Automated QT Interval Measurement in Holter ECGs Recorded at 180 and 1000 samples/second

GK Panicker[1], V Salvi[1], DR Karnad[1], P Macfarlane[2], E Clark[2], A Ramasamy[1], S Kothari[1], D Narula[1]

[1]Quintiles Cardiac Safety Services, Mumbai, India
[2]University of Glasgow, Glasgow, UK

Abstract

To study the effect of sampling rate on automated QT measurements, Holter ECGs were recorded at 180 and 1000 samples/second (s/s) using 2 recorders; 30 ECG snapshots were extracted at varying heart rates from 16 healthy subjects and re-sampled to 180, 500 or 1000s/s using the Antares software. QT interval by CalECG algorithm was longer (5.0±6.3 ms, $p<0.001$) in 180s/s ECGs than in 1000s/s ECGs. It decreased to 2.1±5.8ms when 180s/s ECGs were re-sampled to 500s/s, and to 2.6±6.2ms at 1000s/s. It also decreased progressively on resampling both sets of ECGs to 1000s/s (2.6±6.2ms), 500s/s (1.8±5.5ms) and 180s/s (0.4±5.9ms). Differences in QT interval were independent of the QT measurement algorithm used: University of Glasgow (Uni-G) program and CalECG for 500s/s ECGs; Veritas and CalECG for 1000s/s ECGs. Thus, QT interval is longer in ECGs with lower sampling rates; resampling them to a higher resolution partially compensates for this.

1. Introduction

Digital 12-lead resting ECGs are used in clinical research or drug trials for studying changes in various intervals in the ECG. Regulatory guidelines require that studies designed to detect QTc prolongation by a new drug are able to detect a mean prolongation of 5 milliseconds (ms).[1] Electrocardiographs with a sampling rate of 500 or 1000 s/s are used for this purpose. Improvements in acquisition and storage technology have permitted recording of longer durations of continuous 12-lead Holter ECG recordings at sampling rates of up to 1000 samples per second (s/s). However, due to cost constraints, 12-lead Holters with lower sampling rates are still used in many studies.

Holter ECGs recorded at 180 s/s have data points that are 5.6 ms apart. Is the QT interval in these ECGs comparable with that in Holter ECGs recorded at 1000 s/s where data points are 1 ms apart? This question is more pertinent when a computer algorithm is used for measurement of various intervals as automated QT measurement algorithms place annotations on sample points and not between them. Moreover, many computer programs can only analyze ECGs at a specified sampling rate. Consequently, digital 12-lead Holter recordings acquired at lower sampling rates are often up-sampled to a higher sampling rate, before further analysis. This involves interpolation of data values between actual samples. How up-sampling affects automated QT measurement in digital ECGs acquired at a lower sampling rate is not clear. We, therefore, studied QT interval measurements in Holter ECGs recorded at 180 and 1000 s/s with and without resampling.

2. Material and methods

Two 12-lead Holter recorders (Model H12+, Mortara Instrument, Milwaukee, WI) were connected using dual-snap electrodes and 5 hour recordings acquired simultaneously from 16 healthy volunteers. One Holter device recorded the digital ECG signal at a sampling frequency of 180 s/s and the other at 1000 s/s, with a 16-bit amplitude resolution (2.5 μV). 10-second ECG snapshots were extracted from the simultaneous Holter recordings at 30 identical time-points from each subject. Snapshots were extracted at heart rates between 50-60 bpm, 61-70 bpm, 71-80 bpm, 81-90 bpm, 91-100 bpm and ≥101 bpm. Thus, 480 ECGs at a sampling rate of 180 s/s and 480 simultaneous ECGs at a sampling rate of 1000 s/s from 16 subjects were obtained.

ECG resampling

ECGs recorded at 180 s/s were up-sampled to 500 s/s and 1000 s/s and those recorded at 1000 s/s were down-sampled to 500 s/s and 180 s/s using commercially available software (Antares version 2.2.3, AMPS LLC, New York)[2] and converted to HL7 compliant XML files. Thus, six sets of ECGs were created – 180 s/s without resampling; 180 s/s resampled to 500 s/s, 180 s/s resampled to 1000 s/s and 1000 s/s without resampling, 1000 s/s resampled to 500 s/s and 1000 s/s resampled to 180 s/s. ECGs recorded at 180 s/s were also up-sampled to 1000 s/s using another software application (H-Scribe, Version 4.3, Mortara Inc), thereby creating seven sets.

