An In-Silico Study Into the Impact of Electrophysiological Variability at the Cellular Level on the Re-entry Patterns in Atrial Fibrillation

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Abstract

Modelling the atria in-silico has become an important method in understanding atrial behaviour. Atrial models typically include regional electrophysiological variability, but neglect cellular variability. The aim of the study is to determine the impact of cellular electrophysiological variability on ectopic beats. Using a population of models approach to introduce regional and cellular variability into the atrial model, ectopic beats were initiated in two locations. Six ectopic beats were applied at a BCL of 130-160ms. The variable model was compared with an equivalent regional homogenous model. Using consistent tissue CV between models, in both the healthy and AF remodeled cases the average model total activation time was later than the variable model (a delay of 26ms and 14ms respectively). After matching activation times, repolarization was later in the average than the variable models. Latest APD90 in the AF remodeled cases were 268ms for the average and 256ms in the variable model. This resulted in a difference in propagation of the ectopic beat. In conclusion, cellular variability has a significant impact on both the depolarization and repolarization phases in the atria for the healthy and AF cases.

1. Introduction

In silico modelling is often used to model the behaviour of the atria during atrial fibrillation in order to better understand the mechanisms and therefore improve treatment methods. Much of the modelling associated with AF research focusses on the anatomical variability between patients to determine susceptibility. The research investigating the impact of electrophysiology within the atria is limited by the complexity of the models, whereby variability is included on a regional basis[4] and cell-to-cell variability within each atrial region is neglected. Experimental investigations into the cellular variability within atrial regions shows significant levels of cellular variability within the same atria region[1][5][6][9][12].

When modelling the atrial response to AF it is important to have as accurate a model as possible in order to obtain realistic results. It is typically assumed that cellular coupling masks the variability within atrial regions and therefore a regionally homogenous model is used to predict atrial behaviour. But how much of an impact does cellular variability have on the electrophysiological behaviour of the atria? It is the purpose of this study to determine the impact of cellular variability on the atrial electrophysiological response to both sinus rhythm and the presence of ectopic beats.

2. Methods

2.1. Cellular model

A total of 9 maximum channel conductances were varied +/-100% using the Monte Carlo Sampling Method to create a population of models using the Maleckar cellular model for cardiomyocytes[7]. Each cellular model was stimulated a 1Hz for 10 minutes. The ultimate action potential was used for classification. Any unstable or non-physiological action potentials were discarded.

Using experimental data to define regional characteristics using 5 biomarkers (Table 1), the population of models was divided into regional populations[1][5][6][9][12]. Due to a lack of experimental data regarding the biomarkers for regional tissue in an AF remodeled atria, the AF remodeled populations were created by applying the percentage changes to 5 channel conductances[8], shown in Table 2. Again, any unstable or non-physiological action potentials were discarded.

2.2. Atrial model

	RA	RAA	LA	LAA	AVR	CT/BBra	BBla	PM
RMP	-75+/-12	-76+/-6.6	-75+/-5.4	-71+/-6.6	-71 +/- 1.4	-74+/-1.9	-74+/-1.9	-73+/-12
APA	109+/-14	116+/-19	95+/-3.9	120+/-19	119 +/-21	126+/-19	116+/-19	123+/-16
APD20	7 +/- 6.6	7 +/-6.6	7 +/-6.6	7 +/-6.6	7 +/-6.6	7 +/-6.6	7 +/-6.6	7 +/-6.6
APD50	95+/-37	139+/-36	72+/-17	118+/-13	50 +/-21	157+/-32	124+/-32	98+/-17
APD90	295+/-62	280+/-22	256+/-34	236+/-22	250 +/-29	322+/-64	253+/-32	254+/-19

For each regional population, the action potential representing the mean characteristics of the population was assigned to each node associated with that region in the atrial model. This created the regionally homogenous model used for comparison, shown in Figure 1.

Using the regional populations, each node within the whole atrial model was randomly assigned a single cellular model from the associated population with a uniform distribution. This resulted in four comparable models: healthy average atria, healthy variable atria, AF remodeled average atria, and AF remodeled variable atria. Tissue conduction velocity for the healthy atria models were calibrated using the variable model to adjust

Using a total activation time within the observed physiological range for a healthy atria, the tissue conduction velocity was adjusted until the variable healthy model total activation time fell within this accepted range.

For the AF remodeled atria, tissue conduction velocity was reduced by 15% from the healthy atria CV [8]. The average models were initially simulated using the same conduction velocity as the respective variable models and further adjusted until the total activation times were comparable with the variable models.

	RA regions	LA regions
gTo	-45%	-75%
gKur	-60%	-45%
gKs	+150%	+100%
gK1	+100%	+100%
gCaL	-65%	-65%
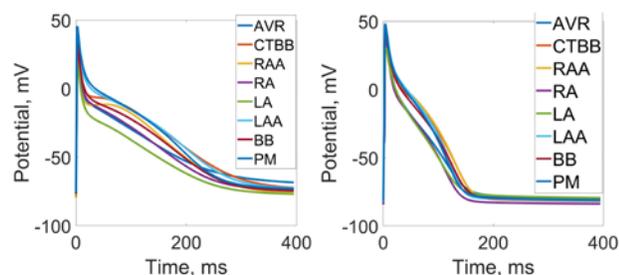
Figure 1 Regional population average models for the healthy atrial regions (Left) and AF remodeled regions (Right) used to create regionally homogenous models.

