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Comparison of automated interval measurements by widely used algorithms in digital electrocardiographs

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ABSTRACT

Background: Automated measurements of electrocardiographic (ECG) intervals by current-generation digital electrocardiographs are critical to computer-based ECG diagnostic statements, to serial comparison of ECGs, and to epidemiological studies of ECG findings in populations. A previous study demonstrated generally small but often significant systematic differences among 4 algorithms widely used for automated ECG in the United States and that measurement differences could be related to the degree of abnormality of the underlying tracing. Since that publication, some algorithms have been adjusted, whereas other large manufacturers of automated ECGs have asked to participate in an extension of this comparison.
Methods: Seven widely used automated algorithms for computer-based interpretation participated in this blinded study of 800 digitized ECGs provided by the Cardiac Safety Research Consortium. All tracings were different from the study of 4 algorithms reported in 2014, and the selected population was heavily weighted toward groups with known effects on the QT interval: included were 200 normal subjects, 200 normal subjects receiving moxifloxacin as part of an active control arm of thorough QT studies, 200 subjects with genetically proved long QT syndrome type 1 (LQT1), and 200 subjects with genetically proved long QT syndrome Type 2 (LQT2).
Results: For the entire population of 800 subjects, pairwise differences between algorithms for each mean interval value were clinically small, even where statistically significant, ranging from 0.2 to 3.6 milliseconds for the PR interval, 0.1 to 8.1 milliseconds for QRS duration, and 0.1 to 9.3 milliseconds for QT interval. The mean value of all paired differences among algorithms was higher in the long QT groups than in normals for both QRS duration and QT intervals. Differences in mean QRS duration ranged from 0.2 to 13.3 milliseconds in the LQT1 subjects and from 0.2 to 11.0 milliseconds in the LQT2 subjects. Differences in measured QT duration (not corrected for heart rate) ranged from 0.2 to 10.5 milliseconds in the LQT1 subjects and from 0.9 to 12.8 milliseconds in the LQT2 subjects.
Conclusions: Among current-generation computer-based electrocardiographs, clinically small but statistically significant differences exist between ECG interval measurements by individual algorithms. Measurement differences between algorithms for QRS duration and for QT interval are larger in long QT interval subjects than in normal subjects. Comparisons of population study norms should be aware of small systematic differences in interval measurements due to different algorithm methodologies, within-individual interval measurement comparisons should use comparable methods, and further attempts to harmonize interval measurement methodologies are warranted.

Measurements of intervals and durations are critical to clinical diagnoses made by automated electrocardiographic (ECG) algorithms.[1,2] Because some ECG measurement points, such as the end of the T wave and

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the end of the QRS complex, have no precise medical definition, individual algorithm manufacturers have evolved different engineering solutions to this problem. As a consequence, different automated algorithms may produce different measurements of the same underlying ECG waveform.[3-5] Even where measurement differences are small, systematic differences might have consequences for automated ECG interpretation that is based on discrete interval partitions, including serial studies of drug effects on the QT interval.[5-8] Furthermore, unrecognized systematic differences might confound measurement-based comparisons of normal values from epidemiological studies that might otherwise use different algorithms from different electrocardiographs.[9-11] A recent study found small differences in ECG interval measurements among 4 major algorithms that are currently widely used in the United States.[3] Since then, some modifications to measurement algorithms were undertaken by study participants. In conjunction with the study results and availability of additional ECGs, other manufacturers asked that the original study be expanded. Accordingly, we examined differences in automated ECG intervals measured by current-generation digital electrocardiographs from 7 different manufacturers in a new database from the Cardiac Safety Research Consortium (CSRC)[12,13] comprising normal subjects, subjects on moxifloxacin, and 2 expanded subgroups of subjects with genetically documented variants of long QT syndrome.[14,15] Our goal was to document whatever systematic differences might currently exist among widely used automated ECG measurement algorithms and to reexamine the hypothesis that the magnitude of interval measurement differences among algorithms is dependent on the degree of abnormality of the selected ECGs.

Methods

Participants

Seven manufacturers of computerized ECG analysis programs that are widely used around the world in automated electrocardiographs agreed to participate in the present study, which was performed during a supervised session at the 2016 annual meeting of the International Society for Computerized Electrocardiography in Tucson, AZ. Included in the study as participants are AMPS-LLC (New York, NY); GE Healthcare (Milwaukee, WI); The Glasgow Program, University of Glasgow (Glasgow, Scotland, United Kingdom); The Modular ECG Analysis System (MEANS) Program, Erasmus University Medical Center (Rotterdam, the Netherlands); Mortara Instrument (Milwaukee, WI); Philips Healthcare (Andover, MA); and Schiller AG (Baar, Switzerland). No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the final paper, and its final contents.

Population and automated measurements

The ECG data set provided by the CSRC[12,13] for the present study is completely different from the digitized tracings used in the 2014 study.[3] The ECGs were randomly selected from available ECGs within the CSRC data warehouse by the study statistician (C. G.) while maintaining balance across sex when possible. All ECGs in the present data set were reviewed by a single investigator (P. K.) to eliminate tracings with excessive noise and also rhythms with no identifiable P wave. Participants agreed to publication of the results in advance of analysis. All measurement data were simultaneously acquired by participants on randomly sequenced media, and the results were immediately given to CSRC for analysis during the supervised analysis period. Measurements of the RR interval, PR interval, QRS duration, and QT interval were made blindly by each of the 7 algorithms from 800 XML files of 500-Hz ECG tracings stored in the US FDA ECG Warehouse.[13] Because all measurements for each algorithm were performed from previous XML conversion of digitized data, there is no variability of repeated measurements within single algorithms such as might have occurred with sequential analysis of analog to digital data conversions. QT intervals presented are the absolute measurements, not corrected for heart rate.

Included were 4 groups selected by CSRC according to expected QT interval and degree of repolarization abnormality, comprising 200 10-second 12-lead ECGs from each of (1) normal subjects during placebo or baseline study period from thorough QT studies, (2) a separate group of normal subjects during peak moxifloxacin effect during thorough QT studies, (3) subjects with genotyped congenital long QT syndrome (LQT) type 1, and (4) subjects with genotyped LQT type 2.[14,15] Other primary and secondary repolarization changes, as well as other causes of atrioventricular and intraventricular block, are also important but extend beyond the scope possible in this report. Because the purpose of the study was to assess and to quantify potential differences among algorithms, no human overreading and no "gold standard" for accuracy of the reported measurements were used. Within each of the normal and moxifloxacin groups, the sex distribution was balanced (100 men and 100 women per group); however, of the 200 subjects within the LQT1 and LQT2 groups, there were 78 men and 122 women and 99 men and 101 women, respectively. Inequality of sex distribution was necessary in the LQT groups to keep all ECG data digitized at 500 samples per second rather than the lower high-frequency cutoff in older tracings. The mean age was similar in all groups, ranging from 29 to 35 years.

