A simulation study on the effect of antiarrhythmic drugs during myocardial infarction

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Abstract

Cardiovascular diseases can lead to sudden cardiac death, most of which were caused by arrhythmias induced by myocardial infarction (MI). However, current simulation researches mainly focus on the effect of myocardial fibrosis on wave propagation in tissues, and few studies gave attention to antiarrhythmic drugs for the treatment of MI. Therefore, the aim of this study is to simulate the therapeutic effect of common antiarrhythmic drugs. Firstly, this paper constructed the human ventricular cell model in MI based on the TP06 model according to the experimental data. Then, the single-cell model was remodeled by adding the change of ion currents after drug action. We simulated the therapeutic effects of the two drugs (telmisartan and nifedipine) at different concentrations, and compared the changes of parameters (APA, APD, RP, dV/dt_{max}) before and after the drug action. At the same time, the co-action of the two drugs were simulated on the cell model in MI. The simulation results showed I_{Na} agonist telmisartan could increase the maximum depolarization rate of cells in MI, but the drug had no effect on APD. On the contrary, I_{CaL} blocker nifedipine mainly affected the APD of myocardial cells and had no effect on the depolarization stage. Under the combined action of the two drugs, APA, RP and APD of myocardial cells in MI basically returned to normal values, and dV/dt_{max} returned to 85% of the normal value. Although at present, there are no drugs that only act on these two targets (I_{Na} and I_{CaL}), new antiarrhythmic drugs acting on these two targets can be designed to treat MI diseases in the future.

1. Introduction

Cardiovascular disease caused more than 4 million deaths in Europe in 2016 [1], most of which were caused by arrhythmias induced by MI [2, 3]. Hypoxia following MI can change the metabolic mode of myocardial cells, and the change of metabolic mode will promote the reconstruction of electrophysiological characteristics of cardiomyocytes, which will lead to arrhythmias[2, 4]. When MI is serious, it will lead to necrosis of some myocardial cells. After necrosis, the cells will be replaced by fibroblasts to stabilize the heart structure [5, 6]. However, when the proportion of fibrotic cells is high, it will slow down the wave propagation on the heart tissue and induce the occurrence of re-entry [7, 8].

The electrophysiological characteristics of cardiomyocytes will also change due to the difference of cell metabolic mode in MI. Experimental studies show that the APD of cells is prolonged in MI, which is the main matrix for inducing arrhythmias [2, 4, 9-11]. These damaged but not necrotic cardiomyocytes can still restore their electrophysiological function at the action of drugs. At present, the drug treatment of cardiovascular diseases mainly includes three categories: β receptor blockers, nitrates and calcium antagonists, which can dilate blood vessels and reduce myocardial oxygen demand [12]. There are few simulation studies related to antiarrhythmic drugs in MI, which restore the electrophysiological function of myocardial cells by acting on ion channels.

Therefore, the purpose of this study is to simulate the effect of common antiarrhythmic drugs (telmisartan and nifedipine) on damaged cardiomyocytes in MI, and provide a treatment scheme which can repair the electrophysiological function of damaged cells in MI. In this paper, the change of the electrophysiological function of damaged cardiomyocytes in MI was simulated when telmisartan and nifedipine acted alone and together at different concentrations. This study could provide new ideas for the drug treatment of MI diseases.

2. Method

2.1. Single cell models in MI

The TP06 model [13] was used in our simulation as shown in equation (1). According to experimental data in MI, I_{Na}, I_{CaL}, I_{Kr} and I_{Ks} decreased by 62% [14], 69% [15], 70% [16] and 80% [16], respectively, compared with normal values.

$$I_{ion} = I_{Na} + I_{CaL} + I_{to} + I_{Kr} + I_{Ks} + I_{K1} + I_{NaCa} +$$
$$I_{NaK} + I_{pCa} + I_{pK} + I_{bNa} + I_{bCa} \qquad (1)$$

Where, I_{ion} represents the total transmembrane current.

The stimulation strength on the single cell was $-86.2\,\text{pA/pF}$, the stimulus duration was 1 ms, and the time step is 0.02ms.

2.2. The cell model of drug action

The calculation of the blocking ratio of drugs to each ion channel was based on the single channel blocking theory proposed by Bernnan et al. [17], as shown in equation (2).

$$V = \frac{1}{1 + \left(D / IC_{50}\right)^{nH}} \qquad (2)$$

Where, V is the blocking ratio of drugs to ion channels, D represents the drug concentration, IC_{50} refers to the corresponding drug concentration when the blocking ratio is 50%, and nH refers to hill constant.

