Automated QT Measurement and Application to Detection of Moxifloxacin-Induced Changes

David W. Mortara, Ph.D.

From Mortara Instrument, Milwaukee, WI

Background: Concern for drug-induced QT prolongation has caused significant investment in QT measurement to safety-test new compounds. Manual methods are expensive and time-consuming. Reliable automatic methods would be highly desirable.

Methods: Twelve-lead Holter recordings were annotated beat-to-beat by an automatic algorithm for global QRS onset and T offset. T offset was established from the time of peak T downslope plus a rate-dependent offset, analogous to the "tangent method," wherein T offset is determined by extrapolating the T downslope to an intersection with the baseline.

Results and Conclusions: Variances of the beat-to-beat QT measurements were in the range 2.5–3.4 ms over three distinct databases, including a large heart failure database. Application to a moxifloxacin/placebo control database of 29 subjects showed excellent results.

Ann Noninvasive Electrocardiol 2009;14(Suppl. 1):S30–S34

QT; Holter; 12-lead; beat-to-beat; moxifloxacin

The last two decades have seen a resurgence of interest in ECG repolarization effects. Initially, this interest was driven by research on long QT syndrome (LQTS) and the correlation of long QT intervals with sudden cardiac death. Subsequently, QT prolongation induced by drugs—acquired LQTS—was found to have a similar risk. Concern about acquired LQTS has resulted in extensive QT safety testing for new pharmacologic compounds.

The QT interval is rate, drug, and autonomic tone dependent. Isolation of a drug effect, if it exists, mandates control of, or correction for, changes due to rate and autonomics. A consequence is the need for multiple assessments of the QT interval over extended periods of time, with positive control and placebo arms included. In this context, manual methods are expensive and time-consuming. Reliable automatic methods would be highly desirable. This report focuses on a successful approach to automated serial QT measurement.

METHODS

The data for this study was acquired from Mortara Instrument H12+ Holter recorders. Twenty-

four hours (sometimes abbreviated) of 12-lead simultaneous data, sampled @ 1000 s/s, with 3.75 microvolt resolution, constituted each recording. Three separate populations were studied: (1) 32 Mortara Instrument employees (CE group), (2) 384 congestive heart failure patients (HF group), and (3) 29 healthy volunteers in a moxifloxacin/placebo "thorough QT" test (MP group). The MP group was part of larger 3-way crossover design study, wherein moxifloxacin was used as a positive control for the detection of QT prolongation in a third test compound. Nine total recordings on each subject in this group were used for this study, composed of three consecutive twenty-four-hour recordings on placebo, a second group of three consecutive recordings with moxifloxacin (400 mg) given on the start of the second day, and a third group taking a test compound (without detected QT change) on the second day. The seventy-two-hour recording periods were separated by at least seven days.

Each of the tested groups included both sexes. Details of the respective profiles are not deemed relevant in this study, as no inferences are drawn from the results regarding particular attributes of any one of the groups.

QT measurement is conventionally a process applied to a single cardiac cycle, possibly averaged. The QT measurement algorithms used in this study are part of the proprietary Mortara Instrument VERITAS algorithm set. The process is multi-lead, using landmarks determined by the earliest QRS onset and the latest T wave offset. The T wave offset itself is set at the point where the local slope magnitude, derived from the available leads, falls below a threshold proportional to the T amplitude. We will refer to this as the static QT measurement process (QT_{Stat}). Although QT_{Stat} is a robust, stable, and accurate method, variability does occur in sequential measurements of QT on the same subject. While some of this variability is physiologic (true), some is false. False changes occur primarily because the signal amplitudes/slopes at the end of T have a poor signal-to-noise ratio.

Continuous QT measurement (QT_{Cont}) is especially appropriate in the context of QT safety testing, where changes in QT are more important than the absolute QT duration. We show in this study that the relative accuracy of QT_{Cont} can be im-

proved by using a well-determined fiducial near, but not at the end of the T wave. We have chosen the point of the maximum downslope (upslope in the case of negative T waves) of the T as the fiducial. In this approach the QT_{Cont} interval has two segments: (1) QRS onset to the point of maximum T downslope (QT_d) and (2) T downslope to T end (T_{d-e}). Figure 1 provides an illustration of these segments. The QT_d segment captures the majority of QT dynamic behavior and can be measured accurately on a beat-to-beat basis. The T_{d-e} segment exhibits only minor beat-to-beat variation and is measured indirectly. The concept is expanded to the multilead environment by substituting the spatial velocity, defined by square root of the sum of squared slopes over the independent leads, for the slope in a single lead.

RR values used for determining cycle length specific averages, and for QT/RR modeling, are a weighted average of individual RR's preceding each beat. The method and rationale of this weighting will be published elsewhere.

