Rotor Termination in Cholinergic Paroxysmal Atrial Fibrillation by Small-Conductance Calcium-Activated K^+ Channels Inhibition and Isoproterenol: a Computational Study

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Abstract

Hyperactivity of the parasympathetic nervous system has been linked to the onset of paroxysmal atrial fibrillation (AF). Recent investigations have proven inhibition of small-conductance calcium-activated potassium (SK) channels to improve adverse cholinergic effects in the atria. It has also been reported that β-adrenergic stimulation by Isoproterenol (Iso) can act as a brake to lessen cholinergic effects on atrial tissue. Furthermore, the combination of SK channel block (SKb) and Iso has been suggested to possibly prolong atrial APD in ACh-stimulated myocytes. In this study, computational modeling was used to test individual and combined effects of SKb and Iso in terminating a stable rotor in a cholinergic AF model of human atria. 2D tissues with uniform ACh concentrations of 0.01 or 0.1 μM were simulated. After stable rotors were initiated, 1 μM Iso and/or complete SKb were progressively applied over time following different application kinetics. Both Iso alone and the combination of Iso and SKb were able to terminate rotors for the two ACh concentrations. SKb was only able to terminate the rotor for the lower ACh concentration. In conclusion, the results from this study support β-adrenergic stimulation and SK channel block, the latter with less efficacy, as potential options to terminate rotors in parasympathetically-stimulated human atria.

1. Introduction

The autonomic nervous system (ANS) has been reported to play an important role in the initiation and maintenaince of atrial fibrillation (AF). Hyperactivity of the parasympathetic branch of the ANS has been linked to the onset of paroxysmal AF (pxAF) [1]. Acetylcholine (ACh) is the neurotransmitter of the parasympathetic nervous system. Once ACh is released from the cholinergic nerve fibers, it binds to muscarinic receptors in atrial myocytes to activate the ACh-activated potassium current, I_{KACh}. This current causes dose-dependent shortening of action potential duration (APD) and hyperpolarization of the resting membrane potential (RMP). In atrial tissue, these effects lead to shortening of the wavelength (WL) of reentry, thus facilitating the establishment of reentrant activity. According to experimental and clinical findings, certain cases of AF are maintained by high-frequency small reentrant sources called rotors [2].

Class III antiarrhythmic drugs bind to and block potassium channels driving AP repolarization, producing an increase in APD and lenghtening of the WL. Among the potassium currents, those preferentially expressed in the atria are sought as possible targets for the treatment of AF, in order to avoid possible dangerous side effects at the ventricular level. In recent years, a growing body of research suggests that small-conductance calcium-activated potassium (SK) channels may constitute a potential atrial-selective target [3]. *In vivo* and *ex vivo* investigations have shown that inhibition of SK channels can counteract parasympathetically-induced effects in the atria by prolonging APD [4].

Isoproterenol (Iso) is a nonspecific β-adrenergic agonist, which modulates the action potential (AP) by acting on many cellular substrates, including calcium and potassium currents and the release of calcium from the sarcoplasmic reticulum [5]. Studies investigating the cholinergic-adrenergic interaction have shown that β-adrenergic stimulation can act in a synergistic way with cholinergic stimulation and facilitate AF induction [6], whereas in other studies β-adrenergic stimulation has been described to act as a brake to decrease the extent of cholinergic-induced APD shortening [7].

In this study, we extend our previous works investigating the ability of different interventions, involving β-adrenergic stimulation and SK channel inhibition, to restore ACh-induced alterations in atrial electrical activity [8, 9]. Using computational simulation, we aim to test the ability of SK block (SKb) and β-adrenergic stimulation by Iso, individually or in combination, to terminate

rotational activity in a cholinergic model of AF. Different levels of cholinergic stimulation and application kinetics of SKb and Iso, representing a range of drug association rates, are considered to evaluate the role of pharmacokinetics in rotor termination.

2. Methods

2.1. Human atrial cell models

The Courtemanche [10] computational AP model was used to describe human atrial cellular electrophysiology. To describe parasympathetic effects, an acetylcholine-activated potassium current, I_{KACh}, as defined in Kneller et al. [11] with the updates proposed in Bayer et al. [12], was included in the model. Sympathetic effects were modeled as proposed in González et al. [5]. Specifically, the maximum conductances of the L-type calcium current (g_{CaL}) and of the slow delayed rectifier potassium current (g_{Ks}) were increased and the maximum conductance of the transient outward current (g_{to}) was reduced according to dose-dependent conductance curves. The I_{SK} current was introduced by adopting the formulation proposed by Engel et al. [13] for neurons. The conductance g_{SK} was adjusted to match the experimentally observed 20% increase in APD after full SKb in atrial myocytes from sinus rhythm patients [4, 8].

