A 3D Electromechanical Model of the Human Atria: a Realistic Framework for the Study of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and it is mainly sustained by rapid ectopic activity, which affects the electromechanical dynamics of the cardiac tissue. The objective of the present work is to develop a highly detailed 3D electromechanical model of the human atria in order to assess how atrial fibrillation-induced electrical remodelling affects atrial mechanical contraction. The model incorporates regional tissue heterogeneities at the cell level by defining different electrical and tissular properties and different conduction areas. The preliminary studies here proposed suggest that the heterogeneity and the mechano-electric feedback is a relevant factor in the intracellular calcium handling and the contractility of the atria in arrhytmogenic dynamics.

1. Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, with a growing prevalence in aging population [1]. Computational modelling and simulations are now an essential part of the mechanistic research in cardiovascular diseases. In particular, the study and understanding of the mechanisms of complex arrhythmia, such as AF, can take profit of computational modelling and multi-scale models. This work aims to computationally test the effect of electrical and mechanical remodelling of AF at the atria organ level.

Multi-scale atrial models are mathematical models that link electrophysiological phenomena at the cell, tissue and whole atria scale. The cell scale includes the equations that describe the kinetics of different ionic channels and proteins, that are coupled to produce the transmembrane potential of an atrial myocyte. The tissue scale includes coupling between cells and fibre orientation that govern electrical propagation. The whole atria scale includes the entire complexity of atrial 3D anatomy, tissue heterogeneity and distribution of fibers. On top of that, atrial mechano-electric feedback is necessary to include the contributions of atrial stretch in the pathophysiology of the atria. Strong electromechanical coupling is done in both senses: the changes in electrophysiological state variables affect atrial tissue deformation, and atrial tissue deformation alters the electrophysiological parameters that determine the action potential and the changes in the ionic currents. The first mechano-electric feedback in left atrial models showing a first relation between stress concentration and the generation of arrhythmia was proposed recently [2]. The study of the mechanial function in the atria has not been highlighted in the cardiac computational models.

The electrical remodelling of AF results in shortened action potential duration (APD), which is associated with disordered Calcium handling. The mechano-electric feedback and the contribution of atrial stretch in the pathophysiology of AF is still challenging, not only because of the lack of experimental studies but also because electromechanical simulations of the atria are computationally expensive. The purpose of this work is to provide a numerical framework for human atrial contraction with an electrical-mechanical coupling of human atrium cell models. The study investigates the effect of the electrical remodelling of persistent AF in the calcium transient and the contractility of the atria.

2. Materials and methods

The 3D atrial model has 5.221.799 tetrahedral elements and different mean thickness depending on the region. The model is an improved and scaled version of the previous human atria [3] and includes 21 anatomical regions accounting for the ionic heterogeneity and different diffusivity regions.

The atrial 3D anatomical model included fibre orientation measured from histological sections of a human anatomy. The mathematical model of human cardiac atrial myocytes proposed by Courtemanche [4] was used to solve the electrophysiology using a monodomain approximation. Furthermore, stretch-activated channels were integrated to the Courtemanche atrial model [5].

To reproduce the experimental heterogeneity in action

potential morphology and activation and repolarisation sequence, different regional electrical regions are defined, together with fibre orientation. The regions are defined by adjusting the maximum conductance of five ion currents I_{to}, I_{CaL}, I_{Kr},I_{Ks} and I_{K1}. A total of nine anatomical regions have been identified, and the principal direction of the fibres within each region have been included, based on anatomical studies, namely: right atria (RA), crista termalis (CT), Bachmann bundle in left atria (BBla), tricuspid valve ring (TVR), mitral valve ring (MVR), right atrial appendage (RAA), left atrial appendage (LAA), left atria (LA) and pulmonar veins (PV). Additionally, tissue heterogeneity has been modelled by tunning in each region the longitudinal conductivites and the anisotropy ratios, to match the activation sequence of experimental data [6].

