3-Dimensionality in Determining the Stability of Atrial Fibrillation

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Abstract

Atrial fibrillation is a progressive arrhythmia with increase in AF stability during its progression. AF progression goes in line with structural and electro-physiological changes. These alterations can make changes in electrophysiological parameters such as increase in number of waves, decrease in wave sizes, and increase in transmural conductions. In order to investigate which parameter has the largest effects on AF stability, we made a novel dual layer computer model and measured different read out parameters. Afterwards, a statistical test, multivariate logistic tests, was performed to extract contributions of different parameters on AF stability. Our study revealed endo-epicardial electrical activity dissociation is the most determinant parameter associate with AF stability.

1. Introduction

Atrial fibrillation is a progressive arrhythmia with increase in AF stability over its progression. Several studies suggested different mechanisms associated with AF stability over time. Disruption of electrical side to side connections between muscle bundles, leading to narrower thus more fibrillatory waves, is considered as one the main mechanisms contributing AF stability [1]. De Groot et al. showed increase in incidence of number of fibrillation waves as well as epicardial breakthroughs in patients in later stage of AF compare to patients with acute AF [2]. The same result reported as well increase in number of transmural conduction and endo-epicardial electrical activity dissociation by several animal studies using simultaneous endo-epicardial mapping [3, 4]. These findings suggest that AF development over time goes in line with more endo-epicardial transmural conductions and electrical activity dissociation. Although these studies conclusively demonstrated several reasons for increase in AF stability over time, but many conceptual questions such as mechanisms behind increase in transmural conduction and more important stability of AF duration remained open.

In this study we tried to investigate on parameters changes during AF progression and their effect on simulated AF episode duration and try to figure out important parameters among all different parameters. For this aim a novel computer model consists of two human atrial tissues were developed [5]. Afterwards different parameters such as number of waves, phase singularities, BTs as well waves lifespan, BT lifespan and electrophysiological parameters such as excitable area (EA), conduction velocity (CV), AF cycle length (AFCL) and endo-epicardial electrical activity dyssynchrony were measured. There after using statistical methods we tried to extract interactions and importance of each or several parameters.

2. Methods

2.1. Model

To investigate effects of different parameters on atrial fibrillation duration, a 'proof-of-principle' dual-layer computer model was developed.[5]

The human atria were modelled with a mono-domain reaction-diffusion model comprising two layers with a size of 4cm × 4cm. Each of the layers was composed of 400 × 400 segments with a size of 0.01cm × 0.01cm. Ionic currents and calcium handling for each segment was described by the Courtemanche-Ramirez-Nattel model [6]. Conductivities were assumed the same in both directions, $\sigma_x = \sigma_y = 0.5\,\mathrm{mS/cm}$, which implies isotropic tissue.

Opposing cells at the site of connection points were connected, in circles with a radius of 0.1 cm, via ohmic conductor

2.2. Simulation protocol

To investigate the effect of the above mentioned parameters on stability of AF, the following simulation protocol was applied:

In one layer, a spiral wave was initiated using an S1-S2 protocol [7], while the other layer was quiescent, as described in our previous study [5]. The simulation was continued for 1 second.

One second after the start of the simulation, 6 connection points were added at randomly chosen sites. These sites were chosen such that two connection points were at least 0.15 cm apart. To exclude possible bias resulting from a particular geometry of connection points, 8 different sets of 6 randomly chosen sites were created. For each of the 8 configurations, the simulation of step 1 was continued for 6 more seconds. This resulted in 8 different simulations that were used to initialize the simulations in the next step.

The 8 simulations from step 2 were continued for another 6 seconds, either without changing the connection points or after adding randomly chosen connection points (at least 0.15cm apart) such that the total number of connections was 6, 12, 24, 48 or 96. In addition, each simulation from step 2 was continued with 100% connectivity, i.e., all opposing segments in the two layers were connected to each other.

As described above, steps 2 and 3 were performed 8 times such that in total 48 simulation runs were performed in step 3.

In our model, 6 and 12 connections represented severely remodelled atria; 24, 48, and 96 connections represented moderately remodelled atria; and 100% connectivity represented a healthy atrium.

