Effects of Sotalol on T-wave Morphology in 24-hour Holter ECG Recordings

TP Brennan, L Tarassenko

Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, United Kingdom

Abstract

This article describes the impact of sotalol, a Class III anti-arrhythmic that is known to prolong the QT interval and induce torsades de pointes*, on ventricular repolarisation. Timing and T-wave morphology-based biomarkers of ventricular repolarisation are extracted from 24-hour Holter electrocardiogram (ECG) recordings from a clinical sotalol study [1]. The results show sotalol produces a significant dose-dependent increase of QT and T-peak to T-wave end (T_{pe}) intervals ($p < 0.0001$). The effect of sotalol tends to significantly increase the morphology-based biomarkers, with the exception of T_{area} and T-wave area-based symmetry (T_{SymA}). The morphology based biomarkers are shown to be more sensitive to the effects of sotalol and the maximum effect on morphology biomarkers tends to take place after the maximum effect on the heart rate, QT and T_{pe} intervals.*

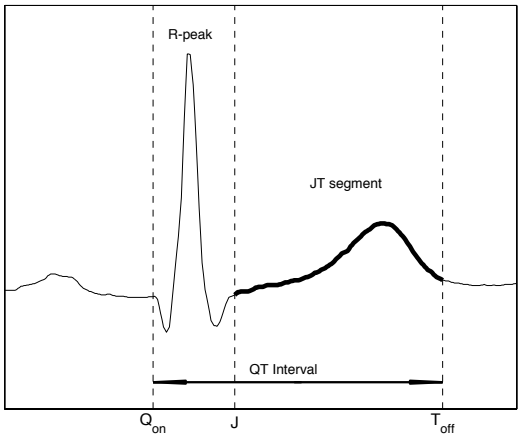

Figure 1. A typical ECG waveform with the critical waveform boundaries identified, namely Q_{on}, J and T_{off}, as well as the JT segment and QT interval.

1. Introduction

In recent years cardiac drug safety has been a growing concern for regulatory agencies because of the increasing number of non-cardiac drugs adversely affecting the heart and inducing life-threatening ventricular arrhythmias, such as *torsades de pointes*. The current "gold standard" in assessing the cardiac safety of new drugs in clinical trials has centered on evaluating ventricular repolarisation duration, namely the QT interval [2]. The QT interval is measured from Q_{on} to T_{off}, as shown in Figure 1. However, the QT interval has several limitations: firstly, T_{off} is difficult to identify because of the varying morphology of the T-wave, the occasional presence of a U-wave and various types of noise and physiological artefacts. Secondly, the sensitivity and specificity of QT interval prolongation as a predictor of drug-induced arrhythmia has been brought into question. Several drugs have been shown to prolong the QTc interval but do not necessarily induce arrhythmia [3].

As a result of the limitations of the QT interval, there has been a growing interest in identifying alternative biomarkers of drug-induced arrhythmia. Studies of the electrophysiological mechanisms underlying drug-induced arrhythmia have suggested that spatial and/or temporal electrophysiological heterogeneities of ventricular repolarisation may provide an indicator of proarrhythmic activity [4]. Both *in vitro* and *in silico* studies suggest that characterisation of T-wave morphology (or the JT segment, as shown in Figure 1) might enable the degree of ventricular repolarisation dispersion to be assessed [5, 6]. This article investigates the effects of sotalol, a Class III anti-arrhythmic that is known to prolong the QT interval and induce *torsades de pointes*, on ventricular repolarisation in 24-hour Holter recordings from a clinical study ($N = 26$) [1].

2. Methods

The method of extracting timing and morphology-based biomarkers of ventricular repolarisation from 24-hour Holter ECG recordings is shown in Figure 2. The method has two parallel tracks; the first segments the ECG by identifying the R-peak, Q_{on}, J and T_{off}; the second track is a wavelet de-noising procedure that removes baseline wander and high-frequency noise so that smooth JT segments can be extracted for morphological characterisation. A segmentation algorithm uses a combination of multi-

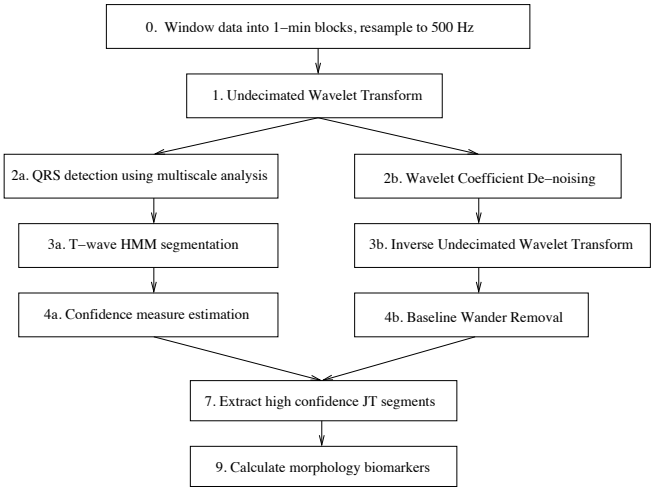

Figure 2. Flowchart of automated ECG analysis system for characterisation of ventricular repolarisation using 24-hour Holter ECG recordings.

