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Simulating Pulmonary Vein Activity Leading to Atrial Fibrillation Using a Rule–based Approach on Realistic Anatomical Data

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Abstract—**Atrial fibrillation (AF) is the most common cardiac arrhythmia leading to a high rate of stroke. The underlying mechanisms of initiation and maintenance of AF are not fully understood. Several findings suggest a multitude of factors to leave the atria vulnerable to AF. In this work, a rule–based approach is taken to simulate the initiation of AF in a computer model for the purpose of generating a model with which the influence of anatomical structures, electrophysiological properties of the atria and arrhythmogenic activity can be evaluated. Pulmonary vein firing has been simulated leading to AF in 65,7 % of all simulations. The excitation pattern generated resemble chaotic excitation behavior, which is characteristic for AF as well as stable re-entrant circuits responsible for atrial flutter. The findings compare well with literature. In future, the presented computer model of AF can be used in therapy planning such as ablation therapy or overdrive pacing.**

I. Introduction

ATRIAL fibrillation (AF) is described by very fast and chaotic excitation of the atria, which leads to a loss of mechanical contraction of the atria and non-physiological contraction of the ventricles. Age, diet, neurohormones and inflammation as well as cardiovascular diseases, structural and physiological changes, genetics and the autonomic nervous system have an influence on the initiation and maintenance of AF [1] – [3]. Ectopic activity in the pulmonary veins and re-entrant circuits are the main mechanisms responsible in the genesis of AF.

A. Initiation of Atrial Fibrillation

The pulmonary veins (PVs) have mostly been targeted as the source of arrhythmogenic activity involved in the initiation of atrial fibrillation. This activity appears to be localized in the myocardial sleeves of the vessels [4], [5]. The anatomic pattern of these sleeves indeed seems to correlate with the relative distribution of PV ectopy [6], [7] if compared with the seminal findings in [8] where 31 foci were located in the left superior PV, 17 in the right superior PV, 11 in the left inferior PV and 6 in the right inferior PV. The mesh-like arrangement of muscle fascicles indicates the complexity of the anatomical structures at the PV ostia [9]. The fiber orientation also seems to play a vital role in the initiation of AF: A conduction block was also associated with the sudden change of fiber orientation [10]. Hence, evidence indicates that the anatomical structures and a non-uniform anisotropy is the key to re-entry and therefore to AF [10], [11]. Conduction delay and short refractory periods have also been identified suggesting a re-entrant mechanism [12] – [14]. Different repolarization times are significantly longer in the endocardium than in the epicardium; it is even longer in the PVs [15]. Reduced intra-atrial conduction timing leaves the atrium vulnerable to AF due to the possibility of re-entrant circuits [16], [17].

Although no evidence of abnormal automaticity or triggered activity was observed in [10], a tight coupled extra–stimulus within a PV would result in unidirectional conduction block and re-entry. It was proposed that a focal trigger may be maintained as a rapid re-entrant circuit in the PVs [15]. Studies in experimental models and in patients have demonstrated that a rapidly firing focus or a reentrant circuit of very short cycle length can cause AF by producing fibrillatory conduction to the rest of the atria [18]. Other findings suggest that the PVs are capable of automaticity [9]. Repetitive focal discharges of about 340 bpm [8] with a cycle length of 108 – 280 ms [19] have been measured. Their occurrence with respect to the sinus beat is 216 ± 34 ms (time from sinus beat to begin of ectopic beat).

While the foci in atrial tachycardia seem to be situated ostially [20], they originate rather distally in the PVs [8], [21]. A single trigger most often is present although multiple foci in multiple veins have been observed. Especially rapid firing activity in one vein could induce firing in another vein [22]. These triggers can be recurrent, especially in patients with paroxysmal AF [23]. The ectopic or premature activation of the atria renders them vulnerable to re-entrant circuits.

B. Maintenance of Atrial Fibrillation

Although some claim ectopic foci to be the cause of AF in 80 % – 95 % of cases [24], re-entrant circuits are also still regarded to initiate AF possibly through a unidirectional conduction block [9], [25]. While pulmonary vein firing appears to be more dominant in the initiation of AF, driving rotors and multiple re-entrant circuits seem to maintain AF.

