A novel ECG-based biomarker quantifying APD restitution dispersion improves risk stratification following sotalol administration

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Abstract

Anti-arrhythmic drugs work by interfering with ion channel activity and may lead to cardio toxicity. In this work, we investigated the effect of sotalol in 2 sets of subjects, one of them consisting of patients who developed Torsades de Pointes after sotalol administration and the other one consisting of healthy volunteers. Biomarkers quantifying rate adaptation of repolarization and restitution dispersion were evaluated and used to predict the effect of sotalol. Results show that restitution dispersion stratifies the arrhythmic risk in individuals following sotalol administration, with a considerably improved performance with respect to classical biomarkers such as the QT corrected interval.

Keywords *Rate adaptation, Restitution dispersion, cardiotoxicity, sotalol*

1 Introduction

Anti-arrhythmic drugs work by interfering with ion channel activity which may lead to cardio toxicity [1]. The class III antiarrhythmic drug sotalol binds to potassium channels, specifically reducing the rapid delayed rectifier current I_{Kr}. This current contributes to the repolarization of the action potential (AP), and therefore, when blocking I_{Kr}, the action potential duration (APD) increases. This effect is reflected on the ECG as a prolongation in the QT and T peak to T end (T_{pe}) intervals. Prolongation of the QT interval or QTc interval (QT corrected by heart rate (HR)) is the main biomarker used to assess cardiotoxicity. The main concern/limitation of the QT/QTc interval prolongation as a biomarker is its low specificity. For instance, not all torsadogenic drugs prolong the QT interval and not all drugs that prolong the QT result in Torsades de Pointes (TdP).

The rate dependency of drug binding to hERG, the gene encoding the I_{Kr} channels, has been suggested as one of the factors that lead class III drugs to become proarrhythmic. In particular, the effect of many I_{Kr} blockers is lower for higher frequencies, which highlights the importance of rate dependence in cardiac safety [2]. Rate dependence of drug action modifies APD restitution (APDR) and may lead to a increased spatial APDR dispersion, which has been proposed to act as a potent arrhythmogenic substrate [3], and has also been associated with the induction of ventricular arrhythmias [4]. In a recent study, spatial APDR dispersion was quantified from the surface ECG by a novel index, $\Delta\alpha$, which accounts for the rate normalized differences of the T_{pe} interval under steady state conditions [5]. In this work, $\Delta\alpha$ is evaluated as a biomarker for improving risk stratification after sotalol administration.

Computation of $\Delta\alpha$ under non-stationary conditions first requires evaluation of repolarization adaptation to HR changes. Rate adaptation of repolarization has been suggested to play an important role in the development of arrhythmias. Biomarkers such as QTc, which include rate dependence, are commonly used. However, QT interval is not only affected by the previous RR interval, but for a history of RR intervals. A methodology to compensate for the T_{pe} and QT memory lag after HR changes will be used in this work [6]. On top of investigating sotalol modulation of APDR dispersion, we will additionally study the effect of sotalol in the QT and T_{pe} rate adaptation and we will assess their use for risk stratification.

Computational modeling and simulation was used to assess the mechanisms underlying the effect of I_{Kr} block, as induced by sotalol, on APDR dispersion and rate adaptation of repolarization.

2 Methods

2.1 Population

The study population was divided in two sets, one consisting of 3 patients with a previous history of TdP and the other one consisting of 8 volunteers. All of them received the same sotalol dosis (2mg/kg body weight). The TdP patients of the first set had a history of syncope or TdP and they were subsequently enrolled for a diagnostic test based on dl-sotalol IV. The test was used to unmask latent repolarization abnormalities. All patients in this first set experienced TdPs after sotalol administration. The second set consisted of healthy volunteers who did not experienced TdP after sotalol administration.

12-lead ECG recordings with a sampling frequency of 180 Hz were obtained for each subject/patient. The lead with a higher signal-to-noise ratio was selected for computation of the different rate dependent biomarkers.

ECG excerpts of 1 hour duration presenting marked HR changes were selected, both before and after sotalol administration in the case of the healthy subjects and just after sotalol administration in the case of TdP patients.

2.2 Rate adaptation of the QT and T_{pe} intervals

A previously proposed model, shown in Fig. 1, was used to compute rate adaptation of the QT and T_{pe} intervals [6].