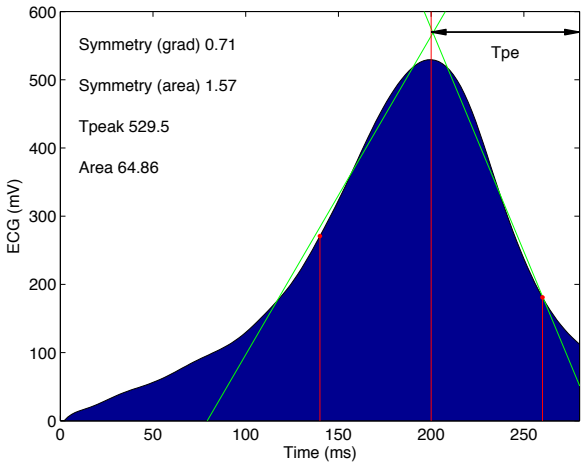

Figure 3. Morphology-based biomarkers extracted from the JT segment, namely T-wave area, T-peak amplitude, gradient-based symmetry and area-based symmetry.

scale wavelet analysis R-peak detection method [7], and hidden Markov model (HMM) segmentation for a subset of the ECG signal in a region near the R-peak [8]. The HMM is trained in a supervised manner and is used to infer the Q_{on}, R, J and T_{off} using the Viterbi algorithm [9]. The inferred annotations are also accompanied by a *confidence measure*, which allow low confidence beats to be excluded from morphology characterisation. The confidence measure is in fact the normalised joint log-likelihood of the observations *and* state sequence given the model, i.e. $p(O, S|\lambda)$, which is determined as part of the HMM inference process [10].

2.1. T-wave morphology biomarkers

A number of different T-wave morphology-based biomarkers of drug-induced arrhythmia have been proposed in the literature. The biomarkers can be broadly classified into five groups: T-wave duration parameters [11, 12], amplitude-based parameters [13, 14, 15], T-wave alternans [16, 17], parameters based on singular value decomposition of multi-lead ECG signals [18, 19] and parameters based on the T-wave loop [20, 21]. A comprehensive review of T-wave morphology based biomarkers is published by Brennan and Tarassenko [22]. The wide variety of morphology-based biomarkers published in the literature necessitates the selection of a subset for further analysis. From the literature is it clear that T-wave area and symmetry are both sensitive to drug effects [12, 15]. Furthermore, *in silico* studies have show that an increase in sotalol concentration resulted in an increase in T-wave area, amplitude and T-wave area-based symmetry [6]. Therefore, the effect of sotalol on the following T-wave morphology biomarkers are investigated:

1. **Area:**

$$\sum_{n=1}^{T} f(n)\Delta x$$

2. **T-peak:** T-wave peak amplitude value.
3. **Gradient-based symmetry:** the ratio of the ascending gradient over the descending T-wave gradient. The ascending and descending gradients are defined as the gradient of the best-fit[1] straight line to T-peak $\pm 0.75 \times T_{pe}$ for the portions of the waveform on either side of T-peak.
4. **Area-based symmetry:** the ratio of the area before T-peak occurs over the area under the descending slope of the T-wave. The area considered, similar to the gradient-based symmetry biomarker, is the area under $\pm 0.75 \times T_{pe}$ either side of T-peak.

Prior to calculating the morphology biomarkers, the JT segment smoothed using a wavelet de-noising and baseline wander removal procedure [8]. The de-noising algorithm applies the fixed threshold estimated using soft thresholding to the same UWT coefficients used for the R-peak detection and HMM segmentation procedure. The inverse UWT is then used to reconstruct the de-noised ECG signal. Low confidence beats, i.e. beats with a confidence measure less than 0.7 [10], are excluded from further analysis. The high confidence JT segments are then "normalised" by subtracting the J-point value from the JT segment. Figure 3 shows morphology-based biomarkers derived from a typical JT segment.

[1] Implemented using MATLAB's *polyfit* function with a least-squares fitting technique.

2.2. Heart-rate correction of biomarkers

Significant work has been undertaken to identify the *optimal* formulae for heart rate correction. Malik et al. investigated the performance of six generic QT/RR regression models on interval data obtained (via automated interval measurement) from 50 healthy volunteers and found that the linear and shifted logarithmic regression models had the lowest residual error [23]. There is also some evidence that T-wave morphology-based biomarkers are also dependent on heart rate [24]. In this study a simple linear regression model of the form $B = \beta + \alpha$RR, where B is the interval or morphology biomarker and RR is the RR-interval of the preceding heart beat, was fitted to data extracted from the baseline day (D0) for each patient.

