Modeling Effects of Strain-Modulated Membrane Capacitance and Conductance of K⁺ Inward Rectifier on Conduction Velocity in Cardiac Tissue

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Abstract

Mechanical deformation of cardiac myocytes has been shown to alter the conductance of various ion channels and possibly membrane capacitance. Here, we studied the strain-modulation of electrical membrane properties at rest. In particular, we studied the conductance of the inward rectifying K⁺ channel ($G_{K1}$) and the membrane capacitance ($C_m$) with respect to cellular electrophysiology and conduction velocity. For this purpose, we applied mathematical models of cardiac myocytes in computational simulations. To explore strain modulation we varied the $C_m$ and $G_{K1}$ in the range of ±25% of their original values. Conduction velocity ($\Theta$) decreased to 39.7 and 45.7 cm/s with ±25% of $C_m$ and $G_{K1}$ respectively. A decrease of 25% in $C_m$ and $G_{K1}$ caused a respective increase of 57.9 and 48.4 cm/s where 47.0 cm/s was the $\Theta$ using default values. Our study indicates that establishing the relationship between strain and $G_{K1}$, as well as strain and $C_m$ at myocyte level will be necessary to understand measured strain-$\Theta$ relationships in myocardium.

1. Introduction

Mechano-electric feedback (MEF) is well established as a modulator of electrophysiology of cardiac myocytes and tissue. Acute strain has been shown to alter conduction velocity ($\Theta$) and can cause conduction block [1–5]. Strain also decreased action potential duration at 20% repolarization ($APD_{20}$) and increased APD at 90% repolarization ($APD_{90}$) of myocytes and has been suggested to prime cardiac tissue for re-entry of electrical activation [6–8]. A proper characterization of the extent of MEF will allow an understanding of electrical activity during physiological contractions and aid in deciphering pathophysiological states.

It is generally accepted that $\Theta$ is affected by membrane excitability, intercellular coupling, and passive membrane properties. Early models of conduction are based on these properties. However, most modeling approaches were based on the assumption that these properties are independent of strain. Experiments within the last two decades have shown that cardiac myocytes possess ion channels that exhibit a strain-modulated conductance [9–12]. A number of experiments demonstrated depolarized resting membrane voltages when axial strain was applied to the myocytes. This was suggested to be caused by activation of non-selective stretch-activated channels ($SAC_{NS}$) and/or decrease in the conductance of the inward rectifying K⁺ channels [10, 12, 13]. In studies on isolated murine myocytes, the conductance of the inward rectifying K⁺ channel ($G_{K1}$) decreased by as much as 33% in response to axial strain [12].

Experimental studies of rabbit ventricular tissue showed a decrease in $\Theta$ during volume load with and without using Gd³⁺ to block SAC$_{NS}$ [14]. This suggests the lack of SAC$_{NS}$ involvement. Similar studies in papillary muscle using streptomycin to block SAC$_{NS}$ led to the same conclusion [5].

Electron micrographs of strained myocytes showed a reduction in ‘slack’ membrane and integration of caveolae into the membrane surface [15]. These effects suggest an increase in membrane capacitance ($C_m$). In a study of rabbit ventricle, space constants were measured for different mechanical loads on tissue [14]. $C_m$ values were estimated based on changes of the space constant using a bidomain model of electrical conduction [16]. This analysis suggests that $C_m$ increases as mechanical load increases.

Strain modulation of inward rectifying K⁺ channels is well established [17]. However, the effects of variation of $G_{K1}$ in combination with variations in $C_m$ are less understood.

The objective of this paper is to study the strain-modulation of electrical properties of cell membranes at rest, in particular $G_{K1}$ and the membrane capacitance ($C_m$), with respect to cellular electrophysiology and con-
duction velocity. We used mathematical models of cardiac myocytes in computational simulations for this study.