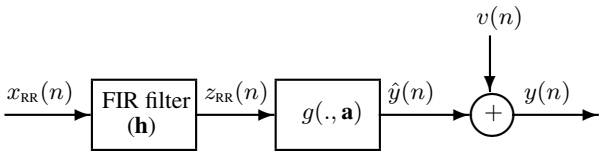

Figure 1: Block diagram describing the relationship between the QT or T_{pe} and RR, which consists of a time invariant FIR filter, with impulse response **h**, and a nonlinear function described by vector **a**.

The scheme in Fig. 1 describes the relationship between the RR interval series (input), $x_{RR}(n)$, and the corresponding QT or T_{pe} interval series (output), generically denoted in the diagram by $y(n)$. A time invariant FIR filter with impulse response **h**, and a nonlinear function described by the vector **a** which relate both series $x_{RR}(n)$ and $y(n)$, are identified. '**h**' includes information about the memory of the system; that is, a characterization of the influence of a history of previous RR intervals on each QT or T_{pe} measurement. From '**h**', the biomarker t_{90} was computed, which measures the time required for the QT or T_{pe} intervals complete 90% of their rate adaptation.

As t_{90} is known to depend on the range of RR intervals included in its computation, we additionally computed m_{90}, expressing the adaptation time measured in beats:

$$m_{90} = t_{90}/\overline{RR} \tag{1}$$

where $\overline{RR}$ is the mean RR interval.

$g_k(.,\mathbf{a})$ represents the relationship between the RR interval and the QT or T_{pe} interval once the memory effect has been compensated for (i.e. under stationary conditions), and it is particularized and optimized for each subject using one ($k, k \in \{1,\ldots,10\}$) of the ten regression models described in [6].

2.3 APD restitution dispersion from the ECG

The index $\Delta\alpha$ proposed in [5], quantifying the spatial APDR dispersion under stationary conditions, was measured in this study. $\Delta\alpha$ was computed using $g_k(.,\mathbf{a})$ of the second block in Fig. 1:

$$\Delta\alpha = \left.\frac{\partial g_k(z_{RR},\mathbf{a})}{\partial z_{RR}}\right|_{z_{RR}=\bar{z}_{RR}} \tag{2}$$

where z_{RR} represents a surrogate of the RR interval series x_{RR} with the T_{pe} memory effect compensated for.

2.4 Simulation of APD rate adaptation and APDR dispersion under the effect of sotalol.

Computational modeling and simulation was used to assess the mechanisms underlying the effect of sotalol (I_{Kr} blocking drug) on repolarization adaptation time t_{90} and APDR dispersion $\Delta\alpha$. The human ten Tusscher AP model describes the principal ionic currents with a high degree of electrophysiological detail for the three types of cells in the ventricular wall: endo-, epi- and midmyocardial cells [7].

The rate adaptation of APD at 90% repolarization was simulated in epicardial and midmyocardial single cells by pacing at a cycle length (CL) of 1000 ms until steady state, followed by a CL of 800 ms for 8 min. APDR dispersion was simulated by subtracting dynamic APDR curves in epicardial and midmyocardial cells. The APDR curves were obtained by plotting the steady-state APD (corresponding to the 600th stimulus of each CL) versus the corresponding steady-state CL. In order to assess the effect of sotalol, a 60% I_{Kr} block was introduced in the AP model of the midmyocardial and epicardial cells.

3 Results and Discussion

3.1 Rate adaptation of the T_{pe} and QT intervals

In Fig.2 first row, t_{90} values, representing the time for 90% adaptation of the T_{pe} and QT intervals after a HR change, are plotted versus the mean RR interval for the TdP patients after sotalol administration and for the healthy volunteers before and after sotalol administration. Also, m_{90} values, representing the time for adaptation measured in beats, are shown. Quantification of these results in terms of mean and standard deviation are shown in Table 1.

Table 1: Mean and standard deviation of adaptation times t_{90} [s] and m_{90} [beats] for QT and T_{pe} intervals in TdP patients after sotalol administration and in healthy volunteers before and after sotalol administration.

