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QUANTITATIVE MODELLING OF EFFECT OF TRANSVERSE-AXIAL TUBULAR SYSTEM ON ELECTRICAL ACTIVITY OF CARDIAC CELLS: DEVELOPMENT OF MODEL II

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Summary: *In this work, we present a new version of cardiac ventricular cell model incorporating the transverse - axial tubular system. The improvements include reformulated description of L-type Ca^{2+} channel, of Ca^{2+} induced Ca^{2+} release from sarcoplasmic reticulum, of intracellular Ca^{2+} buffering and incorporation of potassium currents I_{to}, $I_{K(Na)}$ and $I_{K(ATP)}$. In comparison with the previous model (Pásek et al., 2002), the steady state simulations revealed more profound changes of tubular ionic concentration (12.8 % for Ca^{2+} and 4.7 % for K^+ at 1 Hz). The refined model will be used for more exact quantitative exploration of the effect of transverse - axial tubular system on cellular electrical activity and excitation - contraction coupling.*

1. Introduction

In our previous work (Pásek et al., 2002) we introduced a model of electrical activity of cardiac ventricular cell incorporating the transverse axial tubular (TAT) system. The description of electrical activity of surface and tubular membrane as well as of the intracellular Ca^{2+} handling was based mainly on the model of cardiac ventricular action potential (AP) proposed by Luo & Rudy (1994) with modified formulation of mechanisms of Ca^{2+}-induced Ca^{2+} release from sarcoplasmic reticulum (Nygren et al., 1998). Recent experimental evidence (Puglisi, 1999; Zahradníková et al., 1999; Bers, 2002) clearly showed, however, that the phenomenological description of intracellular Ca^{2+} handling used in these models was highly simplified and could not capture the biophysical details of the mechanisms involved. Several models have been proposed (Jafri et al., 1998; Rice et al., 1999; Stern et al., 1999) to bridge this inconsistency in particular with respect to Ca^{2+}-induced inactivation of L-type Ca^{2+} channels, Ca^{2+}-induced Ca^{2+} release from sarcoplasmic reticulum, adaptation of ryanodine receptors and Ca^{2+} buffering.

In this paper, we introduce the modifications of our model (Pásek et al., 2002) to conform the current view on membrane transport and intracellular Ca^{2+} dynamics in ventricular cells.

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The main modifications are made on the basis of the model published by Jafri et al. (1998). In addition, the currents I_{to}, $I_{K,ATP}$ and $I_{K(Na)}$ that can strongly contribute to K^+ accumulation in the TAT-system are newly included into the model. The improved model is supposed to be used for detailed exploration of the role of TAT-system in electrical activity of cardiac ventricular cells and in excitation-contraction coupling.

2. Modification of the previous model

In the following sections, the modifications introduced to the quantitative description of our previous model (Pásek et al., 2002) are summarized.

The description of calcium current through L-type channels (I_{Ca}) and intracellular Ca^{2+} handling (function of sarcoplasmic reticulum, fuzzy space and Ca^{2+} buffers) is completely adopted from the model of Jafri et al. (1998) to be consistent with current experimental observations (Puglisi, 1999; Zahradníková et al., 1999; Bers, 2002).

The 4-AP-sensitive transient outward current I_{to} is incorporated into the model and described as

$$I_{to} = g_{to}\, r_1\, (V_m - V_K)$$

where V_K is the Nernst reversal voltage of K^+ and g_{to} is a constant conductance (see Table 1). The fraction of open channels

$$r_1 = 1 - r_2 - r_3 - r_4$$

results from the solution of a set of three differential equations

$$dr_2/dt = \beta_r\, r_1 + \alpha_q\, r_3 - (\alpha_r + \beta_q)\, r_2,$$

$$dr_3/dt = \beta_q\, r_2 + 0.05\, \beta_r\, r_4 - (\alpha_q + 0.05\, \alpha_r)\, r_3,$$

$$dr_4/dt = \beta_q\, r_1 + 0.05\, \alpha_r\, r_3 - (\alpha_q + 0.05\, \beta_r)\, r_4.$$

Based on the experimental data (Šimurda et al., 1988; Tseng & Hoffman, 1998) the rate constants α_q, β_q, α_r and β_r are expressed as

$$\alpha_q = 395 / (1+\exp(-0.081(V_m+0.9))),$$

$$\beta_q = 356 / (1+\exp(0.0463(V_m+12.4))),$$

$$\alpha_r = 76 \exp(-(V_m+80)/26.6) / (1+\exp(0.4(V_m+48))),$$

$$\beta_r = 75 \exp((V_m-50)/95.9) / (1+\exp(-0.4(V_m+49.4))).$$

The model is also supplemented by quantitative description of the Na^+-sensitive potassium current ($I_{K(Na)}$) and of the ATP-sensitive potassium current ($I_{K(ATP)}$) according to Faber & Rudy (2000).

