Effect of the Ectopic Beats Location on Vulnerability to Reentries in a Three Dimensional Realistic Model of Human Atria

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia. AF induces changes in atrial properties (atrial remodelling) that helps to perpetuate it. Recent studies have shown that ectopic activity in the pulmonary veins can trigger reentrant mechanisms and lead to AF. However, the influence of ectopic foci location on the likelihood of triggering reentries and AF is not well known. In this work we study the effect of the ectopic beats location on vulnerability to reentries. To carry out the study, the effects of electrical remodelling were incorporated in an atrial cell model and integrated in a realistic three-dimensional (3D) model of human atria. An ectopic beat was applied at four different locations in the left atrium. Pseudo-unipolar electrograms in different regions and spectral analysis of the signals obtained were calculated. The results show the great influence of the ectopic activity location on the vulnerability to reentries.

1. Introduction

Atrial fibrillation (AF) is the most common atrial tachyarrhythmia. The presence of AF is associated with a considerable increase in morbidity and mortality. 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 [1]. This hypothesis was questioned by Haïssaguerre et al. [2] when demonstrating that atrial rapid paces originated within or in the ostium of the pulmonary veins (PVs) could act like triggers and, in some cases, they are responsible for the maintenance of AF. A tight coupled single extrastimulus in PVs can result in unidirectional conduction block and may also result in a rapid reentrant circuit maintained in the atria [3]. The PVs have been found to present the predominant source of ectopic activity involved in the initiation of AF [4]. However, ectopic foci have also been founded in other atrial zones, as in the free wall of the left atrium, appendages, crista terminalis, among others [5].

Additionally, AF induces electrical remodelling of membrane ionic channels in atrial cells [6]. Electrical remodelling causes a decrease in refractoriness by significant action potential duration (APD) shortening, leaving the atria vulnerable to reentrant circuits. Atrial remodelling, anatomical structures, spatial heterogeneity and nonuniform anisotropy are the keys to reentrant activity initiation.

In this work the effects of the ectopic beats location on vulnerability to reentries are investigated in a realistic tree-dimensional (3D) model of human atria with electrical remodelling.

2. Methods

2.1. 3D model of human atria

A computer model of the human atria was developed, its geometry derived from magnetic resonance imaging data of [7], this 3D monolayer geometry was adjusted to the anatomical specifications of Wang et al. [8]. The model includes left and right atrial chambers, inter-atrial septum, pectinate muscles, limbus of the fossa ovalis, Bachmann's bundle, crista terminalis, left and right appendages, coronary sinus, right and left PVs, superior and inferior caval veins, isthmus of right atrium and openings corresponding to the valves (see figure 1). An area near superior caval vein was defined to the sinoatrial node.

The atrial surface was discretized into a hexahedral mesh with 98090 nodes. The spatial resolution ranging

from 320 μm to 900 μm.

A realistic fiber structure was included in the model. Using data from histology on excised atria [9], the model was divided into 22 zones, in which a perpendicular axe was traced to the direction of the main bundles. The perpendicular to these axes was projected on the atrial surface to obtain de fiber orientation.

Regions of high (crista terminalis, Bachmann's bundle and limbus of the fossa ovalis), low (isthmus and fossa ovalis) and medium conductivity (the rest of the tissue) were identified. The conductivity values were 0.25, 0.40 and 0.10 S/cm respectively. A 2:1 anisotropic ratio was considered in the tissue, except in the right isthmus considered isotropic.

2.2. Electrical remodelling

Experimental data reported by Bosh et al. [6] have demonstrated that AF induces changes in ionic channel conductance and kinetics of human atrial myocytes. These changes have been incorporated in the model of human atrial action potential (AP) developed by Nygren et al. [10] to reproduce atrial remodelling.

In order to get the 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 I_{to} 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 atrial myocytes of patients with chronic AF. This modified electrophysiological model was integrated in the 3D model.

2.3. Action potential propagation

Action potential propagation was modelled using the monodomain equation given by:

$$\nabla . D_i \nabla V_m = S_v \left(C_m \frac{dV_m}{dt} + I_{ion} \right) \quad (1)$$

where V_m is the transmembrane potential, C_m = 50 pF/cm^2 is the specific membrane capacitance, S_v is the cell surface-to-volume ratio, D_i is the conductivity tensor, and I_{ion} is the aggregate ion fluxes. The ion fluxes across the membrane are based on the modified Nygren atrial cellular model.

Assuming an extracellular space with infinite resistance, the boundary condition for this equation is:

$$-\nabla . (D_i \nabla V_m) = 0 \text{ en } \Gamma \quad (2)$$

Equation 1 was solved using a finite element method.

