Interplay of Potassium Channels in Modulating the Action Potential of the Human Left Ventricle

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Abstract

The interplay of potassium ion channels in modulating the action potential (AP) of the human left ventricle has not been well elucidated due to the precise nature of some underlying ionic components that are not fully characterized. In the current study, we have developed an allosteric conformation model for rapid delayed rectifier (IKr) and incorporated this into the ten Tusscher's model for human ventricular myocytes. The transmural densities of IKr, the slow delayed rectifier (IKs) and the transient outward channel (Ito) were refined based on the variable expression of the underlying protein subunits. Our results demonstrated that the modified model was able to reproduce an AP duration (APD) of 313 ms in Epi, 349 ms in M and 300 ms in Endo at 1 Hz pacing. A frequency change from 1 Hz to 0.5 Hz resulted in an APD difference of 20 ms for Epi, 32 ms for M and 20 ms for Endo. Ito effected the early phase of AP, however, had no significant influence on APD. An increase of IKr progressively suppressed IKs in Epi and Endo, however, caused a paradoxical change of IKs in M cells. In summary, our results have suggested a coincident decrease of IKs with excessive decrease of IKr in M cells would be a substrate of their high susceptibility to APD prolongation.

1. Introduction

Over the last decade, the kinetics of ionic components and intracellular calcium signaling have been characterized in great detail for a range of species, including mouse, rabbit, guinea-pig and canine [1, 2, 3]. A considerable effort has also been devoted to characterize human ventricular action potential (AP). Ten Tusscher's AP model (TNNP) [4] for human ventricular cardiomyocytes consists of a high level of electrophysiological detail, and be able to reproduce the experimentally observed data on action potential duration (APD) restitution. This model has been extended to study three-dimensional heterogeneity [5], and to simulate the effects of Brugada syndrome on cellular AP and body surface potentials [6]. In contrast to the ventricular models of other species, however, the TNNP model has a number of drawbacks in the replication of some experimentally observed data, This is a result of limited experimental data being available for human ventricular myocytes, and partly due to the precise nature of ionic components which are not yet fully characterized. To be more specific, the densities of the rapid and slow delayed potassium rectifiers from the TNNP model are much larger than measured data; the differences of APD are much smaller, and the rate adaptations in all cells are much less than the values recorded.

In our current work, we have developed a kinetic model for the rapid delayed potassium rectifier (IKr) [7], which characterizes the allosteric activation process and the cooperative transition of its protein subunits in detail. We have subsequently incorporated this newly developed allosteric conformation model into the TNNP model to assess the interdependence of major outward potassium channels in modulating the AP of the human left ventricle. The transmural densities of IKr, the slow delayed rectifier (IKs) and the transient outward channel (Ito) were refined based on recent experimental data [8, 9]. Our results based on the modified TNNP model (MTM) showed that Ito exerted an effect on the early phase of AP, however, had no significant influence on AP duration. An increase of IKr induced a decrease of IKs in Epi and Endo, and a counter-intuitive change of IKs in M cells.

2. Methods

2.1. Kinetic pathway model of IKr

The kinetic pathway of a protein channel describes the transition paths of its conformations in the gating actions, and each state in the paths is kinetically connected. A kinetic pathway with 18 conformation states for IKr has been established which characterizes the allosteric activation through 15-state transitions to a fully activated conformation, followed by two subsequent cooperative open conformation transitions. An inactivation conformation state

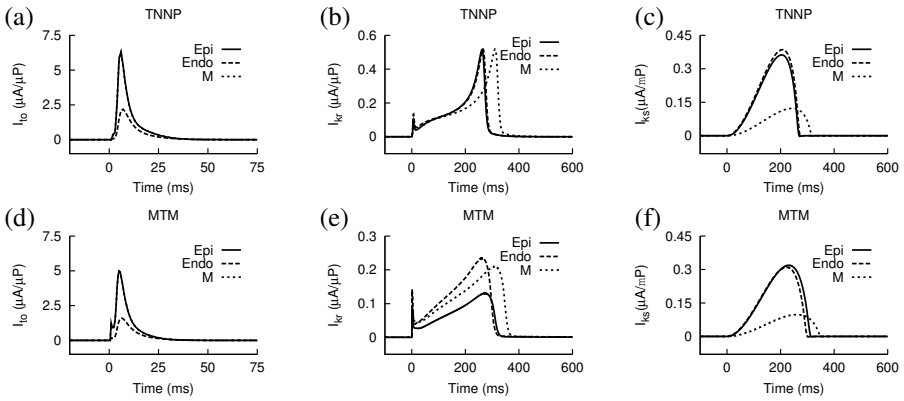

Figure 1. Comparison of transient outward potassium current, the rapid and slow delayed rectifier currents produced by TNNP model (a, b and c) with those reproduced by the modified TNNP model (d, e and f).

is coupled to the open conformation transition. Full details of this model scheme can be found by Wang *et al.* [7]. In the present study, the transition rates of inactivation were refined by characterizing the recovery from inactivation to the first open conformation as a weakly voltage-dependent process.

