Reentrant Mechanisms Triggered by Ectopic Activity in a Three-Dimensional Realistic Model of Human Atrium. a Computer Simulation Study

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Abstract

Atrial fibrillation (AF) is the most common tachiarrhythmia. The pulmonary veins (PVs) have the predominant source of ectopic activity involved in the initiation of AF. Atrial remodelling, due to rapid and irregular activation during AF, leaves the tissue vulnerable to reentries. In this work the effects of electrical remodelling were incorporated in a 3D anisotropic model of human atrium. An ectopic focus was applied near to PVs. Electrograms were computed in simulated-electrodes in back wall of left atrial. The ectopic focus induced a figure-of-eight reentry that degenerated to mother rotor, after collisions and wave breaks were observed. Electrograms were more irregular during figure-of-eight reentry and collisions than during rotor activity. Spectral analysis shows multiple frequency peaks, as a consequence of changes of reentrant patterns. Dominant frequency was similar in all measuring points.

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 [1]. 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 [2]. This hypothesis was questioned by Haïssaguerre et al. [3] when demonstrating that auricular rapid paces originated in the interior or in the proximities of the pulmonary veins (PVs) could act like triggers and, in some cases, they are responsible for the maintenance of AF. The pulmonary veins have been found to present the predominant source of ectopic activity involved in the initiation of AF [4,5]. Recently, Jalife et. al. [6], proposed the rotor hypothesis, which suggests that AF is triggered by ectopic beats emanating from the VPs, the wave fronts would be fragmented generating a figure-of-eight reentry, finally, one of the vortices would be stabilise, generating a rotor. The rotor could act as mechanism to maintain AF.

AF induces electrical remodelling of membrane ionic channels in atrial cells [7-9]. Electrical remodelling causes a decrease in refractoriness by significant action potential duration (APD) shortening, leaving the atrium vulnerable to reentrant circuits [7]. Atrial remodelling, anatomical structures, spatial heterogeneity and nonuniform anisotropy are the keys to reentrant activity initiation.

In this work the initiation and maintenance of re-entrant mechanisms triggered by ectopic activity are investigated in a realistic tree-dimensional (3D) model of human atrium with electrical remodelling.

2. Methods

2.1. 3D model of human atrium

A computer model of the human atria was developed in which the geometry, derived from magnetic resonance imaging data of [10], was represented by a 3D monolayer. The geometry was adjusted to the anatomical specifications of Wang et al. [11] and Cohen et al. [12]. The geometry 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 pulmonary veins, superior and inferior caval veins, isthmus of right atria, 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 [13], the model was divided into 22 zones, in which a perpendicular axle was traced to the direction of the main bundles. The perpendicular to these axles was proyected on the atrial surface to obtain de fiber orientation.

Regions of high (crista terminalis, Bachmann 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 isthmus which was considered isotropic.

2.2. Electrical remodelling

The experimental data of AF induced changes in ionic channel conductance and kinetics of human atrial myocytes are reported by Bosh et al. [14] and Workman et al. [15]. These changes have been incorporated in the model of human atrial action potential (AP) developed by Nygren et al. [16] 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 I_t was decreased by 85%, the kinetics of the fast inactivation of I_{CaL} was increased by 62 %, the activation curve of I_t 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 the 3D model.

2.3. Action potential propagation

Propagation was modeled using assuming a 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 tranmembrane potencial, C_m 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 (FEM).

2.4. Pseudo-electrograms

Pseudo unipolar electrograms were computed in 10 simulated-electrodes located in back wall of left atrial (black dots in figure 3). The extracellular potential (Φ_e) was modelled using a current source approximation for a large volume conductor:

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

where $\vec{r}$ is the electrode location vector, $\vec{r}'$ 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. Pseudo-electrograms 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).

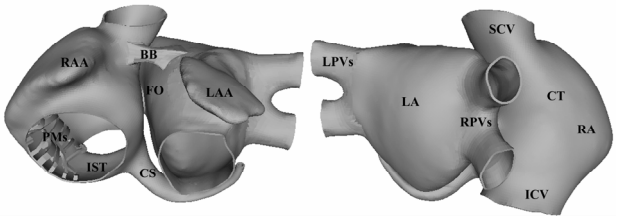

Figure 1. 3D modelo of human atrium, including: Left (LA) and right (RA) atrial chambers, pectinate muscles (PMs), Bachmann´s bundle (BB), crista terminalis (CT), fossa ovalis (FO), isthmus (IST), left (LAA) and right (RAA) appendages, coronary sinus (CS), right (RPVs) and left (LPVs) pulmonary veins, superior (SCV) and inferior (ICV) caval veins.

2.5. Stimulation protocol

A train of stimuli was applied during 10 seconds in the sinoatrial node region, to simulate the sinus rhythm to high frequency. The basic cycle length (BCL) was 300 ms. A single ectopic focus was applied during the repolarization phase of ten sinus beat (3084 ms after start the simulation) in the pulmonary veins region.

