

Identification of Sotalol-induced Changes in Repolarization With T Wave Area-based Repolarization Duration Parameters

Jean-Philippe Couderc, PhD, MBA,* Wojciech Zareba, MD, PhD,*
Arthur J. Moss, MD,* Nenad Sarapa, MD,[†] Joel Morganroth, MD,[‡]
and Borje Darpo, MD, PhD[†]

Abstract: In this study, we investigated the validity of T wave area-based parameters for the identification of drug-induced changes of repolarization. Based on electrocardiograms from 39 healthy patients, we computed the stability of repolarization measurements and compared the sotalol-induced repolarization changes when measured with area-based parameters and traditional QT interval techniques (manual and automatic). Also, we evaluated the effect of different types of heart rate correction on these repolarization measurements. The results show that the stability of the automatic repolarization measurements is higher when measured using computer algorithm than using manual QT measurement. By using a population-based heart rate correction, the area-based parameters reveal significant modification of the overall shape of the T wave in its early, middle, and final part. In conclusion, morphological parameters of T wave are able to identify the changes in repolarization interval induced by sotalol. These parameters are more stable and thus more reliable than the traditional QT interval measurements. **Key words:** Electrocardiogram, repolarization, QT, acquired long QT syndrome.

The manual identification of QT interval relies on the accurate determination of the end of the T wave, which may be visually assessed differently

according to the experience and training of the cardiologist or electrocardiogram (ECG) technician (1). Automatic methods do have a 100% reproducibility but they may fail to identify this location correctly when based on the least-square technique or on the slope approach because the shape of the T wave is abnormal or the T wave has low amplitude (2). These are well-known limitations of the current automatic methods used for the measure of the QT interval.

Another major common limitation of both manual (tangent, intersection with baseline, TU nadir)

*From the *Cardiology Unit, Heart Research Follow-up program, University of Rochester, Rochester, NY; †Pfizer Inc, Skokie, IL; ‡ResearchTechnology Inc and the University of Pennsylvania School of Medicine, Philadelphia, PA.*

Reprint requests: Jean-Philippe Couderc, PhD, MBA, 601 Elmwood Ave, Box 653, Rochester, NY 14642; e-mail: Jean-Philippe.couderc@heart.rochester.edu.

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and automatic (tangent, threshold) measurements of the QT interval is that they do not account for the entire repolarization process, which may include unaccounted terminal portion of T wave, U wave, or merged TU complex. The T-wave area-based method described in this paper, allows for morphological analyses of repolarization duration encompassing the entire repolarization segment. This method takes advantage of combining information about prolongation and shape changes of the repolarization signal.

In this study, we investigated T wave area-based method for quantifying repolarization duration in healthy subjects exposed to sotalol, drug known to produce QT prolongation.

Materials and Methods

The study population consisted of 38 healthy patients (all men, 28 ± 8 years; BMI[body mass index] 24.4 ± 3.4 kg/m²) who underwent repeated digital 12-lead ECG recordings during a 3-day protocol. The first day of the experiment was the baseline; during the second day patients were exposed to a single dose of sotalol (160 mg), and during the third day a double dose of 320 mg of sotalol was used. Sixteen ECGs were recorded each day after 5 minutes in resting condition. Recordings were conducted at the same time each day for each patient. Sotalol blood plasma concentration was measured prior to each ECG. The protocol is described in detailed elsewhere (3). ECGs were acquired after a five-minute resting period using the Mortara ELI 200 12-lead recorder (Mortara Instrument, Milwaukee, WI) and stored in digital format under proprietary XML format.

QT intervals were measured manually (QT-manual) using Digipad board. The end of T wave was identified using intersection between terminal part of T wave and the isoelectric line (eResearchTechnology, Philadelphia, PA).

Automatic QT interval measurements were performed using our software for the Comprehensive Analysis of the repolarization Signal (COMPAS, University of Rochester, NY) that provides repolarization measurements on a beat-to-beat basis for all leads. These repolarization measurements include the QT interval (calculated using the maximum slope method: QT slope) and the T wave area-based parameters. T wave area-based parameters are measures of repolarization duration, which are dependent on the morphology of the T wave. The time needed to reach a certain percentage of the

