Effect of Ectopic Focus Frequency on Fibrillatory Conduction in Atrial Remodelling Tissue. a Simulation Study

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Abstract

Atrial fibrillation (AF) is the most common atrial tachyarrhythmia. Recently, pulmonary vein ectopic focus has been demonstrated that it can trigger reentry in the presence of a vulnerable substrate and lead to AF. We examined the effects of ectopic focus frequency on the generation of AF. In this study, the effects of remodelling on ionic currents were incorporated in a two-dimensional anisotropic model of human left atrial tissue. Ectopic activity initiated a stable reentry around the right pulmonary veins. The interaction of this ectopic activity with a rapid sinus rhythm generated fibrillatory conduction. This fibrillatory rhythm was maintained only at high rates of ectopic focus. Our study suggests that the interaction of high frequency ectopic activity and rapid sinus rhythm facilitates the progress from a stable reentrant mechanism to fibrillatory conduction in remodelling atrial tissue.

1. Introduction

Atrial fibrillation (AF) is the most common auricular tachyarrhythmia. The presence of AF is associated with a considerable increase in morbidity and in mortality [1]. Typically, atrial arrhythmias are characterised by rapid and irregular activation of atrium (300-500 bpm) [2]. Although considerable advances in the treatment of AF have taken place, the results of the pharmacologic treatment and ablation are still suboptimal. This is due, mainly, to the ignorance that still exists on the pathophysiological mechanisms that cause the initiation and maintenance of the arrhythmia.

During the last 50 years, the most widely accepted conceptual model of reentrant activity in AF has been the multiple wavelets hypothesis [3]. This hypothesis was questioned by Haïssaguerre et al. [4] when demonstrating that extrasístoles and auricular rapid paces originated in the interior or in the proximities of the pulmonary veins could act like triggers and, in some cases, they are responsible for the maintenance of AF episodes [5,6]. There are many factors that favour the initiation and maintenance of fibrillatory conduction. One of them is the atrial remodelling, caused by the rapid and irregular activation of the atrium during atrial arrhythmias. The electrical changes induced by atrial remodelling [2,6-8] cause a decrease in refractoriness by significant action potential duration (APD) shortening [2,7,8]. APD shortening is believed to underlie the mechanisms of "AF begetting AF" [6].

A unifying theory suggests that focal tachycardias promote atrial remodelling and are required to trigger and maintain a substrate capable of multiple wavelet reentries [9]. Additionally, experimental studies have demonstrated that a high frequency of this focal activity contributes to the generation of fibrillatory activity [10]. The objective of this work was to examine the effect of ectopic focus frequency on the generation of reentrant mechanisms, when a recurrent focus is applied between right pulmonary veins, in remodelling atrial tissue.

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. [7] and Workman et al. [8]. These changes have been incorporated in the model of human atrial action potential (AP) developed by Nygren et al. [13] to reproduce atrial remodelling. In order to get the atrial remodelling model, several parameters were changed in the AP 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 I_{to} 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 (figure 1).

Transversal to longitudinal ratio of conductivity for the conduction tissue was set to 2:1 with the longitudinal direction being parallel to the main axis of the bundles. The size of atrial tissue was 9.6 cm X 9.6 cm, which was discretized by a spatial resolution of 0.24 mm to form a 400 X 400 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 backwall.

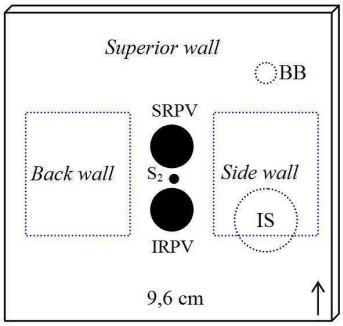

Figure 1. 2D model of human left atrium tissue including orifices for superior (SRPV) and inferior (IRPV) right pulmonary vein. BB, region where Bachman bundle ends. IS, region where Interatrial septum ends. The EGMs are registered into the regions delimited by the blue dotted line. Longitudinal direction is indicated by the arrow.

