Approximate Entropy Can Localize Rotors, but not Ectopic Foci during Chronic Atrial Fibrillation: A Simulation Study

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Abstract

Rotors and ectopic foci are targets for ablation to revert atrial fibrillation (AF). Spectral analysis is not accurate for rotor localization during chronic AF. Studies suggest that complex fractionated atrial electrograms (CFAE) are generated by rotor tips. The aim of this work is to locate rotor tips applying approximate entropy (ApEn), which is a non-linear dynamic measure. For this, a chronic AF episode was simulated in a 3D model of human atria. Electrograms were simulated in the atrial surface and ApEn was calculated. Our results show that high ApEn values matched with rotor tips. This findings suggest that targeting ApEn areas may potentially be effective in identifying rotor tips for ablation in chronic AF.

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. AF is often sustained by rotors and ectopic foci, which are stable over time and thus suitable targets for ablation [1]. Rotor modulation-guided ablation substantially improved long-term freedom from AF over conventional ablation alone [2]. Analyses of dominant frequency and regularity indexes have proven to be effective to localize ectopic foci during paroxysmal AF, but no on chronic AF [3]. Further, it has not been demonstrated its efficacy on rotors localization during AF. Some studies suggest that complex fractionated atrial electrograms (CFAE) are generated by rotor tips [4]. Approximate entropy (ApEn) is a non-linear statistic that can be used as a measurement that quantifies the complexity of a signal [5]. We hypothesized that the ApEn could locate rotors, by means of quantification of irregularity degree of CFAE.

2. Methods

2.1. 3D model of human atria

A realistic 3D model of human atria including fiber orientation and anisotropy was developed previously [4]. The model comprises the main anatomical structures and it includes three different pathways for inter-atrial conduction of electrical propagation: the Bachmanns bundle, limbus of the fossa ovalis and discrete sites of the coronary sinus.

2.2. Electrophysiological model

We used the Courtemanche-Ramirez-Nattel-Kneller [6, 7] membrane formalism. A 0.005 μM of acetylcholine (ACh) concentration was simulated. The electrophysiological heterogeneity reported by Feng et al [8] was included to reproduce action potentials in different zones of the atria.

The monodomain model of the electrical propagation of action potential along the tissue representation is described by the following reaction-diffusion equation:

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

where C_m is the specific membrane capacitance (100 pF), I_{ion} is the total ionic current that crosses the membrane cells, V_m is the membrane potential, I_{stim} is the stimulus current, S_v corresponds to the surface-to-volume ratio and D is the conductivity tensor. The conductivity values were assigned in order to obtain conduction velocities within the ranges reported by literature [9]. Anisotropic conduction was also assumed with transversal to longitudinal conductivity ratio of 1:2.

2.3. Model of chronic atrial fibrillation

To reproduce the atrial electrical remodeling generated by chronic AF, changes in conductance of different ionic

channels of human atrial cells observed in experimental studies of cAF [6, 10] have been incorporated in the electrophysiological model. Several parameters were changed: the conductance for both I_{Kur}, I_{to} was decreased by 50%, the conductance for I_{CaL} was decreased by 70%, while the conductance for I_{K1} was increased by 100%.

2.4. Simulation protocol

Chronic AF episodes were generated by S1-S2 protocol as follows: a train of stimuli, with a basic cycle length of 1000 ms, was applied during 5 s in the sinoatrial node area to simulate the sinus rhythm (S1). After the last beat of the sinus nodal stimulus, a continuous ectopic focus (S2) of high frequency was delivered into the superior pulmonary vein. All simulations were completed within 5 s after chronic AF establishment including last second of S1-S2 protocol.

2.5. Electrograms

Pseudo-unipolar electrograms were simulated in the atrial surface. The extracellular potential (ϕ_e) is given by the following equation:

$$\phi_e(r) = -\frac{1}{4\pi}\frac{\sigma_i}{\sigma_e}\iiint \nabla V_m(r') \cdot \nabla \left[\frac{1}{r'-r}\right] dv \quad (2)$$

CFAE were defined by reported criteria [11].

2.6. Approximate entropy

Approximate entropy (ApEn), mathematically defined [5] as:

1. Given a N-points signal $x(n)$. Form m-dimensional vectors $X(i)$ defined as follows:

$$\begin{aligned} X(i) &= [x(i), x(i+1), \ldots, x(i+m-1)] \quad (3) \\ i &= 1, 2, \ldots, N-m+1 \end{aligned}$$

2. Calculate:

$$d[X(i), X(j)] = \underbrace{max}_{k=0,\ldots,m-1} [|x(i+k) - x(j+k)|] \quad (4)$$

3. Calculate:

$$C_r^m(i) = \begin{cases} \frac{1}{N-m+1} \sum_{j=1}^{N-m+1} \Theta\left(r - d[X(i), X(j)],\right) \\ \text{if } i \leq N-m+1 \\ \\ 0, \text{ if } i > N-m+1 \end{cases} \quad (5)$$

where $\Theta(x)$ is Heaviside function:

$$\Theta(x-a) = \begin{cases} 1 & \text{if } x \geq a \\ 0 & \text{if } x < a \end{cases} \quad (6)$$

4. Calculate:

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_r^m(i) \quad (7)$$

5. Repeat for $m+1$
6. Finally:

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (8)$$

were applied to EGM using a moving window of 500 points without overlapping. Standard parameters $ApEn(2, 0.1, 500)$ suggested in literature [5] were used.

