Influence of Right and Left Atrial Tissue Heterogeneity on Atrial Fibrillation Perpetuation

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Abstract

We propose a biophysical modelling approach to separately investigate the impact of right and left atrial (RA/LA) electrical heterogeneity on atrial fibrillation (AF) perpetuation. The baseline AF substrate was based on a 4:1 anisotropy ratio and uniform membrane properties. AF was initiated by a ramp-pacing protocol applied in the pulmonary veins region. Once AF was observed, random patchy heterogeneities in action potential duration (shorter duration inside the patches) were introduced in the cellular model for the subsequent simulation of AF. The effect of tissue heterogeneity on AF perpetuation was quantified by the duration of AF episodes (an AF episode lasting more than 50 s was considered as sustained). For high percentages of heterogeneities, the mean AF episode duration and the number of non-terminated AF episodes were significantly higher for the RA compared to the LA. This could be indicative of a very probable involvement of the RA substrate into the persistent AF process in this model. A direct link between the spatial localization of tissue heterogeneity and AF duration was also observed.

1. Introduction

Atrial fibrillation (AF) is the most common type of sustained arrhythmia with a very complex behavior and a high incidence rate compared to other cardiac arrhythmias.

It has generally been postulated that the AF process is accompanied by a progressive structural and electrical remodeling which contributes to AF maintenance. In this respect, it is of great interest to learn more about the one-to-one link between the AF process and the AF-induced changes in the atria [1]. AF-induced electrical remodeling has been shown to result in local random heterogeneities over the atria with shortened action potential duration (APD); this mechanism promotes multiple re-entry circuits [2].

The impact of electrical/structural remodeling on AF initiation and maintenance has been previously demonstrated in sheep [3] and human [4, 5] biophysical atria models. A full electrical and structural remodeling has been shown to prolong the duration of reentrant activity, leading to self-sustained AF episodes [5, 6]. Although many studies have investigated reentrant activity initiation and perpetuation due to the electrophysiological heterogeneity, the link between the mechanism underlying AF and the spatial extent and localization of these tissue heterogeneities is not well documented yet.

In the present study we used a previously developed 3D biophysical atrial model [7] to separately investigate the impact of right and left atrial (RA/LA) electrical heterogeneity in APD on AF perpetuation. In what follows, Section 2 briefly describes the biophysical model of AF, the simulation protocol and the analysis of AF perpetuation. Section 3 shows and discusses the experimental results.

2. Methods

2.1. Biophysical model of AF

Several computer models of AF with different accuracies in their representation of electrophysiological and anatomical details have been developed over the last decades (for a detailed review of the major mathematical approaches in modeling AF, see [8]).

In this study, the biophysical model was based on a Courtemanche model of human atrial cell electrophysiology. The model was implemented on an atrial anatomy reconstructed from computed tomography scans of a patient in permanent AF referred for an ablation procedure [7]. The atrial geometry (constructed as a three-dimensional monolayer surface) included all major anatomical obstacles.

In order to simulate self-terminated AF episodes, the Courtemanche model was used with modified channel conductances: the I_{to}, I_{Cal} and I_{Kur} currents were reduced

by 80, 30 and 90%, respectively and the I_{Kr} was increased by 50% [9, 10]. AF substrate was based on a homogeneous atrial tissue with 4:1 anisotropy ratio (longitudinal conductivity over transverse conductivity) and 300 Ωcm resistivity (yielding a conduction velocity of ~ 50 cm/s).

2.2. Simulation protocol and data analysis

AF was initiated by a ramp protocol with a cycle length of 280 ms decremented by 1 ms every beat, applied for 20 s in the pulmonary veins region. AF was observed after 10 s of pacing. During the time-course of AF, 26 instantaneous transmembrane potential maps were selected as initial conditions to form an AF database for further simulations. These transmembrane potential maps correspond to different states of electrical activity in the atrial tissue. They were taken from 15 s to 20 s after the beginning of ramp pacing, with 200 ms steps.

Random patchy heterogeneities in APD (shorter APD inside the patches) were introduced in the cellular model for the subsequent simulation of AF. Figure 1 shows the action potential morphology inside and outside the zones of heterogeneities. Patchy heterogeneities with a characteristic length scale of 7.5 mm were introduced by modifying the local membrane properties of the Courtemanche cell model (namely, the channel conductance associated with the ionic currents I_{to} , I_{Cal} , I_{Kur} , I_{Kr} were altered inside the patches by a factor 3, 0.5, 1 and 3 relative to the original model).