The model was excited by a train of pulses (S_1) that simulate stationary sinus beat arriving to the right atria through the BB and IS. An ectopic beat (S_2) was applied between two right pulmonary veins during the repolarization phase of the last S_1 beat. Ectopic foci were modelled by a supra-threshold stimulus with amplitude of 0.4 uA and duration of 2 ms to a localized area (5 X 5 nodes) between two orifices for right pulmonary veins. Ectopic beats were applied to cycle length (CL) of 130 ms. The basic cycle length (BCL) of sinus rhythm was decreased progressively from 800 to 300 ms. Next, maintaining the BCL of sinus rhythm to 300 ms, the CL of ectopic focus was multiplied by two (CL = 260 ms) and three (CL = 390 ms).

Unipolar electrograms for a sheet of cells under conditions of uniform intracellular anisotropic resistivity was simulated as previously described [14]. The extracellular potential (Φe) is given by the following equation:

$$\Phi_e(P) = \frac{\rho_e}{4\pi} \sum_{i=1}^{M} \sum_{j=1}^{N} \frac{I_{ion(i,j)}}{r_{i,j} V_s} \qquad (1)$$

where M and N are the total numbers of segments in the longitudinal and transversal directions, respectively, $r_{i,j}$ is the distance from the observation point (P) to the center of the volume element (Vs) at node i,j, and ρe is the extracellular resistivity.

Pseudo-Electrograms (EGMs) were computed each two milliseconds, for a simulated-electrode located in the center of two areas of 2.4 cm X 2.4 cm in the backwall and sidewall of the left atrium near to pulmonery veins, 1 mm from the atrial surface. To analysis the frequency content of model electrograms, spectral analysis of signals was performed with fast Fourier transform (FFT). Activity was sampled at 500 Hz (2 ms) for 5000 frames (≈ 5 seconds), providing a spectral resolution of 0.2 Hz.

3. Results and discussion

The electrical remodelling induced a 6 mV hyperpolarization of the resting potential, a 70% reduction in APD_{90} (90% repolarization) and 5% reduction in conduction velocity (CV). The APD was reduced from 312 ms to 92 ms and the effective refractory period (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. [7,8].

In 2D simulations, the applied ectopic foci generated a unidirectional block in the opposite direction to the excited sinus. The vulnerable window (VW), within which unidirectional block occurs, was 9 ms. The wavefront initiated turned around the two pulmonary veins and it continued to propagate constantly, generating anatomical re-entry around the pulmonary veins, maintaining the tissue in tachycardia.

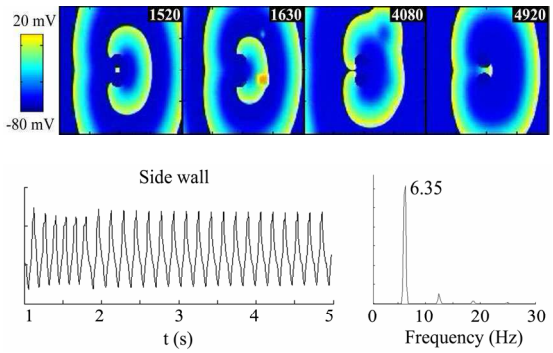

Figure 2. Snapshots of membrane voltage and pseudo-EGM at the sidewall with corresponding FFT, registered during ectopic activity to CL of 130 ms and BCL of sinus rhythm to 800 ms.

Applying the ectopic focus at CL of 130 ms, with a BCL of sinus rhythm to 800 ms, fibrillatory activity was not observed. The reentry around pulmonary veins was the only driver that maintained the tachycardia (figure 2).

Pseudo-EGM demonstrated stable and regular atrial activation. A dominant frequency (DF) peak of 6.35 Hz was present in backwall and sidewall, which corresponded to a 1:1 activation pattern at a mean reentry CL of 158 ms, showing a focal atrial tachycardia.

Decreasing the BCL of sinus rhythm from 600 ms to 450 ms and to 300 ms, maintaining focal beats at CL of 130 ms, figure-of-eight reentries and rotors were generated in sidewall. Pseudo-EGMs of the sidewall show irregular activity in the three cases, FFT analysis shows broadbands with multiple frequency peaks, corresponding to fibrillatory conduction as a consequence of the unstable and irregular electrical activity in this region (figure 3 shows the photograms and pseudo-EGM at the sidewall with its corresponding FFT for 300 ms of BCL). Additionally, the DF peaks in backwall and sidewall were different (7.64 Hz and 7.08 Hz, respectively), suggesting an unstable conduction pattern.

