Impacts of Cellular Electrophysiological Variability on Conduction Velocity Within Isolated Tissue and Depolarization and Repolarization Across the Whole Atrial Model

Jordan Elliott[1], Maria Kristina Belen[1], Luca Mainardi[1], Valentina Corino[1], Jose Felix Rodriguez Matas[1]
[1]Politecnico Di Milano, Milano, Italy

Abstract

Improved understanding of the impact of variability on electrophysiological mechanisms is key to understanding the cause and development of cardiovascular disease. Recent studies suggest cellular variability could have an impact on electrophysiological behavior that homogeneous models are unable to capture. This study investigates the impact of cellular variability on conduction velocity and the depolarization and repolarization phases of the atria. Method: 10 Isolated tissue samples for each atrial region were calibrated for CV and later combined in a detailed anatomical atrial model. Variable models were compared with equivalent homogeneous models. Activation maps and APD maps were used for comparison. Results: In isolated tissue simulations, differences in tissue conductance (Gi) ranged between 5.5% reduction to 5.4% increase as a result of heterogeneity, despite differences in CV being <1%. Activation maps showed no significant differences between regionally homogeneous and heterogeneous atrial models. Repolarization across the atria differed significantly between regionally homogeneous and heterogeneous atrial models. Conclusion: Cellular variability has no significant impact on depolarization but significantly influences atrial repolarization. This could result in increased susceptibility to re-entries and atrial fibrillation.

1. Introduction

A trial models are used to further understand the mechanisms behind common atrial arrhythmias. In order to represent the behaviour of the atria, it is important to create models with the variability observed in the human atria. Due to difficulties incorporating cellular variability, models typically assume cellular coupling masks the impact of electrophysiological variability on the cellular level. Some studies have investigated cellular variability in through the use of a population of models approach but have not extended this to tissue samples [1][7][8], whereas other studies introduce regional variability in tissue samples or atrial simulations, but do not include cellular variability [2][6]. [3] is the only atrial model that includes cellular variability but only looks at the activation across the atria. This study aims to determine the impact of cellular variability on the overall electrophysiological behaviour of the human atria. This study presents the impact of cellular variability on conduction velocity (CV) across isolated tissue samples and on the electrophysiological behaviour in the entire atria.

Atrial studies typically focus on the depolarization across the atria or dominant frequency maps and few look directly at the repolarization across the atria. Atrial simulations in [10] showed the APD map for a regionally homogeneous atria under sinus rhythm. This is the first study to investigate the impact of cellular variability on the repolarization across the atria.

2. Materials and Methods

2.1. Population of models

Using the Courtemanche cellular model for cardiomyocytes [9] 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 create a population of models. Each cellular model was stimulated a 1Hz for 10 minutes. Classification of each cellular model was based on the action potential from the ultimate stimulation. Exclusion criteria included any action potentials with spontaneous depolarization activity, any action potentials with an

Table 1 Mean and standard deviation values used for regional classification. Values based on experimental data for healthy atria tissue for each region.

SR	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	105 ± 13	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

abnormal peak voltage, or peak voltages below zero and any potentials with an APD larger than 1 second or a resting potential less negative than -50mV.

The software packages used to create, stimulate and analyze the population was MATLAB 2019b (The Mathworks Inc., Natick, MA, USA)

Published experimental data was used to classify individual action potentials for each atrial region [1][4][5][6][8]. Regional parameters for the 5 biomarkers used for classification are shown in table 1.

2.2. Isolated tissue calibration

Isolated tissue calibration was performed first on a single homogenous and a single heterogeneous tissue sample for each atrial region.

Tissue sample geometry was 1.8x0.18x0.18mm with an element size of 0.03mm and a hexahedral mesh. Each tissue sample was paced using 10 stimuli at a BCL of 800ms. Each stimulus had a duration of 2ms and an amplitude of 350mV. Using 5 nodes spaced 0.15mm apart in the centre of the tissue sample and a unidirectional propagation, the average CV was calculated using the following equations:

$$CV_n = \frac{\Delta d_n}{\Delta t_n}$$

$$CV_n = \frac{d_n - d_{n-1}}{t_n - t_{n-1}}$$

Whereby CV_n is the conduction velocity between points n-1 and n. Δd_n is the distance between points n-1 and n. Δt_n is the time difference between the stimulus reaching points n-1 and n. Using several iterations, the CV for each tissue sample was calibrated to within 3% of the target CV by adjusting the tissue conductance (Gi). Target CVs were based on published data [10].The relationship between the conduction velocity and tissue conductance is:

$$CV \; \alpha \; Gi^2$$

Where Gi is the tissue conductance and CV is the conduction velocity.

