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A MODIFIED MATHEMATICAL MODEL OF HUMAN VENTRICULAR CARDIOMYOCYTE INCORPORATING SEPARATE T-TUBULAR AND SURFACE DYADS AND SUBMEMBRANE SPACES

M. Pásek*, M. Bébarová, G. Christé*****

Abstract: *Intracellular Ca^{2+} load and Ca^{2+} transient are considerably dependent on distribution of sarcolemmal Ca^{2+} pump and Na^{+}-Ca^{2+} exchanger between the t-tubular and surface membranes in the presence of separate dyadic and subsarcolemmal spaces in rat ventricular cell model. To explore analogical phenomenon in human, we modified our previously published model of human ventricular myocyte. When the t-tubular fractions of Na^{+}-Ca^{2+} exchanger and of sarcolemmal Ca^{2+} pump were increased to the newly proposed value of 0.95 in the modified model, the following changes were observed at 1 Hz steady-state stimulation: a shortening of the action potential duration at 90 % repolarisation by 6 % and an increase of the cytosolic Ca^{2+} transient by 22 %. Further analysis revealed a critical role of Ca^{2+} concentration changes in the subsarcolemmal spaces and consequent change in cellular Ca^{2+} cycling in this effect.*

Keywords: Human ventricular cell model, T-tubules, Dyads, Subsarcolemmal spaces, Calcium cycling.

1. Introduction

In 2003, we first revealed that activity-induced ion concentration changes in t-tubules of cardiac ventricular cells may be large enough to significantly modulate membrane currents and cellular electrical activity (Pásek et al., 2003). Later, works on species-specific models for rat (Pásek et al., 2006) and guinea-pig (Pásek et al., 2008) were published. They demonstrated that, during a single beat at steady-state stimulation, the activation of L-type Ca^{2+} channels that are predominantly localized in the t-tubular membrane caused a transient Ca^{2+} depletion in the t-tubular lumen. This depletion reduced Ca^{2+} entry into the cell, intracellular Ca^{2+} load and, hence, the magnitude of the intracellular Ca^{2+} transient.

Recently, a modified model of rat ventricular cell incorporating separate dyadic and subsarcolemmal spaces at the t-tubular and surface membranes (Pásek et al., 2012) clearly showed that the intracellular Ca^{2+} load and Ca^{2+} transient are also considerably dependent on distribution of sarcolemmal Ca^{2+} pump and Na^{+}-Ca^{2+} exchanger between these two membrane pools (Pásek et al., 2012, 2017). On the contrary, dependency of the intracellular Ca^{2+} transient on membrane distribution of these two transporters was rather small in our model of human ventricular cardiomyocyte (Hrabcová et al., 2013) that did not include the formulation of peripheral dyads and restricted submembrane spaces. To find out whether this simplification in the formulation of the human model was responsible for the difference and to explore the importance of ion concentration changes in subsarcolemmal spaces for activity of human ventricular cardiomyocytes, we modified the model description by incorporating the function of dyads and submembrane spaces at both the t-tubular and surface membranes.

2. Modification of the model

The schematic diagram of the modified model is illustrated in Fig. 1. The presence of peripheral dyads and ion gradients under the membrane is taken into account by incorporation of the following new

* Assoc. Prof. Ing. Michal Pásek, PhD.: Institute of Thermomechanics, Czech Academy of Science - branch Brno; Technická 2; 616 69 Brno; Czech Republic; e-mail: pasek.avcr@centrum.cz

** Assoc. Prof. MUDr. Markéta Bébarová, PhD.: Department of Physiology, Faculty of Medicine, Masaryk University, Kamenice 5; 625 00; Brno; Czech Republic; e-mail: bebarova.lfmu@centrum.cz

*** Dr. Georges Christé.: Laboratoire de Neurocardiologie, EA4612, Université Lyon 1, F-69003 Lyon; France; e-mail: christe.georges@laposte.net

compartments: dyadic space adjacent to the surface membrane (i.e. the surface dyadic space), junctional sarcoplasmic reticulum (JSR) adjacent to the surface dyadic space (JSR_s), and subsarcolemmal spaces adjacent to the surface and t-tubular membranes (i.e. the surface and t-tubular subsarcolemmal space, respectively).

