Simulations of Ventricular Tachycardia under Myocardial Ischemic Conditions and Infarction

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Abstract

In order to investigate myocardial action potential propagation under ischemia and infarction, we present a modified version of the Luo-Rudy I model. The chosen domain is a 2D virtual heterogeneous sheet of myocardial tissue, subdivided in three distinct zones: an ischemic area (CZ), a border zone (BZ, linear transition between physiological and ischemic values) and normal tissue (NZ). Ischemia is simulated through hyperkalemia and acidosis and affected parameters are changed in the CZ and in the BZ at each time after the onset of ischemia.

We study how the interaction between propagating waves and ischemic regions can lead to the onset of cardiac arrhythmias, including ventricular tachycardia (VT) and fibrillation (VF). We investigate pinning and unpinning of rotating waves to and from infarction zones using pulsed electric fields. We will present an example of an interesting dynamics leading the system from a chaotic transient to long-lasting spirals pinned to ischemic heterogeneities.

1. Introduction

Cardiac diseases are one of the most common causes of death in the industrialized world. They are due to irregular electrical activity in the heart, arising from reentrant waves circulating in the tissue and leading, in the most dangerous cases, either to ventricles contracting too rapidly (VT) or to individual ventricular cells contracting asynchronously (VF). There is growing evidence that a specific form of reentries, i.e. spiral waves, is the main cause for the occurrence of such cardiac arrhythmias: in the case of VT, its onset can be caused by a single spiral wave rotating around a stationary core (if monomorphic) or a drifting spiral wave (if polymorphic); VF, in addition, is related to the coexistence of multiple spirals in the same medium. Another considerable issue is the presence of multiple-size heterogeneities in the myocardium, responsible of inducing profound changes in the tissue's electrical properties and responses. Their interaction with propagating waves represents a critical substrate for the onset and, under certain conditions, for the maintenance of spiral wave activity [1]. In our work we simulate the presence of an ischemic region arising in a 2D virtual sheet of heterogeneous myocardial tissue with the aim to investigate its interaction with propagating excitation waves and its role in the arrhythmogenesis process. Myocardial ischemia arises when, after coronary occlusion, blood supply of substrates doesn't meet tissue metabolic demands and it is widely known to be one of the leading causes of ventricular arrhythmias. If this deficit lasts in time and exceeds a critical threshold, the desease can degenerate in acute ischemia and infarction, the last one being related to the death (necrosis) of the tissue. Ischemia is followed by profound metabolic changes mainly caused by hyperkalemia (increment of extracellular potassium concentration), hypoxia (deprivation of oxygen supply) and acidosis (increment of acidity in the blood). In this study, hyperkalemia and acidosis are simulated in a modified Luo-Rudy (LR) I model. The tissue is modelled as heterogeneous and subdivided into a central circular ischemic area (CZ), a ring-shaped border zone (BZ, linear transition between physiological and ischemic values) and normal tissue (NZ) [2]. Affected parameters are changed both in time and in space (in the BZ and in the CZ) after the onset of ischemia, in order to follow its initiation and development. With this approach, the main electrophysiological ischemic effects are observed: reduction of the action potential (AP) duration and upstroke, increment of post-repolarization refractoriness. In addition, an example of the interesting and complex dynamics arising from the interaction waves-heterogeneities is given: overdrive pacing is applied to observe reentrant excitation patterns and mechanisms leading to long-lasting spirals pinned to ischemic heterogeneities.

2. Material and methods

2.1. Mathematical model

For our analysis, a modified LR I mathematical model has been implemented [3]. It describes the mammalian (guinea pig) ventricular cells action potential via trans-

membrane ionic currents [3] and consists of a nonlinear reaction diffusion problem given by

$$\nabla \cdot (\mathbf{D}\nabla V) = C_m \frac{\partial V}{\partial t} + J_{ion}(V, \mathbf{u}) \quad (1)$$

$$\frac{\partial \mathbf{u}}{\partial t} = \mathbf{f}(V, \mathbf{u}, t) \quad (2)$$

where V stands for the membrane potential, $\mathbf{D}$ for the positive definite conductivity tensor, J_{ion} for the sum of transmembrane ionic currents, $\mathbf{u}$ for the vector of gating variables, $\mathbf{f}$ for a vector valued function and t for the time. Eq.1 is a system of linear partial differential equations (PDE) describing electric conduction. Eq.2, instead, represents a system of nonlinear ordinary differential equations (ODE) describing the cellular ionic currents through their gating variables $\mathbf{u}$ (variables expressing the probability for ionic channels to be open or closed depending on membrane voltage V). The transmembrane ionic currents are determined by the ionic gates, whose gating variables are obtained as a solution of the ODE system. The ionic currents, in turn, change V, which subsequently affects the ionic gates and currents.

