Sensitivity Analysis of the QT and JTpeak intervals from a High-resolution Human Left-ventricular Wedge Model

Massimo W Rivolta[1], Roberto Sassi[1], Viatcheslav Gurev[2], John J Rice[2], Coeli M Lopes[3], Jean-Philippe Couderc[4]

[1] Dipartimento di Informatica, Università degli Studi di Milano, Crema, Italy
[2] IBM T.J. Watson Research Center, Yorktown Heights, NY, USA
[3] Aab CVRI, University of Rochester, Rochester, NY, USA
[4] Heart Research Follow-up Program, University of Rochester, Rochester, NY, USA

Abstract

There is an interest in looking at sub-intervals of the QT in the Comprehensive in-vitro Proarrhythmia Assay (CiPA) initiative. Here, we performed a sensitivity analysis of JTpeak and T-wave morphology (TWM) parameters computed on transmural ECGs, generated by a high-resolution human left-ventricular wedge model, with a modified version of the ten Tusscher 2006 cardiac cell model, with respect to the block of the slow and rapid potassium channels (IKs and IKr), and the late sodium channel (NaL), from 0% to 90%. Moreover, we simulated the effects of Dofitilide and Ranolazine. TWM parameters were QT interval (QT), T-peak to T-end (TpTe), T amplitude (Tamp), J to T-peak (JTpeak), Flatness Score (FS), Asymmetry Score (AS), average APD90 (APD90avg), APD Dispersion (APD90Disp) and standard deviation of the repolarization times (s_ρ). Sensitivities were computed as the percentage variation normalized at 50% block and they varied across ion channels and amount of block. QT interval, JTpeak and APD90avg performed similarly across channels (0.29). TpTe and s_ρ provided similar sensitivities (0.80 for both IKr and NaL, and 0.13 for IKs). AS resulted with the highest sensitivity to NaL block (8.35). Morover, the wedge model was capable to simulate the effects of the drugs. In conclusion, TWM parameters reflected ion channel alterations with different proportions.

1. Introduction

The Comprehensive *in-vitro* Proarrhythmia Assay (CiPA) is a new strategy to shift the emphasis away from QT prolongation and focuses on predicting torsadogenic hazard through an expansion of the *in-vitro* component of nonclinical safety evaluation. The initiative is focused on *in-silico* model of the cardiac cells and the effect of novel compounds on the action potential. As of today, the CiPA does not include *in-silico* models of a cardiac wedge or a whole heart because of their complexity and the lack of scientific evidence of the utility of such models. But the clinical components of the CiPA includes novel ECG markers such as the JTpeak interval, a sub-interval of the QT which duration measurement depends on the morphology of the T-wave.

In this work, we explore an *in-silico* high-resolution human left-ventricular wedge model and study the morphology of the T-wave (TWM) recorded from a simulated electrocardiogram. We studied the TWM changes as function of the model's parameters, specifically the variation of conductances of the major ion channels of the cardiac cells. Indeed, accordingly to electrophysiological studies (*e.g.*, [1]) and *in-silico* cardiac model simulations (*e.g.*, [2, 3]), TWM might change depending on alterations of the spatial heterogeneity of the ventricular repolarization. In particular, alterations due to ion channel abnormalities across the cardiac tissue produce TWM patterns identifiable from the surface ECG [4].