Statistical analysis

The following continuous ECG interval parameters were summarized for each group (normal, moxifloxacin, LQT1, and LQT) and subgroup (sex and algorithm) of interest using central tendency analyses: RR, PR, QRS, and QT (not adjusted for rate). Standard summary statistics are presented in the tables including the mean and 95% CIs around the mean. The difference between algorithms was assessed by the ability of each algorithm to perform as expected (ie, detecting known interval differences between sex and between ECG groups), by the intrinsic variability within each algorithm, and by evaluating pairwise differences between algorithms.

To compare the expected means between algorithms, sex, and ECG groups, repeated-measures regression models were used for each interval with ECG serving as the random effect and ECG group, sex, and algorithm as the fixed effects. We assumed a compound symmetry variance structure with equal variances across ECG groups and tested this assumption using likelihood ratio tests comparing models using other possible covariance structures. Two-sided 95% CIs for the difference between subgroups of interest were constructed using the residual error of the regression model and applying the Tukey α adjustment for multiple pairwise comparisons.

Initially, interval and duration measurement differences between algorithms were examined in subjects separated by ECG group (normal, moxifloxacin, LQT1, and LQT2). Measurement differences were then examined within algorithms in subjects separated by sex. Interval data were also examined for differences separated by algorithm and by ECG group; these findings were used to examine the significance of differences within each algorithm associated with normal, moxifloxacin, LQT1, and LQT2 status. By considering seven algorithms, 21 ($7 \times 6/2$) possible unique pairwise comparisons of mean differences between algorithms for each ECG measurement (PR, RR, QRS, and QT) could be made overall and within each subgroup (sex and ECG group). In several instances, automated algorithms were not able to measure a PR interval, slightly reducing the total number of observations within a given subgroup as seen in the tables.

To examine the effects of normal, moxifloxacin, LQT1, and LQT2 group status on overall measurement differences between algorithms, a separate analysis was conducted for each ECG interval (RR, PR, QRS, and unadjusted QT) to evaluate the overall mean and variability of all possible pairwise comparisons between algorithms. For each ECG

Table I
Mean intervals by algorithm in total population

Interval	n	Algorithm	Mean ± SD (ms)	Lower 95% CI (ms)	Upper 95% CI (ms)
RR*	800	AMPS	979 ± 180	966	991
	800	GE	978 ± 180	966	991
	800	Glasgow	978 ± 180	966	991
	800	MEANS	979 ± 182	966	992
	800	Mortara	973 ± 179	960	985
	800	Philips	980 ± 180	967	992
	800	Schiller	979 ± 182	966	992
PR†	800	AMPS	155 ± 22	154	157
	800	GE	154 ± 21	152	155
	798	Glasgow	152 ± 22	150	154
	789	MEANS	156 ± 21	154	157
	785	Mortara	153 ± 23	152	155
	799	Philips	154 ± 22	152	155
	796	Schiller	154 ± 23	152	155
QRS‡	800	AMPS	89 ± 10	89	90
	800	GE	85 ± 12	84	86
	800	Glasgow	89 ± 11	88	90
	800	MEANS	92 ± 13	91	93
	800	Mortara	92 ± 11	91	93
	800	Philips	93 ± 12	92	94
	800	Schiller	90 ± 12	89	90
QT§	800	AMPS	423 ± 47	420	427
	800	GE	429 ± 45	426	432
	800	Glasgow	433 ± 44	430	436
	800	MEANS	430 ± 43	427	433
	800	Mortara	423 ± 43	420	426
	800	Philips	432 ± 45	429	435
	800	Schiller	428 ± 43	425	431

* P = NS by Tukey-adjusted repeated-measures analysis of variance for comparisons of RR between algorithms, except $P < .001$ for AMPS versus Mortara, GE versus Mortara and Philips, Glasgow versus Mortara and Philips, MEANS versus Mortara, and Mortara versus Philips and Schiller.

† $P < .001$ for all comparisons of PR between algorithms except nonsignificant for AMPS versus MEANS, GE versus Mortara, Philips and Schiller, Mortara versus Philips and Schiller, and Philips versus Schiller.

‡ $P < .02$ for all comparisons of QRS duration between algorithms except nonsignificant for AMPS versus Glasgow and Schiller, Glasgow versus Schiller, and MEANS versus Mortara.

§ Note that QT measurements are not rate corrected; $P < .03$ for all comparisons of unadjusted QT between algorithms except nonsignficant for AMPS versus Mortara, GE versus MEANS and Schiller, and Glasgow versus Philips.

group of 200 subjects (normal, moxifloxacin, LQT1, and LQT2), 4,200 (200 x× 21) possible unique paired differences between algorithms can be constructed. These differences are represented by boxplots showing the median, 25th, and 75th percentiles with superimposed mean and whiskers for denoting minimum and maximum values.

All statistical data analyses were completed using SAS software, Version 9.4 (SAS Institute Inc, Cary, NC). A P value ≤ .05 was considered statistically significant unless otherwise noted.

Results

Measurement differences in total population by algorithm

Summary statistics for the entire population of 800 subjects by algorithm, not further separated by ECG group or sex, are shown in Table I. Pairwise differences between each mean interval value were clinically small, ranging from 0.0 to 6.9 milliseconds for RR interval, 0.2 to 3.6 milliseconds for the PR interval, 0.1 to 8.1 milliseconds for QRS duration, and 0.1 to 9.3 milliseconds for unadjusted QT interval, but some systematic differences were present. Several of the 21 possible unique pairwise differences between means among the 7 algorithms for each interval measurement did reach statistical significance as indicated in the table footnote.

Interval measurement differences within algorithm in total population separated by sex

Among the entire population separated by sex but not by ECG group, within each of the 7 algorithms, the mean RR intervals, PR intervals, and QRS durations were significantly longer in men than for women (pairwise Tukey-adjusted $P < .001$) for all comparisons with each algorithm. Interestingly, the mean unadjusted QT intervals in this entire population, half of whom were patients with genotyped LQT1 and LQT2, were similar for women and for men within each of the 7 algorithms (P = not significant [NS] for all comparisons); mean differences were relatively small, ranging from 0.7 to 4.3 milliseconds (Table II and Figure 1). It is emphasized that these values are unadjusted for heart rates or cycle lengths, with significantly shorter cycle lengths in women. The influence of LQT patients on the overall QT differences is further explored by examination of group differences below.

Interval measurement differences within ECG groups by algorithm

Interval measurement differences according to algorithm within each ECG group, but not further separated according to sex, are shown in Table III and Figures 2-4. For the PR interval comparisons (Figure 2), there were trends observed for shorter AV conduction time in the LQT groups than in the normal and moxifloxacin groups, but statistical significance was reached only for LQT1 compared to both normal and moxifloxacin within the AMPS algorithm ($P < .05$) and within the GE algorithm ($P < .005$). QRS durations (Figure 3) were significantly shorter in LQT1 and LQT2 compared to normal and moxifloxacin groups within the GE ($P < .001$), MEANS ($P < .001$), Mortara ($P < .02$), and Schiller ($P < .001$) algorithms. QRS durations were also significantly shorter in LQT1 and LQT2 than in normal ECGs for the Glasgow algorithm ($P < .02$) but did not reach significance for the LQT groups compared with moxifloxacin. All other pairwise QRS differences were not statistically significant. Within algorithms, all differences for unadjusted QT interval between ECG groups (Figure 4) were significantly different ($P < .025$), with progressive QT prolongation from normal to moxifloxacin to LQT1 to LQT2 groups; this includes significantly higher unadjusted QT intervals, ranging from 10.3 to 11.8 milliseconds, in the moxifloxacin compared with normal subjects at comparable cycle lengths for all algorithms.