2.4. Pseudo-electrograms

Pseudo unipolar electrograms (EGMs) were computed in 8 simulated-electrodes located in the free wall of left atrium (black dots in figure 1). The extracellular potential (Φ_e) was modelled using a current source approximation for a large volume conductor:

$$\Phi_e(r,t) = \frac{1}{4\pi\sigma_e} \int dr' \frac{I_m(r',t)}{|r - r'|} \quad (3)$$

where r is the electrode location vector, r' is the current source location vector, I_m is the transmembrane current per unit area of atrial tissue surface, and σ_e is the extracellular conductivity. EGMs were computed every millisecond. This electrograms was then used to calculate the power spectral density using Fast Fourier Transform (FFT) method, which allowed us to obtain the maximum dominant frequency (DF).

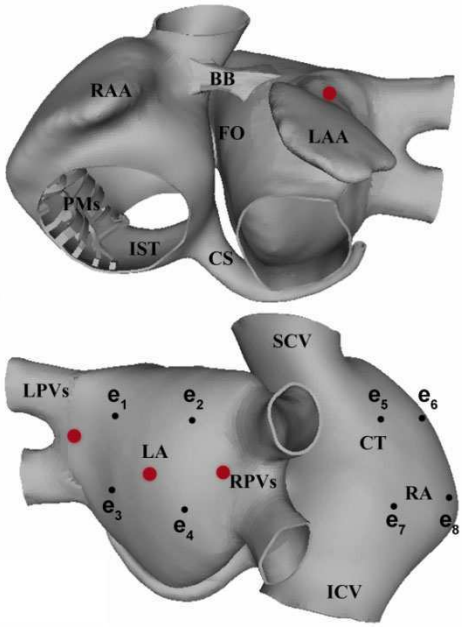

Figure 1. 3D model of human atria, including: left (LA) and right (RA) atrial chambers, pectinate muscles (PMs), Bachmann´s bundle (BB), crista terminalis (CT), fossa ovalis (FO), isthmus (IST), left (LAA) and right (RAA) appendages, coronary sinus (CS), right (RPVs) and left (LPVs) pulmonary veins, superior (SCV) and inferior (ICV) caval veins. The black dots are the eights virtual electrodes (e1 to e8). The red dots are the four different locations where the ectopic beat is applied.

2.5. Stimulation protocol

A train of stimuli was applied during 10 seconds in the sinoatrial node region, to simulate the sinus rhythm. The basic cycle length (BCL) was 1000 ms. An ectopic beat was applied during the repolarization phase of ten sinus

beat, at four different locations in the left atrium: centre of the free wall, basis of the appendage, and ostium of the left and right PVs (red dots in figure 1).

3. Results and discussion

Electrical remodelling induced a 70% decrease in APD. The APD was reduced from 312 ms to 92 ms. These changes are consistent with experimental observations [6].

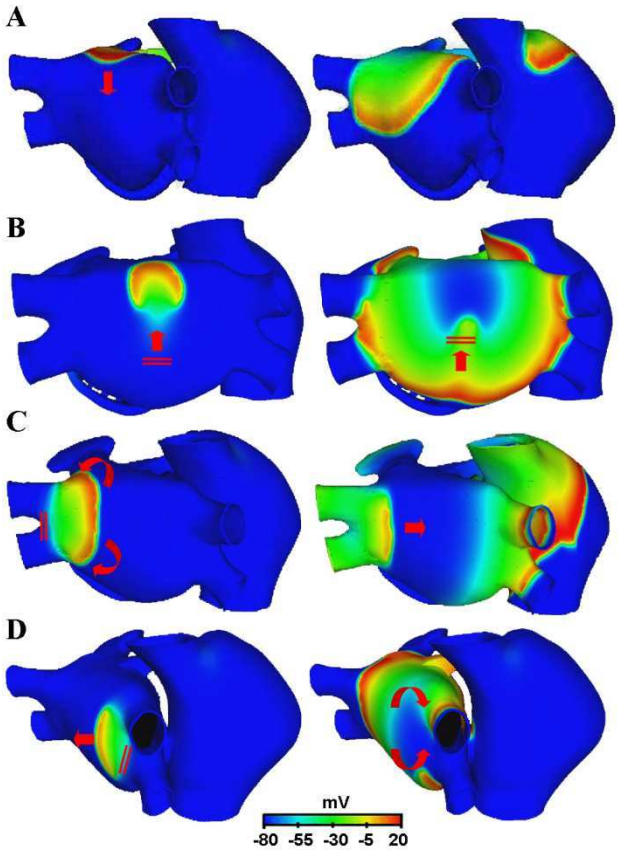

Figure 2. Ectopic beat applied in: A) the left appendage; B) the middle of free wall of the left atrium; C) the left PVs, and D) the right PVs.

When we applied the ectopic beat in the left appendage (see figure 2 A) in the repolarization phase of ten sinus beat, a unidirectional block occurred. However the wavefront propagated through both atriums and became extinct. Reentry was not generated.