ECG interval / duration measurements

ECG intervals were measured by 3 algorithms: CalECG version 2.7 (A.M.P.S. LLC), the University of Glasgow Program version 27.1 (Uni-G) and the Veritas (Mortara Inc) algorithm. All six sets of ECGs were analyzed using CalECG algorithm which can measure ECG intervals on digital ECGs at any sampling rate.[3] ECGs resampled to 500 s/s were also analyzed by the Uni-G algorithm which analyzes ECGs only at 500 s/s.[4] ECGs at 1000 s/s and 180 s/s up-sampled to 1000 s/s using H-Scribe® software were also analyzed by the Veritas algorithm which operates only on ECGs at 1000 s/s.[5]

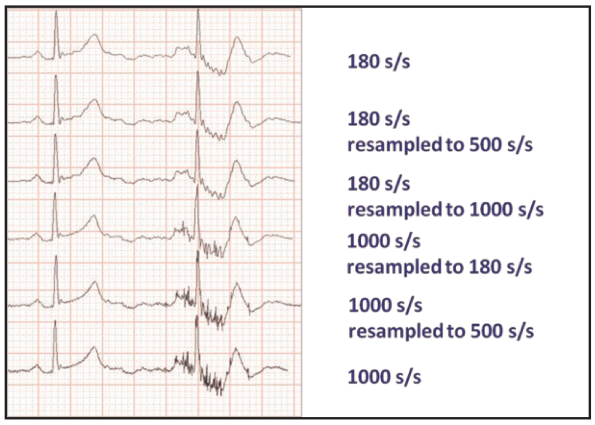
Statistical methods

Means and standard deviations (SD) of differences between original and resampled ECGs were obtained and the Bland-Altman limits of agreement (LOA) calculated. The range of the limits of agreement defines the limits within which 95% of the differences between 2 sets of ECGs lie. Paired t-test was used to compare QT intervals in corresponding ECGs at various sampling rates.

3. Results

QT intervals were measured in ECG sets at their original sampling rate and after resampling to 180 s/s, 500 s/s and 1000 s/s. The effects of resampling ECGs recorded at the original sampling rate of 180 s/s and 1000 s/s is shown in a representative tracing in Figure 1.

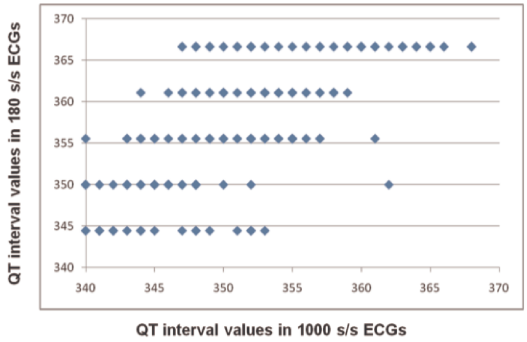
Figure 1. Effects of resampling ECGs recorded at the original sampling rate of 180 s/s and 1000 s/s



Comparison of ECGs at 180 s/s at various resampled rates with ECGs at 1000 s/s

The ECG recorded at 1000 s/s and annotated at 1000 s/s was considered as the 'gold standard'. The mean QT interval in this set of ECGs was 345 ms (SD = 21 ms, minimum 282 ms and maximum 413 ms). In comparison, mean QT interval in the ECGs recorded at 180 s/s was 350 ms (SD = 22 ms, minimum 283 ms and maximum 411 ms). Thus, the QT interval in ECGs recorded at 180 s/s was measured as longer by a mean of 5.0 ms (SD=6.3 ms; $p < 0.001$) (Table 1). The mean difference decreased to 2.1 ms when the ECGs acquired at 180 s/s were up-sampled to 500 s/s and to 2.6 ms when up-sampled to 1000 s/s (Table 1). We also found that automated QT intervals were measured to the nearest 1 ms in ECGs recorded at 1000 s/s while it was 5.6 ms in ECGs recorded at 180 s/s (Figure 2).