2.2. Electrical properties of ventricular myocytes

As demonstrated in the study of Viswanathan *et al.* [10], APD differences are reduced when cells are electrotonically coupled in a multicellular fiber through resistive gap junction. Thus, for each type of cells, we used 2D-sheet of tissues consisting a group of cells instead of a single cell to study the properties of AP and the underlying cellular ionic processes. Mathematically, the electrical activity in tissue is described by the bidomain equations,

$$C_m \frac{\partial V_m}{\partial t} = -\sum_{k=1}^{N} Ion_k - \frac{1}{\beta}\nabla \cdot \sigma_e \nabla V_e \qquad (1)$$

$$\nabla \cdot (\sigma_i \nabla V_e) + \nabla \cdot (\sigma_i \nabla V_m) = -\nabla \cdot (\sigma_e \nabla V_e) \qquad (2)$$

where, σ_i and σ_o are intracellular and extracellular conductivities, and V_m and V_e are membrane and extracellular potentials, and C_m is the capacitance per unit area, and β the ratio of membrane surface area to tissue volume. The term $\sum_{k=1}^{N} Ion_k$ in Equation (1) is the sum of all currents participating in the modulation of action potential activity. Equations (1)-(2) are approximated with finite differences.

2.3. Transmural distribution of potassium channels

The cell-specific expression of ion channel proteins has been reported for ventricular myocytes in many species [8, 9]. In the present study, the variable transmural expression of Ito was specified based on the experimental data of Zicha *et al.* [8]. In particular, a heterogeneity of IKr expression (0.55:0.83:1 for Epi:M:Endo) in human ventricular myocytes [9] was introduced into the modified model. A range of ratios from 1/4 to 1/6 for IKr density in left ventricular myocytes (human vs. guinea-pig) was examined. The conductances of IKs in all the three types of cardiomyocytes were scaled by a factor 0.7 compared to those specified in TNNP model, i.e., 0.98:0.36:1 for Epi:M:Endo.

3. Results

3.1. Electrical property of outward potassium channels

The electrical properties of major outward potassium channels were computed by use of both the TNNP model and the MTM. Figure 1 presents representative results obtained at a basic cycle length (BCL) of 1000 ms (1 Hz pacing). For Ito and IKs, their densities from the MTM were relatively low in comparison to those reproduced by the TNNP model. Regional difference of IKr density was not apparent in the TNNP model, however, much better reproduced by the MTM. The peak densities of Ito, IKr and IKs at 1 Hz pacing are summarized in Table 1. The average IKr density from the TNNP model was 0.0458 pA/pF (Epi), 0.0475 pA/pF (Endo) and 0.0542 pA/pF (M)

Table 1. Current densities (pA/pF) of Ito, IKr and IKs.

	MTM			TNNP		
Cell	Ito	IKr	IKs	Ito	IKr	IKs
Epi	4.938	0.192	0.305	6.329	0.515	0.362
M	4.881	0.229	0.096	6.253	0.519	0.123
Endo	1.597	0.235	0.310	2.190	0.519	0.386

