Cellular Heterogeneity in the Atria: An In Silico Study in the Impact on Reentries

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Abstract

In-silico modelling is increasingly relied upon to gain new insights into the underlying mechanisms of atrial fibrillation. Due to the complex nature of the atria, in-silico models typically exclude cellular heterogeneity. One question that remains unanswered is the impact of cellular heterogeneity on reentrant mechanisms and in the vulnerable window (VW). This study aims to present the impact of cellular heterogeneity on the AF mechanisms and susceptibility to re-entry behaviour. Cellular heterogeneity was introduced into the whole atrial model using the population of models approach and regionally specific node assignment. Each atrial model was stimulated from the SA node, followed by a series of rapid-paced ectopic beats at one of three locations in the left atria. Results showed a small, insignificant increase in re-entrant frequency as a result of cellular heterogeneity, with only minor changes to the re-entrant circuit. However, the vulnerable window was significantly impacted through the introduction of cellular heterogeneity. The results suggest that cellular heterogeneity in the atrial model resulted in an increased VW for reentry depending on EB location. This suggests that local cellular heterogeneity plays a significant role in the susceptibility to re-entries, but does not significantly impact the path or frequency of re-entries.

1. Introduction

Improved understanding of the impact of variability on electrophysiological mechanisms is key to understanding the cause and development of cardiovascular disease. Atrial models are increasingly relied upon to understand the mechanisms behind atrial arrhythmias such as atrial fibrillation. In order to represent the behaviour of the atria, it is important to create representative models of the human atria. Models typically assume cellular coupling masks the impact of electrophysiological variability on the cellular level. Recent studies show cellular heterogeneity can significantly impact repolarization in the atria [1].

This study investigates the impact of cellular variability on the vulnerability to and maintenance of re-entrant activity in the AF remodelled atria. Directly comparing the vulnerability to and maintenance of an arrhythmia in these atrial models will provide valuable insight into the importance of including cellular heterogeneity in in-silico modelling.

2. Materials and Methods

2.1. Model setup

Using the Courtemanche cellular model for cardiomyocytes and the Monte Carlo Sampling method, a total of 9 maximum channel conductances (gNa, gTo, gKur, gKr, gKs, gK1, gCaL, gNaK, gNaCa) were varied -100% to +200% to create a population of 200,000 unique action potential models. Published experimental data was used to divide the population into 8 regional populations based on 5 biomarkers (RMP, APA, APD20, APD50, APD90) with AF remodelled characteristics. Mean and standard deviation values for each region are shown in Table 1.

2.2. Ectopic beat protocol

A heterogeneous atrial model was created using the regional populations and the regional tissue conductance set by the isolated tissue calibration. A comparable

Table 1. Mean and standard deviations of regional biomarkers used for the classification of the population of models.

	RA	RAA	LA	LAA	AVR	CT/BBra	BBla	PM
RMP	−78 ± 12	−79 ± 6.6	−78 ± 5.4	−73.8 ± 6.6	−73.8 ± 1.4	−77 ± 1.9	−77 ± 1.9	−75.9 ± 12
APA	116.6 ± 14	124.1 ± 19	112.4 ±13	128 ± 19	127.3 ± 21	134.8 ± 19	124.1 ± 19	131.6 ± 16
APD20	30 ± 18	30 ± 18	30 ± 18	30 ± 18	30 ± 18	30 ± 18	30 ± 18	30 ± 18
APD50	72.2 ± 37	105.6 ± 36	54.7 ± 17	89.7 ± 13	38 ± 21	119.3 ± 32	94.2 ± 32	74.5 ± 17
APD90	200 ± 62	190 ± 22	174 ± 34	160 ± 22	170 ± 29	219 ± 64	172 ± 32	172 ± 19

regionally homogeneous atrial model was created using the same geometry. The anatomical atrial model presented in [2] was modified for this study.