Figure 2. QT interval measurements in ECGs recorded at 180 s/s for simultaneous ECGs recorded at 1000 s/s



Analysis of the QRS duration and JT intervals in the same set of ECGs showed that the difference in QT interval in the ECGs recorded at 180s/s and at 1000 s/s was primarily due to differences in QRS duration and not the JT interval. (Table 1).

Comparison of ECGs annotated to a common sampling rate

Both sets of ECGs were resampled to the same sampling rate and were analyzed using the CalECG algorithm. The mean difference in QT intervals when both sets were read at 1000 s/s was 2.6 ms. It decreased to 1.8 ms when both sets were resampled and analyzed at 500 s/s, and decreased further to 0.4 ms at 180 s/s. (Table 2)

Comparison of ECGs annotated by different QT measurement algorithms

To compare the performance of QT measurement algorithms, ECGs acquired at 180 and 1000 s/s were resampled to 500 s/s and analyzed using CalECG and the Uni-G algorithms. The difference between sets of ECGs was comparable with both algorithms (Table 3). Similarly, a small difference was also seen when both sets of ECGs were analyzed by CalECG and Veritas algorithms at 1000 s/s (Table 3).

Comparison of up-sampling by two software applications

ECGs recorded at 180 s/s were up-sampled to 1000 s/s using two different software applications: H-Scribe and Antares. The difference between these up-sampled ECGs was 0.6 ms with SD of 5.5 ms (minimum -24 ms, maximum 21 ms), limits of agreement of -10.4 to 11.6 ms and the range of limits of agreement was 22 ms.

Table 1. Comparison of QT intervals measured by the CalECG algorithm in 12-lead digital Holter ECGs recorded at 180 s/s resampled to 500 and 1000 s/s compared to the 'gold standard' i.e. ECGs recorded at 1000 s/s

ECG interval	Comparison between ECG sets	Mean	Standard Deviation	Min Diff	Max Diff	LOA	Range of LOA	P value
QT	180 s/s vs 1000 s/s	5.0	6.3	-35.2	23.1	-7.6 to 17.7	25.3	<0.0001
	180 s/s@500s/s vs 1000s/s	2.1	5.8	-35	25	-9.5 to 13.8	23.3	<0.0001
	180 s/s@1000s/s vs 1000s/s	2.6	6.2	-37	38	-9.8 to 15.0	24.8	<0.0001
QRS	180 s/s vs 1000 s/s	4	5.2	-15.7	33.7	-6.4 to 14.3	20.7	<0.0001
	180 s/s @ 500 s/s vs 1000 s/s	2.1	4.2	-16	17	-6.3 to 10.5	16.8	<0.0001
	180 s/s @ 1000 s/s vs 1000 s/s	2.2	4.6	-16	20	-7 to 11.3	17.3	<0.0001
JT	180 s/s vs 1000 s/s	1.1	5.1	-21.8	17.9	-9.1 to 11.3	20.4	<0.0001
	180 s/s @ 500 s/s vs 1000 s/s	0	4.7	-22	30	-9.3 to 9.4	18.7	0.88
	180 s/s @ 1000 s/s vs 1000 s/s	0.4	4.5	-21	28	-8.7 to 9.5	18.2	0.04

All values in milliseconds. Min: Minimum, Max: Maximum

Table 2. Comparison of QT intervals measured by the CalECG algorithm in 12-lead digital Holter ECGs recorded at 180 s/s and 1000 s/s and resampled to identical sampling rates of 1000 s/s, 500 s/s and 180 s/s

Comparison between ECG sets	Mean	Standard Deviation	Min	Max	LOA	Range of LOA	P value
180 s/s@1000s/s vs 1000s/s	2.6	6.2	-37	38	-9.8 to 15.0	24.8	<0.0001
180 s/s @ 500 s/s vs 1000 s/s@ 500 s/s	1.8	5.5	-16	32	-9.3 to 12.9	22.1	<0.0001
180 s/s vs 1000 s/s @180 s/s	0.4	5.9	-22.2	22.2	-11.3 to 12.2	23.5	0.10