The electroneutral potassium pump (J_{pK}) is removed from the model and the saturation factor of I_{NaCa} at very negative potentials (k_{sat}) is returned to 0.1 according to the original description of Luo & Rudy (1994).

The maximal specific conductivity, permeability or current density of individual ion transfer mechanisms in surface and tubular membrane are set as summarised in Table 1.

Table 1. Electrical properties of surface and tubular membrane transport systems used in the model. In the absence of data, the densities of ion transfer mechanisms were assumed equal in both membrane systems. References: [1]- Petrecca at al., 1997; [2]- Yao et al., 1997; [3]- Mays et al., 1995; [4]- Christé, 1999; [5]-Takeuchi et al., 2000; [6]-Shepherd & McDonough, 1998; [7]-Frank et al., 1992; [8]- Chen et al., 1995; [9]-McDonough et al., 1996; [10]- Iwata et al., 1994.

	unit	surface	tubules	reference
g_{Na}	[mS/cm^2]	30	30	[1, 2]
g_K	[mS/cm^2]	0.18	0.02	[3]
g_{K1}	[mS/cm^2]	0.4838	0.8696	[4]
g_{to}	[mS/cm^2]	0.0645	0.116	[5]
g_{Kp}	[mS/cm^2]	0.002	0.002	
$g_{K,(Na)}$	[mS/cm^2]	0.1285	0.1285	
$g_{K,ATP}$	[mS/cm^2]	2.5157	4.5221	[4]
$g_{Na,b}$	[mS/cm^2]	0.0014	0.0014	
$g_{Ca,b}$	[mS/cm^2]	0.0021	0.0021	
P_{Ca}	[cm/s]	0.0054	0.0054	[6, 2]
$P_{ns(Ca)}$	[cm/s]	1.75e-7	1.75e-7	
$I_{NaCa,max}$	[μA/cm^2]	1290	2319	[7, 8]
$I_{NaK,max}$	[μA/cm^2]	1.5	1.5	[9]
$I_{pCa,max}$	[μA/cm^2]	2.9673	0.3334	[10]

The time constants of ion diffusion between the TAT-system and extracellular space are enhanced to 300 ms for calcium ions and to 120 ms for potassium and sodium ions (Shepherd & McDonough, 1998; Yao et al., 1997).

The modified model (schematic diagram is shown in Fig. 1) was implemented in the program system MATLAB 6.0 and the numerical computation of the system of 57 non-linear differential equations was performed using the solver for stiff systems ODE-15s.

