Role of the Late Sodium Current in Arrhythmias related to Low Repolarization Reserve

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Abstract

The prolongation of action potential duration (APD) is usually related to conditions of low repolarization reserve and leads to long QT syndrome. In these situations, an unbalance between currents can fire early after depolarizations (EADs). This repolarizing disorder has been observed in heart failure situations, where the late sodium current (I\textsubscript{NaL}) has an important role. In this work we evaluate the effects of I\textsubscript{NaL} enhancement in the ventricular wall under normal conditions and we analyze the role of I\textsubscript{NaL} under pathological conditions prone to EADs generation. Human I\textsubscript{NaL} was formulated and introduced in ten Tusscher AP model. Our results show that the increase in the maximum conductance of I\textsubscript{NaL} prolongs APD in a rate-dependent manner especially in M cells. A 10-fold increase of I\textsubscript{NaL} prolongs APD in 35%, 44% and 80% for a stimulation rate of 1 Hz in epicardium, endocardium and M cells, respectively. Finally, the enhancement of I\textsubscript{NaL} under conditions of low repolarization reserve led to EADs formation in M cells.

1. Introduction

QT interval prolongation is usually related to a delay in phase 3 repolarization, and may have arrhythmogenic consequences in the ventricles (1;2), such as the formation of early afterdepolarizations (EADs) and Torsade de Pointes (Tdp). EADs are membrane potential oscillations that occur during the action potential (AP) plateau and may trigger ventricular arrhythmias. An action potential with a long duration increases intracellular calcium (Ca\textsuperscript{2+}) concentration that promotes membrane potential oscillations and formation of EADs, which are also responsible for dispersion of repolarization. These electrical alterations can degenerate into Tdp.

On the other hand, pure class III antiarrhythmics drugs (I\textsubscript{Kr} blockers) can instigate excessive QT interval prolongation due to block of action potential repolarizing currents (3;4). I\textsubscript{Kr} blockers prolong the APD in a frequency reverse dependent manner and may induce EADs in the ventricle, and even Tdp. Drug-induced Tdp remains an important problem, especially in combination with risk factors such as bradycardia, hypokalemia or congenital and long QT syndrome. This repolarizing disorder has been observed under pathological situations, such as heart failure (HF), oxidative stress, ventricular hypertrophy and provoke changes in the AP properties and alterations in the functional expression of depolarizing and repolarizing currents. The most relevant changes are down-regulation of potassium (K\textsuperscript{+}) currents, (repolarization K\textsuperscript{+} ionic currents), changes in calcium (Ca\textsuperscript{2+}) handling, decrease of sodium–potassium pump (I\textsubscript{NaK}) activity and increase of I\textsubscript{NaL} (5).

The late sodium current (I\textsubscript{NaL}) is one of the most important currents during repolarization under pathological conditions (6). Several studies have suggested that the I\textsubscript{NaL} is increased in heart failure and contributes to action potential prolongation and EADs formation (2;7-9). I\textsubscript{NaL} contributes, at least, to two established HF mechanisms: electrophysiological alterations (interruption of repolarization) and altered cell sodium (Na\textsuperscript{+}) and Ca\textsuperscript{2+} cycling (10;11). Several authors have hypothesized that an increase of I\textsubscript{NaL} would potentiate and unmask the proarrhythmic effects of QT prolonging drugs, including drugs that have a very low risk of causing VT (12;13).

The main goal of this study is to evaluate the effects of I\textsubscript{NaL} enhancement in the different cells of the ventricular wall under normal conditions in a human ventricular AP model. Moreover, we analyze the role of I\textsubscript{NaL} under pathological conditions prone to EADs generation to shed light the role of late sodium current under these conditions.