The multiple wavelet theory hypothesizes [26] that AF is sustained by multiple, randomly wandering wavelets that either divide into daughter wavelets or collide and get

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extinguished. Consequently, the atria are re-excited in a chaotic and non-linear fashion. More recent studies have shown that a single source of stable re-entrant activity can also maintain AF [27] – [30].

The PVs and the left atrium seem to have a critical role in maintaining rotors and re-entrant circuits in AF. It has been observed that the cycle length in the PV differs compared with the cycle length in the left atrium. The cycle length was recorded in over 90 % to be shorter in the PVs than in the adjacent atrium [31]. The opposite was found 5 s after AF onset in another study where the posterior left atrium was proposed to be responsible in the maintenance of AF [32]. It can be concluded that the results from mapping electrical activation during AF may differ from that at AF onset.

Finally, the change in substrate contributes to the maintenance of AF. Brief refractory periods and decremental conduction as well as structural changes in the anatomy can be noted in patients with AF [33], which is favorable for the initiation of wavelets. The maintenance of these wavelets seems to be determined by local atrial refractoriness and excitability, which sets their pathways rather than anatomical influences [16].

Whether the arrhythmogenicity of AF is a re-entrant of focal phenomenon, or possibly both, remains unclear. The complex interplay of anatomy and electrophysiology in the PVs and the left atrium as well as their changes can be held to be responsible for the initiation and maintenance of AF. To conclude, among mechanisms recognised for having a role in atrial fibrillation, primarily pulmonary vein focal triggers, rotors and re-entrant circuits can initiate spontaneous activation and sustain fibrillatory conduction [34]. It is unlikely that a single patho–physiology is operative in all or even a majority of cases of AF.

Computer models of the heart describe its functions through mathematical equations or through rule–based approaches. Anatomical structures and electrophysiological properties are included so that their pathologic changes can be analyzed. In this work, pulmonary vein activity is simulated on a realistic anatomical data set to evaluate the role of arrhythmogenic foci in atrial fibrillation.

II. Methods Used

A. Electrophysiological Modeling

The Visible Female dataset of the National Library of Medicine, Bethseda, Maryland, USA was used to give the underlying anatomical structures for the electrophysiological modeling in computer simulations. Its model of the atria consists of 245 x 278 x 305 cubic voxel with isotropic side length of 0.33 mm. 1,696,740 voxel of the dataset represent atrial tissue including sinus node, atrio–ventricular node and parts of the pulmonary veins . The change of transmembrane voltage was calculated by coupled partial differential equations representing the cell model of Courtemanche et al. [35], which is a mathematical description of a human atrial myocyte. 36 different action potentials were calculated giving the transmembrane voltage V_m for nine different stimulation frequencies and for stimulation at four different times during the refractive period. The calculated courses of V_m are used in an adaptive cellular automaton that calculates the excitation propagation on a given anatomy with a rule–based approach. It takes into account a cells history of excitation, the electrophysiological properties of its neighboring cells, fiber orientation, location of the cell and its tissue type, excitation velocity and frequency of excitation, resulting in a dynamic model to compute the excitation propagation in the heart [36].

B. Modelling Atrial Fibrillation

To initiate AF in the computer model, the cardiomyocytes are set to short refractive periods and the propagation velocity is reduced to about 40 % its original value. Then, pulmonary vein firing is simulated by virtually exciting tissue near at the veins ostia: Two stimuli cause a unidirectional block that leads to a rotor wave. The stimuli have a spherical shape with radius around 6.5 mm. The first stimulus was set 200 ms after the onset of a sinus beat. The second stimulus has a position and time offset to the first stimulus of 6.27 mm and 34 ms, respectively (see fig. 1 - 2).

By placing the position of these stimuli in different regions of the atria, a multitude of excitation pattern can be generated. Table 1 shows the location of the ectopic foci to initiate AF.