The total volume of the model cell (V_{tot}) was set to 20.9 pL. The total volumes of myoplasm, network sarcoplasmic reticulum (NSR), JSR and dyadic space (14.2 pL, 1.15 pL, 0.088 pL and 0.00066 pL, respectively) were left the same as in our previous model (Hrabcová et al., 2013). The total volume of subsarcolemmal space (0.412 pL) was set to represent 2 % of V_{tot} (Shannon et al., 2004). The fractional volumes of t-tubular JSR (JSR_t) and t-tubular dyadic space were set to conform with the fraction of L-type Ca^{2+} channels in the t-tubular membrane ($f_{Ca,t}$ = 0.64). The fractional volumes of surface and t-tubular subsarcolemmal spaces ($f_{Vs,s}$= 0.59 and $f_{Vs,t}$= 0.41, respectively) were set to be proportional to the non-junctional area of each membrane (92.3 % of surface membrane and 52 % of t-tubular membrane; Brette et al., 2006).

The time constants controlling the rate of ion diffusion from the dyadic spaces to the subsarcolemmal spaces (τ_{dsss} = 0.547 ms, τ_{dtst} = 0.214 ms) and from the subsarcolemmal spaces to the cytosol (τ_{ssc} = 2.3 ms, τ_{stc} = 3.4 ms) were set to be consistent with the rate of ion diffusion from dyads in our previous model (Hrabcová et al., 2013) and to ensure that during action potential (AP) the physiological magnitude of Ca^{2+} transients under the sarcolemma is higher than in the bulk cytosol (Shannon et al., 2004).