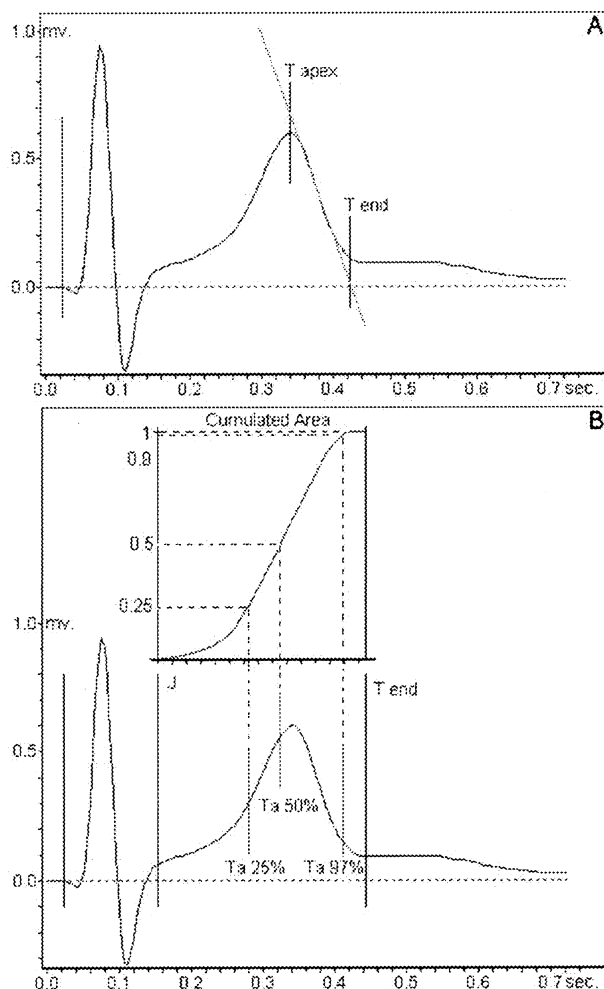


Fig. 1. Measurements of (A) T-wave duration and (B) morphology. The cumulated area of the T wave is plotted above the T wave in (B).

maximum value of the cumulated area under the T wave is computed. Figure 1 shows the method used for locating the end of the T wave (Fig. 1A) and computing area-based parameters (Fig. 1B) for 25%, 50%, and 97%. For instance, the so-called QTa25% is the distance between Q and Ta 25% (see Figure 1B). The beginning of the QRS complex was identified in all 12 leads and the earliest one was used for the measure of the QT intervals in all leads.

The heart rate correction of QT duration was computed using a population-based correction model (data for Bazett's and Fridericia's correction methods for manually measured QTc are also reported for comparison). The correction models were implemented on the baseline recordings using a linear function: $QT = \beta + \alpha RR$. Stability of repolarization measurements was assessed using the Bland-Altman method (4).