Table II
Mean intervals by sex and algorithm

Interval	Sex	n	Algorithm	Mean ± SD (ms)	Lower 95% CI (ms)	Upper 95% CI (ms)
RR*	Men	377	AMPS	1026 ± 181	1008	1044
		377	GE	1026 ± 181	1008	1044
		377	Glasgow	1026 ± 181	1008	1043
		377	MEANS	1026 ± 183	1008	1044
		377	Mortara	1021 ± 180	1004	1039
		377	Philips	1027 ± 181	1009	1045
		377	Schiller	1027 ± 182	1009	1044
	Women	423	AMPS	937 ± 170	920	953
		423	GE	935 ± 168	919	952
		423	Glasgow	936 ± 168	919	952
		423	MEANS	937 ± 171	920	953
		423	Mortara	929 ± 166	913	946
		423	Philips	937 ± 169	921	954
		423	Schiller	937 ± 171	920	953
PR†	Men	377	AMPS	159 ± 23	157	161
		377	GE	157 ± 22	155	159
		377	Glasgow	155 ± 23	153	157
		370	MEANS	160 ± 22	158	162
		369	Mortara	157 ± 24	155	159
		377	Philips	157 ± 24	155	159
		376	Schiller	157 ± 24	155	159
	Women	423	AMPS	152 ± 21	150	154
		423	GE	151 ± 20	149	153
		421	Glasgow	149 ± 21	147	152
		419	MEANS	153 ± 20	151	155
		416	Mortara	150 ± 21	148	153
		422	Philips	151 ± 21	149	153
		420	Schiller	151 ± 22	148	153
QRS‡	Men	377	AMPS	92 ± 12	91	93
		377	GE	90 ± 12	89	91
		377	Glasgow	93 ± 12	92	94
		377	MEANS	96 ± 15	95	98
		377	Mortara	96 ± 12	95	97
		377	Philips	95 ± 13	94	97
		377	Schiller	94 ± 12	93	95
	Women	423	AMPS	87 ± 9	86	88
		423	GE	80 ± 9	79	81
		423	Glasgow	85 ± 8	84	86
		423	MEANS	88 ± 10	86	89
		423	Mortara	88 ± 8	87	89
		423	Philips	91 ± 11	89	92
		423	Schiller	86 ± 12	84	87
QT§	Men	377	AMPS	421 ± 47	416	426
		377	GE	428 ± 44	423	432
		377	Glasgow	431 ± 44	427	436
		377	MEANS	429 ± 43	424	433
		377	Mortara	423 ± 44	418	427
		377	Philips	432 ± 45	427	437
		377	Schiller	429 ± 42	424	433
	Women	423	AMPS	425 ± 46	421	430
		423	GE	431 ± 45	427	435
		423	Glasgow	434 ± 45	430	438
		423	MEANS	431 ± 44	427	435
		423	Mortara	424 ± 43	420	428
		423	Philips	431 ± 45	427	436
		423	Schiller	427 ± 44	423	432

* $P < .001$ by Tukey-adjusted-repeated measures analysis of variance for all comparisons of RR between sex within algorithm.
† $P < .001$ for all comparisons of PR between sex within algorithm.
‡ $P < .001$ for all comparisons of QRS duration between sex within algorithm.
§ $P =$ NS for all comparisons of rate-unadjusted QT between sex within algorithm (including groups with LQT1 and LQT2).

Within individual groups, pairwise differences of means between algorithms for PR interval ranged from 0.2 to 3.6 milliseconds in normal ECGs, 0.3 to 3.3 milliseconds in moxifloxacin, 0.6 to 3.6 milliseconds in LQT1, and 0.0 to 4.1 milliseconds in LQT2 groups. Pairwise mean differences between algorithms for QRS duration ranged from 0.4 to 6.8 milliseconds in normal ECGs, 0.1 to 6.7 milliseconds in moxifloxacin, 0.2 to 13.3 milliseconds in LQT1, and 0.2 to 11.0 milliseconds in LQT2 groups. Pairwise mean differences between algorithms for unadjusted QT interval ranged from 0.1 to 11.3 milliseconds in normal ECGs, 0.3 to 10.2 milliseconds in moxifloxacin, 0.2 to 10.5 milliseconds in LQT1, and 0.9 to 12.8 in LQT2 groups.

Range of interval differences for total paired individual measurements within ECG groups

Within each of the 4 diagnostic ECG groups (200 subjects per group), 4,200 individual paired differences were possible for each of the RR, QRS duration, and QT interval measurements between all single ECGs;

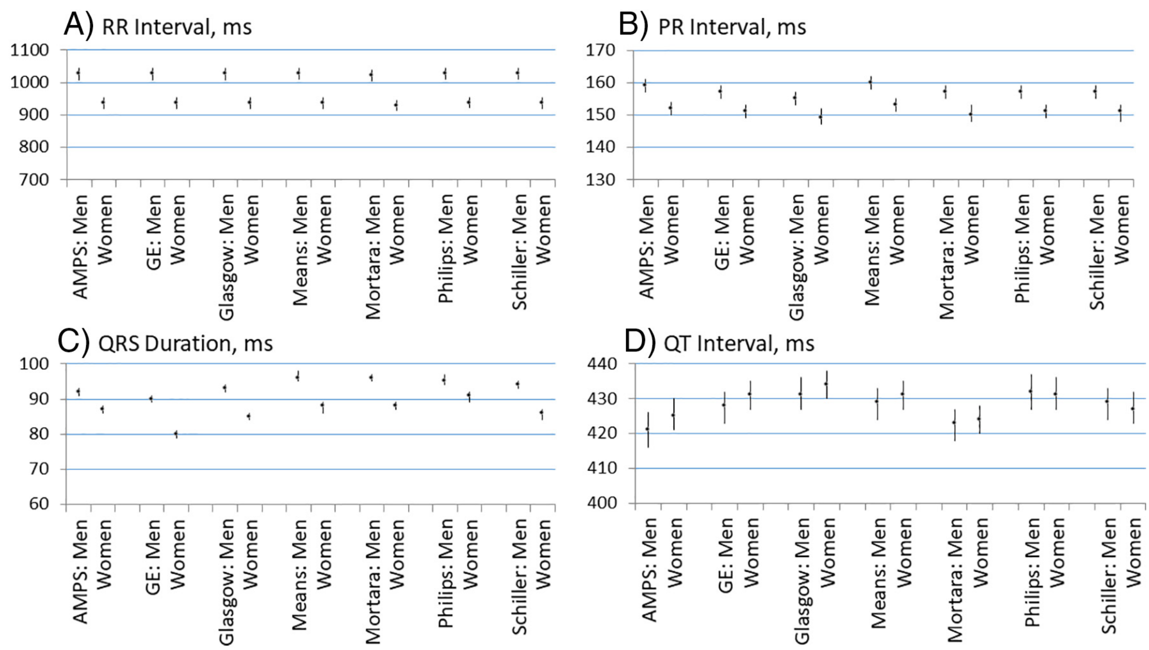

Figure 1. Mean differences (with 95% CIs) between men and women, by algorithm, for automated measurements of (A) RR interval, (B) PR interval, (C) QRS duration, and (D) QT interval in the total population of 800 subjects. Expected sex-dependent differences for RR intervals, PR intervals, and QRS durations are clear, whereas similar unadjusted QT interval values are most likely explained by different RR intervals between men and women (see discussion).

