Study the Effect of Tissue Heterogeneity and Anisotropy in Atrial Fibrillation Based on a Human Atrial Model

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmias in clinic, it is characterized by multiple waves of excitation coursing through myocardial tissue. AF disrupts the normal sinus rhythm and may arise from ectopic foci. In right atrium, there are many different conduction bundles which have different action potential morphology, and they provide a substrate for reentrant activity during AF. Fibre orientation is important in electric propagation and maintaining AF, however, most previous simulation studies didn't consider the fibre orientation. In this paper we studied the effect of tissue heterogeneity and anisotropy on initiation and maintaining of AF based on a realistic human atrial model with fibre orientation and detailed conduction system. The results showed that tissue heterogeneity and anisotropy are important for AF, and in some cases AF is transient due to the lack of anisotropy. Fiber orientation is very important in sustaining of re-entry waves. This investigation suggests that a detail atrial anatomical model should be necessary for AF simulation.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmias in clinic, it can significantly increase the risk of stroke and lead to ventricular tachycardia, and in turn affect the heart's pumping function. AF is characterized by multiple waves of excitation coursing through myocardial tissue, it disrupts the normal sinus rhythm and may arise from ectopic foci [1]. The mechanism of AF initiation and maintaining has been studies by experiment and simulation [2-4]. These researches have shown that the electrophysiological and anatomic heterogeneities in atria have influences on initiation and maintaining of AF.

Different conduction bundles exist in the right atrium, such as Bachmann's bundle (BB), crista terminalis (CT) and pectinate muscles (PM). These bundles have different action potential morphologies, thus lead to electro-physiological heterogeneity in right atrium and provide a substrate for reentrant activity during AF [5-6]. Modeling studies of cardiac tissue also showed that wave break can occur in homogeneous tissue when the action potential duration (APD) restitution curve is steep [7-8], this type of wave break arises from the dynamics of cardiac propagation and the steep APD restitution caused oscillations in wavelength before wave break [9].

Although many studies have been done on the re-entry wave initiation and breakup due to the cell dynamic properties or electrophysiological and anatomical heterogeneities, most of them are based on two-dimensional models [6, 10]. Some of them are based on three-dimensional models [2, 4], but they have some limitations, for instances, the atrial conduction bundles were not included, or only one cell model was used, these factors may influence the results of simulation. Furthermore, most of the three-dimensional models do not consider the fibre orientation in the simulation of AF, since the atria has less organized fibre orientation and it was difficult to be measured. While the experimental results have showed that fibre orientation is important for the electrical propagation [11-12], therefore it is necessary to take the fibre orientation into account in simulation of the normal excitation conduction and AF.

The aim of this paper is to study the effect of tissue heterogeneity and anisotropy on initiation and maintaining of AF based on a recently developed realistic human atrial model with measured fibre orientation. In the simulation, two different stimulus protocols were used to initiate AF with two different atrial action potential (AP) models, furthermore, the anisotropy was considered too [13].

2. Materials and methods

2.1. Atrial anatomical model

The heart specimen in this study was taken from a healthy adult male in Zhujiang Hospital, Southern Medical University, China. The pretreatment and image data collection work were completed in the Southern Medical University, while the follow-up image processing, three-dimensional reconstruction and modelling of the fiber rotation were done by our group. The heart specimen was scanned using a spiral computer

tomography (Philips / Brilliance 64). The size of raw computer tomography data were 512×512, and the total number of images was 531 with the spatial resolution 0.3574mm×0.3574mm×0.33mm.

In the atrial model, the conduction system includes sinoatrial node (SAN), Bachmann's bundle (BB), crista terminalis (CT), pectinate muscles (PM), fast passway (FP) and slow passway (SP). In order to simulate the anisotropy, the fiber orientation of atria and the major conduction system are developed on the atrial model contains. Because of the page limitation, the detail atrial model is not introduced here.

The atrium has inhomogeneous conduction velocity (CV), by assigning different diffusion coefficients, we set heterogeneous conduction velocities for different parts in atria, which were within the physiological ranges. The normal conduction velocity for proximal CT was about 90mm/s, for the distal CT the velocity was about 60mm/s. The average velocity was 70mm/s for atrial muscles, 95mm/s for PM and 80mm/s for BB.

2.2. AP model

We used two atrial cell models to simulate AF. The first one was based on the model developed by Courtemanche et al [14], the APD of which was about 306ms at the basic cycle length of 1s, but this is too long for AF simulation. Therefore we changed the maximum conductance of the inward rectifier K^+ current to 0.27nS/pF which is in accordance with reference [4], instead of the original value in Courtemanche model of 0.09nS/pF. With this modification, the APD decreased to 210ms. In the following sections, we refer this model as Model I. The second one was an AF-induced electrical remodeling cell model which is based on Courtemanche et al [14] and was modified to incorporate the experimental data measured by Bosch et al [15]. The APD of this cell model was 125ms and the APD slope was much stepper than model I, we refer this model as Model II.

