Multi-scale integrative computational model of pulmonary veins: Studying arrhythmogenic substrate for atrial fibrillation

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ABSTRACT. ***In this study, we develop a multi-scale 3D computational model that integrates cellular electrophysiology of the left atrium (LA) and pulmonary veins (PVs) with the respective tissue geometry and fibre orientation reconstructed from the contrast micro-CT data. The model is used to study mechanisms of the most common cardiac arrhythmia, atrial fibrillation (AF). Simulations demonstrate that a break-down of normal electrical excitation wave-fronts can be caused by a combination of tissue anisotropy and electrical heterogeneity between the PVs and LA. This leads to the generation of a high-frequency reentrant source near the PV sleeves. Evidence of such sources have been seen clinically in AF patients. Hence, our modelling results provide new insights into the arrhythmogenic mechanisms of reentrant excitation waves underlying AF.***

I. INTRODUCTION

Atrial fibrillation (AF), associated with irregular electrical activation of the atria, is the most common sustained cardiac arrhythmia [1]. AF is a major cause of morbidity and mortality, and the rate of hospitalization for AF and costs of its treatment are increasing in epidemic proportions [2]. However, mechanisms underlying the genesis of this common disease are not completely understood and its clinical treatments have significant intrinsic limitations. The myocardial sleeves of the pulmonary veins (PVs) in the left atrium (LA) are recognied as primary sources of high-frequency electrical activity during AF, and the PV ablation is used to terminate AF [3]. Results of catheter mapping in AF patients led to suggestions that high-frequency activity in the PV can be sustained by reentry [4]. However, mechanisms by which the PVs can generate arrhythmic substrate were difficult to dissect.

Computational modelling provides a framework for integrating multi-scale and multi-modal data and understanding arrhythmogenesis in the 3D atria [5, 6]. However, structural complexity makes it difficult to quantify fine 3D details of the PV tissue microarchitecture, including fibre orientation. Thus, even the most recent 3D models of atrial activation have not included descriptions of the PV anatomy, and hence also omitted electrophysiology [6]. The aim of this work is primarily to develop and study an integrative biophysically detailed 3D model of the canine PVs and surrounding LA tissue. The details of tissue geometry and fibre orientation are based on a recent contrast micro-CT reconstruction of the 3D tissue geometry of the canine atria [7]. The model is used to dissect the role of electrical heterogeneity and fibre anisotropy in the genesis of reentrant waves in the atria.

II. METHODS

Biophysically detailed models describing individual ionic channel currents and the resulting action potential (AP) have been developed for the canine LA and PV cells [8]. A novel method of contrast micro-CT has been applied recently [7] to reconstruct the detailed 3D tissue geometry of the canine atria and to segment it into distinctive regions - primarily, the PVs. Structure tensor analysis validated by histology has shown that the arrangement of atrial fibres can be quantified using the micro-CT images, and hence fibre orientation in the atrial bundles and PV sleeves has also been reconstructed [7]. Fig. 1 illustrates the 3D model of the entire atria (Fig. 1A) and PVs (Fig. 1B), the latter also including cellular APs and fibre orientations (Fig. 1C). The standard reaction-diffusion PDE formalism [5, 6] was used to simulate the AP propagation in the developed integrative 3D tissue

model. Under normal conditions the tissue was segmented into the PV and LA regions, with different cell-specific AP models used in each region (Fig. 1B). The role of heterogeneity was studied by using the PV cell model only throughout the entire tissue. The role of anisotropy was studied by setting the anisotropy ratio for conduction along and transverse to the fibres to1:1 instead of the normal 10:1. The same pacing protocol was used in all simulations: two S1 stimuli were applied in the PV region at a cycle length of 120 ms, followed by a short-coupled "ectopic" S2 stimulus at 90 ms.

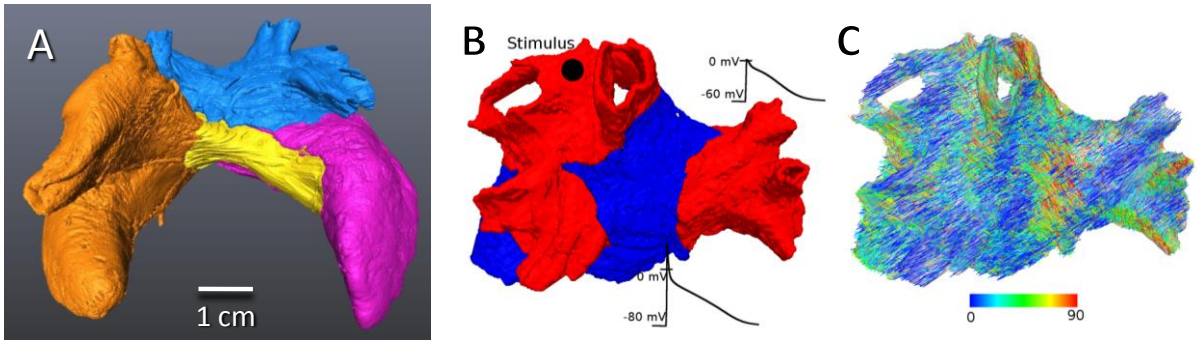

Fig. 1. 3D model of the canine atria including PVs. A: Segmented geometry of the atria. Reconstructions of the right atrium (orange), Bachmann's bundle (yellow), LA (pink) and PVs (light blue) from micro-CT images [7]. B: Geometry of the integrative PV model with two pairs of branching PVs (red) and surrounding LA tissue (blue). Single cell APs for the PV and LA regions are shown. Dot shows to the pacing site. C: Fiber orientation, with the fibers coloured according to their inclination angle ("rainbow" palette). Most fibers are aligned along the PVs, but their arrangement becomes more complex - with multiple changing directions - towards the LA.

