Simple Ablation Guided by ApEn Mapping in a 2D Model during Permanent Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Catheter ablation has become the main therapeutic strategy for the treatment of paroxysmal AF, however, results in permanent AF are not completely satisfactory; complex ablation patterns are needed, thus it is of great interest to look for an ideal pattern with a minimum number of lines. Ablation of complex fractionated atrial electrograms (CFAE) has been proposed for the termination of rotors as mechanisms of AF maintenance. The aim of this work is to characterize the CFAE by implementing approximate entropy (ApEn) and to correlate it with the tip of a simulated rotor, in order to apply simple ablation patterns to terminate the rotor activity. For this, a rotor was simulated in a 2D model of human atrial tissue, under permanent AF conditions. Electrograms were recorded and an algorithm to measure ApEn was developed. Three ablation patterns were proposed and evaluated. The ApEn allowed locating the CFAE with high precision and relating them to the tip of the rotor. The ablation pattern that enclosed the rotor tip and that was extended to a conduction boundary was effective in the termination of the rotor. The ApEn could be very effective in identifying target sites for ablation.

1. Introduction

Atrial fibrillation (AF) is the most common sustained atrial tachyarrhythmia, which affects about 2% of the general population and its incidence is increasing [1], making it one of the most important causes of morbidity and mortality [2]. Its treatment is still far from being fully satisfactory. In patients with permanent AF, complexes ablation patterns with a large number of block lines are necessary, thus, surgeons are looking for the ideal pattern and effectively terminate the FA with few lines. There is evidence that rotors could be drivers that maintain AF. Complex fractionated atrial electrograms (CFAE) were shown to be located in rotor tip areas; however, CFAE is still a controversial tool to locate target sites for ablation [3].Currently, the characterization algorithms of CFAE are being questioned for focusing on cycle length and not on the signal morphology [4, 5]. The development of improved algorithms that allow the mapping of areas with CFAE, based on morphology criteria, could help to improve the effectiveness of treatments for permanent AF.

The aim of this work is to implement approximate entropy (ApEn) to characterize the CFAE obtained from permanent AF simulations, and analyze its relationship with the rotor tip to identify areas susceptible to ablation. Additionally, we apply three single ablation patterns and assess its effectiveness on rotor termination.

2. Methods

2.1. 2D model of human atrial tissue

A 2D model of human atrial tissue was developed, which consists of a 6 x 6 cm matrix. It was discretized at a spatial resolution of 400 μm, to form a mesh of 150 x 150 cm hexahedral elements (22500 elements and 45602 nodes).

2.2. Permanent AF model

The electrophysiological model developed by Courtemanche et al. [6] was integrated into the 2D virtual model. Changes in conductance of different channels observed experimentally [7] were introduced, in order to obtain the electrical remodeling caused by permanent AF: maximum conductance of transient potassium current (I_{to}) and delayed rectifier potassium current (I_{Kur}) were

decreased by 50%; the maximum conductance of L-type calcium current (I_{CaL}) was decreased by 70%; and the maximum conductance of potassium time independent current (I_{KI}) was increased by 100%.

2.3. Electrical propagation model

In the 2D model, the propagation in cardiac tissue defined by the monodomain model of electrical propagation [8] is described by the following reaction-diffusion equation:

$$\frac{1}{S_v}\nabla \cdot (D\nabla V_m) = C_m \frac{\partial V_m}{\partial t} + I_{ion} - I_{stim}$$

where S_v is the surface/volume ratio, V_m is the transmembrane potential, D is the conductivity tensor, C_m is the capacity of membrane (100 pF), I_{ion} is the total ion current, and I_{stim} is the stimulation current. The equation was solved by finite element method (FEM). The tissue was considered isotropic. A conductivity of 0.3 S/cm was assigned in order to obtain a velocity conduction of 60 cm/s.

2.4. Stimulation protocol and contour maps

S1-S2 cross-field protocol was applied in the 2D model (rectangular pulses of 2 ms duration and 6 mA amplitude). The S1 stimulus was plane and was applied at the left boundary of the model (Fig. 1A). The S2 stimulus was rectangular (2 cm x 3 cm) and was applied 40 ms after S1 in a corner of the model (Fig. 1B). Through this protocol, spiral waves are generated in 2D models. For the location of the rotor tip, contour lines of the depolarization wavefront at different times were marked. The rotor tip is the area where these lines converge. The simulation ran for 5 seconds.