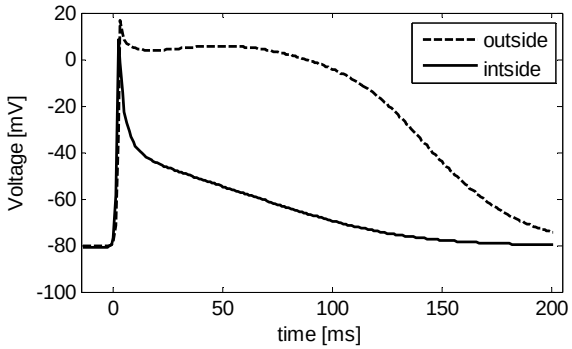

Figure 1. Action potentials morphology inside and outside the zones of heterogeneity.

The patchy heterogeneities were created using a region growth algorithm [10, 11] and the area of altered tissue was progressively increased from 20% to 80% of the size of each atrium.

For each considered percentage, five realization of the spatial distribution of patchy heterogeneities were generated. Figure 2 presents an example of random patchy heterogeneities in the atrial substrate. In the bottom panel, it can be seen how the sharp APD heterogeneity between regions promotes the development of reentrant wavefronts and wavebreaks.

The impact of tissue heterogeneity on AF perpetuation was quantified by the duration of AF episodes. An AF episode lasting more than 50 s was considered as sustained.

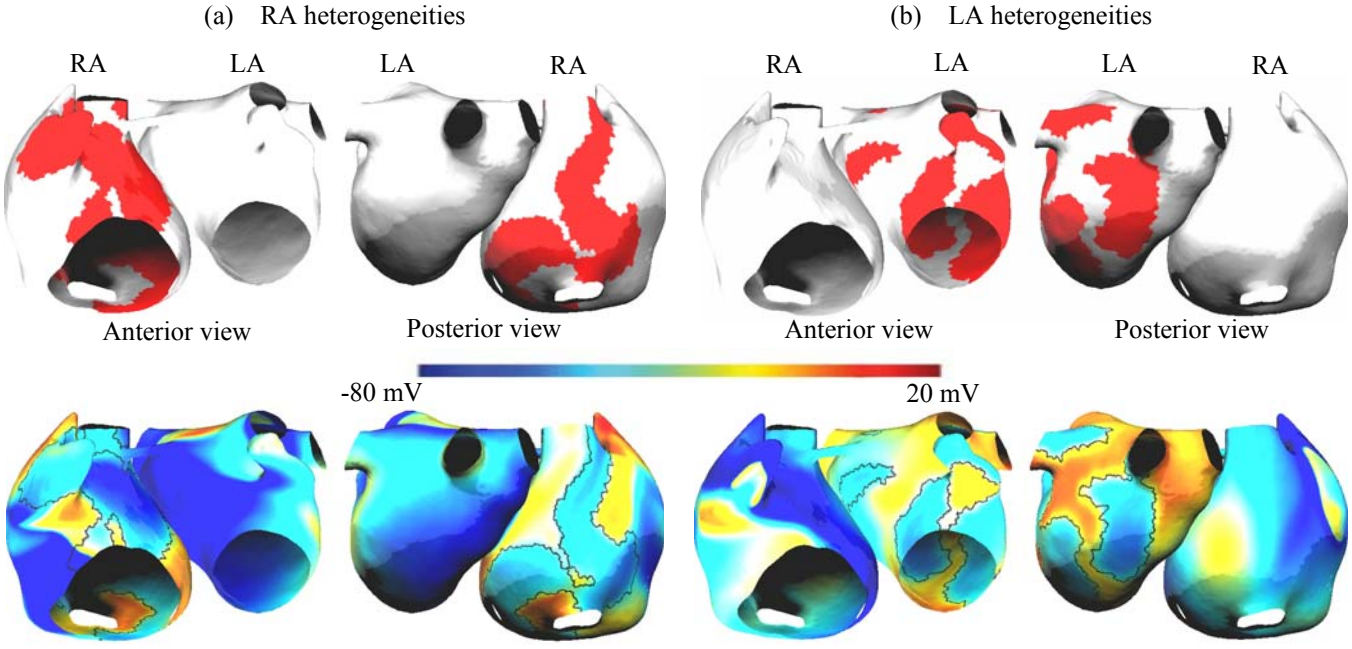

Figure 2. Top panel: Introduction of 40% random patches of heterogeneity in the atrial substrate. Bottom panel: Maps of transmembrane potentials during simulated AF. The patchy heterogeneities locations are indicated on the potential maps with a black line.

Statistical comparison between the RA and the LA for each percentage of heterogeneity was performed using a two-sample *t*-test. One-way ANOVA analysis was used to test whether the spatial localization of the patch heterogeneities significantly affects AF duration.

