Physiological Consequences of Ion Concentration Changes in Transverse Axial Tubular System in A Model of Human Ventricular Cardiomyocyte

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Abstract. A mathematical model of human ventricular cell incorporating the transverse axial tubular system (TATS) was designed and used to explore the role of TATS in human ventricular cell electrophysiological activity. The model is based on the latest quantitative description of guinea pig ventricular cell electrophysiology and modified to respect the published data obtained from human cardiac preparations. Computer simulations suggest that significant transient depletions of Ca^{2+} ions and accumulation of K^{+} ions may (occur) in the human TATS. The preliminary analysis of the effects of tubular Ca^{2+} depletions on the activity of the model cell indicates their role in limitation of intracellular Ca^{2+} overload at higher frequencies of stimulation.

1 Introduction

The transverse-axial tubular system (TATS) of cardiac cells is a structure of surface membrane invaginations that allows rapid propagation of excitation into the cell interior. The results of the latest experimental works suggest that the TATS form a highly specialized region that is important for excitation-contraction coupling because many of key proteins involved in transmembrane Ca^{2+} flux appear to be located predominantly in the TATS [1].

In this paper, we present a model of human ventricular cardiomyocyte in which the TATS is described as a single compartment and the results of preliminary simulations showing the effect of ion concentration changes in the tubular lumen on intracellular Ca^{2+}-transients at different stimulation rates.

2 Methods

The model originally proposed to describe the properties of guinea-pig ventricular myocyte [2] was adopted and modified to cope with recently published results of electrophysiological experiments obtained in current clamp and voltage clamp experiments on isolated human cardiomyocytes. [3]. Geometric parameters of TATS and distribution of ion flux pathways between the surface and tubular membrane of the myocyte were estimated on the basis of published experimental data [4, 5]. A schematic diagram of the model is shown in Figure 1.

The model was implemented using MATLAB 6.5 (The MathWorks, Inc., Natick, MA) and the numerical computation of the system of 81 non-linear differential equations was performed using the solver for stiff systems ODE-15s. The model equations were simultaneously solved using a time step adjusted to keep the estimated relative error of inner variables below a threshold value of 0.001. The stability of the model was tested simulating 1200 s of quiescence and activity at stimulation frequencies 1, 2, and 3 Hz.