To calculate the variability of the conduction velocity in heterogeneous tissue, 10 heterogeneous tissue samples were created for each atrial region using the regional populations, and the mean and standard deviation calculated.

2.3. Whole atrial simulations

A heterogeneous atrial model was created using the regional populations and the regional tissue conductance set by the isolated tissue calibration. A comparable regionally homogeneous atrial model was created using the same geometry and the tissue conductance for the homogeneous isolated tissue samples. The anatomical atrial model used can be found in [10].

Each atrial model was pre-paced from the SA node at a BCL of 800ms for 10 stimuli. Each stimuli had an amplitude of -50mV and a duration of 2ms. Once pre-paced, each model was stimulated using a single sinus rhythm stimulus for comparison during normal atrial behaviour.

Activation maps, APD maps and Repolarization maps were generated for the last beat of each simulation for comparison between the regionally homogenous and heterogeneous atria.

3. Results

When tissue conductance (Gi) remained the same for the heterogeneous tissue as the homogeneous tissue, cellular variability resulted in CV variation of up to 4cm/s.The heterogeneous isolated tissue samples were then calibrated to within 1% of the homogeneous isolated tissue samples.

Table 2 shows the percentage difference between the regional tissue conductance for the homogenous and heterogeneous tissue samples calibrated to within 3% of target CVs. Differences in tissue conductance (Gi) ranged between 5.5% reduction to 5.4% increase as a result of heterogeneity, despite CVs being within 1% of each other.

Table 2 Tissue conduction velocity for calibrated homogeneous and heterogeneous isolated tissue samples.

Region	Heterogeneous tissue CV (cm/s)	Homogeneous tissue CV (cm/s)	% difference CV
RA	92.6	92.4	0.2
CT	102.0	101.8	0.2
PV	69.0	69.0	0.0
BB,PM	117.8	117.8	0.0
IST	78.2	78.0	0.3
SAN	27.3	27.4	-0.4
CS	109.5	109.2	0.3
LA	74.1	74.1	0.0
FO ring	100.0	100.0	0.0

Table 3 shows the tissue conductivity (Gi) for each atrial region for both the homogeneous tissue samples and the heterogeneous samples for each atrial region. The final column shows the percentage increase in tissue conductivity from the homogeneous tissue to heterogeneous tissue.

Tissue conductance values differed between homogeneous and heterogeneous tissues by up to 5.5%. The RA, CT and FO ring regions showed a reduction in tissue conductance as a result of heterogeneity. The BB, PM and LA regions showed an increase in tissue conductance as a result of heterogeneity.

Table 4 shows the conduction velocity for each atrial region for both the homogeneous tissue samples and the mean and standard deviation of the 10 heterogeneous samples for each atrial region. Heterogeneous tissue samples for each region showed small levels of variability in the conduction velocity, with a maximum standard deviation of ±2.4 cm/s in the FO ring and a minimum s.d of 0.19 cm/s in the SAN. Homogeneous tissue CV remained within the range of the calculated CV for the heterogeneous tissue samples.

Table 3 Percentage change in tissue conductance between homogeneous and heterogeneous isolated regional tissue samples.

Region	Gi cm^2/ms Homogeneous	Gi cm^2/ms Heterogeneous	% increase in Gi
RA	0,003000	0,002835	-5.5
CT	0,003229	0,003069	-4.96
PV	0,001700	0,001760	3.53
BB,PM	0,004100	0,004320	5.37
IST	0,002122	0,002122	0
SAN	0,000413	0,000419	1.45
CS	0,004100	0,004100	0
LA	0,001900	0,001967	3.53
FO ring	0,003360	0,003280	-2.38

Table 4 Regional tissue conduction velocity for the homogeneous tissue samples and the mean and standard deviation of the tissue conduction velocity of the heterogeneous tissue samples.

