

# Torsadogenic Drug-induced Increased Short-term Variability of JT-area

Xiao Jie<sup>1</sup>, Blanca Rodriguez<sup>1</sup>, Esther Pueyo<sup>2,3</sup>

<sup>1</sup>Oxford University, Oxford, UK

<sup>2</sup>University of Zaragoza, Zaragoza, Spain

<sup>3</sup>Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Spain

## Abstract

*Increased beat-to-beat variability of repolarization (BVR) has been suggested to indicate increased susceptibility to drug-induced arrhythmia. This study aimed to characterize BVR in patients before and after administration of sotalol, a torsadogenic antiarrhythmic drug, in the search for new biomarkers of proarrhythmic risk. ECG Recordings pre and post sotalol injection in two groups of patients (with and without history of drug-induced torsades de pointes) were obtained from THEW. ECG wave detection and delineation were performed via dyadic wavelet transform. BVR was evaluated by short-term variability (STV) of QTc interval and JT area. In both groups, sotalol resulted in significant increase in STV of JT area, while no significant change occurred in STV of QTc interval. Thus, STV of JT area, as a measure of BVR, has the potential to be a biomarker for drug toxicity.*

## 1. Introduction

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia that can potentially degenerate into life-threatening ventricular fibrillation. QT prolongation is one major characteristics of TdP. But drug-induced QT prolongation, even to a significant extent, might not lead to occurrence of TdP; on the contrary, it might induce significant antiarrhythmia [1]. Moreover, drugs that do not prolong QT interval or even shorten it can be proarrhythmic [2]. Therefore, QT prolongation alone is inadequate for assessment of drug-induced cardiac toxicity.

It has long been suggested that increased beat-to-beat variability of repolarization (BVR), i.e., increased temporal and spatial dispersion of repolarization, indicates increased susceptibility to arrhythmia [1, 3-5]. The goal of this study is to characterize BVR in patients

before and after administration of sotalol, a torsadogenic antiarrhythmic drug, in the search for new biomarkers of proarrhythmic risk. Such biomarkers, either alone or combined with QT interval, may provide a better drug safety assessment than QT interval alone.

Existing studies have assessed BVR in terms of short-term variability (STV) of QTc interval [4-6]. As JT area, i.e., total area of T wave, has been shown to be an indicator of dispersion of repolarization [7, 8], in this study, BVR was evaluated by STV of both QTc interval and JT area in an attempt to compare the two.

## 2. Methods

Electrocardiogram (ECG) datasets that were employed in this study were obtained from the Telemetric and Holter ECG Warehouse (THEW, <http://thew-project.org/>). These datasets consisted of 12-lead surface ECG recordings from individuals without (group I, n=17) and with (group II, n=16) history of drug-induced TdP, and both pre and post injection of sotalol (see detailed descriptions in [9]). The sampling frequency and resolution were of 1 kHz and 5  $\mu$ V respectively.

All analyses reported in this study were performed on the lead II ECG. Specifically, all signals were first filtered (0.05 Hz high-pass filter; 40 Hz low-pass filter) in order to reduce baseline wander and power line noise. The baseline wander was further eliminated using cubic spline technique. ECG wave detection and delineation, i.e., identification of fiducial points (peaks and limits for individual P, QRS and T waves), were performed via the algorithm proposed in [10]. In brief, the dyadic wavelet transform of the ECG signals was computed. QRS complexes were then first detected and subsequently, fiducial points of the QRS complex, the P wave, and the T wave were identified. The algorithm was validated using manually annotated databases comprising different sampling rates and wave morphologies. Its performance has been shown to be accurate and reliable.

For each recording, a 30-consecutive beat interval free of ectopic beats was manually selected under control and sotalol condition, respectively. QT interval was measured as the interval between the onset of QRS wave and the end of the T wave. The heart rate-corrected QT interval, QTc, was calculated using Bazett's formula. JT area of each beat was computed as the area between the curve and the baseline from the J-point to the end point of the T wave [7]. The baseline referred to the isoelectric segment preceding QRS complex. The J-point was defined as 10 ms following the end point of QRS complex. STV was calculated as the mean orthogonal distance from each point in the Poincaré plot to the diagonal ( $STV = \sum |D_{n+1} - D_n| / [30 \times \sqrt{2}]$ , where D is either QTc interval or JT area) [4]. Results were reported as mean $\pm$ SD. Statistical analyses were done by paired Student's t-test or ANOVA, as appropriate. A P value of less than 0.05 was considered significant.

### 3. Results

Tables 1 and 2 present values of electrocardiographic parameters pre and post sotalol administration for groups I and II, respectively. For both groups, sotalol induced significant increase in RR interval, QT interval, QTc interval, JT area and STV of JT area. Specifically, the corresponding mean values increased by 21.5%, 17.9%, 6.7%, 28.0% and 28.6%, respectively, in group I, and by 24.5%, 26.4%, 13.1%, 34.4%, and 54.8%, respectively in group II. STV of QTc interval, however, did not undergo statistically significant change following sotalol administration.

Table 1. Electrocardiographic parameters for group I under control and sotalol condition.

|                   | Control       | Sotalol           |
|-------------------|---------------|-------------------|
| RR Interval (ms)  | 882 $\pm$ 165 | 1072 $\pm$ 162*** |
| QT Interval (ms)  | 397 $\pm$ 29  | 468 $\pm$ 50***   |
| QTc Interval (ms) | 418 $\pm$ 20  | 446 $\pm$ 38**    |
| JT Area (mV•ms)   | 25 $\pm$ 11   | 32 $\pm$ 16*      |
| STV_QTc (ms)      | 14 $\pm$ 12   | 16 $\pm$ 17       |
| STV_JT (mV•ms)    | 3.5 $\pm$ 1.6 | 4.5 $\pm$ 2.3**   |

Note: QTc = heart rate-corrected QT interval; STV\_QTc/STV\_JT = short-term variability of QTc/JT area. \*P<0.05; \*\*P<0.01; \*\*\*P<0.0001.