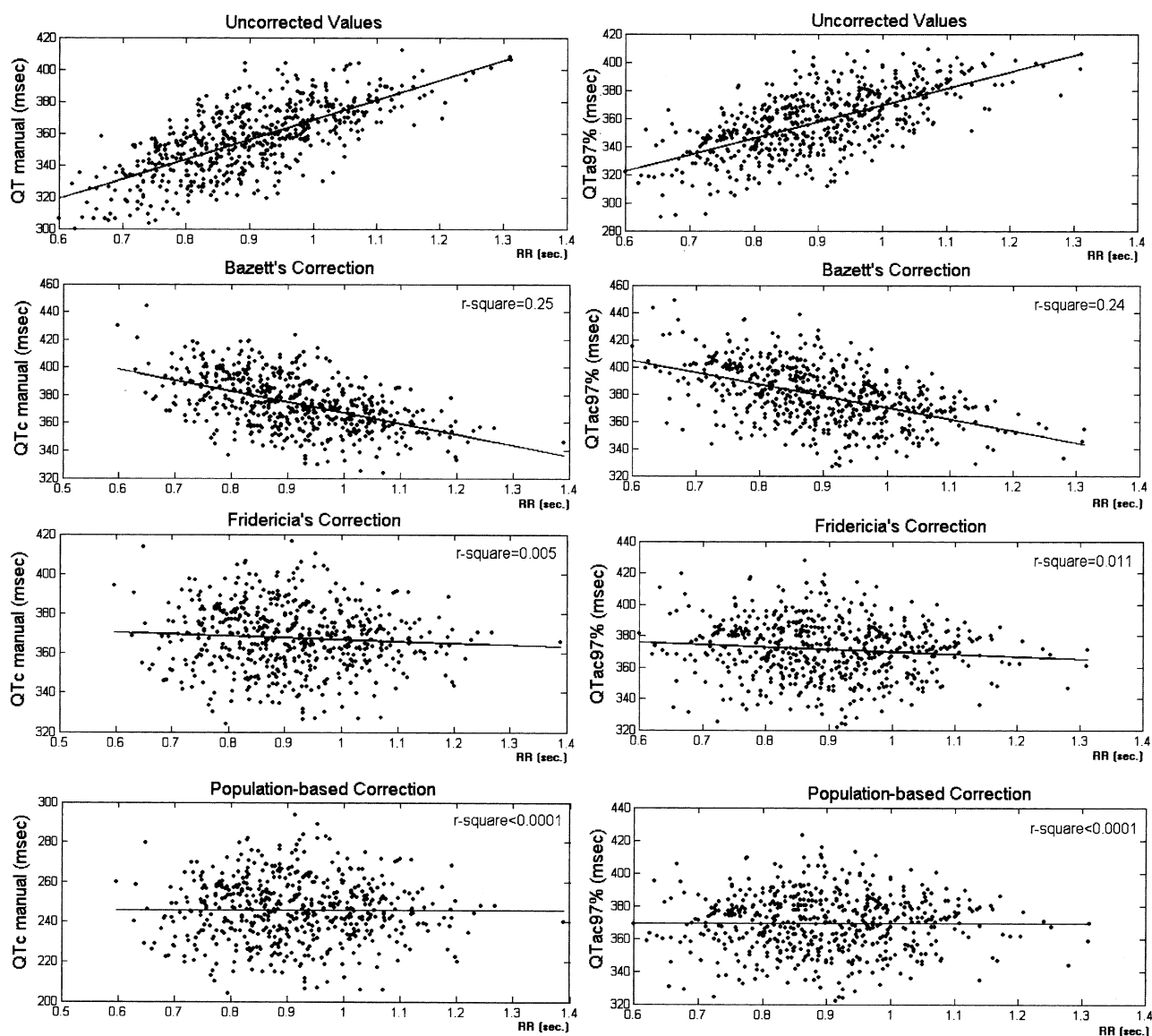


Fig. 2. From lead V5, QT/RR and QTa97%/RR relationships before correction (upper panels) and after heart rate correction using Bazett's formula (2nd row), Fridericia's formula (3rd row) and population-based correction (4th row). With each type of corrections, the graphs report the associated r^2 . The population-based correction provides a better correction whereas Bazett's formula inverts the QT/RR relationship.

Since patients were expected to have a wide spectrum of sotalol plasma concentrations throughout the 24-hour period during which also multiple ECGs were recorded, we analyzed the ability of various repolarization parameters to detect statistically significant changes from baseline observed at lowest plasma concentrations of the drug. A paired t -test was used for comparing changes in parameters between baseline and respective plasma concentration levels.

Results

Thirty-nine patients had 1,411 ECGs recorded. Population-based heart rate correction model was obtained for all parameters resulting in the following α values in Lead V5: 0.12, 0.11, 0.07, 0.09, and 0.12 for QT manual, QT slope, QTac25%, QTac50%, and QTac97%, respectively. Examples of the effects of Bazett's, Fridericia's and population-based corrections on QT manual and QTa97% are

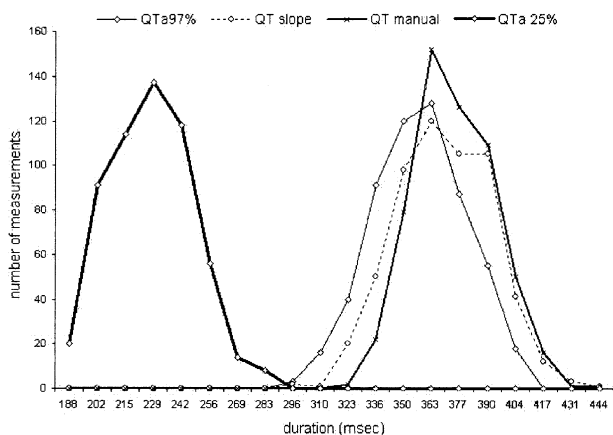


Fig. 3. Histograms of QT manual, QT slope, QTa25% and QTa97% values from the ECGs recorded during baseline in lead V5.

provided in Figure 2. The Bazett's formula inverts the QT/RR relationship with a $r^2=0.25$ ($P < .0001$). Fridericia's correction provides a better correction for QT manual and QTa97% intervals where less than 1.2% of the variation of repolarization changes is explained by the RR value changes ($r^2=.005$ and $r^2=.011$ for QT and QTA97%, respectively). The population-based correction leads to the best correction (Fig 2).