3. Results

The mean AF episode duration was 15.42 ± 3.68 s (mean ± SEM) for the homogeneous tissue. In contrast, in the presence of 80% heterogeneity in the atria, the reentrant activity was sustained (AF episode lasting more than 50 s) in 98% of the simulations. Overall, in the absence of APD heterogeneity, the reentrant activity was more stable and less chaotic with a low number of wavebreaks occurring. For the heterogeneous tissue, the repolarization gradients promoted multiple wavebreaks, which contributed to the maintenance of AF.

The simulations showed that the spatial extend and localization of heterogeneities significantly effects AF maintenance. Figure 3 shows the average AF duration for different percentages of heterogeneity considering separately the following cases: heterogeneities within the LA; heterogeneities within the RA; heterogeneities within both atria (considering together the heterogeneities from the previous two cases).

The mean AF episode duration and the number of sustained AF episodes were significantly higher for the RA compared to the LA only for 80% heterogeneities (47.9 ± 1.5 s *vs*. 31.2 ± 3.7 s, p<0.001). In terms of sustained AF episodes, there were 123 sustained AF episodes in 130 simulations for the RA heterogeneities compared with 68 sustained AF episodes for the LA heterogeneities. No significant differences were found between the RA and the LA for the other percentages of heterogeneity.

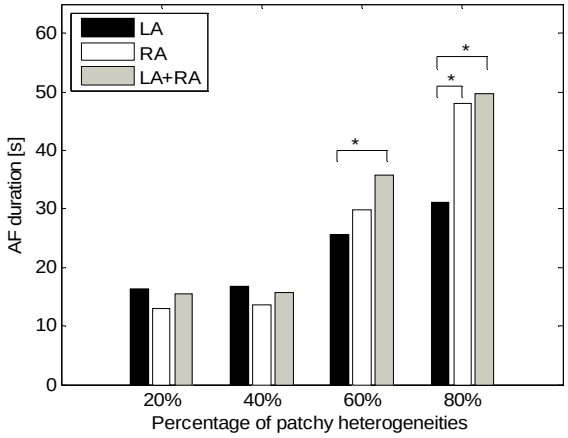

Figure 3. The mean AF duration for different percentages of the patchy heterogeneities. LA: heterogeneity within the LA; RA: heterogeneity within the RA; LA+RA: heterogeneity within the both atria (* : p<0.001).

Regarding the heterogeneities within both atria, the mean AF duration was significant higher only compared to the LA heterogeneity and only for high percentages of heterogeneity (p<0.001 for 60% and 80% heterogeneity). No significant differences were found for low percentages of heterogeneity or between heterogeneities within both atria compared to the heterogeneities within the RA.

Additionally, for low percentages of heterogeneity, a significant variability of the mean AF duration with respect to the spatial localization of the tissue heterogeneities was observed for the RA, but not for the LA. Namely, the mean AF duration among the five spatial distributions of the heterogeneities were significantly different for the RA, but not for the LA. Table 1 presents the *p*-values and the *F*-statistic for one-way ANOVA with the null hypothesis that the means of AF duration among the five spatial distributions of the heterogeneities are equal (*e.g.,* for 20% of heterogeneity, the mean values among the five were significantly different for the RA, $p = 0.02$, but not for the LA, $p = 0.76$).

Table 1. One-way ANOVA results (the *F* statistics and the *p*-values are indicated)

	LA		RA	
	$F_{4,125}$	*p*-value	$F_{4,125}$	*p*-value
20%	0.45	0.76	3.05	0.02
40%	1.04	0.4	4.23	0.003

4. Conclusion

In this study we have investigated the impact of electrical heterogeneity (heterogeneity in ionic channel conductance) on the AF perpetuation in a human atria model. The results suggest that the spatial localization and extent of tissue heterogeneity contribute to AF maintenance.

Although the driving role of the LA in maintaining AF is already well established, our results indicated that an AF-induced electrical remodeling within the RA is very likely to be present in a persistent form of AF. Note, however, that our model did not include left atrial specific AF mechanism such as ectopic foci or rotors, but was rather based on multiple wavelets that propagated after these triggers have induced AF. Another possible reason of the left-right differences that we have observed is the atrial size. Indeed, the area of the right atrial surface was 117 cm^2 *vs.* 104 cm^2 in the left atrium.

Moreover, the simulations showed that the spatial localization of heterogeneities could affect AF perpetuation. The results indicated a significant variability of AF duration for the heterogeneities within the RA, but we were not able to link the AF duration to the anatomical location of the heterogeneities.

The study did not take into account the natural inter-atrial electrophysiological heterogeneities (tissue refractoriness difference between the LA and the RA or action potential morphology variability across the atria). This could be another factor that creates additional left-right difference and would be necessitate further simulations.

Acknowledgements

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