3. Results

3.1. Simulation results of antiarrhythmic effect of telmisartan in MI

Firstly, the effect of telmisartan on myocardial cells in MI was simulated. Telmisartan is an angiotensin II receptor antagonist [18], which is mainly used to treat hypertension and protect cardiovascular system. The side effects of telmisartan are that it may cause bradycardia, premature beat or hypotension. In addition, relevant studies have shown that telmisartan can be used as I_{Na} agonist [19], and its effect on ion currents was shown in Table 1.

Simulation results in Figure 1 showed that telmisartan can restore the depolarization rate of damaged cardiomyocytes and increased the conduction velocity in the tissue. With the increase of the concentration of telmisartan, the effect of cell electrophysiological function recovery was better. Although telmisartan could play a certain therapeutic effect in the MI stage, it basically had no effect on the repolarization stage of cells. So, it is still necessary to further explore a better treatment scheme.

Table 1. The effect of high and low doses of telmisartan on ion channels.

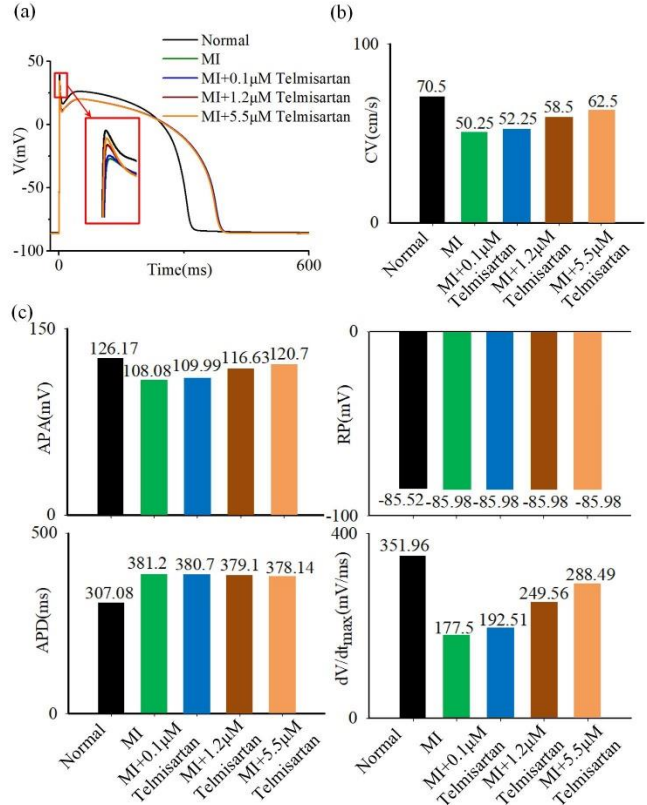| Drug name	Telmisartan
IC_{50}	1.2μM
nH	1.1
	180%（5.5μM）
Conductance	150%（1.2μM）
	110%（0.1μM）
Reference	Chang et al.[19]

Figure 1. (a) Action potential, (b) parameter values on single cells, and (c) CV in MI treated with telmisartan at different doses.

3.2. Simulation results of antiarrhythmic effect of nifedipine in MI

Next, we simulated the therapeutic effect of I_{CaL} blocker on myocardial cells in MI. The representative drug nifedipine was selected and its effect on I_{CaL} was shown in Table 2. The simulation results shown in Figure 2 showed that nifedipine can shorten the APD of the action potential and restore the APD to some extent. However, the drug cannot restore the electrophysiological function of the damaged cells in the depolarization stage, so, there are still some limitations.

Table 2. The effect of high and low doses of nifedipine on ion channels.

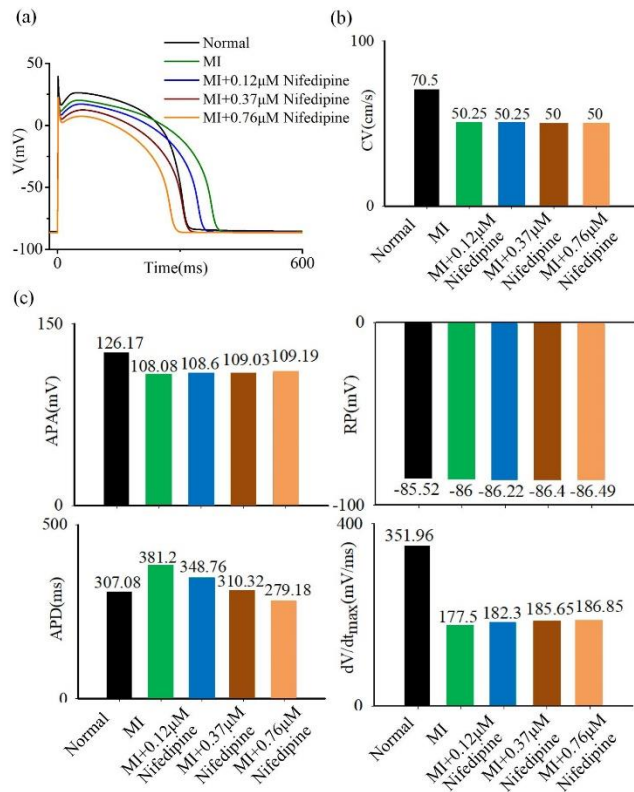| Drug name	Nifedipine
IC_{50}	0.3μM
nH	1.1
Conductance	70%（0.12μM）
	45%（0.37μM）
	30%（0.76μM）
Reference	Shen et al.[20]

