Analysis of sotalol-induced effects on cardiac electrical activity

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Abstract

This study aimed at investigating the effects of the antiarrhythmic drug sotalol on ventricular myocardium. Electrocardiogram (ECG) recordings of two groups of patients, with and without a history of the ventricular arrhythmia Torsades de Pointes, were analyzed prior and after they were administered sotalol. Furthermore, a multi-scale computational model of sotalol action at ionic, cellular and tissue levels was investigated. The model was validated with the results from the ECG analysis as well as with additional data available from the literature.

The study contribution was the determination of biomarkers capable of identifying the cardiotoxicity associated with sotalol treatment. From the results of clinical ECG analysis and simulation of the effects of sotalol administered at different doses, we concluded that sotalol-induced prolongations of the corrected QT (QTc) and Tpe (Tpe_c) intervals over 15% and 20%, respectively, are associated with high arrhythmic risk and, therefore, indicate drug-induced cardiac toxicity.

Keywords: heart, ventricle, drugs, sotalol, arrhythmias.

1 Introduction

1.1 Study background

Cardiovascular diseases are the leading death cause in developed countries. A significant proportion of these deaths are directly related to the generation of malignant cardiac arrhythmias, some of which end up leading to sudden cardiac death. In order to make progress in the prevention and/or treatment of cardiac arrhythmias, it is fundamental to deepen the knowledge of such pathological conditions not only at the surface electrocardiogram (ECG) but also at cellular and subcellular level.

Experimental studies have shown that sotalol, widely used in the treatment of atrial and ventricular arrhythmias, significantly changes the heart electrophysiological activity, being beneficial in some patients but not in others. Recent studies have documented that sotalol acts directly on ventricular myocardium prolonging the action potential (AP) duration of every myocyte. However, this prolongation is heterogeneous across the ventricular wall, with the increase in AP duration (APD) being much more pronounced in midmyocardial cells than in endocardial or epicardial cells. This heterogeneous prolongation could be key to explain the benefits or adverse effects of sotalol treatment.

1.2 Drug cardiotoxicity

The development of a new drug compound is an expensive process that would be useless if it is discovered that the compound is toxic at an advanced stage of the development process or when the drug has already hit the market. Because of that, pharmaceutical companies perform toxicity studies in which they typically analyze three indices: the human ether a-go-go related gene (HERG), which encodes the rapid delayed rectifier potassium current (I_{Kr}) and plays a key role in the AP repolarization phase, the APD and the QT interval. A decrease in I_{Kr} and/or an increase in APD and QT are usually considered pro-arrhythmic.

However, not all drugs that block HERG and/or prolong the QT interval result in the generation of arrhythmias. In recent years new electrophysiological markers that provide a more complete characterization of arrhythmic risk have been proposed (Hondeghem, Carlsson, and Düker, 2001). Some of these new markers are used in this study, namely: T peak to T end interval (Tpe), defined as the time from the peak to end of the T wave, which has been proposed as an indicator of transmural dispersion of repolarization (TDR) (Liu et al., 2006); the ratio between the QT and TQ intervals (QT/TQ), which measures the restitution slope from the ECG; the percentage of beats with a ratio QT/TQ greater than 1 (%QT/TQ>1), which is indicative of the fraction of the restitution slope with potential instabilities (Fossa et al., 2007) based on the association between the restitution slope and the transition from tachycardia to ventricular fibrillation (Karagueuzian, and Chen, 1999).

1.3 Sotalol

Drugs interact with the heart at the molecular level once they have been introduced into the body either intravenously or orally. Sotalol is a racemic compound of two drugs, l-sotalol and d-sotalol (Hohnloser, and Woosley, 1994), which differ in their pharmacology and have Class II and Class III antiarrhythmic effects, respectively. L-sotalol is a beta-blocker that suppresses the sinoatrial (SA) node and slows the atrioventricular (AV) node conduction, which decreases heart rate (HR). On the other hand, d-sotalol prolongs the AP by blocking the I_{Kr} current. At the ECG level, sotalol prolongs ventricular repolarization and can induce TdP.