Table 3. Comparison of QT interval measurements re-sampled to the common sampling rate of 500 s/s (by CalECG and Uni-G) and 1000 s/s (by CalECG and Veritas)

ECG sampling rates	QT measurement software used	Mean	Standard Deviation	LOA	Range of LOA	P value
180 s/s@500s/s vs 1000 s/s @ 500 s/s	CalECG	5.0	6.3	-7.6 to 17.7	25.3	<0.0001
	Uni-G	2.1	5.8	-9.5 to 13.8	23.3	<0.0001
180 s/s @ 1000 s/s vs 1000 s/s	CalECG	4	5.2	-6.4 to 14.3	20.7	<0.0001
	Veritas	2.1	4.2	-6.3 to 10.5	16.8	<0.0001

4. Discussion

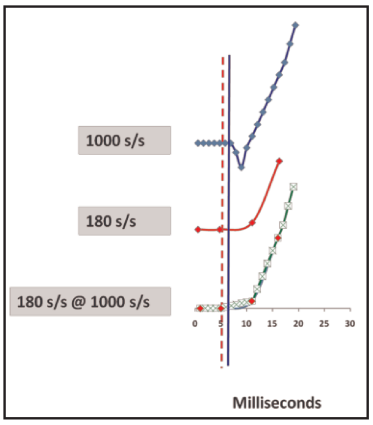
Using the Holter ECGs acquired at 1000 s/s as the gold standard, we found that the mean automated QT interval measurement in corresponding ECGs recorded at 180 s/s was greater than the gold standard by 5.0 ms. This difference decreased to 2.1 ms on up-sampling the 180 s/s ECGs to 500 s/s and to 2.6 ms at 1000 s/s. In order to identify why QT measurements are longer in ECGs recorded at 180 s/s than in corresponding ECGs acquired at 1000 s/s, we compared the QRS duration and JT interval in the same sets of ECGs. While the JT intervals were comparable in ECGs recorded at 180 s/s and 1000 s/s, the QRS duration was greater in the 180 s/s ECGs by a mean of 4 ms, suggesting that the difference in the QT intervals was almost entirely accounted for by the QRS duration and not the JT interval.

Previous studies have shown that sampling rate significantly influences the amplitude of high-frequency components of the ECG waveform; the QRS amplitude is lower in ECGs recorded at lower sampling rates.[6,7] The present study revealed that a lower sampling rate also affects the duration of high frequency components of the ECG waveform like the QRS complex; the QRS duration in ECGs acquired at 180 s/s was 5 ms longer than that in ECGs acquired at 1000 s/s. One possible explanation for this is that automated algorithms can place fiducial points only on sampling points (Figure 2).[3] Since the QRS onset is identified as the last data point on the PR interval and QRS offset as the first data point on the ST segment, these will be further apart on ECGs recorded at 180 s/s (Figure 3).

ECGs acquired at different sampling rates may also have to be re-sampled to a common rate because automated algorithms are programmed to perform at a specific sampling rate. The Uni-G algorithm measures QT interval only at 500 s/s while the Veritas algorithm measures QT intervals only at 1000 s/s. We found that the difference between QT intervals in ECGs recorded at 180 s/s and 1000 s/s decreased when both sets were resampled to the same sampling rate; the difference decreased progressively from 1000 s/s to 500 s/s to 180 s/s. Again, this is possibly because fiducial points are placed only on sample points.[3] Therefore, agreement between the two sets of ECGs is apparently best at 180 s/s where the sample points are 5.6 ms apart rather than when sample points are 1 or 2 ms apart at 1000s/s or 500s/s respectively. However, it must be remembered that ECGs at 180 s/s have a longer measured QT interval than the same ECG recorded at 1000 s/s. Therefore,

while agreement may be better at 180 s/s, this is achieved at the cost of accuracy.

