Study of Simulation Technology for Myocardial Ion Channels on Pharmacological Effects

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Abstract

Computational models of the mammalian ventricular myocyte have become important tools for understanding the biophysical basis of the ventricular action potential (AP), for relating changes in gene/protein expression and effects of gene mutations to alterations of AP and calcium transient morphology, and for investigating mechanisms of arrhythmia. We established the computational model of heart failure and simulated the electrophysiological effects on the action potential of the main myocardial ion channels according to the action of class III antiarrhythmic drugs. This work could be used to study the pharmacological effects of heart disease drugs on transmural propagation and to develop a simulation tool for developing the new drugs for heart diseases.

1. Introduction

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Congestive heart failure (CHF) is generally defined as the inability of the heart to supply sufficient blood flow to meet the needs of the body [1]. Nearly 5 million American people experience CHF and 250 000 die annually. The incidence and prevalence have continued to increase with the aging of the US population [2]. Despite remarkable improvements in medical therapy the prognosis of patients with myocardial failure remains poor with over 15% of patients dying 1 year of initial diagnosis and greater than 80% 6 year mortality [3]. Patients with heart failure experience a number of changes in the electrical function of the heart that predispose to potentially lethal cardiac arrhythmias. Action potential prolongation, the result of functional down-regulation of K currents, and aberrant Ca^{2+} handling is a recurrent theme. Significant alterations in conduction and activation of a number of initially adaptive but ultimately maladaptive signaling cascades contribute to the generation of a highly arrhythmogenic substrate [4].

Congestive heart failure changes ion channel distribution and function, with significant electrophysiological consequences [5], and sudden arrhythmic death contributes importantly to CHF-related mortality [6]. Abnormalities of atrial [7] and ventricular [8] electrophysiology in patients' hearts have been recognized for nearly half a country. Remodeling of ventricular myocyte electrophysiology in both human and animal models of HF is well-described [9]. Prolongation of the action potential (AP) is a hallmark of cells and tissues isolated from failing hearts independent of the cause, which has been observed in isolated myocytes and intact ventricular preparations [10]. The AP prolongation is heterogeneous, resulting in the exaggeration of the physiological inhomogeneity of electrical properties in the failing heart [11].

Patch clamp technology is the common method to study the electrophysiology of cells. We want to take advantage of this technology to do more practical experiments. The operation of patch clamp is complicated. So we have integrated the experimental data to build a cardiac model, which could demonstrate the AP activity of heart. In this paper, we construct a platform based on the model above to simulate the variations in AP under heart failure, and to test some pharmacological effects of heart disease medicine, whose electrophysiological properties are known.

2. Model description

On We assumed that each current across the cell membrane was a linear function of the membrane potential, with a driving force given by the corresponding Nernst potential (Equ.1)

$$I_X = g_X (V - V_X) \quad (1)$$

Where $V_X = (\frac{RT}{F})\ln(\frac{[X^+]_e}{[X^+]_i})$ is the Nernst potential [12]. Propagation of electrical excitation in cardiac tissue can be described by a non-linear cable equation, a reaction-diffusion-type partial differential equation (2)

$$\frac{\partial V}{\partial t} = \nabla(D\nabla V) - \frac{I_{ion}}{C_m} \quad (2)$$

Here V is the membrane potential in mV, t is the time in ms, ∇ is a spatial gradient operator, D is a diffusion coefficient tensor in mm^2ms^{-1} that characterizes electrotonic spread of voltage, and I_{ion} is the total membrane ionic current density in $mAmF^{-1}$ [13]. Families of cardiac cell models have been developed to describe the voltage- and time-dependent current I_{ion} [14] that reconstruct the action potential V(t). These models can be applied hierarchically, with cell models for action potential properties [15]. According to this principle, we develop a detailed description of I_{ion}, and hence a single cell AP, for canine PF cells by modifying the existing canine endocardial cell model [11] based on experimental data for the kinetics of several major ionic currents in canine PFs[13]. These include the L-type and T-type Ca^{2+} currents, $I_{Ca,L}$ and $I_{Ca,T}$, the transient outward current, I_{to}, the fast and slow delayed rectifier currents, $I_{K,r}$ and $I_{K,s}$, and the inward rectifier K^+ current, $I_{K,1}$ [16].

