A Heterogeneous Formulation of the Himeno et al Human Ventricular Myocyte Model for Simulation of Body Surface ECGs

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Abstract

Current multi-scale electrophysiology models capture the processes underlying ECG genesis under physiological and many disease conditions with high fidelity. However, proper representation of the extracellular milieu remains challenging. The human ventricular myocyte model by Himeno et al. is one of the first which faithfully represents the dependence of the action potential (AP) duration on the extracellular calcium concentration ($[Ca^{2+}]_o$). Here, we present a heterogeneous formulation of the Himeno et al. cellular model and integrate it into a multi-scale framework to compute body surface ECGs. We propose 3 variants to account for transmural heterogeneity informed by experimental data and tuned to match AP level features such as repolarization stability. As shown before, an apico-basal gradient of I_{Ks} conductance is a likely mechanism causing concordant T-waves. Therefore, we increased I_{Ks} in the Himeno et al. model at the apex by a factor of 3.5 compared to the base to obtain an APD shortening of 12.5%. The setup comprising transmural and apico-basal heterogeneity yielded a physiological ventricular ECG. Our novel setup allows to study, for the first time, how realistic changes of the AP under hypo- and hypercalcaemic conditions translate to changes in the ECG. Resulting QT prolongation under hypocalcaemic conditions matched human experimental data.

1. Introduction

The T-wave in the body surface ECG is the most accessible measurement to characterize the repolarization of the human ventricles. The ventricular repolarization phase is crucial for normal heart function and plays an important role in arrhythmia initiation [1]. Despite the opposite polarity of depolarizing and repolarizing currents, the T-waves in humans is concordant with the QRS complex (i.e., R-peak and T-wave show the same polarity) implying dispersion of action potential duration (APD). Besides transmural variation of cellular properties, an apico-basal gradient has been discussed [1–3] as a causal underlying factor.

Heterogeneous formulations of ventricular cell models have been proposed and used in simulation studies evaluating T-wave metrics. A relevant but challenging scenario is an altered extracellular milieu like hypo- or hypercalcaemia as occurring in patients with chronic kidney disease, which is a massive population of more than 30 million patients in the European Union [4]. It was shown that most computational models of ventricular cellular electrophysiology do not faithfully represent the experimentally and clinically observed effects of altered extracellular calcium concentrations. While in vitro and in vivo studies consistently report an inverse relation between $[Ca^{2+}]_o$ and APD, virtually all ventricular models behave different [5,6]. Thus, these models are not suited to study the effects of hypo- and hypercalcaemia in silico. A notable exception is the Himeno et al. human ventricular myocyte model [7], which faithfully models calcium-induced inactivation of the L-type calcium current and reproduces the experimentally observed inverse relation between $[Ca^{2+}]_o$ and APD.

Here, we propose and evaluate a heterogeneous formulation of the Himeno et al. cellular model which is suited to be used in multi-scale simulations up to the ECG level allowing to study the effect of hypo- and hypercalcaemia on the T-wave.

2. Methods

Regarding transmural heterogeneity, we derived three variants of the Himeno et al. model for subendocardial (endo), M, and subepicardial (epi) cells from the experimental data provided with the parent O'Hara et al. model [8]. Compared to the parent model for M cells, G_{Kr} was increased to obtain an APD within the experimentally observed range, P_{CaL_Ca} was reduced to avoid early afterdepolarizations, Amp_{NaK} was increased to avoid delayed afterdepolarizations, and P_{RyR} was reduced to

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Table 1. Scaling factors to represent transmural heterogeneities in the Himeno et al. model [7].

Parameter	epi/endo	M/endo
P_{Na}	0.6	1.0
G_{Kto}	4.0	4.0
P_{CaL_Ca}	1.2	2.0
G_{Kr}	1.3	1.0
P_{Ks_K}	1.4	1.0
G_{K1}	1.2	1.3
Amp_{NCX}	1.1	1.4
Amp_{NaK}	0.9	1.5
P_{bNSC_K}	0.6	1.0
P_{RyR}	1.0	1.4
Amp_{SERCA}	1.3	1.0

obtain a notch morphology of the AP. For epi cells, the data from the parent model was adopted without changes except for [CMDN], which is not represented in the Himeno et al. model. Table 1 lists the proposed scaling factors for the transmurally heterogeneous Himeno et al. model variants based on the original Himeno et al. model representing endo cells.

Regarding the apico-basal heterogeneity, Keller et al. identified an I_{Ks}-induced APD shortening of 12.5% at the apex compared to the base as the most likely variant [3]. This degree of APD shortening was obtained using a 3.5x higher maximum I_{Ks} conductivity P_{Ks_K} at the apex compared to the base in the Himeno et al. model (compared to a 2x higher value found for the ten Tusscher et al. model [9] in [3]).

