T-wave morphology depends on transmural heterogeneity in a high-resolution human left-ventricular wedge model

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Abstract

In this study, we used a in-silico cardiac wedge model with high spatial resolution to evaluate the role of transmural heterogeneity on T-wave morphology.

Computer simulations were performed with transmural electrograms recorded with a pacing rate of 60 bpm. QT and TpTe intervals were extracted. The model consisted of: i) a human left-ventricular wedge mesh (∼4 millions cells); and ii) modified version of the ten Tuscher 2006 cardiac cell model with an added late sodium current. Heterogeneity was generated by changing the spatial distribution of cell types, i.e., M-cells and Epi-cells, across the wedge. Three different cell distribution were used in the simulations: i) random; ii) layers; and iii) layered then gradient. The wedge was stimulated to produce a normal activation propagating from endocardium to epicardium.

Our simulations showed that a positive T-wave required the repolarization wave to predominately propagate in opposite direction to the depolarization wave with longer APDs in the endocardial region compared to epicardium. Moreover, QT intervals increased with the amount of M-cells in the wedge model while TpTe intervals were dependent on the transmural heterogeneity.

In summary, we showed that cell distributions highly affect both repolarization and T-wave morphology parameters in a high-resolution human wedge model.

1. Introduction

The spatial heterogeneity of ventricular repolarization of the heart is hypothesized to play a role in the genesis of the T-wave on the surface ECG. However, the role of the spatial heterogeneity on the T-wave morphology remains to be characterized in detail. *In-vitro* experiments show that the T-wave in transmural electrograms is generated from electrical propagation during repolarization [1].

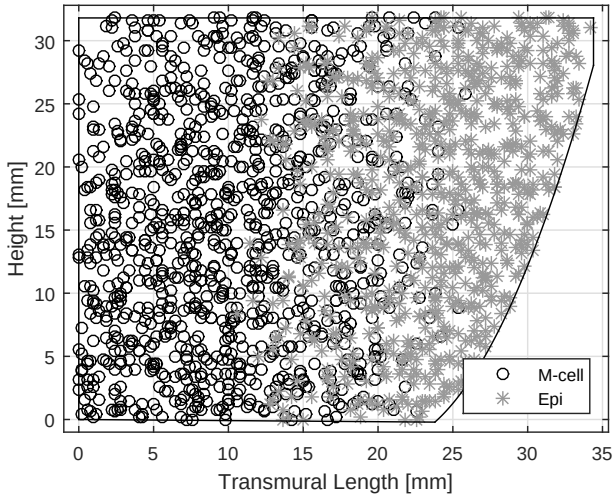

Figure 1. Example of cell distribution in the wedge model showing a transmural view from the endocardium (left) to the epicardium (right). Black O and Grey $*$ symbols correspond to M-cells and Epi cells, respectively.

Several *in-silico* studies have assess the role of the spatial heterogeneity on the T-wave morphology [2, 3]. The main findings were that the action potential duration (APD) must decrease towards the epicardium to obtain reasonable T-wave morphology characteristics.

In this study, we investigated the role of cell distributions and heterogeneity on ventricular repolarization in a high resolution human wedge model. In particular, we designed three experiments to assess the dependence of T-wave morphology on the cell distribution.

2. Methods

2.1. Geometry of the wedge model

The computational wedge model was extracted from an anatomical model of the human left ventricle described elsewhere [4]. The anatomical model was reconstructed by using cryosectional images stored in the Visible Human Project of The National Library of Medicine [5]. 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 comprised of approximately 4 million cells. Figure 1 shows the transmural geometry of the cardiac wedge model.

2.2. Mathematical model

As in [4], 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. The parameters that characterize the different cell types are shown in tab. 1. For the experiments described here, only M- and Epi cells were used. The monodomain formalism was employed and the conductivity was set 0.03 mS/mm for each node in the wedge model. The fiber direction was the same as reported in [7].