however, only 4,111 to 4,188 paired differences for PR intervals were possible because of unmeasurable PR intervals within a small number of subjects. Boxplots of these differences are illustrated in Figure 5 showing the mean, median, 25th and 75th percentiles, and range. Note that these findings represent the mean of all differences rather than a difference of means, and therefore, these data represent the magnitude of variability of measurement between algorithms for the different groups and not the magnitude of the underlying measurements. Considerable overlap was observed between ECG groups for each interval measurement difference, and the range of differences above the 75th percentile was large, indicating larger differences for some of the individual comparisons.

No clinically significant mean individual paired differences for RR intervals between groups were found, but some differences did reach statistical significance, particularly in the LQT1 and LQT2 groups. PR interval mean individual paired differences were not significant between normal and moxifloxacin groups or separately between LQT1 and LQT2 groups. However, despite considerable overlap, mean individual paired differences for PR interval were significantly greater for each of the LQT groups than for the normal group and, separately, also for the moxifloxacin group ($P < .02$). Mean individual paired differences for QRS duration were not significantly different between the normal and the moxifloxacin groups, but the mean individual difference of 7.4 $\pm$ 8.5 milliseconds in the LQT1 group was significantly greater than the 6.5 $\pm$ 5.7 milliseconds mean difference in the LQT2 group ($P = .014$, adjusted for multiple comparison). Mean individual paired QRS duration was larger in the LQT1 group than in either normal or moxifloxacin groups, whereas mean individual paired QRS difference in the LQT2 group was larger than in the normal, but not in the moxifloxacin groups. Mean individual paired difference for unadjusted QT duration was 9.9 $\pm$ 15.3 milliseconds for LQT1 and 12.6 $\pm$ 17.2 milliseconds for LQT2 ($P < .001$, adjusted for multiple comparison), each of which was separately greater than in the normal and moxifloxacin groups.

Discussion

Although all algorithms separate groups with normal and abnormal QT intervals, small but statistically significant group differences in mean interval and duration measurements and means of individual absolute differences exist among the 7 automated algorithms of widely used, current-generation digital electrocardiographs. The overall population differences seen in Table I are not explained entirely by data from the abnormal LQT groups because smaller differences also are seen within the normal and moxifloxacin groups. Although the magnitudes of these differences are unlikely to be clinically significant for any single measurement comparison, systematic differences can have consequences for outcomes when different algorithms are used during the course of longitudinal evaluations such as thorough QT studies,[4,5,7] in comparative studies of normal values and risk prediction in different populations,[9,10,16,17] and for the establishment of normal limits in routine electrocardiography.[18] For such research purposes, attention must be paid to methodologic consistency in the comparison of measured values, particularly for measurements of QRS duration and for QT interval.

It is well recognized that, in general populations, women have systematically shorter RR intervals, PR intervals, and QRS durations but longer heart rate adjusted QT intervals than men.[18-20] Although there are known changes in intervals with age, mean ages are similar for all groups in this study. Differences between sex were found by all algorithms for RR, PR, and QRS intervals. However, as seen in Figure 1 and Table II, overall sex-related differences in unadjusted QT interval are not statistically significantly different in the present analysis. This finding is a consequence of comparison of QT intervals that are not heart rate corrected for the purpose of this study. It can be estimated from the significantly different cycle lengths in men and in women that rate adjustment by any of the standard formulae would result in longer QT values for women than for men in this population. The effect of a 50% admixture of long QT subjects in the total population, half LQT1 and half LQT2, on mean QT values in men and women is uncertain and requires further study.[14,15] As seen in Figure 2, other differences between groups within each algorithm include trends toward shorter PR intervals, shorter QRS durations, and significantly longer QT intervals in the LQT subjects, with longer QT in LQT2 than in LQT1 groups. These findings also require further subanalyses within the LQT groups themselves, with heart rate adjustment, that are beyond the scope of the present report.

Table III
Mean intervals, by algorithm and group, for PR, QRS, and QT intervals

Interval	Algorithm	n	Group	Mean ± SD (ms)	Lower 95% CI (ms)	Upper 95% CI (ms)
PR	AMPS	200	Normal	157 ± 19	155	161
		200	Moxifloxacin	157 ± 18	154	160
		200	LQT1	152 ± 22	149	155
		200	LQT2	154 ± 27	151	157
	GE	200	Normal	157 ± 19	154	160
		200	Moxifloxacin	156 ± 17	153	159
		200	LQT1	149 ± 21	146	152
		200	LQT2	152 ± 26	149	155
	Glasgow	200	Normal	154 ± 20	151	157
		200	Moxifloxacin	154 ± 18	151	157
		199	LQT1	149 ± 24	146	152
		199	LQT2	151 ± 27	148	154
	MEANS	199	Normal	157 ± 19	154	160
		200	Moxifloxacin	157 ± 17	154	160
		195	LQT1	153 ± 22	150	156
		195	LQT2	156 ± 27	153	159
	Mortara	198	Normal	156 ± 20	152	159
		198	Moxifloxacin	155 ± 18	152	158
		195	LQT1	150 ± 23	147	153
		194	LQT2	153 ± 29	150	156
	Philips	200	Normal	155 ± 19	152	158
		200	Moxifloxacin	155 ± 19	152	158
		199	LQT1	151 ± 22	148	154
		200	LQT2	154 ± 28	151	157
	Schiller	199	Normal	155 ± 19	152	158
		200	Moxifloxacin	156 ± 18	152	159
		200	LQT1	151 ± 23	148	154
		197	LQT2	153 ± 29	150	157
QRS	AMPS	200	Normal	91 ± 8	89	92
		200	Moxifloxacin	89 ± 8	87	90
		200	LQT1	89 ± 11	88	91
		200	LQT2	89 ± 14	87	90
	GE	200	Normal	89 ± 10	88	91
		200	Moxifloxacin	88 ± 9	86	89
		200	LQT1	80 ± 11	79	82
		200	LQT2	81 ± 14	80	83
	Glasgow	200	Normal	91 ± 9	88	91
		200	Moxifloxacin	89 ± 9	88	91
		200	LQT1	87 ± 11	86	89
		200	LQT2	88 ± 14	86	89
	MEANS	200	Normal	96 ± 10	95	98
		200	Moxifloxacin	95 ± 10	93	96
		200	LQT1	87 ± 12	85	89
		200	LQT2	89 ± 17	87	90
	Mortara	200	Normal	94 ± 9	93	96
		200	Moxifloxacin	94 ± 8	92	95
		200	LQT1	89 ± 11	88	91
		200	LQT2	90 ± 14	89	92
	Philips	200	Normal	93 ± 10	92	95
		200	Moxifloxacin	92 ± 9	90	94
		200	LQT1	94 ± 13	92	95
		200	LQT2	92 ± 15	91	94
	Schiller	200	Normal	94 ± 10	92	95
		200	Moxifloxacin	92 ± 9	91	94
		200	LQT1	86 ± 14	84	87
		200	LQT2	86 ± 13	85	88
QT*	AMPS	200	Normal	397 ± 27	391	402
		200	Moxifloxacin	408 ± 27	403	414
		200	LQT1	434 ± 54	429	440
		200	LQT2	454 ± 48	449	460
	GE	200	Normal	403 ± 26	398	409
		200	Moxifloxacin	415 ± 27	409	420
		200	LQT1	442 ± 53	347	448
		200	LQT2	457 ± 44	451	462
	Glasgow	200	Normal	408 ± 26	402	413
		200	Moxifloxacin	419 ± 27	413	424
		200	LQT1	444 ± 54	438	439
		200	LQT2	460 ± 43	455	466
	MEANS	200	Normal	408 ± 27	402	413
		200	Moxifloxacin	418 ± 28	413	424
		200	LQT1	441 ± 52	435	446
		200	LQT2	453 ± 45	448	459
	Mortara	200	Normal	400 ± 26	395	406
		200	Moxifloxacin	412 ± 27	406	417

