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Change of short-term memory effect in acute ischemic ventricular myocardium: A computational study

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ABSTRACT

The ionic mechanism of change in short-term memory (STM) during acute myocardial ischemia has not been well understood. In this paper, an advanced guinea pig ventricular model developed by Luo and Rudy was used to investigate STM property of ischemic ventricular myocardium. STM response was calculated by testing the time to reach steady-state action potential duration (APD) after an abrupt shortening of basic cycling length (BCL) in the pacing protocol. Electrical restitution curves (RCs), which can simultaneously visualize multiple aspects of APD restitution and STM, were obtained from dynamic and local S1S2 restitution portrait (RP), which consist of a longer interval stimulus (S1) and a shorter interval stimulus (S2). The angle between dynamic RC and local S1S2 RC reflects the amount of STM. Our results indicated that compared with control (normal) condition, time constant of STM response in the ischemic condition decreased significantly. Meanwhile the angle which reflects STM amount is less in ischemic model than that in control model. By tracking the effect of ischemia on intracellular ion concentration and membrane currents, we declared that changes in membrane currents caused by ischemia exert subtle influences on STM; it is only the decline of intracellular calcium concentration that give rise to the most decrement of STM.

1. Introduction

Cardiac short-term memory (STM), which reflects the impact of pacing history on APD, is an intrinsic electrophysiological property in myocardium [1]. Due to the presence of memory, APD often takes a time to adjust to a new steady-state value after an abrupt change of pacing rate [2,3]. Meanwhile, memory-related changes of APD will modify the entire dynamics of cardiac myocytes, causing the restitution curve (RC) to be dependent on pacing protocols [4–6]. At the ionic level, STM is mediated by multiple factors, including intracellular calcium dynamics and membrane ionic currents [7,8]. In ischemic ventricular myocardium, STM has not been well understood. One approach to evaluate the changes of STM in ischemic myocardium is to use a computer model. Computer

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simulation developed in an attempt to gain insight into the underlying mechanisms for memory allows pathophysiological conditions to be selectively evaluated and mechanisms of STM to be investigated at the ionic level.

In the past decades, computer models based on mammalian cardiac myocytes have been developed to study the properties of cardiac electrophysiology. The Noble model [9], which incorporates formulation of ATP-sensitive potassium current, can simulate the characters of cellular electrophysiology either in normal or in ischemic myocardium. The ionic model proposed by Fox et al. [7] presents a robust feature of the rapidly paced ventricle using formulations based on canine experimental study, and can be used to investigate the relationship between STM and intracellular calcium dynamics. Luo and Rudy [10–12], using data obtained primarily from guinea pig myocytes, developed a comprehensive ionic model (LRd model) to simulate detailed ion channels and intracellular ionic concentration of cardiac ventricular cell. In this paper, we adopted LRd model which is the most recent version of the model taking into account changes made since the original 1994 presentation. As detailed formulas for ionic currents and calcium handling processes are incorporated, LRd model can reproduce physiological and pathophysiological phenomena such as STM and ischemia. Several currents of the model are often used by scholars to investigate pathophysiological behavior of ventricular myocardium [13,14].

According to Shaw and Rudy [15], the major electrophysiological properties of acute myocardial ischemia can be reproduced by LRd model with the changes of parameters in formulation. Acute ischemia, which is characterized by a deficient energetic input as well as a deficient waste removal in the first 20 min of myocardial ischemia, causes redistribution of a number of ions across the cardiomyocyte membrane. Based on the guinea pig ischemic myocardial model developed by Shaw and Rudy, we investigated the STM property of ischemic myocardium in this study. The major pathophysiological component conditions of myocardial ischemia were simulated. Ischemia-induced changing in electrical parameters were studied to evaluate the impact of each parameter on STM. Knowledge of the ionic basis for changes in STM during ischemia may increase understanding of the genesis of arrhythmias and may facilitate the development of new antiarrhythmic agents.