2.2. Simulated domain

The domain adopted for simulations is shown in Fig.1 and consisted of an heterogeneous 2D simulated myocardial tissue developed according to Ferrero et al. [2] and made up of a central circular CZ, a ring-shaped BZ, and NZ. The LR I model was modified in order to reproduce the conditions of hyperkalemia and acidosis arising during ischemia in the CZ: in particular, the effects of hyperkalemia were simulated increasing the potassium concentration, while acidosis was implemented simulating a drop in the sodium and calcium specific conductances [1, 2].

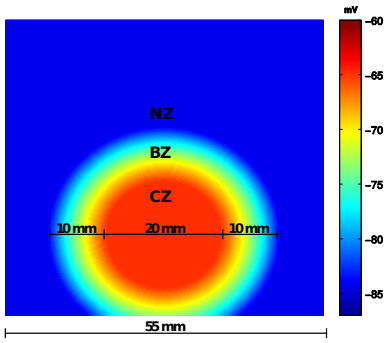

Figure 1. Heterogeneous 2D simulated tissue: a central circular ischemic area (CZ), a ring-shaped border zone (BZ, linear transition between CZ and NZ) and normal tissue (NZ).

In order to follow ischemia initiation and development, affected parameters were then changed both in time (in the CZ) and in space (in the whole tissue, in which BZ represents a linear transition between the ischemic and the healthy zones). The evolutions in time and space are shown in Fig.2a and Fig.2b, respectively.

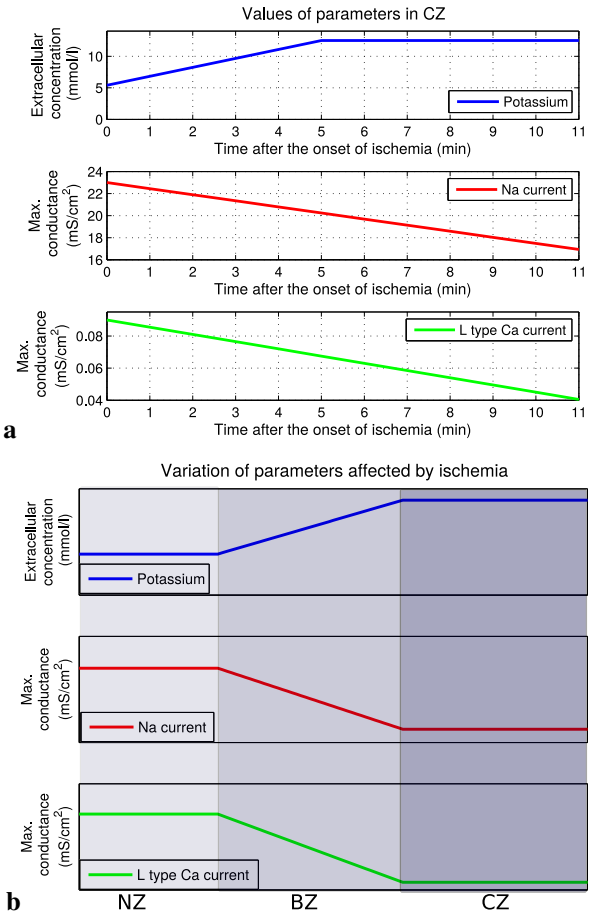

Figure 2. During ischemia development, affected parameters were changed both in time in the CZ (a) and in space in the whole tissue (b), in which the BZ is a linear transitions between CZ and NZ.

3. Results

This formulation of the LR I model allowed us to follow the initiation and the development of an ischemic pathology in the myocardium. In the first phase, simulations were run to investigate the tissue behaviour during the first 5 minutes after the onset of ischemia. Alterations of its electrophysiological properties were observed and are shown in Fig.3, in which the AP is recorded in two different time intervals after the onset. The tissue was periodically paced and, as soon as ischemia developed, its electrophysiological effects became more visible (see the CZ and BZ in Fig.3): among them, the shorter AP duration, the lower AP upstroke and the lower cell excitability. Strictly

connected to these, changes were also visible in the gating variables regulating the currents flow through the ionic channels.

