Pis'ma v ZhETF, vol. 108, iss. 8, pp. 580 – 581

Cardiac excitation waves under strong hyperkalemia condition

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Submitted 18 September 2018

DOI: 10.1134/S0370274X18200110

Introduction. Ischemia in the heart can lead to severe consequences, including ventricular fibrillation and cardiac arrest. With ischemia, blood supply is disturbed; as a result of which hypoxia, acidosis and hyperkalemia occur in the affected area [1]. The resulting arrhythmia leads to impaired pump function, the further progression of ischemia and, as a result, death within a few minutes [2]. Each of the above mechanisms operates at different time scales [3], however, the contribution of these mechanisms in a patient is difficult to distinguish. In this paper, we confine ourselves to examining a biophysical model of the changes in the dynamics of cardiac excitation waves in hyperkalemia condition, playing a decisive role in the first minutes of ischemia development.

Normal blood levels of potassium are critical for maintaining normal heart electrical rhythm. Both low blood potassium levels (hypokalemia) and high blood potassium levels (hyperkalemia) can lead to abnormal heart rhythms. The most important clinical effect of hyperkalemia is related to electrical rhythm of the heart. Acute episodes of hyperkalemia commonly are triggered by the introduction of a medication affecting potassium homeostasis; illness or dehydration also can be triggers. Low potassium levels may cause acquired long QT syndrome (LQTS) easily manifesting in recorded electrocardiogram (ECG). However, taking drugs increasing potassium level in overdose and maintaining diet increasing potassium level may be harmful as well and lead to hyperkalemia and eventually to hyperkalemic cardiac arrest [4].

Thus, hyperkalemia is the most dramatic and life-threatening electrolyte disorder. There appears to be a direct effect of elevated potassium on some of the potassium channels by increasing their activity and speeding up membrane repolarisation. Also, hyperkalemia causes an overall membrane depolarisation that inactivates sodium channels. The faster repolarisation of the cardiac AP causes inactivation of sodium channels causes slow cardiac conduction [1].

The aim of this work was to investigate the effect of potassium concentration on the excitation wave in the cardiac tissue. Results were obtained, both in the experimental model, which is a monolayer of neonatal rat cardiomyocytes, and using the Korhonen computer model, modified in [5], and describing ventricular rat neonatal cardiomyocytes. Thus it was found the existence of non-sodium excitation waves under a strong hyperkalemia (more than 10 mM K + in the extracellular environment) in the cardiomyocyte monolayer, which was also confirmed by inactivation of sodium channels with a specific channel blocker.

To experimentally simulate the effects of hyperkalemia, different amounts of the KCl were added to the incubation medium, thus changing the concentration of extracellular potassium. The initial concentration in the Tyrode solution was 2.68 mM. By addition of KCl, the following concentrations were obtained: 3, 5.4, 8.5, 11, 13, 15, 17, 19.5, 22 .

To inactivate the sodium channels, a tetrodotoxin (TTX) of 0.5 μM was used. For the inactivation of potassium channels, tetraethylammonium (TEA) was used at a concentration of 1 mM.

In order to make sure that sodium channels are inactivated under strong hyperkalemia and only calcium channels are responcible for the excitation generation and conduction, only TEA was initially added to the medium in the experiments. Then, TTX was added, thus guaranteeing inactivation of the sodium channels. The speed of the excitation wave was measured under normal conditions and under conditions of hyperkalemia of varying degrees.

For computational experiments, a detailed model of neonatal rats ventricular myocytes (NRVM) with a modification of the calcium dynamics was used [5, 6]. It is based on the following equations:

$$\frac{\partial V}{\partial t} = \frac{I_{\text{ion}}}{C_m} + D\left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2}\right),$$

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$$I_{\text{ion}} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{Ca(L)} + I_{NaCa} + \\ + I_{NaK} + I_{P(Na)} + I_{p(Ca)} + I_{Ca,b} + I_{Na,b}.$$

To simulate the experimental data, as well as predict the further results, the parameters of the gate variables of the sodium current, L-type calcium current, and also the family of potassium currents have been changed. For this, the results of the patch-clamp experiments of ion-specific currents were used.