2.3. Sotalol Holter ECG data set

The data set consists of 12-lead, 24-hour Holter ECG recordings from 26 healthy volunteers. The recordings were obtained during a controlled study of the effects of sotalol at Pharmacia's Clinical Research Unit (Kalamazoo MI, USA) [1]. The study was based on a three-day protocol; baseline day (D0), administration of 160 mg of sotalol (D1) and administration of 320 mg of sotalol (D2). The drug was administered orally at 08:00 on dosage days under fasting conditions and the subjects were given standard meals at noon and 18:00. Subjects were withdrawn from the study if pre-dose QTc was greater than 410 ms or any QTc within 6 hours after dosing was greater than 450 ms. As a result, data is available from only 11 subjects for D2. This could clearly bias the results to reduce the real change of sotalol induced effects.

3. Results

To assess the effect of sotalol on the interval and morphology biomarkers, a median filter was applied to each of the heart rate corrected biomarkers extracted from the high-confidence beats in each one-minute analysis window. The mean sotalol effect across all subjects (26 for D1 and 11 for D2) for the biomarkers is calculated as a percentage change with respect to baseline. The percentage change between drug and non-drug is calculated for every minute averaged over a 30-minute period. The sensitivity of each biomarker (S) is calculated as the absolute maximum mean effect normalised by the sum of the biomarker variance across all subjects, i.e.

$$S = \frac{\max |\bar{E}_t|}{\sqrt{\sum_{i=1}^{N} \sum_{n=1}^{T} \sigma_{i,n}^2}}, \qquad (1)$$

where $\bar{E}_t$ is the average biomarker effect at time t, and $\sigma_{i,n}^2$ is the variance for the nth 30-minute window for patient i.

	Effect (%)		Time (min)		Sensitivity	
	D1	D2	D1	D2	D1	D2
QT	5.8	6.3	210	210	0.147	0.147
T_{pe}	14.2	12.2	150	120	0.148	0.122
T_{area}	-18.0	-23.3	420	420	0.184	0.227
T_{amp}	16.5	21.0	450	450	0.213	0.246
T_{SymA}	-25.3	-31.5	450	450	0.252	0.284
T_{SymG}	12.0	13.0	240	210	0.247	0.24

Table 1. Summary of the drug effects of 160 mg (D1) and 320 mg sotalol on heart-rate corrected interval and morphology-based biomarkers.

3.1. Effect of sotalol on biomarkers of ventricular repolarisation

Table 1 lists the mean maximum effect, the timing of the maximum effect and a dimensionless measure of biomarker sensitivity. Sotalol results in a significant increase of RR, QT and T_{pe} with $p < 0.0001$ using the Wilcoxon rank-sum test with 95% significance level. The effects of sotalol on the RR, QT and T_{pe} are also dose-dependent ($p < 0.0001$). The timing of the maximum effect of sotalol on RR, QT and T_{pe} occurs between 2 to 4 hours after dosing, which is consistent with the pharmacokinetics of sotalol [25]. Sotalol results in a dose-dependent increase in T_{amp} and T_{SymG} ($p < 0.0001$). In contrast, sotalol results in a dose-dependent decrease of T_{area} and T_{SymA} ($p < 0.0001$).

4. Discussion and conclusions

The results in Table 1 show that the morphology-based biomarkers are more sensitive to the drug effect, with T_{SymA} showing the greatest sensitivity to sotalol concentration. The sensitivity of QT and T_{pe} is comparable. The effect of sotalol tends to exhibit an earlier mean maximum effect on QT and T_{pe} intervals, with the maximum effect for the QT interval occurring around 210 min after dosing on both dosage days. The maximum effect on the morphology biomarkers, with the exception of T_{symG}, tends to occur later, around 420 to 450 min, after dosing.

The varied effect of sotalol on interval and morphology biomarkers has been observed in similar studies of sotalol. Couderc et al. [12] investigated the effects of sotalol on T-wave area-based repolarisation duration parameters found that the increase of repolarisation duration due to sotalol was smallest at 25% total cumulative area (29 ms), larger at the 50% mark (47 ms) and greatest at 97% total cumulative area (73 ms). In other words, the effect of sotalol on the duration of repolarisation is more exaggerated towards the end of the repolarisation process. This might explain the varied effects observed morphology biomarkers.

Acknowledgements

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Address for correspondence:

Thomas Brennan
Institute of Biomedical Engineering
Old Road Campus Research Building
University of Oxford, Headington OX3 7LF, United Kingdom
thomas.brennan@eng.ox.ac.uk