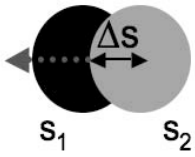

Fig. 1. Spatial distribution of stimulus s_1 and s_2 to create a unidirectional block. The distance Δs between the center of stimulus s_1 and s_2 was set to the radius of stimulus s_1. The dotted arrow indicates the direction of excitation propagation of the second stimulus.

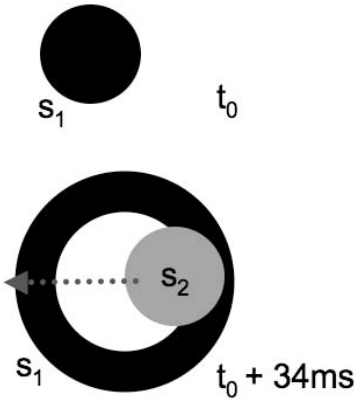

Fig. 2. Temporal delay between stimulus s_1 and s_2 to create a unidirectional block. While stimulus s_1 will propagate concentrically, stimulus s_2 falls partly in an area of absolute refractoryness and partly in an area where the cells are re–excitable. Thus, the excitation will not be propagated to the right and therefore blocked, but in the direction of the dotted arrow to the left. This way, a unidirectional block is created.

III. Results

Out of 35 different locations of the ectopic focus, 23 (65.7 %) lead to AF that lasted for the time period simulated, i.e. 2 s (tab. 1). Only 12 (34.3 %) did not show AF after 1 s. It was possible to create AF by setting the ectopic focus at all pulmonary veins. Comparing the results from placing the focus proximally vs. distally at the left superior pulmonary vein, AF occurred more often if the focus was located proximal.

TABLE I
Location of Simulated Pulmonary Vein Activity

Location	Simulations	AF	No AF
LSPV (proximal)	9	6	3
LSPV (distal)	9	4	5
RSPV	8	5	3
LIPV	5	4	1
RIPV	4	4	0
Overall	35	23	12

LSPV – left superior pulmonary vein: RSPV – right superior pulmonary vein; LIPV – left inferior pulmonary vein; RIPV – right inferior pulmonary vein; AF – atrial fibrillation

The initiating trigger creates a rotor wave at the PV (fig. 3) leading to a recurring excitation pattern as in atrial flutter (AFL) at the beginning. The initial focus is either self-terminating leaving the atria to be excited by the next sinus beat, or it is replaced by other rotor waves (see fig. 3) that are persistent and create AFL.

The stable pattern of AFL is broken up which results in a change of excitation pattern to quasi-chaotic behavior, which is characteristic for AF (fig. 4). Different excitation pattern can occur in different regions of the atria at the same time instance (fig. 5). While the excitation in the area of both atria's roofs is dominated by small wavelets, the regions further out show stable pattern.

The simulation of 2000 ms took less than 30 minutes on a single Apple Macintosh 1.33 GHz PowerPC G4 Processor with 1.25 GB SDRAM.

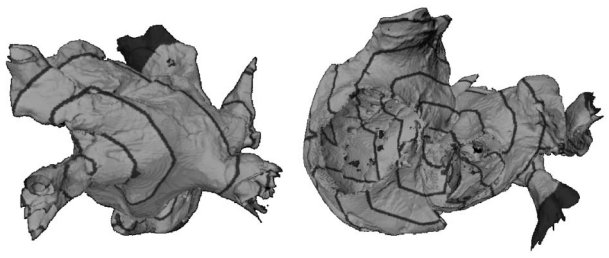

Fig. 3. Left: Latero-dorsal view on the left atrium at 184 ms after the initiating trigger. The rotor wave is situated at the left inferior pulmonary vein with the center around the initial trigger. The stable excitation pattern is characteristic for atrial flutter. Right: View on the valve plane (the ventricles are hidden for visualization) at 716 ms after the initial trigger. A new dominant rotor wave with center between the mitral and tricuspidal valve has replaced the rotor wave around the initial trigger at the left inferior pulmonary vein.

