Cellular Modeling and Simulation of Brugada Syndrome

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Abstract

A mathematical model of the action potential (AP) of human ventricular cell is constructed and used in simulation studies of Brugada syndrome. The model is based on Luo-Rudy model, and refined by recent experimental data on major ionic currents, and the formulations of ten Tusscher et al are also introduced into our model. The results show that the endocardial and midmyocardial cells AP have little changes in Brugada syndrome compared with that of normal heart, but the epicardial cell AP changes obviously. We also investigate the temperature dependent and heart rate dependent Brugada syndrome. The results show that when the body temperature increases to 39.5^{o}C or the cardiac length is larger than 1000 ms, the Brugada syndrome epicardial cell APs may appear suddenly change, which is very likely to induce sudden death. The result may explain why some Brugada syndrome patients easily to die suddenly during a febrile state or during the night when they are sleeping. These results are in good accordance with the experiment findings reported in the literatures.

1. Introduction

The discovery of Brugada syndrome (BS) has created a great deal of interest [1-3]. Brugada syndrome is an inherited disease characterized by an ECG ST-segment elevation in leads V1, V2, V3 and a high risk of sudden cardiac death due to ventricular fibrillation. The experimental research of human ventricular myocardium with BS is very limited so far. Therefore, the use of alternative methods such as computer simulations is of great importance. Most previous simulation studies of BS, however, are mainly based on animal cell models, not human cell models. These animal models provide good references for simulations studies for BS, whereas, as we know that animal hearts used for simulation studies may differ significantly from human hearts (heart size, heart rate, action potential shape, duration, and restitution, vulnerability to arrhythmias, etc). So it needs to use human cell models to investigate the electrophysiological mechanism of BS in simulation studies.

Based on Luo-Rudy model [4-7] and ten Tusscher et al.'s model [8], and refined by recent experimental data on some of the major ionic currents, we constructed a mathematical model of the action potential (AP) of human ventricular cells. This model also includes a basis calcium dynamics [9], allowing for the realistic modeling of calcium transients, calcium current inactivation, and the contraction staircase. According to BS physiological mechanism, simulations are conducted in isolated epicardial, endocardial, and midmyocardial (M) cells, which are simulated by mainly varying the maximum conductance (density) of the slowly activating delayed-rectifier potassium current, the transient outward current and L-type Ca current. Incorporated our model with the temperature sensitivity coefficient Q_{10}, we also investigate the different ventricular cell AP change due to body temperature increasing. Based on our simulation study, we also explain the reason that BS patients often break out during the night when they are sleeping.

2. Methods

The cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps. The electrophysiological behavior of a single cell can hence be described with the following differential equation:

$$dV / dt = -(I_{ion} + I_{stim}) / C_m \qquad (1)$$

where V is voltage, t is time, I_{ion} is the sum of all transmembrane ionic currents, I_{stim} is the externally applied stimulus current, and C_m is cell capacitance per unit surface area. I_{ion} given by the following equation:

$$I_{ion} = I_{na} + I_{ki} + I_{to} + I_{kr} + I_{ks} + I_{caL} + I_{naCa} + I_{naK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa} + I_{naL} \qquad (2)$$

where I_{naCa} is Na^+/Ca^{2+} exchanger current, I_{naK} is Na^+/K^+ pump current, I_{pCa} and I_{pK} are plateau Ca^{2+} and K+ current, and I_{bCa} and I_{bK} are background Ca^{2+} and K+ currents.

The general approach to modeling the heart cell is similar with that of the dynamic Luo-Rudy model of ventricular cells [4-7], but an additional current of I_{naL} is incorporated into our model and I_{naCa} is adopted from Weber et al [10] which is based on human heart data. Other major ionic currents are adopted from the ten Tusscher et al.'s model [8] and modulated in such a way that simulations are widely consistent with available human data.

Simulations are conducted in isolated epicardial, endocardial, and midmyocardial cells, which are implemented by changing the maximum conductance, G_{ks}, of the slowly activating delayed-rectifier potassium current I_{ks} [9]. Ito, the transient outward current [11-12], is incorporated into our model, with maximum conductance (G_{to}) of 0.294mS/uF. The density ratio of I_{ks} to I_{kr} (the rapidly activating delayed rectifier) G_{ks}/G_{kr} is set to be 8. In M cells, G_{to}=0.294mS/uF and G_{ks}/G_{kr}=2. In endocardial cells, G_{to}=0.073 and G_{ks}/G_{kr}=5.

The maximal conductance of IcaL is decreased by 20% to 50% [12-13] in epicardial cells in order to obtain realistic durations of simulated action potentials.

We multiply both rate constants of inactivation gate h of I_{na} by a factor of 2, while leaves steady-state value of Ina unchanged. The faster inactivation of Ina resulted in a 32% [13-14] smaller peak current during upstroke of AP.