3. Results and Discussion

Electrical remodelling induced a 6 mV hyperpolarization of the resting potential and a 70% reduction in APD90. The APD was reduced from 312 ms to 92 ms. These changes are consistents with experimental observations [14,15].

In 3D simulations, the ectopic focus applied near to right PVs generated a unidirectional block. The wavefront turned around the PVs (see figure 2 at 3264 ms) and it continued propagating in back wall of the left

atrium, generating a figure-of-eight reentry (see figure 2 at 3406 ms and 3902), with a vulnerable window of 4 ms.

This result is accord with experimental studies [3-5], which have shown the role of focal activation in the initiation and maintenance of reentrant mechanisms, initiated by triggers in the pulmonary veins (PV's); which could be treated by delivery of radiofrequency energy (RF). Figure-of-eight reentries have been observed experimentally [17] and in simulations of cardiac tissue [18].

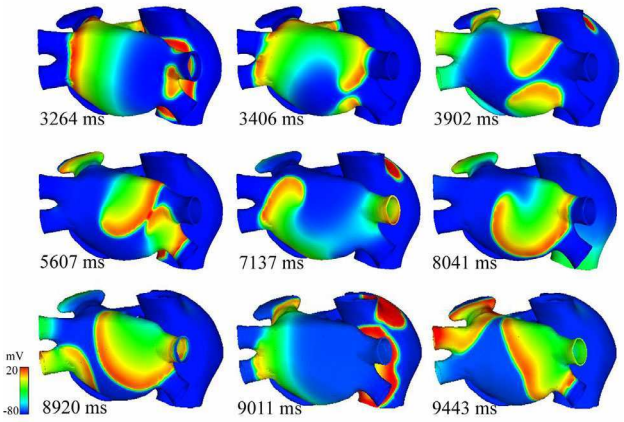

Figure 2. Evolution of the reentrant mechanisms on the atrial surface. The red colour represents the despolarization voltage and blue colour the repolarization voltage.

At 5607 ms of simulation, one of figure-of-eight reentry vortexes was stabilized and converted in a mother rotor in back wall of the left atrium (see figure 2 at 7137 ms and 8041 ms). The rotor was very regular and persisted in back wall for about 3000 ms. This result is agree with rotor hypothesis proposed by Jalife and with another experimental and computational studies [19, 20], which have been obtained rotors in the atrium. After that, collisions and wave breaks were observed in back wall of both, left and right atrium (see figure 2 at 8920 ms, 9011 ms and 9443 ms).

Electrograms were calculated within the region of reentrant mechanisms, after the ectopic focus was applied. In agreement with previous findings that a single reentry is sufficient to produce AF-like electrograms [21], electrogram complexes were rapid, irregular and polymorphous (variability in size and shape). Irregularity and polymorphism was greater during figure-of-eight reentry and collisions, on the other hand, during rotor activity the electrograms shown more uniform and regular complexes (see figure 3).

Spectral analysis of the electrograms shows broadbands with multiple frequency peaks, as a consequence of the unstable electrical activity, which is produced by the changes of reentrant patterns along the all simulation. FFT analysis has had increasing use in helping to study and characterize atrial arrhythmias [19, 22]. Dominant frequency was similar in all measuring points (7.9 Hz), which is more characteristic of focal atrial tachycardia than AF [22], however, would be necessary to calculate electrograms in another regions as right atrium to know the real type of tachyarrhythmia.

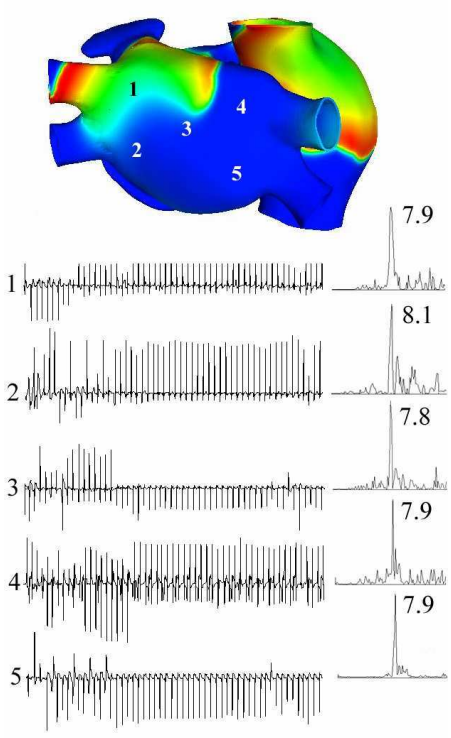

Figure 3. Pseudo-electrograms and its spectral analyse in five measuring points.