Inhibition of the I_{Kr} current by sotalol is dependent on the transmembrane potential and the ion channel state (Sanguinetti and Mitcheson, 2005). Sotalol molecules gain access to the binding site when the channel is activated (open) (Numaguchi et al., 2000). The recovery of the blockade is also subject to the channel state. It is also reasonable to assume that the activation and inactivation dynamics are not affected by the bound drug molecule (Brennan, 2009).

2 Material and Methods

2.1 Signal processing

2.1.1 THEW database

In order to analyze the sotalol effects at ECG level and to compare and validate simulations results, a database containing ECG recordings of patients prior and after receiving sotalol was

analyzed. The database was available from the Telemetric and Holter ECG Warehouse (THEW) of the Center for Quantitative Electrocardiography and Cardiac Safety of the University of Rochester. The THEW database analyzed in this study consists of ECG recordings from 34 patients, including 17 +TdP, i.e. patients who experienced Torsade de Pointes (TdP) in the past induced by a heterogeneous list of drugs with potential to prolong the QT interval, and other 17 -TdP who started taking sotalol to prevent atrial fibrillation (AF).

The study protocol consisted of administering a dose of 2.0 mg/kg body weight of d,l-sotalol intravenously over a 20 minutes interval. In all cases the ECG acquisition was performed in the morning. The recordings were acquired at rest and supine position before and during the sotalol administration. Each recording contains eight leads: I, II, V_1-V_6.

2.1.2 Analyzed clinical indices

The ECG indices analyzed in this study are: RR, QT, TQ and Tpe intervals; QT/TQ, %QT/TQ>1, Tpe/RR, which represents the difference in the Tpe intervals at different RR intervals normalized by the corresponding RR difference. The computation of the later index used a strategy in which a line is fitted to the Tpe interval series and the maximal Tpe difference is computed from the fitted values.

Having obtained the indices series, a median filtering was applied to remove outliers. Additionally, two more indices were computed, namely QTc and Tpe_c, which represent the QT and Tpe intervals corrected by RR. Since the recordings analyzed in this study are of short duration and were acquired at rest, the range of RR is small, and the QTc and Tpe_c series were obtained by the fitting QT-RR and Tpe-RR curves with a line and subsequently projecting onto RR=1 s.

2.1.3 Statistical analysis

The mean and standard deviation (SD) of each of the analyzed indices was computed. Also, mean and SD were obtained independently for the +TdP and -TdP groups.

Finally, a comparison was made between the measurements before and after the sotalol administration (for all of the patients, the +TdP and the -TdP group) as well as between the +TdP and the -TdP groups (for both the recordings acquired before and after the sotalol administration). Population means were compared using the paired Student's t test. Population SDs were compared using the F test. P value <0.05 was considered as statistically significant.

2.2 Computational cardiac modeling

2.2.1 Sotalol effects in simple cells

In this study, d-sotalol effects (i.e., the Class III effects) were modelled only, since it has been shown that I_{Kr} inhibition plays a major role in drug-induced arrhythmias (Brennan, 2009). Drug-induced I_{Kr} inhibition was simulated by using a Markov model to represent HERG activity. These types of model provide the required modeling framework to investigate drugs state-

dependent effects in I_{Kr}, allowing each Markov state to represent a channel protein physical conformation. Figure 1 illustrates the Markov model, as proposed in (Brennan et al., 2007), used in this study to describe the interaction of sotalol with HERG, which is based on the human I_{Kr} Markov model proposed by Fink, Noble and Giles in 2008 (FNG08) (Fink et al., 2008). The model uses the guarded receptor framework to include changes in the I_{Kr} dynamics caused by the sotalol binding.

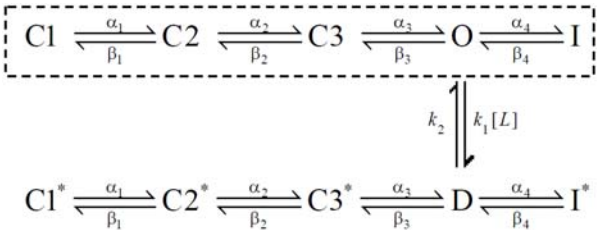

Figure 1: Schematic diagram of I_{Kr} channel Markov model and HERG blockade with sotalol. Inside the box model is the FNG08 model. The channel has three closed states (C1, C2, C3), an open state (O) and an inactivation state (I). [L] is the drug concentration and blocked states are represented by an asterisk (*) (taken from (Brennan, 2009)).

