Computational Modeling of Cardiac Ventricular Action Potentials in Rat and Mouse: Review

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Abstract: Little is known about the ionic mechanisms underlying the action potential heterogeneity in ventricle-associated healthy and disease conditions, even though five decades of histological, electrophysiological, pharmacological, and biochemical investigations exist. The computational modeling in murine ventricular myocytes can complement our knowledge of the experimental data and provide us with more quantitative descriptions in understanding different conditions related to normal and disease conditions. This paper initially reviews the theoretical modeling for cardiac ventricular action potentials of various species and the related experimental work. It then presents the progress of the computational modeling of cardiac ventricular cells for normal, diabetic, and spontaneously hypertensive rats. The paper also introduces recent modeling efforts for the action potential heterogeneity in mouse ventricular cells. The computational insights gained into the ionic mechanisms in rodents will continue to enhance our understanding of the heart and provide us with new knowledge for future studies to treat cardiac diseases in children and adults. Because the dissemination of computational models is very important, we continue to disseminate these models by iCell, the interactive cell modeling resource. iCell (http://ssd1.bme.memphis.edu/icell/) has been developed as a simulation-based teaching and learning tool for electrophysiology and contains JAVA applets that present models of various cardiac cells and neurons and simulation data of their bioelectric activities at cellular level. [The Japanese Journal of Physiology 54: 523–530, 2004]

Key words: computational model action potential, simulation, rat, mouse, ventricle, ionic currents.

The rodent animal models have been well characterized in terms of cardiac mechanics, biochemistry, and basic electrophysiology. The murine ventricular action potential (Fig. 1) is a topic of great interest in cardiac electrophysiology and mathematical modeling for several reasons [1]. First, the murine ventricular action potential is shorter and lacks a prominent plateau phase compared to those in human, dog, guinea pig, and rabbit. Second, most mathematical modeling for ventricular cells has been done in guinea pig and less in rat, mouse, human, and rabbit. Furthermore, the differences in ventricular membrane ionic currents, especially outward K+ currents in different species, have very important practical implications. Different drugs are known to affect different ionic currents and to change action potential waveforms in different mammalian heart preparations under normal conditions of aging and gender and also under various pathophysiological conditions.

Heart diseases are often associated with action potential prolongation. K+ currents are key determinants of cardiac action potential duration and thus also of prime targets in controlling repolarization. For all these reasons, there is great interest in defining the ionic and molecular basis of mouse cardiac currents and especially of K+ currents. Several laboratories are collecting and presenting experimental data on ventricular myocytes; however, there is little mathematical model development for murine ventricular cells using all these available data. Biophysically detailed
models for rat ventricular myocytes and for mouse ventricular myocytes are needed to utilize the data, to be used as predictive tools, and to enhance our understanding of the living systems at the cellular level.

**Cardiac Ventricular Action Potential and Membrane Currents**

Normal cardiac action potentials can be classified into two broad categories [1]: those that are self-oscillatory in nature, such as pacemaker cells, and those that need an external stimulus to be evoked, such as atrial or ventricular cells. The diversity of the action potential configurations can be seen in different regions of the heart. The ventricular tissue in particular displays a wide variety of action potential waveforms. They include pacemaker potentials in purkinje cells and disparate action potential durations (APD) and morphologies in cells from the epicardial, mid-myocardial, and endocardial layers of the ventricle. The ventricular action potential has been studied more frequently than other representative cardiac membrane potentials because ventricular arrhythmias are believed to constitute most reported fatal incidences of cardiac arrhythmias [2].

A typical ventricular action potential in higher mammals, such as dog and human, consists of five distinct phases (Fig. 1A) [1]. Phase 0 corresponds to a rapid depolarization or upstroke of the action potential. Phase 1 is the initial rapid repolarization and is followed by phase 2, which forms the action potential plateau. Phase 3 represents the final repolarization, which allows the ventricular cell to return to its resting state in phase 4. The ventricular action potential characteristics that are commonly measured are the resting membrane potential ($V_{rest}$), the peak overshoot value, which is the maximum positive value achieved during the initial phase 0 depolarization; the maximum upstroke velocity ($dV/dt_{max}$), which occurs during phase 0; and the action potential durations (APDs), measured when the action potentials have repolarized to 50% and 90% of their final repolarization value, also called APD$_{50}$ and APD$_{90}$, respectively (see Fig. 1B). One or more of these characteristics is usually changed in the setting of a pathophysiological condition and helps to quantify the differences between normal and abnormal action potentials.

