Influence of Atrial Dilatation in the Generation of Re-Entries Caused by Ectopic Activity in the Left Atrium

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Abstract

Structural remodeling plays an important role in the genesis and maintenance of atrial arrhythmias. In this work, the influence of atrial dilatation on the generation of reentrant activity trigger by an ectopic beat applied at different locations of the left atrium was studied. We have developed two 3D models of human atria: a model with electrical remodeling only, and a model with electrical and structural remodeling (atrial dilatation). Both models include the Nygren atrial cell model and realistic fiber orientation. When an ectopic beat is applied in the middle of the free wall of the left atrium, a reentry was not generated; however, in dilated left atrium, reentrant activity was generated. For ectopic beats applied between pulmonary veins, the vulnerable window to reentry was higher in dilated atria than in normal atria. This study shows the important influence of atrial dilatation on the vulnerability to reentries, triggered by ectopic activity.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans and it is characterized by rapid and chaotic electrical activity of the atria, causing loss of effective atrial contraction. Clinical studies have shown that AF produces electrical [1,2] and structural [3,4] changes that facilitate its perpetuation; these changes have been called atrial remodeling. Electrical changes cause a significant shortening of the refractory period [5-7], being responsible for the initiation and maintenance of multiple reentrant waves in atrial tissue, as suggest different experimental studies [1,5,6]. Structural changes cause atrial dilatation, principally of the left atrium [8,9]. The relationship between the size of the atria and the generation of diverse types of atrial arrhythmias has been observed in the last 50 years, in both clinical and experimental studies [3,4,8,10-14]. Atrial dilatation has been considered as a cause of arrhythmias, but also as a consequence [15]. For this reason it is necessary to study this mutual dependence more closely. The aim of this paper is to study the effect of dilatation of the left atrium in the generation of reentrant activity, triggered by ectopic beats, using 3D models of human atria.

2. Methods

In this work, we developed two computational 3D models of human realistic atria: a model with electrical remodeling only (normal size), and a model with electrical and structural remodeling (atrial dilatation). Both models include the Nygren atrial cell model [16] and realistic fiber orientation.

Different anatomical regions of the atrial models were adjusted to the anatomical specifications of Wang *et al.* [17] and Chauvin *et al.* [18]. The size of the anatomical regions is in agreement with the sizes defined by Cohen *et al.* [19]. The models include 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 the superior caval vein was defined to be the sinoatrial node. The atrial surface was discretized into a hexahedral mesh with 50906 elements and 100554 nodes. Using data from histology on excised atria [20] the realistic fiber structure was included in the models. 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.

Action potential propagation was modeled using the monodomain equation and was solved using the finite element method, as in previous studies [21,22].

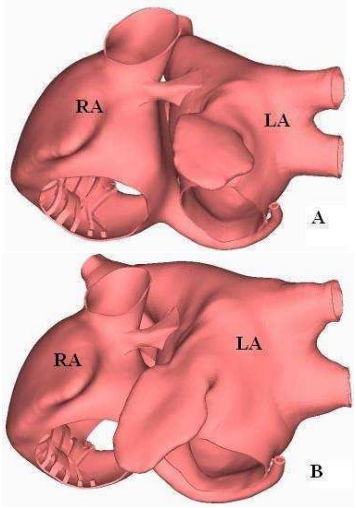

Figure 1. Model of human A) normal atria and B) dilated atria. Left (LA) and right (RA) atrial chambers.

2.1. Electrical remodeling

Experimental data [23-25] have demonstrated that AF induces changes in ionic channel conductance and kinetics of human atrial myocytes. In order to get the remodelling model, several parameters were changed in the cell 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 normal and dilated models.

2.2. Modeling atrial dilatation

Atrial dilation was considered only in the left atrium. To obtain the dilated model, the anteroposterior, mediolateral and superoinferior axes were modified, as shown in Table 1. Maintaining the right atrium unchanged; the left atrium was dilated to obtain values within the range of experimental data of human dilated left atrium [26].

Table 1. Axes in normal and dilated atrial models.

Axis	Normal	Dilated
Anteroposterior	4.31 cm	5.09 cm
Mediolateral	4.49 cm	6.20 cm
Superoinferior	4.11 cm	5.82 cm

2.3. Stimulation protocol

A train of stimuli was applied during 10 seconds in the sinoatrial node region, to simulate the sinus rhythm at high frequency. The basic cycle length (BCL) was 300 ms. A single ectopic beat was applied during the repolarization phase of the last sinus beat at three different zones: in the base of right and left pulmonary veins and in the middle of free wall of left atrium. The foci were modeled by a small group of elements. The ectopic activities were applied at different coupling intervals, to reproduce the studies by Haisaguerre *et al.* [27].

3. Results and discussion

When we applied the ectopic beat in the right pulmonary veins, in both normal and dilated atria, reentrant activity was generated within a period of time called vulnerable window for reentry. However, the length of the vulnerable window was larger in dilated atria (45 ms) than in normal atria (4 ms), which is consistent with experimental observations of [28].

