Analysis and Improvement of a Human Ventricular Cell Model for Investigation of Cardiac Arrhythmias

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Abstract

The use of experiments for studying cardiac arrhythmias, the effect of drugs, or pathologies on cardiac electrophysiology is very limited. This has made mathematical modeling and simulation of heart’s electrical activity a fundamental tool to understand cardiac behavior. In this study several modifications were introduced to a recently proposed human ventricular cell model. Four stimulation protocols were applied to the original and improved models of isolated cell, and a number of cellular arrhythmia risk biomarkers were computed: steady-state action potential (AP) and \([Ca^{2+}]\) transient properties, AP duration (APD) restitution curves, AP adaptation to abrupt changes in heart rate, and intracellular \([Ca^{2+}]\) and \([Na^{+}]\) rate dependence. Our modifications led to: a) further improved AP triangulation (78.1 ms); b) APD rate adaptation curves characterized by fast and slow time constants within physiological ranges (10.1 s and 105.9 s); c) maximum S1S2 restitution slope in accordance with experimental data (\(S_{S1S2} = 1.0\)).

1. Introduction

Ventricular arrhythmias can have their origin in diseases, genetic disorders, drug cardiotoxicity, and a number of other causes. Research in this field has identified a number of potential biomarkers of arrhythmic risk related to cellular electrophysiological properties. However, performing experimental and clinical studies involving human hearts to quantify these biomarkers is very difficult. On the other hand, animal hearts used for experimental studies may differ significantly from human hearts. In addition, ventricular cardiac arrhythmias are three-dimensional phenomena whereas experimental observations are still largely constrained to surface recordings. Under this circumstances, mathematical models of myocardial cells and computer simulations of cardiac activity in the human heart can overcome some of these problems.

Recently, a new model has been proposed by Grandi et al. [1] (GR) that improves the response to frequency changes and has a better performance against current blocks with respect to the model proposed by ten Tusscher and Panfilov [2] (TTP06). This article introduces several modifications to the GR model by accounting for recent experimental measurements of potassium currents [3] and the introduction of fast and slow inactivation of L-type calcium current [2]. The performance of the proposed model, herein denoted by CRR, has been tested against the GR and TTP06 models by applying four stimulation protocols and computing twelve cellular arrhythmic risk biomarkers following the methodology proposed in [4]. The results show that the introduced modifications have brought most biomarkers into the physiological range, and considerably improved others with respect to the GR and TTP06 models of AP.

2. Methods

2.1. Biomarkers of arrhythmic risk

Four stimulation protocols have been applied and twelve cellular biomarkers of arrhythmic risk have been computed as in [4]:

Steady-state AP and intracellular \([Ca^{2+}]\) concentration properties. Systolic and diastolic \([Ca^{2+}]\), levels under steady-state pacing at frequencies of 0.5 and 1 Hz and APD and AP Triangulation at 1 Hz have been calculated. These biomarkers have been proposed as arrhythmic risk biomarkers in the literature [5–7].

APD restitution (APDR) curves. APDR curves have been obtained using the S1S2 and the dynamic restitution protocols as in [4]. In both cases, the maximum slope, suggested as a risk marker in the literature [8, 9], has been computed.

APD rate adaptation to abrupt changes in cycle length (CL). APD rate adaptation dynamics have been proposed as a clinical marker in [10]. Dynamics have been fitted to two exponentials with time constants \(\tau_{fast}\) and \(\tau_{slow}\) [11].

Rate dependence of steady-state \([Na^{+}]\), and \([Ca^{2+}]\).
The importance of $[Na^+]_i$ and $[Ca^{2+}]_i$ interactions in arrhythmogenesis has been reported [12, 13]. The systolic values of both concentrations have been measured at different frequencies (0.25, 0.5, 1, 1.5, 2, 2.5 and 3 Hz) and normalized to the level of the minimum frequency. The maximum value has been computed and used as biomarker.

2.2. Modifications of the model

Two ionic currents have been reformulated and some model parameters have been redefined in the GR model:

$L$-Type Calcium Current ($I_{Ca}$). The voltage-dependent inactivation gate $f$ has been replaced with the product of a fast, $f_1$, and a slow, $f_2$, inactivation gates as in [2]. Based on available experimental data, the value of the opening rate $\alpha_{f_2}$, associated with $f_2$, has been modified to:

$$\alpha_{f_2} = 300 \cdot e^{-\frac{(V_m+425)^2}{10}},$$

where $V_m$ denotes the transmembrane potential.