2.3. Analysis

In all 48 simulations of step 3 the following parameters were analyzed:

- Number of phase singularities (PSs)
- Phase singularity lifespan
- Breakthrough rates (BTRs)
- Breakthrough lifespan
- Number of fibrillation waves
- Wave front lifespan
- Atrial fibrillation cycle length (AFCL)
- Conduction velocity (CV)
- Excitable area (EA)
- Degree of endo-epicardial dyssynchrony
- Atrial fibrillation survival rate

2.3.1. Number of PSs and PS lifespan

A phase singularity (PS), which forms the tip of a reentrant wave, was defined on the basis of a transform of membrane potential distribution into phase as described earlier.[8] The algorithm used to detect PSs was based on the algorithm proposed by Zou et al[9].

To investigate the dynamics of PSs propagation, they were tracked in time and space as follows. The distance was calculated between all PSs detected at simulation time $t + 1$ ms and all PSs detected at simulation time t. If the minimum distance was less than 1mm, the two PSs were assigned the same ID. If for a PS the minimum distance was larger than 1mm, the PS was considered as an independent PS and was assigned a new ID. By choosing 1mm as a threshold, it was assumed that a PS cannot move faster than 1m/s [8].

2.3.2. BTR and BT lifespan

A breakthrough (BT) is a wave that appears in one layer and cannot be related to the propagation of other waves in the same layer. To detect BTs, areas containing connection points were studied per each 1ms. If a wave appeared at a connection point, this wave was followed for 2ms as a candidate breakthrough. If the breakthrough candidate increased in size within 2ms, it was labelled as a breakthrough.

Dynamics of breakthrough propagation was explored using the wave chain tracking algorithm described in our previous work.[8] In this algorithm, labelled wave(s) as well as breakthrough(s) were tracked through time and space. Lifespan of a breakthrough was defined as the time duration between breakthrough appearance and either extinction or fusion with a bigger wave. Breakthroughs were tracked in time by comparing AF patterns each 1ms, similar to the approach reported by Ten Tusscher et al [10] and Clayton et al.[11]

2.3.3. Waves and wavefront lifespan

A wave was defined as a contiguous area in which all segments have trans-membrane voltages above the excitation threshold of -60mV. Number of waves was calculated each 1ms of simulation time.

The propagation of fibrillation waves in our model was analyzed by tracking wave fronts through time and space. Wave fronts were detected using maximum positive slope in trans-membrane potentials.

Wave fronts were tracked in time by comparing AF wave front patterns in each 1ms, similar to the approach reported by Ten Tusscher et al[10] and Clayton et al [12]. For all wave fronts found in each layer at simulation time t, overlap (amount of segments) is computed with all wave fronts found in that layer at simulation time $t + 1$. If a wave front in one layer at simulation time t does not have overlap with any wave fronts in that layer at simulation time $t + 1$, it means that the wave front was extinguished. If a wave front at simulation time $t + 1$ has overlap with two or more wave fronts at simulation time t, fusion occurred that wave get the identification number of biggest wave front among two fused wave fronts. If a wave front at simulation time t has overlap with two or more wave fronts at simulation time $t + 1$, wave break occurred and a new wave was generated. The biggest size

among generated waves kept identification number of original wave front and the rest acquire new wave identification number. Finally, if a wave appeared at simulation time $t + 1$ and has no overlap with any wave fronts at simulation time t, breakthrough occurred also resulting in a new wave front and identification number.

2.3.4. Dyssynchrony

Dyssynchrony was defined as the percentage of segments that were excited (membrane potential above -60 mV), while the opposing segment was not excited (membrane potential below -60mv), i.e.

$$\text{Dyssynchrony} = \frac{\text{number of cells activated in one layer}}{\text{total number of cells}} \times 100\% \quad (2)$$

2.3.5. Excitable Area (EA)

Total number of segments in both layers with trans-membrane potentials below –60mv is considered as amount of excitable area calculation.

3. Results

In this study total number of 48 simulations, as mentioned in simulation protocol section, were used.

As illustrated in Figure 1 decrease in amount of transmural connections significantly increase amount of endo-epicardial electrical activity dyssynchrony.

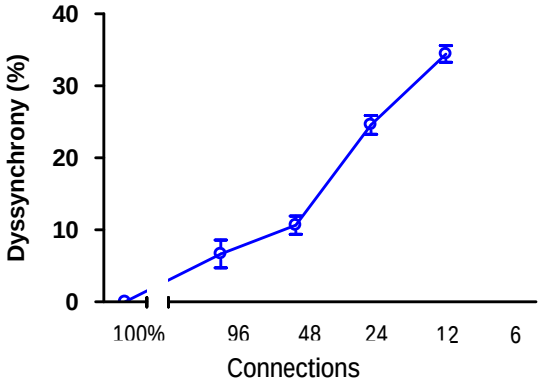

Figure 1. Averaged dyssynchrony percentage in different number of connections.