In order to simulate the effect of sotalol binding with HERG in ventricular cellular APs, we incorporated the I_{Kr} Markov model into the ten Tusscher and Panfilov human ventricular AP model published in 2006 (TP06) (ten Tusscher, and Panfilov, 2006). For the purpose of ensuring that the I_{Kr} current for a sotalol zero-concentration did not alter the APD restitution and dynamics of the TP06 model, the maximum conductance G_{Kr} was rescaled to 0.043 mS/nF (its value in the FNG08 model is 0.024 mS/nF) (Brennan, 2009).

2.2.2 Sotalol effects in tissue

In order to investigate the sotalol effects in tissue we used a one-dimensional (1-D) model to simulate impulse propagation along the ventricular wall. The equation to describe the propagation in the 1-D fiber is given by:

$$\frac{\partial V_m}{\partial t} = D\frac{\partial^2 V_m}{\partial x^2} - \frac{I_{ion}+I_{stim}}{C_m}. \quad (1)$$

In the above equation the diffusion coefficient D was set to 1.171 cm^2/s based on experimental results reported in the literature (Bueno-Orovio, Cherry, and Fenton, 2008). According to previous studies, the diffusion coefficient can be considered constant through the fiber, except for one-fifth reduction in the transition zone between the midmyocardium and the epicardium (Gima and Rudy, 2002). For all simulations we have used a temporal resolution dt=0.02 ms and a spatial discretization dx=150 μm (which is approximately the length of a human myocyte: 148 μm (Li et al., 1999)). The length of the fiber was considered as 1.5 cm, in accordance with experimental data (Drouin et al., 1995; Gima and Rudy, 2002). That fiber length corresponds to a 1-D model consisting of 100 cells. Furthermore, the transmural heterogeneity was included in the fiber by considering 30% of endocardial cells, 30% of midmyocardial and 40% of epicardial cells (Drouin et al., 1995). The fiber was stimulated at the endocardial side.

Finally, pseudo-ECG (pECG) signals (extracellular unipolar potentials) were computed at a point surrounding the heart tissue model:

$$\emptyset_e(x',y',z') = -\int_{\Omega} \beta \nabla V \cdot \nabla \frac{1}{\mathrm{r}} dx \quad (2)$$

where β is the diffusion coefficient in the electrical environment around the heart, Ω denotes the ventricular tissue length, r is the Euclidean distance from a source point (x, y, z) to the electrode point (x', y' ,z') and dx is the fiber spatial resolution. In the simulations, the virtual electrode for the pECG calculation was placed 2 cm away from the epicardial surface of the heart.

2.2.3 Analyzed preclinical and clinical indices

At cellular level, the preclinical indices computed in this study were: APD at 1 Hz steady-state pacing, APD restitution (APDR) curves and their slopes obtained with the dynamic protocol (Koller, Riccio, and Gilmour, 1998).

Finally, the clinical indices computed from pECG signals were: QT, QTc, Tpe and Tpe_c intervals, the slopes of Tpe restitution (TpeR) curves obtained using the dynamic protocol.

3 Results

3.1 Signal processing

3.1.1 Sotalol-induced effects on ECG

The percentage of sotalol-induced change in the indices analyzed in this study is shown in Table 1, which presents mean±SD computed over all patients in the studied database. Sotalol induced an increase in all of the tested intervals (RR, QT, QTc, TQ, Tpe, Tpe_c), a reduction in the QT/TQ index and an increase in the %QT/TQ>1 and Tpe/RR indices (the latter index has negative values both before and during the sotalol administration, so its increase is in absolute value). The differences in all of the intervals and the Tpe/RR index between the recordings acquired before and after the sotalol administration were statistically significant.

	(n=34)		
RR	21,5± 11,6	%	*
QT	22,2± 11,0	%	*
QTc	18,8± 11,7	%	*
TQ	20,8± 17,1	%	*
Tpe	14,2± 34,0	%	*
Tpe_c	4,9± 58,6	%	*
QT/TQ	-0,5± 20,8	%	
%QT/TQ>1	2,8± 174,2	%	
Tpe/RR	95,4± 973,0	%	*

Table 1: Percentage of change (mean±SD in the study population) after the sotalol administration with respect to the recordings taken before sotalol administration for the studied intervals and indices. * Denotes statistical significance, P<0.05.