Figure 1a depicts $\tau_f$ and $\tau_{f_2}$ along with experimental data [2]. The time constant ($\tau_d$) of the activation gate $d$ has been replaced with the description given in [2]. The relative permeabilities of the $L$-type calcium channels have been adjusted to: $p_C = 1.458 \cdot 10^{-4} \, cm/s$, $p_K = 7.290 \cdot 10^{-8} \, cm/s$, $p_Na = 4.050 \cdot 10^{-9} \, cm/s$.

This new definition of $I_{Ca}$ is compared against experimental data and the original definition of the GR model in Figure 1b. Experimental data is from [14–16].

$Inward Rectifier K Current$ ($I_{Ks}$). This current has been re-adjusted based on experimental data from [3]. The re-adjusted current is formulated as follows:

$$V_{k_i} = V_m - E_K$$

$$a_{ki} = 4.094 \cdot \frac{1.0 + e^{0.1217(V_{k_i}-49.934)}}{1.0 + e^{0.0674(V_{k_i}-3.257) + 0.0618(V_{k_i}-594.31)}}$$

$$b_{ki} = 15.720 \cdot \frac{1.0 + e^{-0.1629(V_{k_i}+14.207)}}{1.0 + e^{0.0674(V_{k_i}-3.257) + 0.0618(V_{k_i}-594.31)}}$$

$$K_{1s} = \frac{a_{ki}}{a_{ki} + b_{ki}}$$

where $I_{K1}$ denotes the extracellular $K^+$ concentration, and $E_K$ is the $K^+$ reversal potential. $I_{K1}$ has been reduced by 45%.

$I_{Ks}$ and $G_{Ks}$. A more physiological value of $[K^+]_i$ (138 $mM$) has been used in the model. In this regard, in order to get physiological values for the maximal upstroke velocity, $\frac{dV}{dt}$, the maximum conductance of the sodium current, $G_{Na}$, has been reduced to 18.86 $mS/\mu F$.

2.3. Blocking Currents

We have also studied the behavior of the model under total and partial block of potassium currents, comparing the results against those reported in [17]:

$I_{Ks}$: To simulate the effect of 1 $\mu M$ of HMR-1556, $I_{Ks}$ has been completely blocked.

$I_{Ks}$: To simulate the effect of 50 $nM$ of dofetilide, $I_{Ks}$ has been completely blocked.

$I_{Ki}$: To simulate the effect of 10 $\mu M$ of BaCl2, $I_{Ki}$ has been blocked at 50%.

2.4. Numerical implementation and simulation

Model differential equations were implemented in Fortran. Cells were stimulated with square transmembrane current pulses twice the diastolic threshold at $CL = 1000 \, ms$ and 1-ms duration. Forward Euler integration with a time step $\Delta t = 0.002 \, ms$ was used to integrate the system of differential equations governing the cellular electrical behavior. The Rush and Larsen integration scheme was used to integrate the Hodgkin-Huxley type equations for the gating variables of the various time-dependent currents.
Table 1. Biomarkers of arrhythmic risk for the TTP06, GR and CRR human models. Green color indicates within physiological range. Blue color indicates out of physiological range but better than previous models. Red color indicates out of physiological range.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>TTP06</th>
<th>GR</th>
<th>CRR</th>
<th>Physiolo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD&lt;sub&gt;90&lt;/sub&gt;</td>
<td>301.2</td>
<td>285.0</td>
<td>306.1</td>
<td>271-366</td>
</tr>
<tr>
<td>Triangulation</td>
<td>28.4</td>
<td>51.5</td>
<td>78.1</td>
<td>44-112</td>
</tr>
<tr>
<td>Sys [Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt;, 1 Hz</td>
<td>0.886</td>
<td>0.383</td>
<td>0.602</td>
<td>1.59-2.01</td>
</tr>
<tr>
<td>Sys [Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt;, 0.5 Hz</td>
<td>0.199</td>
<td>0.345</td>
<td>0.522</td>
<td>0.71-1.68</td>
</tr>
<tr>
<td>Dia [Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt;, 1 Hz</td>
<td>0.104</td>
<td>0.089</td>
<td>0.097</td>
<td>0.20-0.33</td>
</tr>
<tr>
<td>Dia [Ca&lt;sup&gt;2+&lt;/sup&gt;]&lt;sub&gt;i&lt;/sub&gt;, 0.5 Hz</td>
<td>0.068</td>
<td>0.085</td>
<td>0.091</td>
<td>0.14-0.32</td>
</tr>
</tbody>
</table>

3. Results

3.1. Biomarkers of arrhythmic risk

Table 1 shows the computed biomarkers for the modified model, CRR. Results are compared against those obtained with previous models (TTP06 and GR) and against a variety of physiological data described in [4].