Table III (*continued*)

Interval	Algorithm	n	Group	Mean ± SD (ms)	Lower 95% CI (ms)	Upper 95% CI (ms)
		200	LQT1	433 ± 54	428	439
		200	LQT2	448 ± 44	442	453
	Philips	200	Normal	406 ± 26	400	412
		200	Moxifloxacin	418 ± 27	412	423
		200	LQT1	444 ± 55	438	449
		200	LQT2	459 ± 45	453	464
	Schiller	200	Normal	406 ± 27	401	412
		200	Moxifloxacin	417 ± 27	412	423
		200	LQT1	438 ± 54	432	443
		200	LQT2	451 ± 42	445	456

* QT intervals are unadjusted for cycle length.

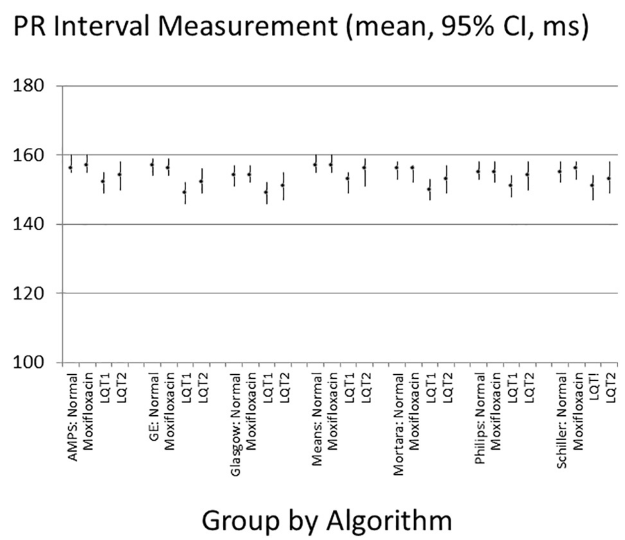

Figure 2. Mean differences (with 95% CIs) in PR intervals between normal, moxifloxacin, LQT1, and LQT2 groups by algorithm. Note trends toward shorter PR intervals in the LQT groups.

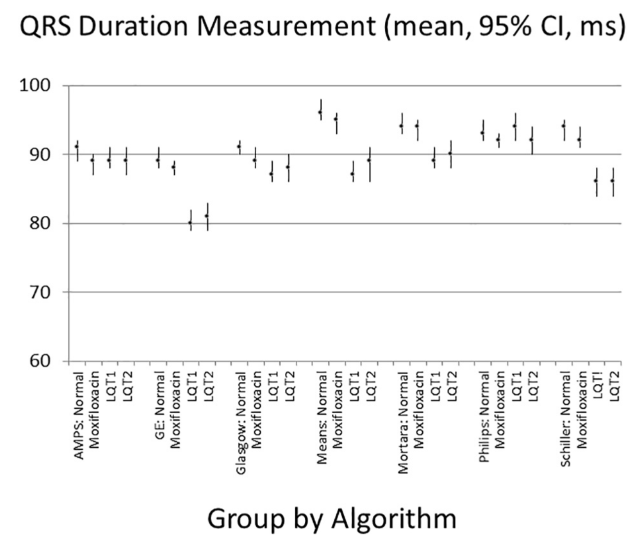

Figure 3. Mean differences (with 95% CIs) in QRS durations between normal, moxifloxacin, LQT1, and LQT2 groups by algorithm. Note trends toward shorter QRS durations compared with normal and moxifloxacin subjects in some but not all algorithms.

Our current findings support the hypothesis that the magnitude of difference between measurements by different automated algorithms increases with the degree of abnormality of the underlying ECGs.[3,6] Computer-based ECGs measure intervals on differently implemented "global" as opposed to single-lead basis, which increases measurement precision and reproducibility within algorithms and should remove uncertainty regarding waveform onset and offset obtained in any individual lead.[1,21] But even so, the lack of a formal medical definition of the end of the QRS complex and the end of the T wave leaves the concept of "global" intervals subject to individual engineering solutions by different algorithm developers.[4] Because these solutions vary, as noted in the appendix, different results might be expected for automated measurement of the QRS and QT intervals, and perhaps also for PR intervals which are dependent on the detection of smaller, low-frequency waveforms. Thus, for example, it is well recognized that T-wave offset measurement is highly dependent on T-wave amplitude and shape and separately confounded by isoelectric projection of rounded T-wave loops that are more common in abnormal subjects than in normals.[22-29] Interestingly, despite longer QT intervals apparent in the moxifloxacin versus normal subject groups (Figure 4), differences between automated algorithms remained comparably small in these 2 groups (Figure 5). These findings are consistent with the relative preservation of T-wave shape and amplitude in subjects receiving moxifloxacin in contrast with other types of QT prolonging drugs.[30]

Of note, 2 of the original 4 algorithms were modified in response to (or following) the original comparison study published in 2014. There seems to have been some harmonization of QT interval measurement as a result: among the 4 original comparisons, the longest mean QT difference between algorithm pairs in the long QT population (then comprising mixed LQT1 and LQT2 subjects) was 18 milliseconds. In the present study of 7 algorithms, which include the original 4 algorithms with some methodologic modification, the maximum mean QT interval difference was only 10 milliseconds for the LQT1 patients and 12 milliseconds for the LQT2 patients. Because this represents an overall trend within which the original algorithms are included, it argues for improvement in differences in QT measurement compared with the original study.

