Dependence of Action Potential Duration on Extracellular Calcium Concentration in a Model of Human Ventricular Myocyte

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Abstract

The mechanisms underlying the inverse relation between extracellular calcium concentration ($[Ca^{2+}]_o$) and action potential duration (APD) in ventricular myocytes are not fully clear.

We computationally analysed the effects of $[Ca^{2+}]_o$ variations on APD of human cardiac myocyte by means of the Ten Tusscher (2004) model. The I_{CaL} current description was then modified in order to make the simulated results coherent with experimental findings.

The original model formulation produced opposite results with respect to the expected trend, i.e. an increase of APD when increasing $[Ca^{2+}]_o$ was observed. By strengthening the Ca^{2+}-dependent inactivation of I_{CaL} it was possible to reproduce the reduction of APD when increasing $[Ca^{2+}]_o$.

The mechanism of Ca^{2+}-dependent I_{CaL} inactivation seems to be an high sensible pathway for APD adaptation to variations in $[Ca^{2+}]_o$.

1. Introduction

It is well known that changes in serum calcium influence the cardiac electrical activity particularly affecting the ventricular repolarization [1,2]. The primary electrocardiographic manifestation of hypocalcemia is the QTc interval lengthening. Prolongation of the QTc interval is associated with early after-depolarizations and triggered dysrhythmias. On the other hand, hypercalcemia exerts an opposite effect on the electrocardiogram with the hallmark of abnormal shortening of the QTc interval. These observations have been confirmed in humans in the specific setting of uremic patients undergoing hemodialysis, where prolongation of QTc was found to inversely correlate with variations in plasma Ca^{2+} by several authors, suggesting that patients with the greatest reduction in Ca^{2+} had the greatest increases of QTc at the end of dialysis session [3,4].

At the cellular level, depolarization and repolarization of cardiac myocytes strongly depend on the electrolyte gradients between intra- and extracellular compartments and these gradients affect genesis, duration, morphology and propagation of the cardiac action potential (AP). In guinea pig ventricular myocytes the rise in extracellular Ca^{2+} concentration ($[Ca^{2+}]_o$) has been shown to induce shortening of phase 2 of AP and consequent AP duration (APD) decrease [5]. To our knowledge, no experimental data are available on the effects of hypo- and hyper-calcemia on human ventricular myocyte AP.

The mechanisms underlying the inverse relation between extracellular Ca^{2+} and AP duration are not fully clear. The action potential duration is mainly determined by the equilibrium of the inward calcium current I_{Ca}, active during phase 2, and the outward delayed-rectifier potassium currents, I_{Kr} and I_{Ks}, playing a major role in ventricular repolarization (phase 3), and all these currents are influenced by $[Ca^{2+}]_o$. A theoretical model of the ventricular myocyte AP allows the investigation of the ionic mechanisms involved in ventricular repolarization. In the recent years a large number of voltage–clamp data from human myocytes has become available, and their integration in computer models has led to the formulation of models of human cardiac cell AP.

The aim of the present study was to explore the possible role of Ca^{2+}-dependent inactivation of I_{CaL} in the dependence of APD on $[Ca^{2+}]_o$ by using the Ten Tusscher-Noble-Noble-Panfilov (TNNP) model of the human ventricular myocyte [6].

2. Methods

The ventricular action potential was simulated using the TNNP model of human ventricular cell. It describes the main membrane currents and active transport mechanisms participating in the AP and the processes that regulate intracellular Ca^{2+} concentration. The model has been validated against a wide set of experimental data [6] and it is able to reproduce human epicardial,

endocardial, and M cell action potentials based on different assignment of the transient outward and slow delayed rectifier current conductances.

Model differential equations were implemented in Simulink (Mathworks Inc., Natick, MA, U.S.A.). APD was measured as the interval between the AP upstroke and the 90% repolarization level (APD_{90}). The dependence of simulated APD on different levels of $[Ca^{2+}]_o$ ranging from 1 to 2 mM was analysed.