2. Methods

This study explores potential effects of strain-modulated $G_{K1}$ and $C_m$ on cellular and tissue electrophysiology, in particular, $\Theta$, upstroke velocity of the transmembrane voltage ($dV_m/dt$), and action potential duration (APD). Electrical conduction was described by a computational monodomain model of a one dimensional tissue strand using the cable equation as follows:

$$\frac{a}{2} \frac{\partial}{\partial x} \left( \frac{1}{\rho(x)} \frac{\partial V_m(x, t)}{\partial x} \right) = I_{ion} + C_m \frac{\partial V_m(x, t)}{\partial t}$$ (1)

with the cellular diameter $a$, the resistivity $\rho$, the transmembrane voltage $V_m$, and membrane currents $I_{ion}$. Resistivity $\rho$ was calculated using the coupling resistance ($R_c$). The strand had a length of 2.4 mm and was discretized every 0.1 mm. Parameters of the model are presented in table 1. Myocytes were represented by the Noble et al. model of the electrophysiology of guinea-pig ventricular cells [18]. The ordinary differential equations underlying the arrangements were solved using the Euler method with a time step of 1 $\mu$s. Inter cellular currents were updated every 1 $\mu$s. A stimulus frequency of 0.5 Hz was used. The stimulus current applied to myocyte 0 was 25 nA until a threshold voltage, -50 mV, was reached. The resulting stimulus duration was kept shorter than 1 ms to avoid significant overlap of sodium and stimulus current. Simulation results were analyzed after the $10^{th}$ simulation.

The equations used to describe $I_{K1}$ were as follows:

$$I_{K1} = G_{K1} \frac{[K]_e}{[K]_e + k_{m,K1}} \left( \frac{V_m - E_K}{1 + e^{(V_m - E_K) / \theta_{\text{Thr}}}} \right)$$ (2)

$$E_K = \frac{RT}{F} \ln \left( \frac{[K^+]_i}{[K^+]_e} \right)$$ (3)

with the respective extra- and intracellular $K^+$ concentrations $[K]_e$ and $[K]_i$, the Michaelis constant $k_{m,K1}$, the Nernst potential for $K^+$ (eq 3) $E_K$, the Faraday’s constant $F$, the gas constant $R$, and the absolute temperature $T$.

To explore strain modulation we varied both the original $C_m$ and the original $G_{K1}$ (table 1) in the range of $\pm 25\%$ in 5% increments. The analysis yielded $\Theta$, $dV_m/dt$, APD, and resting membrane voltage.

3. Results

We performed simulations varying $C_m$ and $G_{K1}$ using the described model of electrical conduction in tissue. As $C_m$ was incrementally increased from -25 to +25% there was a consistent decrease in $\Theta$, $dV_m/dt$, and an increase in APD$_{90}$. A similar increase in $G_{K1}$ caused a decrease in $\Theta$, $dV_m/dt$, and in APD$_{90}$. All changes to the resting membrane voltage, originally at 92.1 mV, through varied values of $C_m$ and $G_{K1}$ were <2%.

Increases in $C_m$ caused a near linear decrease in $\Theta$ (Fig 1). When $C_m$ was increased from 71.25 (holding $G_{K1}$ constant at 0.50 $\mu$S) to 76.0 $\mu$S the $\Theta$ decreased by 4.6% cm/s from 57.94 to 55.3 cm/s. As $C_m$ increased the change in $\Theta$ decreased such that the difference in $\Theta$ between the largest two iterations of capacitance in the simulation had a decrease of 3.1% cm/s. Over all, $\Theta$ increased by 23.4% and decreased by 18.3% with a respective 25% decrease and increase in $C_m$.

A decreasing relationship was also found as $G_{K1}$ was increased . The trend for the change in $\Theta$ to decrease as $G_{K1}$ increased also held, though smaller in magnitude. The decrease in $\Theta$ from changing $G_{K1}$ from 0.375 to 0.400 $\mu$S (holding $C_m$ constant at 95 pF) was 0.32 cm/s from 48.40 to 48.08 cm/s, while the increase from 0.600 to 0.625 $\mu$S was 0.22 cm/s. $\Theta$ increased by 3.1% and decreased by 2.6% with a respective 25% decrease and increase in $G_{K1}$.

When $C_m$ was increased from -25 to -20% the decrease in $dV_m/dt$ was 3.0%. An increase from +20 to +25%the caused a decrease in $dV_m/dt$ of 2.2%. When $C_m$ was in-

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creased from -25% to 0% \(dV_m/dt\) decreased by 13.1% from 269.7 V/s. The increase in \(C_m\) from 0% to +25% caused \(dV_m/dt\) to decreasing by 10.9% from 234.4 V/s (Fig 2).

