Evaluating Effects of Fibrosis in Atrial Arrhythmogenesis using 3D Computational Modelling

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Abstract

Fibrosis is strongly linked with the mechanisms of atrial fibrillation (AF), the most common arrhythmia. Direct electrotonic coupling between atrial myocytes and fibroblast has been suggested to contribute to these mechanisms. We use a 3D biophysical model of the atria to study the effects of fibrosis on atrial electrophysiology. Realistic tissue geometry, regional heterogeneity and myofiber anisotropy are integrated in the model. The model also accounts for the effects AF induced ionic remodeling, which has been shown to promote AF. The model simulations demonstrated that fibrosis significantly reduced both the atrial conduction velocity and action potential duration. Both these factors contributed to a large (45%) reduction of the atrial activation wavelength. This is comparable with the wavelength reduction (65%) due to ionic remodeling. As a result, the sustenance of re-entrant waves in the 3D atria was substantially increased with both fibrosis and remodeling. Hence, the elecrotonic changes induced by fibrosis can be comparable to those due to ionic remodeling, and both factors can provide substrate for re-entry in the 3D atria model.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Although the disorder itself is not life-threatening, it is progressive and can lead to severe complications such as embolic stroke or congestive heart failure. AF is also responsible for a greatly reduced quality of life for the patient. Current clinical treatments are relatively ineffective due to the complexity and patient specific nature of the disorder [1, 2].

The asynchronous electrical activations characteristic of AF are linked with multiple re-entrant wavelets propagating around the atria. For re-entry to occur, either the activation wavelength must be reduced or the atrial substrate size increased by changes to the tissue function or structure. Multiple conditions have been suggested to provide substrate for the re-entrant wave to circulate within the atria, including AF induced ionic and action potential (AP) remodelling and fibrosis [3-6].

Histology shows that AF patients present significantly larger amounts of fibrosis than healthy subjects [3]. Longer AF duration is linked with a larger quantity of fibrosis [7]. Fibrosis is characterised by structural remodelling that occurs in all tissues of the body. In AF fibrosis results in an increased deposition of extracellular collagen in the atria [1], which produces a relative decrease in conductive atrial tissue. This affects the propagation of the electrical activations in the atria and may provide substrate for AF [8]. Fibrosis results from the proliferation of fibroblasts, which can be electrically coupled to atrial myocytes. Although the fibroblasts cannot generate an AP, they maintain a resting potential. Hence, electrotonic effects arising from coupling with fibroblasts can affect the AP in myocytes [4, 6, 9, 10].

AF is likely to arise from a combination of multiple pathophysiological factors. Modelling provides means for dissecting the relative contributions of these factors in atrial arrhythmogenesis. Several aspects of fibrosis [5] and ionic remodeling [11] have been investigated as AF substrates previously. The aim of this work is to compare the effect of fibrosis and ionic remodeling on the genesis of AF in an anatomically and electrophysiologically detailed 3D model of the human atria.

2. Methods

The electrophysiological cell models have been developed to describe the AP in human atrial myocytes [11, 12] and the effects of myocyte-fibroblast electrotonic coupling [6]. The atrial geometry was derived from the Visual Human dataset, providing detailed segmentation of atrial regions and distinctive conductive bundles, as well as rule-based fibre orientation [13, 14]. Atrial AP models were specific to the segmented regions [11].

The cell models were integrated with the 3D atrial geometry using the mono-domain formulation described previously [13]. Diffusion coefficients characterising gap junctional coupling between neighbouring cells were set to produce physiological conduction velocities of ~0.9

and 0.3 m/s along and transverse to atrial fibres [13]. In all pathological conditions the diffusion coefficients were reduced 2-fold, and hence the longitudinal velocity was reduced to ~0.6 m/s, which in characteristic of AF [11].

