Balance between sodium and calcium currents underlying chronic atrial fibrillation termination: An *in silico* intersubject variability study

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BACKGROUND Atrial remodeling as a result of long-standing persistent atrial fibrillation (AF) induces substrate modifications that lead to different perpetuation mechanisms than in paroxysmal AF and a reduction in the efficacy of antiarrhythmic treatments.

OBJECTIVE The purpose of this study was to identify the ionic current modifications that could destabilize reentries during chronic AF and serve to personalize antiarrhythmic strategies.

METHODS A population of 173 mathematical models of remodeled human atrial tissue with realistic intersubject variability was developed based on action potential recordings of 149 patients diagnosed with AF. The relationship of each ionic current with AF maintenance and the dynamics of functional reentries (rotor meandering, dominant frequency) were evaluated by means of 3-dimensional simulations.

RESULTS Self-sustained reentries were maintained in 126 (73%) of the simulations. AF perpetuation was associated with higher expressions of I_{Na} and I_{CaL} ($P < .01$), with no significant differences in the remaining currents. I_{CaL} blockade promoted AF extinction in 30% of these 126 models. The mechanism of AF termination was related with collisions between rotors because of an increase in rotor meandering ($1.71 \pm 2.01 cm^2$) and presented an increased efficacy in models with a depressed I_{Na} ($P < .01$).

CONCLUSION Mathematical simulations based on a population of models representing intersubject variability allow the identification of ionic mechanisms underlying rotor dynamics and the definition of new personalized pharmacologic strategies. Our results suggest that the underlying mechanism of the diverging success of I_{CaL} block as an antiarrhythmic strategy is dependent on the basal availability of sodium and calcium ion channel conductivities.

KEYWORDS Atrial fibrillation; Ionic currents; Rotor dynamics; Calcium current; Mathematical modeling

Introduction

Pharmacologic treatment of atrial fibrillation (AF) has modest efficacy in terminating the arrhythmia and sustaining sinus rhythm in patients with long-standing persistent AF.[1,2] One of the explanations for this lack of success in chronic AF patients is the remodeling process of atrial tissue. Prolonged periods of AF result in changes in the characteristics of AF drivers (e.g., dominant frequency [DF], rotor meandering, wavefront curvature) and promote AF maintenance.[3] Understanding the ionic mechanisms that govern AF drivers will allow the development of more effective antiarrhythmic drug treatments in remodeled substrates. However, the remodeling process and its effects on the interaction between ion channel currents depend on the underlying clinical scenario and genetics of each patient,[4,5] which may result in perpetuation mechanisms that differ among patients.

Pharmacologic treatments have traditionally attempted to prolong the action potential duration (APD) and refractory period of cells, resulting in an increase of wavelength. However, this strategy has limited efficacy for AF termination and sinus rhythm maintenance.[1] Another potential strategy, based on most recent knowledge about perpetuation of AF by rotors, is to focus on destabilizing rotor cores. An increase in rotor core movement may promote its extinction

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by collision with other wavefronts or anatomic obstacles[3] and thus appears to be an attractive target for antiarrhythmic drugs. Therefore, an in-depth understanding of the ionic mechanisms that govern self-sustained reentries under remodeled conditions is needed. The voltage-dependent sodium current I_{Na} probably is the main ionic current governing wavefront propagation properties during sinus rhythm and reentrant activity. Blockade of this current results in deceleration of reentrant activity and increase in reentry meandering, which facilitates termination of the arrhythmia.[6] However, I_{Na} block can increase vulnerability to ventricular fibrillation caused by decreased conduction velocity.[2] In addition, the role of the L-type calcium current I_{CaL} in rotor dynamics remains controversial. It has been observed that I_{CaL} blockade can result in acceleration of fibrillation activity,[7] consistent with APD shortening,[8] and in a reduction of fibrillation frequency.[9,10] The specific mechanisms for these discrepancies remain unclear and can be related to the role of I_{CaL} in terms of propagation.[11] Our hypothesis is that the effect of I_{CaL} block on atrial rotor dynamics is modulated by the strength of I_{Na} in the specific tissue preparation. Consequently, the specific mechanisms that govern functional rotors may change between patients depending on the relative expression of sodium and calcium currents, opening new venues for personalized pharmacologic strategies to terminate the arrhythmia.