In the experiments of measuring action potential (AP) conduction velocity for hyperkalemia, it was shown that the velocity decreases strongly, however do not go to zero – the excitation is still possible even with a high degree of hyperkalemia.

It can be seen that when $[K^+] > 10$ the sample is still conducting the excitation wave, albeit at a much slower rate than under normal conditions ($[K^+] = 5.4$). Since at such a high concentration of potassium, most of the sodium channels are inactivated, then the conduction becomes possible due to the work of the calcium channels. In order to verify that sodium channels are inactivated under severe hyperkalemia and only calcium channels are responsible for the conduction, TEA and TTX consequently were added to the medium in for lowering the availability of potassium channels. It was shown that when the TTX was added under normal conditions, the wave velocity fell by 50 %. (see Fig. 1a). However, under the significant hyperkalemia of the order of 20 mM, the wave velocity after the addition of TTX did not practically change (it decreased by 8 %).

Under acidosis, it has been shown that the conduction velocity increases with more progressive stages of acidosis. However, the velocity increases quite insignificantly: by no more than 1 %, and taking into account the measurement error, the change in the conduction velocity can in general be neglected. The acidosis affects much greater the length of the action potential (Fig. 1b). The length of the AP under the acidosis is greatly reduced and this can lead to the shortening of the refractoriness compare to that under normal conditions. In combination with hyperkalemia, it will lead to the reduction of size of the obstacle at which reentry can originate. Thus, on the scale of the heart, the danger of a fibrillation will be greatly amplified. The results obtained may suggest in clinical procedures the thorough monitoring of blood calcium when treating patients with the high doses of medicines increasing blood potassium level.

The work was supported by the Russian Science Foundation grant # 16-14-10091.

Full text of the paper is published in JETP Letters journal. DOI: 10.1134/S002136401820002X

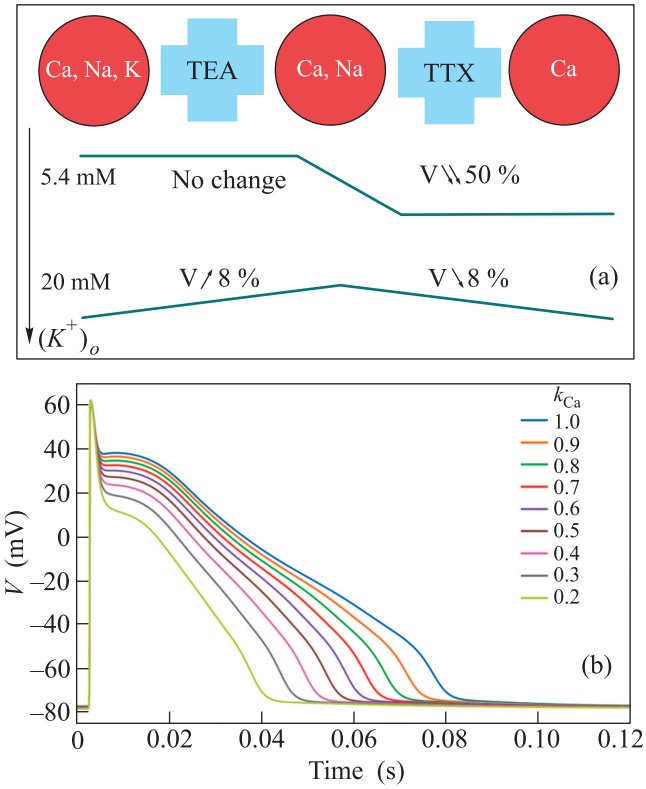

Fig. 1. (Color online) Excitation wave propagation in conditions of strong hyperkaliemia and acidosis. (a) – Dependence of the excitation wave velocity on the added blockers under normal conditions (5.4 mM) and strong hyperkalemia (20 mM). (b) – Action potential under the acidosis. Y – membrane potential in mV, X – time in seconds

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