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Electrophysiological Substrate for a Dominant Reentrant Source During Atrial Fibrillation

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Abstract—**Experimentally observed differences in the action potential (AP) properties between the left (LA) and right (RA) atria are believed to be important in maintaining reentrant sources during atrial fibrillation. We incorporate AP models for single LA and RA cells, as well as major intra- and interatrial conduction pathways, into a 2D atrial tissue model and study the role of tissue heterogeneity in global interactions between reentrant spiral waves in both atria. Our simulations show that shorter AP refractoriness in the LA translates into a shorter period of spiral rotation, and as a result, reentry in the LA dominates the overall excitation patterns in the atria.**

I. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, as well as the major cause of stroke [1-3]. Several lines of evidence point to a particularly important role of the left atrium (LA) in maintaining AF. Primarily, activation patterns mapped in isolated animal tissues [4, 5] or patients [6] have revealed regular and repetitive activation within the LA, whereas activation in the RA was complex and chaotic [5, 6]. Hence, it has been suggested that the LA contains "driver" regions acting as localized high-frequency excitation sources during AF.

Action potential (AP) refractoriness in the LA is shorter than in the RA [7-9], which provides a potential explanation for the driving role of the LA. AF is widely associated with reentrant electrical activity in the heart [2, 3], whereas the period of a reentrant spiral wave rotation is proportional to the refractoriness. If two spiral waves in a heterogeneous excitable medium (such as atrial tissue) have different rotation periods, the boundary between their domains of influence will move away from the faster spiral towards the slower one, suppressing the latter [10, 11]. As shorter refractoriness in the LA means shorter period (i.e., higher frequency) of rotation than in the RA, reentry in the LA should dominate the overall excitation patterns in the atria and become the high-frequency engine that maintains AF.

Relationships between atrial electrical heterogeneity and interactions of reentrant activation sources are difficult to dissect experimentally. In this work we construct computer models reproducing known electrophysiological differences between the LA and RA tissues [7-9], as well as major intra- [12-14] and interatrial [15, 16] conduction pathways, and study the role of atrial heterogeneity in global interactions between reentrant spiral waves in the LA and RA.

II. Methods

A. Model Development

The dynamics of electrical activation in cardiac tissues can be described by the following well-known equation [11]:

$$\frac{\partial V}{\partial t} = \nabla \cdot \mathrm{D} \nabla V - \frac{I_{\mathrm{ion}}}{C_m} \,. \qquad (1)$$

Here V (mV) is the membrane potential, t – time (s), ∇ – spatial gradient operator, D – diffusion coefficient (mm^2/ms) that characterizes electrotonic spread of voltage via gap junctional coupling, I_{ion} – the total membrane ionic current (pA), C_{m} (pF) – the membrane capacitance.

Biophysically detailed models for individual membrane ionic currents comprising I_{ion} have been developed for rabbit atrial cells [17, 18]. Primarily, they accurately reproduce AP morphologies for rabbit LA and RA cells (Fig. 1A), as well as the AP differences between the bundles (Fig. 1B) of the crista terminalis (CT) and pectinate muscles (PM). Similarly, AP models for two major interatrial conduction pathways – the Bachmann's bundle (BB) and coronary sinus (CS) – are constructed (Fig. 1C) based on extant voltage-clamp datasets from rabbit [15]: steady-state activation and inactivation kinetics and current-voltage relationships for the L-type Ca^{2+} current, I_{CaL}, and the transient outward current, I_{to}, are fitted to the experimental data [15]. All AP models (Fig. 1) are validated against experimental data from rabbit [7, 13, 16] and incorporated into a 2D tissue model with substantial AP and ionic heterogeneity (Figs. 1-3) between major cell types (LA, RA, PM, CT, BB and CS) within the atria.

Equation (1) was solved for the respective 30 × 30 mm^2 LA and RA tissues using the explicit Euler method with time and space steps Δt = 0.01 ms and Δx = 0.1 mm. The