2.5. Unipolar electrograms

Unipolar electrograms (EGM) were simulated according to previous studies [9]. The measurement of extracellular potential is obtained from:

$$\emptyset_e(r) = -\frac{1}{4\pi}\frac{\sigma_i}{\sigma_e}\int\int\int \nabla` V_m(r`)\cdot\nabla`\left[\frac{1}{|r`-r|}\right]dv$$

EGM are calculated at 0.2 mm far from the surface of each element of the 2D model, for a total of 22500 EGM. CFAE are defined as EGM with low voltage and fragmented potentials formed by two or more deflections.

2.6. Approximate entropy

Approximate entropy (ApEn) was calculated for all EGM, in order to quantify the degree of complexity of signals. ApEn is defined as [10]:

$$ApEn(m,r,N) = \emptyset^m(r) + \emptyset^{m+1}(r)$$

$$\emptyset^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} log\ (Ci^m(r))$$

The calculation of ApEn depends on three parameters: number of data points N, embedding dimension m and threshold r. *ApEn(m, r, N)* allows to measure regularity by calculating the probability that patterns of length m remain close on next incremental comparisons within a signal of length N, with $m < N$ [10]. We used the standard parameters *ApEn(2, 0.1, 1000)*. In order to localize high ApEn areas in the 2D model, false color maps were developed: the red color corresponds to the maximum ApEn value and blue corresponds to the minimum value.

2.7. Simple ablation patterns

Three different lineal ablation patterns were designed, composed by two element of thickness; to which null conductivity were assigned in order to convert them to conduction block lines. The patterns as described as follows: Pattern #1, a line that does not pass through the rotor tip and ends at the tissue boundary (1 in Fig. 1C). Pattern #2, a line passing through the rotor tip and ends before touching the tissue boundary (2 in Fig. 1C). Pattern #3, a line passing through the rotor tip and ends at the tissue boundary (3 in Fig. 1C). To evaluate the patterns effectiveness to terminate rotors, each pattern was applied into the 2D model after 5 seconds of the rotor activity.

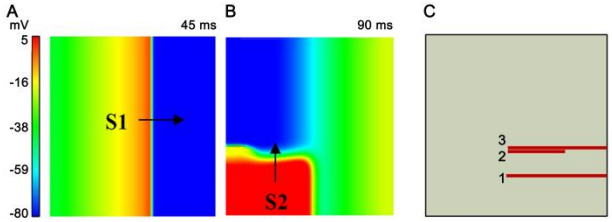

Figure 1. S1-S2 cross-field protocol. A) Plane S1 stimulus. B) Rectangular S2 stimulus. C) Simple ablation patterns (red lines).

3. Results

The atrial electrical remodeling introduced into the cell model simulating conditions of permanent AF, caused an action potential duration reduction of 70%.

By using the S1-S2 cross-field protocol in the 2D model previously remodeled, a stable clockwise rotor (Fig. 2A) was generated. The tip of the rotor is located where the contour lines converge (Fig. 2B).

During 5 second of rotor simulation, EGM were calculated over whole surface of the 2D model. 98.9% of the EGM presented simple morphology, with ApEn values lesser than 0.1 (average 0.093±0.011). The remaining 1.1%, calculated on the rotor tip and

characterized as CFAE, presented potentials composed of two or more deflections, with ApEn values greater than 0.15 (average 0.164±0.014). These results can be seen on the ApEn map generated in the 2D model, where the area of highest entropy (red region in Fig. 2C) corresponds with the CFAE. Figure 2D shows a CFAE from the rotor tip and a simple EGM from a region far to the rotor tip (* in Fig. 2C).

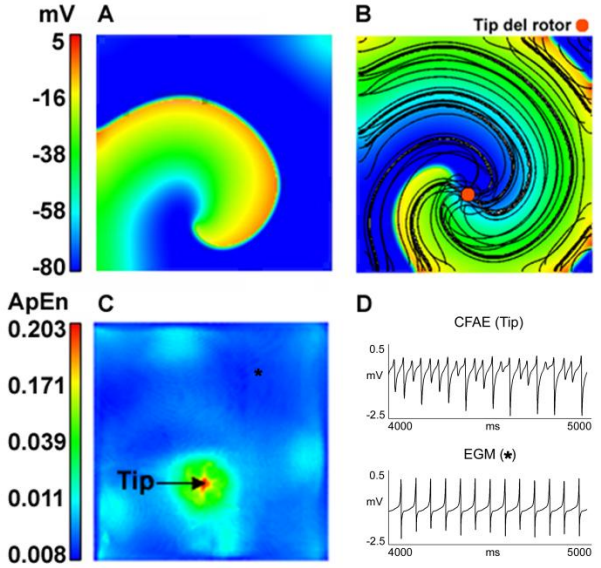

Figure 2. A) Stable rotor. B) Contour map, the red point indicates the rotor tip location. C) ApEn map, high ApEn area matches with the rotor tip. D) CFAE calculated in the rotor tip and simple EGM calculated in (*).