To simulate fibrillatory atrial activations, the 3D atria model was rapidly paced 10 times at the basic cycle length (BCL) of 275 ms. A cross-field protocol was applied afterward to initiate a re-entrant rotor in the right atrium. Evolution of the rotor was followed for 5 seconds, with the simulation outputs visualised using Paraveiw^{TM}. The model was parallelised using MPI and run on a local SGI HPC machine. Simulating 1 second of atrial activity on 72 cores of the HPC took approximately 7 hours.

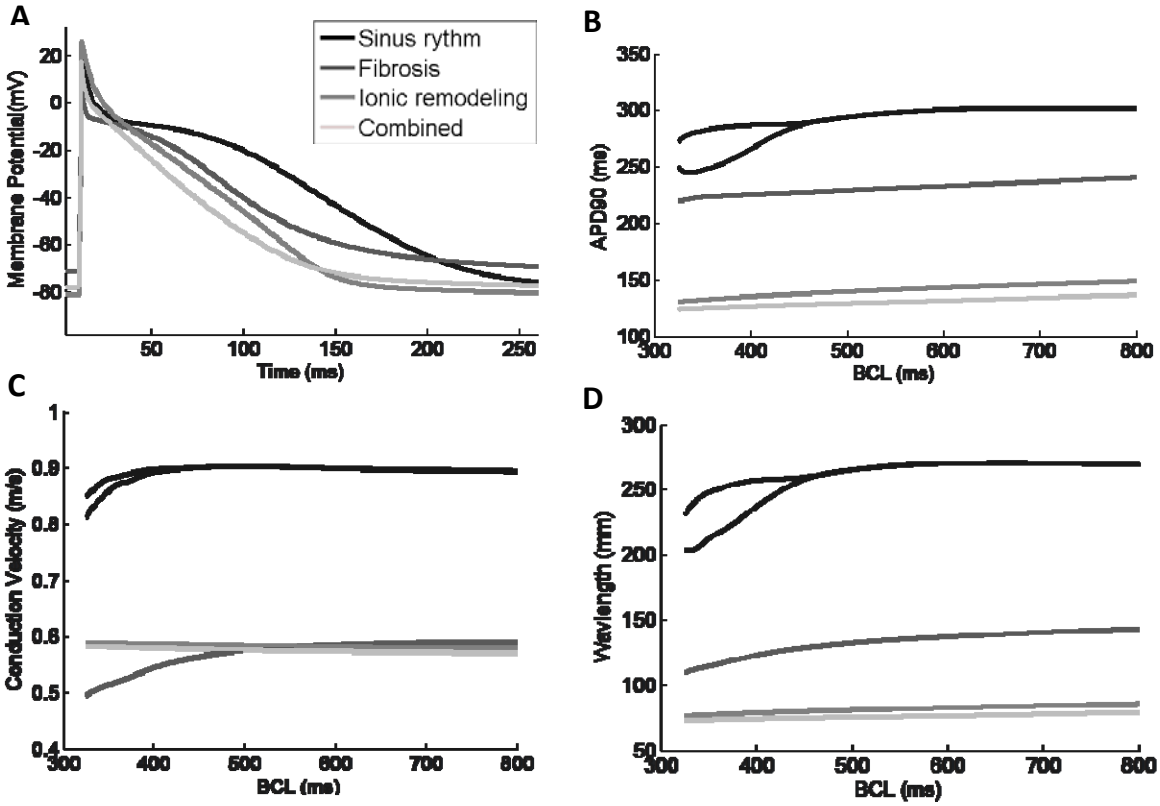

Figure 1. AP characteristics in the atrial cell model [12] under different conditions. Plots in ascending greyscale colour intensity are control, fibrosis, ionic remodeling and fibrosis and ionic remodeling combined. A: The AP morphology. The cell is paced at the BCL of 350 ms. B: The action potential duration (APD) restitution curves. C: The conduction velocity restitution curves. D: The wavelength restitution curves corresponding to B & C.