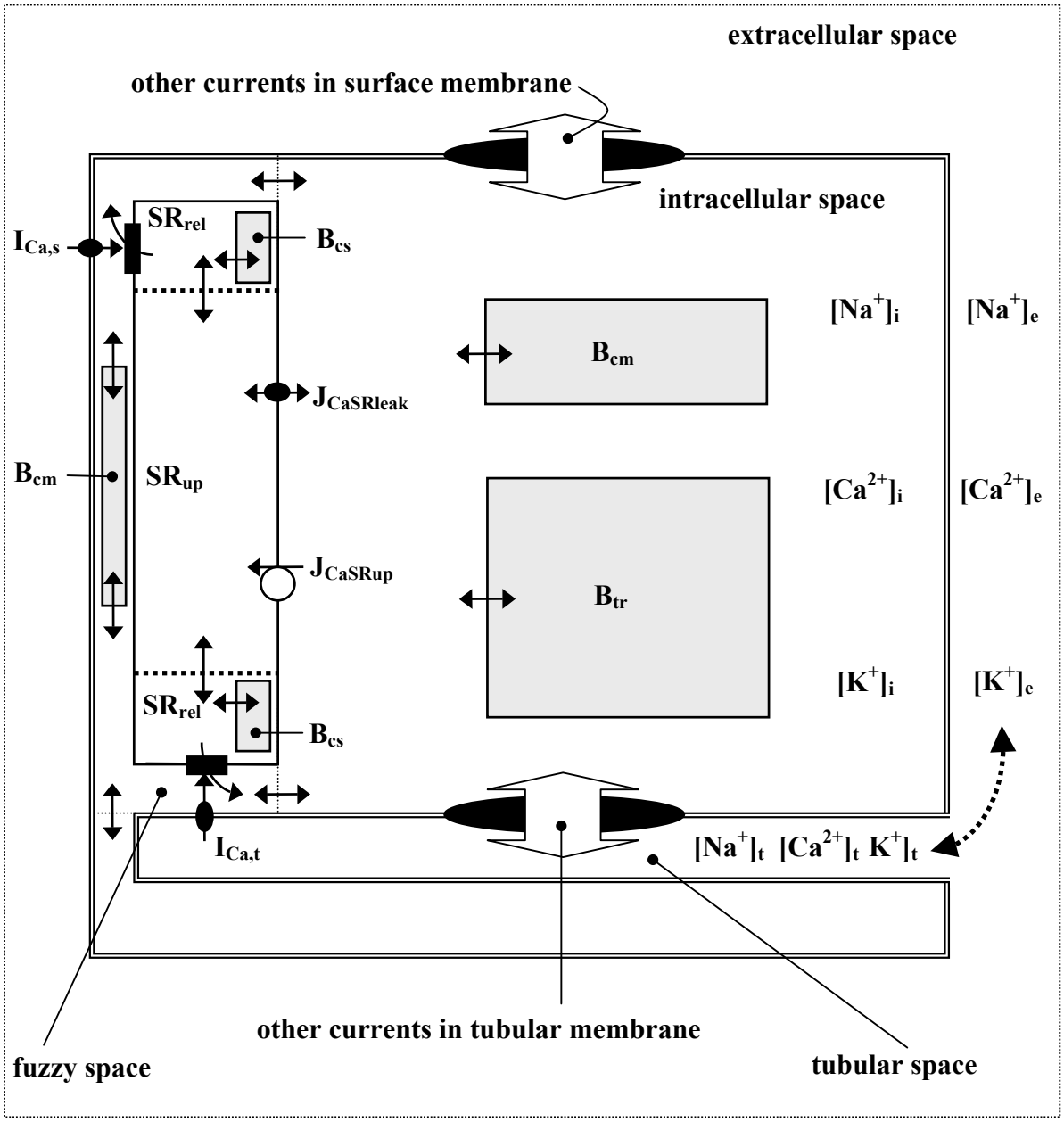

Figure 1. Schematic diagram of the cardiac ventricular cell model. The description of electrical activity of surface (s) and tubular (t) membrane comprises ion currents (I_{Na}, I_{Ca}, I_K, I_{K1}, I_{Kp}, $I_{K(Na)}$, $I_{K(ATP)}$, $I_{ns(Ca)}$, $I_{Na,b}$, $I_{Ca,b}$, I_{NaCa}, I_{NaK}, I_{pCa}) introduced by Luo & Rudy (1994) and by Faber & Rudy (2000). In addition, 4-aminopyridine-sensitive transient outward current I_{to} was incorporated. The intracellular space contains the fuzzy space, the Ca^{2+}-uptake and Ca^{2+}-release compartments of sarcoplasmic reticulum (SR_{up}, SR_{rel}) and the Ca^{2+} buffering by calmodulin (B_{cm}), troponin (B_{tr}) and calsequestrin (B_{cs}). The small filled rectangles in SR_{rel} membrane represent ryanodine receptors. The small bidirectional arrows denote Ca^{2+} diffusion. Ionic diffusion between tubular and bulk space is represented by the dashed arrow.

3. Results of quantitative modelling

Fig. 2 and Fig. 3 illustrate the basic behaviour of the model. Fig. 2 depicts steady state electrical responses of surface and tubular membrane to stimulation pulses (12 nA, 1 ms) applied at 1Hz. Included are action potentials and main ionic currents underlying depolarization (I_{Na}, I_{Ca}) and repolarization (I_K, I_{K1}, I_{to}) of surface and tubular membrane. The carrier mediated currents I_{NaK} and I_{NaCa} maintain ionic homeostasis. The other currents, of lesser importance with respect to modulation of AP, are not illustrated. The differences between APs of both membrane systems appeared to be negligible. The striking differences between the magnitudes of the surface (solid lines) and the tubular (dotted lines) membrane currents result from different area of tubular membrane versus surface membrane as well as from unequal densities of some channels, exchangers or pumps (see Table 1).