When we applied the ectopic beat in the middle of the free wall of the left atrium (see figure 2 B), also a unidirectional block occurred, the wavefront travels towards the superior wall, the two vertices turned by themselves in the opposite direction and collided. Reentry was not generated.

On the other hand, the ectopic beats applied in the ostium of right and left PVs generated a unidirectional block. The wavefronts turned around the PVs (see figure 2 C and D) and they continued propagating in free wall of the left atrium, generating a reentry. The width of the vulnerable window (Vw) to reentry (see figure 3) was greater in the left PVs (16 ms) than in the right PVs (2 ms). During 10 seconds of simulations, figure-of-eight reentries and rotors were observed in both atriums (see figure 4), generating fibrillatory conduction.

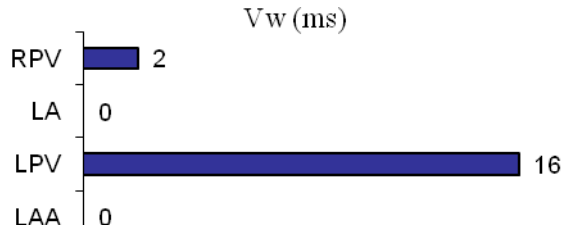

Figure 3. Width of the vulnerable window to reentry in left PVs (LPV), right PVs (RPV), free wall of the left atrium (LA) and in the left appendage (LAA).

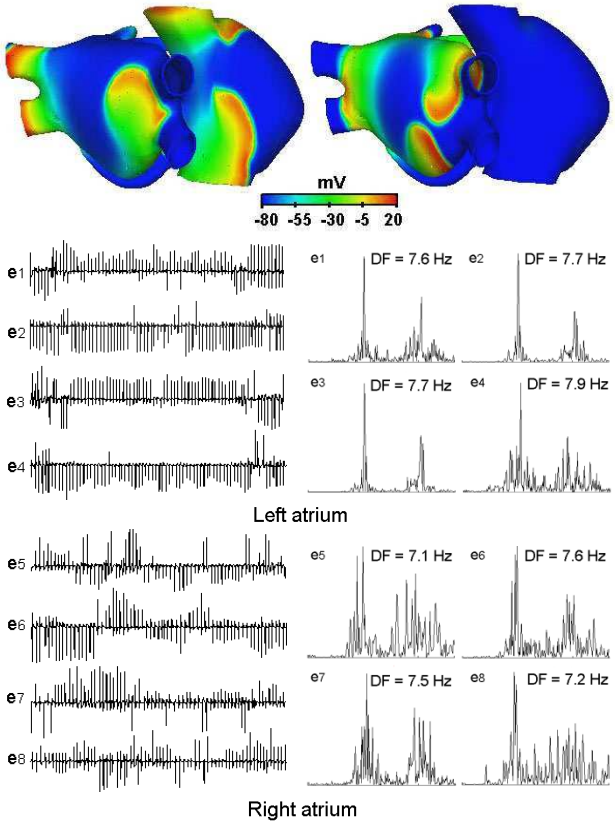

Figure 4. AF generated by the ectopic beat applied at left PVs. The 8 EGMs calculated in both atriums, their spectral analyses and the DF values are showing.

This result is accord with experimental and clinical studies [3,11], which have shown the role of focal

activation in the initiation and maintenance of reentrant mechanisms, initiated by triggers in the PVs, mainly in the left PVs; which could be treated by delivery of radiofrequency energy (RF). Arentz et al. [12] in a study with 35 patients, recorded ectopic beats in left PVs that triggered AF in 39% of the cases. Haissaguerre et al. [11], in a study with 45 patients identified 65 ectopic foci in PVs, of which 42 (65%) are in the left PVs.

During fibrillatory activity, after the ectopic beat applied in left PVs, electrograms were calculated in the free wall of the left and right atriums (see figure 4). In agreement with previous findings, a single reentry is sufficient to produce AF-like EGMs [13]. Electrogram complexes were rapid, irregular and polymorphous (variability in size and shape).

Spectral analysis of the EGMs shows multiple frequency peaks, as a consequence of the unstable electrical activity. FFT analysis has had increasing use in helping to study and characterize atrial arrhythmias [14]. Dominant frequency peaks at different values were found, been lower in right atrium. We obtained a DF gradient from right atrium to left atrium. This indicates that the activation pattern is heterogeneous, consistent with the presence of AF. These results are in agreement with experimental studies [15] that have obtained DF gradient during AF episodes.

4. Conclusions

The results show that ectopic beat location affects the vulnerability to re-entry triggered by ectopic activity. Reentry was obtained applying an ectopic beat in PVs. The width of the vulnerable window was greater in the left PVs.

Electrograms and its spectral analysis allow characterizing AF.

Biophysical modelling can be considered as a useful tool for understanding the underlying mechanisms of AF.

Acknowledgements

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