Mutual Influence between Dyssynchrony and Transmural Conduction Maintains Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) and other structural heart diseases cause structural remodeling in the atria. Structural remodeling leads to local heterogeneities of conduction between muscle bundles as well as between the epicardium and endocardial bundle network which enhances endo-epicardial electrical activation time differences and breakthroughs. In order to investigate the mutual influence between endo-epicardial activation time differences, breakthrough rates, and stability of AF episodes, a novel dual-layer computer model was developed. This model was composed of two layers connected by randomly distributed connection points. Two groups of simulations were selected: dual-layer and single-layer. In the dual-layer group, the amount of dyssynchrony and breakthrough rate was calculated during the course of the simulation and good correlations between dyssynchrony and breakthrough rate were observed. Stability of AF episodes was significantly higher in the dual-layer group. We conclude that transmural conduction, or 'breakthrough', can be an explanation for the larger AF stability in the dual-layer group.

1. Introduction

Atrial Fibrillation (AF) and other structural heart diseases cause structural remodelling in the atria favouring local heterogeneities of conduction. These conduction disturbances can occur in side-to-side connections between muscle bundles, but also between the epicardium and endocardial bundle network. Impaired coupling between the two layers increases endo-epicardial electrical activation time difference and, therefore, transmural conduction.

Clinical studies revealed increase in amount of breakthroughs in patients who were in later stages of AF [1]. Experimental studies showed increase in the amount of endo-epicardial electrical activation time differences in goats in 3 weeks AF, 3 months AF, and 6 months AF[2].

These studies suggest that fibrillatory conduction during atrial fibrillation shows a much more three-dimensional character. To address the question whether endo-epicardial electrical activation time difference increases breakthrough rate as well as stability of AF episodes, we developed a novel dual-layer proof-of-principle computer model. Simulation results obtained with the dual-layer model were analysed and compared to results obtained with a single-layer model of the same size.

2. Methods

To investigate the effect of dyssynchrony in endo-epicardial electrical activity on transmural conduction, a proof-of-principle dual-layer computer model was developed. We describe the model structure, simulation protocol, and analysis of the simulation results.

2.1. Model

Atrial tissue was described by a mono-domain reaction diffusion model consisting of two layers of size 4cm × 4cm (Figure 1). Each segment had a size of 0.01cm × 0.01cm and atrial membrane behaviour was modelled using the Courtemanche-Ramirez-Nattel model [3]. Ionic membrane current I_{ion} was defined by

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kur} + I_{Kr} + I_{Ks} + I_{Ca,L} + I_{p,ca} + I_{NaK} + I_{NaCa} + I_{b,Na} + I_{b,ca}, \quad (1)$$

where I_{Na} is fast inward Na^+ current, I_{K1} is inward rectifier K^+ current, I_{to} transient outward K^+ current, I_{Kur} is ultra-rapid delayed rectifier K^+ current, I_{Kr} is rapid delayed rectifier current, I_{Ks} is slow delayed rectifier K^+ current, $I_{Ca,L}$ is L-type Ca^{2+} current, $I_{p,ca}$ is Ca^{2+} pump current, I_{NaK} is Na^+-K^+ pump current, I_{NaCa} is Na^+/Ca^{2+} exchanger current, and $I_{b,Na}$ and $I_{b,ca}$ are background Na^+ and Ca^{2+} currents, respectively. To incorporate changes in ionic currents as observed in atrial fibrillation, maximum conductivity for I_{to} was reduced with 60%, maximum conductivity for $I_{Ca,L}$ was reduced with 65%, and maximum conductivity for I_{K1} was increased with 100% [4].

The mono-domain model was described by

$$\chi\left(C_m \frac{\partial V_m}{\partial t} + I_{ion} + I_{stim}\right) = \nabla \cdot (G \nabla V_m), \quad (2)$$

where χ is membrane surface-to-volume ratio, C_m is membrane capacitance, I_{ion} is ionic membrane current, I_{stim} is externally applied stimulus current, and G is the mono-domain conductivity tensor [5]. In the present study, $\chi = 2000$ cm^{-1}, $C_m = 1\mu$F/cm^2, and conductivities were the same in both directions $\sigma_x = \sigma_y = 0.5$mS/cm, which implies isotropic tissue.

Electrical connections between the two layers were incorporated by adding resistances between opposing segments in a circular area with radius 0.1cm (conductivity $\sigma_z = 0.5$mS/cm). Connections can be introduced or removed at any time during the simulation (Figure 1).

