Familial Atrial Fibrillation: Simulation of the Mechanisms and Effects of a Slow Rectifier Potassium Channel Mutation in Human Atrial Tissue

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Abstract

Atrial fibrillation (AF) is a critical pathology due to the risk of secondary diseases like thromboemboli and ventricular arrhythmia. A recent study identified a familial type of AF based on a mutation influencing the cardiac I_{Ks} channel. The mutant channel is characterized by a gain-of-function and a nearly linear current-voltage relationship.

The kinetics and density of I_{Ks} in a model of atrial myocytes was adjusted to the measured characteristic to describe the mechanisms and effects of the mutation. A schematic anatomical model of the right atrium was designed to simulate the excitation propagation.

The action potential duration of the mutant cell was reduced to 105 ms and the effective refractory period to 148 ms. Both factors lead to a reduction in wavelength and thus the risk of an initiation and perpetuation of AF rises.

The results support the understanding of the complex behavior of cardiac cells. The described model will be used to investigate AF and potential treatments.

1. Introduction

Atrial Fibrillation (AF) is an abnormal rapid activation of the atrial muscle, which results in the massive reduction of contractility in the atria. The atrial rate, which is normally given by the rate of the primary pacemaker (the sinoatrial node) with 60 beats per minute (bpm), is fastened to 400 – 600 bpm for the atrial cells due to e.g. re-entry mechanisms [1]. The effects of sustained AF can be e.g. severe congestive heart failure, thromboembolism, cardiomyopathy, ventricular arrhythmia, and electrical remodeling of the atria, which supports stabilization of AF [1].

The occurence of AF rises with age. 0.5% of the 50 years old and over 10% of the 70 years old are effected [1]. But AF can also have the reason in a genetic mutation, which occurs on a familial basis. Chen et al. studied a family with persistent AF [2]. The family has a mutation in the KCNQ1 gene, which normally forms the α subunit of the slow delayed outward rectifier potassium channel I_{Ks}. The mutation (S140G) causes a gain-of-function effect, an instantanious activation and deactivation as well as a nearly linear current-voltage relationship. These effects lead to a shortened action potential duration (APD) and reduced effective refractory period (ERP), which could support the initiation and perpetuation of AF [1].

In this work, the gating and kinetic properties of this mutation were quantitatively included into the Courtemanche, Ramirez, and Nattel (CRN) ionic model of human atrial cardiomyocytes [3]. The influences were visualized in a single-cell and a multi-cell environment. The multi-cell environment describes schematically a part of the right atrium. The APD and ERP changes could be reconstructed within this model.

2. Materials and methods

By sequence analysis in a four-generation family Chen et al. identified the missense mutation S140G, which replaces the normal α subunit encoding KCNQ1 gene of the cardiac I_{Ks} channel [2]. The mutant channel function was recorded by whole cell patch-clamping in transfected COS-7 cells. The current-voltage relationship was measured by a step protocol. Starting from the holding potential of -80 mV, the potential was stepped for each 3 seconds between -130 mV and 50 mV in a 10 mV increment. Fig. 1 shows the measured steady state current-voltage relationship at the end of the 3 second voltage step. The current density in COS-7 cells was increased significantly. The current and the voltage had a nearly linear dependency.

The CRN ionic model was utilized to describe the mutant characteristics in human atrial electrophysiology [3]. The model describes the electrical behavior of human atrial cells with a set of nonlinear-coupled first-order ordinary differential equations. These equations reconstruct intracellular and extracellular ion concentrations, states and dynamic changes in ion channels, ionic currents through the cell membrane, the behavior of intracellular structures, and the transmembrane voltage. The differential equations were solved using the Euler method and a time increment of 10 μs.

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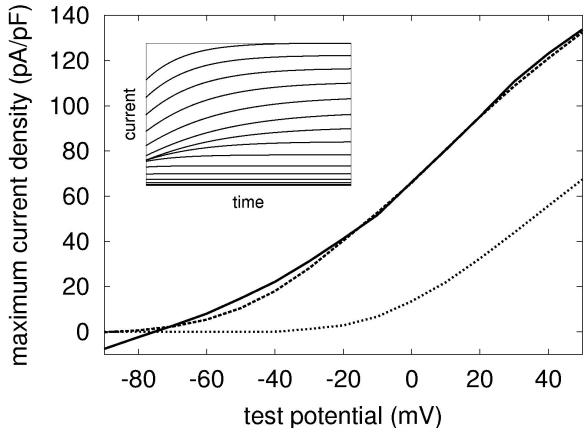

Figure 1. Steady state current-voltage relationship of the measured (solid) and simulated (dashed) mutant I_{Ks} channel. The inset shows the simulated current traces. The physiological current-voltage relationship measured by Chen et al. is displayed dotted.