After I_{CaL} activation, the L-type Ca^{2+} channel undergoes a voltage and Ca^{2+} dependent inactivation [7]. In the TNNP model I_{CaL} is described by a Goldman-Hodgkin-Katz formulation with a voltage-dependent activation gate (*d*), a voltage-dependent inactivation gate (*f*), and an intracellular Ca^{2+}-dependent inactivation gate (f_{Ca}), as follows:

$$I_{CaL} = G_{CaL} d \cdot f \cdot f_{Ca} \cdot 4 \cdot \frac{VF^2}{RT} \cdot \left[\frac{0.341[Ca]_o - [Ca]_i e^{\frac{2VF}{RT}}}{1 - e^{\frac{2VF}{RT}}} \right]$$

$$\frac{df_{Ca}}{dt} = k \frac{f_{Ca\infty} - f_{Ca}}{\tau_{fca}} \qquad \tau_{fca} = 2\ ms$$

$k = 0$ if $f_{Ca\infty} > f_{Ca}$ and $V > -60mV$,

$k = 1$ otherwise

$$f_{Ca\infty} = \frac{\alpha_{fca} + \beta_{fca} + \gamma_{fca} + 0.23}{1.46}$$

$$\alpha_{fca} = \frac{1}{1 + (\frac{[Ca]_i}{0.000325})^8}$$

$$\beta_{fca} = \frac{0.1}{1 + e^{\frac{([Ca]_i - 0.0005)}{0.0001}}}$$

$$\gamma_{fca} = \frac{0.2}{1 + e^{\frac{([Ca]_i - 0.00075)}{0.0008}}}$$

We modified the f_{Ca} expression in order to increase the dependence of inactivation on $[Ca^{2+}]_i$ according to studies demonstrating that the Ca^{2+} channel inactivation process depends more strongly on local Ca^{2+} than on membrane potential [7,8]. In particular, we modified the expression of $f_{Ca\infty}$ as follows, so obtaining the trend shown in Figure 1.

$$f_{Ca\infty} = \frac{\alpha_{fca} + \beta_{fca} + \gamma_{fca}}{1.3156}$$

$$\alpha_{fca} = \frac{1}{1 + (\frac{Ca_i}{0.000600})^8}$$

$$\beta_{fca} = \frac{0.1}{1 + e^{\frac{(Ca_i - 0.0009)}{0.0001}}}$$

$$\gamma_{fca} = \frac{0.3}{1 + e^{\frac{(Ca_i - 0.00075)}{0.0008}}}$$

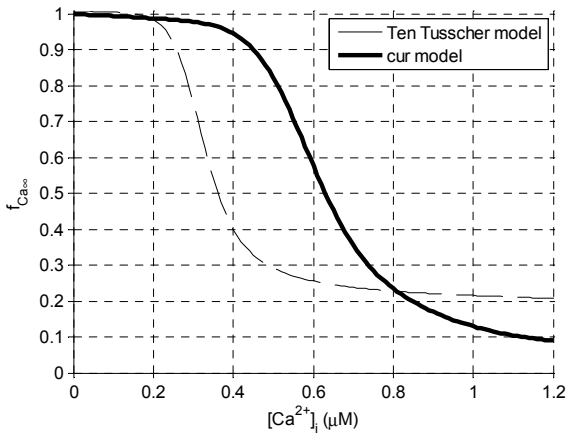

Figure 1. Steady-state Ca^{2+}-dependent inactivation curve of the L-type calcium current. Inactivation curves of the TNNP model and our modification (cur model) are shown: in the new formulation the Ca^{2+}-dependent inactivation can reach up to 90 percent of the current and the dependence on $[Ca^{2+}]_i$ is still present (i.e. the curve is not flat) for $[Ca^{2+}]_i$ = 1 μM.

