Low-Voltage Defibrillation in Bidomain Virtual Ventricular Tissue: Effect of the Bath

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Abstract

Mechanisms for termination of re-entry and defibrillation still remain a challenge. Using the Luo-Rudy family of virtual ventricular tissues we simulate termination of re-entrant spiral waves with a periodic low-voltage shock, studying a new mechanism for defibrillation. Essential for the simulations is extension of the bidomain tissue representation in order to account for the existence of an external bath ("tridomain"), where the shock is applied. The bidomain model with the bath reproduces periodic patterns of depolarization in the virtual tissue - standing waves, previously observed in experiments. In contrast to the classical exponential decay of voltage near the electrodes, standing waves entrain the whole tissue, thus canceling the spiral waves. The mechanism of this far-field effect is based on redistribution of the externally applied current by the external conductive bath.

1. Introduction

During ventricular fibrillation the synchronized, mechanical pumping action of the ventricles is lost, and irregular trembling of the ventricular muscle is produced by irregular excitation. The irregularity is believed to be produced by re-entrant propagation of a number of interacting rotors of excitation in the ventricles [1, 2]. In 2-dimensional excitable media formed by electrically coupled cardiac cells re-entry can be idealised as a spiral wave rotating around a phase singularity, called the core [3, 4]. Re-entry is no longer sustained if the singularity is eliminated, e.g. by a defibrillating shock [3-6].

1.1. Defibrillation

Defibrillation is commonly achieved by applying a strong electric shock, which eliminates the asynchronous activity and brings cardiac tissue back to the resting state. Several mechanisms of the phenomena have been proposed, assuming that the defibrillating shock either uniformly excites all the cells, or brings them to the resting potential, thus terminating wave propagation. However, classical microelectrode measurements by Weidmann [7] have demonstrated that changes of the membrane potential decay exponentially with distance from the electrode, with a space constant of about 1 mm. Thus, as the experiments show, the external voltage cannot effect regions of the tissue several millimeters away from the site of stimulation.

1.2. Model mechanisms

Several attempts to overcome the small space constant restriction have been undertaken. Using mathematical models of cardiac tissue, Krinsky and Pumir showed that spatial heterogeneity, such as intercellular clefts, lead to generation of sawtooth-shaped potentials oscillating through the tissue, and mediating the external voltage stimulation in far-field [8]. However, such spatially oscillating potentials were never observed in experiment.

Alternatively, Trayanova with co-workers [5, 6] suggested the role of "virtual electrodes" emerging in bidomain models [9] of cardiac tissue. The virtual electrodes are dog-bone shaped patterns of depolarization and hyperpolatization formed around the site of the electrode application. Such patterns were observed in both computational and *in vitro* experiments [5], and their interaction with cores can terminate the spiral waves. However, such a mechanism of defibrillation is highly dependent on the spatial location of the electrode – if it does not coincide with the spiral wave core, the virtual electrodes otherwise lead to generation of new spirals and fibrillation [5]. Thus, the mechanism based on the virtual electrodes was assumed probabilistic [6].

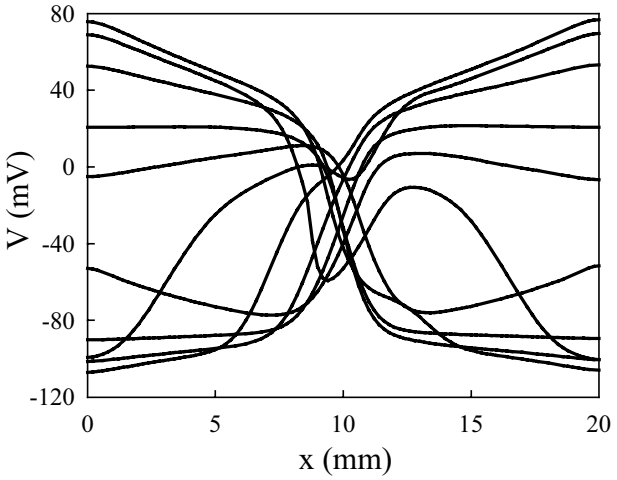

Figure 1. Standing wave in a strand of virtual ventricular tissue stimulated at 10 Hz, 30 V. Spatial profiles of the membrane potential are shown over a period of the stimulation.

1.3. Standing waves

Recently a new possible mechanism for cardiac defibrillation was described both experimentally and computationally [10]. *In vitro* experiments showed that periodic forcing of the heart with low-voltage pulses (amplitude 20-30 V, frequency 5-20 Hz) applied in the bathing solution through bipolar mesh electrode resulted in steady periodic patterns of depolarization on the heart surface - standing waves (Figure 1). Such waves stopped propagating activity in the cardiac tissue, including re-entry and fibrillation, in 100% of the experiments.

Simple cable or bidomain models of cardiac tissue fail to reproduce the experimentally observed phenomena. However, extension of the bidomain model for the intra- and extracellular spaces of the tissue [9] to account for existence of the bathing solution - originally called the "tridomain" model - allows simulation of the standing waves in both 1 and 2 dimensions [10, 11]. After the experiments, preliminary numerical simulations in 2 dimensions have demonstrated that standing waves induces by low-voltage forcing of the bidomain virtual ventricular tissue with a bath eliminate re-entry in form of a single stably rotating spiral wave, thus providing a defibrillating effect [11].