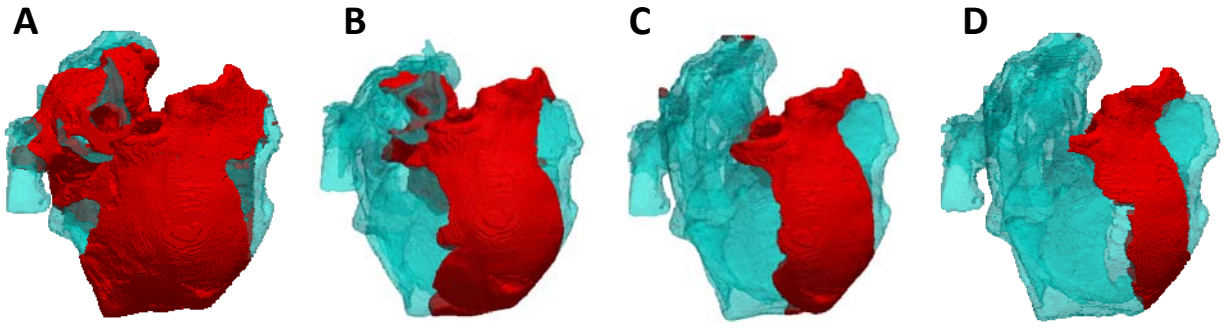

Figure 2. Wavelength changes in the 3D human atria model under different conditions. A: Sinus rhythm (control); B: Fibrosis (myocyte-fibroblast coupling); C: Ionic remodeling, D: Fibrosis and ionic remodeling combined. Waves in the 3D atria (transparent blue) are shown as iso-surfaces of the cell membrane potential at -40 mV (red). In sinus rhythm (A) the wave occupies most of the atria, and hence re-entry could not be generated under this condition.