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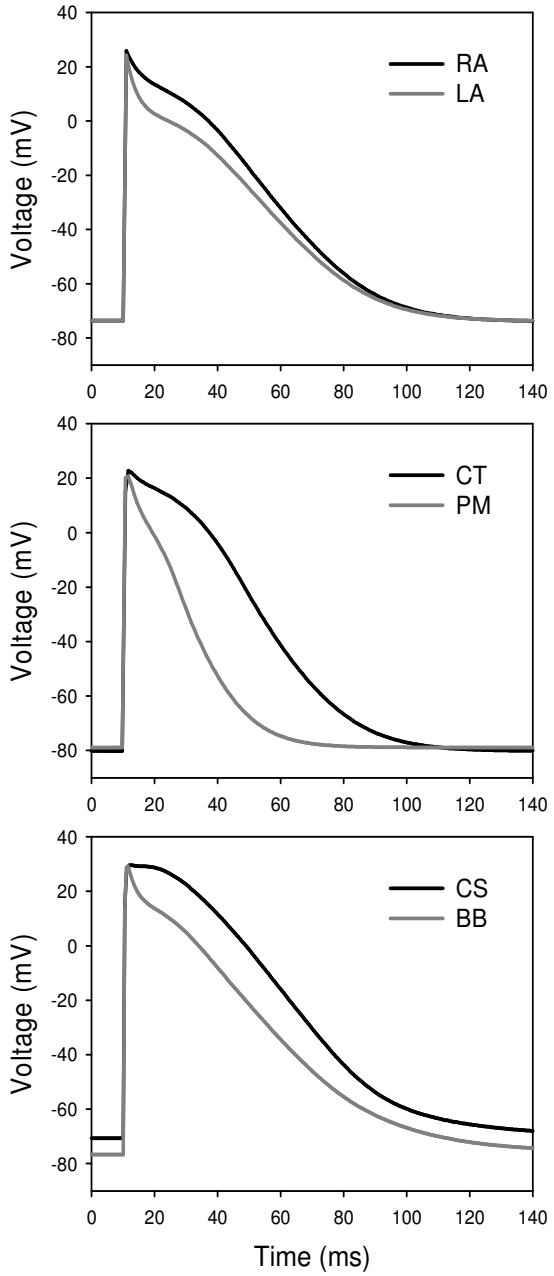

Fig. 1. Electrophysiological AP differences between atrial cell types. Basic cycle length (BCL) is 1000 ms. AP morphologies are in a good agreement with experimental recordings from rabbit [7, 13, 16].

diffusion coefficient was set to the value D = 0.1 mm^2/ms, which produced the planar AP conduction velocity of ~0.5 m/s, as seen in experiments with atrial tissue [19].

III. Results

Fig. 1 shows APs simulated using single cell atrial models, Fig. 2 focuses on the AP differences between the LA and RA cells and tissues, and Fig. 3 summarizes properties of major ionic currents varying through the atria and responsible for the AP heterogeneity. Primarily, Fig. 2 illustrates potential electrophysiological mechanisms of faster reentrant rotation in the LA: cellular AP restitution curves show that the AP duration APD is shorter in the LA for all rates. Hence, the tissue refractory period – which is correlated to the APD, primarily in atrial cells [17] – is proportionally shorter in the LA. This difference translates into the respective difference in the reentry rotation period in 2D tissue (normally, a reentrant spiral tries to occupy all non-refractory tissue), which is also shorter in the LA than in the RA (Fig. 2).

Fig. 4 shows initiation and rotation of reentrant spiral waves in the LA and RA tissues. Two counter-rotating spirals arise from forced wave-breaks of the respective plane waves (i.e., propagating APs). Although both waves are generated from similar initial conditions and using similar protocols, their rotation pattern is not symmetrical due to the electrophysiological differences between the LA and RA (Figs. 1-3). A shorter AP in the LA (79 ms against 82 ms in the RA at the physiological cycle length of 500 ms) translates into shorter tissue refractoriness (98 ms against 100 ms in the RA) and a shorter period of reentry in the LA tissue (119 ms against 121 ms in the RA). Hence, waves from the reentrant source in the LA reach the interatrial connections (BB and CS) first and invade into the RA. Wavefronts from the LA reach the BB and CS faster with each period of rotation, and as a result, move deeper into the RA. Thus, patterns in the LA and RA become different after

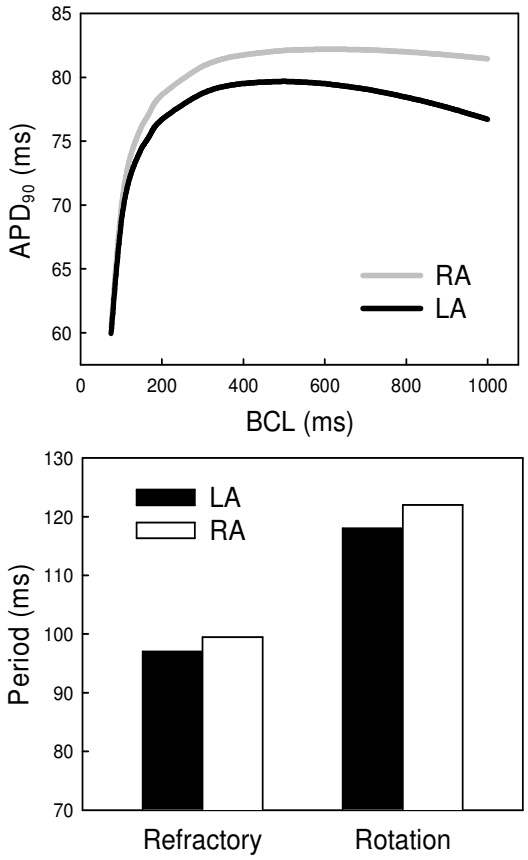

Fig. 2. Mechanisms of differential reentrant patterns in the LA and RA. Top: APD restitution curves for the LA and RA cell models. Bottom: computed refractory periods and reentry rotation periods for the LA and RA tissues. The refractory period was defined as the longest S1-S2 interval that failed to initiate AP propagation.