Three locations were used to initiate a re-entrant: The left pulmonary vein ostia (LPVO), right pulmonary vein ostia (RPVO) and the left atrial posterior free wall (LAPFW). Following a stimulus from the SA node, a series of 9 rapid pacing (RP) stimuli were applied in one of the locations, with a 10ms decrease in the coupling interval from 200ms to 130ms.

$$CI = \{200, 190, 180, \dots, 140, 130\ ms\}$$

Initial simulations were conducted in the absence of continues SA stimulation, these were then repeated with continued SA stimulation at BCL =800ms.

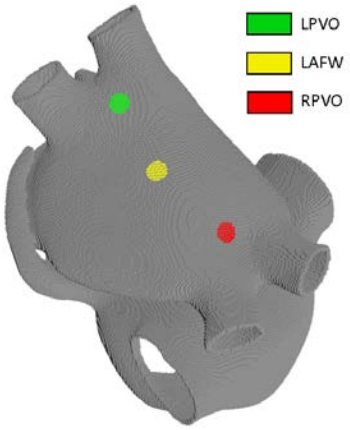

Figure 1. Ectopic beat locations in the left atria.

Vulnerability was determined by systematically moving the rapid pacing start time, RP1. The critical path of re-entry was also compared, along with the impact of continued SA stimulation.

2.3. Model solution

Electric propagation in the atria was modelled through the monodomain model [3]. The monodomain model is defined as:

$$\nabla \cdot (\mathbf{D}\nabla \mathrm{V}) = \mathrm{C_m}\frac{\partial \mathrm{V}}{\partial \mathrm{t}} + \mathrm{I_{ion}}(\mathrm{V}, \mathbf{u})$$

$$\frac{\partial \mathbf{u}}{\partial \mathrm{t}} = \mathbf{f}(\mathbf{u}, \mathrm{V}, \mathrm{t})$$

Whereby $\mathbf{D} = {}^{\lambda}/_{1+\lambda}\,\mathbf{D_i}$ is the effective conductivity tensor. The monodomain model is subject to the boundary condition:

$$\mathbf{n} \cdot (\mathbf{D}\nabla \mathrm{V}) = 0$$

For this study, the monodomain model was used, together with the Courtemanche cellular model to describe the cellular ionic behaviour. The monodomain model was solved by means of the finite element method in combination with operator splitting numerical scheme as described in [4].

3. Results

Heterogeneity resulted in an increased VW in the LAPFW location compared with the regionally homogeneous atria. In the RPVO location, heterogeneity prevented re-entrant behaviour, where in the regionally homogeneous atria, the VW was the full cycle length. Heterogeneity resulted in marginally increased re-entrant frequency. In all cases whereby a re-entry was obtained, the re-entry followed the pathway presented in Figure 2.

Table 2. Vulnerable windows and reentrant frequency for the regionally homogeneous and heterogeneous atrial models at each EB location.

	Homogeneous		**Heterogeneous**	
	VW	Freq. Hz	VW	Freq. Hz
LPVO	0-800	5.66	0-800	5.74
LAPFW	0-325	5.68	0-800	5.72
RPVO	0-800	5.74	*No Re-entry*	

3.2. LPVO

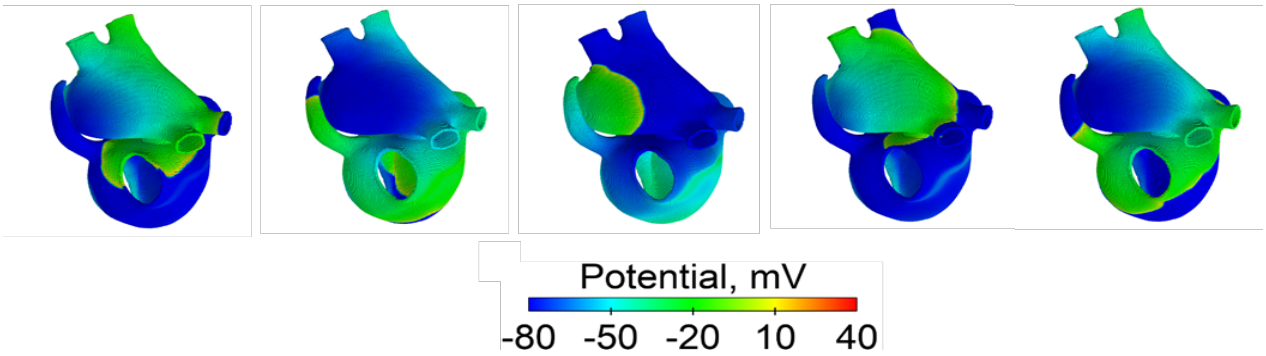

Figure 2. Re-entry pathway obtained from each of the EB locations.