3. Results

3.1. APs simulation results of normal epicardial, endocardial and M cells

Wettwer et al [12] found that I_{to} current and I_{Ks} current are different in epicardial, endocardial and M cells. In endocardial cell, G_{to} is 0.073nS/pF, different from that in epicardial cell of 0.294 nS/pF. In M cell, the G_{to} is same as that of epicardial cell. In addition, Pereon et al [15] found that I_{Ks} in epicardial cell is similar with that in endocardial cell (G_{ks} =0.245nS/pF), but greatly different from that in M cell (G_{ks} =0.062 nS/pF). Based on these findings, we simulated APs of normal epicardial, endocardial and M cells as shown in Fig.1.

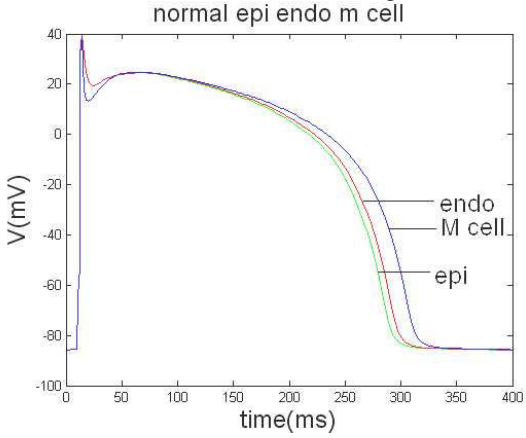
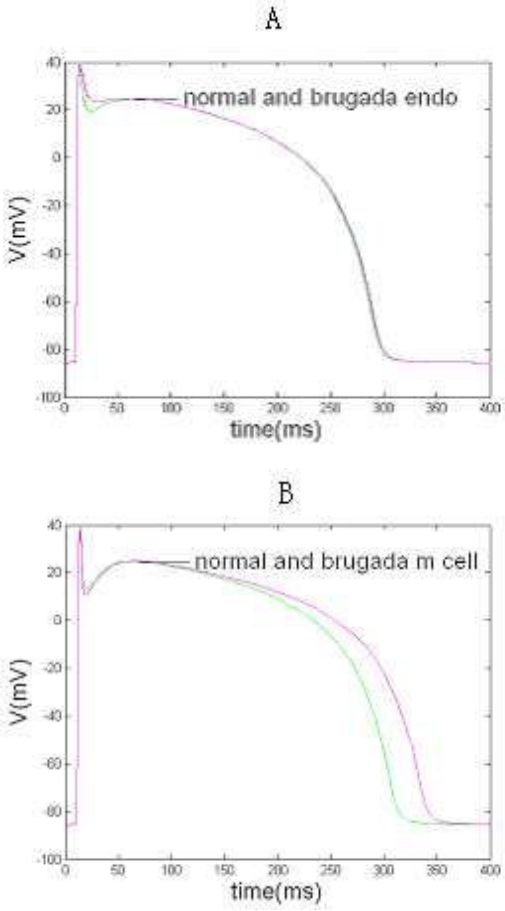


Fig.1. Simulated APs of normal epicardial, endocardial and M cells.

3.2. APs simulation results of epcardial, endocardial and M cells with BS

From Fig.2A and Fig.2B, we can see that normal endocardial and M cell APs are very similar with those of Brugada syndrome. From Fig.2C, we can see that BS epicardial cell APs are greatly different from that of normal epicardial cell. In BS epicardial cells, Na current greatly decreases compared with that of normal cell, which make the maximum AP peak value decreases. At the same time, the increasing I_{to} current destroys the current balance during the plateau, all these reasons lead to an accentuation of the spike and dome morphology of the action potential, resulting in a delay in the development of the dome, and the action potential notch disappears. A further shift in the balance of current leads to loss of the action potential dome and marked abbreviation of the epicardial response. The dome fails to develop because the outward currents flowing at the end of phase 1 overwhelm the inward currents that normally give rise to the secondary upstroke and action potential plateau. Our simulation results are similar with the experiment result of Antzelevitch et al [16-18]. From Fig.2D, we can see that with I_{to} increasing, in the beginning, AP change is not obvious, but if the I_{to} current value increases to some degree, we can find that there is a sudden AP change. This AP sudden change may explain why Brugada syndrome patients are easy to sudden cardiac death.