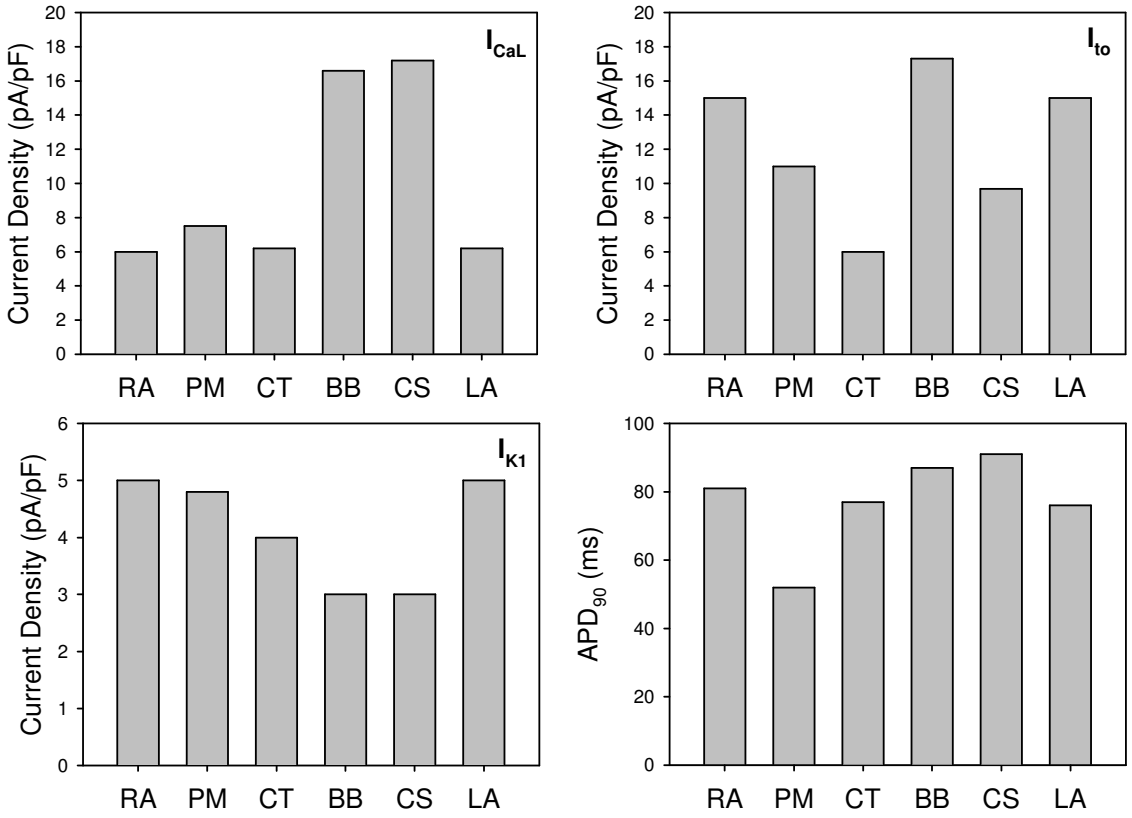

Fig. 3. Ionic and AP heterogeneity of the rabbit atria. Differences in the current densities of three ionic currents (I_{CaL}, I_{to} and I_{K1} as indicated in the respective panels) and the resultant APD differences (at BCL = 500 ms) between major atrial cell types are illustrated.

several seconds of activity: there is a single high-frequency reentrant source in the LA, whereas the RA is characterized by multiple sources (the intrinsic reentrant source and faster sources at the BB and CS) and irregular wavefronts due to higher heterogeneity of the RA (primarily, AP differences between RA, CT and PM cells). This is consistent with electrical activation patterns mapped in isolated animal tissues [5] or patients [6] during AF.

IV. Conclusion

Despite many years of research and speculation, the mechanisms underlying maintenance of AF are poorly understood. Optical mapping studies in isolated sheep hearts [5] have suggested that at least some cases of AF can be maintained by high-frequency reentrant spiral waves (rotors), usually located in the posterior LA, which result in spatially distributed frequency gradients. According to the mother rotor hypothesis [2, 3], rapidly succeeding wavefronts emanating from an ectopic focus may break when conditions of heterogeneity are appropriate, and initiate two counter-rotating rotors. Eventually, only one of the rotors survives and becomes the high frequency engine that maintains AF through fibrillatory conduction to the remainder of the atria.