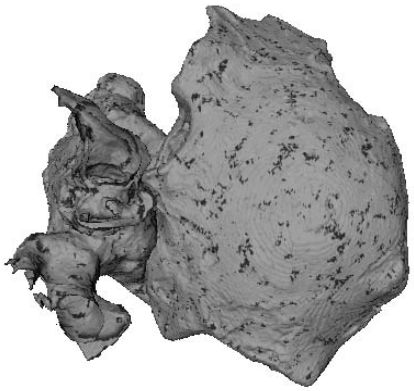

Fig. 4. View onto the right atrium at 17266 ms after the initial trigger at the left inferior pulmonary vein (fig. 3) The chaotic excitation pattern can be classified as atrial fibrillation.

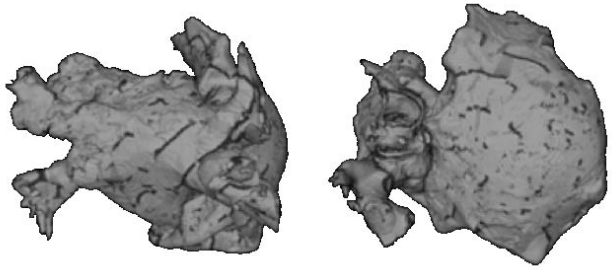

Fig. 5. Excitation of the atria at 1658 ms after the initial trigger. The ectopic focus was set in the left superior pulmonary vein. The excitation pattern differs in separate regions of the atria. While the excitation is dominated by multiple wavelets at the roof of the right atrium (right), stable wave fronts can be observed at the right pulmonary veins (left).

IV. Discussion

The timing of the initiating trigger reflects the findings in literature with respect to focal discharges and occurrence to sinus beat [8], [19]. The computer simulations further show that the initial trigger does not sustain AF. It rather leaves the atria vulnerable for re-entrant circuits created by rotor waves at another location. A break up of rotor waves can lead to AF and multiple wavelets dominate the excitation pattern of the atria only a few seconds after the onset of AF confirming Moe's wavelet theory [26].

Regarding differing cycle lengths at the onset and at a later time instance of AF, the computer simulations show both findings discussed in [31], [32]. While the cycle length is shorter in the pulmonary veins than in the atria at the onset of AF, the longer the fibrillation persists the more chaotic the excitation pattern becomes in the atria. At a later time instance, the regions further from the roof of the atria, e.g. the pulmonary veins, often show stable re-entrant circuits and hence a longer cycle length compared with the atria.

The maintenance of AF seems to depend on the local refractoriness and excitability in all computer simulations at a later stage of the simulation when the stable rotor wave breaks up and wavelets appear. Since wavelets have a small radius, their pathways are not so much influenced by anatomical structures. This behavior has been observed in [16]. Still, the complex anatomical structures play an important role in the initiation of AF. Since the conduction

velocity of the tissue was homogeneously reduced, fragmented conduction was not included. Still, a high percentage of pulmonary vein triggers lead to a chaotic excitation pattern. Whether the trigger initiates AF or whether it is completely self-terminating depends on its location in the pulmonary vein. The minimum radius of the focus to initiate a rotor wave depends on the conduction velocity. The smaller the conduction velocity the smaller can be the radius to create a rotor wave. Nevertheless, the results indicate that foci situated ostial more often create AF. Also, AF was generated due to ectopic foci situated at all pulmonary veins in one anatomical model. Thus, the computer model presented allows to simulate different set–ups of AF initiation. The results reflect literature findings that indicate multiple factors responsible for the initiation and maintenance of AF.

V. Conclusion

Chaotic excitation pattern that resemble atrial fibrillation can be generated with a rule–based computer model. The rule–based approach offers a fast calculation of excitation pattern based on a complex anatomical data set. Different set-ups of AF initiation can be modeled. Since the results reflect the findings in literature, this model can be used to further evaluate therapeutical strategies. Different ablation lesion sets could be simulated based on the presented results and an optimal strategy could be obtained. Future research will focus on individualization of the model both anatomically and electrophysiologically. A clinical evaluation of the model will be carried out in due future.

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