3. Method

3.1. Simulation of heart failure

We have designed a myocardial ion channel simulation platform (See in Fig.1) based on the computational model above. This platform provides an electrophysiological simulation hierarchically, including purkinje fiber cells, endocardial cells, midmyocardial cells and epicardial cells, under normal condition and drugs when conductance of ion channel have changed.

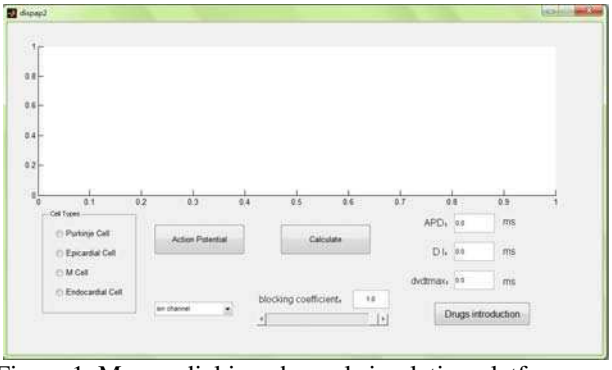


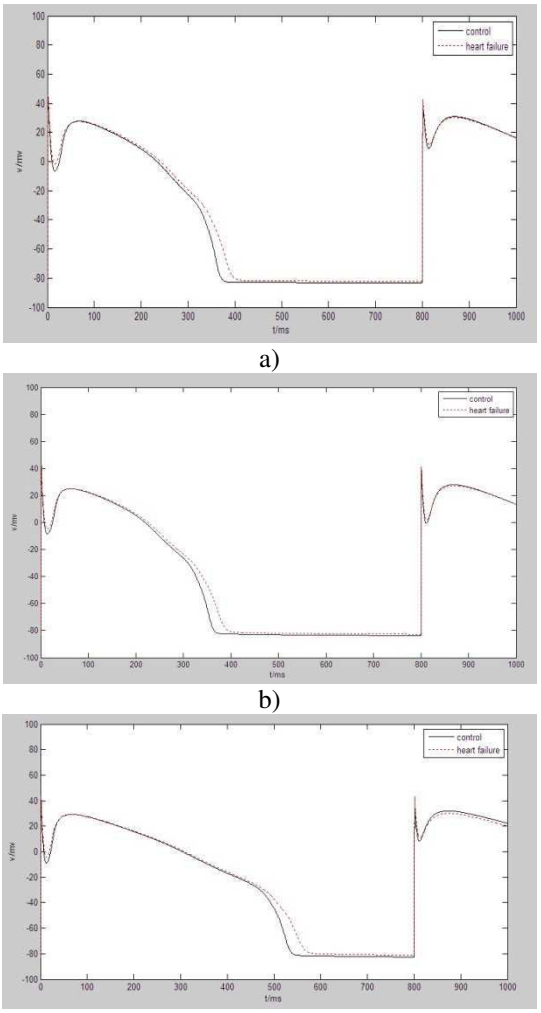
Figure 1. Myocardial ion channel simulation platform.

Many ionic channels remodeling under HF experiment results have been reported. We gathered the reliable conclusions to alter the conductance of the ionic channel. Transient outward current density was reduced in CHF PCs without change in voltage dependence or kinetics. CHF also reduced inward-rectifier current (I_{K1}) density, with no change in form of the current-voltage relationship. Densities of L-type and T-type calcium, rapid and slow delayed rectifier (I_{Kr},I_{Ks}), and Na^+-Ca^{2+}exchange currents were unaltered by CHF, but L-type calcium current inactivation was slowed at positive potentials. Purkinje fiber AP from CHF dogs showed decreased phase 1 amplitudes and elevated plateau voltages and demonstrated twice as much prolongation on exposure to the rapid delayed rectifier blocker as control Purkinje fibers [15]. The ventricular myocyte consists of epicardial, midmyocardial, and endocardial cells, and they perform differently in the electricity activities. Therefore, $\boldsymbol{I_{K1}}$ density was significantly decreased in the three cell types of failing hearts at -70 to -30 mV. I_{K1} density at -60 mV was reduced by 40.9%, 40.7%, and 41.1%, respectively. The slow component of the delayed rectifier K^+ current ($\boldsymbol{I_{Ks}}$) was significantly down-regulated by 57%, 49%, and 58%, respectively, in epicardial, midmyocardial, and endocardial cells, whereas the rapid component of the delayed rectifier K^+ current was not altered. I_{to1} was decreased by 43%, 45%, and 43%, respectively [17].