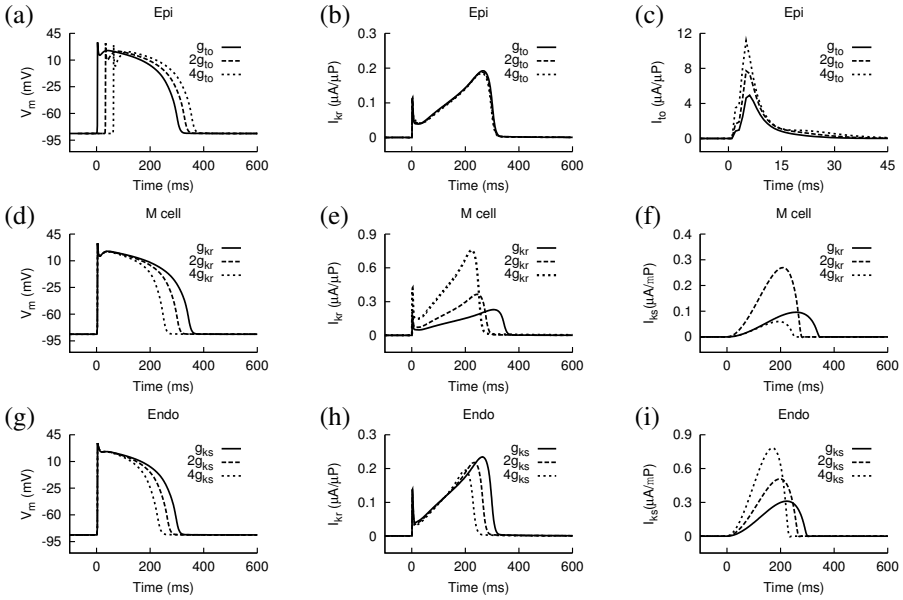

Figure 2. Effect of varying conductivities of the individual channels under 1-Hz pacing. Changes of AP (a), IKr (b) and Ito (c) in Epi with varying Ito conductance (g_{to}); Changes of AP (d), IKr (e) and IKs (f) in M with varying IKr conductance (g_{kr}); Changes of AP (g), IKr (h) and IKs (i) in Endo with varying IKs conductance (g_{ks}).

and those from the MTM were only slightly reduced, i.e., 0.0321 pA/pF for Epi, 0.0386 pA/pF for Endo and 0.0442 pA/pF for M cells.

3.2. Ionic remodeling in cardiomyocytes

Using the MTM model, we investigated interdependence of Ito, IKr and IKs in the determination of AP by varying the conductance of each channel. The ionic remodeling of these channels contribute to AP changes in different ways. An increase in Ito density by 2-fold and 4-fold (Figure 2c) reduced the AP upstroke (Figure 2a), however, exerted neither significant influence on the AP duration of all the three types of cells, nor on the densities of IKr (Figure 2b) and IKs (not shown). An increase in either IKs or IKr shortened APD (Figures 2d and 2g). In Epi and Endo cells, the increase of either IKr or IKs tended to suppress one another progressively, as shown in Figure 2h and Figure 2i. In M cells, an increase of IKs suppressed IKr (not shown), however, an increase of IKr caused IKs changes in different ways: a coincident augmentation of IKs density and a left-shift of peak IKs with a 2-fold increase in IKr, and a reduction of IKs density and a right-shift of peak density with a 4-fold increase in IKr, as shown in Figure 2f.

3.3. Rate dependence of APD

The rate dependence of Epi, Endo and M cells were examined at the pacing frequencies of 1.3 Hz (BCL 750 ms), 1 Hz (BCL 1000 ms), 0.5 Hz (BCL 2000 ms). APD from the TNNP model at a BCL of 750 ms was 270 ms for Epi, 273 ms for Endo and 317 ms for M. In contrast, with a conductance ratio (Epi:Endo:M) of 0.0065:0.0078:0.0071 for IKr, 0.1715:0.1715:0.0434 for IKs and 0.2099:0.0521:0.2099 for Ito, the MTM reproduced an APD of 295 ms for Epi, 292 ms for Endo and 332 ms for M cells. The results at the pacing frequencies of 0.5 Hz and 1 Hz are summarized in Table 2. With a change of frequency from 1 Hz to 0.5 Hz, APD in M cells increased by 9.3% from the MTM, and only 4.4% by the TNNP model. The response of AP to single channel blockade in different types of cells was also verified based on the TNNP model and the MTM. The APD prolongation in response to IKr and IKs block at 1 Hz and 0.5 Hz are listed in Table 3. By the MTM model at 1 Hz, a 100% block of IKr led to a prolongation of APD90 (AP duration at 90% repolarization) by 11% in Epi, 23% in M and 15% in Endo cells, whereas a 100% block of IKs caused a prolongation of APD90 by 27% in Epi, 9.5% in M and 24% in Endo

Table 2. APD at 0.5 Hz and 1 Hz pacing frequencies.

	MTM		TNNP	
Cell	1 Hz	0.5 Hz	1 Hz	0.5 Hz
Epi	303 ms	323 ms	272 ms	280 ms
M	344 ms	376 ms	321 ms	335 ms
Endo	299 ms	319 ms	275 ms	283 ms

cells, respectively.