2.3. Numerical method

The monodomain model [16] was used to study the propagation of action potential, it was described by the following partial differential equation,

$$\frac{\partial V_m}{\partial t} = D\left(\frac{\partial^2 V_m}{\partial x^2} + \frac{\partial^2 V_m}{\partial y^2}\right) - \frac{I_{ion}}{C_m} \quad (1)$$

where V_m is transmembrane voltage, D represents the diffusion coefficient, C_m is the membrane capacitance, and I_{ion} is the sum of ionic currents.

Equation (1) was solved based on the explicit Euler method with a time step 0.01ms and space step 0.35mm respectively. The simulation was performed on the Dawning TC4000L server, its hardware architecture is symmetric multi-processor shared-memory, and contains one management node, 10 computation nodes. Each computation node contains two Intel Xeon 5335 processors, 4G memory and 160G hard disk. The total theoretical computing capacity is up to 184Gflops. We used MPI to implement the communication between the nodes.

2.4. Initiation of AF

We used two pacing protocols to initiate AF. The first one is the cross-field protocol [17]: a first stimulus was applied at the edge of left atria, after a sufficient time the second stimulus was applied in the half bottom of whole atria. The second one was as follows: give a stimulus at the SAN, after a sufficient time, a train of ectopic foci was delivered from the ectopic focus location of interest at a cycle length [4]. The first one was simple and in most cases it can initiate a sustained AF. The second one needs more time to induce AF and much sensitive to the parameters of cell models, but it was often used in experimental study to initiate AF.

3. Results

3.1. Cross-field protocol

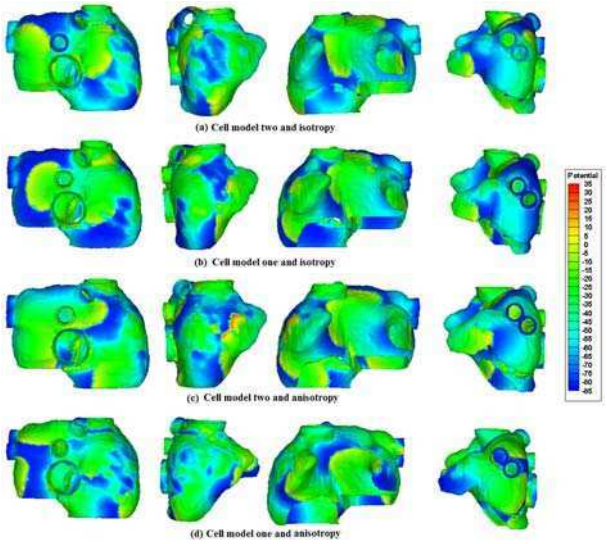

Figure 1. The simulated AF using the cross-field protocol. The four columns represent the frontal, right lateral, back and left lateral views of the distribution of AP in atria. Rows 1-4 represent the cases of Model I and isotropy; Model I and anisotropy; Model II and isotropy; and Model II and anisotropy, respectively.

For the cross-field protocol, both Model I and Model II can initiate a sustained AF lasts for more than 5ms, while the cell properties and anisotropy have different influences on the spire wave patterns.

In isotropy conduction, Model I and Model II have similar re-entry waves in left atrial frontal and posterior wall: there is a sustained re-entry wave rotating around left auricular appendage, the re-entry in posterior wall is meandering around the pulmonary veins. In the right atrial lateral and posterior wall the re-entry waves have some differences: electrophysiological heterogeneity in right atria is high, and the re-entry wave break into many sub-waves. The Model II's property with shorter APD and steeper APD restitution, may lead to more inhomogeneous in right atrium, thus the re-entry wave in Model II is more chaos than that in Model I (Seen first and second row in Fig.1).

With the same cell model, anisotropy has influence on the re-entry waves too. The re-entry waves in left auricular appendage is more chaos than isotropy conduction in both cell models: the re-entry waves in posterior wall become planer waves in anisotropy conduction, the re-entry waves in right atrial lateral and posterior wall are less influenced using anisotropy conduction compared with isotropy conduction in Model II. The reason may be due to the larger electro-physiological heterogeneity in Model II, so that the effect of anisotropy does not play the main role in AF.

3.2. Ectopic foci pacing protocol

In the ectopic foci pacing protocol, a voltage stimulus of 10mv at the SAN is given for 1ms, after 400ms a train of ectopic foci ($\leq$5) is delivered at the atria next to left superior pulmonary vein, the voltage stimulus strength is 20mv for 1ms, after a sufficient time, the planer wave breaks into wavelets.

As shown in Fig. 2, in isotropy conduction with Model I and Model II, they have similar conduction patterns, after a train of ectopic foci pacing, the re-entry waves are initiated. They meander around the atrial tissue and do not break into wavelets until they get the right atrial lateral and posterior wall, however, the wavelets are short-lived. After about 3s, the re-entry wave in the whole atria comes into an end and then the propagation ends too.