Our study gives solid computational evidence to support the rotor hypothesis. Our 2D model, although geometrically simple, nevertheless captures one of the most essential and recognized features of the atria [7-9] – electrophysiological heterogeneity between the LA and RA. Simulations with the model show how shorter refractoriness in the LA tissue translates into a shorter period of reentrant spiral wave rotation, making a rotor in the LA the dominant high-frequency wave source.

Note that 3D features of atrial geometry are not included in our 2D model. Our recent study [18] has developed an electrophysiologically and geometrically detailed 3D model of rabbit RA, but not LA. Heterogeneous 3D model has been developed for both human atria [20], although interatrial heterogeneity (and hence, dominant frequency) has not been considered. Diffusion tensor MRI experiments aimed at reconstructing geometry of both rabbit atria are in progress in our group. Thus, the next step of our model development will aim to include the detailed 3D anatomy of the atria.

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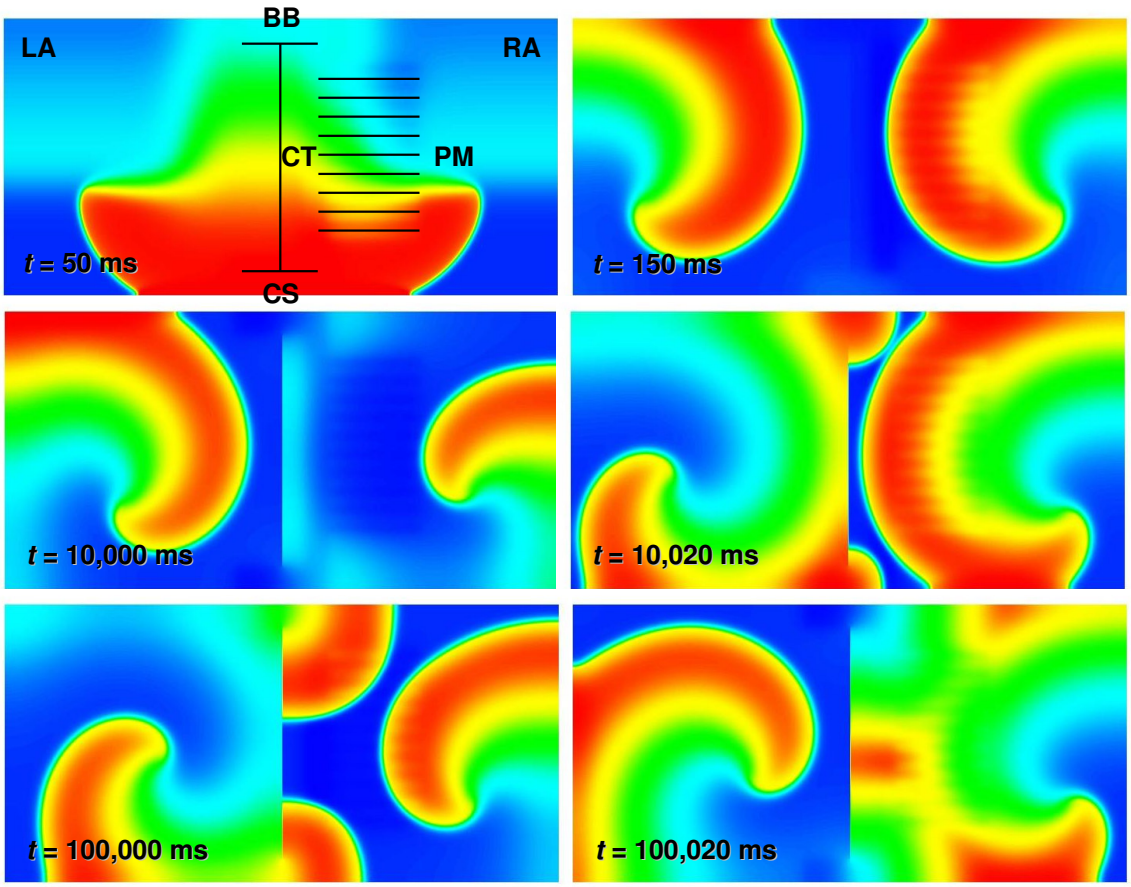

Fig. 4. Differential electrical activation patterns in the LA and RA. Spiral waves are initiated simultaneously in both atria (top), but rotate with different periods in the LA and RA due to the differential AP morphologies. As a result, the spiral in the LA reaches the interatrial connections faster and invades into the RA (middle). After ~100 s of rotation, LA has a single spiral wave source, whereas the activation pattern within the RA is more complex (bottom). Voltage distributions in the tissue are shown using the standard rainbow palette for successive moments of time, *t*.

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