2.2. Human atrial tissue models

Two-dimensional (2D) square tissues of 5x5 cm with a longitudinal (y-axis) diffusion coefficient of 0.002 cm^2/ms and a transverse-to-longitudinal diffusion coefficient ratio of 0.5 were considered. The monodomain model was used to describe electrical propagation in tissue. We simulated a homogeneous spatial ACh distribution with ACh concentrations of 0.01 and 0.1 μM, which are within ACh ranges tested in previous studies [12].

2.3. Simulation protocols

A temporal resolution of 0.005 ms was used for cell and tissue simulations. A space step of 0.02 cm was considered. To reach steady-state, single cells were paced at a fixed basic cycle length of 1000 ms for 1 minute. The values of the state variables at steady-state were used to initialize tissue simulations.

A cross-stimulation protocol was applied onto the tissue to initiate reentrant activity: a first stimulus was applied at the bottom edge of the tissue while a second stimulus was applied onto a 2.5x2.5 cm square at the bottom right corner. The timing of the second stimulus was dependent on the considered ACh concentration, which influenced the APD and the conduction velocity. The initiated rotor was considered stable if it did not vanish spontaneously during a 30-second simulation.

To test Iso and SKb ability to stop the initiated rotor, 1 μM Iso and complete SKb, individually or in combination, were progressively applied after the first two seconds of simulation following the curves shown in Fig. 1 [14]. These curves are aimed to represent different drug association rates to assess whether the kinetics of application could have an impact o rotor termination. The correspondent times Δt_a to go from 0 to maximum (Iso dose or SKb block) were equal to 0.1, 1, 4 and 8 s. The simulations were run for a total of 12 seconds.

Cellular simulations were run in MATLAB. Tissue simulations were run using the in-house software ELECTRA implementing the Finite Element and Meshfree Mixed Collocation methods for the solution of the monodomain model [15,15,16]. In this work, the Finite Element Method was used.

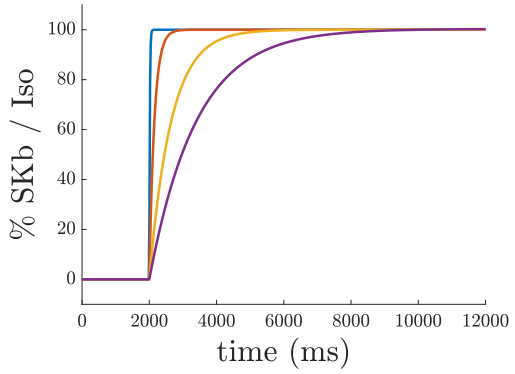

Figure 1. Load curves for Iso and SKb expressed as percentage of SKb and Iso concentration with respect to 1μM Iso, respectively.

3. Results

When applying Iso and/or SKb over Δt_a = 1 s (red curve in Figure 1), different results were observed depending on the underlying level of ACh. Iso, individually and in combination with SKb, was able to terminate the rotors in 0.4 s from the application start time for both ACh concentrations. However, in the case of ACh=0.1 μM, SKb alone was not able to terminate the rotor within the 12-second simulation and it took it 2.8 s to terminate it for ACh=0.01 μM. Voltage maps over time, for ACh = 0.01 μM, are reported in Fig. 2 for the different cases.

When applying Iso and Skb over over Δt_a = 0.1, 4 and 8 s (blue, yellow and purple curves in figure 1), we found that the timing of application did not change the results in terms of the ability to terminate the rotor with only one exception (ACh 0.1 μM, SKb, Δt_a = 8 s). A slight delay