2. Methods

In this work, the late sodium current was formulated as an individual ionic current. I\textsubscript{NaL} was modeled previously by Hund and coworkers (14) for dog ventricular cells, using Hodgkin Huxley formalism (see equations 1 to 4).

\[ I_{NaL} = \bar{g}_{NaL} \cdot m^3_{L} \cdot h_{L} \cdot (V - E_{NaL}) \] (1)

\[ \alpha_{m,L} = \frac{0.32 \cdot (V_m + 47.13)}{1 - e^{(-0.1(V_m+47.13))}} \] (2)
\[
\beta_{m,i} = 0.08 e^{-\frac{V_m}{1}}
\]
(3)

\[
h_{l,\infty} = \frac{1}{1 - e^{-\frac{V_m + 91}{6.4}}}
\]
(4)

Time constant of inactivation (\(\tau_h\)) and the maximum conductance (\(g_{Na_0}\)) were modified to reproduce experimental data taken from human (15). The \(g_{Na_0}\) was fitted to data provided by Tsurugi et al. (16) and Maltsev et al. (17). In their experiments, they measured an \(I_{Na_0}/I_{Na_0}\) ratio of 0.5% approximately, and \(g_{Na_0}\) was fitted in our model accordingly. The conductance yielded 0.055 mS/\(\mu\)F. It is to be noted that the ratio does not change with temperature (18). Moreover, experimental data demonstrated that the time constant of inactivation is modified by temperature, for this reason, we multiplied \(\tau_h\) by the factor Q10 (2.2), so \(\tau_h\) yielded 233 ms at 37°C (7:18). Next, we introduced the model of \(I_{Na_0}\) into the human action potential model formulated by ten Tusscher et al. (TP06) (19). The TP06 includes the formulation of membrane ionic currents following Hodgkin-Huxley formalism, ionic pumps and exchangers that regulate ionic concentration changes, as well as dynamic changes of intracellular calcium.

To measure the APD_{90} and its rate-dependence, we paced continuously with a basic train of pulses (BCL) of 2 ms in duration and 1.5 times diastolic threshold in amplitude. In all measurements obtained the steady-state was achieved and in the three types of cells: epicardium (epi), endocardium (endo) and M cells. The BCL was modified to observe the APD rate-dependency with \(I_{Na_0}\) enhancement. Next, we calculated the substraction between APD for the maximum and minimum BCL stimulated for M cells (APD_{Max} (4000 ms) - APD_{Min} (666 ms)). APD_{90} is assessed as the time between the maximal AP upstroke (dV/dt_{max}) and 90% repolarization from peak amplitude (peak potential minus resting potential).

To analyze the arrhythmogenic role of \(I_{Na_0}\), pathological conditions of the cell prone to EAD generation, such as heart failure, ventricular hypertrophy or oxidative stress, were modeled and combined with \(I_{ca}\) block, mimicking the effects of class III antiarrhythmic agents. Specifically, L-type calcium current (\(I_{ca}\)) was 2.4-fold enhanced as well as \(I_{Na_0}\). In these simulations, the cell was paced with a BCL of 2000 ms.

3. Results and Discussion

Firstly, we incorporated the \(I_{Na_0}\) in the TP06 human AP model. APD was prolonged when the current was enhanced, as expected and demonstrated experimentally (20:21). Figure 1 shows an AP when the different types of cells were stimulated with a BCL of 1000 ms. APD_{90} underwent an increase of 7.3 %; 7.4 % and 42 %, when \(I_{Na_0}\) was included in epi; endo and M cells, respectively. When we increased 10-fold \(I_{Na_0}\), APD was prolonged in 44 %, 45 % and 80 %, respectively.

![Figure 1](image)

Figure 1. Effects of \(I_{Na_0}\) on the action potential duration using TP06 (19) (black line), modified TP06 incorporating \(I_{Na_0}\) (gray line) and 10-fold increased \(I_{Na_0}\) (dotted line). Panel A) Epicardium; B) endocardium and C) M cells.