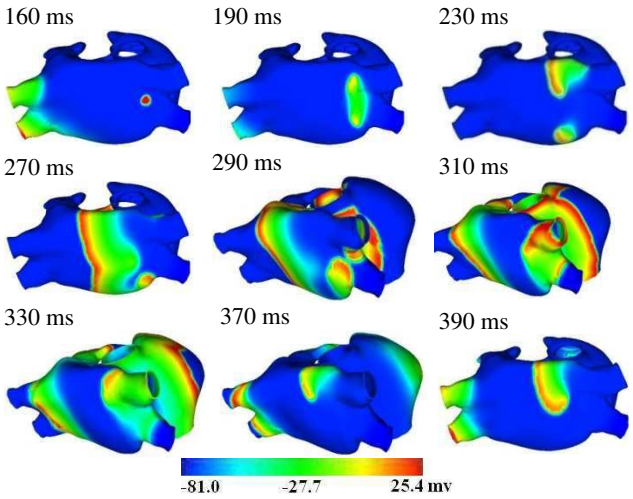

Figure 2. Ectopic beat in the right pulmonary vein in dilated left atrium.

Figure 2 shows the ectopic beat applied in the right pulmonary veins in dilated atria, at 160 ms of coupling

interval. The ectopic beat provoked unidirectional conduction block, inducing propagation only in the free wall direction (190 ms in figure 2). The wavefront was fragmented generating reentrant waves. Figure-of-eight reentries and rotors were observed.

Similary, when we applied the ectopic beat in the left pulmonary veins, in both normal and dilated atria, reentrant activity was generated. The duration of the vulnerable window was larger in dilated atria (18 ms) than in normal atria (7 ms), which is consistent with experimental studies [27]. Figure 3 shows the ectopic beat applied in the left pulmonary veins in dilated atria, at 209 ms of coupling interval.

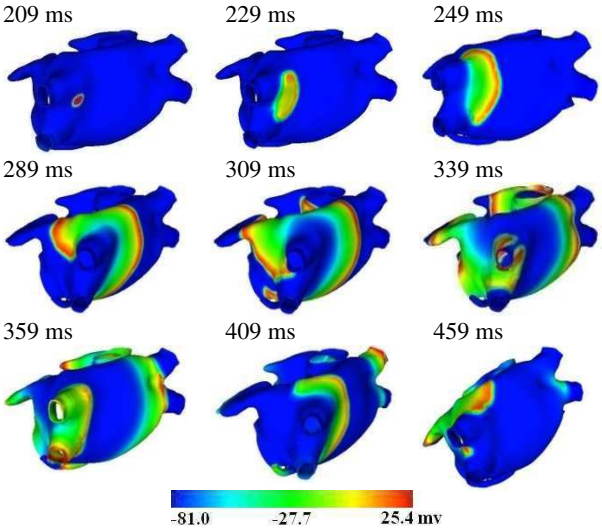

Figure 3. Ectopic beat in the left pulmonary vein in dilated left atrium.

On the other hand, when we applied the ectopic beat in the middle of the free wall of the normal atria, reentrant activity was not generated (not shown), which is in agreement with experimental observations [27]. When the ectopic beat was applied in the repolarization phase of the last sinus activity a unidirectional block was generated, inducing propagation only in the superior wall direction. The wavefront turned and collided with its own refractory tail and became extinct.

On the contrary, in dilated atria, the wavefront generated by unidirectional block turned, finding excitable tissue and continued propagating. This is due to the fact that the dilated atria has a greater mass of tissue, in which the wavefronts can reenter. The length of the vulnerable window for reentry was 8 ms. Figure-of-eight reentries and rotors were observed.

Figure 4 shows the ectopic beat applied in the middle of free wall of the left dilated atrium, at 159 ms of coupling interval.

These results show the important role of the expansion process in the vulnerability to reentry, consistent with studies of Eckstein *et al.* [29].

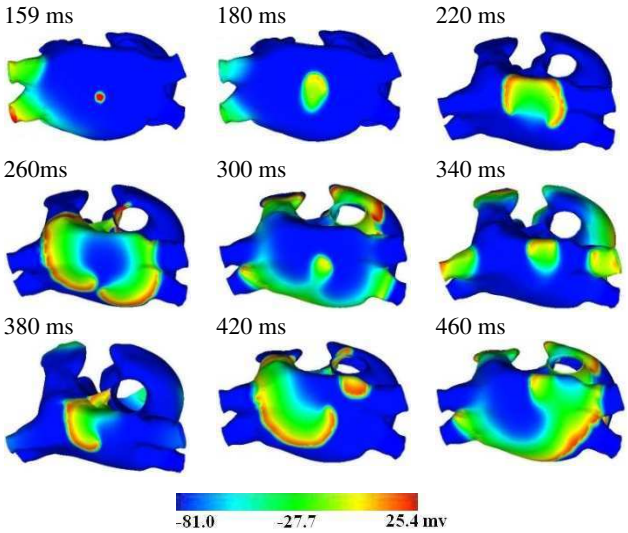

Figure 4. Ectopic beat in the middle of the free wall of the dilated left atrium.

4. Conclusions

In this study we developed a 3D model of human atria with normal size and another 3D model of dilated atria. Electrical remodeling was incorporated in both models to reproduce the action potential of patients with chronic AF. The results show a greater vulnerability to reentries in dilated atria than in normal atria. This study demonstrated by simulation, the important role of the atrial dilatation in the development of reentries.

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