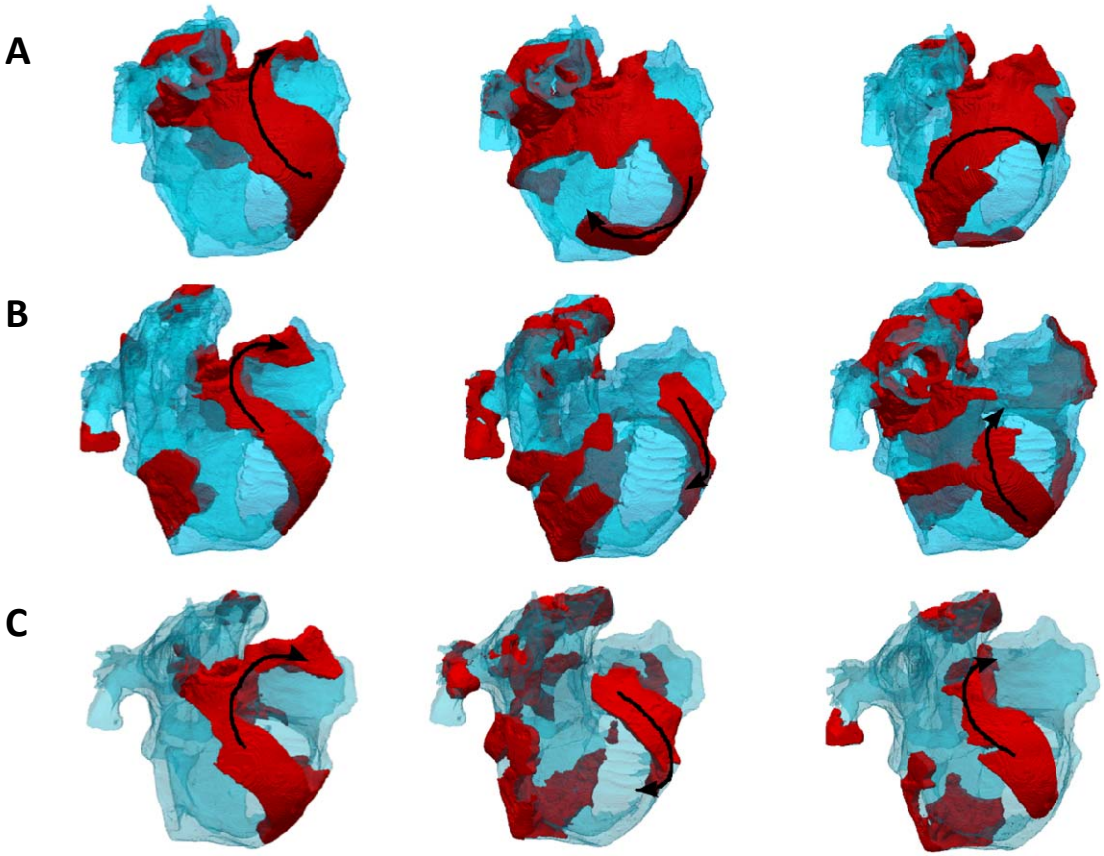

Figure 3. Wave propagation in the 3D human atria model. Each row shows three successive positions of atrial activation waves under a specific condition. A: Fibrosis (myocyte-fibroblast coupling), B: Ionic remodeling, C: Fibrosis and ionic remodeling combined. Waves in the 3D atria (transparent blue) are shown as iso-surfaces of the cell membrane potential at -40 mV (red). The black arrows indicate the wave propagation direction.

3. Results

Models combining region specific electrophysiology and ionic remodeling have demonstrated the breakdown of normal activation waves into re-entry and AF [11, 13]. The current study focuses on the effectiveness of fibrosis as AF substrate, and its effects are compared to the well characterized effects of ionic remodeling [11].

The AP simulated for a single atrial myocyte coupled with 3 fibroblasts was significantly shorter than that for a control (uncoupled) myocyte (Fig. 1A). This effect was comparable to the AP shortening due to ionic remodeling. With fibrosis and remodeling combined, the simulated AP yielded a more triangular morphology and higher resting potential, both characteristic of AF (Fig. 1A).

Restitution curves were calculated for the APD, tissue conduction velocity and the wavelength (Figs. 1B-D). Fibrosis produced an APD reduction of approximately 20%, which was smaller than >50% reduction caused by ionic remodeling. Combined remodeling and fibrosis resulted in only a marginal further reduction (Fig. 1B).

Conduction velocity was also significantly reduced in all pathological conditions (Fig. 1C). Although there was little difference between the velocity restitution curves at lower rates (BCL > 500 ms), fibrosis resulted in a more pronounced velocity decrease at higher pacing rates.

Note also that the Courtemanche model [12] presents large alternans in both the APD and conduction velocity.

Wavelength, estimated as a product of the APD and velocity, was reduced approximately by 120 mm in fibrosis and by 140 mm in both ionic remodeling and the combined condition. A larger restitution slope was seen in fibrosis compared that in ionic remodeling (Fig. 1D).

Simulations of the 3D atria model show similar results, with substantial reductions of the wavelength in fibrosis, ionic remodelling and the combined condition (Fig. 2). Such short wavelengths enable the generation of re-entry in the atria (Fig. 3). In sinus rhythm condition, the wavelength is too large for re-entry to occur in the atria. This is representative of propagation in healthy subjects.

In all three pathological conditions, a re-entrant rotor was initiated by the cross-field stimulation of the atria and maintained for the duration of simulations (5 seconds).

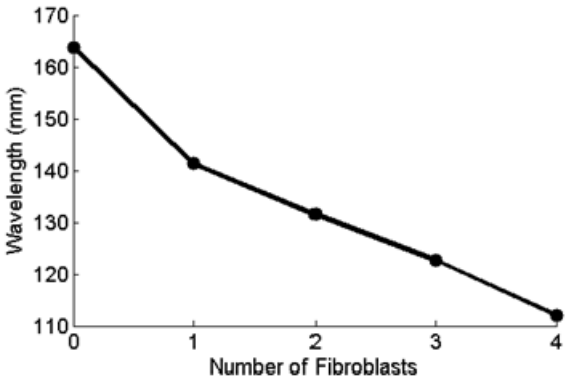

Figure 4. Effect of the variation of fibrosis level on the wavelength. As the number of fibroblasts coupled to a myocyte is increased, the wavelength is reduced. Note that the diffusion coefficients [11] in these simulations are reduced 2-fold compared to control.