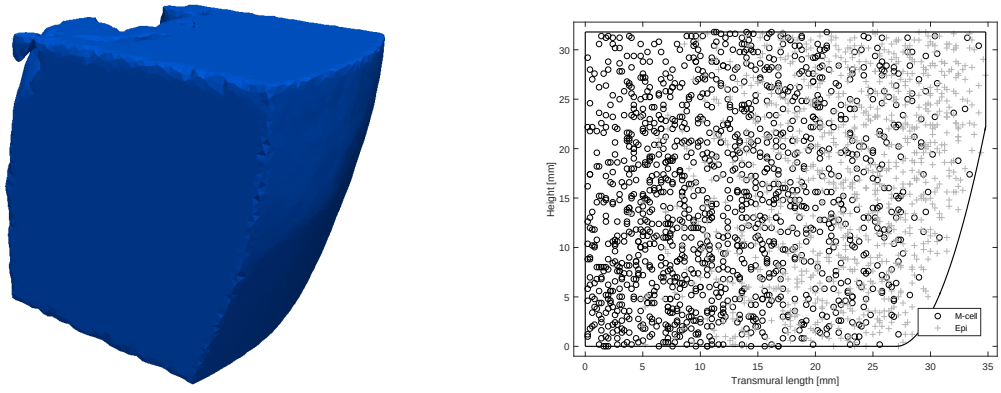
2. Methods

2.1. Geometry of the wedge model

The computational wedge model was extracted from an anatomical model of the human left ventricle. Cryosectional images, stored in the Visible Human Project of The National Library of Medicine [5], were used to reconstruct such anatomical model.

The dimensions of the wedge model were $32 \times 35 \times 32$ mm (35 mm was the transmural length) with a spatial resolution of 0.2 mm. The model was composed of approximately 4 million cells. Figure 1a shows the wedge model.

 ISSN: 2325-887X DOI:10.22489/CinC.2017.062-263



(a) (b)

Figure 1: 3D wedge model (a) along with an example of possible cell distribution (b). The first 20% of the transmural length (approximately 7 mm from the endocardium) contains only M-cells then, from 20% to the total length, a gradient of M- and Epi-cell was used. The "curved" surface is the epicardium.

2.2. Mathematical model

Endocardial cells (Endo), M-cells (M) and Epicardial cells (Epi) were modeled using a modified version of the ten Tusscher 2006 model [6] in which the late sodium current (NaL) was added. In this study, only M- and Epi cells were used.

The monodomain formalism was employed with a conductivity of 0.03 mS/mm for each node in the wedge model.

The model has been described elsewhere [7].

2.3. Spatial cell distribution

Cell types were assigned to each node of the wedge model using three strategies as in [7]: "Random", "Layered" and "Gradient". Briefly, the "Random" strategy selected cell types randomly from a Bernoulli distribution of parameter p, in which p was defined as the probability of having an M-cell and $1-p$ as the probability of having an Epi-cell. The "Layered" strategy forced all the cells within a layer of width d to be of the same type, *i.e.*, p set to either 0 or 1 in the "Random" strategy. The "Gradient" strategy allowed to vary the parameter p linearly between two parallel planes. Using these strategies, we created gradients of repolarization time (RT) along the transmural length of the wedge by means of the following approximated model

$$\begin{aligned} \mathrm{RT}(x) &= \mathrm{DT}(x) + \mathrm{APD}(x) = \dots \\ &\dots = \mathrm{DT}(x) + \dots \\ &\cdots + p(x) \times \mathrm{APD_M} + (1 - p(x)) \times \mathrm{APD_{Epi}} \end{aligned} \tag{1}$$

where x was the distance from the endocardium, $\mathrm{DT}(x)$ and $\mathrm{RT}(x)$ were the depolarization and repolarization times at distance x from endocardium, and $\mathrm{APD}(x)$ was the action potential duration. Figure 1b) shows an example of cell distribution in which the "Layered" and "Gradient" strategies were used.

In this study, we built a spatial cell distribution as follows. A layer of M-cells was positioned on the endocardium with a width of 20% (approximately 7 mm) of the total transmural length. Then, a gradient of M- and Epi-cells was used to cover the mid-cardium and the epicardium. The parameter p was linearly changed to have $p(20\%) = 1$ and $p(100\%) = 0.3$. Such spatial distribution provided a APD gradient similar to the one showed in [1] and was used for the simulations (see sec. 2.4).

2.4. Simulations

We performed a sensitivity analysis of nine parameters at different ion channel blocks, *i.e.*, from 0% to 90% (step 10%), of the slow and rapid potassium channel, and late sodium current (IKs, IKr and NaL, respectively), by running 10 simulations each. The average sensitivity for each parameter was computed as follows

$$S_j^c = \frac{100}{50} \frac{j_c(50\%) - j_c(0\%)}{j_c(0\%)} \tag{2}$$

where $j_c(X)$ was a parameter value at $X\%$ block for the ion channel c.

For each simulation, three stimuli were triggered on the endocardial side at cycle length of 1 s and only the last generated beat was analyzed. Then, the transmural ECG (tECG) was computed by the difference between two virtual electrodes located in the epicardium and endocardium. In this study, we analyzed only the tECG and the myocyte's action potentials (AP). The sampling frequency was 100 Hz for AP and 200 Hz for tECG.