2. Model and methods

2.1. Ventricular cell model

We adopted the advanced numerical formulations developed by Shaw and Rudy in 1997 to study ischemia-dependent pathophysiological features because it is a robust and complete ionic model that can address dynamic activities of ischemia and can reflect electrophysiological properties including STM. Three major ischemic conditions were respectively investigated:

(1) Elevated extracellular potassium: $[K^+]_o = 12$ mM vs. 4.5 mM in control condition.
(2) Intracellular and extracellular acidosis: pH = 6.5 vs. 7.0 in control condition. Intracellular potassium $[K^+]_i = 125$ mM vs. 141 mM in control condition; membrane voltage $V_{m,acid} = V_m - 3.4$ for all sodium current computations; conductance of sodium channel $g_{Na,acid} = 0.75 \times g_{Na}$; conductance of calcium channel $g_{Ca,acid} = 0.75 \times g_{Ca}$.
(3) Anoxia: intracellular ATP concentration $[ATP]_i = 3.0$ mM vs. 7.0 mM in control condition. Anoxia is simulated by lowering ATP and activating the ATP-dependent potassium current $I_{K(ATP)}$. Conductance of ATP-dependent potassium channel $g_{ATP} = 1/[1 + ([ATP]_i/0.25)^H]$, where $H = 2$ is Hill coefficient; conductance of calcium channel $g_{Ca,ATP} = 1/[1 + (1.4/[ATP]_i)^H]$, where $H = 2.6$ is Hill coefficient.

The ischemic model simulates a number of changes in ion concentration including: extracellular potassium ($[K^+]_o$), intracellular potassium ($[K^+]_i$), intracellular sodium ($[Na^+]_i$), intracellular calcium ($[Ca^{2+}]_i$). Among these changes which affect STM, intracellular calcium concentration is an important factor [8]. Changes in intracellular calcium cycling are modeled as follows [10,11]:

$$I_{rel} = G_{rel} \cdot RyR_{open} \cdot RyR_{close} \cdot ([Ca^{2+}]_{jsr} - [Ca^{2+}]_i) \quad (1)$$

$$G_{rel} = \frac{150}{1 + e^{(I_{CaL} + I_{Cab} + I_{p(Ca)} + I_{CaT} - 2I_{NaCa} + 0.5)/0.9}}$$

$$RyR_{open} = \frac{1}{1 + e^{(-t_{CICR} + 4)/\tau_{on}}}$$

$$RyR_{close} = 1 - \frac{1}{1 + e^{(-t_{CICR} + 4)/\tau_{off}}}$$

where I_{rel} refers to Ca^{2+} release from junctional sarcoplasmic reticulum (JSR) to myoplasm; G_{rel} is rate constant of Ca^{2+} release from JSR; RyR_{open} and RyR_{close} are proportion of activating (on) and deactivating (off) of Ca^{2+} release from JSR, respectively.

$$I_{up} = \bar{I}_{up} \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,up}} \quad (2)$$

$$I_{leak} = K_{leak}[Ca^{2+}]_{nsr} \quad (3)$$

$$I_{tr} = \frac{[Ca^{2+}]_{nsr} - [Ca^{2+}]_{jsr}}{\tau_{tr}} \quad (4)$$

where I_{up} refers to Ca^{2+} uptake from myoplasm to network SR (NSR); I_{leak} refers to Ca^{2+} leakage from NSR to myoplasm; I_{tr} refers to Ca^{2+} transfer from NSR to JSR; $K_{m,up}$ is half-saturation concentration of Ca^{2+}; K_{leak} is rate constant of Ca^{2+} leakage from NSR.

The fourth-order Runge–Kutta method was applied to integrate the single cell model with a time-step of 0.005 ms. Decreasing the time step to 0.001 ms was not found to change the simulation results.

2.2. STM response

The STM response (also called APD accommodation), which reflects the transient characteristic of STM, is a slow monotonic change in APD after an abrupt increase of pacing rate.