Figure 2. (a) Action potential, (b) parameter values on single cells, and (c) CV in MI treated with nifedipine at different doses.

3.3. Simulation of co-action of telmisartan and nifedipine on myocardial cells in MI

The above simulation results showed that telmisartan and nifedipine can play a certain therapeutic effect, but the effect is unilateral. Therefore, this paper will further simulate the therapeutic effect of the two drugs when acting together. Simulation results in Figures 1 and 2 showed that the effect of telmisartan at 5.5 μM and nifedipine at 0.37 μM was the best. Therefore, these two concentrations were used to simulate the recovery of myocardial cells in MI when the two drugs act together.

The simulation results in Figure 3 showed that when

telmisartan and nifedipine were used together, they can restore the electrophysiological function in the depolarization and the repolarization stage of myocardial cells at the same time. Under the combined action of the two drugs, the values of APA, RP and APD of action potential in MI basically returned to normal, and dV/dt$_{max}$ returned to 85% of the normal value, as shown in Figure 3. Therefore, the above experimental results show that telmisartan and nifedipine can restore the electrophysiological function of damaged cells from different aspects in the treatment of MI diseases, and the therapeutic effect of the two drugs is significant when used together.
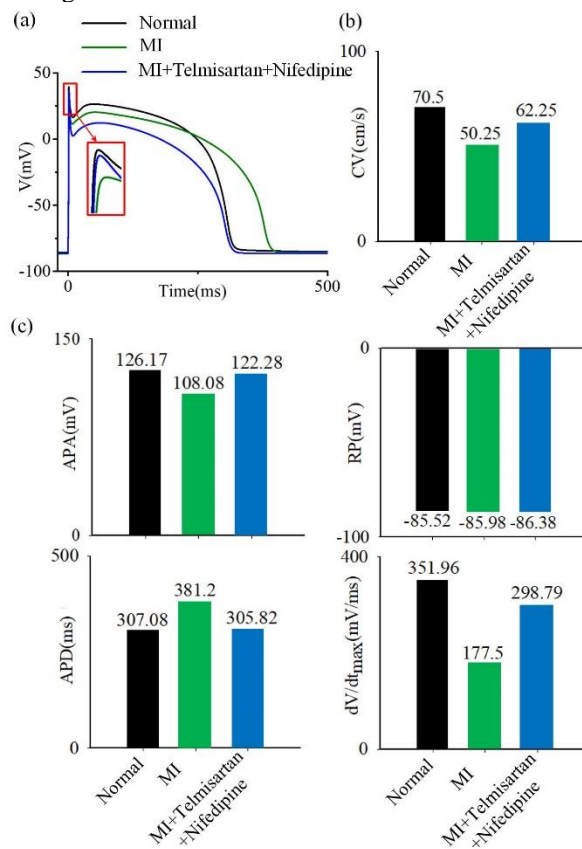

Figure 3. (a) Action potential, (b) parameter values on single cells, and (c) CV in MI treated with 5.5μM telmisartan and 0.37μM nifedipine.

4. Discussion and conclusions

The aim of this study was to use an electrophysiological model to simulate the therapeutic effect of common antiarrhythmic drugs for MI diseases. Furthermore, our study could provide a new treatment scheme that can repair the electrophysiological function of damaged cells in MI.

Our research showed that I_{Na} agonist telmisartan and I_{CaL} blocker nifedipine can restore the

electrophysiological characteristics of damaged cardiomyocytes in MI from different aspects. When the two drugs act together, the therapeutic effect is significant. Although at present, there are no drugs that only act on these two targets (I_{Na} and I_{CaL}), new antiarrhythmic drugs can be designed for these two targets to treat MI diseases in the future.

Acknowledgements

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