2.3. Experiments

Experiments were designed to assess the effect of cell heterogeneity on the repolarization profile and transmural ECG. Three different configuration of cell types were used: "Random", "Layered", "Layered then Gradient". Then, T-wave morphology was characterized based on several measures, *i.e.*, QT and T-peak to T-end (TpTe) intervals, APD at 90% of repolarization (APD90) and polarity of the T-wave. (T-end was computed considering the longest repolarization time among all cells).

Table 1. Parameters that differentiate the cell types: conductivity values of the slow and rapid potassium currents (G_{K_s} and G_{K_r}), transient net outward current (G_{t_o}) and late sodium current (G_{NaL}), and the sodium-potassium pump parameter P_{NaK}.

Parameter	M	Epi	Unit
G_{K_s}	0.196	0.392	(pS/pF)
G_{K_r}	0.450	0.450	(pS/pF)
G_{t_o}	0.294	0.294	(pS/pF)
G_{NaL}	0.300	0.150	(pS/pF)
P_{NaK}	3	3	(pA/pF)

Three stimuli were triggered on the endocardial side at cycle length of 1 s. Using the last beat of the experiment, we analyzed: i) the transmural potential computed by the difference between two virtual electrodes located to the epicardium and the endocardium; and ii) the APD90 computed using a single threshold at 10% of the difference between the maximum and the minimum electrical potential. The sampling frequency was 100 Hz for APs and 200 Hz for the transmural potential.

2.3.1. Experiment 1: Random

In the first experiment, cell types were selected randomly from a Bernoulli distribution of parameter p, in which p was defined as the probability of having an M-cells. The parameter p was varied between 0 and 1, with zero being a wedge of only Epi cells and one a wedge with only M-cells.

As function of the parameter p, we characterized the repolarization parameters: i) T-wave polarity; ii) QT and TpTe intervals; and iii) average APD90.

2.3.2. Experiment 2: Layered

A layer of M-cell covering all the endocardial surface was varied from 0% to 100% of the total transmural length with an increment of 10%. 0% corresponded to the wedge with only Epi cells and 100% a wedge of only M-cells. In each of the 11 simulations, we determined the: i) QT and TpTe intervals from the transmural electrogram; and ii) the APD Dispersion (max[APD90]-min[APD90]) and the standard deviation of the repolarization times (STD[RT]) as measures of heterogeneity of the ventricular repolarization (the latter was recently proposed in [8]).

2.3.3. Experiment 3: Layered then Gradient

A layer of M-cell was placed at the endocardial surface up to the 30% of the transmural length. Adjacent to this layer, a random mixture of M- and Epi-cell was set up to 53%, 76% and 100% of the transmural length, creating a gradient interface. The parameter p (see sec. 2.3.1) was decreased linearly in the region with the mixture. All remaining cells in the wedge were set to Epi cells. The direction of the ventricular repolarization wavefront was characterized for all three constructed cases. A representative example of the second cell distribution is shown in fig. 1.

3. Results

The typical conduction velocity was 66.3 cm/s.

3.1. Experiment 1: Random

The polarity of the T-wave was negative for all the value of p in the range 0-1.

