Contribution of Electrophysiological Remodelling to Generation of Anatomical Re-Entries around the Right Pulmonary Veins in Human Atrium: a Simulation Study

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Abstract

Atrial arrhythmias are characterised by rapid and irregular activation of atrium. In this study, the effects of remodelling on ionic currents were incorporated in a model of human atrial action potential and were integrated in a two-dimensional (2D) model of human left atrium tissue including orifices for right pulmonary veins. We examined the effects of atrial remodelling on atrial arrhythmias when ectopic beats between pulmonary veins were applied. Under normal tissue conditions, no re-entry phenomenon was induced. In atrial remodelling, action potential duration (APD), effective refractory period (ERP) and conduction velocity (CV) were decremented and stable re-entries around the right pulmonary veins were produced. Our study suggests that the electrical remodelling is a key factor to generate anatomical re-entries around the pulmonary veins.

1. Introduction

Atrial arrhythmias (flutter and fibrillation) are the most common tachyarrhythmia. The presence of atrial fibrillation (AF) is associated with a considerable increase in morbidity and in mortality [1,2]. Typically atrial arrhythmias are characterised by rapid and irregular activation of atrium (300-500 bpm) [3], which results in the massive reduction of contractility in the atria. This rapid and irregular activation causes atrial remodelling. Atrial remodelling have been described in various animal models [4] and in the human [5,6]. It induces a set of changes in atrial properties that include anatomical structure [7], electrical changes [3-6] and intercellular gap junction coupling [8,9].

For humans, the electrical changes are: an increase in the regulation of I_{K1} channel density, decrease in the regulation of I_{CaL} and Ito channel densities and changes in the kinetics of Ito, I_{CaL} and I_{Na} channels [5,6].

These electrical changes cause a decrease in refractoriness produced by significant APD shortening [3,5,6,10]. In the human a more hyperpolarized resting potential and decreased maximal upstroke velocity has also been observed [5,6]. APD shortening is believed to underlie the mechanisms of "AF begetting AF" [4]. APD shortening is expected to allow the initiation and favour the maintenance of multiple reentrant wavelets in a limited mass of atrial tissue [3,4].

There are two possible mechanisms for the rapid and irregular activation of the atria: abnormal spontaneous electrical activity of ectopic foci and multiple re-entrant wavelets.

Experimental studies have identified the muscular sleeve of the pulmonary veins as a source of tachyarrhythmias and atrial premature beats that could trigger of AF [11]. In animal models, electroanatomic [12] and optical mapping [13] have demonstrated complex wavefronts within or emanating from the pulmonary veins. Therefore, focal discharges may trigger multiple wavelet re-entry. Different experimental results suggest that atrial remodelling provocked by ectopic activity facilitate the induction of wavelet reentry. Thus, the unifying theory suggest that focal tachycardias (which originate mostly in or around the pulmonary veins) promote atrial remodelling and are required to trigger and maintain a substrate capable of multiple wavelet reentry [14].

The aim of this work is to study the effects of atrial remodelling on the generation of anatomical re-entries around the pulmonary veins.

2. Methods

The experimental data of AF induced changes in ionic channel conductance and kinetics of human atrial myocytes are reported by Bosh *et al*. [8] and Workman *et al*. [9]. These changes have been incorporated in the

model of human atrial action potential developed by Nygren *et al*. [15] to reproduce atrial remodelling. In order to get the atrial remodelling model, several parameters were changed in the atrial model: the channel conductance for I_{K1} was increased by 250 %, the channel conductance for I_{CaL} was decreased by 74%, the channel conductance for Ito was decreased by 85%, the Kinetics of the fast inactivation of I_{CaL} was increased by 62 %, the activation curve of Ito was shifted by +16 mV and the inactivation curve of I_{Na} was shifted by +1.6 mV. With these changes, the modified model can reproduce the action potential of human atria myocytes of patients with chronic AF.

This modified electrophysiological model was integrated in an anisotropic two-dimensional (2D) model of human left atrium tissue including two orifices for right pulmonary veins.

Transversal to longitudinal ratio of conductivity for the conduction tissue was set to 1:2 with the longitudinal direction being parallel to the main axis of the bundles.

The size of atrial tissue was 48x48 mm, which was discretized by a special resolution of 0.12 mm to form a 400x400 node discrete lattice. We added two circular regions of 11 mm diameter and null conductivity for simulate the orifices of the right pulmonary veins (SRPV, IRPV). The tissue includes part of the right sidewall of the atrium (Interatrial septum (IS) ends in this wall), superior wall (Bachmann bundle (BB) ends in this wall) and back wall.