3. Results

During AF activity, two stable rotors were observed in the simulation, one located in posterior wall of left atrium near to left pulmonary vein and the remaining in superior vena cava. Figures 1A-B show the action potential propagation during AF simulation in the 3D model, the two rotor tips and ectopic focus are marked. Figure 1C shows the ApEn map, there are two areas with high ApEn values (ApEn$>$ 0.37), which matched with the rotor tips. Low values of ApEn were observed in the rest of the atria. The area corresponding to the ectopic focus has low entropy values, with ApEn$<$ 0.12.

Figure 2 shows four EGM recorded over different sites from the atrial model. EGM fromm rotor tip zones are showed in Figures 2A-B, these signals present higher ApEn values than signals from ectopic focus and from a site with plane waveform showed in Figures 2C-D, respectively. Small ApEn values agree with highly regular morphology of EGM from ectopic focus and passive activation site.

4. Discussion

Principal finding in this work is that ApEn maps are capable to locate rotor tips during chronic AF.

Studies have shown that FA in humans can be sustained by rotors, which are CFAE sources [2]. Thus, CFAE ablation can be useful in AF termination [2, 11]. However, CFAE mapping is still a questionable technique, for the phenomenon behind CFAE has not been fully understood [12]. Different authors have shown that CFAE can be characterized by entropy measure [13–15]. Novak et al [15] reported the presence of nonlinear dynamics in EGM. They found that ApEn, as a nonlinear tool, is able to discriminate CFAE between 4 classes

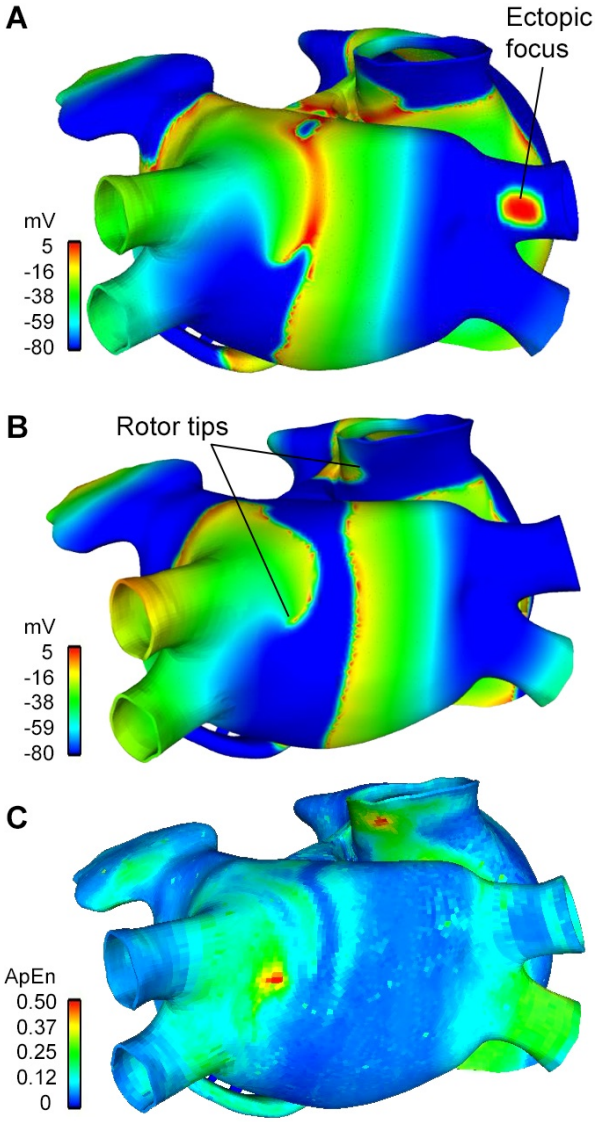

Figure 1. A) Chronic AF propagation, ectopic focus location are shown. B) Chronic AF propagation, rotor tips are shown C) ApEn map showing high values in the rotor tips. Ectopic focus is not marked on ApEn map.

of fractionation. This work presents evidence about the relationship between ApEn and CFAE in a modeled and simulated physiopatological case. High ApEn values were located over the rotor tip zone, therefore, virtual EGM with high fragmentation degree were related with rotor tip in the AF simulated episode. This result shows that ApEn maps could be use as a tool for rotors detection as ablation targets.

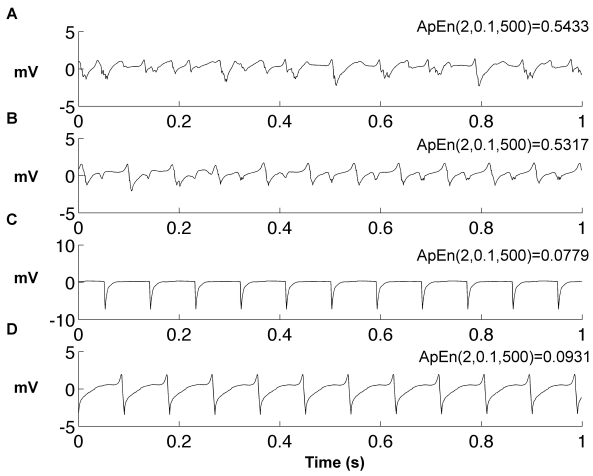

Figure 2. A) EGM from R1 rotor tip. B) EGM from R2 rotor tip. C) EGM from ectopic focus. D) Low ApEn EGM from an area with plane depolarization wavefront. ApEn values are shown. A) and B) exhibit CFAE with high ApEn values, while C and D are regular EGM with low ApEn values. Ectopi focus is not marked on the map of entropy

5. Conclusion

Targeting high ApEn areas may potentially be effective in identifying rotor tips but not ectopic foci, for ablation in chronic AF. Thus, it could be used as a specific tool for AF rotor mapping.

Future studies, using EGM record during AF ablation procedures, might prove the performance of ApEn maps for rotor detection in clinical practice and its utility as a tool for EGM-guided AF ablation strategies.

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