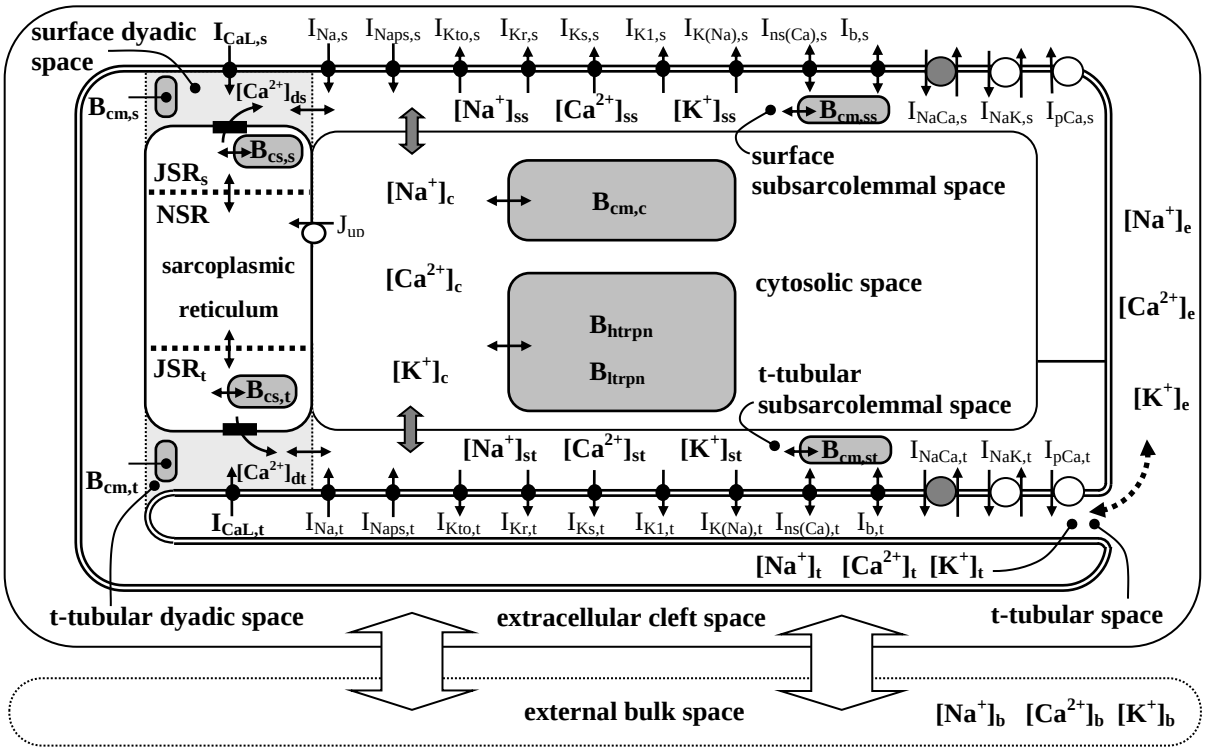

Fig. 1: Schematic diagram of the modified model of human ventricular cell. Description of electrical activity of the surface (s) and t-tubular (t) membranes comprises formulations of the following ion currents: fast sodium current (I_{Na}), persistent sodium current (I_{Naps}), L-type calcium current (I_{CaL}), transient outward potassium current (I_{Kto}), rapid and slow components of delayed rectifier potassium current (I_{Kr} and I_{Ks}), inward rectifying potassium current (I_{K1}), background currents (I_b), sodium-activated potassium current ($I_{K(Na)}$), calcium-activated non-specific current ($I_{ns(Ca)}$), sodium-calcium exchange current (I_{NaCa}), sodium-potassium pump current (I_{NaK}), and calcium pump current (I_{pCa}). The intracellular space contains the cytosolic space (c), surface and t-tubular subsarcolemmal subspaces (ss, st), surface and t-tubular dyadic spaces (dt, ds), and network and junctional compartments of sarcoplasmic reticulum (NSR, JSR_s, JSR_t). J_{up} represents Ca^{2+} flow via SR Ca^{2+} pump and the small filled rectangles in JSR membrane ryanodine receptors. The small black and grey bi-directional arrows denote intracellular ion diffusion. Ion diffusion between the t-tubular and cleft spaces is represented by the dashed arrow, and between the cleft and external bulk spaces by the thick white arrows.

To reliably simulate changes of the human action potential induced by inhibition of membrane ionic currents, a partial modification of membrane transport system description was also necessary. A block of I_{K1} was shown to induce only small prolongation of action potential duration (APD) in human ventricular myocytes (Fink et al., 2008). However, our previous human model showed a substantially larger effect (Pásek et al., 2014). To resolve this inconsistency, we have adopted the formulation of I_{K1} from the work published by Fink et al. (2008) in the modified model. This change, however, resulted in unphysiological prolongation of control APD due to smaller I_{K1}. To compensate for this effect, the conductivities related to I_{Ks} (g_{Ks}) and I_{Kr} (g_{Kr}) had to be increased. Their new values were found to simulate the experimentally proved human epicardial APD_{90} (action potential duration at 90 % repolarisation) and 3 % prolongation of APD_{90} when I_{Ks} was blocked by 90 % (Li et al., 1998 and Jost et al., 2013, respectively). The conductivities, permeabilities or maximum current densities of all ion transporters related to total membrane area and their t-tubular fractions ($f_{x,t}$) are specified in Tab. 1.

*Tab. 1: Electrical properties of ion transporters in the modified model of human cardiomyocyte. The t-tubular fractions of ion transporters ($f_{x,t}$) were adopted from Hrabcová et al. (2013). *Modified values.*

g_{Na}	25 mS cm^{-2}	$f_{Na,t}$	0.57	$g_{K(Na)}$	0.129 mS cm^{-2}	$f_{K(Na),t}$	0.56
g_{Naps}	0.01 mS cm^{-2}	$f_{Naps,t}$	0.56	g_{Nab}	0.141 μS cm^{-2}	$f_{Nab,t}$	0.56
P_{CaL}	0.00185 cm s^{-1}	$f_{CaL,t}$	0.64	g_{Cab}	2.413 μS cm^{-2}	$f_{Cab,t}$	0.56
P_{KL}	0.0000032 cm s^{-1}	$f_{KL,t}$	0.64	$P_{ns(Ca)}$	1.75 nm s^{-1}	$f_{ns(Ca),t}$	0.56
g_{Kto}	0.132 mS cm^{-2}	$f_{Kto,t}$	0.56	k_{NaCa}	0.15 nA cm^{-2} mM^{-4}	$f_{NaCa,t}$	0.56
g_{Kr}	0.216 mS cm^{-2}*	$f_{Kr,t}$	0.56	I_{NaK}	0.975 μA cm^{-2}	$f_{NaK,t}$	0.56
g_{Ks}	0.074 mS cm^{-2}*	$f_{Ks,t}$	0.56	I_{pCa}	1.725 μA cm^{-2}	$f_{pCa,t}$	0.20
g_{K1}	0.682 mS cm^{-2}*	$f_{K1,t}$	0.80				

