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 du-

ration (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 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.
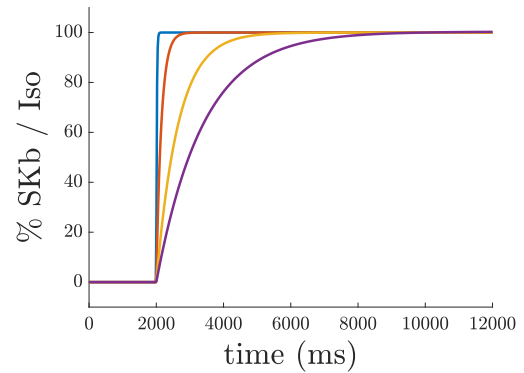

Figure 1. Load curves for Iso and SKb expressed as percentage of SKb and ratio with respect to 1μM Iso, respectively.

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

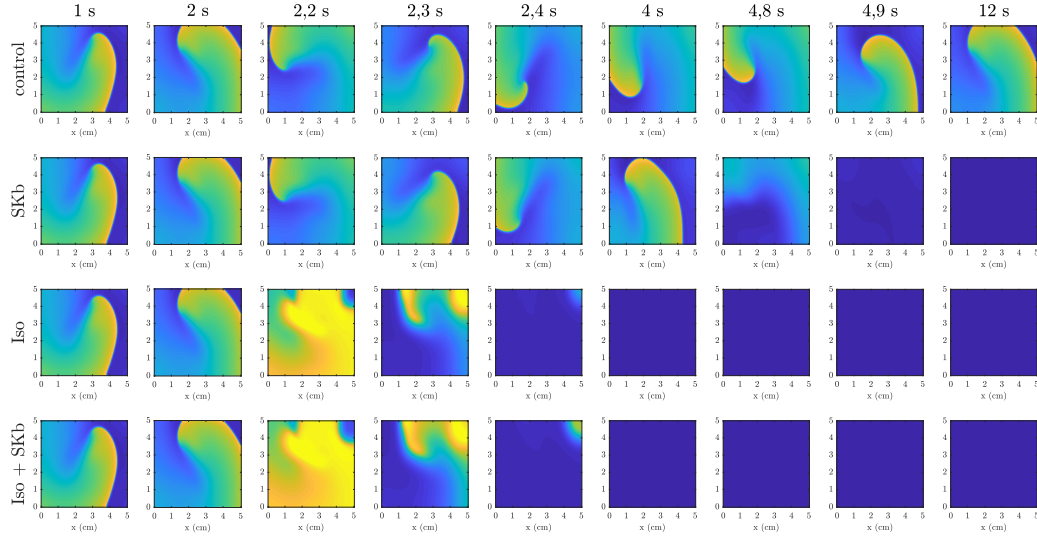$$\text{ACh} = 0.01 \ \mu\text{M}, \ \Delta t_a = 1 \ \text{s}$$

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.

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

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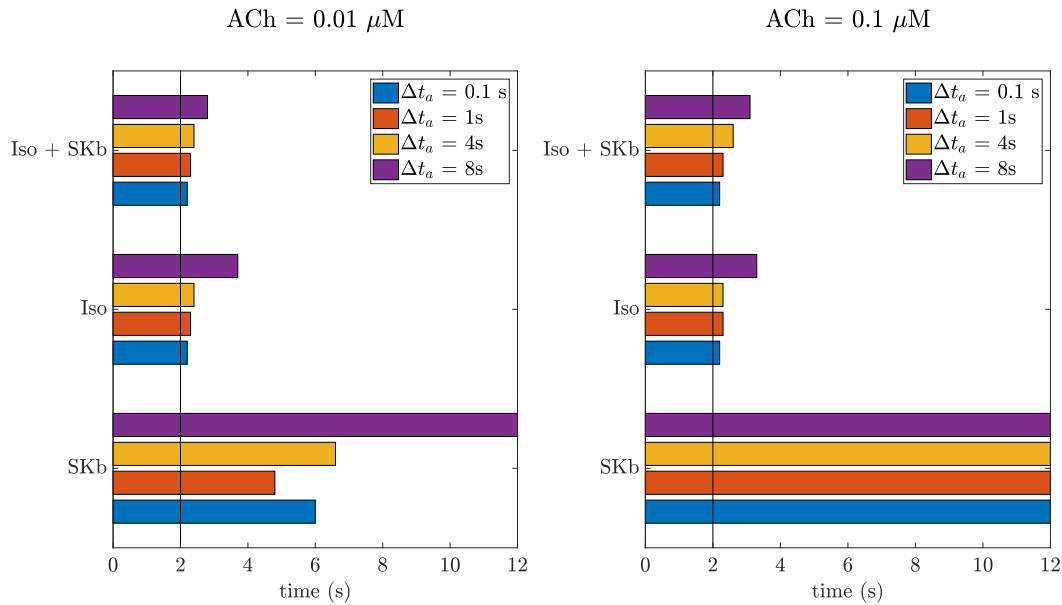
Figure 3. Time for rotor termination in the different simulated cases. The vertical black line represents the start time of Iso and SKb application.

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