose the simple power-law relation in Equation 3.

Equation 3: Estimation of the reproducibility of the QT interval. The purpose of the constant 0.000001 in the nominator is to prevent division by zero.

$$w_i = (SD_{QT_i})^{-1} \text{ and } SD_{QT_i} = e(f_i + 0.000001)^{-g}$$

Symbols: w_i is the weight and SD_{QT1} is the predicted standard deviation of the measurement errors of the QT interval in lead "i"; e and g are constants to be identified; f_i is the magnitude of the apex preceding the endpoint of the T wave or the slope of the tangent in lead "i".

The reproducibility of the mean QT interval and QTD3 with and without weighing is calculated as the SD of two measurements of the same ECGs made by the same observed. The optimal value for the constant g in Equation 3 is identified by minimizing the standard deviation of the measurement errors of the mean weighed QT interval for the training data. Inserting Equation 3 into Equation 1-2 reveals that the constant e can be removed and that it does not need to be identified. Notice that the amplitude is measured on the apex preceding the intersection between the tangent and the baseline. This amplitude may be much smaller than for example the amplitude of the first phase of a biphasic T wave.

Different Types of Measurement Errors

The data were measured at two occasions. We distinguished between three types of measurement errors 1) mismatch which occurs when the QT interval was measured at the first occasion but not the second or vice-versa, 2) small measurement errors below 75 ms 3) large measurement errors above 75 ms.

Statistics

Two variances were compared by the F-test. Statistical significance was defined as $P < 0.05$. The measurement errors were, in order to be consistent, always considered normally distributed. A few very large measurement errors invalidated this assumption for some distributions. There are different causes for mismatch QT intervals, the small to medium measurement errors, and the very large measurement errors. The different types of error might mask the benefit of a method that only reduced one type of error. To avoid this problem and to understand how the weighing works, we stratified the reproducibility analysis according to the type of measurement error.

RESULTS

The correlation between the amplitude and the slope of the T waves was $R^2 = 0.94$. The correlations between the logarithm of the measurement errors of the QT interval and the logarithm of the amplitude and the logarithm of the slope were $R^2 = 0.05$ and 0.07, respectively.

We used stratified reproducibility tables like Tables 1 and 2 to optimize and validate the model for prediction of the reproducibility in Equation 3. Tables 1 and 2 should be read as follows. The reproducibility is stratified row-by-row with respect to the size of the measurement errors and left-to-right with respect to mismatch QT intervals. The table's left section "All Data" shows the reproducibility with mismatch QT intervals included. The right section "Mismatch Excluded" shows the reproducibility after exclusion of mismatch QT intervals. Each row shows the reproducibility after rejection of leads with measurement errors above the threshold shown in the first column of the row. The number of rejected leads is shown in the column "Outliers" in the left and right section of the table for each row.

The training data (34 ECGs) were used to identify the optimal value of g in Equation 3. We calculated stratified reproducibility tables like Table 1 for g in the interval from 0 to 2 in steps of 0.01. The reproducibility in each stratification layers was subsequently plotted against g. We found that g was close to optimal in a region that was so large that multiple constraints could be taken into consideration as follows. The primary endpoint for the optimization was the best overall reproducibility of QTw and secondarily QTD3w. When possible, we identified the best compromise between the reproducibility of all stratification layers. We found that g = 1 was the best choice for weighing with the

Table 1. Validation of Weighing the QT Interval with the Amplitude of the T Wave Using $g = 1$ in Equation 3

	All Data				Mismatch Excluded			
Threshold (ms)	**Outliers (N)**	**QTw**	**QT**	**QTw/QT**	**Outliers (N)**	**QTw**	**QT**	**QTw/QT**
25	48	2.4	3.2	0.7	68	2.1	1.9	1.1
75	30	3.4	4.1	0.8	50	3.5	3.6	1.0
325	0	14.8	12.0	1.2	15	14.9	12.0	1.2
Threshold	**Outliers N**	**QTD3w**	**QTD3**	**QTD3w/QTD3**	**Outliers N**	**QTD3**	**QTD3**	**QTD3w/QTD3**
25	48	8.0	8.1	1.0	68	6.2	5.4	1.2
75	30	11.9	10.7	1.1	50	11.1	9.3	1.2
325	0	35.7	34.2	1.0	15	35.6	34.2	1.0

slope and weighing with the amplitude. Weighing the QT intervals with the amplitude improved the reproducibility of QTw and QTD3w by 20% and 39%. Weighing with the slope improved the reproducibility of QTw and QTDw by 39% and 54%.

We validated $g = 1$ in Equation 3 by calculating the reproducibility of the validation data (80 ECGs). The total reproducibility changed as follows. Weighing the QT intervals with the amplitude reduced the reproducibility of QTw and QTDw by 20% and 0% (see Table 1). Weighing with the slope improved the reproducibility of QTw by 41% ($P < 3\ 10^{-6}$), whereas the reproducibility of QTDw decreased by 1% (see Table 2).