In order to validate this hypothesis, a population of 173 mathematical models capturing variability in experimental measurements from 149 AF patients was used to evaluate the role of each ionic current in the dynamics of functional reentries. The effect or I_{CaL} blockade on reentrant biomarkers and its efficacy for AF extinction by destabilizing the core of rotors were evaluated. Intersubject variability allows identification of the mechanisms that produce diverging effects on AF characteristics by the same antiarrhythmic treatment depending on the basal expression of ion channels.

Methods

Experimental dataset and biomarkers

Action potential (AP) recordings in atrial trabeculae samples (n = 215) of right atrial appendages from 149 patients diagnosed with chronic AF were available.[2,5] The following AP biomarkers were quantified at 1 Hz (Figure 1): APD at 20%, 50%, and 90% of repolarization (APD_{20}, APD_{50}, APD_{90}, respectively), action potential amplitude (APA),

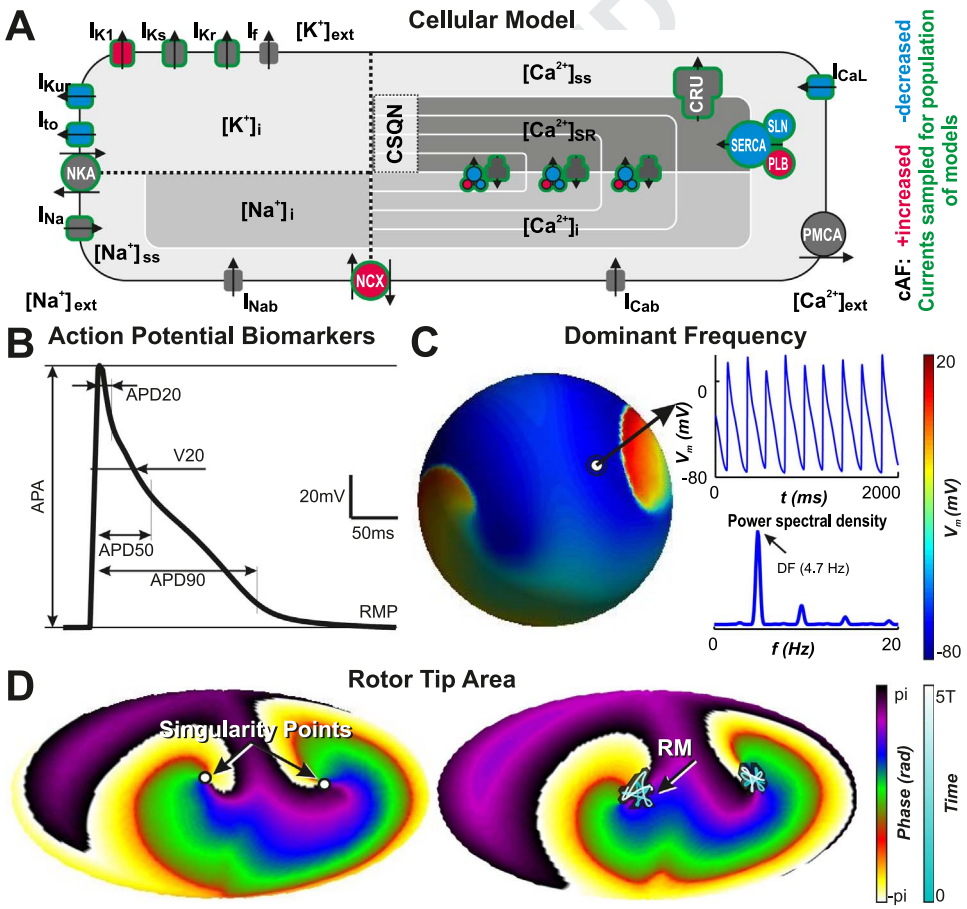

Figure 1 Parameters and biomarkers evaluated in the study. **A:** Koivumaki model. Atrial fibrillation modifications are depicted in *red* and *blue*.[8] Currents sampled to obtain the population of models are shown in *green*. **B:** Action potential biomarkers: APD_{20}, APD_{50}, APD_{90}, action potential amplitude (APA), resting membrane potential (RMP), and V_{20}. **C:** Membrane voltage in sphere simulations according to color scale. *Insets* show transmembrane voltage and power spectral density for a given node, illustrating the dominant frequency (DF). **D:** Phase maps in Aitoff projection of the sphere. **Left:** Detection of the rotor core. **Right:** Meandering of the core according to color scale. APD = action potential duration.