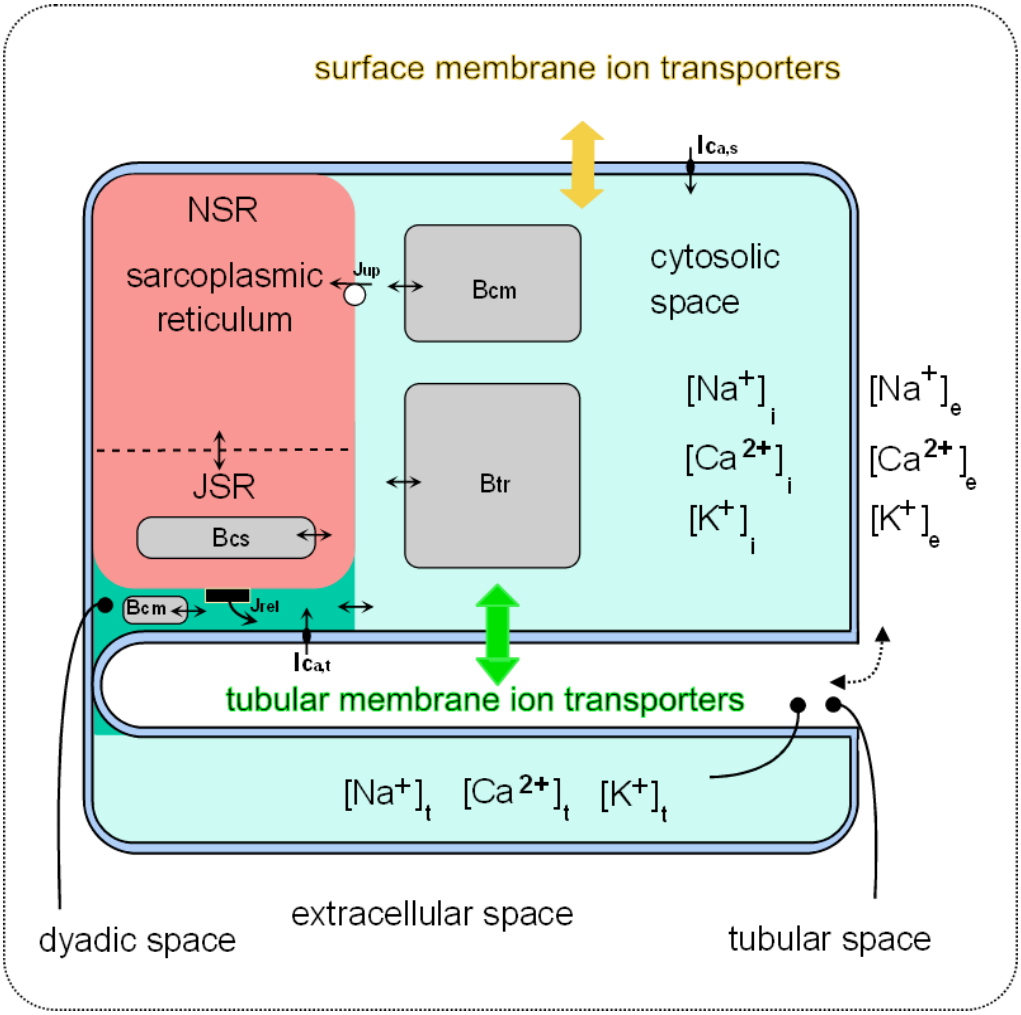

Fig 1. Schematic representation of the model of human ventricular myocyte. The description of electrical activity of surface (s) and tubular (t) membrane includes formulation of the following ion currents: fast sodium current I_{Na}, L-type calcium current $I_{Ca,L}$, L-type potassium current $I_{K,L}$, time-dependent transient outward potassium current I_{to}, rapidly-activating delayed rectifier potassium current I_{Kr}, slowly-activating delayed rectifier potassium current I_{Ks}, time-independent inwardly rectifying potassium current I_{K1}, persistent sodium current I_{Naps}, Na^+-activated potassium current $I_{K(Na)}$, non-specific Ca^{2+}-activated current $I_{ns(Ca)}$, background sodium current I_{Nab}, background calcium current I_{Cab}, Na/Ca-exchanger current I_{NaCa}, electrogenic Na^+-K^+-ATPase pump current I_{NaK}, sarcolemmal Ca-pump current I_{pCa}. The intracellular space contains the cytosol, the dydadic space, the network and junctional compartments of sarcoplasmic reticulum (NSR, JSR) and the Ca^{2+} buffers calmodulin (B_{cm}), troponin (B_{ltrpn},B_{htrpn}) and calsequestrin (B_{cs}). J_{rel} and J_{up} represent the Ca^{2+} release flux from JSR into the dyadic space and the Ca^{2+} uptake flux from the cytosol into NSR respectively). The small filled rectangle in JSR membrane represent ryanodine receptors. The small bi-directional arrows denote Ca^{2+} diffusion. The dashed arrow represents ionic diffusion between the tubular and the bulk extracellular space.

3 Results

The basic behavior of the model at a stimulation rate of 1 Hz (resting heart rate characteristic for human) is shown in Figure 2. The panel A depicts the steady state electrical responses of surface and tubular membranes to 4.5 nA stimuli (1 ms) showing action potentials (V_m), Ca^{2+} - currents through L-type Ca^{2+}-channels (I_{Ca}) and intracellular Ca^{2+}-transient ($[Ca^{2+}]_i$. The differences between action voltages of both membranes are negligible. The observed differences between tubular and surface membrane I_{Ca} result from a different distribution of Ca^{2+}-channels between both membrane subsystems (fraction of I_{Ca} in tubular membrane is 64 %) as well as from changes of Ca^{2+}-concentration in the tubular lumen. The changes of tubular ion concentrations ($[Ca^{2+}]_t$, $[K^+]_t$, $[Na^{2+}]_t$) are displayed in panel B. While $[Ca^{2+}]_t$ and $[K^+]_t$ exhibited a significant depletion (about 9 %) and accumulation (about 3 %), respectively, the relative changes of $[Na^{2+}]_t$ appeared to be negligible. The effect of ion concentration changes in TATS on intracellular Ca^{2+}-transient ($[Ca^{2+}]_i$) at different steady state stimulations is shown in Figure 3. As follows from the figure, the activity-dependent depletions of tubular Ca^{2+} reduced the $[Ca^{2+}]_i$ transient in the whole range of physiological stimulation frequencies .