III. RESULTS

Fig. 2 shows propagation of excitation wave-fronts initiated by S1-S2 stimulation in the PV region in 3 cases (see also Methods): the full model (Fig. 2A), the model with anisotropy but no heterogeneity (Fig. 2B), and the model with AP heterogeneity but no anisotropy (Fig. 2C). Application of a short-coupled "ectopic" S2 stimulus resulted in a break-down of the regular excitation wave-front and generation of a reentrant wave (Fig. 2A). Thus, whereas the wave initiated by the S1 stimulus has propagated into the superior LA after ~15 ms and throughout the tissue in 40 ms, the wave initiated by the S2 stimulus failed to propagate superiorly as the LA tissue has not fully repolarised after 25 ms (Fig. 2A). Instead, the wave entered the inferior LA after 45 ms, by which time the entire LA has fully repolarised. The wave then spread through the LA in multiple directions and reached the initial stimulus point in the PV after 65 ms (Fig. 2A). Hence, the full reentrant circuit has been completed.

Fig. 2B shows the effect of the removal of AP heterogeneity between the PV and LA: in the homogeneous tissue, there is no longer a conduction block towards the superior LA. Hence, a regular excitation wave-front propagates throughout the tissue, similar to the normal conduction seen after the S1 stimulation. In the isotropic tissue (Fig. 2C), the initial conduction block towards the LA is present due to the AP heterogeneity between the PVs and LA. However, the absence of anisotropy (primarily, fast and slow conducting pathways) results in the elimination of the reentrant circuit (Fig. 2C). These results are in good agreement with recent computational [6] and experimental [9] studies.

IV. CONCLUSION

We developed a biophysically detailed 3D computational model (Fig. 1) that integrated the PV and LA cell electrophysiology [8] with the respective 3D tissue geometry and fibre orientation based on micro-CT data [7]. The model simulations showed that a combination of tissue anisotropy and electrical heterogeneity near the PV sleeves caused a break-down of the regular electrical excitation wave-

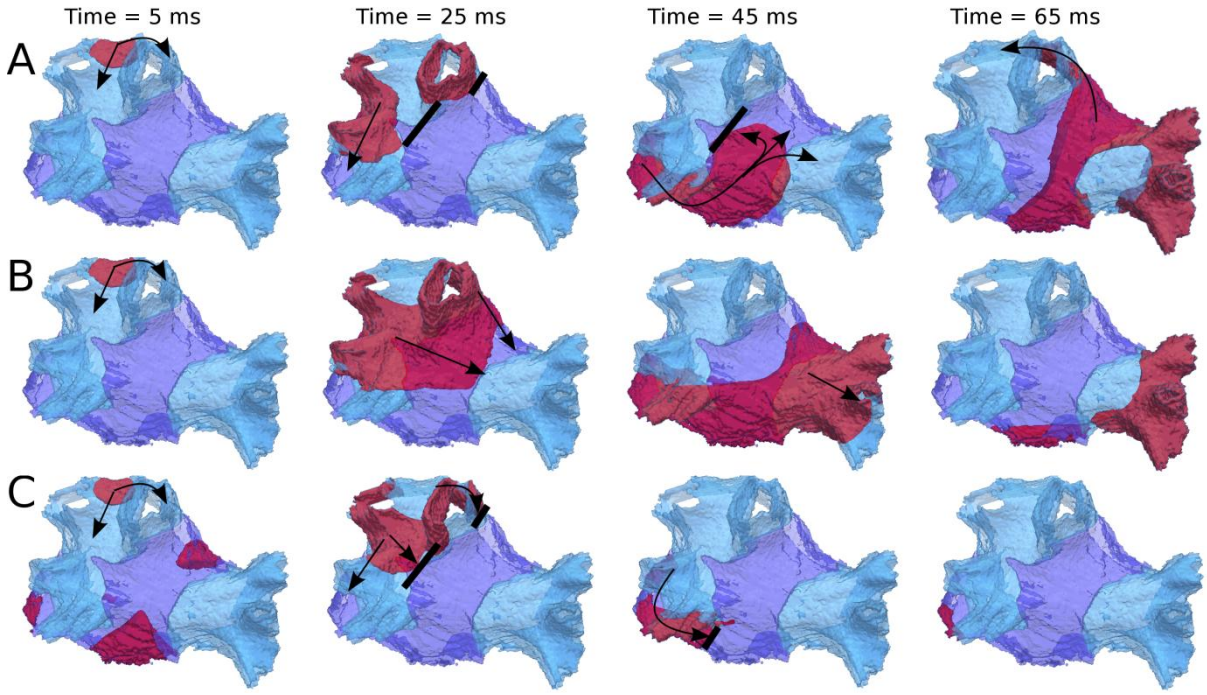

Fig. 2. The role of tissue heterogeneity and anisotropy in re-entry initiation and sustenance. A: Reentry in the full model. B: Regular wave-front in the homogeneous tissue. C: Initial conduction block does not lead to reentry in the isotropic tissue. The PV and LA tissue regions are shown in transparent light and dark blue colours, respectively. Snapshots of the wave are shown as the voltage iso-surfaces (dark red) for 4 moments of time. Black arrows show direction of wave-front propagation and black lines mark areas of the conduction block.

fronts, leading to the generation of a high-frequency reentrant source near the PVs (Fig. 2). Evidence of such reentrant sources have also been seen clinically in AF patients [3, 4]. Our computational study for the first time dissected the mechanisms of such reentry initiation (Fig. 2), providing new insights into the arrhythmogenic dynamics of reentrant excitation waves underlying AF. The developed 3D tissue model of the PVs also provides a missing link in the large-scale computational modelling of the entire 3D atria and heart, and hence, organ-level studies of AF arrhythmogenesis.

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