Electrical Propagation Patterns in a 3D Regionally Ischemic Human Heart: A Simulation Study

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Abstract

In this work, we have studied the different propagation patterns displayed in a human heart during acute ischemia. A 3-D geometrically and anatomically accurate regionally ischemic human heart was simulated. The ischemic region was located in the anterior side of the left ventricle mimicking the occlusion of the circumflex artery. Realistic heterogeneity and fiber anisotropy has been considered in the model. The electrical activity of each cell was reproduced using a modified version of the ten Tusscher 2006 action potential model. The model predicts the generation of figure-of-eight re-entries which cross the central ischemic zone formed in the epicardial surface due to the longer refractory period of the midmyocardial layers. Also, focal activity experimentally observed in the epicardium could be caused by re-entrant wavefronts propagating in the mid-myocardium that re-emerge in the heart surface.

1. Introduction

Ventricular tachycardia and fibrillation are known to be two types of cardiac arrhythmias that usually take place during acute ischemia and frequently lead to sudden death. Even though these arrhythmias arise from different clinical conditions, ischemic heart disease is the foremost perpetrator among them. During ischemia, the delivery of substrates, primarily oxygen, to the myocardium stops, causing metabolic changes which result in a progressive deterioration of the electric activity in the injured region and subsequently to a loss of function and ultimately pump failure [1]. These metabolic changes are mainly hypoxia, increased concentrations of the extracellular K^+ (hyperkalemia), increased concentrations of intracellular Na^+, and Ca^{2+}, decreased concentration of extracellular Na^+, decrease of intracellular ATP, and acidosis [2]. In addition, the impact of ischemia in the myocardium is characterized with a high degree of heterogeneity. Due to diffusion of ions and metabolites, the core of the tissue suffering from the lack of blood (the central ischemic zone, (CIZ) is surrounded by a border zone (BZ) which comprises changes in electrophysiological properties between the healthy and ischemic regions [3-6]. These heterogeneities are produced not only intramurally, but also transmurally, in the depth of the ventricular wall. From an electrophysiologic point of view, these changes imply alterations in action potential configurations, excitability, conduction velocities, refractive period among others, which enormously favour reentrant activity, and therefore arrhythmias and fibrillation [4-6].

In this work, we have studied the different propagation patterns displayed in a human heart during acute ischemia.

2. Methods

The electrical activity of each cell was reproduced using a modified version of the ten Tusscher 2006 action potential model [7]. The tissue was modelled according to the monodomain equation

$$\nabla \cdot \left(D \nabla V \right) = C_m \frac{\partial V}{\partial t} + J_{ion} + J_{stm},$$

where V is the transmembrane potential, D is the second order anisotropic diffusion tensor, C_m the membrane capacitance, J_{ion} the ionic current, and J_{stm} the stimulus current.

Acute ischemia was simulated taking into account its three main components by setting the values of the parameters affected by ischemia to those experimentally observed at minute ten of ischemia. Hypoxia was considered by partially activating the ATP-sensitive K^+ ccurrent ($I_{K(ATP)}$), formulated by Ferrero et al [8] for guinea pig and adapted for the tenTusscher model of action potential. I this regard, the $I_{K(ATP)}$ current has been formulated as follows

$$I_{KATP} = g_0 \left(\frac{[K_o^+]}{5.4} \right)^{0.24} f_M \, f_N \, f_T \, f_{ATP} \left(V - E_K \right),$$

where g_0 is the maximum channel conductance, f_M, f_N, f_{0T} are correction factors, f_{ATP} is the fraction of opened channels, V the transmembrane potential, and E_K is the inversion potential of the channel. The maximum channel conductance and the fraction of opened channels, f_{ATP}, have been modified with respect to its original formulation

$$f_{ATP} = \frac{1}{1+\left([ATP\}_i / K_m\right)^H},$$

$$K_m = \alpha\left(35.8 + 17.9[ADP]_i^{0.256}\right),$$

$$H = 1.3 + 0.74\beta\exp\left(-0.09[ADP]_i\right).$$

Parameters a, b, and g0 where identified by fitting experimental data available for different animal models. The results are given in Table 1 for the different cell types.