Abnormal notching, symmetry, and low amplitude are features of abnormal ECGs in our LQT subjects,[31-34] which are also found in many forms of established heart disease and in other acquired channelopathies.[23,35,36] This complicates the identification and measurement of the T wave in subjects with abnormal ECGs. When the T wave is abnormal, therefore, different engineered solutions for recognition of the end of the T wave would be expected to result in the most QT variation between algorithms, as noted here (Figure 5) and also in our prior report.[3] Other differences between ECG waveforms, based on ion channel variations, structural disease, or drug effect, might similarly affect QRS measurement differences between study groups as well as in other populations. It is therefore of interest to note the increased variability among algorithms for the measurement of QRS duration in our long QT subjects compared with normals and subjects taking moxifloxacin, a finding also noted in our prior report.[3] The mechanisms affecting QRS fiducial waveform point ascertainment in LQT1 and LQT2 accordingly require specific investigation.

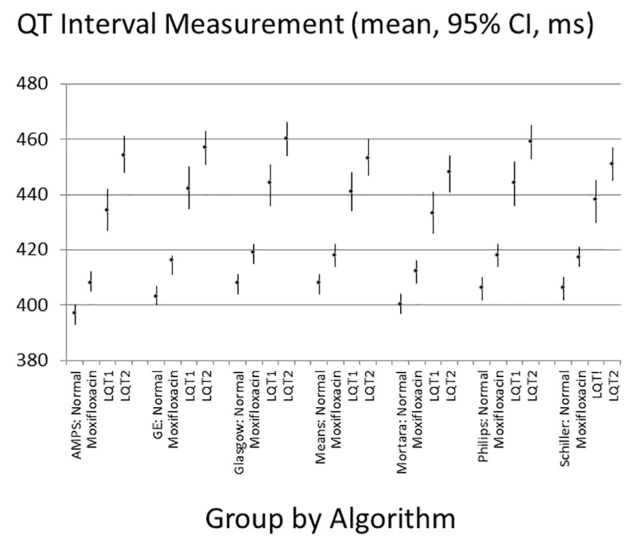

Figure 4. Mean differences (with 95% CIs) in QT intervals between normal, moxifloxacin, LQT1, and LQT2 groups by algorithm. There is progressive increase in QT for all algorithms from normal to moxifloxacin to LQT1 to LQT2 groups.

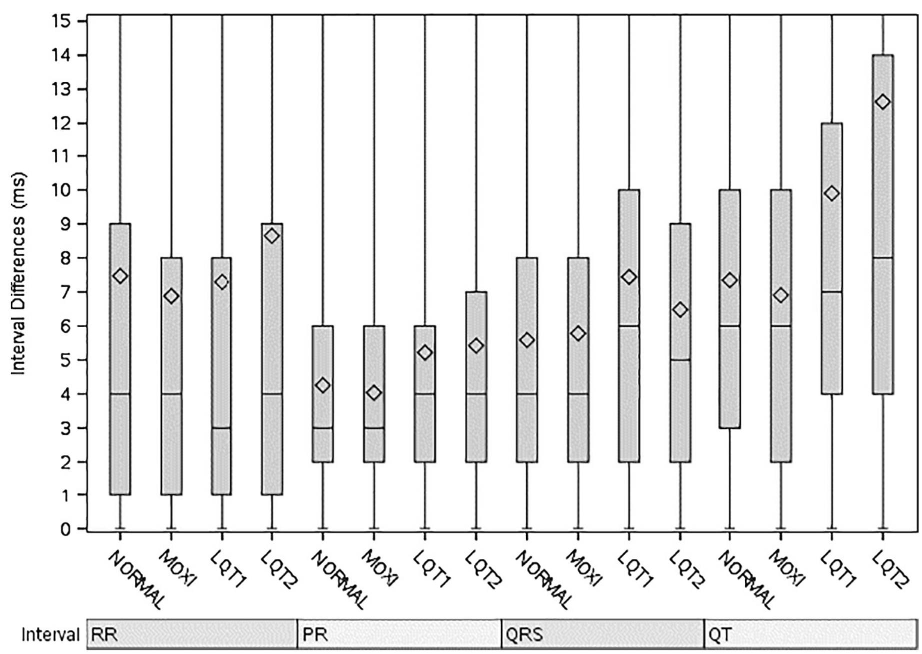

Figure 5. Boxplots with median, 25% and 75% range, and superimposed mean values (diamonds) for all possible 2-way comparisons of differences between 7 algorithms in RR intervals, PR intervals, QRS durations, and QT intervals according to study group. Both median differences and mean differences for PR, QRS, and QT are greater within the LQT1 and LQT2 groups than within the normal and moxifloxacin groups, suggesting that differences between algorithms are greater in the most abnormal ECGs.

The major purpose of this cooperative trial was to establish whether systematic differences in measurement among these widely used algorithms might have consequences for clinical and epidemiological research and, if so, how these differences relate to the extent of ECG abnormality. Weighted averaging of expert cardiologist opinions has been used for comparison of computer diagnosis of standard ECG statements such as ventricular hypertrophy and myocardial infarction in the CSE database (European Working Party on Common Standards for Quantitative Electrocardiography).[37] By design, there was no attempt to establish a physician-adjudicated "gold standard" for the automated interval measurements examined in this study. There is one major reason and a subsidiary rationalization for this decision. Most importantly, the suggestion that one proprietary engineering solution to ECG interval measurement is more "correct" than another would have introduced a competitive commercial aspect to participation. Absence of imputed relative performance was essential to accomplishing this cooperative study; under the present conditions, any of the tested algorithms might be closest to an undetermined "truth," if there is one. But separately, in the absence of absolute medical definition of waveform fiducial points, the stability of any human adjudicated "gold standard" for interval measurements is itself subject to uncertainty. Expert ECG overreaders, like algorithms, also vary in interval determinations, perhaps in part based on cumulative experience with manual and semiautomated adjudication using different single-lead and global methodologies.[5,7,38-40] This makes absolute acceptance of any collective "gold standard" arguable, even when quantifiable.

In summary, systematic differences among ECG interval measurements by current, widely used computer-based algorithms are small.

Even so, comparisons of ECG population norms should be aware of potential differences in interval measurements that might result from different algorithm methodologies. In addition, within-individual interval measurement comparisons with clinical implications should use comparable methods, and further attempts to harmonize interval measurement methodologies among algorithms are warranted.