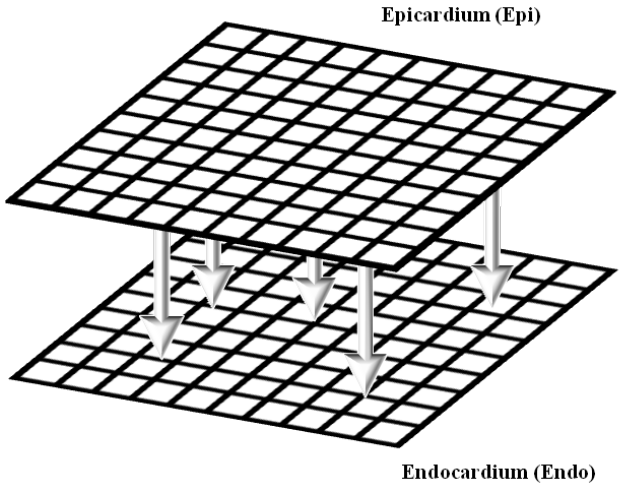

Figure 1. Model structure with two layers (epi- and endocardium) and transmural connections (gray arrows).

2.2. Simulation protocol

To investigate the effect of transmural connections on fibrillatory behaviour and stability of AF episodes, the following simulation protocol was applied:

1. A spiral wave was initiated in of the layers using an S1-S2 protocol [6] while the other layer was quiescent. This simulation was continued for 7 seconds.
2. Eight different sets of six randomly chosen connection points were introduced between the two layers of the model. The simulation state after the first second of the simulations in step 1 was used to initialize these simulations. Connection points for each simulation were chosen such that two connections were at least 0.2cm apart. All simulations were continued for 6 more seconds.
3. 7 seconds after the start of the simulations, all simulations were continued for another 6 seconds, either without changing the connections or with removing all connections.

Steps 2 and 3 were performed 8 times such that together with the continued simulation of step 1 in total 17 simulations were performed.

2.3. Analysis

2.3.1. Dyssynchrony

Dyssynchrony was defined as the number of segments that were excited in one layer, but for which the opposing segment in the other layer was not excited, divided by total number of segments, i.e.,

$$Dyssynchrony = \frac{number\ of\ avitvated\ segments\ in\ one\ layer}{total\ number\ of\ segments} \times 100\% \quad (3)$$

Dyssynchrony percentage was calculated at each 1ms in each simulation.

2.3.2. Breakthrough detection

A breakthrough (BT) is a wave (a closed area in which all segments have trans-membrane voltage above −60mV) that suddenly appears in one layer and cannot be related to the propagation of other waves in that layer (Fig. 2). BTs were detected as follows. Areas containing connection points were monitored each 1ms. If a new wave appeared in one of these areas and could not be related to the propagation of other waves in that layer, and it had a size at most the size of the connection area, it was marked as a candidate breakthrough. If a candidate breakthrough increased in size within the next 2ms, it was labelled as a breakthrough. The moment that the breakthrough appeared as well as the location was saved and the breakthrough rate (BTR), defined as the number of BTs per 50ms, was calculated at each 1ms.

3. Results

The total number of 17 single-layer simulations (8 simulations in which connections were removed, one simulation in which the spiral wave was continued without adding connections) and 8 dual-layer simulations with different sets of six randomly distributed connections were used to investigate the effect of dyssynchrony on BTs and stability of AF episodes.

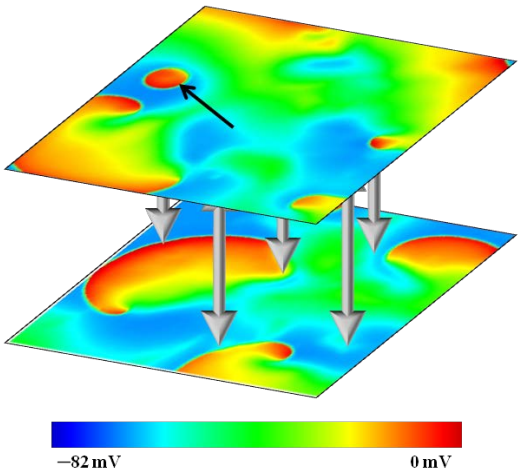

Figure 2. Dissociation of electrical activity between the two layers and transmural conduction resulting in a breakthrough wave in the top layer (black arrow).

3.1. Relation between dyssynchrony and BTR

In Figure 3, dyssynchrony (red line) and BTR (black line) were traced in time for one of the dual-layer simulations. This figure indicates that BTR and dyssynchrony are well correlated in time. Interestingly, on those moments that dyssynchrony increased with some delays also BTR started to increase, leading to a decrease in dyssynchrony. Then, as a consequence, dyssynchrony decreased. This phenomenon continues, which means that as soon as dyssynchrony increased, BTR increases and vice versa. Similar results were obtained for all dual-layer simulations.

