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Effects of refractory gradients and ablation on fibrillatory activity

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ABSTRACT

Background: The mechanisms involved in onset, maintenance, and termination of atrial fibrillation are not well understood. A biophysical model could be useful to determine how the events unfold.
Method: A two-dimensional cellular automaton consisting of 576 × 576 grid nodes was implemented to demonstrate the types of electrical activity that may occur in compromised atrial substrate. Electrical activation between nodes was made anisotropic (2:1), and the refractory period (RP) was adjusted from 74 to 192 ms in the spatial domain. Presence of collagen fibers were simulated as short lines of conduction block at many random grid sites, while ablation lesions were delineated as longer lines of block. An S1-S2 pulse from one grid corner was utilized to initiate simulated electrical activity. Simulations were done in which 1. no ablation lines, 2. random ablation lines, and 3. parallel ablation lines were added to the grid to determine how this affected the formation and annihilation of rotational activity after S1-S2 stimulation.
Results: As the premature (S2) wavefront traversed the grid, rotational activity formed near boundaries where wavefronts propagated from shorter to longer refractory regions, causing unidirectional block, and were anchored by fiber clusters. Multiple wavelets appeared when wavefronts originating from different driving rotational features collided, and/or by their encounter with RP discontinuities. With the addition of randomly orientated simulated ablation lesions, followed by reinduction of fibrillatory activity, mean activation interval (AI) prolonged from a baseline level of 144.2 ms–160.3 ms ($p < 0.001$ in most comparisons). During fibrillatory activity, when parallel ablation lines were added to short RP regions, AI prolonged to 150.4 ms ($p < 0.001$), and when added to long RP regions, AI prolonged to 185.3 ms ($p < 0.001$). In all cases, AI prolongation after simulated ablation resulted from reduced number and/or from the isolation of local drivers, so that distant drivers in short RP regions activated long RP regions N:1, while distant drivers in long RP regions activated short RP regions at a relatively slow rate.
Conclusions: An automaton model was found useful to generate and test hypotheses concerning fibrillatory activity, which can then be validated in the clinical electrophysiology laboratory.

1. Introduction

Atrial fibrillation (AF) is the commonest heart arrhythmia [1] and of major research importance to address in the quest for improved public health [2]. The incidence of AF increases with age [3]. As average lifespan improves, it is likely that global AF occurrence will also increase. Treatment with antiarrhythmic drugs is effective in some cases [4]. However, in other instances the arrhythmia is refractory to pharmacologic intervention, and electrophysiologic (EP) study with radiofrequency catheter ablation is then often used to neutralize arrhythmogenic regions. However, the precise areas to ablate are difficult to ascertain [5], and it is time consuming to create lesions in all candidate regions. Furthermore, patients typically require follow-up treatments to further eliminate sources of arrhythmia [6].

Currently, the mechanisms of AF onset, maintenance, and termination are unknown. Candidate drivers for creating the observed electrical activation pattern include swirling vortices or rotational activity [7] which may be stationary or migrating, the presence of multiple electrical activation wavelets [8], or some combination of both. However, to date, their role in driving AF is murky. Breakthrough from epicardial regions further adds to the complexity of the observed phenomena [9]. Although ion channel models can be useful to recreate the local properties of the electrical activation wavefront [10,11], they can be unwieldy, may be slow running on PC-type computers, and do not completely reproduce all

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of the conditions leading to AF. If a less complex biophysical model of fibrillatory activity were to be developed that could approximate some of the conditions that are observed, it would potentially be useful to generate and test hypotheses, which could then be validated in the EP laboratory for development of improved treatments.

In previous work, a cellular automaton was described to simulate the formation and annihilation of rotational electrical activity, using a computerized grid, with source code provided [12]. Similar characteristics to actual AF substrate were incorporated when defining the model parameters. In this prior study, it was found that the number of rotational regions forming per unit area depended in part upon the density of nonconducting fibers, as well as on the length of boundaries between regions with differing refractory period. A requirement for stable rotational activity was that the time for one spin was greater than that of any refractory period along the path, so as to maintain an excitable gap. Otherwise, the rotational features would migrate to other regions, where anchors around which a longer available pathlength existed, or they would extinguish. Elimination of anchors by simulated ablation prevented the continuance of rotational activity at a particular location where it would otherwise occur.

In the current study, the presence of spatial refractory period (RP) gradients and the addition of simulated linear ablation lesions were investigated to determine how rotational features form, when and where multiple wavelets appear, and how ablation lines cause changes to fibrillatory activity. Besides the construction of electrical activation maps as in prior work [12], the extracellular signal and the dominant frequency were calculated, to be used in the quantitative analysis.

2. Method

The automaton model was developed in-house as a computer software program, and its basic configuration has been published previously [12]. Emphasis was placed on simplicity, limited lines of code, and speed of calculation. The model was run on a Lenovo Yoga 2 Pro laptop with Intel Core i7 processor, and 64-bit Windows 8.1 operating system. The only bottleneck in program speed was in writing the large image files to disk. However, the simplicity of their file structure was useful for analysis. The basic arrangement of the automaton is summarized below.