The change in reproducibility is expressed in the ratios QTw/QT and QTD3w/QTD3. Stratified analysis of the measurement errors below 75 ms revealed that the biggest relative advantage of weighing was seen when mismatch QT intervals were included. Table 3 shows that the reason was that mismatch QT intervals contributed less to the mean weighed QT interval and the weighed QT dispersion, because the amplitude and the slope of mismatch QT intervals were about 60% smaller than for the remaining QT intervals ($P < 10^{-6}$).

DISCUSSION AND CONCLUSION

The very high correlation between the amplitude and the slope of T waves confirmed that both can be used in a weighing algorithm.

The weighing of the QT intervals was optimized on training data including 34 ECGS. We found that setting $g = 1$ in Equation 3 optimized the reproduc-

Table 2. Validation of Weighing the QT Interval with the Slope of the Tangent Using $g = 1$ in Equation 3

	All Data				Mismatch Excluded			
Threshold (ms)	**Outliers (N)**	**QTw**	**QT**	**QTw/QT**	**Outliers (N)**	**QTw**	**QT**	**QTw/QT**
25	48	2.7	3.2	0.87	68	1.9	1.9	1.00
75	30	3.0	4.1	0.74	50	3.7	3.6	1.04
325	0	7.1	12.0	0.59	15	7.8	12.0	0.65
Threshold	**Outliers N**	**QTD3w**	**QTD3**	**QTD3w/QTD3**	**Outliers N**	**QTD3**	**QTD3**	**QTD3w/QTD3**
25	48	8.4	8.1	1.03	68	6.1	5.4	1.13
75	30	11.1	10.7	1.04	50	10.1	9.3	1.08
325	0	34.5	34.2	1.01	15	34.4	34.2	1.00

Table 3. Amplitude and Slope of Selected QT Intervals. The Number of QT Intervals is Indicated for Each Row

	Slope Times 1000 Mean ± SD	Amplitude Mean ± SD
	QT Intervals with versus without Mismatch	
Mismatch (N = 20)	0.7 ± 0.8	0.13 ± 0.14
No mismatch (N = 905)	1.8 ± 1.7	0.37 ± 0.36
	Large versus Small Measurement Errors	
Large (>75 ms, N = 30)	1.5 ± 1.1	0.37 ± 0.42
Small (≤75 ms, N = 875)	1.8 ± 1.7	0.37 ± 0.36

ibility and simplified the weighing technique. The weighing was done by summing the QT intervals multiplied by the magnitude of the slope of the tangent. The sum was subsequently divided by the sum of the magnitudes of the slopes.

The effect of weighing was validated using a second dataset with 80 ECGs. Weighing the QT intervals with the slope improved the reproducibility by 41% ($P < 3\ 10^{-6}$) relative to the nonweighed mean QT interval. Excluding measurement with errors above 25 ms and 75 ms reduced the improvement to 13% ($P < 0.11$) and 26% ($P < 0.004$), respectively. Weighing the QT intervals with the amplitude reduced the overall reproducibility of the validation data by 20% ($P = 0.02$), but it improved it by 20% ($P = 0.02$) if measurement with errors above 75 ms were excluded.

Weighing the QT intervals with either the slope or the amplitude did not improve the reproducibility of QTD3w compared with QTD3.

Mismatch QT intervals are QT intervals that the operator judged measurable the first but not the second time or vice versa. Table 3 shows that the amplitude and slope of mismatch QT intervals were about 60% lower than for the remaining QT intervals ($P < 10^{-6}$). Weighing was therefore, particularly efficient in presence of mismatch QT intervals. This was observed for almost all levels of measurement errors for both the mean weighed QT interval and the weighed QT dispersion.

Inconsistent evaluation of the morphology of the T wave resulted in very large errors. The same wave might have been classified as a U wave versus a part of a biphasic T wave during the first versus the second measurement of the ECG with a large measurement error as consequence. Table 3 shows that the 30 QT intervals with measurement errors above 75 ms (mean ± SD = 163 ± 63 ms) had practically the same amplitude and a slightly smaller slope compared with the QT intervals with errors below 75 ms (mean ± SD = 5 ± 8 ms). One would therefore not expect this type of errors to be reduced substantially by weighing. Furthermore, correlation analysis confirmed that only a small part (5%–7%) of the measurement errors (excluding mismatch QT intervals) could be explained by the amplitude or the slope.

The results showed that the large measurement errors (> 75 ms) cannot be reduced sufficiently by weighing. Well-defined criteria for selection of the terminal part of T waves are required to avoid these errors. However, mismatch QT intervals will always exist. Small variations in the amplitude from beat to beat and day to day will result in inconsistent rejection and acceptance of QT intervals. Fortunately, this study showed that weighing was an efficient way to limit the reduction in reproducibility caused by mismatch QT intervals.

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