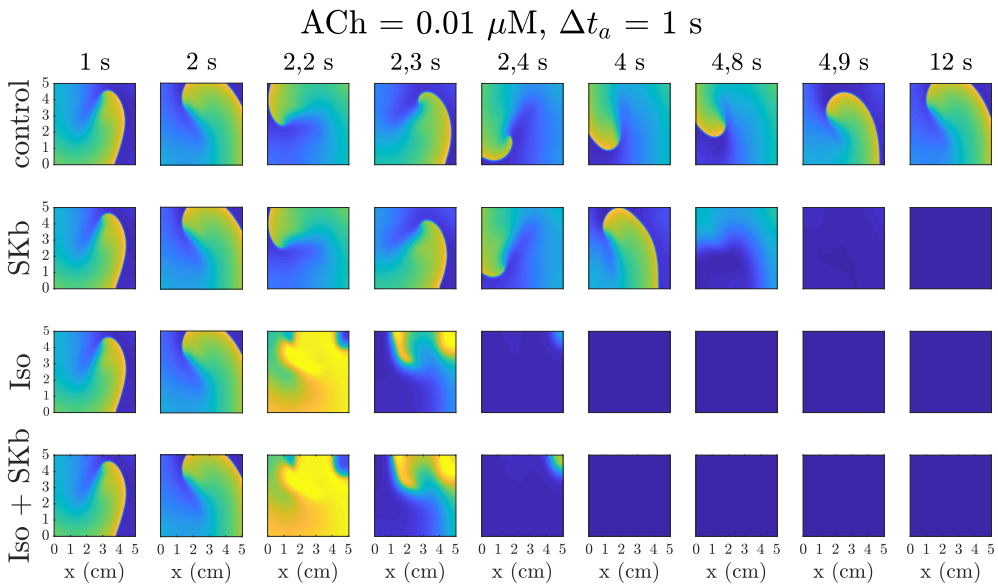

Figure 2. Rotor simulation in 2D human atrial tissue, under 0.01 μM ACh. Voltage maps at different time instants. First row: control, second row: + SKb, third row: + 1 μM Iso, fourth row: + SKb + 1 μM Iso. Iso and/or SKb are applied progressively between seconds 2 and 3.

in rotor termination in the Iso and Iso + SKb cases when increasing Δt_a was observed.

Fig. 3 summarizes the times required to terminate the rotors in each of the simulated cases.

4. Discussion

In this study, the ability of SKb and Iso, individually or in combination, to terminate a stable rotor in a computationally simulated 2D atrial tissue stimulated with ACh was investigated. Iso and Iso + SKb proved to be able to terminate a rotor for all tested ACh concentrations, while SKb alone stopped the rotor only with the lower ACh concentration of 0.01 μM. The different drug application curves did not have an impact on the final output in terms of rotor termination, with the only exception of SKb on top of 0.1 μM ACh, which terminated the rotor only with the three faster application kinetics. Future studies could investigate the mechanisms by which the rotor was terminated and characteristics like WL and rotor meandering could be evaluated. Furthermore, computational studies on realistic 3D atria could be conducted to evaluate rotor dynamics in a more realistic setting.

Acknowledgments

This work was supported by the EU under ERC-StG 638284 and H2020 Marie Skłodowska-Curie ITN grant no.766082 MY-ATRIA, by MICINN (Spain) through projects PID2019-105674RB-I00 and PID2019-104881RB-I00 and by Gobierno de Aragón, BSICoS Group T39-20R.

References

[1] Iso K, Okumura Y, Watanabe I, Nagashima K, Takahashi K, Arai M, Watanabe R, Wakamatsu Y, Otsuka N, Yagyu S, Kurokawa S, Nakai T, Ohkubo K, Hirayama A. Is Vagal Response During Left Atrial Ganglionated Plexi Stimulation a Normal Phenomenon? Circulation Arrhythmia and Electrophysiology October 2019;12(10):e007281.

[2] Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable Microreentrant Sources as a Mechanism of Atrial Fibrillation in the Isolated Sheep Heart. Circulation January 2000;101(2):194–199.

[3] Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the Autonomic Nervous System in Atrial Fibrillation. Circulation Research April 2014;114(9):1500–1515.

[4] Skibsbye L, Poulet C, Diness JG, Bentzen BH, Yuan L, Kappert U, Matschke K, Wettwer E, Ravens U, Grunnet M, Christ T, Jespersen T. Small-Conductance Calcium-Activated Potassium (SK) Channels Contribute to Action Potential Repolarization in Human Atria. Cardiovascular Research July 2014;103(1):156–167. ISSN 1755-3245.

[5] González de la Fuente M, Barana A, Gómez R, Amorós I, Dolz-Gaitón P, Sacristán S, Atienza F, Pita A, Pinto Fernández-Avilés F, Caballero R, Tamargo J, Delpón E. Chronic Atrial Fibrillation Up-Regulates 1-Adrenoceptors Affecting Repolarizing Currents and Action Potential Duration. Cardiovascular Research February 2013;97(2):379–388. ISSN 0008-6363.