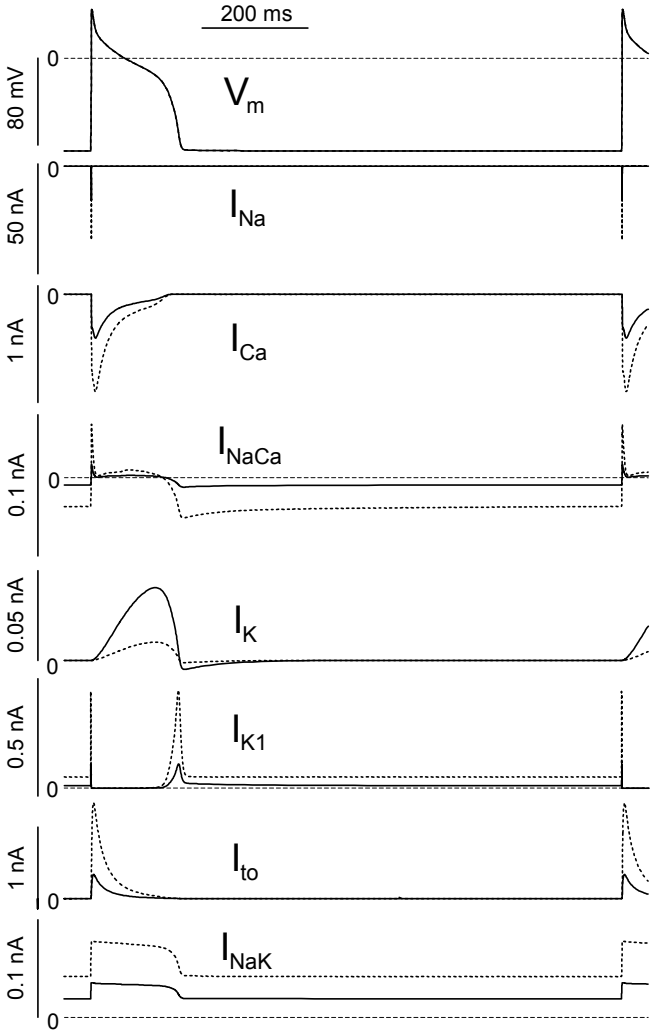

Figure 2. Action potentials (V_m) and main ionic currents in surface (solid lines) and tubular (dotted lines) membrane in response to stimulation pulses (12 nA, 1 ms) applied at steady state (1Hz). The currents visualised here are: fast sodium current (I_{Na}); calcium current through L-type channels (I_{Ca}); delayed rectifier potassium current (I_K); inwardly rectifying potassium current (I_{K1}); transient outward current (I_{to}); sodium-calcium exchange current (I_{NaCa}) and sodium-potassium pump current (I_{NaK}).

Fig. 3 depicts the changes of ionic concentrations in the sarcoplasmic reticulum, cytoplasm and TAT-system accompanying the electrical responses of Fig. 2. The transient increase in $[Ca^{2+}]_i$ from diastolic level (140 nmol/l) to 1.4 μmol/l occurs early after the onset of AP and reflects the rapid release of Ca^{2+} from the release compartment SRrel (Fig. 1). It is mirrored as a fall of $[Ca^{2+}]_{SRrel}$ from 2.33 mmol/l to 0.1 mmol/l. The subsequent decline of $[Ca^{2+}]_i$ caused by concurrent Ca^{2+} uptake into the uptake compartment SR_{up} and calcium extrusion by the Na/Ca exchanger is considerably modulated by intracellular Ca^{2+} buffers (troponin and calmodulin). The relative changes of $[Na^+]_i$ and $[K^+]_i$ at steady state are low. All diastolic levels of the intracellular concentrations lie in the range of measured values at 1Hz stimulation frequency (Baumgarten et al. 1981; Siri et al. 1991; Harrison et al. 1992).

The relative changes of ionic concentrations in TAT-system during regular action potential at 1 Hz are 12.8 % for $[Ca^{2+}]_t$, 4.7 % for $[K^+]_t$ and 0.3 % for $[Na^+]_t$.