The effects of \(G_{K1}\) were smaller on \(dV_m/dt\) compared to the effects of \(C_m\). Increasing the conductance from -25% to 0% decreased upstroke velocity by only 1%, while the change from 0% to +25% \(G_{K1}\) decreased \(dV_m/dt\) by less than 1%.

The change in APD\(_{90}\) remained almost constant at 1% change for every 5% increment change in \(C_m\). APD\(_{90}\) decreased by 4.9% and increased by 4.6% with a coinciding decrease and increase of 25% \(C_m\).

The change in APD\(_{90}\) was closer to exponential while \(G_{K1}\) was varied (Fig 3). When \(G_{K1}\) was increased from -25 to -20% APD\(_{90}\) decreased from 357.2 ms by 10.1%, but the total change from -25% to normal conductance was 31.7%. The change from normal conductance to +25% was 20%. The maximal variation caused an APD\(_{90}\) of 195.1 ms, 4.0% smaller than at +20% conductance.

Figure 2. Simulated \(dV_m/dt\) for varied \(C_m\) and \(G_{K1}\). As with \(\Theta\), the negative relationship between \(C_m\) and \(dV_m/dt\) was larger than that with \(G_{K1}\). The change in response to \(C_m\) appeared to be near linear.

Figure 3. Change in APD\(_{90}\) with respect to varied \(C_m\) and \(G_{K1}\). APD is effected more dramatically by a change in \(G_{K1}\), than by a change in capacitance. Note that the x-axis is \(G_{K1}\) and the y-axis is \(C_m\).

4. Discussion and conclusions

It has been hypothesized that increased strain will induce an increase in \(C_m\) [14, 15]. As suggested by the presented simulations, a small increase in \(C_m\) will cause a large reduction in \(\Theta\). However, the extent of \(C_m\) changes during physiological function is still unknown as well as the relationship between strain and \(C_m\).

The effects of varied \(G_{K1}\) in the same range as \(C_m\) variations are less significant in the presented simulations with regards to \(dV_m/dt\) and \(\Theta\). For example, it would take more than a 25% decrease in \(G_{K1}\) to match the effects of a 5% decrease in \(C_m\) for both \(dV_m/dt\) and \(\Theta\).

As \(C_m\) was the dominant determinant of \(dV_m/dt\) and \(\Theta\), \(G_{K1}\) was the dominant determinant of APD\(_{90}\). For a 5% decrease in \(G_{K1}\), there would need to be an increase greater than 25% in \(C_m\) for the same effect. This implies that conductances of depolarizing ion channels will in general have a larger effect on APD\(_{90}\) than \(C_m\).

A graphical representation of the effects of \(G_{K1}\) and \(C_m\) on APD\(_{90}\), \(\Theta\), and \(dV_m/dt\) is shown in Fig. 4. As strain increases \(G_{K1}\) decreases while it is hypothesized that \(C_m\) will increase [12–15]. Such an effect would imply a decrease in \(\Theta\) and an increase in APD\(_{90}\). We suggest that these results are highly relevant for dissection of the various biophysical mechanisms that underlie measured strain-\(\Theta\) relationships.

Limitations of this study. Limitations are associated with the rather simple model of cellular and tissue electrophysiology used in this study. We did not intend to develop a physiologically accurate model, but focussed on two important aspects of MEF. We characterized the effects of varied \(G_{K1}\) and \(C_m\) that may occur due to stretch. There are a number of other stretch activated ion channels that were not taken into account in our simulations. A more complete description of stretch effects has been recently published [12]. Here, three groups of stretch-sensitive ion channels were distinguished. One group was a conglomeration of outwardly rectifying K\(^+\) channels (I\(_{oth}\)). The other groups were the SAC\(_{NS}\) and channels responsible for I\(_{K1}\). Using this approach, a modeling study showed that the combination of I\(_{oth}\) and I\(_{nax}\) will decrease the APD\(_{20}\) while increasing APD\(_{90}\) [19]. Considering the
small effects of varied $C_m$ on $\text{APD}_{90}$, it is conceivable that stretch induced changes on $C_m$ will remain too small to prevent shortening of $\text{APD}_{20}$ or lengthening of $\text{APD}_{90}$ while causing a decrease in $\Theta$.

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References


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