3. Results

The original model formulation produced opposite results with respect to the expected trend, i.e. an increase of APD when increasing $[Ca^{2+}]_o$ was observed (Figure 2). The relation between APD_{90} and $[Ca^{2+}]_o$ was found to be almost proportional for all the cell types (Figure 3).

On the basis of this result, suggesting an incomplete description of $[Ca^{2+}]_o$ effects on the ionic currents responsible for the action potential generation, we modified the Ca^{2+}-dependent inactivation gate of I_{CaL} (f_{Ca})

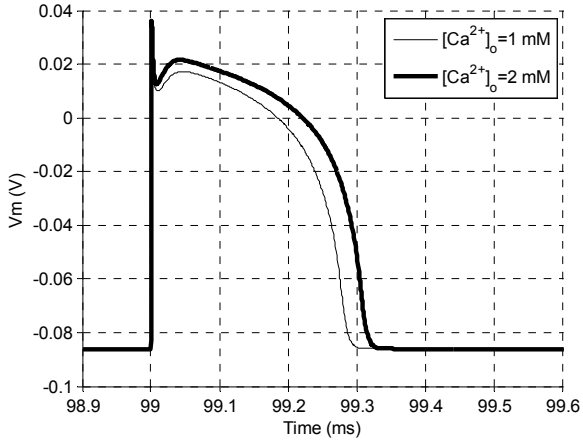

Figure 2. Example of simulated ventricular action potentials with different extracellular $[Ca^{2+}]$, produced by the TNNP model. Higher Ca^{2+} levels lead to prolonged AP.

as described in the Methods section. Thanks to this model modification it was possible to computationally reproduce a faster repolarization for higher $[Ca^{2+}]_o$, as shown in Figure 4.

The trend initially observed was significantly inverted: data obtained after modification of the ventricular myocyte model qualitatively reproduced the experimental results, showing a reduction of APD when increasing $[Ca^{2+}]_o$ for all the cell types (Figure 5).

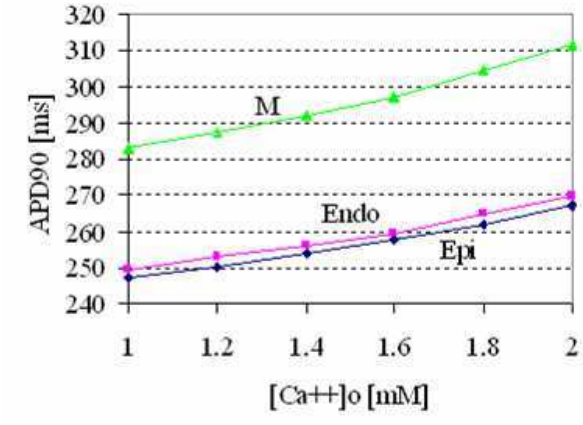

Figure 3. Sensitivity analisys of the dependence of epicardial, endocardial, and M cell APD_{90} on $[Ca^{2+}]_o$ in the TNNP model. A positive correlation between APD_{90} and $[Ca^{2+}]_o$ was found for all the cell types.

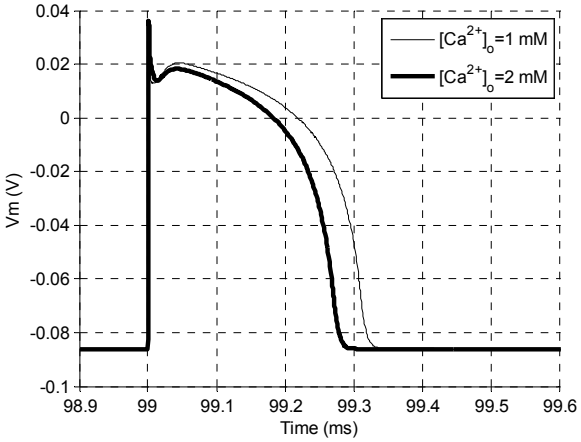

Figure 4. Example of simulated ventricular action potentials with different extracellular $[Ca^{2+}]$, produced by the model after modification of the Ca^{2+}-dependent inactivation of I_{CaL}. Higher Ca^{2+} levels lead to shortened AP.