2.1. Nodes

The computerized grid consisted of a two-dimensional matrix with 576×576 nodes. Each node was designated as having the capacity to electrically activate or not. At any particular 2 ms time epoch, nodes capable of activation occupied one of three states: excitable, activating, or recovering/refractory to activation, as in earlier work [13,14]. Electrical activation of adjacent nodes in the horizontal or vertical direction with respect to an activating node was enabled (i.e., each node was considered to be adjacent to four other nodes, except at the edge of the field). The distance between nodes was set to 1 mm. As an analog representation of actual myocardial tissue, the surface area of one node would thus consist of many myocytes. The duration of nodal activation was set to one time epoch. The grid size was made substantially larger than atrial surface area, which was done so that more of the types of events that might occur could be observed over each simulation run.

2.2. Anisotropic conduction

Simulated electrical activation from node to node was made anisotropic [15,16]. The conduction velocity in the vertical direction of the grid was set to 0.5 mm/millisecond. Thus, the wavefront traveled from one node to the next along the vertical axis, a 1 mm distance, in 2 ms, i.e. one time step. The conduction velocity in the horizontal direction of the grid was set to 0.25 mm/millisecond. Wavefronts traveled from one node to the next along the horizontal axis in 4 ms, equivalent to two time epochs. Analogous to actual cardiac electrophysiology, the vertical axis would be considered to be in parallel with and the horizontal axis transverse to myocardial fibers.

2.3. Refractory period

During atrial fibrillation, an excitable gap is often maintained [7], which may result from spatiotemporal gradients in RP. In the current study, for simulations, spatial RP gradients were created in the range that is observed in actual atrial substrate. In canine atria, the effective RP during AF can be as low as 69 ms [17], and has been generally found to be 80–180 ms [18]. In domestic swine atria with inducible AF, RPs can range from 75 to 250 ms [19]. Thus in the simulations described herein, RP was uniformly changed to confer a gradient along the vertical direction (Fig. 1), using the approximate range found in the prior works. Two configurations were used to impart an RP gradient in the vertical direction: from 76 to 188 ms in increments of 2 (panel A) and from 186 to 74 ms in increments of 2 (panel B). Therefore, each of 57 refractory levels encompassed 10 grid rows, except that the bottom level consisted of 16 grid rows (total of 576 rows in the grid). In order to initiate rotational activity, the S1-S2 coupling interval needed to be shorter than the refractory period in the distal direction at a portion of the grid, so that unidirectional block would occur. Thus, a refractory patch was needed, as depicted in Fig. 1A, lower right (RP = 192 ms), but not in 1B, when the premature stimulus pulse was positioned at the lower right grid corner node.

2.4. Conduction block

The presence of collagen fibers was implemented as nonactivating nodes of dimension 1×5 or 5×1 in accord with prior observations [20], which were randomly distributed throughout the grid. In the simulations, 5000 fibers were incorporated into the grid in the horizontal and 5000 in the vertical directions, to duplicate the approximate coverage of collagen fibers that are typically present in the atrial myocardium of AF patients; thus: 10,000 fibers · 5 nodes/576×576 total nodes = 15%, also in accord with prior observations [21].

2.5. Premature stimulation

A simulated S1-S2 stimulus pulse train was applied to the lower right grid corner to initiate activity. This corner node was activated at the start of the simulation run (S1), and subsequently the S2 pulse was applied prematurely, i.e., so that portions of the grid would not yet have recovered excitability upon the arrival of S2, due to their possessing a longer refractory period. The result was the propagation of the S1 and S2 waves across the field from lower right toward the upper left, except that block of S2 occurred at refractory regions, and both wavefronts blocked when nonconducting fibers and ablation lines were encountered.

2.6. Electrogram synthesis

The method of Spach et al. was used for synthesis of the extracellular signal [22,23]. Briefly, the extracellular voltage ϕ_e caused by activation wavefront propagation can be described using the following equation:

$$\varphi_e(P,\ t_o) \quad = \quad \left(\frac{1}{4\pi\sigma_e}\right) \quad \frac{\sum_j \left[\frac{\partial}{\partial x}\left(\sigma_{ix}\frac{\partial\varphi_i}{\partial x}\right) + \frac{\partial}{\partial y}\left(\sigma_{iy}\frac{\partial\varphi_i}{\partial y}\right)\right]}{\left[(a+b)^2 + d^2\right]^{1/2}} \quad (2a{\cdot}dx{\cdot}dy) \qquad (1)$$

where P is the observation point at time t_o, the intracellular voltage is ϕ_i, the intracellular conductivity is σ_i, the XY coordinate plane aligns with the direction of propagation, b is the distance between the observation point and the myocardial surface, which is equal to zero when the observation point is on the two-dimensional grid surface, d is the distance in the XY plane from the source of activation to the observation point, which can be projected as distances x and y along the X and Y axes,