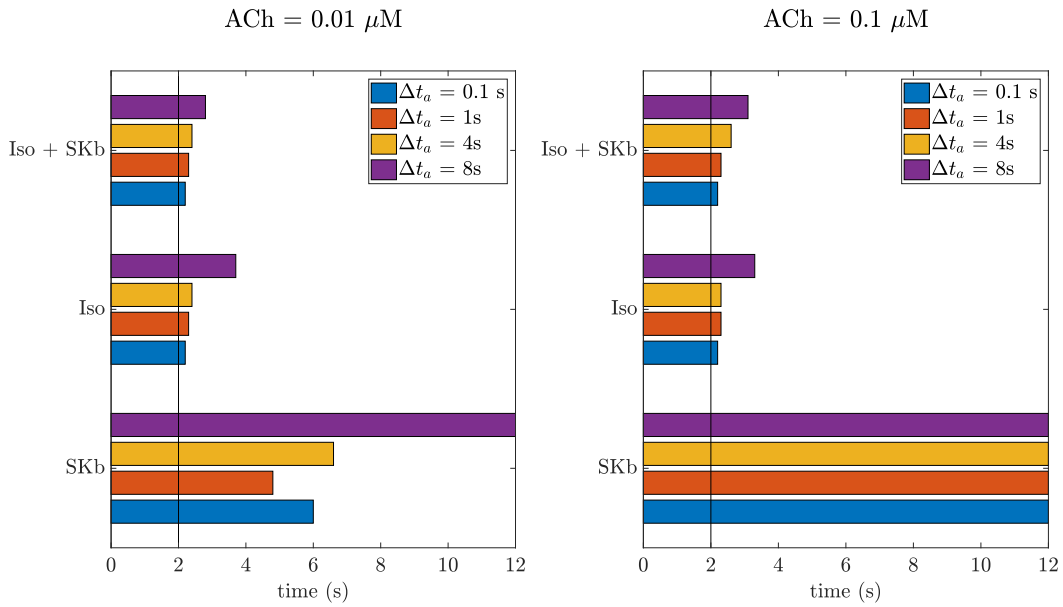

Figure 3. Time for rotor termination in the different simulated cases. The vertical black line represents the start time of Iso and SKb application.

[6] Arora R. Recent Insights Into the Role of the Autonomic Nervous System in the Creation of Substrate for Atrial Fibrillation: Implications for Therapies Targeting the Atrial Autonomic Nervous System. Circulation Arrhythmia and Electrophysiology August 2012;5(4):850–859. ISSN 1941-3084.

[7] Sosunov EA, Anyukhovsky EP, Rosen MR. Adrenergic-Cholinergic Interaction that Modulates Repolarization in the Atrium is Altered with Aging. Journal of Cardiovascular Electrophysiology April 2002;13(4):374–379. ISSN 1045-3873.

[8] Celotto C, Sánchez C, Laguna P, Pueyo E. Calcium-Activated Potassium Channel Inhibition in Autonomically Stimulated Human Atrial Myocytes. December 2019; .

[9] Celotto C, Sanchez C, Mountris KA, Laguna P, Pueyo E. SK Channel Block and Adrenergic Stimulation Counteract Acetylcholine-Induced Arrhythmogenic Effects in Human Atria. In 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). Montreal, QC, Canada: IEEE. ISBN 9781728119908, July 2020; 2303–2306.

[10] Courtemanche M, Ramirez RJ, Nattel S. Ionic Mechanisms Underlying Human Atrial Action Potential Properties: Insights from a Mathematical Model. American Journal of Physiology Heart and Circulatory Physiology July 1998; 275(1):H301–H321. ISSN 0363-6135, 1522-1539.

[11] Kneller J, Zou R, Vigmond EJ, Wang Z, Leon LJ, Nattel S. Cholinergic Atrial Fibrillation in a Computer Model of a Two-Dimensional Sheet of Canine Atrial Cells With Realistic Ionic Properties. Circulation Research May 2002;90(9). ISSN 0009-7330, 1524-4571.

[12] Bayer JD, Boukens BJ, Krul SPJ, Roney CH, Driessen AHG, Berger WR, van den Berg NWE, Verkerk AO, Vigmond EJ, Coronel R, de Groot JR. Acetylcholine Delays Atrial Activation to Facilitate Atrial Fibrillation. Frontiers in Physiology September 2019;10:1105. ISSN 1664-042X.

[13] Engel J, Schultens HA, Schild D. Small Conductance Potassium Channels Cause an Activity-Dependent Spike Frequency Adaptation and Make the Transfer Function of Neurons Logarithmic. Biophysical Journal March 1999; 76(3):1310–1319. ISSN 00063495.

[14] Matene E, Vinet A, Jacquemet V. Dynamics of Atrial Arrhythmias Modulated by Time-Dependent Acetylcholine Concentration: a Simulation Study. Europace European Pacing Arrhythmias and Cardiac Electrophysiology Journal of the Working Groups on Cardiac Pacing Arrhythmias and Cardiac Cellular Electrophysiology of the European Society of Cardiology November 2014;16 Suppl 4:iv11–iv20. ISSN 1532-2092.

[15] Mountris KA, Sanchez C, Pueyo E. A Novel Paradigm for In Silico Simulation of Cardiac Electrophysiology Through the Mixed Collocation Meshless Petrov-Galerkin Method. In 2019 Computing in Cardiology (CinC). IEEE, 2019; Page–1.

[16] Mountris KA, Pueyo E. The Radial Point Interpolation Mixed Collocation Method for the Solution of Transient Diffusion Problems. Engineering Analysis with Boundary Elements 2020;121:207–216.

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