ECG MEASUREMENT OF QT INTERVAL

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The QT interval of the ECG is the duration of time from the onset of ventricular depolarization (QRS onset) to the end of ventricular repolarization (T wave offset). Measurement of the QT interval is strongly dependent on ECG methodology and evolving ECG technology. A recent AHA/ACC/HRS document has reviewed in detail the often profound effect of changing digital ECG methodology on measurements and diagnostic statements.[1]

Other presentations in this symposium address why we need to measure the QT interval. This presentation addresses the methodological questions and choices that affect QT measurement outcome.[1,2] What do we measure to derive a QT interval? This varies, from a single lead individual QT duration from the raw ECG tracing, to a single lead "representative" (averaged) QT duration, to a "global" QT duration from the earliest onset of the QRS complex to the latest offset of the T wave in multiple leads. How do we measure a QT interval? This also varies, from manual measurement from a paper ECG, to computer-based measurement from an automated algorithm, to manual adjustment of a computer-based automated measurement.

Even the definition of QT interval varies, from physician and research organization custom to different proprietary engineering solutions that are applied by manufacturers of electrocardiographs and ECG review stations. How do we define the end of the T wave? The end of single lead raw ECG and single lead "representative" complex QT intervals can be derived by drawing a tangent from the descending limb of the T wave to the baseline or it can be derived from visual estimation of the return of the T wave to the baseline. Inclusion or exclusion of a prominent U wave in one or more leads will change the measurement, and measurement is altered by ECG gain. The end of a "global" QT interval can be derived from clustering of lines of superimposed "representative" complexes from all leads, or by averaging of multiple individual leads with low noise, or by measuring from a spatial vector T wave derived from all leads. Each produces a different result.

Current generation digital electrocardiographs are able to reduce beat to beat signal noise in a single lead by averaging all normal complexes in that lead during a 10 second acquisition period, to produce a "representative" complex for that lead. Most automated measurements in single leads of digitized ECGs are made from the representative complexes.

See Figures 1 and 2

It must be recalled that the 12 leads of the standard ECG represent specified locations of recording of the electrical activity of the heart from the body surface.

However, the underlying electrical activity of the heart occurs in a 3 dimensional space. Projection of this activity onto specific locations on the body surface results in multiple views of the same electrical events. At some locations, the earliest electrical activity of a waveform might not be apparent, and at some locations, the latest electrical acitivity of a waveform might not be apparent (when these electrical forces are perpendicular to the lead axis). With respect to the QT interval, therefore, the earliest onset of the QRS complex and the latest offset of the T wave might not be apparent in any single lead—indeed, each measurement point might be present on different ECG leads, and this is often the case.

How can we detect the earliest onset and latest offset of waveforms in a multilead ECG? Because digital aquisition allows all 12 ECG leads to be recorded simultaneously, it is possible for the electrocardiograph to align and measure all complexes at once, including the representative complexes that are constructed for each lead. This can be visualized as superimposition of all 12 of the representative complexes, as shown below, but the actual process may involve creation of a spatial vector signal from multiple leads that eliminate the isoelectric measurement problem that occurs with single leads. Simultaneous representative complexes allow the earilest onset of a waveform in any lead and the laterst offset in any lead to be used for measurement of the interval, which is known as a “global” duration. From the definition of “global,” it should seem intuitively likely that “global” durations should exceed durations measured from individual “representative” complexes.

See Figures 3 and 4

As a result of the available choices regarding how QT is defined and measured, and what type of ECG signal is measured, it is not surprising that the measurement of QT interval is dependent on ECG methodology.[3-5] This means that a QT interval derived in one way will be different from a QT interval derived in a different way, and the differences can be substantial. An immediate consequence is that all QT measurements within subjects, and all direct comparisons of QT measurements between subjects, must be made with identical methodology. Examples of QT measurements from 3 averaged sequential raw lead II ECG cycles, from the lead II representative complex by both baseline and tangent methods, and from the global complex formed by superimposition of all 12 representative complexes are shown below.

