QT Interval Measurement: What Can We Really Expect?

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Abstract

This study is an effort of measuring QT interval with an automatic computerized algorithm. The aims of the algorithm are consistency as well as accuracy. The general methodology adopted in this algorithm is to seek more consistent QT interval measurement by using multi-lead and multi-beat information from a given segment of ECG. 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 catches 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.

In the study, we tested the algorithm by using clinical databases and also a modeling based simulation signals. The modeling approach provided a more objective test for the estimation. The modeling approach allowed us to evaluated the QT measurement vs. Action potential duration (APD). The results show that the mean error between the algorithm and cardiologist QT intervals is 3.95± 5.5 msec based on a large clinical trial database consisting of 15910 ECGs. The results also show that the correlation coefficient between QT intervals and maximum APD is 0.99 and a consistent bias of 17 msec.

1. Introduction

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 trails based on ECG. The main reasons behind the difficulties are due to 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 to the heart electrical activity. A general assumption is that global QT interval is corresponding to the maximum action potential of cardiac muscle. There are generally two approaches we can use to evaluate that assumption: animal study and computerized modeling. The former approach has been used to show QT intervals on the surface ECG are correlated to the APD changes [1]. Since such animal study is very difficult to conduct and the number of experiments can be very limited, whereas, the computer model approach can be used for more frequent and large number of simulation.

As for the QT interval measurement from the surface ECG, there are two parts that need to be detected, i.e. QRS onset and T wave offset. The former is usually a less difficult task due to relative sharp deflection change in QRS onset in 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 the T wave goes back to the isoelectric line of T-Q segment, which is also corresponding to the final ending of the repolarization process on the cardiac muscle cells. However, in real practice, this simple definition can lead to quite a variation from reviewer to reviewer in manual editing cases, or from algorithm to algorithm in automatic methods due to varies T wave morphologies and different noise sources [2].

There can be many different automatic approaches to measure ECG intervals. In general, they can be divided 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, we might want to use a global approach, 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 (QT dispersion), or beat to beat QT changes (QT dynamicity), we will need to estimate individual QT values. In this individual QT interval case, a major challenge is to differentiate the changes due to physiological causes and the changes due to noise (muscle noise, device noise, environmental noise,

etc).

2. Methods

A flowchart of 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.

2.1. Estimate QRS onset

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

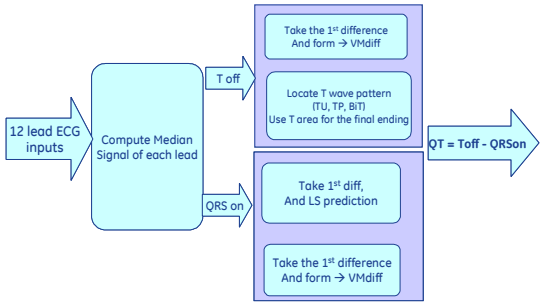

Figure 1. A flow chart of QT interval measurement.

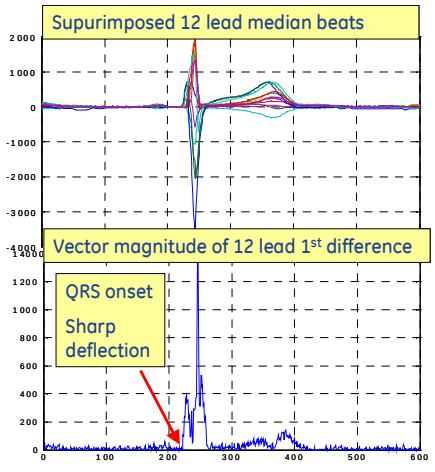

Figure 2. Superimposed 12 lead median beats and the vector magnitude of the 1st difference of the median beats.

2.2 Estimating T offset

It is a bigger challenge to detect T wave offset in most situations. As the example shown in figure 2, even for this very clean T wave, the end of T wave is much less obvious when compared to the start of QRS complex. The rhythm and morphology of ECG from clinical recording can be much more complicated. For example, biphasic T wave, connected T-U pattern or non-connected T-U pattern, T-P pattern when heart rate is high, just name a few. Therefore the first step is to differentiate T wave patterns.

2.2.1. Determine patterns

There can be many different T wave patterns, some of that are shown in figure 3. In our automatic algorithm, we need to differentiate the T wave pattern first. In all examples shown in Figure 3, none of them show a clear T wave offset. The most important is to differentiate between biphasic T wave and T-U, or T-P patterns. The vector magnitude of the multi-lead ECG is used to examine global pattern of the T wave. In the T-U pattern, v2 and v3 are used, since these leads usually have largest U wave amplitude. T-P pattern is 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.

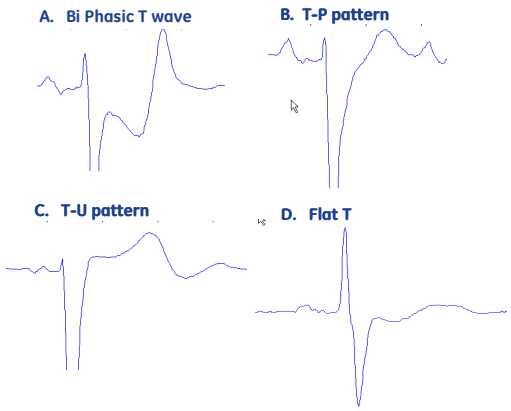

Figure 3. Examples of different T wave patterns.