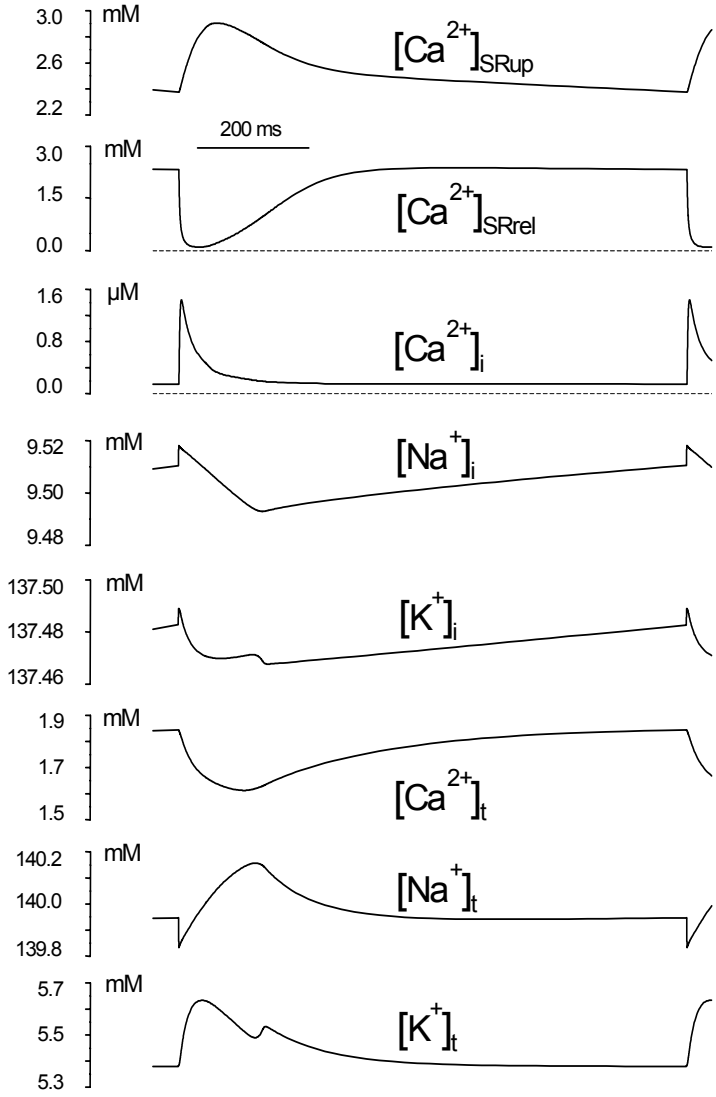

Figure 3. Concentration changes of Ca^{2+} in uptake and release compartments of sarcoplasmic reticulum ($[Ca^{2+}]_{SRup}$, $[Ca^{2+}]_{SRrel}$), and of Ca^{2+}, K^+, Na^+ in myoplasm ($[Ca^{2+}]_i$, $[Na^+]_i$, $[K^+]_i$) and TAT-system ($[Ca^{2+}]_t$, $[Na^+]_t$,$[K^+]_t$). Steady state simulation at 1 Hz.

4. Conclusion

The model presented here represents the next stage of our attempt to explore quantitatively the contribution of the TAT-system to cardiac cellular activity. It includes previous knowledge of key importance concerning the distribution of ionic pumps, exchangers and channels between the membrane of the TAT-system and the rest of the ventricular cell membrane (see table 1). It also takes into account the restricted diffusion of ions between the lumen of the TAT-system and the bulk extracellular medium (Yao et al., 1997; Shepherd & McDonough, 1998). The considerable modification in its quantitative description is, however, made with respect to intracellular Ca^{2+}-dynamics that was adopted from the model proposed by Jafri et al. (1998).

The idea that transient accumulation-depletion of ions may take place in the TAT-system is confirmed and quantified: Ca^{2+} ions are depleted by about 13% and K^+ ions are accumulated by 5% during the course of a single action potential of a train at 1 Hz.

The possible role of these phenomena in physiological conditions (e.g.: rate-dependent changes) and in pathological ones (e.g.: hypoxia-ischaemia, or other proarrhythmogenic conditions) is the subject of detailed analyses to be published in subsequent works.

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