See Figures 5 – 9

These differences in QT interval according to method are not an issue of “right” and “wrong,” but rather an issue of recognition of consequential differences between methods.[4-6] As predicted, QTc intervals from global measurements are significantly greater, by 10-15 ms, than measurements made from individual representative complexes.[6] Although QTc (Bazett) rather than absolute QT is

shown here, rate correction has no confounding effect on these differences because the rates are identical for each set of measurements. Interestingly, time alignment of the representative complexes indicates that not all of the differences are due to variation in determination of the end of the T wave—about a third of the greater QT with global measurement is due to earlier detection of the onset of the QRS complex.

See Figures 10 and 11

Whether one or another method for the measurement of QT is "better" has not been established. It is clear that each of the methods is capable of detecting differences in QT caused by QT prolonging drugs and the small differences in QT interval caused by moxifloxacin when used as an active control.[3,4] It seems likely that the "best" method will evolve from the measurement that has high sensitivity to change with the smallest intertest variability (ie, greatest reproducibility). These methodologic characteristics should favor smaller numbers of subjects in costly thorough QT studies, but it must be acknowledged that experience with different methods varies among users, and often what is familiar and comfortable is what tends to be done best.

The key point is that both within and between studies, the QT method must be constant throughout acquisition and analysis of data. If not, QT differences may reflect technical rather than biologic change. As a simple example, changing from single lead tangent measurement of QT to global measurement of QT during the course of a drug study would likely result in marked QT prolongation, even with no drug effect on QT. Similarly, changing from global to single lead QT measurement during a drug study would likely mask a QT prolonging effect. As another example, statistical data on QT intervals within one population cannot be reliably compared with similar data in another population if the recording methods and analytic methods are not identical.

Can automated measurements of QT interval provide stability of methodology for the evaluation of drug effects on the heart? This is possible, but at present (with no consistent medical defininition available) algorithms for measurement of QT represent proprietary engineering solutions that vary from manufacturer to manufacturer. Even within manufacturers, evolving algorithm development can result in different QT measurements according to specific generation of software used in otherwise technically similar electrocardiographs. Rate corrected QT intervals from two generations of algorithms from simultaneous recordings with electrocardiographs from Philips Medical Systems and from General Electric Healthcare are shown below.[7] Each of the 4 algorithms are in current use in the US. Note that evolving algorithms of both manufacturers have resulted in substantially longer "global" QT measurements that are 15-26 ms greater than earlier generation results.

See Figure 12

The newest generation equipment of each manufacturer provides similar mean values for QT in a hospital based population, as seen above. However, a Bland-Altman plot comparing the algorithms indicates considerable scatter around the mean difference, indicating important disagreement regarding individual results.

See Figure 13

Differences in QT measurements between newest generation algorithms are greatest for abnormal ECGs, as might be expected from differences in methodologic definition of the end of the T wave in these programs. Again, disparity here is not necessarily a matter of “right” and “wrong,” but it does highlight the dependence of automated output on method.

See Figure 14

In summary, QT interval measurements are strongly dependent on ECG technology and methodology. “Global” ECG intervals are systematically larger than intervals from individual single lead “representative” complexes. Automated interval measurements evolve and vary with the measurement algorithm, and differences between manufacturers increase as ECGs become more abnormal. From a practical standpoint, the “best” method for measurement of QT should be the method with high sensitivity for the detection of change that has the greatest reproducibility.

References

1. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, van Herpen G, Kors JA, Macfarlane P, Mirvis DM, Pahlm O, Rautaharju P, Wagner GS, Josephson M, Mason JW, Okin P, Surawicz B, Wellens H. Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation*. 2007;115:1306-24.

2. Kautzner J. QT interval measurements. *Card Electrophysiol Rev*. 2002;6:273-277.

3. Sarapa N, Morganroth J, Couderc JP, Francom SF, Darpo B, Fleishaker JC, McEnroe JD, Chen WT, Zareba W, Moss AJ. Electrocardiographic identification of drug-induced QT prolongation: assessment by different recording and measurement methods. *Ann Noninvasive Electrocardiol*. 2004;9:48-57.

4. Azie NE, Adams G, Darpo B, Francom SF, Polasek EC, Wisser JM, Fleishaker JC. Comparing methods of measurement for detecting drug-induced changes in the QT interval: implications for thoroughly conducted ECG studies. *Ann Noninvasive Electrocardiol*. 2004;9:166-174.

5. Malik M. Errors and misconceptions in ECG measurement used for the detection of drug induced QT interval prolongation. *J Electrocardiol*. 2004;37 Suppl:25-33.