4. Discussion

Zwermann has reported there exists a transmural difference of IKr current density in human ventricular myocytes [9]. The transmural difference has also been evidenced in other experimental studies based on the expression of IKr channel protein in canine and human myocytes [8]. With a maximum IKr conductance of 0.0043 nS/pF for Epi, 0.0078 nS/pF for Endo and 0.0065 nS/pF for M, the MTM was able to reproduce an APD of 313 ms in Epi, 300 ms Endo and 349 ms in M cells at 1 Hz pacing. Compared to the TNNP, the MTM reproduced APDs closer to experimental data recorded from human left ventricular preparations paced at a BCL of 1 s (324 ms for Epi, 316 ms for Endo and 432 ms for M) [11].

Table 3. Response to simulated IKr and IKs block.

	IKr Block		IKs Block	
Cell	TNNP	MTM	TNNP	MTM
Epi	42.47 ms	34.81 ms	82.63 ms	85.35 ms
M	77.68 ms	79.90 ms	33.59 ms	26.44 ms
Endo	42.71 ms	45.34 ms	90.62 ms	72.63 ms

It has been suggested that IKs plays a role in limiting excessive APD lengthening when ion channels such as IKr are compromised by disease or drugs [3], whereby an available reserve of IKs accounts for the molecular mechanism. Our study demonstrated that the ionic remodeling of IKr and IKs could balance somewhat the increase or decrease of one another in Epi and Endo, thus helping prevent AP prolongation. Nevertheless, there was a counter-intuitive behavior of IKs in response to IKr change in M cells. An excessive decrease of IKr in M led to a decrease of IKs, thus contributing to AP prolongation.

The TNNP model has major drawbacks in reproducing the APD difference and APD rate dependence. The current densities for IKs and IKr are substantially larger than experimentally measured densities [4]. By replacing the native IKr formulation with our newly developed allosteric kinetic model, the MTM model could reproduce larger APD differences, while the current densities of IKr and IKs and Ito are close to the physiological ranges.

5. Conclusions

In summary, the modified TNNP model reproduced APD, the differences in APD and the rate dependence between Epi, Endo and M cells much closer to the experimental observations. Ito exerted an effect on the early phase of AP, however, had no significant influence on APD. Our results suggested that a coincident decrease of IKs with excessive decrease of IKr in M would be a substrate of the high susceptibility of M cells to APD prolongation.

References

[1] Bondarenko VE, Szigeti GP, Bett GCL, Kim SJ, Rasmusson RL. Computer model of action potential of mouse ventricular myocytes. Am J Physiol Heart Circ Physiol 2004; 287(3):H1378–1403.

[2] Decker KF, Heijman J, Silva JR, Hund TJ, Rudy Y. Properties and ionic mechanisms of action potential adaptation, restitution, and accommodation in canine epicardium. Am J Physiol Heart Circ Physiol 2009;296(4):H1017–1026.

[3] Silva J, Rudy Y. Subunit interaction determines IKs participation in cardiac repolarization and repolarization reserve. Circulation 2005;112(10):1384–1391.

[4] ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. Am J Physiol Heart Circ Physiol 2004;286(4):H1573–1589.

[5] Weiss D, Seemann G, Keller D, Farina D, Sachse F, Dossel O. Modeling of heterogeneous electrophysiology in the human heart with respect to ecg genesis. Computers in Cardiology 2007;34:49–52.

[6] Xia L, Zhang Y, Zhang H, Wei Q, Liu F, Crozier S. Simulation of brugada syndrome using cellular and three-dimensional whole-heart modeling approaches. Physiological Measurement 2006;27(11):1125–1142.

[7] Wang C, Beyerlein P, Hammer P, Krause A, Nugent C, Dubitzky W. Allosteric interaction of rapid delayed rectifier protein and its role in cardiac repolarization. Computers in Cardiology 2008;35:589–592.

[8] Zicha S, Xiao L, Stafford S, Cha TJ, Han W, Varro A, Nattel S. Transmural expression of transient outward potassium current subunits in normal and failing canine and human hearts. The Journal of Physiology 2004;561(3):735–748.

[9] Zwermann L. Kardiale Delayed Rectifier Kaliumkanle: Bedeutung in humanem Myokard, Speziesunterschiede, transmurale Verteilung und Regulation bei Herzinsuffizienz. Ph.D. thesis, Medizinischen Fakultaet der Ludwig-Maximilians-Universitaet zu Muenchen, 2007.

[10] Viswanathan PC, Shaw RM, Rudy Y. Effects of IKr and IKs heterogeneity on action potential duration and Its rate dependence: a simulation study. Circulation 1999; 99(18):2466–2474.

[11] Pereon Y, Demolombe S, Baro I, Drouin E, Charpentier F, Escande D. Differential expression of KvLQT1 isoforms across the human ventricular wall. Am J Physiol Heart Circ Physiol 2000;278(6):H1908–1915.

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