The significant differences of the action potential between control and HF (shown in Fig.2) are described by variation of specific ion channel. The action potential characteristic values are also calculated and displayed, including APD_{90}, DI, $(dv/dt)_{max}$. The action potential duration in three kinds of cell in HF is all longer than in control. APD prolongation could be seen in many heart diseases, like Heart failure, myocardial infarction and atrial fibrillation [5]. Moreover, the prolongation in HF is the cause of sudden cardiac death (SCD) [4].

3.2. Simulation of heart disease medicine when heart failure happens

On the basis of the simulation of myocyte under heart failure, we could study the influence on action potential under the heart disease medicine. We will use the pharmacological and electrophysiological effects of the heart diseases to simulate the influence in patients who suffering heart failure. In this experiment, the effects of medicine should be definitely described the conditions in which type of myocyte, in respect that the computational model contains purkinje fiber, epicardial, midmyocardial and endocardial cells. The simulation of drugs for myocardial ion channels works by changing the value of the related parameters in the model above.



a)

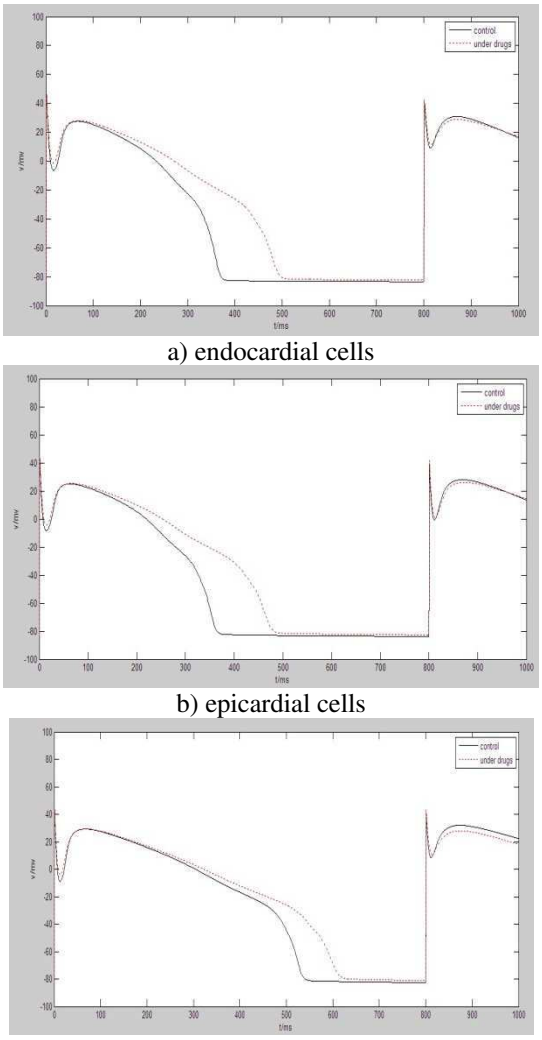
b)

c)

Figure 2. Simulation result of endocardial, epicardial and midmyocardial between the heart failure and control. a) endocardial cells; b) epicardial cells; c) midmyocyte.

Class III agents predominantly block the potassium channels, thereby prolonging repolarization[18]. Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is less likely to interact with tissue that has become refractory). Drugs include: amiodarone, ibutilide, sotalol, dofetilide, and dronedarone.

