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TISSUE STRUCTURE AND Ca^{2+} -MEDIATED ECTOPIC BEATS

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Abstract

Ectopic focal excitations due to abnormal calcium (Ca) cycling at the cellular level are believed to underlie cardiac arrhythmias. The mechanisms linking subcellular Ca and focal excitations remain elusive though. This work employs a detailed model of spontaneous Ca release (SCR) to study the formation of Ca-mediated triggered activity in tissue. Due to the stochastic nature of SCR, hundreds of simulations were performed to build statistics regarding frequency, first latency and location of the first ectopic beats. It could be shown that Ca-overload as well as the strength of electrotonic coupling between cells clearly influence the occurrence of ectopic foci. Cable-like structures resembling those in the Purkinje system are more prone to Ca-mediated foci. Further, foci were not evenly distributed, rather they clustered at tissue boundaries.

Keywords

Triggered activity; calcium abnormalities; electrotonic coupling; monodomain simulations

Introduction

Abnormalities in the calcium (Ca) cycling at the cell level have been shown to be intimately related to cardiac arrhythmias [1]. Under pathological conditions, such as Ca-overload, spontaneous Ca release (SCR) from the sarcoplasmic reticulum (SR) may occur due to random openings of Ryanodine receptors. These spontaneous Ca sparks can induce delayed after-depolarizations (DADs), via Ca-sensitive currents, which can trigger action potentials (APs) capable of disturbing the normal sinus rhythm. However, it is not yet understood how such instabilities in Ca cycling within myocytes can overcome the electrotonic load in tissue to become triggered excitations. In this study, we use computer simulations to investigate the role of electrotonic load in the formation of Ca-mediated ectopic foci.

Methods

Phenomenological Ventricular Myocyte Model of SCR

The modified Mahajan-Shiferaw (MSH) model [2, 3] of the rabbit ventricular AP was used to investigate the formation of Ca-mediated triggered activity in cardiac tissue. The model

describes dynamics of membrane currents, main intracellular ionic concentrations as well as SCR from the SR in cardiac myocytes.

To generate triggered activity, some key parameters of the MSH model were modified, as previously described [3, 4], in order to create a DAD-prone myocyte model. Accordingly, the maximum conductance of the inward rectifier K^+ current (g_{K1}) was decreased to 30% of its control value; the electrogenic Na-Ca exchange current was doubled; Ca-overload was induced by increasing external Ca concentration.

Cardiac Tissue Models

Computer models of a 1D 27 mm strand, a 2D 27×27 mm slab and a 3D $27 \times 27 \times 6$ mm cardiac tissue preparation were established to investigate the relation between electrotonic load and Ca-mediated ectopic beats. The dimensions were chosen to be representative of rabbit Purkinje system and ventricular walls. Tissue models were meshed using line, quadrilateral and hexahedral elements with $300 \mu\text{m}$ edge length. Monodomain conductivities were adjusted to obtain a conduction velocity of 0.6 m/s in all directions axes, i.e., enforcing isotropic conditions to the 2D and 3D geometries.

Simulation Protocols

Single-cell Simulations—The MSH cell model was simulated using the Cardiac Arrhythmia Research Package (CARP) [5] with a time step of $10 \mu\text{s}$. In order to investigate the properties of SCR, different SR loads were considered. During each simulation run, the cell was paced at a basic cycle length of 400 ms for 100 beats. The state variables at the end of the protocol were stored and used later as an input for the tissue scale simulations.

Tissue Simulations—The initial state of the tissue was defined by populating the cells using state vectors as computed previously in the single-cell pacing protocol. Electrical activity in tissue was described by the monodomain equations [6] using CARP. In all tissue simulations, no stimulus was applied mimicking thus, a pause following a sequence of paced beats. In this situation, the unstimulated tissue fires due to a depolarization caused by Ca-sensitive membrane currents.

Data Analysis

Tissue simulations were performed $N = 100$ for different SR loads. Each simulation corresponds to a period of 800 ms. The number of simulations n , where an ectopic beat was observed was used to compute the probability $p = n/N$. In addition to that, location and first latency of Ca-mediated excitations were also analyzed.

Results

Computational studies were carried out to investigate the relation between Ca-overload and ectopic beats in the context of simplified tissue geometries. Fig. 1 A presents the statistics of Ca-mediated excitations on a 1D cable. Note that the probability of ectopic excitations increases for higher SR loads. The relationship between electrotonic load (tissue dimension) and probability of ectopic foci is demonstrated in Fig. 1 B. SR load was increased to 1500

μM and simulations were performed also with a 2D slab and a 3D wedge preparation. Note that the frequency of ectopic beats decreases from 83% on the cable to 52% on the 3D case. The average first latency increased with tissue dimension being 351.6 ms, 371 ms and 379.7 ms for the 1D, 2D and 3D cases respectively. Foci were not found to be evenly distributed (not shown), they clustered at tissue boundaries instead.

Discussion

Alterations in the subcellular Ca handling have been shown to be arrhythmogenic [1]. Understanding how instabilities in the Ca cycling, at the single-cell scale, can summate and overcome electrotonic source-sink mismatches to form ectopic foci remains elusive. In this work, we make use of a computational framework [5] to assess the stochastic properties of Ca-mediated ectopic foci in the context of simplified tissue geometries. Our hypothesis is that occurrence, timing and location of ectopic foci are dependent on the spatial synchronization of SCR and the electrotonic load imposed by the cardiac tissue. Indeed, simulations have demonstrated that Ca-overload increases probability of triggered excitations while reducing first latency, favoring thus synchronization of neighboring cells. Interestingly, ectopic foci appeared with higher frequency in 1D tissue than in the 2D and 3D cases demonstrating that the strength of electrotonic coupling plays a role as well. These findings suggest that cable-like structures resembling those in the Purkinje system are more prone to Ca-mediated foci than the myocardium. In addition to that, foci were not found evenly distributed. They rather clustered at boundaries due to the lesser degree of electrotonic load on these cells.

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Figure 1.

Dependency of ectopic focal excitations on SR load and strength of electrotonic coupling.

A) Probability of foci in 1D cardiac strand of cells for different SR loads. B) Probability of foci on a 1D (cable), 2D (slab) and 3D (wedge) cardiac geometries for a SR load of 1500 μM .