Appendix A. Methodologic statements by participating algorithms

A.1. AMPS: fiducial point detection

The BRAVO algorithm provides automated measurements from the 10-second raw ECG data and also from mathematically derived single-beat representative waveforms (averaged or median beats). In the latter case, measurements can be performed from each individual lead or, as in this study, from a "global" lead computed as the vector magnitude of the independently acquired leads. On the global lead, the QRS onset and offset detection points are based on the resampled (1,000 Hz) and normalized waveform and on the combined implementation of an adaptive threshold moving average and of a high-pass regressive filter. The QRS onset is searched starting from the R-peak position going backward, identifying the right edge of an interval of contiguous samples with minimal variability. Similarly, the QRS offset detection point is assigned on the high-pass filtered signal as the left edge of a 5-millisecond interval which is constantly below a threshold that is iteratively increased until the condition is met. Lower-frequency segments (P and T waves) are then analyzed by a series of signal processing steps that include nondistorting low-pass filtering (bidirectional fourth-order Butterworth) and first- and second-derivative analyses. *P-onset* and *T-wave offset markers* are defined as the backward or forward sample points where the first derivative of the signal goes below a fixed percent of the maximum value (reached at the maximum ascending or descending slope of each wave).

A.2. GE Healthcare

In the GE Healthcare 12SL ECG Analysis Program, all intervals and measurements are made from the median complex. The median complex is the representative 12-lead complex formed by time-aligning all beats of the dominant morphology and using a proprietary nonlinear type of signal averaging. After the median complex is formed, the onsets and offsets are determined in the following order: QRS onset, QRS offset, T offset, P onset, and P offset. Immediately after the T offset is determined, the median complex is searched for a synchronous P wave. The P onset and offset are determined only if a P wave is found. The exact method for identifying each onset and offset is tuned for each of the markers, but all use variations of the same approach. The fundamental detection function for each marker search is a "superlead," which is the sum of the absolute value of all independent leads (I, II, V1,… V6). In some cases, the first or second derivatives of the superlead are calculated, and in other cases, the derivatives are calculated first and then summed to form the superlead. Such detection functions accentuate the slope changes that accompany a wave onset or offset. After the onset and offset points are found, the intervals are calculated from the time differences between the appropriate markers. See Xue J, QT Interval Measurement: What Can We Really Expect? *Computers in Cardiology* 2006;33:385-388.

A.3. Glasgow Program

Based on the availability of an average beat, different approaches to finding fiducial points have been tried, including a simple form of threshold crossing to a more complex template matching technique. Ultimately, a combination of these approaches has been adopted where, for example, QRS onset was found to perform best with respect to a noisy test set using a threshold technique. On the other hand, T end performed best using a template matching method. All QRST amplitudes are referred to QRS onset, as are P-wave measurements. Individual QRS and T-wave fiducial points are derived for all leads, and a method of selecting the earliest QRS onset for example is used to determine a global QRS onset. A similar approach is adopted for QRS termination, and the difference between the 2 global measurements is taken as the overall QRS duration. It was found optimum to use a common P onset and P termination in view of the unreliability of P-wave detection in many ECGs.

A.4. MEANS Program, Erasmus University Medical Center, Rotterdam, the Netherlands

MEANS locates the QRS complexes using the spatial velocity, which is computed from the reconstructed vectorcardiographic X, Y, and Z leads. The QRS complexes are typed as dominant and nondominant, and a representative P-QRS-T complex per lead is obtained by averaging the time-aligned dominant complexes. Complexes affected by sudden baseline shifts or other major disturbances are excluded from averaging. MEANS determines common inflectional points (P onset, P offset, QRS onset, QRS offset, T offset) for all 12 leads together. The spatial velocity derived from the representative complexes is used as the detection function. For determination of QRS onset and offset, the detection function is matched with a template. The template matching method takes into account information on the time-amplitude distribution of the detection function in a window around the inflectional point. For T offset, the template is heart rate dependent to take care of the P-on-T phenomenon that may occur at higher heart rates. When the template match is not good enough, MEANS enters a thresholding algorithm to locate the minimum of the spatial velocity, which is then taken as the end of the T wave. For determination of P onset and offset, MEANS uses thresholding algorithms. PR interval, QRS duration, and QT interval are calculated from the time differences between the pertinent fiducial points.

A.5. Mortara Instrument

All ECG landmarks, P onset/offset, QRS onset/offset, and T offset, are global, with a single index spanning all leads for each landmark. The detection of these landmarks is generally done using a *spatial velocity magnitude*, defined as the absolute differences of neighboring samples, summed over the available leads. The first step in landmark detection is the formation of a representative cardiac cycle from the cycles labeled as part of the dominant rhythm. Premature beats, even with QRS morphologies similar to the dominant rhythm, are excluded to avoid influencing P-wave and repolarization details. The representative cycle is referred to as a *median*, although the actual process is a median of 3 averages, with the 3 averages found from modulo 3 normal beat cycles (that is, average 1 of beat 1, 4, 7, 10…, average 2 of beat 2, 5, 8, 11…, average 3 of beat 3, 6, 9, 12…). The representative cycle is recursively low-pass filtered until the high-frequency noise is brought below a threshold, with the aim of robust landmark detection in the presence of noise. P-wave landmark detection first requires locating the peak spatial magnitude of a high-pass filter applied to the T-P segment. Onset and offset are determined by fitting straight lines to 16-millisecond linear segments and locating the boundaries where the straight line fit improves (decreases) below a threshold. This straight line model allows P onset/offset to be properly located even when the P is superimposed on the terminal part of a T wave. QRS landmarks use a similar straight line fit to refine the details of onset/offset. Initially, spatial velocities are used to crudely locate estimates of the onset and offset. The straight line tests again work well in cases of steeply sloped PR/ST segments. T-wave offset detection poses special problems because there is no precise end of repolarization. To avoid too early/late offset marking in cases of low-/high-amplitude T waves, the offset slope threshold is scaled to the amplitude of the largest T wave in any lead. (It can be noted in

Tables I and II that the average RR interval measured by the Mortara VERITAS program is approximately 6 milliseconds shorter than the average of the other programs. This shorter RR interval is not real and an artifact of the measurement methodology used in this particular study; it does not represent a difference that is present in actual Mortara products.)

A.6. Philips Healthcare

The Philips DXL algorithm measures each lead first and then determines the global PR interval, QRS duration, and QT interval from the set of fiducial points on each lead. The process starts with detecting QRS and then segmenting into P, QRS, and T on an activity or envelope function which is a weighted sum of first and second differences. Next, beats are compared and classified as normal or ectopic, with the normal beats making up the representative averaged beat. Each lead of the average beat is measured based on deflections characterized by maxima and zero crossings of smoothed first and second differences. The end of the T wave is estimated from the maximum distance between the signal and a secant line drawn from the peak of the T wave out a fixed time duration to a point beyond the end of the T wave. The end of the QRS is measured with a similar secant line from the last S or R wave into the T wave. The final global PR interval, QRS duration, and QT interval come from the earliest onset and the last end point across leads with logic to prevent choosing an outlier or a value from a noisy lead.