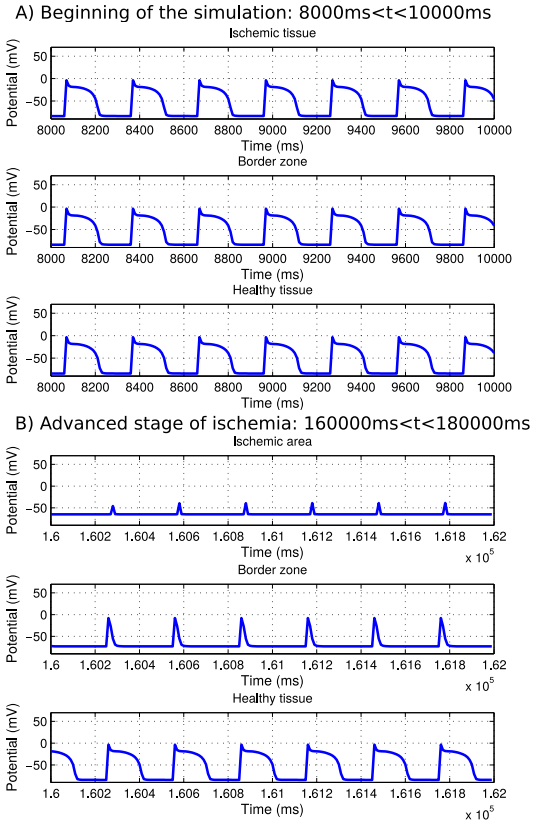

Figure 3. Membrane potential recorded in each area of the tissue (periodically paced) at two different time intervals after the onset of ischemia.

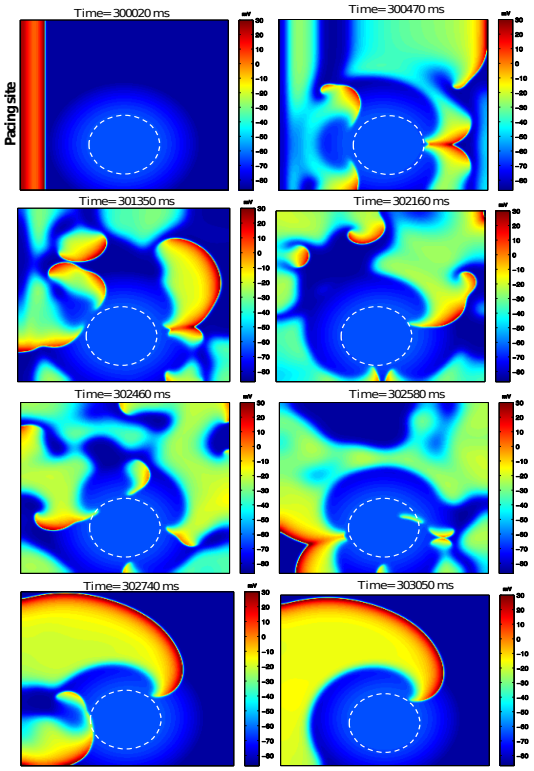

Figure 4. Different times of the simulation run after conditions of hyperkalemia were reached. Decremental pacing protocol was applied. Pulses were delivered locally (to the left hand row of elements), intervals were kept constant for a limited time and then suddenly decreased. After a chaotic transient, the system dynamics evolved to a long lasting spiral wave pinned to the ischemic heterogeneity (marked in the pictures).

In literature, it is well known that during ischemia development, strong hyperkalemia is needed in order to produce reentries in the tissue. These conditions are reached after 5 min. after the onset of ischemia [2]. In addition, during wave propagation the differences in velocity due to nonuniform excitability of the myocardium create a visible tendency of reentry at the interface normal region-pathological tissue [4].

