Robust QT Interval Estimation—From Algorithm to Validation

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Background: This article presents an effort of measuring QT interval with automatic computerized algorithms. The aims of the algorithms are consistency as well as accuracy. Multilead and multibeat information from a given segment of ECG are used for more consistent QT interval measurement.

Methods: A representative beat is generated from selected segment of each lead, and then a composite beat is formed by the representative beats of all independent leads. The end result of the QT measure is so-called global QT measurement, which usually correlates with the longest QT interval in multiple leads. Individual lead QT interval was estimated by using the global measurement as a starting point, and then adapted to the signal of the particular lead and beat. In general, beat-by-beat QT measurement is more prone to noise, therefore less reliable than the global estimation. It is usually difficult to know if difference of beat-by-beat QT interval is due to true physiological change or noise fluctuation.

Results: The algorithm was tested independently by a clinical database. It is also tested against action potential duration (APD) generated by a Cell-to-ECG forward-modeling based simulation signals. The modeling approach provided an objective test for the QT estimation. The modeling approach allowed us to evaluate the QT measurement versus APD. The mean error between the algorithm and cardiologist QT intervals is 3.95 ± 5.5 ms, based on the large clinical trial database consisting of 15,910 ECGs. The mean error between QT intervals and maximum APD is 17 ± 2.4 , and the correlation coefficient is 0.99.

Conclusions: The global QT interval measurement method presented in this study shows very satisfactory results against the CSE database and a large clinical trial database. The modeling test approach used in this study provides an alternative “gold standard” for QT interval measurement.

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METHOD

The accuracy of QT interval measurement of ECG has become more important due to the need of identifying possible pro-arrhythmia adverse affects of new drugs during clinical trials based on ECG. The main reasons of the difficulties can include complex nature of cardiac repolarization and ambiguous definition of the end of repolarization in surface ECG. Therefore, to improve the QT measurement from the surface ECG, we also need to understand what we are measuring regarding the heart electrical activity. A general assumption is that global QT interval corresponds to the final ending of action potential of cardiac cells. There are generally two approaches we can use to evaluate that assumption: animal study and computer-

ized modeling. The former approach has been used to show that QT intervals on the surface ECG are correlated to the APD changes.¹ Since such animal study is very difficult to conduct, the number of experiments conducted were very limited. The computer model approach can be used for conducting more rigorous and frequent simulations.

As for the QT interval measurement from the surface ECG, both QRS onset and T-wave offset need to be measured. The former is usually a less difficult task due to relative sharp deflection change in the QRS onset for most cases, which also corresponds to a sharp rise of the action potential in the cardiac muscle cells at the beginning of the depolarization. Whereas, the T-wave offset measurement is much more difficult in most cases. The textbook definition of a T-wave offset is when

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the T wave goes back to the isoelectric line of the T-Q segment, which also corresponds to the final ending of the repolarization process on the cardiac muscle cells. However, in real practice, this simple definition can lead to some variations from reviewer to reviewer in manual editing cases or from algorithm to algorithm in automatic methods due to various T-wave morphologies and different noise sources.²

There can be many different automatic approaches to measure ECG intervals. In general, we can divide them into global approach or individual lead/beat approach. If what we need is a general QT interval value from a segment of multi-lead ECGs, a global approach can be used, where the purpose is to use information from all leads/beats to obtain a most representative QT value. On the other hand, if we need to evaluate lead-to-lead changes of the QT interval (e.g., QT dispersion) or beat-to-beat QT changes (e.g., QT dynamicity), we will need to estimate individual QT values. Major challenge of lead/beat based QT measurement is to differentiate the physiological changes from changes caused by various noise (muscle noise, device noise, environmental noise, etc.).

Estimate Global QT Interval

QT interval consists of both estimations of QRS onset and T offset. A flowchart for computing global QT interval is shown in Figure 1. A segment

of multi-lead ECG (usually 10 seconds) is sampled, and then the representative beats of each lead are computed by either median or mean method.

The QRS onset is determined by taking the 1st difference of all leads whose noise level are low and then searching the relatively sharp deflection based on the sum of the vector magnitude of the 1st differences, as shown in Figure 2.

T-offset estimation of the algorithm include several steps: (1) classifying different T-wave patterns, for example, biphasic T wave, connected T-U pattern or nonconnected T-U pattern, T-P pattern, etc.; (2) identifying final T-wave segment; and (3) determining end of T-wave from the final T-wave segment.

Most QT algorithms put attentions on the end of T-wave detection. However, a general purpose ECG measurement algorithm needs to handle various rhythms and complex ECG morphologies. The end of T-wave detection will only be meaningful if the final segment of T wave is judged correctly. Among ECG components, P and U waves have most influence on T-wave segment detection. Some of the T-wave patterns are shown in Figure 3, in which, none of ECGs show a clear T-wave offset. Different T-wave morphology such as biphasic T wave and T-U or T-P patterns are separated. The vector magnitude of the multilead ECG is used to examine global pattern of the T wave. In the T-U pattern, V_2 and V_3 are used, since these leads usually have largest U wave amplitude. T-P pattern is

Figure 1. A flow chart of QT interval measurement. Here the input is 10-second segment of 12-lead ECG, the median beat is formed for each lead, QRS onset and T offset are estimated separately from the vector magnitude of multiple leads, and finally the QT interval is calculated.