Region	Homogeneous tissue CV (cm/s)	Average CV of heterogeneous tissue (cm/s)	s.d. of heterogeneous tissue CV (cm/s)
RA	92.37	92.024	1.76
CT	101.79	101.827	1.59
PV	68.99	69.045	0.65
BB,PM	117.79	119.458	2.17
IST	77.96	78	0.66
SAN	27.4	27.217	0.19
CS	109.2	112.73	1.31
LA	74.11	74.672	1.29
FO ring	100	99.423	2.40

Figure 1 shows the variability in CV of isolated tissue samples for each atrial region. The largest range of CV was observed in the BB/PM tissue and the FO ring tissue. All regions showed small amounts of variability across the 10 heterogeneous tissue samples.

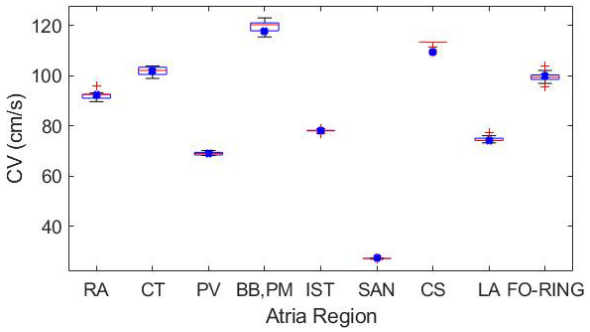

Figure 1 Boxplot showing the variability in conduction velocity across 10 different heterogeneous tissue samples for each atrial region. The blue dot for each region represents the CV for the equivalent homogeneous atrial tissue.

Activation across heterogeneous and homogeneous models were comparable after isolated tissue calibration. As is shown in figure 2, there are no observable or significant differences in activation maps between regionally homogeneous and heterogeneous models.

Repolarization times differed between homogeneous and heterogeneous models despite equivalent activation times and activation across the atria. Figures 3 and 4 show the APD maps and the repolarization maps for the homogeneous atrial model and heterogeneous atrial model.

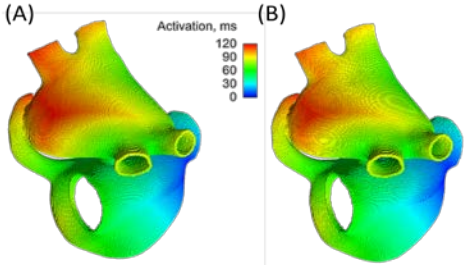

Figure 2 Activation maps for the regionally homogeneous atria (A) and heterogeneous atria (B). The scale shown in the middle of the figure applies to both A and B with activation times ranging from 0ms to 120ms.

Despite no significant differences in activation across the atria, the repolarization of the atria differed significantly as a result of heterogeneity. The action potential duration in the RA, RAA, LAA and CT regions were reduced as a result of heterogeneity. The largest observable drop in action potential duration is in the LAA where in the homogeneous model the APD is 300ms, whereas in the heterogeneous simulations the LAA ranges between 225ms and 250ms. The LA, PV and AVR APDs were increased as a result of heterogeneity. The overall result of the cellular variability resulted in a reduction in the repolarization time across the atria. Further to this, the regionally homogeneous atrial models showed smoother gradients in APD than that of the heterogeneous model.

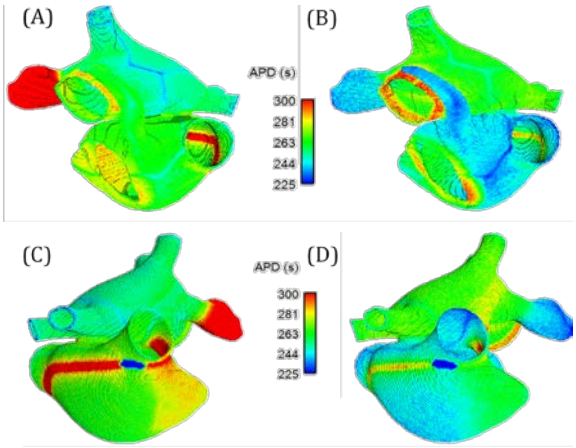

Figure 3 APD maps of the regionally homogeneous atria (A, C) and heterogeneous atria (B, D).