6. Kligfield P, Tyl B, Maarek M, Maison-Blanche P. Magnitude, mechanism, and reproducibility of QT interval differences between superimposed global and individual lead ECG complexes. *Ann Noninvasive Electrocardiol*. 2007;12:145-152.

7. Kligfield P, Hancock EW, Helfenbein ED, Dawson EJ, Cook MA, Lindauer JM, Zhou SH, Xue J. Relation of QT interval measurements to evolving automated algorithms from different manufacturers of electrocardiographs. *American Journal of Cardiology*. 2007;99:711-713.

Fig 1

DIGITAL ACQUISION AND ALIGNMENT OF 12 SIMULTANEOUS LEADS

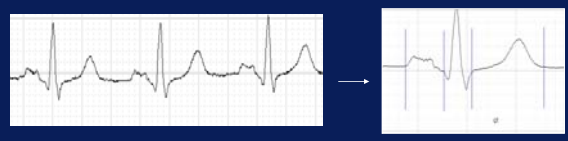
10 seconds of data in each lead can be averaged

Fig 2

FORMATION OF SINGLE LEAD "REPRESENTATIVE COMPLEX"

Creation of representative single complexes:

- Formation of "representative complex" for each lead during 10 sec of recording, with digital synthesis of a single average or median complex

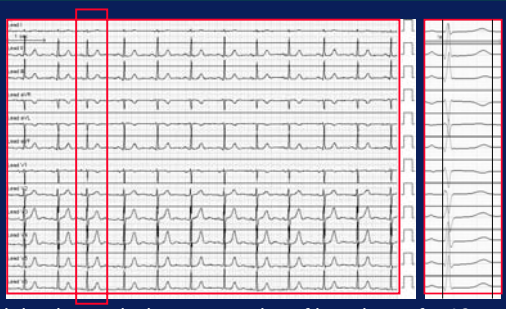


Sequential complexes with variation

Single average complex for each of 12 leads

Fig 3

DIGITAL ACQUISION AND ALIGNMENT OF 12 SIMULTANEOUS LEADS



Each lead records the same series of heartbeats for 10 sec, and each aligned representative complex comes from same beats

Fig 4

FORMATION OF MULTIPLE LEAD "GLOBAL" SIGNAL

Creation of global temporal signal:

- "Superimposition" of all temporally coherent representative complexes by alignment or by formation of a single spatial vector magnitude complex from individual lead data

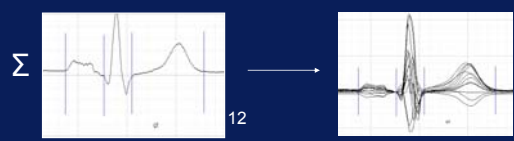


Fig 5

EFFECT OF METHOD: QT FROM STANDARD SIGNAL COMPLEXES

Measurements from 3 sequential raw lead II complexes

Lead II

Average QT = 377 ms

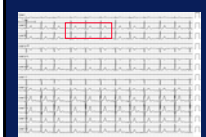
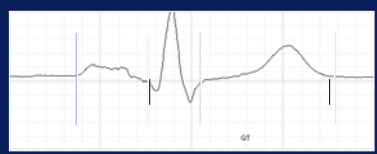


Fig 6

EFFECT OF METHOD: QT FROM REPRESENTATIVE COMPLEX

Baseline measurement from lead II representative complex

Lead II



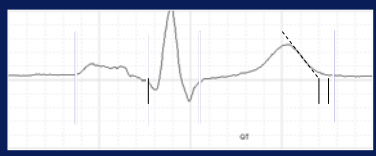
End of T: QT = 390 ms
(vs 377 ms average)

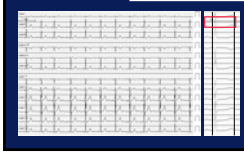
Fig 7

EFFECT OF METHOD: QT FROM REPRESENTATIVE COMPLEX

Tangent measurement from lead II representative complex

Lead II



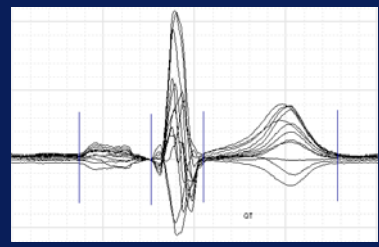


Tangent: QT = 370 ms
(vs 390 ms end of T)
(vs 377 ms average)

