Computers in Biology and Medicine 83 (2017) 166–181

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Development of an automaton model of rotational activity driving atrial fibrillation

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ARTICLE INFO

Keywords:
Atrial fibrillation
Conduction block
Rotational activity
Rotor
Vortex

ABSTRACT

Background: Atrial fibrillation (AF) is difficult to treat effectively, owing to uncertainty in where to best ablate to eliminate arrhythmogenic substrate. A model providing insight into the electrical activation events would be useful to guide catheter ablation strategy.

Method

A two-dimensional, 576×576 node automaton was developed to simulate atrial electrical activity. The substrate field was altered by the presence of differing refractory period at varying locations. Fibrosis was added in the form of short, randomly positioned lines of conduction block. Larger areas of block were used to simulate ablation lesions. Anisotropy was imposed in a 2:1 ratio. A premature electrical impulse from one of four grid corners was utilized to initiate activation.

Results: Rotational activity was uninducible when refractory patch dimensions were less than 20×20 mm. For larger refractory regions, a single premature stimulus was capable of inducing an average of 1.19 ± 1.10 rotors, which often formed near the patch edges. A maximum of 5 rotors formed when refractory patch dimensions approached the size of the entire left atrial virtual field. Rotors formed along a refractory patch edge, after wavefront arrival was delayed at turning points or due to the presence of a fiber cluster of sufficient size. However, rotational activity could also occur around a large fiber cluster without the need of spatially variable refractoriness. When obstacles to conduction were lacking in size, nascent rotors drifted and either extinguished, or stabilized upon anchoring at a sufficiently large fiber cluster elsewhere in the field. Transient rotors terminated when traversing a region with differing refractory periods, if no obstacle to conduction was present to sufficiently delay wavefront arrival beyond the longest refractory period. Other rotors were annihilated when a nearby rotor with faster spin rate gradually interrupted the activation pathway. Elimination of anchors by removal, or by simulated ablation over a sufficient region, prevented rotor onset at a particular location where it would otherwise form.

Conclusions: The presence of obstacles to conduction and spatial differences in refractory period are important parameters for initiating and maintaining rotational activity in this simulation of an atrial substrate.

1. Introduction

Atrial fibrillation (AF) is the commonest arrhythmia and is a major public health concern. Left untreated it can lead to stroke, cardiomyopathy, and heart failure [1]. When AF is refractory to antiarrhythmic drugs, catheter ablation can be used to eliminate arrhythmogenic regions from which AF originates [2]. Typically, the pulmonary veins, which are sources for pulse stimuli initiating AF, are isolated during electrophysiologic study [3]. However, alone this may be insufficient to prevent reinduction of AF. Moreover, at the present time, follow-up visits are often needed to isolate all possible sources of AF and to prevent their recurrence. If a model were available to faithfully recreate the conditions present during atrial electrical activation that lead to rotational activity during AF, it could go a long way toward improving the planning and guiding of treatment procedures.

Presently, many characteristics that are important for understanding the mechanism of AF onset and maintenance are undetermined. It is not known for instance, the precise interactions by which the vortices or rotors are formed that are often evident in AF activation maps [4]. It is not known with complete certainty whether the vortices actually drive the arrhythmia or are byproducts, or manifestations, of it [5]. And it is not known whether the pattern of activation evident during

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http://dx.doi.org/10.1016/j.compbiomed.2017.02.008
Received 10 November 2016; Received in revised form 13 February 2017; Accepted 21 February 2017

AF, which is often random or chaotic appearing, is caused by the presence of one or multiple rotors, and/or by other discontinuities present in the substrate leading to multiple wavelets. In prior computer model studies, cellular-level and macroscopic anatomical structures have been shown to influence excitation propagation during AF [6–8]. Herein, a two-dimensional automaton model is described to simulate the conditions under which rotors and the spiral waves emanating from them [4], arise and are perpetuated. It is shown that based on the timing, varying refractory period, and fixed conduction block simulating fibrosis and ablation lesions, that this model can be helpful for understanding rotor formation and annihilation that may pertain to AF.

2. Method

The model that was developed is entirely computer-based, and was designed with the goal of understanding and reproducing the electrical activation phenomena that occur during actual AF. An automaton was used to simulate the conditions. In this section, the various components of the model will be described.