The first segment of the QT interval, QT_d , is well determined by landmarks at QRS onset and peak T downslope. The second segment, T_{d-e} , is bounded by peak T downslope and T end. This latter segment is more difficult to measure on a beat-to-beat basis. Since the typical magnitude is ~ 50 ms, it is a relatively small portion (10–15%) of the total repolarization cycle. Our initiative is to model this small segment to have a linear dependence on cycle length. Our QT_{Cont} reflects a direct measure of 85–90% of the repolarization cycle, and a patient-specific modeling of the remaining 10–15%. The model parameters are the slope of the linear T_{d-e} /RR dependence and a "pivot" cycle length. Values of T_{d-e} are determined using average cardiac cycles, wherein the determination of T end (QT_{Stat}) is made more robust by the lower noise of the average cycles. Using multiple average cardiac cycles, each average made up of cycles with a preceding RR in a specific range, allows the cycle length dependence of T_{d-e} to be evaluated. The pivot cycle length is selected from the most populous cycle length range. Expressed algebraically:

$$QT_{Cont}(i) = QT_d(i) + T_{d-e}(i)$$

and

$$T_{d-e}(i) = T_0 + S_2 \times (RR(i) - RR_p),$$

Figure 1. Graphic portrayal of QT interval segments used in this study. The onset of the T_{d-e} interval is at the peak of the spatial velocity (absolute slope) of the descending limb of the T wave.

where “i” is a beat number, T_0 is the value of $T_{d-e}(i)$ at the pivot cycle length (RR_p), S_2 is the linear slope reflecting $T_{d-e}(i)$ dependence on cycle length, and $RR(i)$ is the cycle length for a given beat. The T_{d-e}/RR slope, S_2 , is derived by least squares from values of $QT_{Stat} - QT_d$ measured in RR interval selected average cycles at 50 ms increments. T_0 , S_2 , and RR_p are constants for each twenty-four-hour recording.

Not every cardiac cycle will yield a meaningful QT_{Cont} . Examples include periods of noisy data, cycles with no identifiable T peak,—without which the downslope is undefined, and ectopic cycles. We also exclude cycles with potential QT_{Cont} values more than 30 ms from an “expected” value, determined by an adaptive average of prior measurements. Apart from this last limitation, each value of QT_{Cont} is statistically independent. Six percent of the total available cycles were excluded for all of the above reasons in the most extreme case (HF group).

QT/RR slopes were determined for QT_{Cont} , using a linear model. The RR interval used was not the prior RR, but a composite, weighted average of previous intervals based on a method to be published separately. The QT/RR slope was obtained from all measured cycles over the full 24 hours.

RESULTS

Table 1 summarizes the significant results from each of the studied populations. The standard deviation ($QT-RMSSD$) of QT_{Cont} was calculated for each recording as the standard deviation of the suc-

cessive differences of QT_{Cont} over valid cycles, divided by the square root of two, based on the assumption of statistical independence of the each cycle’s measurement.¹ To the extent that the true QT_{Cont} does not vary significantly on a beat-to-beat basis, $QT-RMSSD$ reflects the measurement error. Table 1 reports the average $QT-RMSSD$ in each of the different populations, and the 90th percentile value. The proximity of latter to the former is a measure of the consistency within each population. The HF group shows the greatest disparity, and this is attributed to the more complex, lower amplitude, and greater range of T wave morphologies in this group.

Another perspective on QT_{Cont} variation is provided by the root-mean-square (RMS) deviation of QT_{Cont} from an optimum QT/RR slope ($QT-RMS$). The mean values of $QT-RMS$ from each of the studied populations show little difference (6.1–6.8 ms). $QT-RMS$ is presumed to reflect primarily the inadequacies of the linear model for QT as function of RR interval and the variation of QT with other physiologic parameters, such as autonomic tone. The values for the MP group include those where moxifloxacin was taken the same day, although this pertains to only 1/9 of the total recordings for the group.

Included in Table 1 are the total QT/RR slope and the T_{d-e}/RR slope. The total slope values are rather high in all groups, possibly reflecting the use of the weighted RR to derive the slopes.² The rate dependence of the terminal T_{d-e} segment is shown graphically in Figure 2 and observed to be reasonably linear with, and to have only modest dependence on, cycle length.

Table 1. Various QT Measures from Study Groups

Group	CE	MP	HF
Number of subjects	32	29	384
Number of recordings	32	261	384
QT-RMSSD (ms)	3.1 ± 0.8	2.5 ± 0.5	3.4 ± 1.5
QT-RMSSD 90th percentile (ms)	4.3	3.7	6.1
QT-RMS (ms)	6.6 ± 1.4	6.1 ± 1.1	6.8 ± 2.1
QT/RR slope	0.20 ± 0.04	0.19 ± 0.05	0.24 ± 0.07
T_{d-e}/RR slope	0.02 ± 0.03	0.02 ± 0.02	0.04 ± 0.06

All measurements are the averages for the groups, apart from the $QT-RMSSD$ 90th percentile. Standard deviations (±) are included where appropriate.
CE = Company employees; MP = Moxifloxacin/placebo clinical trial; HF = Heart failure group; $QT-RMSSD$ = Root-mean-square of successive differences of QT_{Cont} , divided by square root of two; $QT-RMS$ = Root-mean-square deviation of QT_{Cont} from linear QT/RR model; QT_{Cont} = Beat-to-beat QT; QT/RR slope = Least-mean-square slope from linear QT/RR model, using individual cycles; T_{d-e}/RR slope = Linear dependence of the terminal segment of QT on RR interval.