3.1.2 Effects in both patient groups

We additionally investigated whether the sotalol-induced changes were more or less pronounced in one of the two groups of patients. Sotalol induced more notable changes in the +TdP group than in the -TdP group, as assessed by measuring RR, QT, QTc and Tpe intervals. The change was greater in the +TdP group than in the -TdP group with respect to the TQ and Tpe_c indices (Table 2). These results show that the known sotalol effects on ventricular repolarization were more accentuated in the +TdP group, as expected for the history of TdP, which makes those patients more susceptible of having drug-induced ventricular abnormalities. With respect to the Tpe/RR index, sotalol increased in the +TdP group and decreased in the -TdP group.

	Values before sotalol (ms)		Change after sotalol (ms)			
	-TdP (n=17)	+TdP (n=17)	-TdP (n=17)		+TdP (n=17)	
RR	920 ± 162	905 ± 150	180 ± 101	*	212 ± 111	*
QT	**403 ± 30**	**422 ± 51**	**73 ± 28**	*	**110 ± 52**	*
QTc	**410 ± 27**	**430 ± 57**	**67 ± 38**	*	**91 ± 57**	*
TQ	517 ± 141	482 ± 110	107 ± 87	*	101 ± 87	*
Tpe	**79 ± 8**	**88 ± 14**	**7 ± 14**		**17 ± 38**	*
Tpe_c	**80 ± 9**	**104 ± 64**	**6 ± 21**	*	**3 ± 74**	*
QT/TQ	0,83 ± 0,19	0,93 ± 0,21	**-0,04 ± 0,14**		**0,03 ± 0,22**	
%QT/TQ>1	18,14 ± 30,95	21,98 ± 31,56	**-9,86 ± 33,08**		**10,98 ± 34,56**	
Tpe/RR	**-0,43 ± 1,79**	**-0,21 ± 0,71**	**0,44 ± 1,78**	*	**-1,05 ± 3,99**	*

Table 2: Values (mean±SD) before and change after sotalol administration for the +TdP and the -TdP group. Bold numbers denote statistical significance when comparing between the -TdP and the +TdP group, and * denotes statistical significance when comparing between the situation before and after sotalol administration ($P < 0.05$).

From Table 2 it is also possible to observe that intervals and indices were significantly different between the +TdP and the -TdP group. Before sotalol administration, QT, QTc, Tpe and Tpe_c were lower in the +TdP group than in the -TdP group, while the Tpe/RR index was higher in the +TdP group than in the -TdP group. After sotalol administration, the same intervals and also the Tpe/RR index and the QT/TQ and %QT/TQ>1 indices were significantly different between the +TdP and -TdP group.

3.2 Computational cardiac modeling

3.2.1 Validation of the sotalol model

The sotalol model described in section 2 was validated using the ECG data from the THEW database analyzed in this study as well as additional experimental and clinical data available from the literature. Considering that both a 2.0 mg/kg intravenous and a 200 mg oral d-sotalol dose are equivalent to a 320 μM sotalol concentration in our computational model, we found that simulated sotalol effects reproduced the observations made from the available experimental and clinical data. Specifically, as illustrated in Figure 2, Figure 3, and Figure 4, we found that our sotalol model provided increases in the APD comparable to those found in the study by

Huikuri et al (Huikuri, and Yli-Mäyry, 1992), reverse-rate dependence in agreement with experimental data (Huikuri, and Yli-Mäyry, 1992), as well as prolongations of the QT and Tpe intervals matching clinical observations (Fossa et al. 2007).