Our aim is to study the mechanism of such "defibrillation", namely to show importance of the bath in generation of the far-field effect.

2. Methods

A convenient method for studying fibrillation and re-entry is using the current generation of ventricular cell models [12], allowing idealization of the cardiac tissue as an excitable medium supporting rotation of spiral waves. We use the Luo-Rudy family of virtual ventricular tissues [13] extended to account for the existence of external solution bathing the tissue. Equations for the bidomain representation of cardiac tissue with a bath are similar to those used in [10], but the Laplace's operators are now written for 2 rather then 1 spatial dimensions.

Spiral waves are first initiated in 3x3 cm square uniform bidomain virtual ventricular tissue by the phase distribution method, then after 200 ms of simulation external sinusoidal forcing of opposite polarity is applied along two opposite boundaries of the tissue. We solved the resulting equations numerically using an explicit scheme with time step of 50 μs and space step of 0.2 mm.

3. Results

For the bidomain model without a bath rotation of a spiral wave is stable both before and after the stimuli application (Figure 2). In the bidomain with a bath, there is a threshold forcing strength of about 12 V below which the spiral wave rotation is also stable in respect to the stimuli. For such forcing no standing wave is generating and only regions of the tissue close to electrodes are effected by the external voltage (thus, the activity pattern in the tissue is similar to that seen in the previous case).

However, increasing the forcing strength above the threshold leads to formation of standing waves in the tissue, which eliminate the spiral wave (Figure 3). Existence of such a defibrillation threshold is in agreement with the experiment [10]. Note that as in the experimental observations, the simulations results were robust in respect to the frequency variations in the range of 5-20 Hz.

We measure a current flowing from the external solution into the tissue during forcing and show that it is non-localized, at each moment of time having almost linear profile (Figure 4) - whereas in absence of the bath only edges of the tissue near the electrodes are effected by the external voltage (see Figure 2). Hence, although our model possesses the space constant property, the far-field effect is achieved through linear redistribution of the electrode current in the conductive external bath.

4. Discussion

Our simulations show that the bidomain model without a bath cannot reproduce the transition from re-entry and fibrillation to standing waves, which is observed in experiments, whereas the model with a bath can. The mechanism of such "defibrillation" is based on generation of a distributed electric current source in the bathing

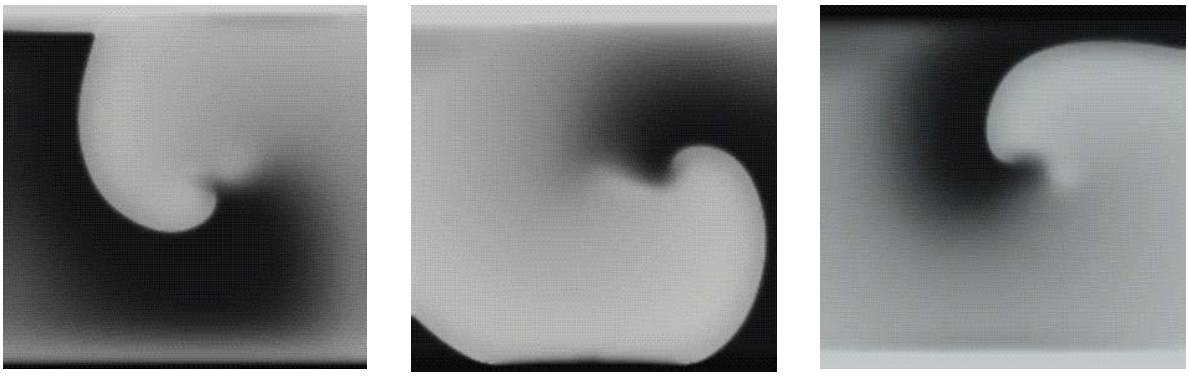

Figure 2. Rotation of a spiral wave in 3x3 cm square isotropic bidomain virtual ventricular tissue without a bath. Spatial distribution of the membrane voltage is shown by gray color palette (white corresponding to the maximum depolarization and black to the maximum hyperpolarization) for the moment of time t = 250, 300, 350 ms. Black and white areas near top and bottom edges correspond to voltage decaying from the electrodes.