2.1. Nodes

The two-dimensional matrix size was selected as 576×576 nodes to provide a field of sufficient resolution to observe the details of simulated electrical activation, and to generate images of sufficient quality for analysis. Nodes consisted of those that could be electrically activated and those that were nonactivating. Each node capable of electrical activation occupied one of three states: excitable, activating, or recovering / refractory to activation, as in prior work [7,8]. The duration of the excitable state was unconstrained. An excitable node activated on a following time step whenever an adjacent node had been activated. Each node, except the nodes at the edge of the field, was considered to be adjacent to four other nodes – two along the x-axis (horizontal adjacency) and two along the y-axis (vertical adjacency). The distance between nodes was set to 1 mm. Thus each node represented clusters of myocardial cells rather than a single cell. An activating node was defined as one that was in the process of electrical activation. In prior work, a time of 0.6 ms was used for a cell to depolarize [7,8]. Since one node represents multiple cells in the present work, the duration of this state was set equal to one time epoch, or 2 ms. Thus, at any particular time epoch, activating nodes were those at the leading edge of the activation wavefront or wavefronts. A recovering node was described as being refractory to activation. The duration of this state was the refractory period of the node, and was set during initialization so as to study the effects of refractoriness on the pattern of activation.

2.2. Fibrosis

Fibrosis was simulated by imparting thin random lines of fixed conduction block to the field. The dimensions of actual myocardial collagen fibrils are on the order of 0.5 mm in diameter and several millimeters in length [9]. For the automaton, a rough approximation for collagen fibers of 1 mm in diameter (1 node) and 5 mm in length (5 nodes) was used. None of these nodes was made excitable. In an animal study, the collagen volume fraction in control hearts has been found to be 3%, and under pathologic conditions it could range up to 27.5% [10]. According to this finding, as a first approximation, an intermediate fiber density of 15% was used to simulate fibrosis in the automaton model. Thus 10,000 fibers were incorporated into the grid, which comprised 15% of the total grid area, i.e.:

$$10000\ \ fibers\ \ \bullet\frac{5\ \ nodes}{fiber}=50000\ \ nodes$$

$$\frac{50000\ \ nodes}{576\ \ x\ \ 576\ \ nodes}=\frac{50000\ \ nodes}{331776\ \ nodes}\bullet 100=15\%$$

For other tests of the model, other fiber densities ranging from 0 to 50,000 total fibers were imposed on the grid. A random number generator was used to position all fibers. Each random number defined the center node of a particular fiber. Fibers could be oriented horizontally, vertically, or diagonally.

2.3. Ablation lesions

Each ablation lesion consisted of a nonconducting area, with nonexcitatory nodes. The shape and orientation of each ablation lesion was overlapped with anchor points contributing to rotor formation. Various shapes and sizes overlapping the anchor points were used in attempting to prevent rotor formation upon premature excitation. Disruption of rotational activity was also investigated by removing anchor points.

2.4. Anisotropic conduction

The grid was made anisotropic. Prior model studies have used a 2:1 [11] or 3:1 [12] ratio of velocities in the longitudinal versus transverse wavefront propagation directions for well-recovered medium. Hence, the conduction velocity in the anisotropic grid was given a 2:1 ratio in the automaton. Either the speed of conduction along the x direction was made one node per time epoch (0.5 mm/ms) and the speed along the y-axis one node per two time epochs (0.25 mm/ms) or vice versa.

2.5. Refractory patches

Refractory patches were added to the grid. Using an average left atrial diameter of 40 mm [13–15], the circumference is 125 mm. Therefore any atrial electrophysiologic structures should be less than 125 mm for the longest dimension. We set the maximum length of the refractory patches to 120 mm (120 nodes). The atrial effective refractory period can range from 95 to 146 ms when a fibrillation pacemaker is used to artificially maintain AF in an animal model [16]. In agreement with this range, the refractory period of the patches was set to 106 ms, and the refractory period of the background was set to 98 ms. For most simulations, two refractory patches were positioned in proximity, with dimensions of 20×50 and 50×20 nodes. The patches were located toward the lower right corner of the grid and are shown in Fig. 1A, along with simulated fibrosis in the periphery (denoted as small black lines). For simplicity, fibrosis was not added to the refractory patch regions themselves.

2.6. Rotor induction

An S1-S2 stimulus was used to initiate rotor formation as in prior studies [17,18]. The stimuli were imparted at one corner of the grid. The S1-S2 coupling interval was made to be longer than the background refractory period but shorter than the patch refractory period. For simplicity and to show the efficacy of the method, the coupling interval for premature stimulation was set to a constant value of 102 ms.

2.7. Implementation of the algorithm

Several parameters used on different runs of the algorithm were adjusted. The adjusted parameters were: the grid corner for stimulation, the direction of anisotropy (longitudinal axis horizontal or vertical), the fiber density, and the size of any ablation lesions imposed on the field. Fibrosis was simulated in most simulations by having half of all random fibers oriented in the horizontal direction and half in the vertical direction, and using different fiber densities. For two simulations, fibers were oriented diagonally with differing densities.