In order to investigate the complex and interesting reentrant dynamics, simulations were then run after 5 min of ischemia development. A *decremental pacing protocol* (stepwise decrease of the pacing interval) was applied and results are shown in Fig.4. Pulses were periodically and locally applied to the left hand row of elements in the sheet. The interval between pulses was held constant for a limited time and then suddenly stepped to a shorter interval, reaching a burst cycle length (BCL) of 90, 80, 74 and 71 ms. Due to the electrophysiological changes already shown in Fig.3, the ischemic zone turned out to be a not excitable area and behaved like an obstacle to the wave propagation. In addition, the BZ seemed to play an important role due to its hybrid properties, in the middle between healthy and ischemic. The higher excitability compared to CZ but higher refractoriness compared to NZ seemed to affect wave propagation, especially when the frequency of stimulation was increased. The chaotic transient arising from waves collision and break up lead then the system dynamics to a long lasting spiral wave pinned to the ischemic heterogeneity (marked in the pictures). During the simulation, the membrane potential was recorded during both the chaotic transient and the stable pinned spiral regime. Results in the last case are shown in Fig.5. Looking more carefully at the membrane potential, it seems that when a stable spiral is pinned to the heterogeneity the tissue shows alternans in the BZ and NZ. When observed, this property might be then considered as a sort of *marker*, a sign transmitted by the tissue when this kind of reentrant activity is going on.

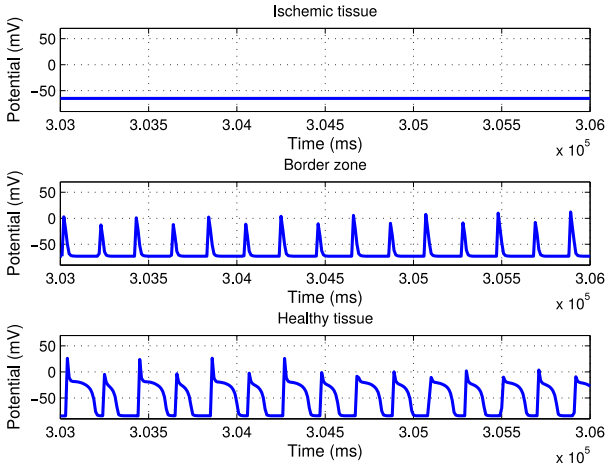

Figure 5. Membrane potential showing alternans in the BZ and NZ during the stable pinned spiral regime.

4. Discussion

Reentrant activity in the heart has been found to be one of the major causes of the occurrence and development of cardiac arrhythmias [1]. However, the complex mechanisms underlying spirals' behaviour during these arrhythmias are still not clearly understood. There is also little knowledge about the central role played by the interaction between such spiral waves and the multiple-size heterogeneities characterizing the myocardial tissue. In the present study, we simulate the effects that the occurrence of an ischemic area in a 2D myocardial tissue exerts on the wave propagation and give an example of how the complex interaction between waves and ischemic area can evolve to a maintained spiral wave pinned to the heterogeneity.

We chose to implement the LR I model that, compared to the Beeler-Reuter model, introduced a new formulation of the fast inward sodium current (leading to a more realistic and higher upstroke velocity), formulated a new current (the plateau potassium current) leading to a more realistic description of the inwardly rectifying potassium current and introduced the extracellular potassium concentration as a parameter [3]. We modified affected parameters simulating the development of hyperkalemia and acidosis, profound metabolic changes induced by ischemia, in a 2D heterogeneous tissue. The developed model allowed to track the progression of ischemia at each time step after its onset and to detect the changes caused to the cell electrophysiology (the shorter AP duration, the lower AP upstroke and the lower cell excitability) at different time intervals. These results are in agreement with previous investigations [4]. We focused our attention on arrhythmogenesis once favourable conditions for reentries were reached. In agreement with Xu et al.[1], a decremental pacing protocol was performed. Our simulations showed an interesting and complex behaviour of the ischemic area, not excitable anymore due to its metabolic changes and thus acting like an obstacle. The last one, together with an increment of the frequency of stimulation, lead the system to a chaotic dynamics arising from waves collision and break up. It is worth to highlight the role that the BZ might play in this process, being less excitable than a healthy tissue, but still preserving part of its properties of conductivity. Compared to previous investigations, our simulations showed the transition from the chaotic to the stable regime, in which among all the breaking spirals only one survives and stays pinned to the ischemic heterogeneity. From our analysis, this state is shown by alternans in the AP registered in the BZ and in the NZ. These results, further investigated, may provide a sort of marker to reveal the presence of spiral waves pinned to heterogeneities in the tissue and to detect conditions of reentrant arrhythmias. Moreover, future developments of this study can be framed in a more general approach in which defibrillation techniques for the termination of VT can be deeply investigated, focusing on the interconnections between VT, strength of the electric field needed for spirals unpinning and size of the tissues heterogeneities. In addition, development and optimization of low energy control of cardiac arrhythmias including LEAP [5] can be pursued.

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