3. Sensitivity of the model to changes in membrane distribution of I_{NaCa} and I_{pCa}

The t-tubular fractions of Na^+-Ca^{2+} exchanger and of sarcolemmal Ca^{2+} pump ($f_{NaCa,t}$ and $f_{pCa,t}$, respectively) in the basic model are 0.56 and 0.2 (Tab. 1). The recently published studies (Pásek et al., 2017 and Chase and Orchard, 2011) however indicated that the t-tubular fractions of both transporters might be even higher than 0.9 in ventricular cardiomyocytes. To explore whether such redistribution of these transporters affects the behavior of the model, we compared the simulated AP and Ca^{2+} transients in control with those when both $f_{NaCa,t}$ and $f_{pCa,t}$ were increased to 0.95. The results illustrated in Fig. 2 show that this change would lead to a shortening of APD_{90} by 6 % and to an increase of cytosolic Ca^{2+} transient by 22 % at steady state under 1 Hz stimulation. This change of Ca^{2+} transient is about tenfold higher than in our previous human model (Hrabcová et al., 2013). However, it is comparable with our recent simulations on the model of rat ventricular cardiomyocyte showing a rise of the steady state Ca^{2+} transient by 19 % when $f_{NaCa,t}$ was increased from 0.48 to 0.93 at 1 Hz stimulation (Pásek et al., 2017). Deeper analysis of the simulations revealed a critical role of Ca^{2+} concentration changes in the subsarcolemmal spaces (see $[Ca^{2+}]_{st}$ and $[Ca^{2+}]_{ss}$ in Fig. 2) and consequent change in cellular Ca^{2+} cycling in this effect (see Pásek et al., 2017 for detailed explanation). Repeating the same simulations under conditions of high

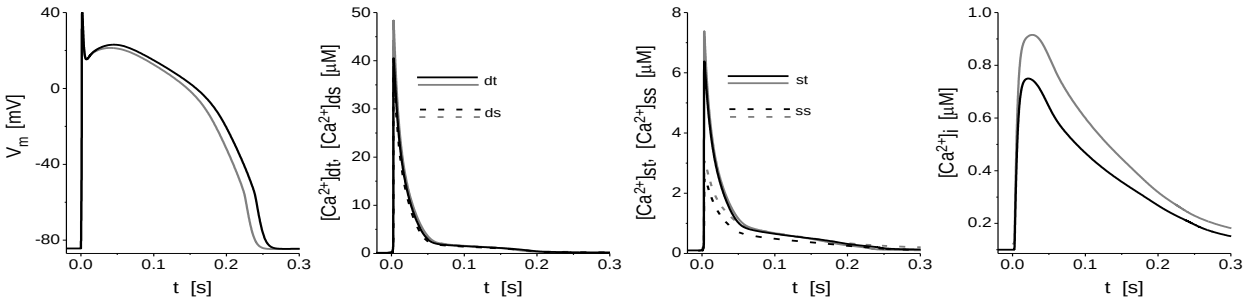

Fig. 2: Action potential and Ca^{2+} transients in t-tubular and surface dyadic spaces ($[Ca^{2+}]_{dt}$, $[Ca^{2+}]_{ds}$), subsarcolemmal spaces ($[Ca^{2+}]_{st}$, $[Ca^{2+}]_{ss}$) and cytosol ($[Ca^{2+}]_i$) at 1 Hz steady state stimulation (after 600 s) in the basic model (black lines) and after an increase of $f_{NaCa,t}$ and $f_{pCa,t}$ to 95 % (gray lines).

rate of ion exchange between the subsarcolemmal spaces and cytosol (to eliminate the ion concentration differences between these spaces), the steady state change of cytosolic Ca^{2+} transient in response to the increase of $f_{NaCa,t}$ and $f_{pCa,t}$ was substantially lower (relative increase of peak $[Ca^{2+}]_i$ was ~2 %). This explains the small sensitivity of our previous human model to membrane redistribution of Na^+-Ca^{2+} exchanger and sarcolemmal Ca^{2+} pump. Notably, it highlights the importance of restricted Ca^{2+} diffusion and formation of Ca^{2+} concentration gradients under sarcolemma in the control of intracellular Ca^{2+} load and Ca^{2+} transient. The present model also showed that the role of activity-induced variations of $[K^+]_{ss}$, $[K^+]_{st}$, $[Na^+]_{ss}$ and $[Na^+]_{st}$ in this effect is minor (not shown).

4. Conclusion

The presented modification of the model of human ventricular cell represents a further step to reliably simulate the electrophysiological activity of human cardiomyocytes in different conditions. Our simulations revealed that distribution of Na^+-Ca^{2+} exchanger and sarcolemmal Ca^{2+} pump between the t-tubular and surface membranes governs restricted Ca^{2+} diffusion and formation of Ca^{2+} concentration gradients between the corresponding submembrane spaces and cytosol. These are of key importance in the control of intracellular Ca^{2+} load and Ca^{2+} transient and, hence, of excitation-contraction coupling features in human ventricular cells.

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