The heterogeneous model variants were characterized in a single cell environment regarding AP morphology and duration, cycle length restitution, and the dependence on $[Ca^{2+}]_o$. Converged steady states on the single cell level were used to initialize biventricular monodomain tissue simulations followed by forward calculation to the body surface similar to [3]. A transmural distribution of 35/30/35% endo/M/epi cells was assumed together with a continuous apico-basal gradient multiplying P_{Ks_K} with 1 at the base and 3.5 at the apex. Tissue conductivities were matched to obtain transverse and longitudinal conduction velocities of 600 and 970 mm/s, respectively. A stimulation profile mimicking the Purkinje system was tailored to match the measured QRS complex [10].

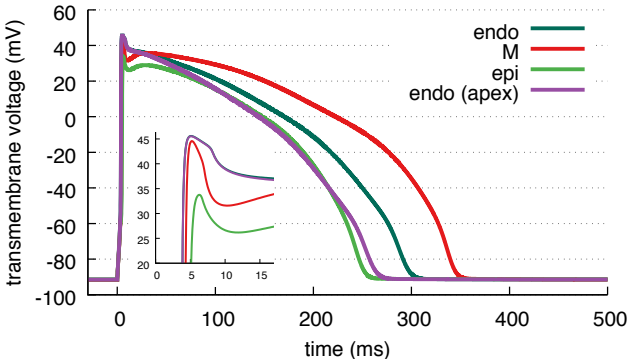

Figure 1. APs of the transmurally heterogeneous model variants and an endo cell at the apex (P_{Ks_K} x3.5). The inset shows phase 1 of the AP.

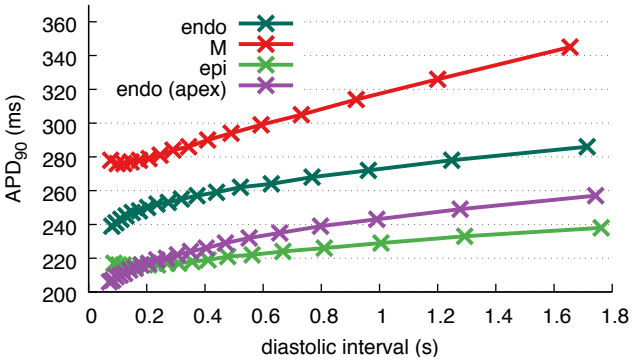

Figure 2. APD restitution of the Himeno et al. model variants.

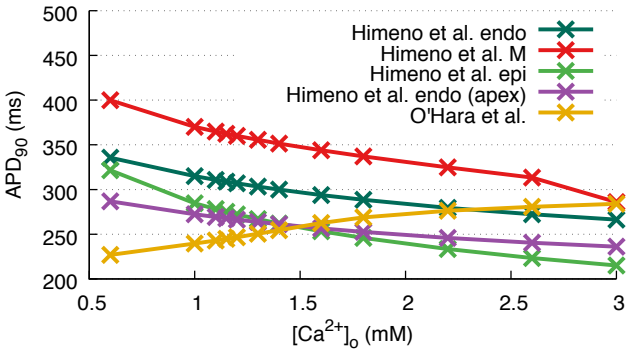

Figure 3. Dependence of APD_{90} on $[Ca^{2+}]_o$ for the model variants. Note the fundamental difference between the O'Hara et al. and Himeno et al. model.

3. Results

Figure 1 shows the APs of the model variants representing transmural heterogeneity and an endo cell at the apex. APD_{90} at a cycle length of 1 s is 289/337/245/254 ms for endo/M/epi/endo (apex) cells, respectively. M and epi cells show a notch in AP phase 1. For longer diastolic intervals, the APD restitution is steepest for the M cells (Figure 2). M and epi cells show a biphasic restitution curve with slight AP prolongation for very short diastolic intervals. Apart from that, the restitution behavior does not differ markedly between model variants.

The dependence of the APD on the $[Ca^{2+}]_o$ is as desired inverse for the Himeno et al. model opposed to the O'Hara et al. model (Figure 3). This behavior is preserved for the heterogeneous model variants with AP prolongation under hypocalcaemic conditions being most pronounced for the epi cells.

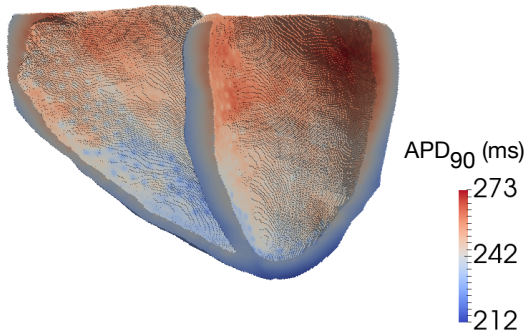

Figure 4. APD_{90} distribution in the ventricles for a setup comprising both transmural as well as apico-basal heterogeneity of the Himeno et al. model. Stimulus sites show shortened APD compared to surrounding tissue.