The ablation pattern #1 was not effective to terminate the AF activity; the rotor continued turning around the ablation line, which behaved as an anatomical barrier to the rotor (Fig. 3A). The ablation pattern #2 neither was effective to ending the AF; the rotor became a figure of eight reentry, because the ablation line fragments the spiral wave, generating a new rotor turning in the opposite direction (Fig. 3B). Ablation pattern #3, composed by a line through the rotor tip and ending at the tissue boundary, was effective in terminating the AF activity, the rotor stopped at 200 ms (Fig. 3C), this is due to the ablation line eliminates the singular point through which the rotor is maintained and the boundary prevents reentry of the propagation wave.

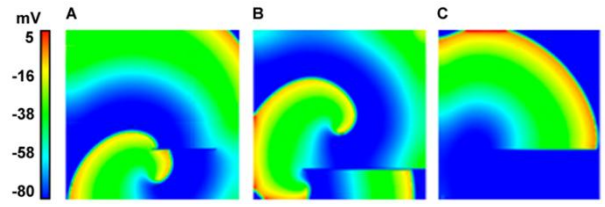

Figure 3. Only one of the three ablation patterns (pattern # 3) was effective in ending the AF activity (C).

4. Discussion

The main results of the study suggest that: 1) there is a direct relationship between CFAE and rotor tip. 2) ApEn is able to locate CFAE related to the rotor tip with a high precision. 3) Under the conditions of this study, the simple ablation pattern must pass through the rotor tip and extend itself to the boundary to be effective in order to terminate the rotor.

Our results simulating atrial electrical remodeling are consistent with studies published by [11] in isolated myocytes from patients with permanent AF; where observed an APD shortening of 70% approximately was observed. The APD shortening due to electrical remodeling, allowed rotor stability over time. Different experimental studies have suggested that remodeling is a substrate necessary to maintain reentrant patterns [12] and contributing to increased reentrant stability after onset [13]. The rotor propagation pattern obtained in the simulation is consistent with the "rotor hypothesis" given by Jalife et al. [14], which states that some episodes of AF may be sustained by one or few mother rotors in the left atrium.

The results suggest a relationship between CFAE and the center of the rotor (tip). These results are consistent with recent studies, which provide evidence that AF in humans can be sustained by rotors and are sources of CFAE [15]. In this context, CFAE ablation may be an alternative for permanent AF treatment [15], but the CFAE mapping is still a debatable technique [16]. Other studies have shown that areas with AF substrates are characterized by a high degree of disorganization of the EGM [17]. In this study, we implemented the ApEn in order to characterize CFAE, because it is a method able to quantify degrees of complexity of signals. Ng et al. [18] showed that the Shannon entropy (ShEn) can be used to identify CFAE sites for AF ablation. Additionally, Ganesan et al. [19] implemented this method in stable rotor mapping; however, they failed to accurately associate CFAE with areas of greater ShEn. On the other hand, ApEn was used to characterize the increasing irregularity of EGM during atrial arrhythmia [20].

Three simple ablation patterns were developed in order to terminate successfully the rotor activity, as a mechanism for permanent AF maintenance. Only one of the three ablation patterns, composed by a line through the rotor tip and ending at the tissue boundary, was effective in terminating the rotor. Experimental studies [21] have developed modifications to the Maze procedure, in order to simplify the surgical technique, reducing time, adverse effects and postoperative complications.Intuitively, the ideal ablation pattern should be able to prevent arrhythmias with a limited number of lines, with minimum length and to allow the mechanical activity recovery of the atria during sinus rhythm [22].

The results of this study suggest the importance of determining the location of the rotor tip and generate ablation lines which pass through the tip, in combination with the line extension until touch a conductive boundary. In real atrium, these boundaries could be atrioventricular rings, cavas or pulmonary veins or other additional ablation lines.

5. Conclusion

ApEn may be effective in identifying rotor tips for ablation in permanent AF. The results suggest the importance to localize the rotor tip and identifying anatomical boundaries for effective ablation.

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