These results indicate that the GR model performs better than the TTP06 model, with respect to the following biomarkers: triangulation, systolic and diastolic [Ca<sup>2+</sup>]<sub>i</sub>, at 0.5 Hz and rate dependence of steady-state [Na<sup>+</sup>]<sub>i</sub> and [Ca<sup>2+</sup>]<sub>i</sub>. However, according to other analyzed biomarkers, the GR model renders worse results than the TTP06 model. Particularly, in [18] two phases of APD rate adaptation curve were reported: a first phase with a rapid time constant and a second phase with a slower time constant. The GR model does not present this first phase. Also, the S1S2 restitution curves of the TTP06 model (Figure 3c) are in better agreement with experimental data.

For the CRR model, most of the twelve analyzed biomarkers are within the physiological range or otherwise closer to the physiological range as compared to GR and TTP06 models, except for systolic and diastolic [Ca<sup>2+</sup>]<sub>i</sub> levels at 0.5 Hz where TTP06 outperforms CRR.

3.2. Blocking Currents

Table 2 summarizes the effect of current block on the different models. Results are given as percentage of variation of the APD value in control conditions. In those cases where more than one current is blocked, the variation refers to the APD obtained when the first current is blocked. Experimental values have been taken from [17].

4. Discussion and conclusions

This study introduces several modifications to the GR model by accounting for recent experimental measurements of potassium currents, and by reformulating the L-type calcium current so as to introduce fast and slow voltage-dependent inactivation. All the modifications have been made with the aim of maintaining the advantages that the GR model presents over previous models while improving the performance on other electrophysiological aspects.

For the proposed CRR model, the introduction of fast and slow I<sub>Ca</sub><sup>L</sup> inactivation has led to a more physiological rate adaptation response as compared to the original GR model. The other modifications have rendered most biomarkers to be within the physiological range or otherwise closer to the physiological range as compared to the GR and TTP06 models, except for systolic and diastolic [Ca<sup>2+</sup>]<sub>i</sub> levels at 0.5 Hz where TTP06 outperforms CRR. These modifications, however, have altered the behavior of the model against current blocks minimally.

The results of the analysis conducted in this study points out the importance that calcium dynamics have over differ-
ent biomarkers. This suggests the need for continuing with the development of more reliable calcium dynamic models that allow improving the performance of whole cell AP models.

Further developments of the proposed model will include conducting a sensitivity analysis of the studied models.

Table 2. Percentages of variation in the APD caused by blocking different currents. Green color indicates within physiological range. Blue color indicates out of physiological range but better than previous models. Red color indicate out of physiological range.

<table>
<thead>
<tr>
<th>Current</th>
<th>Ref.</th>
<th>TT</th>
<th>GR</th>
<th>CRR</th>
<th>Exper.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{K}$ 0% Control</td>
<td>74.9</td>
<td>0.7</td>
<td>0.6</td>
<td>&lt; 2.8</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$ 0% Control</td>
<td>15.9</td>
<td>18.6</td>
<td>14.1</td>
<td>44 ± 4</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$ 0%</td>
<td>—</td>
<td>1.4</td>
<td>0.8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$ 50% Control</td>
<td>3.6</td>
<td>11.5</td>
<td>14.6</td>
<td>4.8 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$ 0%</td>
<td>—</td>
<td>1.4</td>
<td>0.8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$ 50% B</td>
<td>8.9</td>
<td>15.6</td>
<td>21.1</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Acknowledgements

This study was financially supported by grants TEC2007-68076-C02-02 from Ministerio de Ciencia e Innovación, Spain, and PI144/2009 from Gobierno de Aragón, Spain, and fellowship B040/2010 from Gobierno de Aragón, Spain.

References


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