The whole-atrial simulations showed that the heterogeneity in the atrial model has no significant impact on the activation across the atria. This would suggest that cellular coupling masks any differences in activation as a result of cellular variability. The whole atrial simulations also showed that cellular heterogeneity has a significant impact on the repolarization across the atria.

4. Conclusion

In conclusion, small levels of variability of conduction velocity occur in all atrial regions as a result of heterogeneity. Cellular variability across isolated tissue can result in CV variation of up to 4cm/s. For this reason, it is important to calibrate heterogeneous tissue separately from the regionally homogeneous tissue. The small amount of variability observed between heterogeneous tissue samples from the same region, and the activation maps from the whole atrial simulations suggest the variability in conduction velocity observed in experimental data is due to anatomy, rather than electrophysiological variability. However, cellular variability clearly has an impact on the repolarization across the atria. This could have significant impacts on the susceptibility to atrial fibrillation and the impact of re-entries in the atria. This is something we plan to determine next.

5. Limitations

These results only present the difference in repolarization across the atria between a single regionally homogeneous atrial model and a single regionally heterogeneous atrial model. Future work would include multiple heterogeneous atrial models and the use of a variety of anatomical models to determine the combined impact of anatomical and electrophysiological variability on the repolarization patterns. Additionally, the consistency of the impact of heterogeneous tissue on the repolarization patterns can be mapped through the use of multiple heterogeneous models using the same anatomy.

Acknowledgments

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No. 766082.

References

[1] C. Sánchez *et al.*, "Inter-Subject Variability in Human Atrial Action Potential in Sinus Rhythm Versus Chronic Atrial Fibrillation," *PLoS One*, vol. 9, no. 8, 2014.

[2] D. Li, L. Zhang, J. Kneller, and S. Nattel, "Potential Ionic Mechanism for Repolarization Differences Between Canine Right and Left Atrium," *Circ. Res.*, vol. 88, no. 11, pp. 1168–1175, 2001.

[3] Elliott J, Dössel O, Loewe A, Mainardi L, Corino V, Rodriguez Matas JF. An In-Silico Study into the Impact of Electrophysiological Variability at the Cellular Level on the Re-entry Patterns in Atrial Fibrillation. *2020 Computing in Cardiology*, 2020, pp. 1-4, doi: 10.22489/CinC.2020.436.

[4] H. Zhang, O. Dössel, G. Seemann, F. B. Sachse, A. V Holden, and C. Höper, "Heterogeneous Three-Dimensional Anatomical and Electrophysiological Model of Human Atria," *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.*, vol. 364, no. 1843, pp. 1465–1481, 2006.

[5] J. Feng, L. Yue, Z. Wang, and S. Nattel, "Ionic Mechanisms of Regional Action Potential Heterogeneity in the Canine Right Atrium," *Circ. Res.*, vol. 83, no. 5, pp. 541–551, 1998.

[6] O. V. Aslanidi *et al.*, "3D Virtual Human Atria: A Computational Platform for Studying Clinical Atrial Fibrillation," *Prog. Biophys. Mol. Biol.*, vol. 107, no. 1, pp. 156–168, 2011.

[7] U. Ravens *et al.*, "Balance Between Sodium and Calcium Currents Underlying Chronic Atrial Fibrillation Termination: An In-Silico Intersubject Variability Study," *Hear. Rhythm*, vol. 13, no. 12, pp. 2358–2365, 2016.

[8] X. Liu *et al.*, "From Ionic to Cellular Variability in Human Atrial Myocytes: An Integrative Computational and Experimental Study," *Am. J. Physiol. Circ. Physiol.*, vol. 314, no. 5, pp. H895–H916, 2017.

[9] Courtemanche M, Ramirez RJ, Nattel S. Ionic Mechanisms Underlying Human Atrial Action Potential Properties: Insights from a Mathematical Model. Am J Physiol [Internet]. 1998;275(1 Pt 2):H301-21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9688927

[10] Godoy EJ, Sánchez-Quintana D, Rodríguez JF, Ferrer A, Saiz J, Martínez L, et al. Detailed Anatomical and Electrophysiological Models of Human Atria and Torso for the Simulation of Atrial Activation. PLoS One. 2015;10(11):e0141573.

Address for correspondence:
Jordan Elliott
LabS, Piazza Leonardo da Vinci, 32, 20133 Milano MI
Jordan.elliott@polimi.it