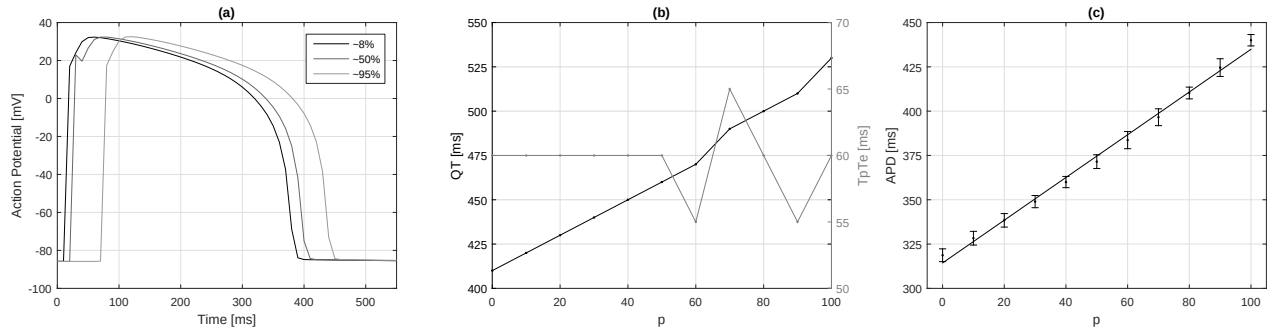

Figure 2. Results of the first experiment are shown. Fig. (a): examples of AP extracted in three regions of the wedge model, *i.e.*, at $\sim$8%, $\sim$50% and $\sim$95% distance from the endocardium, when the probability to select a M-cell (p parameter) was 50%. Fig. (b): QT and TpTe intervals as a function of the p parameter. Fig. (c): mean and standard deviation of the APD90 across the wedge as a function of the p parameter. Moreover, the regression line is shown ($R^2 = 0.99$; $p < 0.05$).

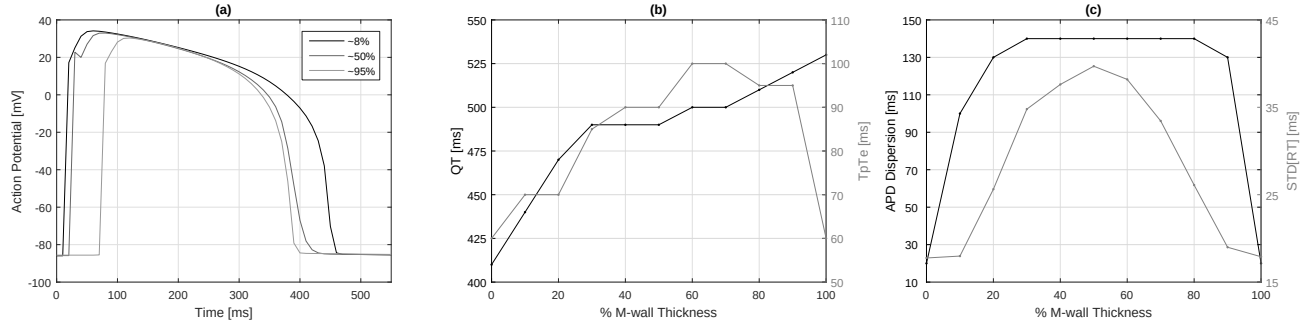

Figure 3. Results of the second experiment are shown. Fig. (a): example of AP extracted in three regions of the wedge model when a layer of M-cell was placed to cover the 50% of the total transmural length. Fig. (b): QT interval duration and TpTe interval while varying the thickness of the M-cell layer. Fig. (c): APD Dispersion and STD[RT] while varying the thickness of the M-cell layer.