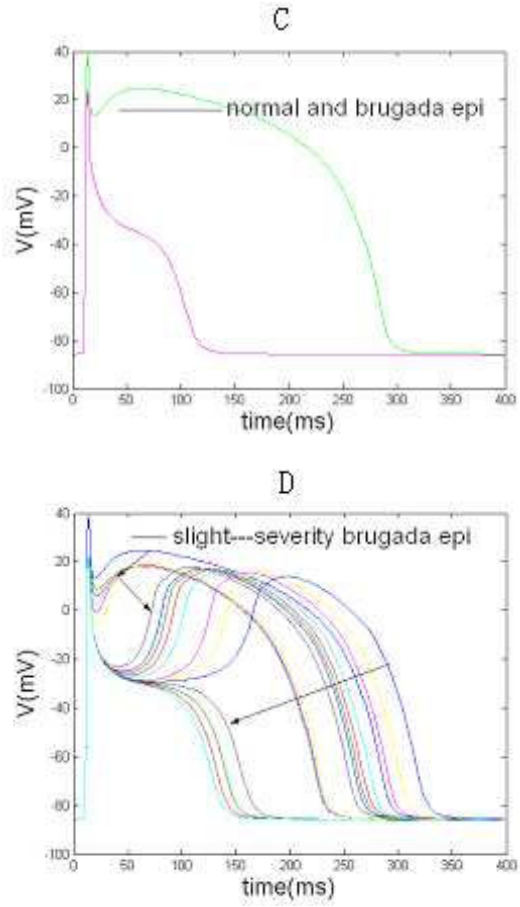


Fig.2. Simulated APs of epicardial, endocardial and M cells with Brugada syndrome. A: Normal and Brugada endocardial APs. B: Normal and Brugada M cell APs. C: Normal and Brugada epicardial APs. D: From silght to severity Brugada epicardial APs.

3.3. Simulation of temperature dependent Brugada syndrome

Clinical findings show that some BS patients are easy to sudden death during a febrile state. This means BS is temperature dependent. By multiplying a temperature sensitivity coefficient Q_{10} [19] to inactivation gate h in I_{na}, to G_{caL} in I_{caL}, and to G_{to} in I_{to}, respectively, we can simulate BS epicardial APs with different body temperatures. Fig.3 shows the simulation results of BS epicardial APs at the body temperatures range from 37 ^{o}C to 40 ^{o}C. From Fig.3, we can see that it is very similar with Fig.2D, the APs change with the temperature increasing, when the temperature increases to some value, the APs appear a sudden change. In our simulation investigation, this body temperature value is 39.5^{o}C, BS patient maybe very easy to sudden death his/her body temperature increases to 39.5^{o}C.

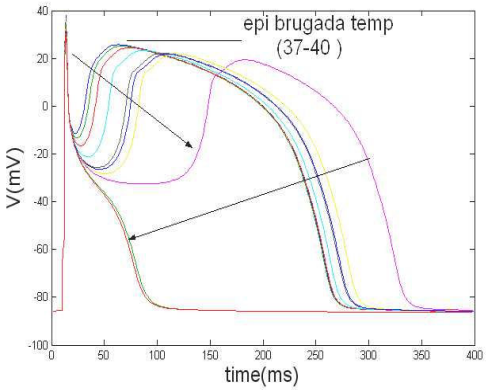
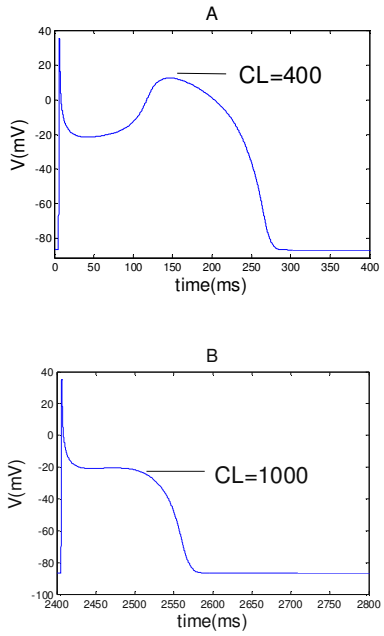


Fig.3. Simulated BS epicardial APs at different body temperatures.

3.4. Simulation of cardiac length dependent Brugada syndrome

Why BS patients are easy to sudden death during night? One of the general clinical explanations is that the activity of vagus nerve increases during night, as the heart rate decreasing, the activity of I_{to} increasing, thus lead to induce the Brugada syndrome. In other words, BS is very likely heart rate dependent. Based our model, we investigated the BS epicardial cell AP at different heart rates as the results shown in Fig.4. From Fig.4, we can see that the APs change obviously with heart rate decreasing. When the cardiac length (CL) is larger than 1000 ms, the action potential plateau duration of BS epicardial cell may disappear, which may induce BS sudden death.



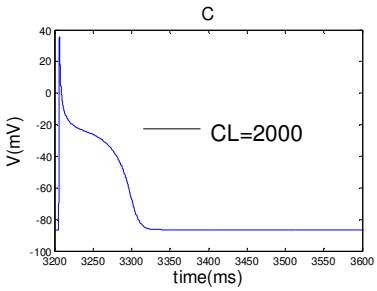


Fig.4. Simulated APs of BS epicardial cell at three different cardiac lengths.

4. Discussion and conclusions

In this study, a mathematical model of the human ventricular cell action potential was constructed and used to simulate Brugada syndrome. The results show that the endocardial and M cells AP have little changes in Brugada syndrome compared with that of normal heart, but the epicardial cell AP changes obviously. The Brugada syndrome is temperature dependent and heart rate dependent. Our simulation results show that when the body temperature increases to 39.5°C or the cardiac length is larger than 1000 ms, the Brugada syndrome epicardial cell APs may appear a sudden change, which is very likely to induce sudden death. The simulation results are in good accordance with the experiment findings reported in the literatures. Our simulations suggest that the proposed model can reproduce a variety of electrophysiological behaviors and thus provide a basis for studies of Brugada syndrome.

Acknowledgements

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