If considering the anisotropy, the re-entry wave can last for a long time ($\geq$10s) in both cell models, but they have different re-entry characteristics. In Model I, the re-entry wave breaks into wavelets only at the right atrial lateral and posterior wall, while the wave in the remaining parts is only a repeated excitation like a planner wave. In Model II, the re-entry wave meanders around inferior vena cava almost in the entire simulation. When the wave arrives at the right atrial lateral and posterior wall, it will break into wavelets too. Compared to Model I, the wavelets in Model II are more chaos.

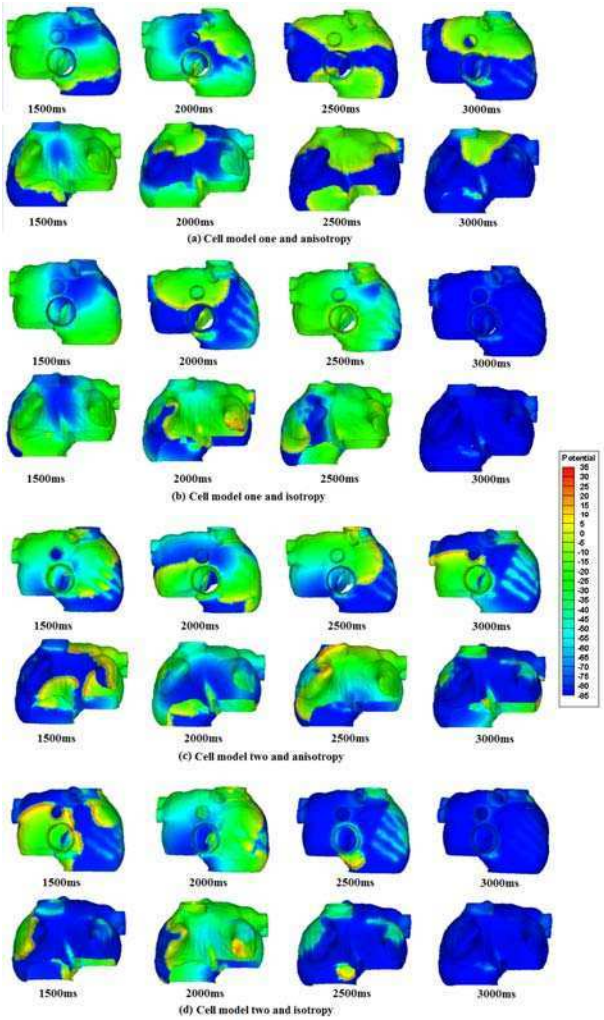

Figure 2. The simulated AF using ectopic focus stimulation. There are four groups of stimulations: (a) Cell model I and isotropy; (b) Cell model I and anisotropy; (c) Cell model II and isotropy; (d) Cell model II and anisotropy. In each case, the AP distribution of four different time step was recorded. The upper row of each case was the back view; the lower row in each case was the frontal view.

4. Discussion and conclusions

In this paper, based on a realistic human atrial model with detailed conduction system and fibre orientation, we investigated the effect of electrophysiological heterogeneity and anisotropy on initiation and maintaining of AF. Two cell models and two common pacing protocols were used to initiate AF. The results showed that re-entry can be initiated by cell model whose APD restitution was not steep (<1) if the electrophysiological heterogeneity exists in atria. In our simulation, the APD restitution in Model I was flat and in

Model II was steep (>1), however, the simulation results showed that the re-entry pattern in the two cases have no obvious differences at the right atrial lateral and posterior wall since the tissue heterogeneities were high there.

In ectopic focus stimulation, the result shown that fiber orientation plays a very important role in sustaining of re-entry waves. The re-entry waves in both cell models were successfully initiated, although the re-entry patterns had some differences. The re-entry waves, however, can not last for a long time (>4s). When the fiber orientation was added in the simulation, the re-entry waves can last for more than 10s, and they were easier to break into wavelets to form AF.

It should be pointed out that some limitations existed in this simulation study. Firstly, the parameters of atrial cell model were not intensively investigated. We only changed one parameter to study the influence of APD and APD restitution on re-entry waves. Secondly, we used only one ectopic focus stimulation position to study the influence of fiber orientation and tissue electro-physiological heterogeneity on re-entry waves. Thirdly, we have not quantitatively measure the re-entry waves.

In all, we have used an anatomically detailed atrial model containing major conduction bundles and fiber orientation to simulate AF. The simulation results showed that re-entry waves could be initiated using the controlled state cell models if the electrophysiological heterogeneity exists in atria tissue, the APD restitution does not play the main role in the areas where the tissue heterogeneities are high. Fiber orientation is very important in sustaining of re-entry waves in the ectopic focus stimulation.

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