Medical Engineering and Physics 000 (2016) 1–8

Contents lists available at ScienceDirect

Medical Engineering and Physics

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

Termination of atrial spiral waves by traction into peripheral non 1:1 conducting regions – A numerical study

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ARTICLE INFO

Article history:
Received 31 March 2016
Revised 20 July 2016
Accepted 28 August 2016
Available online xxx

Keywords:
AF termination
Numerical modeling
Persistent AF
Spiral waves

ABSTRACT

Atrial ablation has been recently utilized to treat atrial fibrillation (AF) by isolation or destruction of arrhythmia drivers. In chronic or persistent AF patients these drivers often consist of one or few rotors at unknown locations, and several ablations are commonly conducted before arrhythmia is terminated. However, the irreversible damage done to the tissue may lead to AF recurrence. We propose an alternative strategy to terminate rotor activity by its attraction into a non 1:1 conducting region. The feasibility of the method was numerically tested in 2D models of chronic AF human atrial tissue. Left-to-right gradients of either acetylcholine (ACh) or potassium conductance were employed to generate regions of 1:1 and non 1:1 conduction, characterized by their dominant frequency (DF) ratios. Spiral waves were established in the 1:1 conducting region and raster scanning was employed using a stimulating probe to attract the spiral wave tip. The probe was then linearly moved towards the boundary between the two regions. Successful attraction of spiral waves to the probe was demonstrated when the probe was <8 mm from the spiral wave tip. Maximal traction velocity without loss of anchoring increased in a non-linear way with increasing values of ACh. Success rate of spiral wave termination was over 90% for regional DF ratios of as low as 1:1.2. Given that normally much higher ratios are measured in physiological atrial tissues, we envision this technique to provide a feasible, safer alternative to ablation procedures performed in persistent AF patients.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults and is associated with increased morbidity and mortality [1]. AF is characterized by uncoordinated and irregularly rapid electrical activity of the atria leading to impaired cardiac function. AF is classified into three main categories [2]: paroxysmal, persistent and chronic AF. While paroxysmal AF episodes terminate spontaneously, persistent AF and chronic AF do not terminate without intervention. AF recurrence is a medical condition in which at least two episodes of AF occur in the same patient. While the physiological mechanisms underlying AF induction and maintenance are multi-factorial and poorly understood, there is a considerable agreement regarding two major AF drivers. The first involves local ectopic foci of depolarization, which under certain conditions such as rate and location may mask the natural sinoatrial node pacemaker activity and induce wavebreaks. The second mechanism, which is in the focus of the present study, involves one or a few number of abnormal reentrant conduction circuits in the atria, mostly driven by rotors [3]. Recently, it has been established that the restoring procedure of the heart to its normal sinus rhythm becomes more challenging as the amount of time in which the heart remains in AF increases [2], signifying the importance of its effective treatment. In the first stage of AF treatment, patients are normally given antiarrhythmic drugs in order to restore and maintain a regular sinus rhythm. In addition to the antiarrhythmic drugs, anticoagulation therapy is required for AF patients in order to reduce the risk of stroke. Unfortunately, in too many cases the pharmacological treatment is found ineffective in the long-term [4,5]. Recently, catheter ablation techniques have been utilized to eliminate the drivers for the arrhythmogenic activity. In this procedure, radiofrequency (RF) energy is delivered in order to permanently ablate atrial tissue suspected to sustain an arrhythmogenic driver, such that the source of focal activity or reentry is annihilated [6,7]. Traditionally, ablation is performed empirically and its outcome largely relies on the expertise of the performing physician. However, this procedure may lead to massive injury to healthy atrial tissue and may in fact promote arrhythmogenesis due to the reduced tissue homogeneity, resulting in the need for repeating ablations. A clinical 3-year follow-up study of patients with chronic AF that underwent catheter ablation procedure

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http://dx.doi.org/10.1016/j.medengphy.2016.08.006
1350-4533/

resulted in a recurrence-free rate of only 28.4% after the first ablation, 47.7% after the second procedure and 51.1% after the third procedure [8]. In another study, a 5-year follow-up of catheter ablation patients showed a recurrence free rate of 29% after a single procedure, and of 63% after up to 3 ablation procedures [9]. Indeed, the success rate of catheter ablation is considered low and varies greatly between different clinical studies. However, the irreversible damage done to the atrial tissue may lead to recurrence of chronic AF within months or few years after the ablation procedure. Electrogram-guided ablation is a technique in which the ablation procedure is done while recording endocardial electrograms in order to improve the ablation procedure success rate by providing guidance regarding the localization of the arrhythmia drivers and the atrial electrical conduction patterns. The electrograms are analyzed for characterizing the myocardial electrical activity and the arrhythmia dynamics during the ablation procedure via measures such as fractionation and activation rate [10]. In many clinical realizations, a dominant frequency (DF) map is presented during the ablation process by performing spectral analysis on the electrograms in order to better locate the arrhythmogenic activity source. This approach relies on studies showing that regions exhibiting the highest activation rate (i.e., maximal dominant frequency, or DF_{max}) are likely to contain the arrhythmogenic driver, at least in rotor-driven AF cases [3,10,11]. Typically, DF mapping results with one or few regions of 1:1 conduction exhibiting DF_{max}, surrounded by peripheral non 1:1 conducting regions with lower DFs. Still, the 1:1 conducting regions may span large part of the atrial tissue so that the exact localization of the arrhythmogenic driver can be challenging. Other types of electrogram analyses have been proposed in mostly pre-clinical studies, including the localization of the pivot points of stable rotors using Shannon entropy calculations [12] or principal component analysis [13], or the characterization of fractionated signals that may be the manifestation of an arrhythmic driver causing irregular activity. Nonetheless, to date, electrogram-guided techniques have not shown significant advantage over empirical ablations in terms of procedural success rates [14], and there is a clear need for improving these techniques by increasing the robustness of arrhythmogenic driver annihilation.