4. Conclusions

In conclusion, in this simulation work, reentrant patterns of activation in a tree-dimensional model of human atrium with electrical remodelling have been analyzed. We observed different reentrant mechanisms triggered by a single ectopic focus, applied near to right PVs. A figure-of-eight reentry was generated in back wall of the left atrium, which degenerated in a rotor, after collisions and wave breaks was observed. This study provides evidence in support of the hypothesis of rotor and hypothesis of AF begetting AF [7].

The electrograms calculated were more irregular and polimorphous during figure-of-eight reentry and collisions than during rotor activity. Spectral analysis shows multiple frequency peaks, as a consequence of changes of reentrant patterns. Dominant frequency was

similar in all measuring points.

Acknowledgements

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References

[1] Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The Natural-History of Atrial-Fibrillation - Incidence, Risk-Factors, and Prognosis in the Manitoba Follow-Up-Study. American Journal of Medicine 1995; 98(5):476-84.

[2] Moe GK, Abildskov JA. Atrial fibrillation as a selfsustaining arrhythmia independent of focal discharges. Am. Heart. J. 1959; 58:59-70.

[3] Haïssaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N. Engl. J. Med. 1998; 339:659-66.

[4] Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins. Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999; 100:1879-86.

[5] Kumagai K, Yasuda T, Tojo H, Noguchi H, Matsumoto N, Nakashima H et al. Role of rapid focal activation in the maintenance of atrial fibrillation originating from the pulmonary veins. Pace-Pacing and Clinical Electrophysiol. 2000; 23(11):1823-7.

[6] Jalife J. Rotors and spiral waves in atrial fibrillation. J. Cardiovasc. Electrophysiol 2003; 14:776-80.

[7] Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial-fibrillation begets atrial-fibrillation - a study in awake chronically instrumented goats. Circulation 1995; 92(7):1954-68.

[8] Bosch RF, Zeng X, Grammer JB, Popovic CM, Kuhlkamp V. Ionic mechanisms of electrical remodelling in human atrial fibrillation. Cardiovasc. Res. 1999; 44:121-31.

[9] Workman AJ, Kane AK, Rankin AC. The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. Cardiovasc. Res. 2001; 52(2):226-35.

[10] Harrild DM, Henriquez CS. A computer model of normal induction in the human atria. Circ. Res. 2000; 87:25e-36e.

[11] Wang K, Ho SY, Gibson DG, Anderson RH. Architecture of Atrial Musculature in Humans. British Heart Journal 1995; 73:559-65.

[12] Cohen GI, White M, Sochowski RA, Klein AL, Bridge PD, Stewart WJ, Chan KL. Reference values for normal adult transesophageal echocardiographic measurements. J. Am. Soc.Echocardiogr. 1995; 8:221-30.

[13] Ho SY, Sanchez-Quintana D, Anderson RH, Can anatomy define electric pathways?, in International Workshop on Computer Simulation and Experimental Assessment of Electrical Cardiac Function 1998:77-86.

[14] Bosch RF, Zeng X, Grammer JB, Popovic CM, Kuhlkamp V. Ionic mechanisms of electrical remodelling in human atrial fibrillation. Cardiovasc. Res. 1999; 44:121-31.

[15] Workman AJ, Kane AK, Rankin AC. The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. Cardiovasc. Res. 2001; 52(2):226-35.

[16] Nygren A, Fiset C, Firek L, Clark JW, Lindblad DS, Clark RB et al. Mathematical model of an adult human atrial cell - The role of K+ currents in repolarization. Circulation Research 1998; 82(1):63-81.

[17] Uno K, Kumagai K, Khrestian CM, Waldo AL. New insights regarding the atrial flutter reentrant circuit: Studies in the canine sterile pericarditis model. Circulation 1999; 100:1354-60.

[18] Vigmond EJ, Tsoi V, Kuo S, Arevalo H, Kneller J, Nattel S, Trayanova N. The effect of vagally induced dispersion of action potential duration on atrial arrhythmogenesis. Heart Rhythm 2004; 3:334-44.

[19] Mandapati R, Skanes AC, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000; 101:194-9.

[20] Kharche S, Garratt CJ, Holden AV, Zhang H. Stability of scroll excitation waves in human atria during fibrillation: a computational study. Computers in Cardiology 2007; 34:285-8.

[21] Ikeda T, Czer L, Trento A, Hwang C, Ong JJC, Hough D, Fishbein MC, Mandel WJ, Karagueuzian HS, P-S Chen. Induction of meandering functional reentrant wave front in isolated human atrial tissue. Circulation 1997; 96:3013-20.

[22] Ryu K, Sahadevan J, Khrestian CM, Stambler BS, Waldo AL. Use of fast fourier transform analysis of atrial electrograms for rapid characterization of atrial activation-implications for delineating possible mechanisms of atrial tachyarrhythmias. J. Cardiovasc. Electrophysiol. 2006; 17:198-206.

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