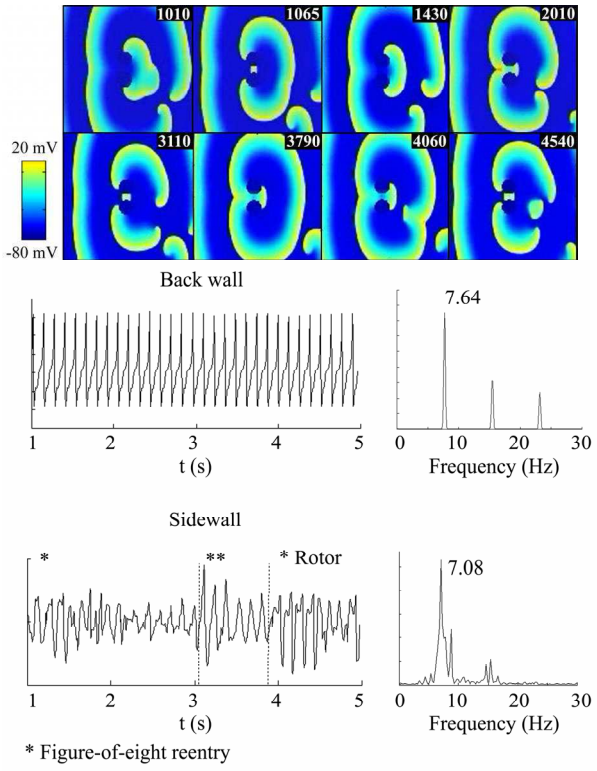

Figure 3. Snapshots of membrane voltage and pseudo-EGM at the sidewall with corresponding FFT, registered during ectopic activity to CL of 130 ms and BCL of sinus rhythm to 300 ms. Figure-of-eight reentry are represented by the regions with "*".

These results are consistent with experimental studies. Observations published by Hobbs et al. [15], demonstrated the role of electrical remodelling in the progression of focal atrial ectopy to persistent AF. Others studies published by Haissaguerre et al. [4], Chen et al. [5], and Kumagai et al. [16], show 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).

Additionally, experimental studies have demonstrated that high sinus frequency favour the induction of a focal automatism [4,17].

Duplicating the CL of ectopic focus to 260 ms, fibrillatory conduction was observed. Figure-of-eight reentries and rotors were generated in sidewall. Pseudo-EGMs shows irregular activity, FFT analysis shows broadbands with multiple frequency peaks, corresponding to fibrillatory conduction. The DF peak was 6.89 Hz (mean CL of 145 ms) in sidewall.

Triplicating the focal CL to 390 ms, a figure-of-eight reentry episode of short duration was observed, but fibrillatory conduction was not generated, on the contrary, at 3 s of simulation the reentry around PVs was finished by interaction with the sinus rhythm, ending the tachycardia. FFT analysis shows a first large peak at 3.17 Hz which correspond with sinus rhythm frequency and a second large peak at 6.59 Hz which correspond with tachycardia pattern.

Experimental studies have demonstrated that a greater duration and a high frequency of this focal activity contribute to the generation of fibrillatory activity [10]. When the source frequency exceeds the sinus rhythm frequency, the source is converted to the main heart pacemaker; on the contrary, it is suppressed by the upper index of sinoatrial node. Our studies support this idea, when we decreased the focal frequency below the sinus rhythm, all reentrant activity ended, maintaining only the sinus rhythm activity in the tissue.

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. Our results support the idea that an ectopic focus localized near the pulmonary veins, acting in remodelling tissue, is an initiator of reentrant mechanisms, which are localized in the sidewall of the left atrial. These reentrant circuits generate fibrillatory activity when interacting with a rapid sinus rhythm and high ectopic focus frequency (higher than sinus rhythm frequency).

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