The measurement data of Chen et al. was used to modify the channel kinetics and density of I_{Ks} in the CRN model by numerical experiments. The environmental conditions for the simulation were adopted from the measurement conditions: Temperature was set to 22 °C and intracellular and extracellular potassium concentration was set to 5 nM and 150 nM, respectively. The original mathematical description of I_{Ks} in the CRN model was left unchanged, only the parameters of the rate constants and the maximum conductance of the I_{Ks} channel were modified. The optimal values for the parameters of the channel characteristics were found using a gradient optimization method to minimize the mean square error between measured and simulated maximum current for each voltage step [4].

An anatomical representation of the cardiac muscle and a method that defines the electrical coupling of excitable cells is required to describe a multi-cellular environment. In this work, the multi-cellular environment was used to determine excitation propagation and the ERP. It was build of cubic volume elements with a side length of 0.2 mm. The anatomical model is a schematic representation of a part of the right atrium. It consists of the terminal crest (CT), some pectinate muscles (PM) and the atrial working myocardium (WM) (Fig. 4 A). For CT and PM adapted electrophysiological parameters were used to quantify the AP shapes of these structures [5]. WM was set to isotropic conductivity. For CT and PM the conductivity was adapted for anisotropy so that CT had an excitation velocity in longitudinal direction of 1.2 m/s and PM of 1.6 m/s as described in [6]. The fast longitudinal direction was set to the main axis of each of PM and CT. The initiation of the excitation propagation in the model was done by applying a stimulus current at the upper end of the CT.

A bidomain model represented the electrical coupling of myocytes by calculating the intercellular current flow, which is given by the flow through gap junctions and through the intra- and extracellular space [7]. The bidomain model was calculated with aid of two Poisson equations for stationary electrical fields for each domain. The finite difference technique was chosen to implement the equations. For the solution an iterative Gauß-Seidel method was used with a time step of 10 μs.

3. Results

The best fit of the simulated characteristics of the mutant I_{Ks} channel to the measured data is given by:

$$
\begin{aligned}
I_{Ks} &= g_{Ks} X_s^2 \left(V_m - E_K\right) \\
\frac{dX_s}{dt} &= \frac{X_{s_\infty} - X_s}{\tau_{Xs}} \\
X_{s_\infty} &= \left[1 + \exp\left(-\frac{V_m + 30}{22}\right)\right]^{-\frac{1}{2}} \\
\alpha_{Xs} &= 1.2 \cdot 10^{-5} \frac{V_m + 30}{1 - \exp\left(-\frac{V_m + 30}{10}\right)} \\
\beta_{Xs} &= 1.1 \cdot 10^{-4} \frac{V_m + 30}{\exp\left(\frac{V_m + 30}{8.5}\right) - 1} \\
\tau_{Xs} &= \frac{1}{2}\left[\alpha_{Xs} + \beta_{Xs}\right]^{-1}
\end{aligned}
$$

with $g_{Ks} = 1$ nS/pF the maximum conductance of the COS-7 cell, the gating variable X_s, the transmembrane voltage V_m, the Nernst potential of potassium E_K, the rate constants α_{Xs} and β_{Xs}, the steady state constant X_{s_∞}, and the time constant τ_{Xs}. Fig. 1 shows the measured and simulated steady state current-voltage relationship of the mutant channel as well as the measured relationship of the normal channel in COS-7 cells [2] .

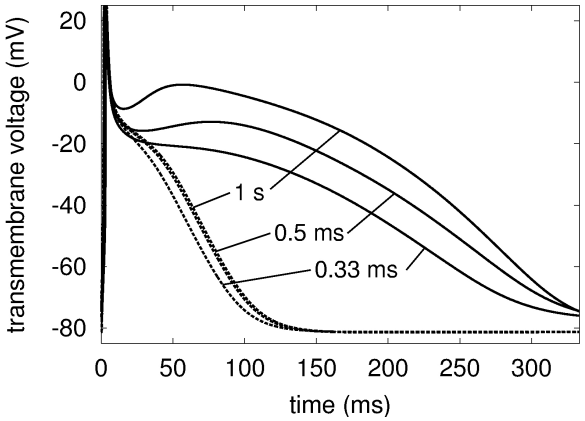

Figure 2. Action potential of physiological (solid) and mutant (dashed) cells of the CRN model at different basic cycle legths.