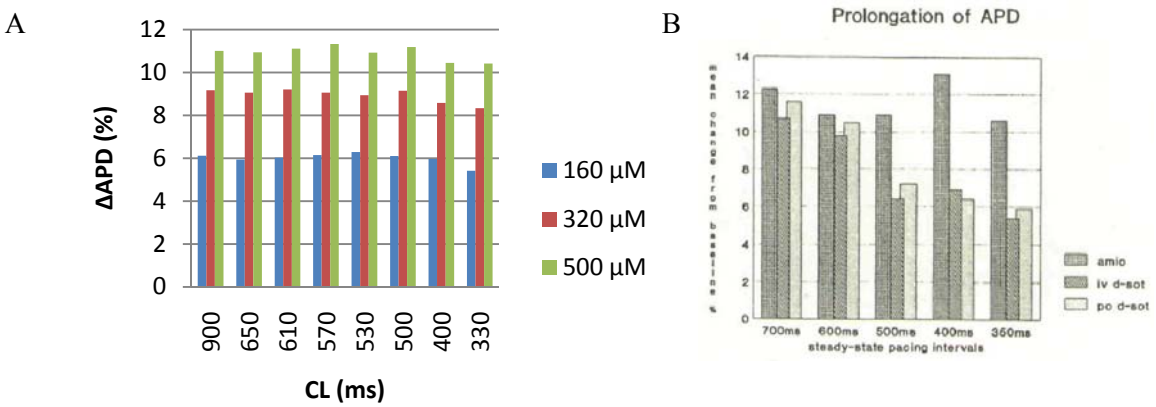

Figure 2: A: Endocardial central cell APD prolongation (%) of for 900-330 ms CL and different sotalol concentrations. B: Mean APD prolongation (%) after an intravenous (iv) and oral (po) d-sotalol (d-sot) dose and amiodarone for different CL (taken from (Huikuri, and Yli-Mäyry, 1992)).

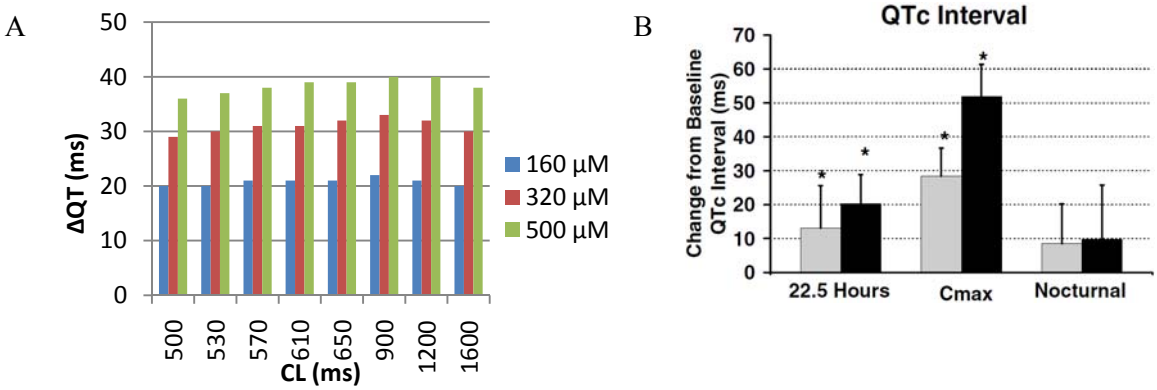

Figure 3: A: Model QT interval prolongation respect to the zero sotalol concentration for different CL and sotalol concentrations. B: Median QTc interval mean change from the situation without sotalol during the peak concentration (Cmax) after 160 mg (gray) and 320 mg (black) oral sotalol doses (taken from (Fossa et al. 2007)).

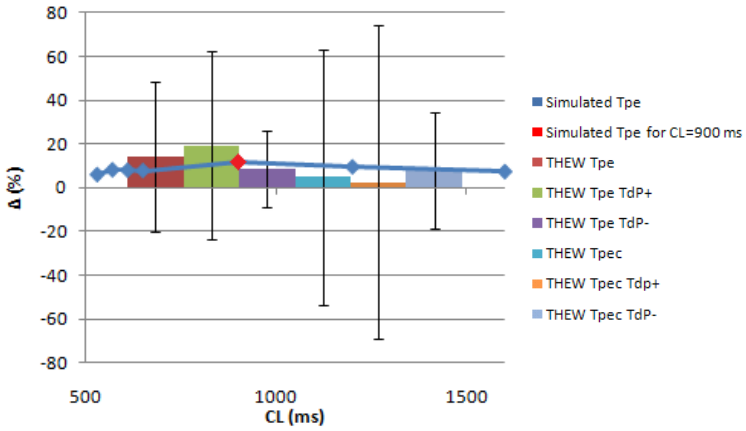

Figure 4: Model Tpe interval prolongation (%) compared to the zero sotalol concentration for a 320 μM sotalol concentration, and THEW database Tpe and Tpe_c (mean±SD) for the overall population study, the +TdP and -TdP group.