In the absence of continued SA stimulation, heterogeneity results in minor changes to the critical path of re-entry, whereby the re-entry enters the LA through the earliest route from the coronary sinus (CS), and enters from further along the CS in the regionally homogeneous atria. This resulted in the marginally higher re-entrant frequency in the heterogeneous atria. In both models, the re-entry was obtained irrespective of when the rapid pacing was initiated.

When continued SA stimulation was applied, the critical path of re-entry was unchanged. Dynamic repolarization heterogeneity occurred across the atria due to cellular heterogeneity. The most notable resulted in the CT and BB acting as temporary blocks in regionally homogeneous. This however did not impact the critical path for re-entry. Figure 3 shows the impact of the BB block in the regionally homogeneous atria, which is not present in the heterogeneous atria.

3.3. LAPFW

When no continued SA stimulation was applied, the heterogeneous model resulted in a re-entry through the CS. The re-entry obtained in the LAPFW was independent of RP1 start time. The regionally homogeneous atria, however, had a significantly reduced VW, whereby re-entries could not be obtained beyond RP1 = 325ms.

When continued SA was applied, the dynamic repolarization heterogeneity in the regionally homogeneous atria was altered in the area surrounding the BB, causing a left-BB block and resulting in a continued re-entry with the same critical path as the heterogeneous atria.

3.4. RPVO

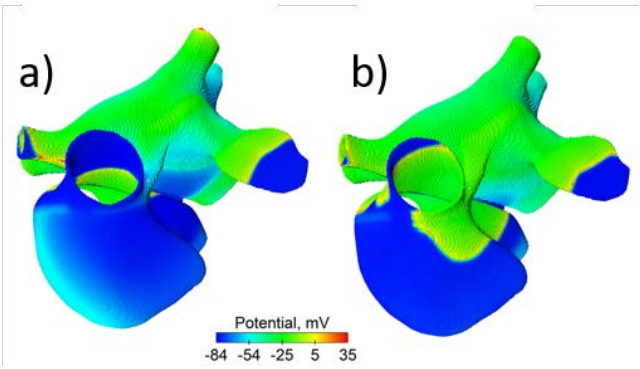

Figure 3. Bachmann's Bundle block present in the regionally homogeneous atria (a), and absent in the heterogeneous atria (b), in response to rapid pacing in the LPVO location.

When rapid pacing was applied to the RPVO, the regionally homogeneous model resulted in a re-entry through the CS that was independent of RP1. The heterogeneous atria, however, did not result in a re-entry, irrespective of RP1. This was the case for both simulations in the absence of continued SA stimulation, and in the presence of continued SA stimulation.

4. Discussion

The results of this study suggest that cellular heterogeneity in the atrial model resulted in an increased VW for the LA free wall location. However, in the right PV ostium, re-entry was obtained in the regionally homogeneous atrial model and not in the heterogeneous atria. This suggests that in some instances, cellular heterogeneity can act in a way that increases re-entrant susceptibility, but in other instances, provides protection against re-entry. Further investigation into the potential