Figure 2. Cycle length dependence of terminal QT segment (T_{d-e}) duration. The mean duration of the T_{d-e} interval, plotted against cycle length, for each of the three studied populations.

The foregoing methodology has been applied to the MP group data to derive what is known as the " Δ - Δ " plot. This plot is constructed by first subtracting a baseline twenty-four-hour period from the rate-corrected QT (QT_c) trend over 24 hours following a drug dose and then subtracting a similar twenty-four-hour trend of QT for the placebo less

the placebo baseline. Figure 3 shows this plot for our MP data. Sample points are taken at 15-minute intervals and show one standard deviation limits. Each sample point is derived from the median QT_c over valid measures within ± 1 minute of the time point. Rate-correction was performed using individual QT/RR slopes. The last hour is not plotted

Figure 3. Delta-delta plot showing QT prolongation due to moxifloxacin. Δ - Δ plot ((Moxifloxacin - Moxifloxacin control) - (Placebo - Placebo control)), sampled at 15 minute intervals and showing one standard deviation limits.

due to missing data from some of the recordings. The mean (over all sample points) standard deviation is 2.0 ms.

Interestingly enough, the dynamic behavior of QT_c is not dependent on the T_{d-e}/RR slope. In the linear QT/RR model,

$$QT_c(i) = QT_{Cont}(i) + (S_1 + S_2) \times (1000 - RR(i))$$

or

$$QT_c(i) = QT_d(i) + S_1 \times (1000 - RR(i)) \\ + S_2 \times (1000 - RR_p) + T_0,$$

where S_1 is the QT_d/RR slope. The last two terms above are constants for a given recording, and thus, QT_c dynamically depends only on QT_d and RR . Consequently, the $\Delta-\Delta$ plot only has a constant offset when the T_{d-e}/RR slope correction is applied to the QT_d measures (1.2 ms in the present study).

CONCLUSIONS

The results show that the time of the maximum downslope of the T wave can be measured accurately over a diverse population of ECG morphologies, including a large sample of congestive heart failure recordings. Unaccounted for variation of QT was as small as 2.5 ms, and only 3.4 ms in the HF group.

Direct comparison with alternative QT measurement methodologies is hampered by the lack of common databases used for reporting. The use of databases with dissimilar noise levels and T wave morphologies limit the conclusions that may be drawn. Even the definition of QT variation varies—while this study measures the internal consistency of QT values, others use external manual QT measures as the reference. Nevertheless, the results obtained in this study compare favorably with those found by Hnatkova et al.,³ who report a range of QT variation from 5.5 to 9.5 ms from two clinical

studies, using healthy volunteers. Moreover, our result of 2.5 ms in a similar population is based on single-beat measurements, while the former is based on noise-reduced composite cardiac cycles over 10 seconds.

A litmus test for a successful QT measurement methodology is the appropriate detection of moxifloxacin-induced QT prolongation in the positive control arm of a drug study. The data in Figure 3 clearly demonstrates such a success. A maximum QT prolongation of 13 ms is observed 4–5 hours after dosage, with a 6 ms residual prolongation after 23 hours. The mean RMS variability is 2.0 ms, with minor fluctuation over the observation period. Remarkably, this result is achieved with only 29 subjects in the study.

Hypothetically, a limitation of the use of the T downslope maximum as a surrogate for T end would occur in a situation where the increase of QT occurs primarily in the T_{d-e} segment. In all cases where the T_{d-e} segment changes disproportionately to the other components of the repolarization interval, the extent of QT change will be underestimated.

Acknowledgments: Thanks are due to Terrence Fullerton of Pfizer for providing the MP data set and to the GISSI-HF investigators⁴ for permission to use the HF data set.

Conflicts of Interest: None.

REFERENCES

1. Glantz S. Primer of Biostatistics, 6th Edition, McGraw Hill, 2005, pp. 77–80.
2. Coumel P, Fayn J, Maison-Blanche P, et al. Clinical relevance of assessing QT dynamicity in Holter recordings. *J Electrocardiogr* 1994;27:62–66.
3. Hnatkova K, Gang Y, Batchvarov V, et al. Precision of QT measurement by advanced electrocardiographic equipment. *Pace* 2006;29:1277–1284.
4. Tavazzi L, Tognoni G, Franzosi MG, et al., for the GISSI-HF Investigators. Rationale and design of the GISSI heart failure trial: A large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004;6:635–641.