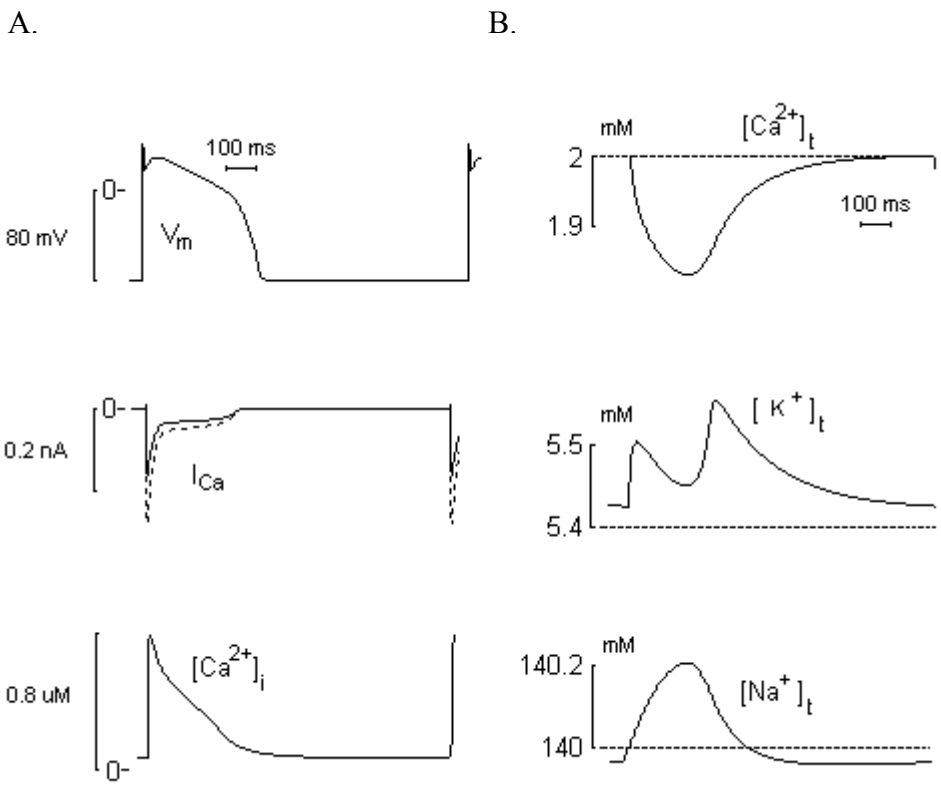

Fig 2. Electrical events and ion concentration changes at steady-state at 1 Hz stimulation of the model cell. A. V_m - action voltage in surface and tubular membranes (the differences are negligible), I_{Ca} - L-type Ca^{2+} currents through surface membrane (dashed line) and tubular membrane (dotted red line), $[Ca^{2+}]_i$ - intracellular Ca^{2+}-transient. B. Corresponding changes of Ca^{2+}, K^+ and Na^+ concentrations in TATS. Horizontal dashed lines refer to extracellular ion concentrations.

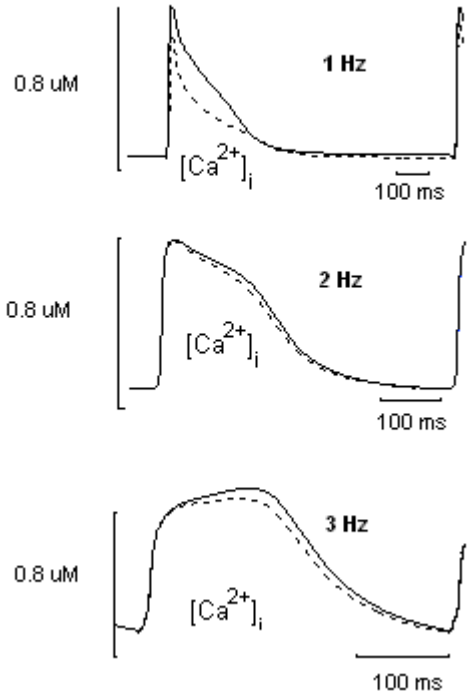

Fig 3. Steady state intracellular Ca^{2+}-transients ($[Ca^{2+}]_i$) under presence (dashed line) and absence (solid line) of ion concentration changes in TATS at 1 Hz, 2 Hz and 3 Hz stimulation frequency.

3 Conclusions

The present model is the first to explore the extent of ion concentration changes in the TATS of human ventricular cardiomyocytes and their physiological consequences. Computer simulations suggest that significant transient depletions of Ca^{2+} ions and accumulation of K^+ ions may occur in the human TATS. The preliminary analysis of the effects of tubular Ca^{2+}depletions on the activity of the model cell indicates their role in limitation of intracellular Ca^{2+} overload at higher frequencies of stimulation.

References

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