2.3. Simulations

To stabilise the atrial models, each model was pre-paced using 10 stimuli at a BCL of 800ms, stimulus duration 2ms, amplitude -50mV. After pre-pacing, each model was stimulated using a single SR for comparison during normal atrial behaviour.

To determine the impact of cellular variability during AF, ectopic beats were applied in two regions: the right and left pulmonary vein ostium[10]. SR stimulation was continued throughout ectopic beat stimulation. A total of 719 and 791 nodes were stimulated in the LPVo and RPVo respectively. Six ectopic beats were applied at a BCL ranging from 130-150ms, stimulus duration 2ms, amplitude -50mV. SR stimuli were applied at a BCL of 800ms, stimulus duration 2ms, amplitude -50mV.

	Av. model	Var. model	Increased Av. CV	%increase CV
Healthy	150	124	128	26%
AF remodeled	168	144	144	8%

2.4. Analysis

Models were compared through total activation time, the time at which the latest APD90 was reached in each model, and visual differences in propagation patterns throughout both healthy atrial behaviour and ectopic beat behaviour.

3. Results

3.1. Population variability

Populations showed a reduction in APD50 and APD90 from the healthy atrial regions to the AF remodeled regions. Figure 2 shows the reduction observed in regional populations for the APD50 and APD90 biomarkers.

3.2. Healthy atrial behavior
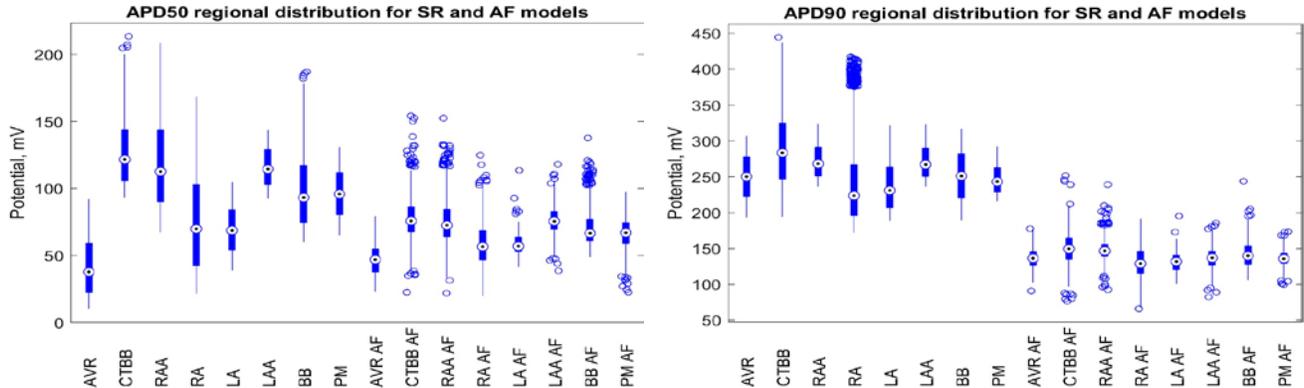
Figure 2 Population distribution of APD50 (left) and APD90 (right) for healthy (first 8) and AF remodeled atria regions (last 8).

Using consistent tissue CV between models, in both the healthy and AF remodeled cases the average model total activation time was later than the variable model (a delay of 26ms and 14ms respectively). Table 3 shows the total activation times for the average and variable models in both the healthy and AF remodeled cases.

The average models were recalibrated to match the variable model TAT. In the healthy model this required a 26% increase in CV to bring the average TAT within 5% of the variable TAT. In the AF remodeled case, the CV increase was smaller, requiring an 8% increase to match TAT between models.

After matching activation times, repolarization was later in the average than the variable models. Latest APD90 in the AF remodeled cases were 268ms for the average and 256ms in the variable model. Additionally, in both the healthy and AF remodeled cases, small differences in propagation patterns were observed.

Additionally, in both the healthy and AF remodeled cases, small differences in propagation patterns were observed. In both the healthy and AF remodeled cases the variable model propagation had a faster propagation with different morphology from initial stimulation. This can be seen in Figure 3 whereby the left shows the average model propagation and the right shows the variable propagation

for both the healthy (top) and AF remodeled (bottom) atria. This results in a different propagation across the right atria as shown in Figure 4 at t=88ms in the average model and t=80ms in the variable model. The black boxes highlight regions in which the propagation differs between models.
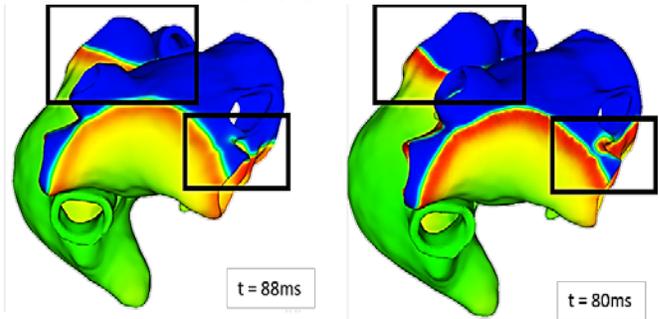
Figure 4 Later sinus rhythm propagation in average model with increased CV (left) and variable (right) healthy atrial models. Black boxes show regions where propagation differs between average and variable models