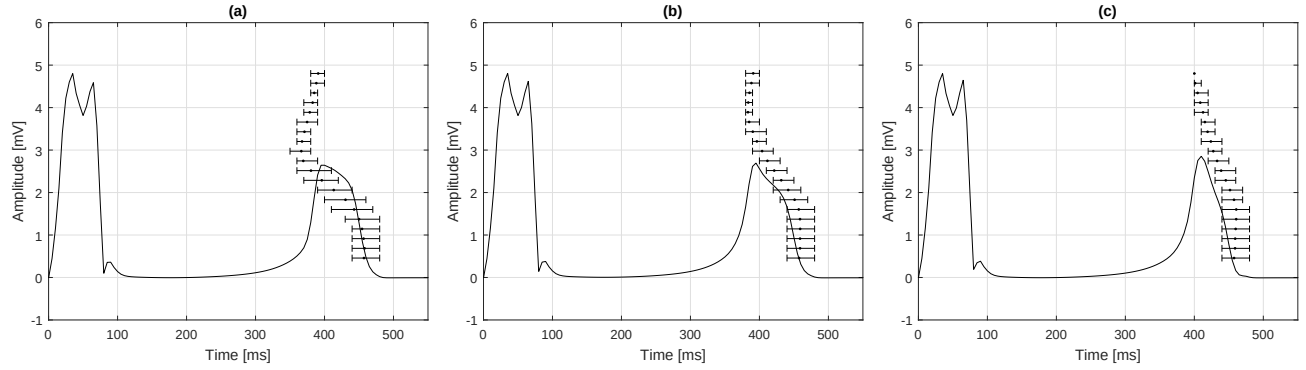

Figure 4. Results of the third experiment are shown. Electrograms obtained from three different cell distributions in which a layer of M-cells was placed at the endocardial surface up to 30% of the transmural length. Then, a gradient interface was set up from 30% to 53% (a), 76% (b) and 100% (c) of the transmural length. Each horizontal bar indicates the time interval in which the first and last cell repolarized in an incremental layers of 5% wall thickness, ordered from the endocardium (bottom line) to the epicardium (top line).

Figure 2a shows an example of the AP measured in the endocardium, middle of the wedge and epicardium. In all cases, the first cell that depolarized was also the first cell to be completely repolarized.

QT interval increased with increasing the percentage of M-cells, while TpTe interval remained constant (fig. 2b).

Finally, we tested the linear correlation between the parameter p of the Bernoulli distribution, *i.e.*, probability to set a cell as M-cell, and the average APD90 across the wedge, and we obtained a very high linear correlation (fig. 2c; $R^2 = 0.99$; $p < 0.05$).

3.2. Experiment 2: Layered

A negative T-wave was obtained when the wedge was constructed from a single cell type, *i.e.*, the M-cell layer was either 0% or 100%; in all the other cases, the polarity of the T-wave was positive. In particular, the epicardium repolarized before the endocardium when the thickness was between 20% to 90% (fig. 3a) of the total transmural length. However, when the thickness was 10%, the epicardium repolarized last, creating a double peaked T-wave.

QT interval duration monotonically increased with the thickness of the M-cells layer. In contrast, TpTe interval was longest when the layer of M-cells was approximately 60% of the total transmural length (fig. 3b).

APD Dispersion and STD[RT] were maximum when the M-cell layer was covering the half of the wedge model (fig. 3c).

3.3. Experiment 3: Layered then Gradient

The polarity of the T-wave was positive independently of the thickness of the interface layer between M- and Epi cells. However, the propagation of the repolarization wavefront was different. Indeed, in the first and in the second simulation, the repolarization started approximately in the middle of the wedge and propagated toward both the endocardium and epicardium (fig. 4a and fig. 4b). Only in the third simulation, where there was not a well defined single cell epicardial layer, the repolarization wavefront propagated from the epicardium toward the endocardium (fig. 4c). Figure 4a, figure 4b and figure 4c show the electrograms obtained considering three complex cell distributions. Each horizontal bar indicates the time interval in which the first and last cell repolarized in a layer of 5% from the endocardium (bottom line) to the epicardium (top line). Such time intervals showed how the repolarization times affected the T-wave morphology.

4. Conclusion

In this study, we investigated the effects of the cell distribution on the heterogeneity of the ventricular repolarization using a high-resolution human left-ventricular wedge model.

In general, a positive T-wave required a repolarization wavefront that propagated from the epicardium towards the endocardium, consistently with the scheme proposed in [1]. The proper repolarization direction required longer APDs in the endocardial region compared to epicardium (fig. 3a). However, a positive T-wave could be obtained even when repolarization wavefront did not propagated towards the endocardium exclusively (fig. 4a and fig. 4b).

T-wave morphology parameters were dependent on the cell distribution. However, QT interval duration was more sensitive to the presence of M-cells in the wedge than TpTe (fig. 2b and fig. 3b). The latter were more correlated to the heterogeneity of the cell distribution (fig. 3b and fig. 3c), measured by APD Dispersion and STD[RT].

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