Figure 2. Superimposed 12-lead median beats and the vector magnitude of the 1st difference of the median beats forms the detection function. The QRS onset and offset can be detected from this enhanced detection function.

detected based on heart rate. If heart rate is above 100 beats per minute and there is no other P-wave detected in front of the next QRS, then the possibility of T-P pattern is high. In general, P waves also have higher frequency content than U waves.

Figure 3. Examples of different T-wave patterns. None of those examples have clear T-wave offset based on the original definition, where T wave is back to the isoelectric line.

Figure 4. Detect final T-wave offset based on the T-wave area comparison. The displayed signal is the vector magnitude of 12-lead 1st difference median beats. The T offset is detected when newly added small window area contributes smaller than 2% to total accumulated T-wave area.

Based on the result of T-wave pattern recognition, the final segment of the T wave is identified. If it is a monophasic T wave, final segment of the T wave is the portion after the T peak. If it is biphasic T wave, final segment of the T wave is after the 2nd peak of the T wave. If it is T-U or T-P pattern, the final segment is the portion before the connection nadir.

In the case of non-T-U or T-P connected patterns, the final T-wave offset is determined by the ratio of the incremental new area contributed by the new point to the total T-wave area accumulated based on the vector magnitude shown in the Figure 4. T-wave offset is defined when the ratio is smaller than 2%. In the case of T-U pattern, the T offset is set at the nadir of T-U connection. The same rule is applied to the T-P pattern.

Estimate Individual Lead T-Wave Offset

Lead-by-lead QT interval is useful for calculating QT dispersion, beat-by-beat QT variations, and the thorough QT study of drug clinical trials. The strategy of measuring lead-by-lead based QT interval in this study is to utilize the global QT interval calculated as previously described and then apply following steps: the first step is to match the final segment of individual T wave by using the median beat as a template. A match window of ± 30 ms around global T-offset point is used; and the 2nd step is to use a least-square-fitting method to determine the final T offset by determining the cross

Figure 5. Using Least-square fitting method to determine T-end. The intersection of two least-square-fit lines is the initial T offset. A nonlinear correction method is used to determine final T offset.

point of the LS fitting line of the final segment of the T wave to the baseline of the T-P segment, as shown in Figure 5. Finally, a nonlinear correction is used to obtain final individual T end.³ The reason the slope method is used instead of threshold method used in the global QT measurement is that the final portion of the T wave of individual lead usually has higher noise level than composite beat. The amplitude based threshold method can have more fluctuation in the low signal-to-noise ratio. At the meantime, the LS fitting line is more consistent in this situation. Therefore, the cross point between the LS fitting line and the isoelectric line can also be more robust than threshold based method, although the former tends to have a shorter T end. If the end point of the QT study is to find the changes of the QT interval, no additional correction is needed. However, if the absolute value of T end is needed, the correction can be applied to mimic the manual and the automatic measurements of the T end.

Test Method and Databases

One of the major difficulties of QT measurements is the lack of standard reference to compare with. A common method is to compare QT intervals estimated by automatic methods with those annotated by cardiologists. The Common Standards for Electrocardiography (CSE) database is one of such databases, which include 125 ECGs annotated by five cardiologists and the median value were used as the final result for each ECG. In the test, 100 ECGs¹ are used for the test based on the regulation by CSE committee.

¹Based on requirement of AAMI standard, the test can be conducted with 100 ECGs by excluding some outliers from original 125 ECGs.

Figure 6. The relationship of QT interval from ECG to the action potential duration (APD) of the cardiac cells. The action potentials were generated from the PB cell model.² The dispersion between Epi- and Endocardial cell APDs were created by alter the I_{ks} , I_{kr} , I_{k1} conductance, where the epicardial cells have the highest conductance (normalized to 100%), and Endocardial and Midmyocardial have the reduced ion channel conductance, varied from 40% to 80%. ECGs were then generated based on the APs and a forward model transfer matrix.

We also tested the global QT algorithm by a large pharmaceutical clinical trial database including 15,194 ECGs annotated by two cardiologists.⁴

All those databases were not used in training phase, and the large clinical trial database is tested in another independent lab, never seen by the algorithm developer.

In the mean time, we also developed a new model based validation approach in this study. This method used an ion channel based cardiac cell model and a cell-to-torso forward model to generate many pair of cell and corresponding ECGs. We then compare the APD of the simulated cardiac cells with the QT interval measurements from the ECGs using the ECG QT algorithm. The advantage of using modeling approach is that the true reference can be established, since the QT measurement from torso ECGs is assumed to match the maximum APD from the cardiac cells, as shown in Figure 6. By using this approach, we also hope to learn the accuracy limit of the QT measurement in this more clearly defined situation.