4. Discussion and conclusions

In the present study we explored the possible role of Ca^{2+}-dependent inactivation of I_{CaL} in the dependence of APD on $[Ca^{2+}]_o$ by using the TNNP model of the human ventricular myocyte. We pointed out that in its original formulation the model was not able to reproduce the experimentally observed inverse relation between extracellular Ca^{2+} and AP duration. A minor modification to the Ca^{2+}-dependent inactivation gate of I_{CaL} was however sufficient to invert the relation between APD and $[Ca^{2+}]_o$. The negative correlation between APD_{90} and $[Ca^{2+}]_o$ that we obtained is in agreement with experimental in vitro observations on animal ventricular myocytes [5], whereas, to our knowledge, no experimental data are available on human ventricular myocytes.

The modification we made to the f_{Ca} expression originated from studies demonstrating that the Ca^{2+} channel inactivation process depends more strongly on Ca^{2+} than on membrane potential. For example, Linz and Meyer [7] by means of action potential clamp experiments showed that the Ca^{2+}-dependent component of inactivation can lead to almost complete current inactivation. Accordingly, our formulation allows the f_{Ca} to inactivate up to 90 percent of the current in the physiological range (see Figure 1). Moreover, the dependence of f_{Ca} on $[Ca^{2+}]_i$ is still present (i.e. the curve is not flat) for $[Ca^{2+}]_i$ = 1 μM, this was necessary in order to achieve a significant dependence of APD on small

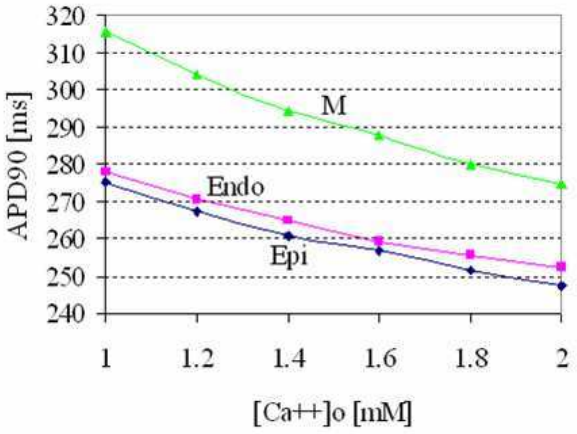

Figure 5. Sensitivity analisys of the dependence of epicardial, endocardial, and M cell APD_{90} on $[Ca^{2+}]_o$ after modification of the Ca^{2+}-dependent inactivation of I_{CaL}. A negative correlation between APD_{90} and $[Ca^{2+}]_o$ was found for all the cell types, in agreement with experimental observations.

variations of $[Ca^{2+}]_o$. It should be considered that the TNNP model has been mainly developed on the basis of data from cells in standard Tyrode solutions and it has not be validated as far as concern its response to variations in extracellular fluid composition. In this context our investigation provide an upgraded formulation of the model being able to reproduce the experimentally observed relation between APD and $[Ca^{2+}]_o$.

Action potential duration is determined by the equilibrium of I_{CaL} and the outward delayed-rectifier potassium currents, I_{Kr} and I_{Ks}, playing a major role in ventricular repolarization (phase 3), since all these currents (not only Ca^{2+} transporters) are influenced by $[Ca^{2+}]_o$ a more detailed analysis involving all these membrane currents is needed.

Our computational analysis pointed out that the mechanism of Ca^{2+}-dependent I_{CaL} inactivation seems to be an high sensible pathway for APD adaptation to variations in $[Ca^{2+}]_o$. This observation can have important *in vivo* implications, where APD prolongation might lead to arrhythmias when patients undergo to calcium depletion (e.g. during hemodialysis therapy).

References

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