	TdP patients	Healthy	Healthy+Sotalol
t_{90} QT	277 ± 9	148 ± 65	124 ± 50
t_{90} T_{pe}	271 ± 21	135 ± 99	112 ± 41
m_{90} QT	286 ± 49	167 ± 66	136 ± 46
m_{90} T_{pe}	279 ± 49	155 ± 113	125 ± 49

Results show no significant differences among the healthy volunteers before and after sotalol administration. For the three patients developing TdP, t_{90} and m_{90} for QT and T_{pe} show moderately higher values. We hypothesize that these higher values are due to the arrhythmogenic substrate of these patients and not solely due to

the sotalol administration, as sotalol did not affect the rate adaptation of repolarization in the healthy subjects. These results are in agreement with previous findings which associate a slower rate adaptation of repolarization with higher propensity of suffering life-threatening arrhythmias [6].

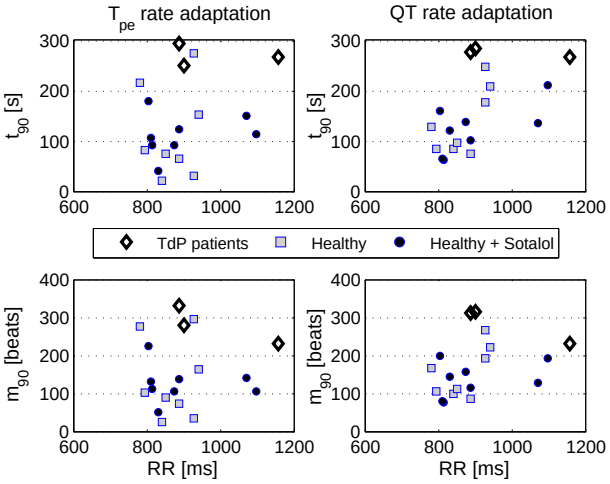

Figure 2: t_{90} and m_{90}values computed for T_{pe} and QT intervals for TdP patients after sotalol administration and for healthy volunteers before and after sotalol administration.

Fig. 3 shows simulated APD adaptation in humans for RR intervals (or cycle lengths) of 1000 to 800 ms for epicardial and midmyocardial cells in control and with 60% I_{Kr} block simulating the effect of sotalol.

From these simulations, adaptation times t_{90} were computed resulting in 290 s for epicardial cells and 230 s for midmyocardial cells in both control and after 60% I_{Kr} block. Therefore, results suggest that sotalol administration should not affect rate adaptation as observed in clinical results in Fig. 2.

Differences in adaptation time are due to the fact that the initial fast phase of the APD adaptation following an abrupt HR change in midmyocardial cells present a faster decay than in epicardial cells, while the slow APD adaptation is similar in both [8]. The fast initial phase was suggested to be related to L-type calcium and slow-delayed rectifier potassium current while the subsequent slow phase is driven by intracellular sodium concentration dynamics [8]. Therefore, I_{Kr} block produced by sotalol administration hardly changes t_{90}, as it is not within the mechanisms underlying any of the two adaptation phases.This explains the results presented in Fig. 2 and Table 1 for subjects before and after sotalol administration.

3.2 APD restitution dispersion

Fig. 4 shows the proposed APDR dispersion measured from the ECG, $\Delta\alpha$, and the mostly used biomarker, QTc. Quantification of the results are shown in Table 2.

APDR dispersion was higher for TdP patients than for healthy subjects after sotalol administration (see table 2)

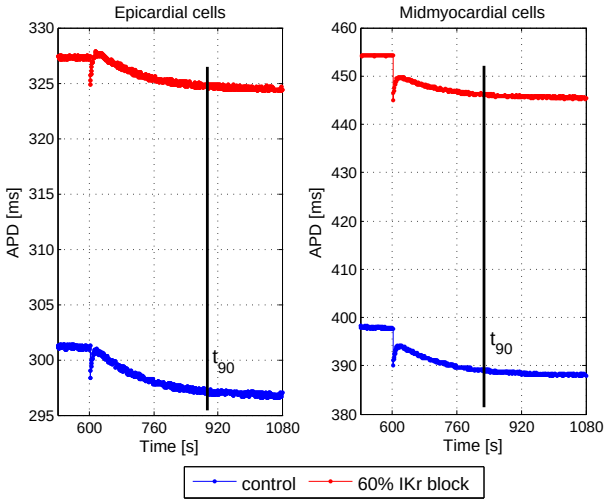

Figure 3: Simulation of APD adaptation from 1000 ms to 800 ms in control and with 60% I_{Kr} block reproducing the effect of sotalol for epicardial and midmyocardial cells. 90% of the complete adaptation is marked with a solid line for both cell types.