Figure 3: Diagrammatic representation of the QRS onset in an ECG recorded at 1000 s/s, 180 s/s and the 180 s/s ECG up-sampled to 1000 s/s. A small negative deflection at the onset of the QRS complex is seen in the ECG recorded at 1000 s/s. In the same ECG recorded at 180 s/s the last point on the baseline comes earlier; the next sample point 5.6 ms later falls on the positive deflection of the QRS complex. Thus QRS onset is identified 2 ms earlier than in the 1000 s/s ECG and the negative deflection is missed by the lower sampling rate. When the 180 s/s ECG is up-sampled to 1000 s/s, additional points are placed between the second and third sample but they all have positive values. Thus QRS onset will probably be the same as in the ECG recorded at 180s/s or, possibly, on a data point one or two ms later. However, up-sampling will not recreate the negative deflection at QRS onset because the information in the 180 s/s ECG gives no indication of its presence to the up-sampling algorithm.



To compare the performance of two re-sampling software applications, we evaluated QT measurements in ECGs recorded at 180 s/s when up-sampled to 1000 s/s using H-Scribe® and Antares® and found no difference in QT intervals in ECGs up-sampled by the two applications. Similarly, QT interval measurements differed only minimally when ECGs at 500 s/s were analyzed by the Uni-G and CalECG applications and those at 1000 s/s were analyzed by the Veritas and CalECG applications. This suggests that QT measurements in ECGs acquired at 180 s/s and 1000 s/s were not affected by the QT measurement algorithms, but are largely affected by the acquisition rates.

In conclusion, a number of studies still use Holter ECGs acquired at 180 s/s to study drug-induced QT prolongation. Our study shows that the QT intervals measured in ECGs recorded at 180 s/s are significantly longer than in Holter ECGs at 1000 s/s. The limits of agreement too are wide and the measured QT interval in the two sets of ECGs may differ by up to 25 ms. This difference, largely due to data loss from high-frequency components of the ECG signal, is only partly compensated for by up-sampling the 180 s/s ECGs or re-sampling both sets of ECGs to a common sampling rate. These differences assume importance in a scenario where regulatory authorities require more accurate and reproducible technology for ECG acquisition and analysis to detect a QT prolongation of 5 ms.

Our conclusions are in agreement with the AAMI guidelines which recommend the use of ECGs acquired at 500 s/s or more for measurement of amplitudes and durations; lower sampling rates may be satisfactory for detection of arrhythmias and ischemia.[8,9] Up-sampling low resolution ECGs may theoretically improve performance of automated algorithms by providing more data points to the mathematical model to identify QRS onset and T offset. However, our data shows that the incremental benefit of resampling from 180 s/s to rates above 500 s/s is minimal, if indeed there is any.

References

[1] ICH Harmonized Tripartite Guideline E14 (2005). The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.Available at: www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf.

[2] Badilini F, Vaglio M, Sarapa N. Automatic extraction of ECG strips from continuous 12-lead holter recordings for QT analysis at prescheduled vs optimized time points. Ann NoninvasiveElectrocardiol. 2009;14(1 Suppl): S22-9

[3] Badilini F, Sarapa N. Implications of methodological differences in digital electrocardiogram interval measurement.J Electrocardiol. 2006;39(4 Suppl):S152-6

[4] PW Macfarlane, B Devine, E Clark.The University of Glasgow (Uni-G) ECG Analysis Program. Computers in Cardiology. 2005; 32: 451-4.

[5] Mortara DW. Automated QT measurement and application to detection of moxifloxacin-induced changes. Ann Noninvasive Electrocardiol. 2009;14(1 Suppl): S30-4.

[6] Gregg RE, Zhou SH, Lindauer JM, Helfenbein ED, Giuliano KK. What is inside the electrocardiograph? J Electrocardiol. 2008;41(1):8-14

[7] Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology. J Am Coll Cardiol. 2007 ;49(10):1109-27.

[8] Association for the advancement of medical instrumentation. Diagnostic electrocardiographic devices. ANSI/AAMI EC11:1991/(R) 2001. American National Standard.

[9] Association for the advancement of medical instrumentation. Ambulatory electrocardiographs. ANSI/AAMI EC38:1998 Standard. American National Standard.

Address for correspondence.

Gopi Krishna Panicker
Quintiles Cardiac Safety Services,
502 A, Leela Business Park,
Andheri, Mumbai- 400059 India.
gopi.panicker@quintiles.com.