The ion channels, the pumps, and the exchanger are the major ionic currents that form an action potential in mathematical representations. A summary of these currents that are present in a typical cardiac ventricular cell, their postulated molecular correlates or candidate genes, and their contributions to the ventricular action potential are summarized in Table 1. In short, the ventricular action potential is the result of a delicate “balance” of the inward currents, outward ion currents, and the active transporters (pump and exchanger).

**Review of Theoretical Modeling Research and Experimental Research in Murine Ventricular Cells**

After the first models of the mammalian ventricular cells by [3] and [4], sophisticated mathematical models have been published in the past decade that simulate the cardiac action potentials in ventricular cells from different species, such as canine [5, 6], guinea pig [7–11], human [12, 13], frog [14], and rabbit [15]. The model equations have usually been based on the Hodgkin and Huxley [16] paradigm, wherein an ionic current is described by a set of nonlinear differential equations, and the parameters within these equations are constrained by experimental data obtained via voltage-clamp experiments in ventricular myocytes. There is a growing recognition that it is important to understand the complex, nonlinear interactions among the ionic milieu of the cardiac cell, which ultimately influence the action potential [17].

The mathematical models have demonstrated to be useful didactic tools in research and have also quantified the important functional differences in the action potential properties among different species. Furthermore, the computational models have also provided valuable semiquantitative insights into the diverse ionic mechanisms underlying the normal/abnormal action potential behavior in different animal models. It is not always possible to make precise experimental measurements regarding the con-
distribution of a particular ionic mechanism to an aberrant action potential. The simulation results from these cardiac models have helped in planning for future experimental studies and in making predictions in cases where suitable technology is unavailable (or not developed) to make direct experimental measurements (such as visualizing the transmural activity within the ventricular wall). Besides experimental studies, these models will play increasingly important roles in the design and development of future drugs and devices [18]. An additional and important feature of these ventricular models has been their ability to simulate intracellular Ca^{2+} transient ([Ca^{2+}]_{i}). Thus these models incorporate the feedback mechanism between the action potential duration (APD) and the intracellular calcium [Ca^{2+}]_{i}. APD is known to influence the amplitude of the [Ca^{2+}]_{i} in ventricular cells [19], and [Ca^{2+}]_{i} in turn influences the action potential waveform by Ca^{2+}-induced Ca^{2+} inactivation of I_{CaL}, and by determining the peak magnitude of I_{NaCa} [20].

The previously developed mathematical models of human, dog, guinea pig, rabbit, and frog provide good bases for the understanding of the ionic mechanisms responsible for the generation of the cardiac action potential. However, there are significant differences in the action potential waveforms and their corresponding properties between different species. The unique nature of the rat cardiac action potential coupled with the recent available experimental data for the ionic mechanisms involved in the genesis of the action potential in isolated rat myocytes provided the motivation for us to develop the first detailed mathematical model of the rat ventricular action potential. We have constructed an adult male rat ventricular myocyte model [21] and used this model to study the ionic basis underlying the action potential heterogeneity in the adult rat left ventricle. We have obtained important insights into the role of long-lasting Ca^{2+} current (I_{CaL}), the Ca^{2+}-independent transient outward K^{+} current (I_{t}), and the steady-state outward K^{+} current (I_{ss}) in determining the electrophysiological differences between epicardial and endocardial cells. This ventricular cell model has been used to investigate the ionic mechanisms that underlie altered electrophysiological characteristics associated with the short-term model of streptozotocin-induced, type-I diabetic rats [22] and spontaneously hypertensive rats [23]. We also further utilized our rat ventricular myocyte model to develop models for the mouse apex and septal left ventricular cells [1]. Thus these model simulations reproduce a variety of experimental results and provide quantitative insights into the functioning of ionic mechanisms underlying the regional heterogeneity in the adult rat and mouse ventricle.