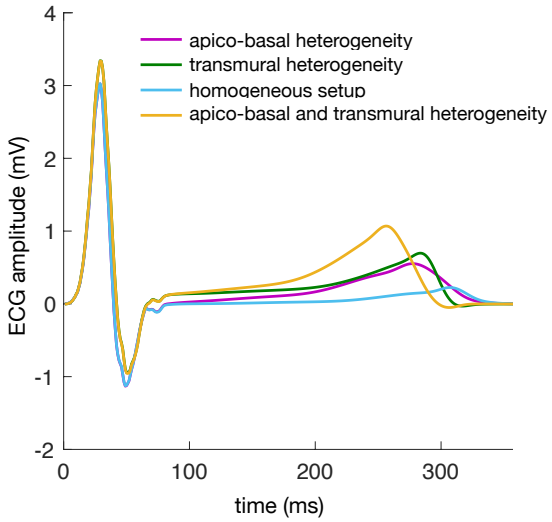

Figure 5. Simulated ECG (Einthoven II) for setups comprising different heterogeneities of the Himeno et al. model.

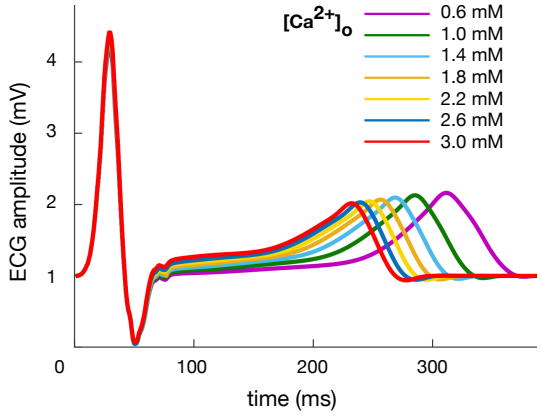

Figure 6. Simulated ECG (Einthoven II) for different $[Ca^{2+}]_o$ values obtained with the heterogeneous Himeno et al. model.

The APD_{90} distribution in the biventricular simulation with a cycle length of 1 s ranges between 212 ms for epi cells at the apex to 273 ms for endo cells at the base (Figure 4). The long APD of the M cells seen on the single cell level (Figure 1, Figure 2) was attenuated by electrotonic coupling in the tissue simulation.

The effect of the apico-basal and the transmural heterogeneity as well as a combination of both on the simulated ventricular ECG is shown in Figure 5. The homogeneous setup lacks a pronounced T-wave. An asymmetric T-wave with a gradual ascent and steep descent is generated by both heterogeneities. The transmural heterogeneity causes a slight elevation of the whole ST-segment due to the transmural transmembrane voltage differences in phase 1 and 2 of the AP (Figure 1). A combination of both heterogeneities produces the highest and most symmetric T-wave.

The inverse $APD/[Ca^{2+}]_o$ relation on the single cell level (Figure 3) translates to an inverse $QT/[Ca^{2+}]_o$ relation on the ECG level (Figure 6). Moreover, an increase of $[Ca^{2+}]_o$, i.e., hypercalcaemia, is associated with a T-wave amplitude decrease and ST-segment elevation.

4. Discussion

In this study, we suggested variants of the Himeno et al. cell model to represent transmural and apico-basal heterogeneity informed by previous work [3] and the parent O'Hara et al. model [8]. The changes for the M cells compared to the parent model are within the experimentally reported error margins [8] except for Amp_{NaK}.

The main findings of this study are that i) the Himeno et al. model reproduces the inverse $APD/[Ca^{2+}]_o$ relation observed experimentally [6]; ii) the proposed model variants faithfully represent heterogeneity on the action potential level and generate a concordant T-wave on the

ECG level comparable to setups based on the ten Tusscher et al. model [3]; iii) the inverse APD/$[Ca^{2+}]_o$ relation is preserved for the derived variants of the Himeno et al. model and translates to an inverse QT/$[Ca^{2+}]_o$ relation on the ECG level seen clinically [11,12]; iv) alterations of $[Ca^{2+}]_o$ induce distinct ECG changes.

We should keep in mind that the default $[Ca^{2+}]_o$ value of 1.8 mM for both the Himeno et al. as well as the O'Hara et al. model represents Tyrode's solution and differs significantly from the physiological range in humans, which is 1.1-1.3 mM [5]. The simulation setup proposed here allows to vary $[Ca^{2+}]_o$ towards physiological in vivo conditions. The observed slight ST-segment elevation (Figure 5) could potentially be due to the high reference $[Ca^{2+}]_o$ value of the Himeno et al. model of 1.8 mM representing severely hypercalcaemic conditions in vivo [13].

The observed QT-interval shortening of 3.8%/3 ms when increasing $[Ca^{2+}]_o$ by 0.4 mM (prolongation of 5.8%/5 ms when decreasing by 0.4 mM) matches well with the available human in vivo data [11,12].

The setup presented here, which faithfully represents the effects of extracellular ion concentration changes on cellular electrophysiology, can be used to study the effects of such changes in silico as shown in our recent work [14]. As the ion concentrations in the extracellular milieu are closely linked to plasma concentrations which fluctuate significantly in chronic kidney disease patients [5], such approach can be used to better understand and optimize the ECG as a diagnostic tool [15,16]. Eventually, this could permit continuous monitoring of the blood electrolyte levels of chronic kidney disease patients.

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