Persistent AF is characterized by recurrent fibrillation episodes. The electrical remodelling was introduced by modifying the main ion channels, following [7] which was based on an extensive review of the available experimental data. Table 1 summarizes the modifications made to the healthy electromechanical single cell models.

	I_{CaL}	I_{to}	I_{K1}	I_{Ks}	I_{Kur}
RA	-65%	-45%	200%	250%	-60%
CT-BBra	-65%	-45%	200%	250%	-60%
BBla	-65%	-45%	200%	250%	-60%
TVR	-65%	-45%	200%	250%	-60%
MVR	-65%	-75%	200%	200%	-45%
RAA	-65%	-75%	200%	200%	-45%
LAA	-65%	-75%	200%	200%	-45%
LA	-65%	-75%	200%	200%	-45%
PV	-65%	-75%	200%	200%	-45%

Table 1. Variations in the ionic channel currents used to reproduce the electrical remodeling experimentally observed under persistent AF conditions.

Due to the complex geometry, heterogeneity and anisotropic properties of the atrial tissue, the behaviour at the cell level cannot be extrapolated into similar activity and results at the organ level. Hence, simulations using realistic human 3D anatomical atrial geometries considering the intrinsic heterogeneity in the atria are mandatory.

The model is coupled to the tissue mechanics, with the solid mechanics tissue constitutive model of Holzapfel and Ogden [8]. The biomechanical model is based on a continuum mechanical approach. The passive mechanical properties of the atrial tissue are described by the model of Holzapfel [8], while the contraction was driven by the excitation-contraction model [9]. In cardiac tissue models [**?**], stress is assumed to be a combination of passive and active parts:

$$\sigma = \sigma_{pas} + \sigma_{act}(\lambda, [Ca^{2+}])f \otimes f, \qquad (1)$$

accounting for the passive and the contractile parts respectively. Here f denotes fiber direction and λ the stretch. Note that the active force is only enforced in the fiber direction, highlighting the relevance of the fibrotic structure of the atria into the contractility.

Before running the 3D model, the electromechanical single cell models were prepaced for 1000 beats or up to calcium steady state. Then, the 3D model is initialized by incorporating the single-cell steady state into the tissue model and stabilized for a basic cycle length of 1000ms by stimulating the sinoatrial node (SAN) for 2ms of duration and 28pA/pF of amplitude for control (healthy condition). For persistent AF, electrical remodeling with normal sinus rhythm is applied. This conidtion simulates the state of the atrial tissue after successful cardioversion.

3. Results

The simulations were run using the multi-schale and high performance software, Alya solver [10, 11], in Marenostrum supercomputer.

Electro-mechanic simulations produced a shortening of the action potential and a reduced concentration of calcium for AF simulations as compare to normal conditions, resulting also in a reduced active force. Figure 1 shows the simulated electromechanical dynamics of action potential for the different heterogeneity cell regions. The measured action potential duration at 90% repolarisation (APD90) is shown in table 2 for healthy conditions with electrophysiological simulations (Healthy EP), persistent AF with electrophysiological simulations (peAF EP) and persistent AF with electromechanical simulations (peAF EM). It can be observed that the mechanical feedback tends to homogenize the length of the APD, while maintaining the reduction of the AP with respect to the healthy EP case.

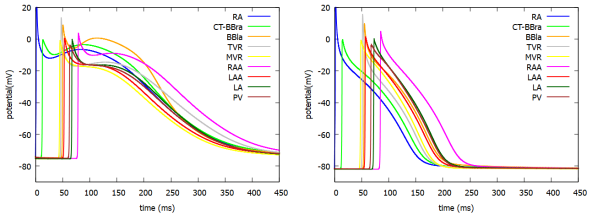

Figure 1. Action Potential for the different regional atrial zones under healthy (left figure) and AF (right figure) conditions.

Figure 2 shows the Calcium concentration within each heterogeneity region for Healthy and persistent AF cases, both with electromechanical simulations. A reduction of the levels of ca is observed in all cell types leading to reduced cell shortening. Despite the notorial cell reduction in the 3D electro-mechanical simulation, this fact does not imply a considerable reduction in the contraction of atria.