The APD rate-dependence in the different types of cells in presence of \(I_{Na_0}\) is represented in Figure 2. It can be observed that the APD rate-dependence was more pronounced in M cells than epi and endo cells. The raise in APD difference was 666 ms versus 228 ms and 360 ms in epi and endo, respectively, when \(I_{Na_0}\) was enhanced with respect with TP06, as indicated in Table 1. For BCLs higher than 2000 ms the APD was the same to epi and endo cells. Additionally, we show the prolongation in APD in all BCL values studied, and especially at high BCLs (see Figure 2). Experimentally, Wu et al. also observed the rate-dependence, as the increase of APD was significantly higher at longer BCLs (22). Milberg and co-workers observed how verapamil, an activator of \(I_{Na_0}\), had more important effects at higher BCLs (8).
Figure. 2 Influence of the stimulation rate on APD₉₀ in epicardium (black line), endocardium (dashed line) and M cells (dotted) when I_{nat} was enhancement 10-fold.

Table 1. APD difference between BCL of 4000 ms (maximum) and BCL of 666 ms (minimum BCL for M cells).

<table>
<thead>
<tr>
<th></th>
<th>EPI</th>
<th>ENDO</th>
<th>M cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP06</td>
<td>17.8</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>With I_{nat}</td>
<td>22</td>
<td>28.2</td>
<td>70.9</td>
</tr>
<tr>
<td>I_{nat} x 10</td>
<td>39.5</td>
<td>87.7</td>
<td>123.3</td>
</tr>
</tbody>
</table>

In order to simulate cellular conditions prone to EADs formation and characterize the role of I_{nat} in the firing of such AP irregularities, some ionic currents were altered. Specifically, a 2.4-fold increase of I_{Cal} was considered, mimicking adrenergic stimulation observed in cases of HF (5) or oxidative stress, as well as the increase of I_{nat} (15).

In this study, we tested the action of enhancement I_{nat} (10-fold) combined with a complete block of I_{Kr} under conditions of low repolarization reserve in the different types of cells (endo, epi, M cells). Figure 4 shows alternant EADs under conditions of enhanced I_{nat} (solid line), highlighting the proarrhythmic effects of this current.

In the case of increased I_{nat}, EADs arose alternatively and Ca²⁺ overload seemed to be the major responsible for this repolarization irregularity. Intracellular Ca²⁺ overload due to long APD has been implicated as a trigger of spontaneous Ca²⁺ release from sarcoplasmic reticulum causing membrane potential oscillation via Ca²⁺ sensitive currents. In our simulations, we found that EADs arose more easily in M cells than epi and/or endo. The mechanisms for EADs generation have been suggested by the experiments of Choi et al. (23), who found how in M cells the primary of EADs was Ca²⁺ overload. Our study supports this observation and provides a powerful tool to get more understanding on the underlying mechanisms.

Furthermore, we found that the increase in I_{nat} favored the initiation of this mechanism.

Figure 3. Effects of I_{nat} enhancement (10-fold) in EADs generation using TP06 (solid line) and modified TP06 with enhanced I_{nat} (dotted line). Panel A) Epicardium, B) endocardium, C) M cells.

4. Conclusion

In this work, we formulated I_{nat} for human ventricular myocyte and showed its determinant role in the three different types of cells. Also, we found how I_{nat} enhancement is proarrhythmic especially in M cells under pathologic conditions prone to EAD generation in the presence I_{Kr} blockers. Finally, our study suggests that targeting I_{nat} block would have antiarrhythmic effects.

Acknowledgements

This work was partially supported by the European Commission preDiCT grant (DG-INFOS-224381), by the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica del Ministerio de Ciencia e Innovación of Spain (TEC2008-02090), by the Programa de Apoyo a la Investigación y Desarrollo (PAID-06-09-
2843) de la Universidad Politécnica de Valencia, and by the Dirección General de Política Científica de la Generalitat Valenciana (GV/2010/078).

Reference


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