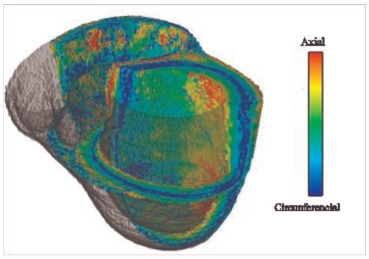
Table 1. Value of the parameters for the $I_{K(ATP)}$ current adapted to the ten Tusscher model

Cell Type	g_0, (mS)	α	β
EPI	2.01	1.0	6.0
ENDO	1.92	0.32	6.0
MID	2.01	0.86	6.0

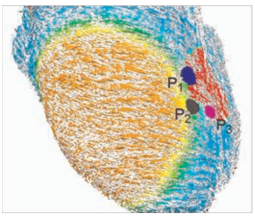
The model of regional ischemia followed closely the proposed in [9]. It was composed by realistically dimensioned transitional border zones (BZ) for the three main components of acute ischemia, connecting the normal zone (NZ) and the central zone (CZ) of ischemia an a thin layer of wash-out in the epicardium. In the central zone of ischemia, the extracellular potassium concentration was set to 9.9 mM to mimic hyperkalemia [3], the inward Na+ current and Ca2+ current through L-type channels were scaled by a factor of 0.85 to imitate acidosis [10,11], and the intracellular ATP and ADP concentration were set to 5 mM and 99 uM respectively [12].

A 3-D geometrically and anatomically accurate model of the heart was constructed from MRI-DTI data [13]. The ischemic region was located in the anterior side of the left ventricle mimicking the occlusion of the circumflex artery. A 1.0 mm thick wash out zone was introduced in the endocardium to simulate the effect of the interaction of the endocardial tissue with the blood in the ventricular cavities [14]. Realistic heterogeneity and fiber anisotropy has been considered in the model. Figure 1 shows the finite element model of the human heart and a detail of the considered ischemic region.

The stimulation protocol consisted on the delivering five stimulation pulses at normal excitation position in the endocardium of the heart at a frequency of 1.25Hz, for preconditioning the tissue, followed by an extra-stimulus located in the border zone with different coupling intervals (CI). Figure 1 depicts the location of the extra-stimulation points. P1 and P2 are located in the border zone, while P3 is located just outside the ischemic zone. The location of the ectopic focal activity obeys to experimental observations by Janse et al. [5].



(a)

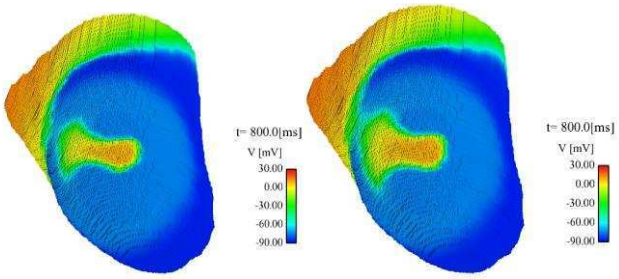


(b)

Figure 1. a) Finite element model of the human heart with the fiber orientation; b) Detail of the circumflex occluded ischemic region considered.

3. Results

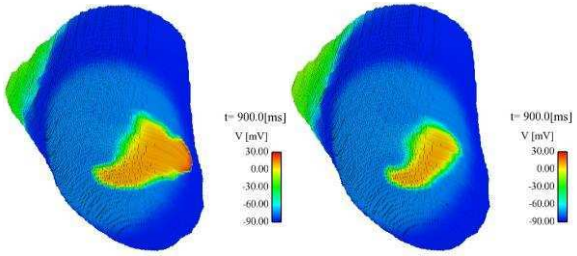
Our simulations have shown spatial heterogeneities in the propagated action potential, as reported experimentally, throughout the regional ischemic tissue, such as resting membrane potential (-86.1 mV in NZ, and –70.3 mV in the CZ, with potentials varying between these values in the BZ). Secondly, different patterns of activation were found depending on the CI. For CIs in the range 418-428 ms, reentry occurred at the epicardium whereas the mid-myocardium remained in refractory period. The reentrant front quickly aligned and propagated along the fiber direction on the epicardium as shown in Figure 2 for two CI.



(a) (b)

Figure 2. Reentrant front in the ischemic heart a) CI=418 ms b) CI=428 ms.