	Healhty EP	peAF EP	peAF EM
RA	301	96	99
CT	321	114	98
TVR	274	84	94
RAA	280	92	93
LA	284	107	92
LAA	271	96	94
PV	287	109	93
MVR	273	97	95
BBla	285	110	94

Table 2. APD90 duration in ms within the different atrial regions for control electrophysiological simulation (Healthy EP), persistent AF electrophysiological simulation (peAF EP) and persistent AF electromechanical simulation (peAF EM).

Figure 3 shows some snapshots of one beat for the contraction of the atria after peAF electrical remodelling. The activation pattern are depicted with the contractility of the atria. At 100ms the whole atria has completely activated and at 310ms relaxation was completed. The contraction time is faster than in normal conditions, due to the significant reduction in Calcium and APD.

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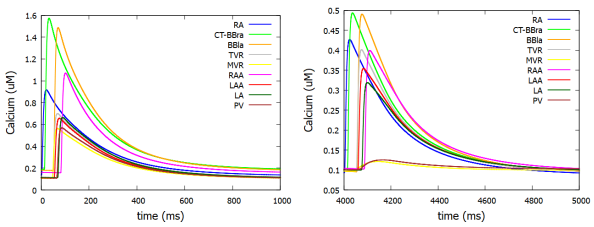

Figure 2. Calcium for the different regional atrial zones under healthy (left figure) and AF (right figure) conditions.

4. Conclusions

This study develops a 3D electromechanical model of the human atria coupling with and excitation-contraction model the different heterogeneous regions of the human atria, and using single cell models for each region. From the study it can be observed that the mechanical coupling produces a reduction in the calcium concentration as well as a shortening of the potential, with respect to purely electrophysiological models. The purpose of this work was to develop a computational framework for human atrial contraction modelling. The current model is a first approach to the creation of electromechanical studies including heterogeneity with single cell models. Next steps will be directed to simulate AF-remodeled tissue with multiple reentrant activity.

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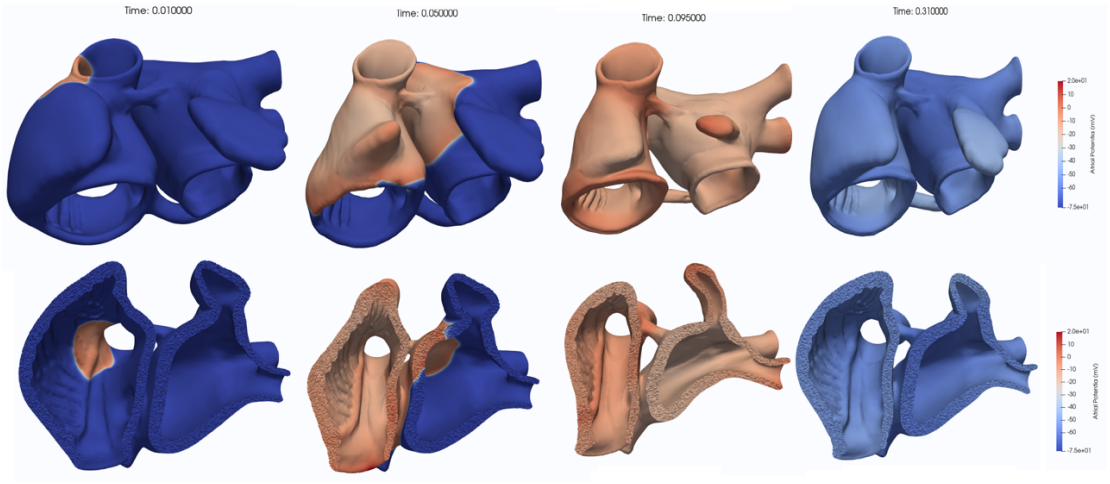

Figure 3. Electrical propagation patterns during a sinus rhythm simulation showing contractility of the atria for different stages (top: full RA and LA, bottom: slice.

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