In our current study, an alternative method to eliminate a single rotor activity is suggested and numerically investigated. In this method, low-energy continuous local depolarizing probe is employed to systematically scan the 1:1 conducting region containing DF_{max} in order to attract and trap the rotor core. Once trapped, the probe is used to pull the rotor into peripheral non 1:1 conduction regions. The use of low-energy local depolarization overcomes the main caveat of ablation procedures by preventing the creation of lesions, thus maintaining the viability of the atrial tissue. We hypothesize that using a continuous low-energy depolarizing probe will render the tissue just under the probe and in its close vicinity refractory due to a decrease in the sodium channel availability. As previous studies have shown, rotors and spiral waves tend to drift towards local low excitability regions [15], thus, such technique is expected to attract and trap the core of the rotor in vicinity to the probe, allowing its traction following the probe's movement towards the desired location. We also hypothesize that the rotor traction into a non 1:1 conduction region will result in local wavebreaks at the border between the 1:1 and non 1:1 regions due to the differences in the sustainable maximal activation rates that will ultimately annihilate the reentrant activity.

To test our hypotheses, 2D computational model of a human atrial tissue was employed in numerical simulations of spiral wave activity. Trapping and traction of the spiral wave via low-energy local depolarization was simulated, and the success rate of spiral wave annihilation was assessed for various scenarios of DF distributions. Our findings demonstrate the feasibility of the proposed technique and provide theoretical basis for its potential prospective implementation in treatments of rotor driven AF.

2. Methods

2.1. Geometrical and electrophysiological modeling

The electrical activity in the atrial model was simulated by numerically solving the following reaction diffusion equation under the mono-domain approximation:

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

where V_m [mV] is the transmembrane voltage, I_{ion} [pA] is the total membrane ion current (originating from ion channels, pumps and exchangers), I_{stim} [pA] is the low-energy depolarization current of the simulated probe, C_m [pF] is the cellular membrane capacitance, and D [mm^2/ms] is the diffusion coefficient, taken as a constant scalar under the isotropy assumption. The human atrial ionic kinetics model of Courtemanche et al. [16] was employed for the calculation of I_{ion}. The original kinetics were modified to simulate chronic AF conditions by reducing the maximal conductivities of I_{to}, I_{kur} and $I_{Ca,L}$ by 50%, 50% and 70%, respectively, and by doubling the maximal conductivity of I_{K1} in order to stabilize the rotor as expected in chronic AF [17,18]. In some simulations an additional I_{KACh} inward-rectifying potassium channel was incorporated as in the work by Kneller et al. [19] with acetylcholine concentrations ranging between 0.02 and 0.16 mM to further stabilize reentrant activity and to generate heterogeneous DF distribution in the tissue model.

Two-dimensional geometrical models of either a 30×30 mm^2 or a 30×45 mm^2 atrial tissue were employed and discretized using spatial resolution of $\Delta x = \Delta y = 0.1$ mm. Eq. (1) was numerically solved using the finite difference approximation for spatial derivatives and Euler method for temporal integration with a time step of $\Delta t = 0.005$ ms, with no-flux boundary conditions. D was set to 0.05 mm^2/ms to achieve a physiological planar wave conduction velocity of 0.33 m/s. Simulations were performed using C++ code, running on a high performance cluster (Altix X86-PTO, Silicon Graphics) with a master node (8 cores, Xeon 2.5 GHz Intel) and 2 computational nodes (48 cores, Xeon 2.8 GHz Intel). Data analysis and visualization were performed with MatLab R2014b (MathWorks).

2.2. Spiral wave attraction and traction

The feasibility and robustness of spiral wave attraction and traction by low-energy depolarizing probe was first tested for different scanning directions and for different locations of the spiral wave center. Forty second long simulations were performed on a uniform tissue of size 30×30 mm^2 with [ACh] = 0.02 μM. A stable spiral wave activity with a rotation frequency of 8.5 Hz was initiated using a standard S1–S2 cross-field stimulation. A low-energy scanning probe of size 1.1×1.1 mm^2 was modeled by setting I_{stim} in Eq. (1) to −30 pA over an area of 11×11 pixels. Raster scanning pattern was employed in a total of $n = 7$ simulations with the stimulation probe being moved with a constant velocity of 1.5 cm/s. In 4 out of 7 simulations the raster scanning direction was changed in 4 patterns as schematically depicted in Fig. 1. In the other 3 simulations, the cross-field stimulation parameters were modified resulting in different spiral wave tip trajectories, while using raster scan pattern B. Next, simulations were conducted to assess the traction capabilities of the probe at various scanning velocities. For that part, spiral waves were generated at the left side of tissue models of size 30×45 mm^2. Four model configurations were simulated, varying by the [ACh] of either 0.02, 0.04, 0.08 or 0.16 μM.

Please cite this article as: A. Rozner, S. Zlochiver, Termination of atrial spiral waves by traction into peripheral non 1:1 conducting regions – A numerical study, Medical Engineering and Physics (2016), http://dx.doi.org/10.1016/j.medengphy.2016.08.006