The cardiac cell model is based on the ionic channel model proposed by Priebe and Beuckelmann.⁵ By changing the parameters of the slow-Potassium and rapid-Potassium ionic channels (I_{ks} ,

Ikr), a table of action potentials was generated with APD range 377–500 ms. The heart propagation model was based on Durrer,⁶ which was used as a reference to adjust the initial excitation points and propagation velocity of the model. The difference between the repolarization ending time and the depolarization start time is defined as the APD. To calculate the ECG from the AP at cell level, a simplified representation of this relation is: $Y = A \times X$, where Y is the potential on the body surface, X is the cell AP. A is the transfer matrix, which is determined by the geometry shapes and the conductivities of different tissues. Finite-element and boundary-element methods were applied to calculate the transfer matrix.

RESULTS

The test results of the CSE database show that the mean difference between the algorithm and the reference QT intervals is 0.30 ms, and the standard deviation is 8.2 ms.

The test results with the large clinical trial database show a mean difference between the algorithm and the reference QT intervals is 3.95 ms, and the standard deviation is 5.5 ms (Fig. 7).

For the test of QT interval versus APD, the correlation coefficient is 0.99 and the root-mean-square

difference is 17 ms, as shown in Figure 8. We can also see that there is a consistent bias across all QT range. The QT interval measured in torso ECGs are about 10 ms shorter than the maximum APD.

DISCUSSIONS

The global QT interval measurement method presented in this study shows very satisfactory results against the CSE database and a large clinical trial database.

The modeling test approach used in this study provide an alternative "gold standard" for QT interval measurement, since the end of action potential profiles provides an objective reference point for T offset. Although the link between the QT interval and the duration of the action potential has been already established before, our study is the first to directly use the model simulated ECGs to test the automatic QT detection algorithm. The results show that the QT measurements using the developed algorithm have excellent correlation with the end of APD profiles. However, the end of T wave measured from ECG is generally not up to the final end of action potential, mainly due to very small amplitude reflected on the torso and different noise sources. For any automatic ECG algorithm, the thresholds used for the onset/offset detection

Figure 7. Bland-Altman plots of QT difference between the algorithm and cardiologists. Total ECGs 15,194. The mean difference is 3.95 ± 5.5 ms.

Figure 8. The cross-correlation between QT estimation and the maximum action potential durations (APDs). The cross correlation between estimated QT interval and the maximum APD is 0.99, whereas the mean error of 17 ms indicates a bias of estimated QT interval. This is because the final portion of action potentials have such a low amplitude when they propagate to the torso that they are below the noise threshold set for detecting end of T wave.

cannot be set to 0 due to noise issues. We can reasonably assume that even very high quality ECG recordings still have some noise. That's why it is not practical to pursue to the end of APD. In our opinion, a consistent high correlation between ECG QT interval measurement and APD is a more practical goal. In spite of the gap between the model and real cell and tissue characteristics, it is reasonable to assume that the real situation would only generate more discrepancy between QT measurement and APD. We will extend our study to analyze detection accuracy for more specific ion channel changes, for example, fast- and slow-potassium channels (I_{Kr}, I_{Ks}).

How accurate we can achieve for the QT interval measurement? This is the question we kept asking ourselves these years. But before we can answer this question, we might need to answer another question first, that is, "What are the relevant QT accuracy we need?" These two questions are related, since if we could measure QT interval within 1 ms of margin versus the true target value, people would think it is good enough. However, in reality, not only this accuracy is not reachable, but it cannot be defined clearly either. It might be bene-

ficial to divide the major applications into clinical patient care (hospitals and clinics) and pharmaceutical clinical trial.

In the patient care field, QT interval measurement is used for detecting long QT, either congenital or induced. A threshold of QT correction between 460 to 480 ms is usually used to make "QT prolongation" call, although women can have larger threshold than men. If we would use manual measurement as a reference in this case, the fine grid in a standard ECG report is 40 ms. Most experienced cardiologists would agree the reasonable accuracy margin they could make is between half and one grid, meaning 20-40 ms. This assumption is consistent with the interobserver variations measured in several studies.⁷

In the clinical trial applications, the demand for higher QT measurement accuracy is driven by a small margin allowed for QT interval changes between baseline and regulated dosage of tested drugs. According to the Guideline of Clinical Evaluation of QT/QTc E14 document,⁸ 5 ms QT interval change is a marginal sign of warning, and 15 ms drug induced QT prolongation is a very concerned sign of warning. Please note that here 5 ms is not for individual ECG measurement, instead, it is more for a whole study base. A more meaningful study can test how accurate the algorithm can reflect some QT changes induced by know positive control drugs such as moxifloxacin.

In terms of lead-by-lead or beat-by-beat QT interval measure, the general approach adopted in our QT algorithm is using global measurement as a base if it is available, then extend to individual lead or beat measure. The global information for multilead and multibeat signals has a higher signal-to-noise ratio and therefore provides a more robust initial estimation. However, the accuracy of individual lead or beat QT measurement will be degraded due to lower signal-to-noise ratio.

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