A.7. Schiller AG

Global ECG Measurement: A QRS detector determines the positions of all heart beats within a given ECG signal. These positions are the basis for the calculation of the average RR interval. All detected heart beats are assigned to one or several beat classes based on their morphological similarity. The morphological similarity is determined by cross-correlation calculations in the range of the QRS complexes. The beat class that contains the largest number of beats with the shortest QRS duration corresponds to the predominant normal beat class. The heart beats that are assigned to this predominant normal beat class are used for the average beat construction. They are first time-aligned by means of cross-correlation and then averaged by calculating a robust mean value sample by sample. Based on derived vectorcardiographic leads X, Y, and Z and their time derivatives dX, dY, and dZ, the absolute spatial velocity $ASV = sqrt(dX^*dX + dY^*dY + dZ^*dZ)$ is calculated. The ASV of the average beat is used to determine the global time marker positions (P-wave onset/offset, QRS complex onset/offset, and T-wave offset). These markers are placed at the positions where the ASV gets to a stable minimum before/after the P wave, before/after the QRS complex, and after the T wave. The PR interval, QRS duration, and QT interval are the time differences between pairs of these global markers.

References

1. Kligfield P, Gettes LS, Bailey JJ, et al. 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. Garg A, Lehmann MH. Prolonged QT interval diagnosis suppression by a widely used computerized ECG analysis system. Circ Arrhythm Electrophysiol 2013;6:76-83.
3. Kligfield P, Badilini F, Rowlandson I, et al. Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs. Am Heart J 2014;167:150-9.
4. Kligfield P, Hancock EW, Helfenbein ED, et al. Relation of QT interval measurements to evolving automated algorithms from different manufacturers of electrocardiographs. Am J Cardiol 2006;98:88-92.
5. Hnatkova K, Gang Y, Batchvarov VN, et al. Precision of QT interval measurement by advanced electrocardiographic equipment. Pacing Clin Electrophysiol 2006;29:1277-84.
6. Tyl B, Azzam S, Blanco N, et al. Improvement and limitation of the reliability of automated QT measurement by recent algorithms. J Electrocardiol 2011;44:320-5.
7. Azie NE, Adams G, Darpo B, et al. Comparing methods of measurement for detecting drug-induced changes in the QT interval: Implications for thoroughly conducted ECG studies. Ann Noninvasive Electrocardiol 2004;9:166-74.
8. Couderc JP, Garnett C, Li M, et al. Highly automated QT measurement techniques in 7 thorough QT studies implemented under ICE Ech e14 guidelines. Ann Noninvasive Electrocardiol 2011;16:13-24.
9. Robbins J, Nelson JC, Rautaharju PM, et al. The association between the length of the QT interval and mortality in the cardiovascular health study. Am J Med 2003;115:689-94.
10. Dekker JM, Crow RS, Hannan PJ, et al. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: The aric study. J Am Coll Cardiol 2004;43:565-71.
11. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam study. Eur Heart J 1999;20:278-84.
12. Kligfield P, Green CL, Mortara J, et al. The cardiac safety research consortium electrocardiogram warehouse: Thorough QT database specifications and principles of use for algorithm development and testing. Am Heart J 2010;160:1023-8.
13. Kligfield P, Green CL. The Cardiac Safety Research Consortium ECG database. J Electrocardiol 2012;45:690-2.
14. Donger C, Denjoy I, Berthet M, et al. KVLQT1 c-terminal missense mutation causes a forme fruste long-QT syndrome. Circulation 1997;96:2778-81.
15. Dausse E, Berthet M, Denjoy I, et al. A mutation in herg associated with notched t waves in long QT syndrome. J Mol Cell Cardiol 1996;28:1609-15.
16. Oikarinen L, Nieminen MS, Viitasalo M, et al. QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: The losartan intervention for endpoint reduction in hypertension study. Hypertension 2004;43:1029-34.
17. Porthan K, Viitasalo M, Jula A, et al. Predictive value of electrocardiographic QT interval and T-wave morphology parameters for all-cause and cardiovascular mortality in a general population sample. Heart Rhythm 2009;6:1202-8.
18. Macfarlane PM, Chen CY, Chiang BN. Comparison of the ECG in apparently healthy chinese and caucasians. IEEE Comput Cardiol 1988:143-6.
19. Macfarlane PW, McLaughlin SC, Devine B, et al. Effects of age, sex, and race on ECG interval measurements. J Electrocardiol 1994;27(Suppl):14-9.
20. Mandic S, Fonda H, Dewey F, et al. Effect of gender on computerized electrocardiogram measurements in college athletes. Phys Sportsmed 2010;38:156-64.
21. Kligfield P, Tyl B, Maarek M, et al. Magnitude, mechanism, and reproducibility of QT interval differences between superimposed global and individual lead ECG complexes. Ann Noninvasive Electrocardiol 2007;12:145-52.
22. Batchvarov V, Malik M. Measurement and interpretation of QT dispersion. Prog Cardiovasc Dis 2000;42:325-44.
23. Couderc JP, Zareba W, Moss AJ, et al. Identification of sotalol-induced changes in repolarization with T wave area-based repolarization duration parameters. J Electrocardiol 2003;36(Suppl):115-20.
24. Kautzner J. QT interval measurements. Card Electrophysiol Rev 2002;6:273-7.
25. Kligfield P, Okin PM, Lee KW, et al. Significance of QT dispersion. Am J Cardiol 2003;91:1291.
26. Kors JA, van Herpen G. Measurement error as a source of QT dispersion: a computerised analysis. Heart 1998;80:453-8.
27. Lee KW, Kligfield P, Dower GE, et al. QT dispersion, T-wave projection, and heterogeneity of repolarization in patients with coronary artery disease. Am J Cardiol 2001;87:148-51.
28. McLaughlin NB, Campbell RWF, Murray A. Influence of T wave amplitude on automatic QT measurement. IEEE Comput Cardiol 1995:777-80.
29. Andersen MP, Xue JQ, Graff C, et al. New descriptors of T-wave morphology are independent of heart rate. J Electrocardiol 2008;41:557-61.
30. Couderc JP, Vaglio M, Xia X, et al. Impaired T-amplitude adaptation to heart rate characterizes I(Kr) inhibition in the congenital and acquired forms of the long QT syndrome. J Cardiovasc Electrophysiol 2007;18:1299-305.
31. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995;92:2929-34.
32. Zareba W, Moss AJ, Konecki J. TU wave area-derived measures of repolarization dispersion in the long QT syndrome. J Electrocardiol 1998;30(Suppl):191-5.
33. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000;102:2849-55.
34. Zareba W. Genotype-specific ECG patterns in long QT syndrome. J Electrocardiol 2006;39:S101-6.
35. Chiang CE. Congenital and acquired long QT syndrome. Current concepts and management. Cardiol Rev 2004;12:222-34.
36. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010;121:1047-60.
37. Willems JL, Abreu-Lima C, Arnaud P, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. N Engl J Med 1991;325:1767-73.
38. Darpo B, Agin M, Kazierad DJ, et al. Man versus machine: Is there an optimal method for QT measurements in thorough QT studies? J Clin Pharmacol 2006;46:598-612.
39. Hnatkova K, Malik M. Automatic adjustment of manually measured QT intervals in digital electrocardiograms improves precision of electrocardiographic drug studies. IEEE Comput Cardiol 2002:697-700.
40. 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.