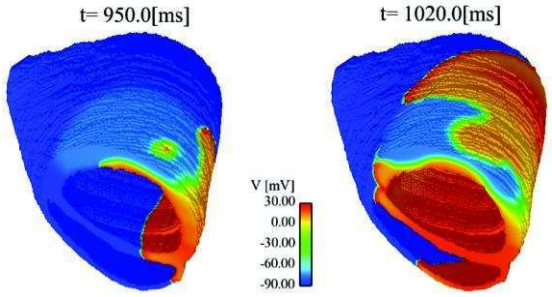
Whereas for a CI=418 ms, the reentrant front was able to exit the ischemic zone propagating through the normal tissue of the heart, for larger CI, i.e., CI=428ms, the re-entrant front is not able to abandon the ischemic zone generating a an spiral pattern that cease activity within the central zone with no further propagation into the normal cardiac tissue. Figure 3 shows a snapshot of the re-entrant front leaving the ischemic zone and completing an eight shape figure for CI=418 ms, and the spiral pattern for the CI=428 ms.



(a) (b)

Figure 3. a) Reentrant front completing the eight shape figure for CI=418 ms; b) Spiral pattern formed for CI=428 ms.

After the first re-entrant circuit, mid-myocardial layers were excited by the reentrant wavefront causing rather complicated patterns within the ischemic zone in the epicardium due to the re-entrant wavefront coming from the mid-myocardium. On the other hand, the faster propagation of the electrical activity through the endocardium, due to the wash-out zone prevented the perpetuation of the re-entrant activity in the ischemic zone. These re-entrant patterns generate a pathway within the central ischemic zone through which reentrant circuits can be sustained in the epicardium for high enough CIs as shown in Figure 4.



(a) (b)

Figure 4. Detailed of the re-entrant activity for CI=418 ms a) Reentrant wave front coming form the midmyocardium b) Premature completion of the re-entrant circuit through the endocaridum.

4. Discussion and conclusions

The main results of the performed simulations can be summarized as follows: i) As a consecuence of the applied extra-stimulus that originates an ectopic beat, reentrant activity is generated in all cases considered. This activity corresponds ot a eight shape figure in some cases (CI=418 ms) whereas in other cases it corresponds to a spiral like shape (CI=428 ms); ii) The reentrant activity generated as a consequence of the extra-stimulus ceases in all cases as a consequence of the interaction between wavefronts emerging from the from the wash-out zone into the ischemic zone.

For the eight shape reentrant pattern, the mechanisms governing the reentrant activity is similar to that obtained in 2D. The propagating wavefront is blocked when trying to invade the ischemic zone since the tissue is still in the refractory period. The electric wave then bypasses the zone of block propagating through the normal tissue and later reentering the ischemic zone retrogradely. However, this pattern of excitation only occurs at the epicardium in the ischemic heart since the mid-myocardium tissue remains in the refractory period.

In other cases, the reentry pattern corresponds to a single spiral. In this case, the reentrant front is not able to reexcite the normal tissue since it finds the tissue in the border zone within the refractory period forcing the wavefront to initiate a rotor that does not perpetuates within the ischemic zone.

Both described patterns from the simulations has been reported in the experimental work by Janse et al [5,6] in pig and dog hearts. For instance, Figure 3, panels A and B in ref [6] shows the eight shape reentrant pattern also obtained in our simulations, whereas panel X in the same figure shows the spiral pattern obtained for the larger CI.

However, differently to the experimental studies by Janse et al., none of the cases studied lead to self perpetuating reentrant activity. In all our simulations the reentrant

activity did not last more than three cycles. The main reason for this behavior was the existence of the wash-out zone. In our simulations, the interaction of epicardial wavefronts coming from the subendocardial wash-out zone with reentrant wave fronts caused the last to disappear preventing the perpetuation of reentrant activity in the ischemic heart. Additional studies on larger ischemic zones are required in order to determine if this effect is reduced as the area affected by ischemia becomes larger.

In conclusion, the model predicts the generation of figure-of-eight re-entries which cross the central ischemic zone formed in the epicardial surface due to the longer refractory period of the midmyocardial layers. Also, focal activity experimentally observed in the epicardium could be caused by re-entrant wavefronts propagating in the mid-myocardium that re-emerge in the heart surface..

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