We reproduced the relative changes to canine action potential characteristics reported by Sicouri et al. [19]: for simulating the application of 100 mM d-sotalol to isolated cells, we scale IKr maximal conductance by 0.5 in endocardial cells, 0.3 in M cells and 0.8 in epicardial cells; for simulating application of amiodarone (30–40 mgkg-1 per day), I_{NaL} maximal conductance was scaled by 0.2 in M cells only, and I_{Ks} maximal conductance was scaled by 0.2 in endocardial and 0.7 in epicardial cells, with I_{CaL} remaining as in control cells [13,14]. The simulation result can be seen in Figure 3. And the action potential duration (90%) of the simulation results are shown in the Table 1.



a) endocardial cells

b) epicardial cells

c) midmyocyte

Figure 3. Simulation result of endocardial, epicardial and midmyocardial between the under drugs when heart failure happens and control. a) endocardial cells; b) epicardial cells; c) midmyocyte.

4. Discussion and conclusion

Based on the experimental results above, heart failure would prolong the APD in epicardial and endocardial cells, change little in midmyocardial cells. And class III antiarrhythmic medicine would also prolong the action potential duration in three types. So even if heart failure may cause arrhythmias, it may be dangerous to take any antiarrhythmic medicine. In case class III antiarrhythmic is taken, the symptom would be worse, and may cause

SCD. Once we know the electrophysiological change of a drug, especially the conductance. So the model could be used to test the Pharmacological effect in ion channel action potential.

Table 1. Action potential duration of ventricular myocyteunder control, hart Failure and with drugs.

	APD90 (control)	APD90 (HF)	APD90 (drug)
EPI	446.85	459.95	542.95
MCELL	586.59	589.84	597.86
ENDO	467.48	479.30	563.81

References

[1] Dorland's Medical Dictionary, Philadelphia: W.B. Saunder, 2008, ISBN: 7117043857.

[2] American Heart Association. Heart disease and stroke statistics-2003, Update. Dallas, Tex: American Heart Association, 2002.

[3] Konstam MA, Remme WJ. Treatment guidelines in heart failure. Prog Cardiovasc Dis 1998; 48: 65-72.

[4] Tomaselli GF, Zipes DP. What Causes Sudden Death in Heart Failure? Circ Res 2004; 95: 754-763.

[5] Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev 2007; 87: 425-456.

[6] Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study. N Engl J Med 1986; 314: 1547-1552.

[7] Van Dam RT, Durrer D. Excitability and electrical activity of human myocardial strips from the left atrial appendage in cases of rheumatic mitral stenosis. Circ Res 1961; 9: 509-514.

[8] Trautwein W, Kassebaum DG, Nelsol RM, Hecht HH. Electrophysiological study of human heart muscle. Circ Res 1962; 10: 306-312.

[9] Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 1999; 42: 270-283.

[10] Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. Circ Res 2003; 93: 638-645.

[11] Fedida D, Giles WR. Regional variations in action potentials and transient outward current in myocytes isolated from rabbit left ventricle. J Physiol 1991; 442: 191-209.

[12] Keener J, Sneyd J. Mathematical Physiology. 2007; 75. ISBN: 0-387-98381-3.

[13] Benson AP, Aslanidi OV, Zhang H, Holden AV. The canine virtual ventricular wall: a platform for dissecting pharmacological effects on propagation and arrhythmogenesis. Progress in Biophys and Molecular Biology 2008; 96: 187-208.

[14] Noble D, Rudy Y. Models of cardiac ventricular action potentials: iterative interaction between experiment and simulation. Philos Trans R Soc London A 2011; 359: 1127-1142.

[15] Han WD. Li CD, Nattel S. Ionic remodeling of cardiac Purkinje cells by congestive heart failure. Circulation 2001: 104: 2095-2100.

[16] Aslanidi OV, Stewart P, Boyett MR, et al. Optimal velocity and safety of discontinuous conduction through the heterogeneous purkinje-ventricular junction. Biopuysical Journal 2009; 97: 20-39

[17] Li GR, Lau CP, Ducharme A, et al. Transmural action potential and ionic current remodeling in ventricles of failing canine hearts. Am J Physiol Heart Circ Physiol 2002; 283: H1031-H1041.

[18] Lenz TL, Hilleman DE. Dofetilide, a New Class III Antiarrhythmic Agent. Pharmacotherapy 2000; 20: 776-786.

[19] Sicouri S, Moro S, Litovsky S, Elizari MV, Antzelevitch C. Chronic amiodarone reduced transmural dispersion of repolarization in the canine heart. J Cardiovasc Electrophysiol 1997b; 8: 1269-1279.

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