Table 2. Electrocardiographic parameters for group II under control and sotalol condition.

|                   | Control       | Sotalol           |
|-------------------|---------------|-------------------|
| RR Interval (ms)  | 857 $\pm$ 155 | 1067 $\pm$ 143*** |
| QT Interval (ms)  | 405 $\pm$ 39  | 512 $\pm$ 35***   |
| QTc Interval (ms) | 433 $\pm$ 28  | 490 $\pm$ 32***   |
| JT Area (mV•ms)   | 32 $\pm$ 19   | 43 $\pm$ 31*      |
| STV_QTc (ms)      | 19 $\pm$ 19   | 17 $\pm$ 17       |
| STV_JT (mV•ms)    | 3.1 $\pm$ 2.3 | 4.8 $\pm$ 2.6**   |

Comparisons between groups I and II showed that sotalol induced a larger increase in QT and QTc interval in group II than in group I. No other significant differences were found under either condition between these two groups.

### 4. Discussion

This study assessed BVR quantitatively by evaluating STV of QTc interval and STV of JT area before and after administration of a torsadogenic drug, sotalol, in groups of individuals with and without history of drug-induced TdP. Sotalol increased STV of JT area significantly, while no significant change was observed in STV of QTc interval, suggesting that STV of JT area might be a better measure of BVR and thus a potential ECG biomarker for drug-induced cardiac toxicity.

Repolarization abnormalities can facilitate both the genesis and sustenance of life-threatening arrhythmias. Not surprisingly, a body of work has demonstrated a statistical link between increased BVR and enhanced susceptibility to arrhythmias [1, 3-5]. BVR has been evaluated as variations of repolarization in time, such as monophasic action potential duration and QT interval [1, 4, 5], and in morphology, such as T wave amplitude [11]. As shown by both experimental and computational studies [7, 8], JT area, a parameter characterizing repolarization both in time and morphology, appeared to be an indicator of transmural dispersion of repolarization. Thus, in this study, the predictive value of both JT area and its STV was evaluated. We observed a significant sotalol-induced increase in both JT area and its STV for patients either with or without history of TdP, which confirmed the torsadogenic effects of this class III antiarrhythmic drug. Moreover, sotalol-induced increase in STV of JT area appeared to be more important (smaller P value) than that in JT area.

Our results also revealed a significant increase in RR/QT/QTc interval following administration of sotalol in both groups, consistent with the results in the study conducted by Couderc et al. [9] which employed the same

datasets as current study and performed all analyses on continuous 5-minute recordings. This suggests that analyzing 30 consecutive beats, as done in current study, could be as effective as analyzing a much longer recording.

It is noted that although there were individuals in both groups exhibiting QTc interval of up to 522 ms following sotalol injection, which is well above the established safety cut-off values (450 ms for men and 460 ms for women [12]), no episodes of TdP were observed among all individuals. This, along with previous studies, suggests the unreliability of using QT prolongation alone as the biomarker for drug toxicity assessment and urges the need for identification of a new biomarker.

In both groups examined, STV of QTc interval, a common measure of BVR, remained unchanged after sotalol injection. This is consistent with the finding in Couderc et al's study [9] where QT variability, quantified as the ratio between median absolute deviation of QT interval and that of RR interval, did not vary after sotalol injection. Considering the observed significant increase in STV of JT area, STV of JT area might be a more sensitive measure of BVR than STV of QTc interval.

In conclusion, sotalol induced significant increase in STV of JT area, suggesting the promising role of STV of JT area as an indicator of BVR and susceptibility to drug-induced arrhythmias. It has the potential to serve as a surrogate or supplemental ECG biomarker other than QT prolongation. Further investigation, both experimentally and computationally, is needed in order to confirm and establish the predictive value of this electrocardiographic parameter in drug safety assessment, and furthermore, in risk stratification and early disease detection.

## 5. Limitations

The ECG datasets employed in this study, albeit consisting of the largest number of patients with a history of TdP [12], were collected from a limited number of patients. In addition, the datasets only examined the effects of one type of drugs. Future studies with a larger sample size and more varieties of drug compounds, such as classes I and IV antiarrhythmic drugs that block sodium and calcium channels respectively, are feasible and will help establish and define the predictive value of STV of JT area. Moreover, in this study, we observed significant sotalol-induced change in STV of JT area, but not in that of QTc interval. It is noted that our analyses were performed on a single lead (lead II), which yielded the highest absolute value of JT area among all leads as seen in experiments on dogs [7]. As to QTc interval, one previous study has shown that leads V3 and V4 yielded the highest accuracy and sensitivity, respectively, for predicting drug-induced QT prolongation [13]. Thus the result of comparisons between STV of JT area and QTc interval may vary depending on the lead selection.

Additionally, in this study, QTc was computed using Bazett's formula as a common practice, which, however, might often underestimate or overestimate its value. This could also contribute to the finding of unchanged STV of QTc.

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Address for correspondence:

Xiao Jie, Ph.D.  
Computing Laboratory  
Oxford University  
Oxford OX1 3QD, UK  
E-mail: xiao.jie@comlab.ox.ac.uk