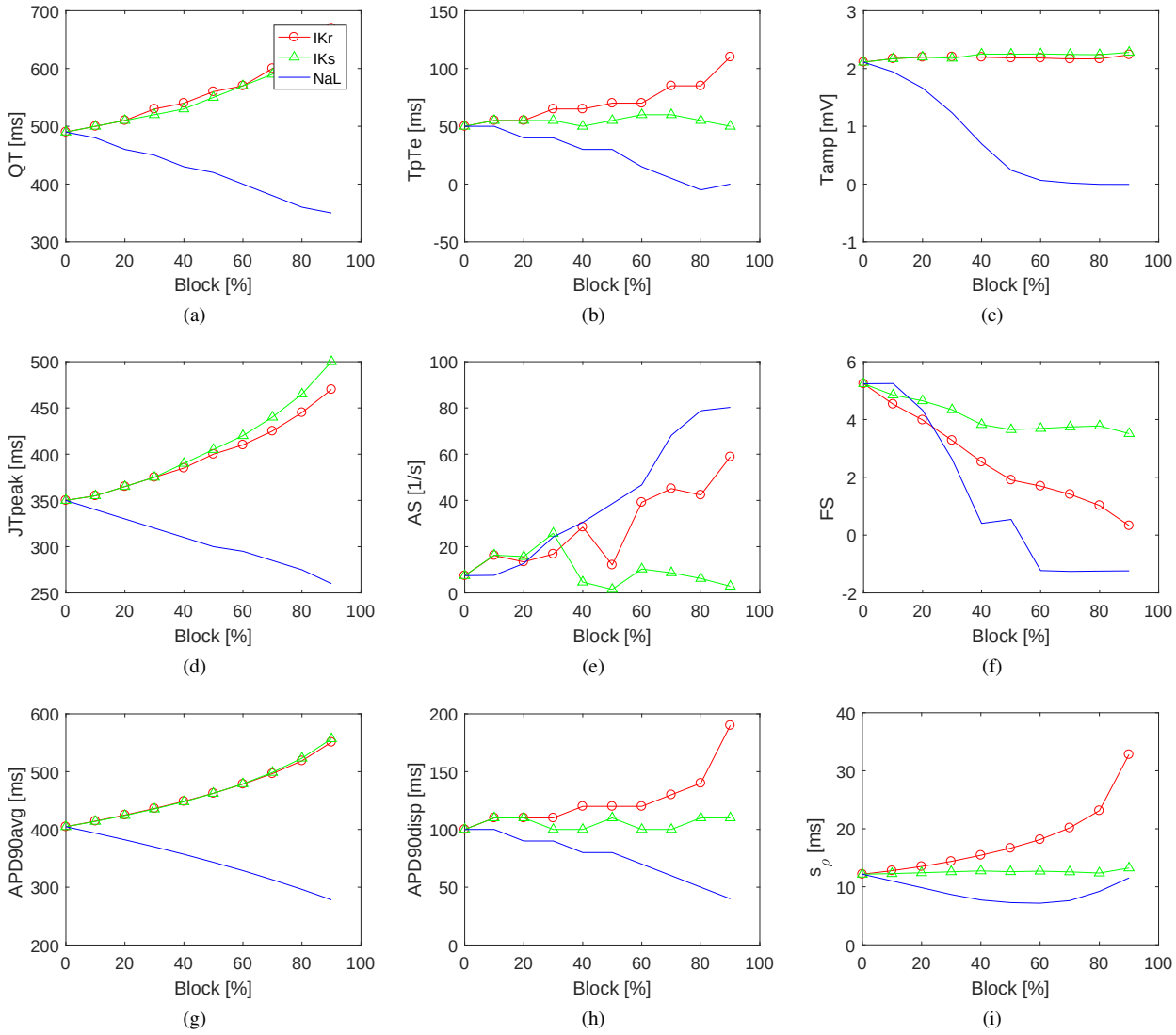


Figure 2: Values of the nine parameters as function of the ion channel block percentage.

Data generated by each simulation were firstly used to determine DT and RT of each synthetic myocyte. DT was defined as the time instant in which the AP had the maximum positive slope, while RT was computed by checking when the AP went below a pre-set threshold. The threshold was set to 10% of the difference between the maximum and minimum electrical potential.