The ventricular cell models of dog, guinea pig, human, and rabbit described in the previous section have been mainly used to simulate the so-called spike and dome configurations for action potentials (Fig. 1) commonly observed in ventricular cells from higher mammalian species [24]. However, no mathematical model had been published to represent the murine (rat or mouse) cardiac action potential until our rat ventricular model [21]. The murine ventricular action potentials have a much shorter APD (typically the APD.

### Table 1. Major membrane currents underlying a typical ventricular action potential.

<table>
<thead>
<tr>
<th>Membrane currents</th>
<th>Description</th>
<th>Gene (α-subunit)</th>
<th>Contribution to action potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inward ionic currents</td>
<td>(I_{Na}) Na^{+} current</td>
<td>SCN5A</td>
<td>Initial depolarization of action potential</td>
</tr>
<tr>
<td></td>
<td>(I_{CaL}) L-type Ca^{2+} current</td>
<td>(\alpha_{1C}, \alpha_{1D})</td>
<td>Maintains plateau phase of action potential</td>
</tr>
<tr>
<td></td>
<td>(I_{CaT}) T-type Ca^{2+} current</td>
<td>(\alpha_{1G}, \alpha_{1I})</td>
<td>Present in the late plateau phase</td>
</tr>
<tr>
<td>Outward ionic currents</td>
<td>(I_{t}) Ca^{2+}-independent transient outward K^{+} current</td>
<td>Kv4.2, Kv4.3, Kv1.4</td>
<td>Responsible for early repolarization</td>
</tr>
<tr>
<td></td>
<td>(I_{Kv}, I_{Ks}) Rapid and slow delayed K^{+} rectifier currents</td>
<td>HERG, KvLQT1</td>
<td>Aids repolarization during plateau</td>
</tr>
<tr>
<td></td>
<td>(I_{ss}, I_{ss low}) Slow inactivating K^{+} currents</td>
<td>Kv2.1, Kv1.5, Kir2.1, Kir2.2</td>
<td>Aids late repolarization</td>
</tr>
<tr>
<td></td>
<td>Inward rectifier K^{+} current</td>
<td></td>
<td>Late repolarization, helps establish (V_{rest})</td>
</tr>
<tr>
<td>Other ionic currents</td>
<td>(I_{NaCa}) Na^{+}-Ca^{2+} exchanger current</td>
<td>NCX1, NCX2</td>
<td>Late depolarization</td>
</tr>
<tr>
<td></td>
<td>(I_{NaK}) Na^{+}-K^{+} pump current</td>
<td>Na^{+}-K^{+}-ATPase (α)</td>
<td>Late repolarization</td>
</tr>
</tbody>
</table>
at 90% repolarization (APD<sub>90</sub>) is less than 100 ms) and lack a well-defined plateau phase (triangular in shape) [25–27]. A comparison of the experimentally recorded ionic currents underlying action potentials in rat, mouse, and other mammalian ventricular cells shows that they display markedly different amplitudes and time-dependent behavior. In fact, despite the similarity of action potential waveforms in rat and mouse, the underlying nature of the repolarizing K<sup+</sup> currents are different [27–30]. Thus the unique action potential characteristics and the lack of models to quantify these membrane properties provide the motivation to develop the rat and mouse ventricular cell models. However, the mere absence of a mathematical model for a particular species cannot alone justify its development. The other justification in this case is provided by the widespread use of the murine cardiovascular system for the investigation of the cellular and molecular physiology of the compromised cardiovascular function [31].