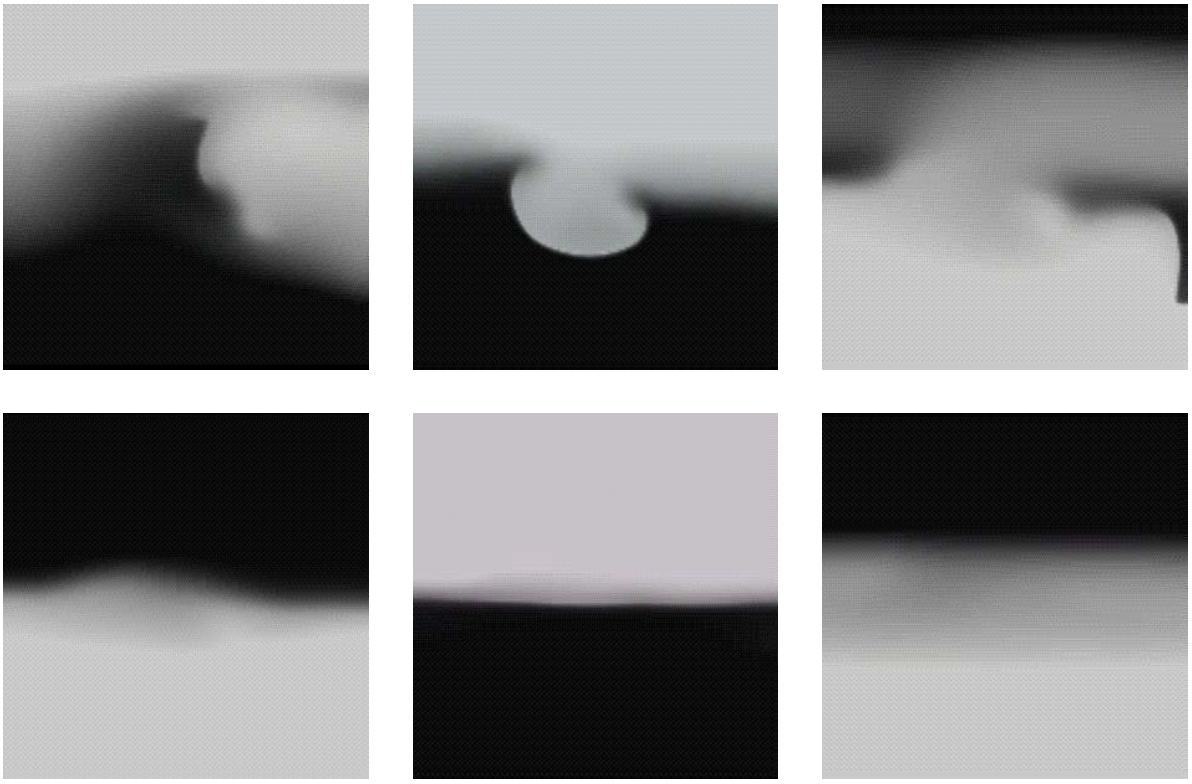

Figure 3. Defibrillation of a spiral wave in 3x3 cm square isotropic bidomain virtual ventricular tissue with a bath. Spatial distribution of the membrane voltage is shown by gray color palette (white corresponding to the maximum depolarization and black to the maximum hyperpolarization) for the moment of time t = 220, 250, 280, 300, 350, 400 ms. The spiral wave decays due to interaction with large areas of depolarization and hyperpolarization near the electrodes (top row), and a standing wave is established in the tissue (bottom row).

solution with applied electrodes, which mediates effects of the external low-voltage forcing to the whole tissue. Flowing into the tissue, the current effects areas far from the electrodes, either exciting them, or bringing to unexcitable refractory state, thus leaving no space for the spiral wave to rotate.

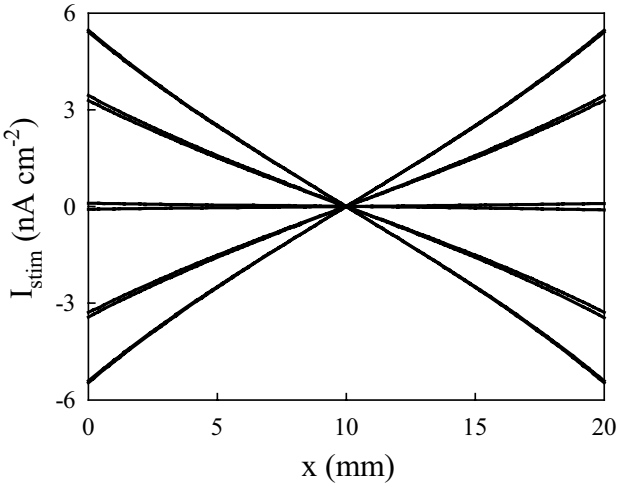

Figure 4. Mechanism for standing waves: quasi-linear periodic current, flowing into the strand of virtual ventricular tissue from the conductive bath stimulated at 10 Hz, 30 V. Spatial profiles of the current are shown over a period of the stimulation.

Future studies of the bath effects will introduce anisotropy in the bidomain model, which may lead to more complex patterns of activity in the tissue, e.g. caused by interaction of standing waves and virtual electrodes with the rotating spiral waves.

Another promising approach is combination of the voltage defibrillation with the strategy for pharmacological antiarrhythmic action [13], aimed at increasing spatial extent of the spiral wave meander and probability of its self-termination. The pharmacological actions increases meander of the spiral wave core, whereas a low-voltage electrical shock effectively reduces size of the tissue available for the spirals wave movement – thus, applied simultaneously, they should reduce both the defibrillation threshold and the degree of blocking the target ion channels, required for termination of the respective cardiac arrhythmias.

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