3.2.2 Sotalol-induced changes in the ECG

Sotalol-induced changes on ventricular repolarization were evaluated at different levels using the computational heart model described in 2.2.1 and validated in 3.2.1, which allowed us to assess the potential benefits or adverse effects presented by this drug when administered at different doses. Figure 5 presents QT restitution (QTR) and TpeR curves. At all CLs, sotalol prolonged the QT and Tpe intervals, with that prolongation being more accentuated for higher drug concentrations. For a CL of 900 ms, QT prolongation was of 16% and Tpe prolongation of 22% for a sotalol dose of 5000 μM. These results are consistent with reported sotalol Class III effects, according to which sotalol prolongs ventricular repolarization, which manifests as an increased QT interval (Fossa et al. 2007). Moreover, as the sotalol-induced prolongation in ventricular APD is more pronounced for midmyocardial cell than for the endocardium and epicardium, this is reflected as an increased Tpe interval, also in agreement with clinical data (Yan and Antzelevitch, 1998).

Sotalol effects in the ECG were additionally investigated by varying by 30% the diffusion coefficient D and the midmyocardial cells proportion, so as to represent intra-subject variability. By reducing or increasing the diffusion coefficient D the QTR and TpeR curves increased or decreased, respectively, with the effects being more pronounced for higher sotalol concentrations. Conversely, reducing or increasing the proportion of midmyocardial cells led to a decrease or increase, respectively, of QTR and TpeR curves, again with the effects being more marked for higher sotalol concentrations. Our results suggest that differences in the electrical impulse conduction and the ventricular wall cause significant changes in the QT interval and, more importantly, in the Tpe interval, which has been proposed as a proarrhythmic marker in clinical studies. This, in turn, implies that sotalol- induced effects may be considerably different in two patients with distinct ventricular electrophysiological characteristics.

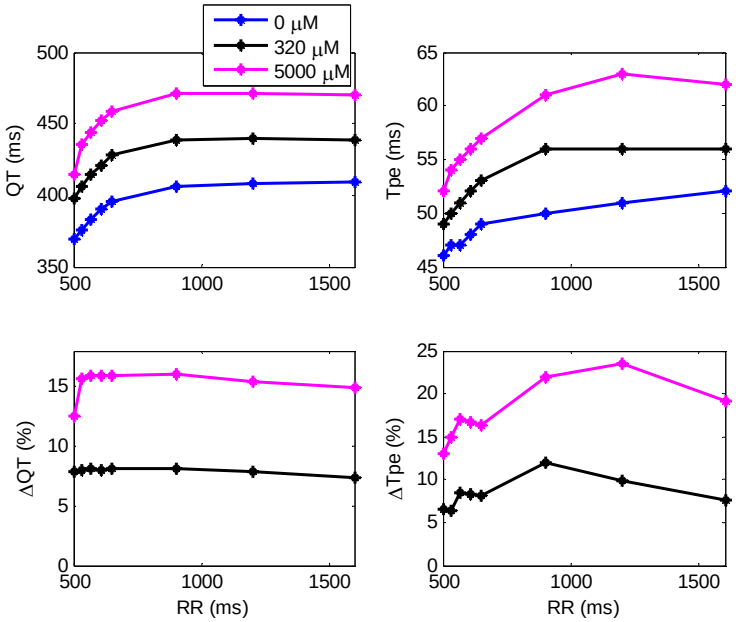

Figure 5: QTR and TpeR curves against RR for different sotalol concentrations (above). Model QTR and TpeR curves prolongation (%) compared to the zero sotalol concentration for different sotalol concentrations (bottom).

3.2.3 Mechanisms of sotalol-induced changes in the ECG

In order to elucidate the mechanisms of sotalol-induced changes in the Tpe interval, we investigated the relationship between TDR and the Tpe interval. For a zero-sotalol concentration, we compared the APD of the first and last cell to repolarize in the 1-D fiber and the Tpe interval. While Tpe was of 49 ms, the APD difference plus the activation time difference was of 50 ms. This agreement between Tpe and TDR measurements had already been observed in experimental studies in canine ventricle (Yan and Antzelevitch, 1998) as well as in theoretical studies using the Luo-Rudy dynamic guinea pig ventricular model (Gima and Rudy, 2002).