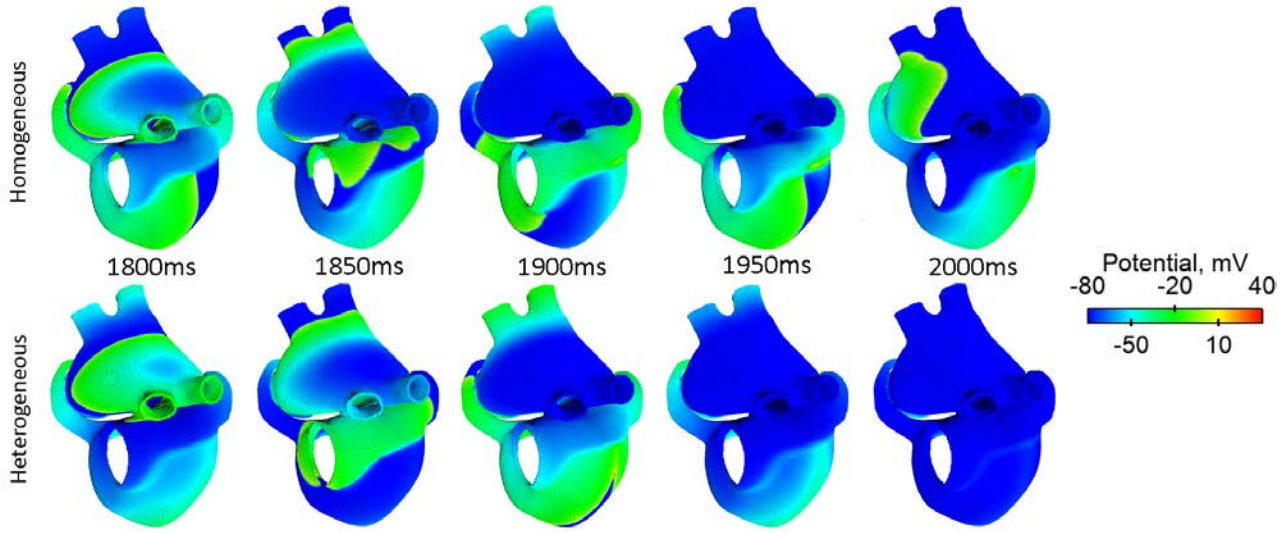

Figure 4. RPVO reentry occurring in regionally homogeneous atria, and no reentry occurring in heterogeneous atria

causes of this are needed. In each of the EB locations, cellular heterogeneity did not result in significant changes to the frequency of reentry or the path of reentry.

In [5], using the same geometric model but different tissue and cellular properties, a re-entry in the LAPFW was unobtainable. In this study, however, a re-entry was obtained in both the regionally homogeneous and heterogeneous models. The heterogeneous atrial model had a much larger VW than the regionally homogeneous model in this case. This suggests that susceptibility to non-PV foci resulting in re-entry is increased as a result of cellular heterogeneity.

In this study, re-entries were obtained in both regionally homogeneous and heterogeneous atria in the LPVO, whereas a re-entry was obtained in the RPVO only in the regionally homogeneous atria. This location in [5] also resulted in a re-entry. In [6], it was reported that LPVO had increased VW to re-entry compared with RPVO. Whereas in this study, both VWs were the same and large, the inability to induce a re-entry in the heterogeneous model in the RPVO location would further support the results in [6], suggesting LPVO is more vulnerable to re-entry.

Interestingly, [7] and [8] reported that foci occurring inside the PV induced re-entrant behavior (54% occurrence) more than foci occurring outside the PV (30% occurrence). This is consistent with the results of this study, whereby VW was larger in PV locations than in the EB locations outside the PV.

5. Conclusion

Cellular electrophysiological heterogeneity has a significant impact on the vulnerability to re-entrant behaviour. Cellular heterogeneity can modify the critical path of re-entry and increase the re-entrant frequency. In the LA free wall, cellular heterogeneity increased the susceptibility to re-entry, whereas the reverse is true in the RPVO. This suggests that local cellular heterogeneity plays a significant role in the susceptibility to re-entries. Furthermore, in both the left atrial free wall and in the left pulmonary vein ostium, cellular heterogeneity prevented temporary blocks in the CT and BB regions, that were observed in the regionally homogeneous atria, suggesting cellular heterogeneity in fast conduction pathways can significantly impact the wavefront by enabling propagation due to variability in local refractory periods.

Acknowledgments

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