3.2. AF remodeled atria ectopic beats

Figure 5 shows the propagation of a RPV ectopic beat across the variable (top) and average (bottom) AF remodeled As shown in figure 5, the variable model propagates through into the right atria through the coronary sinus whereas the same ectopic beat is blocked in the average model. This results in a different wavefront morphology and therefore a different pattern of repolarization. This is likely due to the difference in repolarization times between the average and variable AF remodeled atria.

Similarly, the difference in repolarization times between the average and variable AF remodeled atria resulted in an ectopic beat propagating in the variable model while failing to propagate in the average model. These differences observed as a result of ectopic beats could lead to differences in behavior during reentries in AF. Similar differences between models were observed in the LPV ectopic beat simulations.
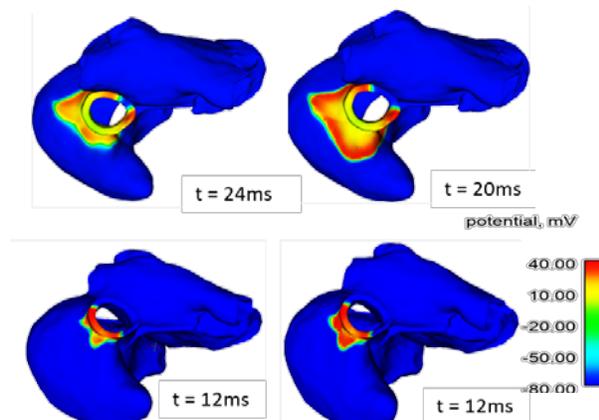
Figure 3 Sinus rhythm propagation in healthy (top) and AF remodeled (bottom) average (left) and variable (right) models during early stages of propagation

4. Conclusion
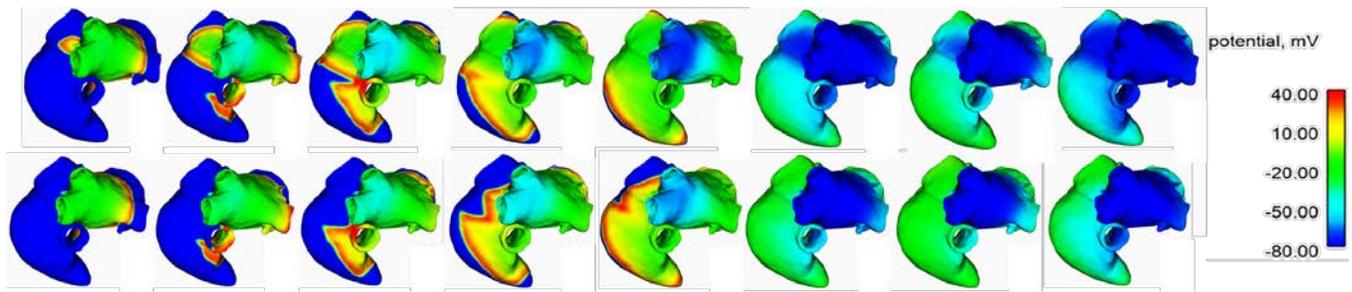
Figure 5 Propagation of RPV ectopic beat in the variable AF remodeled atria (top) and the average AF remodeled atria (bottom), from left to right t = 456ms, 480ms, 492ms, 504ms, 516ms, 580ms, 568ms, 592ms.

In conclusion the inclusion of cellular variability in atrial modelling results in a need for a reduction in tissue conduction velocity to maintain physiological total activation times observed in regionally homogenous models. In both the healthy and AF remodeled cases, using comparable total activation times results in small differences in wavefront morphology between the average and variable models.

Additionally, in both the SR and AF remodeled cases, the repolarization across the atria was slower in the average model than the variable model. This shows that even with accounting for the increased propagation velocity across the variable model, the behaviour in depolarisation differs significantly compared with the regionally homogenous model. When applying ectopic beats to the average and variable models with comparable total activation times, differences in propagation patterns are observed to the extent that an ectopic beat that propagates in the variable model fails to propagate in the average model. Similarly, interatrial blocks observed in the average model EB are not present in the variable model EB. This could result in a difference in susceptibility to atrial fibrillation.

5.   Limitations

These results only observe the difference in propagation resulting from cellular variability using one cellular model. Future work includes using the Courtemanche cellular model[2] and different combinations of cellular variability using the Maleckar model[7]. Additionally, the impact of variability on ectopic beats in other locations and on re-entry patterns during AF are to be investigated[10].

Acknowledgments

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