Experimental studies indicate that the patterns of action potential waveforms are somewhat similar in rodents (rat or mouse), although the APD is shorter in mouse, and the complement of the K<sup+</sup> currents, underlying the cardiac repolarization in mouse are also different than those in rat [29, 32]. The cardiac repolarization in rat is controlled by two distinct depolarization-activated K<sup+</sup> currents, the Ca<sup>2+</sup>-independent transient outward K<sup+</sup> current (I<sub>t</sub>) and the steady-state outward K<sup+</sup> current (I<sub>ss</sub>) [26, 33]. In mouse ventricular myocytes, an additional current, the 4-AP-sensitive, inactivating, delayed rectifier K<sup+</sup> current (I<sub>K<sub>t</sub>slow</sub>) has been deemed to play an important role [27, 34]. The properties of the depolarization-activated K<sup+</sup> currents have now been well characterized in rat [26, 35] and mouse [30, 34], and appear to be significantly different. It is therefore interesting to investigate in computational modeling whether the reported differences in the properties of the depolarization-activated K<sup+</sup> currents can account for the dissimilar nature of the action potential configurations observed in rats and mice.

**Computational Modeling of the Rat and Mouse Ventricular Action Potentials**

Our goal has been to unify different experimental data and to develop biophysically detailed models for the rat and mouse ventricular cells, and also to determine the underlying ionic channels responsible for differences in cardiac action potential variations in rats and mice under normal and diseased conditions. We have developed a computational model for the rat cardiac ventricular cell based on electrophysiology data. Our control model [21] represents the bioelectric activity in the left ventricular cells in adult male rats. We have formulated the differences in the membrane properties within the left ventricle to simulate the action potential variations of the endocardial and epicardial cells. We also built a right ventricular cell model from our control model (the left ventricular cell model) to investigate ionic mechanisms in diabetic rats [22]. Our right ventricular cell model was also the template for us to develop a mouse ventricular cell model by utilizing experimental data [36, 37].

The left (LV) and right (RV) ventricular cell models for the rat consist of a Hodgkin-Huxley type membrane model that is described by the membrane capacitance; various ionic channels; the fast Na<sup+</sup> current (I<sub>Na</sub>); the long-lasting Ca<sup>2+</sup> current (I<sub>CaL</sub>); the 4AP-sensitive, Ca<sup>2+</sup>-independent transient outward K<sup+</sup> current (I<sub>t</sub>); the steady-state outward K<sup+</sup> current (I<sub>ss</sub>); the inward rectifier K<sup+</sup> current (I<sub>K</sub>); the hyperpolarization-activated current (I<sub>h</sub>); the linear background current (I<sub>b</sub>); the Na<sup+</sup>/Ca<sup>2+</sup> ion exchanger (I<sub>NaCa</sub>); and the Na<sup+</sup>/K<sup+</sup>/Ca<sup>2+</sup> membrane (I<sub>CaP</sub>) pumps that are experimentally observed in rat ventricular cells.

We constructed the mouse ventricular cell model by using the rat right ventricular cell model as the template. We developed the mouse LV apex cell by adding the 4AP-sensitive slowly inactivating, delayed rectifier K<sup+</sup> current (I<sub>K<sub>t</sub>slow</sub>) based on the data of Fiset et al. [38] and Zhou et al. [34], and by reformulating I<sub>t</sub> and I<sub>ss</sub> based on experiments performed by Agus et al. [39] and Zu et al. [30] in mice. Further, we developed a mouse LV septum cell model by formulating a new current I<sub>tor</sub> based on the data of Xu et al. [30] and by reducing the densities of I<sub>tor</sub>, I<sub>K<sub>t</sub>slow</sub>, and I<sub>ss</sub> by 70%, 23%, and 1%, respectively, based on the data of Gussak et al. [32].

The important results of our simulation studies are:

1. The action potential heterogeneity (Fig. 2) in the adult rat LV is mainly due to the changes in the density and recovery kinetics of I<sub>t</sub> and to the altered density of I<sub>Na</sub> [21].
2. Based on experimental data, the RV cell model can be developed from the LV cell model by changing the densities of I<sub>t</sub>, I<sub>ss</sub>, I<sub>CaL</sub>, and I<sub>K<sub>t</sub>slow</sub>.
3. The changes in the density and the reactivation kinetics of I<sub>t</sub> can account for the action potential prolongation differences in RV myocytes of diabetic (type-I, short-term) rats [22] and in LV
myocytes of spontaneously hypertensive rats [23] (Fig. 3).