Figure 3 describes the histogram of distribution of repolarization values for QTac 97%, QTac25%, and QTs when determined manually (QT manual) and automatically (QT slope) during baseline conditions. All distributions are normal; the average and standard deviation values of these parameters are reported in the first row of Table 1. This row provides normal values for the repolarization parameters in healthy subjects for baseline condition. The averaged values of computer-based repolarization parameters are also reported for 3 ranges of sotalol plasma concentration (SPC) and for various heart rate corrections: Bazett (B), Fridericia (F) and population-based correction (N). All parameters

were significantly increased in comparison to baseline when the SPC was superior to 600 ng/mL. For a low SPC (between 0 and 300 ng/mL), QTc intervals were not significantly prolonged in comparison to baseline value when using Bazett's correction whereas the same measurement shows significant differences when using Fridericia's or population-based correction. Similar findings were found for manual measurements. The area-based measurements were significantly increased at all levels of SPC. At the highest SPC (>600 ng/mL), the smallest change was found for QTac25% with a 29 ms increase, prolongation was then increased when moving toward the end of the T wave: QTac50% increases by 47 ms and QTac97% increases by 73 ms. These results evidence that the effect of the drug is different along the T wave and therefore that the drug affects T-wave morphology.

Figure 4 provides the Bland-Altman plots for the estimation of stability of QTc manual, automatic and area-based measurements (QTac50% and QTac97%). The analysis is based on 29 ECGs reflecting the stability of 2 measurements conducted at 1-day interval without drug. The Bland-Altman plots reveal a higher stability for automatic measurements in general. QTc manual was less stable with an average difference equal to -8.4 ms and a confidence interval (CI) equal to 68 ms. Automatic measurements showed higher stability with an average difference close to 5 ms and an averaged CI close to 40 ms.

Discussion

Sotalol is known to prolong the QT interval by mainly increasing the action potential durations of the midmyocardium cells (5). The potassium channels blockade increases dispersion of transmural repolarization providing a substrate for intra mural re-entry. This leads to a higher risk for ventricular

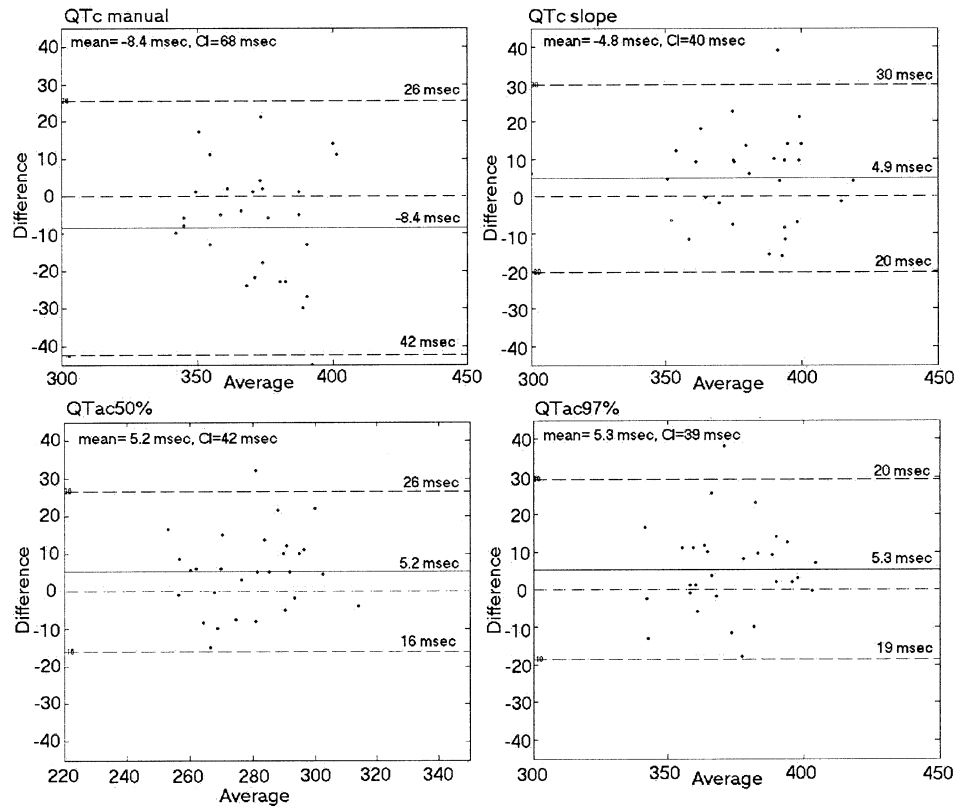
Table 1. QT Repolarization Measurements Associated With 3 Ranges Sotalol Plasma Concentration