Under the effect of sotalol, we observed APD prolongation, with that prolongation being larger in midmyocardial cells than in endocardial and epicardial cells (APD increases by up to 16-18% for endocardium, 18-20% for midmyocardium and 17-19% for epicardium (Figure 6)). That heterogeneous prolongation resulted in increased transmural dispersion of repolarization in ventricular tissue, which has been proposed as an arrhythmogenesis indicator in previous studies (Antzelevitch, Yan, and Shimizu, 1999) and has been associated with changes in the ECG T wave morphology. The sotalol-induced APD prolongation also led to an increase in the QT interval. Additionally, we evaluated the endocardium, midmyocardium and epicardium APDR curves slope, and the TpeR curve slope (S_{Tpe}) for CL values between 600 and 1600 ms in 100 ms steps. For each CL value the difference between the maximum and minimum APDR curves slopes (Smax-Smin) was calculated, and represented against S_{Tpe}, under different sotalol concentrations (Figure 7). It can be observed that for each sotalol concentration the relationship between Smax-Smin and S_{Tpe} was almost linear.

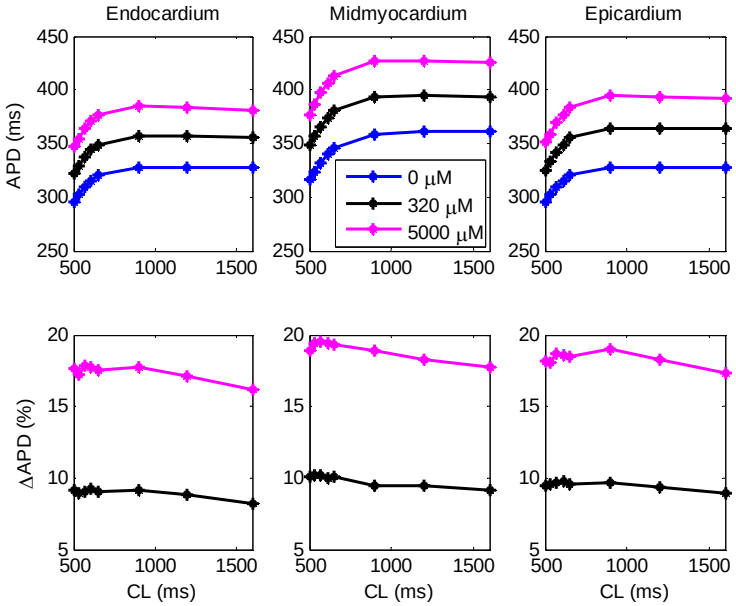

Figure 6: Endocardium (left), midmyocardium (center) and epicardium (right) APDR curve versus CL for different sotalol concentrations (above). APDR curve prolongation (%) referred to the zero-sotalol concentration in endocardium, midmyocardium and epicardium for different sotalol concentrations (bottom).

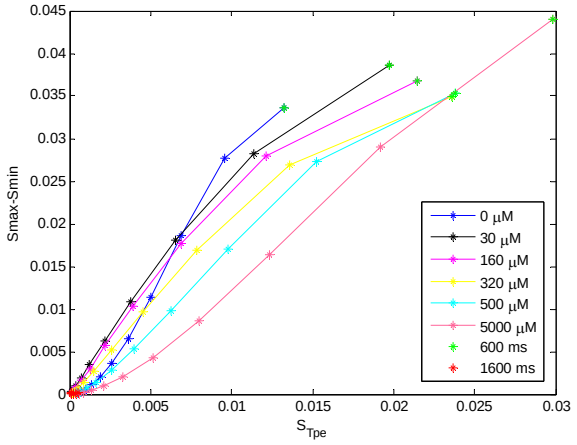

Figure 7: Smax-Smin against S_{Tpe} for CL from 600 to 1600 ms in 100 ms steps. It shows the curves for 0, 30, 160, 320, 500 and 5000 μM sotalol concentrations.