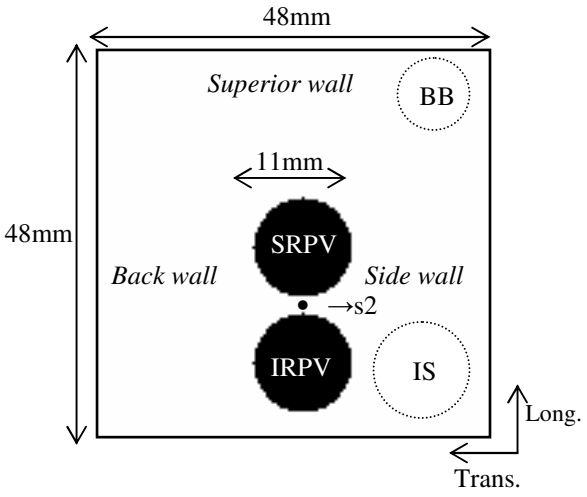

Figure 1. 2D model of human left atrium tissue including orifices for superior (SRPV) and inferior (IRPV) right pulmonary vein. BB, region where Bachman bundle ends. IS, region where Interatrial septum ends. The longitudinal and transversal direction is indicated.

Both, normal and remodelling models were excited by a pulses train (s1) that simulate stationary sinus beat arriving to the right atria through the BB and IS, at a cycle length (CL) of 300 ms. An ectopic beat (s2) was applied between two right pulmonary veins during the repolarization phase of the last s1 beat (10^{th}). Ectopic foci were modelled by a supra-threshold stimuli with amplitude of 0,4 uA and duration of 2 ms to a localized area (5x5 nodes) between two orifices for right pulmonary veins.

The wavelength of excitation (λ) was calculated by the equation:

$$\lambda = \theta t_r$$

where θ is the conduction velocity and t_r is the refractory period.

3. Results and discussion

The model-generated action potentials under normal (control) and under remodelling conditions were shown in Figure 2.

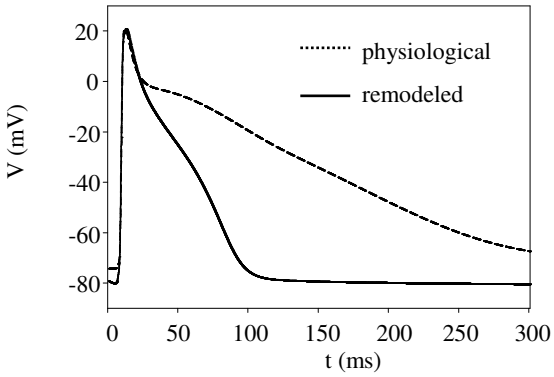

Figure 2. Simulated APs for a physiological atrial myocyte and a cell with electrophysiological remodelling.

Under normal conditions, the longitudinal conduction velocity was 40 cm/s and the transversal conduction velocity was 21 cm/s.

The electrical remodelling induced a 6 mV hyperpolarization of the resting potential, a 70% reduction in APD_{90} (90% repolarization) and 5% reduction in CV. The APD was abbreviated from physiologically 312 ms to 92 ms and the ERP were shortened from 284 ms to 86 ms. These changes are quantitatively similar to the experimental data observed by Bosch and Workman et al. [5,6], and to the simulations carried out by Zhang et al. [17] and Semman et al. [18].

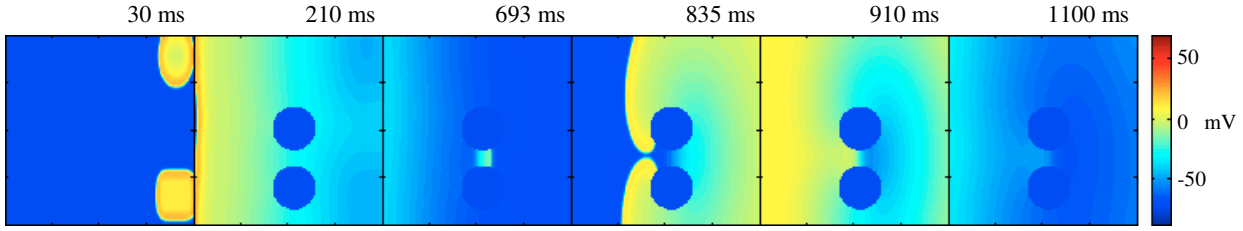

Figure 3. Model of normal atrial tissue with 2 orifices for right pulmonary veins. Sinus rhythm (s1) arriving to the right atria through the interatrial septum and Bachmann bundles at (A) 30 ms and (B) 210 ms after the last s1 beat (10^{th}). (C) Ectopic beat (s2) at repolarization phase of s1. (D) Ectopic beat generates UB turning around the two pulmonary veins. (E) Wavefront collides with its own refractory tail. (F) Wavefront extinct.