Table 2: Mean and standard deviation of $\Delta\alpha$ [ms/ms] and QTc [ms] for TdP patients after sotalol administration and for healthy volunteers before and after sotalol administration.

	TdP patients	Healthy	Healthy+Sotalol
$\Delta\alpha$	0.17 ± 0.04	0.05 ± 0.03	0.04 ± 0.01
QTc	486 ± 59	402 ± 11	400 ± 10

with P-value < 0.001. QTc showed lower statistical differences with P-value < 0.01. Moreover, sotalol administration did not affect APDR dispersion for healthy subjects.

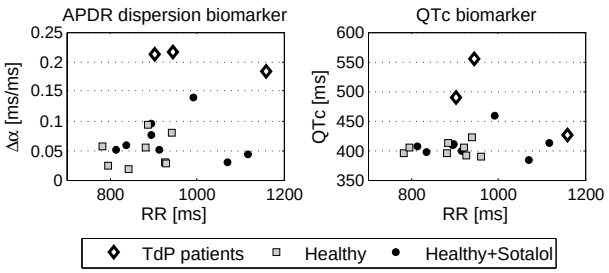

Figure 4: APDR dispersion and QTc at mean RR interval for TdP patients after sotalol administration and healthy volunteers before and after sotalol administration.

APDR dispersion is lower at higher RR intervals. Then the APDR dispersion at a mean RR interval of 1150 is the highest of all TdP patients with respect to the RR interval value, and corresponds to the first one developing TdP (1 hour after sotalol administration).

In summary, $\Delta\alpha$ seems to be a promising biomarker to

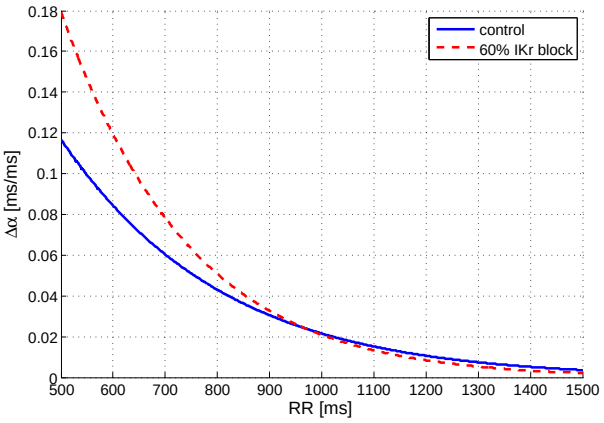

Figure 5: Simulation of APDR dispersion for a range of RR intervals in control and with 60% I_{Kr} block simulating the effect of sotalol.

stratify arrhythmic risk after sotalol administration. Sotalol needs an arrhythmogenic substrate, to be cardiotoxic and $\Delta\alpha$ is able to evaluate that substrate. Despite the limitation due to the number of patients developing TdP after sotalol administration, all of them present higher $\Delta\alpha$ values.

Fig. 5 shows the simulation of APDR dispersion in control and with 60% I_{Kr} block, simulating the sotalol effect. Results suggest that both in control and after 60% I_{Kr} block, APDR dispersion is higher at low RR intervals and considerably decreases for RR intervals above 800 ms. Regarding the effect of I_{Kr} block, substantial differences in APDR dispersion were only found for RR intervals well below 800 ms, while practically no differences were found for RR intervals above 800 ms.

This could explain the results presented in Fig. 4 where $\Delta\alpha$ hardly increased after sotalol administration for healthy subjects, as most of them presented RR intervals above 800 ms.

4 Conclusions

In this work, APDR dispersion has been shown to provide better stratification of TdP patients after sotalol administration than standard ECG-biomarkers such as QTc. This novel rate-dependent biomarker $\Delta\alpha$ which provides information about the arrhythmogenic substrate did not show significant differences among healthy volunteers before and after sotalol administration. However, for patients with an arrhythmogenic substrate who developed TdP after sotalol administration an increased restitution dispersion was observed. Moreover, rate adaptation biomarkers of repolarization features QT and T_{pe} do not show changes after sotalol administration as expected from simulations.

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