SPC (ng/mL)	N	RR	QTc slope (B)	QTc slope (F)	QTc slope (N)	QTac 25% (N)	QTac 50% (N)	QTac97% (N)
0	558	899 ± 128	391 ± 24	384 ± 21	359 ± 32	220 ± 25	261 ± 27	346 ± 34
<0-300	69	1011 ± 122	391 ± 25	391 ± 22*	393 ± 35	240 ± 29	288 ± 30	384 ± 36
≤300-600	135	1000 ± 129	394 ± 22	393 ± 19	393 ± 34	236 ± 26	285 ± 28	380 ± 36
≤600	649	1052 ± 134	419 ± 32	421 ± 39	434 ± 43	249 ± 31	308 ± 34	419 ± 46

Comparing mean values in reference to plasma concentration free of sotalol, the values in bold are significantly higher ($P < .001$) than baseline values. Sotalol Plasma Concentration (SPC) is expressed in ng/ml, all other parameters are in msec. Bazett's (B), Fridericia's (F) and population-based (N) corrections are reported for QT slope (automatic measurements).

* $P = .07$, values in bold $P < .001$

Fig. 4. Bland-Altman plots for the assessment of 1-day reproducibility of QT manual, slope and area-based measurements. Mean: average differences between ECGs (in 29 patients) under baseline condition; CI: confidence interval for the measurements reflecting spread of differences between measurements.



arrhythmias such as torsades de pointes. The association between morphological changes of the T wave and the occurrence of arrhythmic events is less clear. The literature contains scattered studies that have used morphological quantifier of T-wave morphology showing that this information may be associated or even used as a significant marker for the risk of ventricular arrhythmias. It was conducted in animal models (6), in humans with idiopathic LQTS patients (7), and in LQTS patients (8,9). Also, morphology of T loop could improve the risk stratification of post myocardial patients for sudden cardiac death when combined with other parameters such as ejection fraction and HR (10) confirming that repolarization morphology may be an important phenomenon.

The use of heart rate correction is crucial in the estimation of QT interval prolongation. The type of correction used can have a significant effect on the analysis of the repolarization as shown in Table 1. Bazett's correction formula was inadequate; it inverted the relationship between QT and RR values as shown in the second row of graphs in Figure 2. Fridericia's formula provided a better correction than Bazett's with very small QT/RR and QTa97%/RR relationships. As expected, the correction method designed on the population was the

most efficient. Using a linear model, the QT/RR relationship was better corrected than with any other model. The contribution of heart rate to QT changes was inferior to 0.01 % for both QTa97% and QT manual.

Our analysis is a preliminary validation of the area-based parameters for the identification of the effect of an I_{Kr} blocker on the ventricular repolarization segment from the surface ECG. These parameters are, at least, as good as standard QT interval measurements for identifying drug-induced repolarization changes. They are HR dependent and they can be HR corrected with the same techniques as QT interval, but more importantly: 1) their stability is higher than that of manual QT measurements; 2) they extend the analysis of repolarization to its morphology and to the assessment of the changes across the entire repolarization. This may potentially bring interesting and useful information for the evaluation of the safety of new pharmacological compounds.

Currently, our efforts are directed toward the design of more specific morphological indexes based on the T wave area parameters. They are designed to focus on the symmetry of the T wave and on the end of the T wave where the effect of I_{Kr} blocker is supposed to be greater.

Conclusions

The area-based repolarization parameters are affected by sotalol administration indicating drug-induced changes in T-wave morphology. Our results revealed that changes in repolarization are associated with sotalol-induced morphological changes of T wave across the entire repolarization segment. Our automatic measurements including the area-based parameters provide higher stability of repolarization than manual QTs. These observations may create new incentives for using both automatic and morphological parameters of repolarization, rather than, or in addition to QT prolongation when evaluating safety of tested drugs.

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