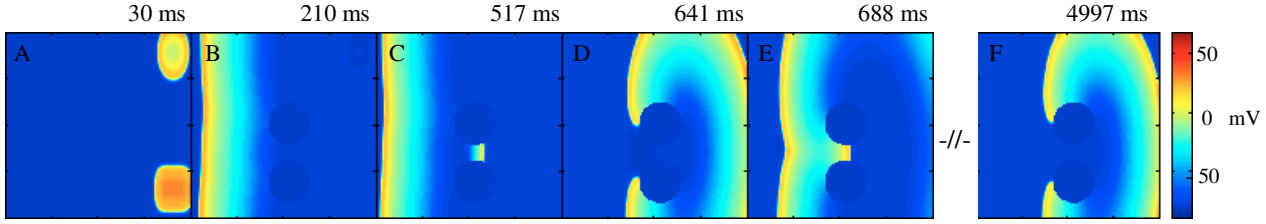

Figure 4. Model of pathological atrial tissue. Sinus rhythm at (A) 30 ms and (B) 210 ms after the last s1 beat (10^{th}). (C) Ectopic beat (s2) at repolarization phase of s1. (D) Ectopic beat generates UB turning around the two pulmonary veins. Stable re-entries propagating around pulmonary veins at (E) 688 ms and (F) 5000 ms.

In 2D simulations, when we used the model under normal conditions, the applied ectopic foci generated a unidirectional block in opposite direction to the excited sinus. The vulnerable window (VW) range, within which UB occurs, was 3 ms.

The wavefront initiated by the UB turned around the two pulmonary veins. Nevertheless, an anatomical re-entry was not obtained because the refractory period was sufficiently long so that the wavelength of excitation (λ=7.2 cm) was longer than the trajectory length (L=3.5 cm) for each pulmonary vein. Therefore, the wavefront collided with its own refractory tail (not-yet-recovered unexcitable tissue) and became extinct in the first turn (Figure 3).

When we used the model under remodelling conditions, the width of the VW was triplicated (9 ms), due to the changes in several electrophysiological properties. The wavefront initiated by the UB also turned around the pulmonary veins, but in this case the wavefront continued to propagate constantly, generating anatomical re-entries around the pulmonary veins, one in clockwise, and the other counterclockwise. This occurs because when the refractory period and the conduction velocity were decreased, the wavelength of excitation (λ=2.1 cm) is shorter than the trajectory length, thus, the wavefront encounters excitable tissue producing a stable re-entry propagating around each pulmonary vein. In a 5 s simulation was observed 26 turns for each re-entry around pulmonary veins (Figure 4).

This reentrant behavior would cause a possible abnormal contraction of the atrium (tachyarrhythmia), being able to trigger another episode of AF or to help its maintenance.

These results are consistent with experimental studies. Observations published by Hobbs et al. [19], demonstrated the role of electrical remodelling in the progression of focal atrial ectopy to persistent AF. Others studies published by Haissaguerre et al. [11], Chen et al. [20], and Kumagai et al. [21], shows the role of focal activation in the initiation and maintenance of AF, initiated by triggers in the pulmonary veins (PV's); which could be successfully treated by delivery of radiofrequency energy (RF).

4. Conclusions

In this study, we developed an anisotropic 2D computer model of the electrical activity of human left atrial tissue, which reproduced the effects of electrical remodelling caused by AF in tissue.

Using the model, we investigated the importance of remodelling to generate re-entries.

Ectopic activity between right pulmonary veins activated within the vulnerable window of sinus rhythm wavefront generated a unidirectional block.

In simulations with normal tissue, no re-entry phenomenon was induced, while with a remodelling tissue stable re-entries around the right pulmonary veins

was produced.

Our results suggest that the electrical remodelling is a key factor to generate anatomical re-entries triggered from ectopic foci around the right pulmonary veins in human atrium.

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