2.2.2. Determine final T wave segment

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 patterns, the final segment is the portion before the connection nadir.

2.2.3. Fine tune of the T wave offset

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.

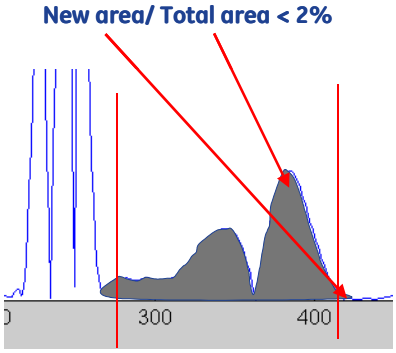

Figure 4. Detect final T wave offset based on the T wave area comparison. The displayed signal is the vector magnitude of 12 lead 1st difference median beats.

2.3. Estimate individual lead / beat T wave offset

After a global QT interval is obtained, individual QT interval is measured in 2 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 msec 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 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].

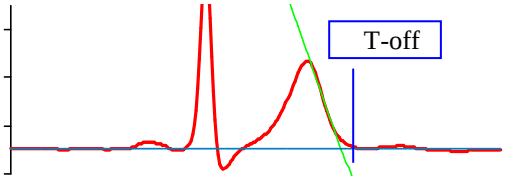

Figure. 5. Using Least-square fitting method to determine T-end. The intersection of 2 lines is the initial T offset. A non-linear correction method is used to determine final T offset.

2.4. Test method and databases for global QT interval measurement

One of the major difficulties of QT measurements is the lack of standard reference to compare to. A common method is to compare QT estimates of automatic method to those of annotated QT measurements by cardiologists. The CSE database is one of such databases, which include 125 ECGs annotated by 5 cardiologists and the median values were taken as the final results for each ECG. In the test, 100 ECGs are used for the test based on the regulation by CSE committee.

We also tested the global QT algorithm by a large pharmaceutical clinical trial database including 15,194 ECGs annotated by 2 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.

At the mean time, we also used a new model based validation approach in this study. The idea is to use 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 action potential duration of the simulated cardiac cells to 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 action potential duration (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 relatively more ideal situation.

The cardiac cell model is based on the ionic channel model proposed by Priebe and Beuckelmann [2]. By changing the parameters of the slow-Potassium and rapid-Potassium ionic channels, a table of APs was generated with APD range 377~500. A 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*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.

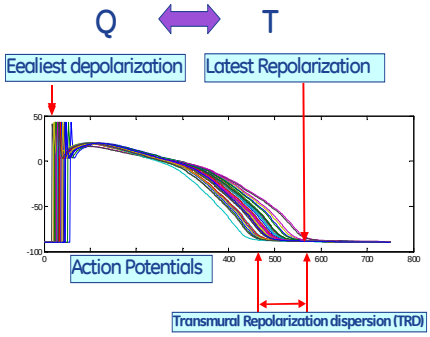

Figure 6. The relationship of QT interval from ECG to the action potential duration of the cardiac cells.

3. Results

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

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

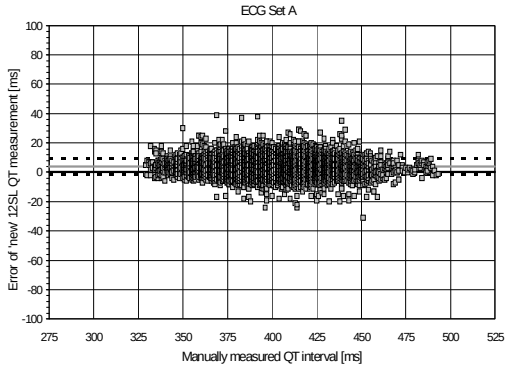

Figure 7. Bland-Altman plots of QT difference between the algorithm and cardiologists. Total ECGs 15,194. The mean difference is 3.95 ±5.5 msec.

For the test of QT interval vs. APD, the correlation coefficient is 0.99 and the root-mean-square difference is 17 msec, 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 msec shorter than the maximum APD.

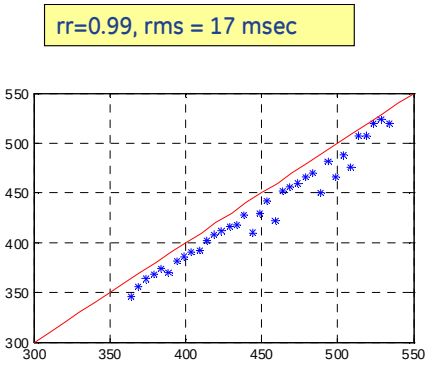

Figure 8. The cross-correlation between QT estimation and the maximum action potential durations

4. Discussion and conclusions

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

The modeling test approach used in this study revealed essence of what QT measurement is against to, i.e. the action potential duration of the cardiac cells. Therefore, comparing QT intervals to APD can make a more objective comparison. The results show that the QT measurements using the developed algorithm has an excellent correlation with the APD. 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. For any automatic ECG algorithm, the thresholds used for the onset/offset detection cannot be set to 0 due to noise issues. We can reasonably assume that even so called clean ECGs have noise. That's why it is not practical to chase 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.

The general approach adopted in our QT algorithm is from global to individual. The global information for multi-lead and multi-beat signals has a higher signal-to-noise ratio, therefore provides a more robust estimation. Any necessary individual estimation can be derived based on the global result.

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