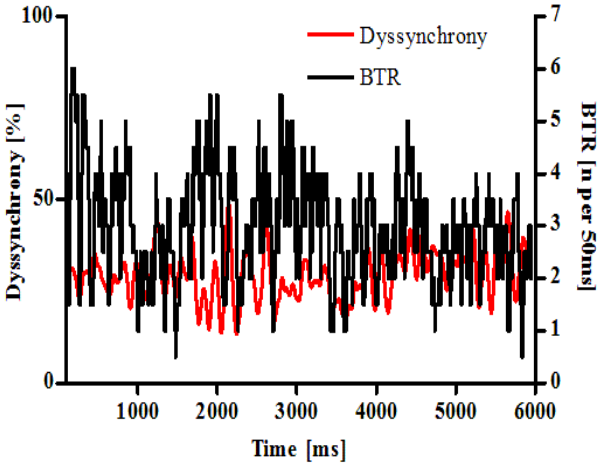

Figure 3. Dyssynchrony (red line) and BTR (black line) traces in time.

3.2. Stability

The total number of simulations in the single-layer group was 17 (8 simulations in which connections were removed and one simulation in which the spiral wave was continued without adding connections). The double-layer group contained 8 different simulations with 6 connections. Stability results of the simulations are presented in Table. 1. The percentage of AF episodes that were still active after 6 seconds was greatly higher in the dual-layer group compared to the single-layers group. Only one AF episode out of 8 AF episodes in double-layer simulations was quiescent within 6s, while for the single-layer group, 10 out of 17 were quiescent within that time period.

Table 1. AF persistence percentage.

Stability	Persistence percentage
Single-layer	41.18% (10 out of 17)
Dual-layer	87.5% (1 out of 8)

4. Discussion

A novel dual-layer computer model was developed to study the effect of endo-epicardial dissociation of electrical activity and transmural conduction on stability of AF. To the best of our knowledge, this model is the first model simulating dyssynchronous electrical activity in two separate layers – representing epicardium and endocardium – connected by electrical connection points enabling transmural conduction and 'breakthrough' of fibrillation waves from one layer to the other. This study demonstrates that adding the third dimension to the substrate of AF greatly enhanced the stability of the simulated arrhythmia, which was explained by occurrence of breakthroughs.

Most computer models of AF treat the atrial wall either as a single two-dimensional sheet [7] or three-dimensional structure. Most three-dimensional atrial models are three dimensional in the sense that a two-dimensional atrial sheet is folded into the shape of an atrium having two main cavities, atrial appendages, and connections between the two atria by a septal ring [8-10]. As a step forward, some computer model studies incorporated heterogeneities in the thickness of the atria wall [2, 11-14]. These simulation studies have shown the effect of spatial differences of anisotropy in specific muscle bundles on normal conduction in the atria and that the heterogeneity of the atrial wall thickness significantly increases the stability of AF episodes. However, none of these studies took disruption of transmural connections

and endo-epicardial electrical dissociation (EED) into account.

The novelty of our model is that it describes 'transmural conduction' between an endocardial and an epicardial layer. The important conceptual consequence is that this model introduces a new type of simulated fibrillation waves. After transmural conduction from one layer to the other, conduction showed radial spread of activation away from the electrical connection point, thereby resembling breakthroughs as also observed in experimental [2] and clinical [1] studies. Using a dual-layer model, we were able to investigate dyssynchrony, BTR, relation between the amount of dyssynchrony and BTR, and effect of transmural conduction on the stability of AF episodes.

Our simulation results indicate a good correlation between dyssynchrony and BTR, increase in dyssynchrony led to increase in amount of breakthroughs. Another finding from this study showed a great increase in stability of AF episodes in dual-layer simulations compared to single-layer simulations. The explanation for the increased stability of the AF episodes lies in an altered dynamic behavior of the AF waves caused by transmural conductions and occurrence of breakthroughs.

Our dual-layer model clearly is a simplified representation that does not reflect the anatomical complexities of the atria, the role of specialized structures such as the pulmonary veins or heterogeneity in ionic membrane currents. Even though we used a simple geometry, we clearly demonstrated that endo-epicardial dissociation of electrical activity and 'truly' three-dimensional conduction strongly increased complexity and stability of AF. As breakthroughs significantly contribute to the stability of AF, mathematical models investigating the perpetuation of AF as well as future AF therapies need to address this phenomenon.

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