Fig 8

EFFECT OF METHOD: GLOBAL QT

All 12 leads



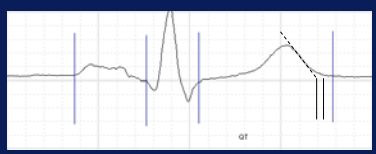
QT = 410 ms
(390 ms)
(370 ms)
(377 ms)

Superimposed representative complexes (average or median for each lead) indicate earliest onset and latest offset of waveform in any lead

Fig 9

GLOBAL MEASUREMENTS DIFFER FROM REPRESENTATIVE LEAD MEASUREMENTS

Lead II



QT = 410 ms
(390 ms)
(370 ms)

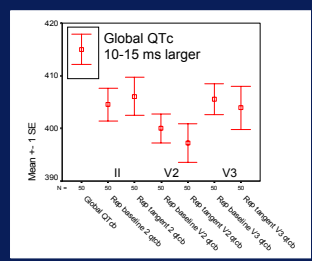
"Global" QT is longer than apparent QT of lead II "representative complex," for both baseline and tangent methods

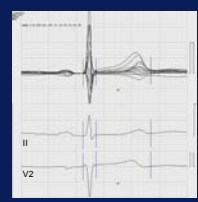
This is not necessarily an issue of "right" and "wrong," ....but it is an issue of consequential differences

Fig 10

GLOBAL AND REPRESENTATIVE QTc INTERVALS

QTc (rate corrected QT)





p<0.001 for Global QTc vs each of the other methods
(by repeated measures anova with post-hoc Bonferroni)

Fig 11

GLOBAL AND REPRESENTATIVE MATRIX QRS ONSET AND T WAVE OFFSET

QRS onset

T wave offset

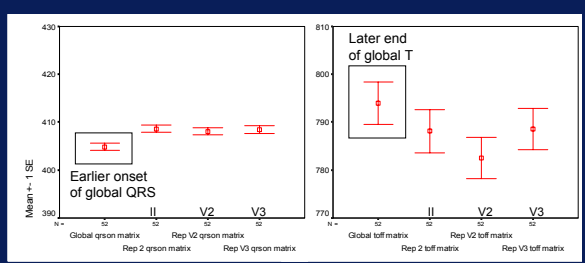
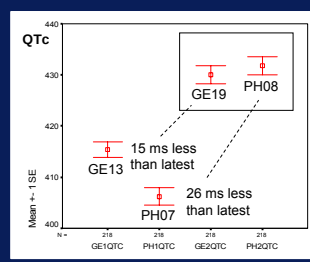


Fig 12

EVOLUTION OF GE AND PHILIPS AUTOMATED QTc ALGORITHMS

QTc from currently used GE and Philips algorithms



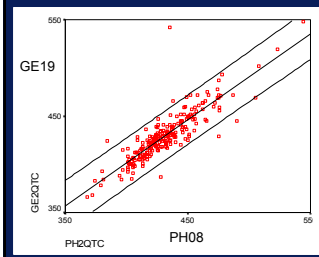
Mean PH08-GE19 difference= 1.8 ms, p = ns
SD diff = 13.2 ms

(n=218)

Fig 13

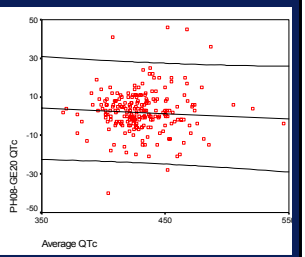
COMPARISON OF MOST RECENT GE AND PHILIPS AUTOMATED QTc ALGORITHMS

Regression (QTc, ms)



r2 = 0.76, SEE = 13.0 ms

Bland-Altman (95% confidence)

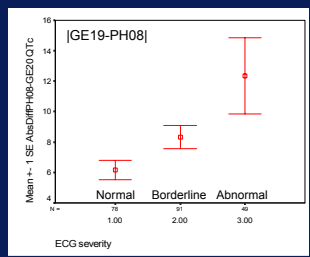


r2 = 0.003
95% confidence ± 26 ms

Fig 14

ECG ABNORMALITY AND DIFFERENCE IN AUTOMATED QTc INTERVAL

Absolute difference in QTc by current PH and GE algorithms



Measurement difference increases with ECG abnormality