4. The presence of $I_{K_{\text{slow}}}$ in mouse is a main factor contributing to the faster rate of repolarization seen in mouse compared to rats (Fig. 4) [36].

5. The LV septum cell model had prolonged action potentials than the apex cells (Fig. 5A), and these simulation results are qualitatively similar to the experimental data of [40].

6. The rat epicardial and endocardial ventricular cell models were more rate-sensitive than the mouse ventricular cell model, and these simulation data match the experimental data well.

In conclusion, the mathematical modeling study of murine ventricular myocytes complements our knowledge of the biophysical data with simulation data and provides us with quantitative descriptions to understand the ionic currents underlying the cardiac action potential variations in different species. This kind of computational work will enhance our understanding of the ionic mechanisms that contribute to the cardiac action potential variation in normal and diseased animals and will provide us with better treatments for diseases in humans.

**Impact of Computational Modeling in Ventricular Cells**

The following information summarizes the impacts of the computational model development of ventricular bioelectric activity and the model-generated data in different disciplines of life sciences. *I. Biophysics and Physiology:* The results of the computational studies expand our knowledge of the living systems...
at the cellular level in electrophysiology. II. Clinical Physiology and Medicine: The insights gained and the conclusions derived from the computational studies enhance our understanding of the biocomplexity of the heart and provide us with better knowledge to be used in future treatments for diseases in humans. We will also better understand cardiac cell responses to various pathophysiological states with simulation data. III. Pharmacology: The differences in ventricular membrane ionic currents, especially outward K⁺ currents in different species, have very important practical implications. Different drugs are known to affect different ionic currents and to change action potential waveforms in different mammalian heart preparations under various conditions of development, aging, and gender. A better understanding of the role of the ionic currents that control repolarization in the ventricular myocytes obtained from various species, including rat and mouse, as presented in this paper will provide motivation and explanations for species differences in treatment and drug actions. It will also promote pharmacological research that may lead to the development of more specific drugs to be used in children and adults.

Dissemination of the Computational Models and Simulation Data by iCell

An interactive Internet site, iCell (http://ssd1.bme.memphis.edu/icell/), was initially developed over which to disseminate our computational models and others. We integrated research and education on iCell and developed it further into an interactive cell modeling tool for electrophysiology that also promotes simulation-based teaching, learning, and collaboration. The site consists of JAVA applets representing models of various cardiac cells and neurons and provides simulation data of their complex bioelectric activities at cellular levels. Each JAVA-based model gives an overview of the cell, illustrates the cell membrane with an electrical equivalent circuit, and cites the published modeling paper for further information. The cell models in iCell are grouped into versions and into cardiac or neuron “model boxes.” The applets developed for the two cardiac model boxes are for (i) the rabbit sinoatrial node cell model [41], [A60] as seen in Fig. 6, (ii) the guinea pig ventricular cell model [8], [A61] (iii) the rabbit atrial cell model [42], [A62] (iv) the human atrial cell model [43], [A63] (v) the dog ventricular cell model [5], [A64] (vi) the bullfrog atrial cell model [44], [A65] (vii) the frog ventricular cell model [14], [A66] and (viii) the rat ventricular cell model [21], [A67]. The applets for the neuron model box are (i) the squid axon model [16], [A68] and (ii) the Aplysia sea slug R15 bursting neuron model [45], [A69]. Each JAVA-based model allows the user to go through menu options to change model parameters and to run and view simulation results. The site also has a glossary section for scientific terms.

iCell has integrated research and education and has been used as a teaching and learning tool for five graduate courses at the Joint Biomedical Engineering Program of the University of Memphis and the University of Tennessee. This modeling tool was also used as a collaboration site among our colleagues interested in the simulations of cell membrane activities. Scientists and students from the fields of biosciences, engineering, life sciences, and medical sciences in Argentina, Belgium, Brazil, Canada, China, England, Germany, Ireland, the Netherlands, New Zealand, Spain, Taiwan, Turkey, and the United States have used iCell as a simulation-based teaching, learning, and collaboration environment. The platform-independent software, iCell, provides us with an interactive and user-friendly teaching and learning resource and also a collaboration tool for electrophysiology to be shared over the Internet.

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