From the tECG, we extracted six parameters: i) QT interval (QT; difference between the longest RT and shortest DT); ii) T-peak to T-end (TpTe; difference between the longest RT and the time instant of the T-peak); iii) T-wave amplitude (Tamp; electrical potential at T-peak); iv) J to T-peak (JTpeak; the longest DT was considered as J); v) Flatness Score (FS); and vi) Asymmetry Score (AS). Flatness Score[1] and Asymmetry Score were computed as in [8].

Other three parameters were evaluated from AP: i) average APD90 (APD90avg); ii) APD dispersion (APD90disp; max(APD90) - min(APD90)); and iii) standard deviation of the RTs (s_ρ).

Moreover, we simulated the effects of Dofitilide and Ranolazine using ion channel blocks as reported in [4] (50% for IKr, and 26% and 21% for IKr and NaL, respectively).

[1]FS was defined as $\frac{m_4}{m_2^2} - 3$ where m_4 and m_2 were the central fourth and second moments of the normalized T-wave, respectively. Normalized T-wave was computed by removing the offset and rescaling the T-wave to its area.

Table 1: Average sensitivity for each parameter and ion channel, and TWM parameter values for Dofitilide and Ranolazine simulations. The values in parenthesis represent the rounded percentage variation with respect to no block.

	TWM parameter	IKr	IKs	NaL	No block	Dofitilide	Ranolazine
tECG	QT [ms]	0.29	0.24	−0.29	490	560 (+14%)	490 (+0%)
	JTpeak [ms]	0.29	0.31	−0.29	350	400 (+14%)	350 (+0%)
	TpTe [ms]	0.80	0.20	−0.80	50	70 (+40%)	50 (+0%)
	Tamp [mV]	0.07	0.13	−1.77	2.11	2.18 (+3%)	1.81 (−14%)
	FS	−1.27	−0.61	−1.79	5.24	1.91 (−64%)	4.31 (−18%)
	AS [1/s]	1.24	−1.59	8.35	7.46	12.09 (+62%)	11.03 (+48%)
AP	APD90avg [ms]	0.29	0.29	−0.30	404.72	462.61 (+14%)	407.72 (+1%)
	APD90disp [ms]	0.40	0.20	−0.40	100	120 (+20%)	100 (+0%)
	s_ρ [ms]	0.74	0.07	−0.80	12.17	16.65 (+37%)	11.42 (−6%)

3. Results

All the parameters were sensitive to ion channel blocks (fig. 2). However, the average sensitivity value was different across parameters and channels (tab. 1). QT interval, JTpeak and APD90avg performed similarly across channels (average of 0.29). TpTe and s_ρ provided similar sensitivities (0.80 for both IKr and NaL and 0.15 for IKs). AS resulted with the highest sensitivity to NaL block (8.35), along with Tamp (1.77) and FS (1.79). APD90disp obtained similar sensitivities for both IKr and NaL (0.40) and a lower one for IKs (0.20).

The main results for the Dofitilide simulation were: i) same effect of QT and JTpeak; ii) increase of TpTe and JTpeak. This pure hERG blocker was detectable from all the TWM parameters. For Ranolazine: i) no change in JTpeak; ii) no prolongation of QT and TpTe. Tamp, FS, AS and s_ρ were sensitive to the drug. Both simulations provided very similar results to what found on real ECGs [9]. Table 1 reports TWM parameters for both simulations.

4. Conclusion

In this study, we performed a sensitivity analysis of QT, JTpeak and TWM parameters by changing the amount of ion channel block of IKr, IKs and NaL, using a high-resolution human left-ventricular wedge model with a realistic spatial distribution of cells. As expected, TWM parameters reflected alterations of the ion channels with different proportions, suggesting that only their combined use might highlight proarrhythmic effects of new compounds in cardiac drug-safety assessments. Moreover, the *in-silico* wedge model was capable to replicate the effects of Dofitilide and Ranolazine.

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Address for correspondence:

Massimo W Rivolta
Dipartimento di Informatica, Università degli Studi di Milano, Via Bramante 65, 26013, Crema (CR), Italy
massimo.rivolta@unimi.it