3.2.4 Sotalol cardiotoxicity

It is known that the sotalol physiological effects are dependent on the concentration in plasma (Lance, Möller, and Hill, 1995). A study performed in dogs (Schneider et al., 2005) showed that a 3mg/kg dose did not alter QTc and its variability, while a 10 mg/kg dose increased QTc (15%) and its variability, which has been related to proarrhythmic effects in other studies (Schneider et al., 2005).

In this study, we associated a 200 mg oral or a 2.0 mg/kg intravenous dose with a simulated concentration of 320 μM. The results by (Kimura et al., 1996) allow us to establish the relationship between the known sotalol effects and the concentrations used in this study.

Relating this to the study (Schneider et al., 2005), the 3 mg/kg dose is in the range of beta-blocking effects and antiarrhythmic activity, and the 10 mg/kg dose is in the range of toxic levels. However, we obtained statistically significant QTc prolongations for a 2.0 mg/kg dose from the database analyzed in this study. This difference may be due to the species. On the other hand, the increase produced by the 320 μM sotalol concentration is significantly lower than that observed in the THEW database for 2.0 mg/kg sotalol dose, which may be because the THEW database contains patients that have suffered TdP. Finally, although the 5000 μM concentration simulated in the toxic levels range is greater than the 10 mg/kg dose, both prolong QT about 15%. Given the observed effects for the different simulated concentration, it can be concluded that TDRc, QTc and Tpe_c increases above 30, 15 and 20%, respectively, involve proarrhythmiticity (Table 3).

Concentration (μM)	ΔTDRc (%)	ΔQTc (%)	ΔTpe_c (%)	
30	3	1	4	
160	9	5	8	Beta-blocking
320	13	8	12	Antiarrhythmic
500	19	10	14	activity
5000	31	16	22	Toxic levels

Table 3: Simulated plasma concentrations (μM), TDRc, QTc and Tpe_c (we consider corrected its value for a 900 ms CL) increases (%) referred to a zero-sotalol concentration, and effects range.

4 Discussion

In this study a database of patients with and without a history of the ventricular arrhythmia TdP that were administered the drug sotalol has been analyzed. In addition, we have used a computational model to simulate the electrophysiological behaviour of human ventricular myocytes in the presence of sotalol. The model was validated with experimental and clinical data from the literature as well as with the results obtained from the analysis of the THEW database. From the ECG processing, we observed that sotalol prolongs the RR, QT, QTc, TQ, Tpe and Tpe_c intervals, and increases the Tpe/RR index, with significant differences between the +TdP and the -TdP group. As expected, sotalol effects were more pronounced in the +TdP group since it is composed of patients with previous ventricular pathologies. From the computational modelling, we observed the heterogeneity in sotalol-induced endocardium, midmyocardium and epicardium APD prolongation at the cellular level, with the drug-induced APD prolongation being more pronounced in the midmyocardium. At the ECG level, we observed prolongation of the QT and Tpe intervals. The relationship between the difference of maximum and minimum APD in the ventricular wall and the ECG Tpe interval (or their slopes) in a 1-D fiber was found to be almost linear. These relationships confirm the results obtained in experimental studies in canine ventricle (Yan and Antzelevitch, 1998) and in theoretical studies using the Luo-Rudy dynamic guinea pig ventricular model (Gima and Rudy, 2002). Differences in electrical impulse conduction and ventricular wall composition produce changes in endocardium, midmyocardium and epicardium APDR curves, QTR and TpeR curves.

In (Couderc et al., 2009) the same database than in this study was analyzed. In general, the intervals that are greater or less in a group than in the other and the statistical significance between the situation before and after sotalol administration, and between the +TdP and -TdP group before and after sotalol administration, agree in both analysis. We must highlight the importance of the Tpe interval in both studies. Both the results of our study and those obtained in (Couderc et al., 2009) suggest that QT prolongation before and after administration in the +TdP group is associated with a delay not evenly distributed across the repolarization interval. These observations highlight the important of Tpe prolongation as an important proarrhythmic factor. Moreover, from our modeling and computer simulation study, we conclude that corrected Tpe interval prolongations over 20% are highly proarrhythmic and indicate drug-induced cardiac toxicity.

5 Acknowledgments

This research was supported by the I3A Fellowship Program.

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