Wave breakdowns occurred sporadically in all cases and secondary rotors in the left atrium were observed for the ionic remodeling and combined conditions. The wave breakdown can be explain by the anisotropy of atrial tissue [13, 15]. A difference in the number of rotors from a previous study of ionic remodeling in the 3D atria [11] can be explained by the different cell model used there.

Note that the vulnerability window (range of timings for the second wave in the cross-field protocol) varied from ~25 ms with fibrosis to <5 ms with ionic remodeling. This may be explained by a large reduction of electrical heterogeneity in the atria due to ionic remodeling [15].

4. Conclusion

Better understanding of complex AF mechanisms requires the dissection and analysis of key factors of arrhythmogenesis. This modelling study shows that fibrosis (specifically, electrotonic coupling between myocytes and fibroblasts) yields a suitable substrate for re-entry in 3D atria. The pattern of re-entrant waves in fibrotic atria is comparable to that resulting from AF induced ionic remodeling of the atria. Both fibrosis and ionic remodeling have been characterised *in vivo* at the cellular scale and may contribute to the maintenance of AF at the whole organ scale - the 3D human atria model enables linking the genesis of AF across multiple scales. The current study did not consider structural changes of the atria associated with fibrosis [2, 7, 8]. Such changes will be integrated into the model in future studies.

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References

[1] Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-2429.

[2] Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev 2011; 91: 265-325.

[3] Gramley F, Lorenzen J, Koellensperger E, et al. Atrial fibrosis and atrial fibrillation: the role of the TGF-β1 signaling pathway. Int J Cardiol 2010; 143: 405-13.

[4] Gaudesius G, Miragoli M, Thomas SP, Rohr, S. Coupling of cardiac electrical activity over extended distances by fibroblasts of cardiac origin. Circ Res 2003; 93: 421-8.

[5] McDowell KS, Vadakkumpadan F, Blake R, Blauer J, Plank G, MacLeod RS, Trayanova NA. Methodology for patient-specific modeling of atrial fibrosis as a substrate for atrial fibrillation. J Electrocardiol 2012; 45: 640-5.

[6] MacCannell KA, Bazzazi H, Chilton L, Shibukawa Y, Clark RB, Giles WR. A mathematical model of electrotonic interactions between ventricular myocytes and fibroblasts. Biophys J 2007; 92: 4121-32.

[7] McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol 2014; 7: 23-30.

[8] Kawara T, Derksen R, de Groot JR, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. Circulation 2001; 104: 3069–75.

[9] Souders C, Bowers SL, Baudino TA. Cardiac fibroblast: the renaissance cell. Circ Res 2009; 105: 1164-76.

[10] Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections. Pacing Clin Electrophysiol 1997; 20: 397-413.

[11] Colman MA, Aslanidi OV, Kharche S, Boyett MR, Garratt C, Hancox JC, Zhang H. Pro-arrhythmogenic effects of atrial fibrillation induced electrical remodelling - Insights from 3D virtual human atria. J Physiol 2013; 591:4249-72.

[12] Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am J Physiol 1998; 275: H301-21.

[13] Aslanidi OV, Colman MA, Stott J, et al. 3D virtual human atria: A computational platform for studying clinical atrial fibrillation. Prog Biophys Mol Biol 2011; 107: 156-68.

[14] Krueger MW, Schmidt V, Tobon C, et al. Modeling atrial fiber orientation in patient-specific geometries : A semi-automatic rule-based approach. Lect Note Comp Sci 2011; 6666: 223-32.

[15] Colman MA, Varela M, Hancox JC, Zhang H, Aslanidi OV. Evolution and pharmacological modulation of the arrhythmogenic wave dynamics in canine pulmonary vein model. Europace 2014; 16: 416-23.

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