In order to investigate which parameter or parameters has the most important role in determining AF duration and their interactions, we categorized all simulations in two different categories, stable (25 simulations) and non-stable AF (23 simulations). Using multilevel logistic regression analysis among measured parameters allowed us to investigate on association of measured parameters on AF stability. Results were shown in Table 1. The average number of waves, wave lifespan, phase singularities, phase singularity lifespan, breakthrough rate, breakthrough lifespan, and dyssynchrony percentage were calculated for whole simulation period at each group. Afterwards multilevel logistic regression analyses were used to figure out contributions and associations of all parameters on AF stability. As illustrated in Table 1, two parameters were significantly correlated to AF stability. Using outcome coefficients of multilevel logistic regression and comparing them allowed us finding the parameter with the strongest influence on AF persistence. Dyssynchrony had highest amount of coefficient among all significant associated parameters, therefore was the strongest determinant of AF persistence.

In Figure 2 predicted probabilities of significant associated parameters were illustrated. As it shown in this figure, increase in dyssynchrony; increases the probability of AF episodes to sustain (see figure 2A). Figure 2B indicates that increase in excitable area led to decrease probability of AF continuation.

Table 1. Multi level logistic regression model parameters.

EP Parameters	P Values	Coef.
PSs	0.639	0.0519
PS Lifespan	0.270	0.0053
BTs	0.369	-0.164
BT Lifespan	0.244	-0.0035
Waves	0.720	0.116
Wave Front Life Span	0.957	0.0015
AFCL	0.245	-0.0348
CV	0.207	-65.4
EA	0.027*	-0.0013*
Dyssynchrony	0.004***	0.132***

4. Conclusions

A novel dual layer computer model was developed to study the effect of electrophysiological and structural alterations during AF progression on AF stability. This model so far is the only model simulating endo-epicardial electrical activity dyssynchrony using two separate layers, as representations of endocardium and epicardium, and transmural conductions between these two layers. In this study we tried to demonstrate that adding the third

dimension to AF substrate enhanced AF stability.

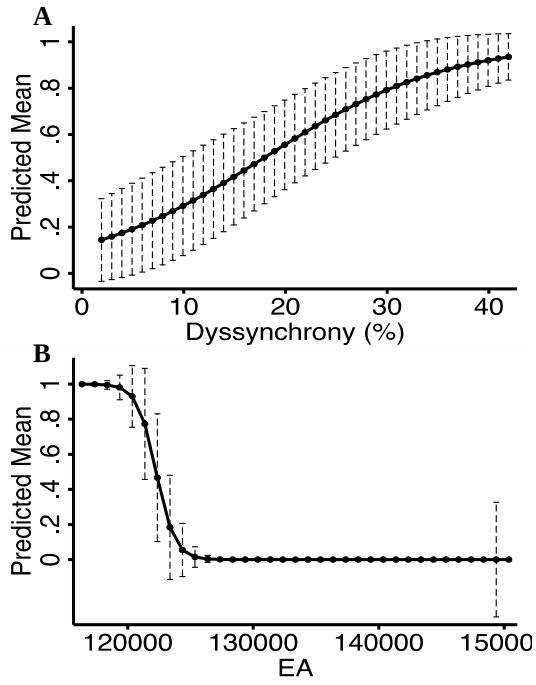

Figure 2. Predicted probabilities of dyssynchrony and excitable area (EA) on AF stability.

We showed that a decrease in number of transmural coupling increases endo-epicardial electrical activity dyssynchrony and as a consequence AF stability. Revealed by statistical analysis, comparing two groups (stable and non-stable AF) not all of the important determinants of AF stability were altered by the different degrees of endo-epicardial coupling. No significant changes were observed in conduction velocity or AF cycle length. Only the excitable area was slightly but significantly altered. Importantly, AF duration increased with increased in dyssynchrony and we identified this parameter as the strongest predictor for AF stability. Surprisingly increase in EA led to decrease the probability of AF to stop. Conclusively these findings clearly suggest that considering three-dimensionality in the conduction pattern in itself plays an important role in determination of the stability of the arrhythmia.

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