The root mean square error of this solution was 2.92 pA/pF given by the equation:

$$E_{RMS} = \sqrt{\frac{\sum_{i=1}^{N} (s_i - m_i)^2}{N}}$$

with the simulated maximum current densities s_i, the measured values m_i, and the number of voltage steps N.

This mutant I_{Ks} channel was incorporated into the CRN model. The maximum conductance g_{Ks} was set for the simulations with the ionic atrial model to the original value of 0.129 nS/pF used in [3]. The normal and the mutant action potentials (AP) are displayed in fig. 2 for different basic cycle lengths (BCL). The APD of the mutant cells is always shorter than the physiological one, but has a lower APD-BCL relationship. The physiological APD_{90} is 302 ms at 1 Hz. The mutant one is reduced to 105 ms. Fig. 3 illustrates the I_{Ks} current for both physiological and mutant case at 1 Hz. The rectifier characteristic of the physiological channel switches to a current, which acts comparable to a very large background current due to the nearly linear current-voltage relationship. This is visible in fig. 3 by the AP-like shape of the mutant I_{Ks}. Thus, in the mutant cells the larger current during the plateau phase is responsible for the shortening of the APD.

The excitation propagation in the schematic model of the right atrium is shown in fig. 4. The velocity of the excitation is not reduced by the mutation. The differences between the physiological and the mutant excitation propagation is only visible during the repolarization propagation (Fig. 5). The mutant model is earlier repolarized than the physiological one. This effect is decreasing the wavelength and thus builds a substrate for the initiation and maintenance of AF.

The ERP was simulated in the schematic right atrial model by applying 5 beats with 1 Hz and then one premature beat was followed. The lowest time at which the excitation from the premature beat was able to produce an excitation propagation is called ERP. For the normal CRN model the ERP was 324 ms. For the mutant one the ERP was reduced to 148 ms.

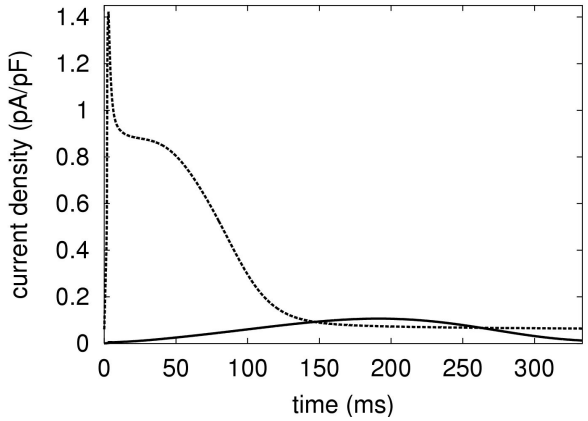

Figure 3. Current I_{Ks} for the physiological (solid) and mutant (dashed) cell during the AP presented in fig. 2 at a stimulus frequency of 1 Hz.

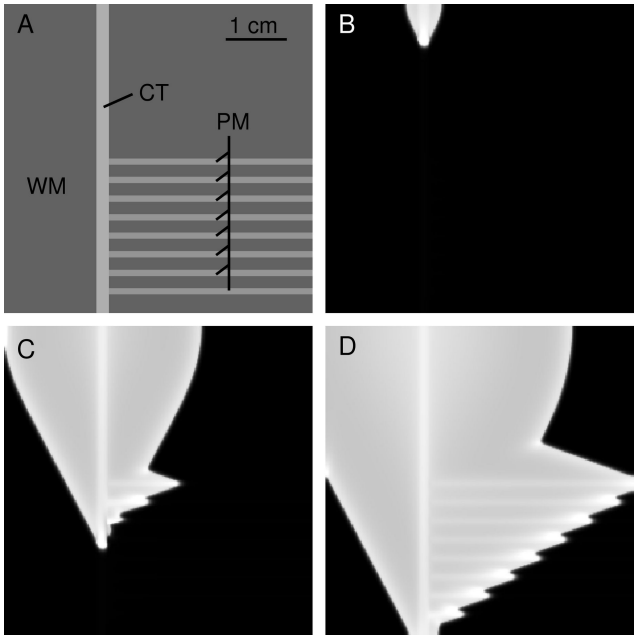

Figure 4. (A) Schematic model of a part of the right atrium. Transmembrane voltage distribution during depolarization at (B) 5 ms, (C) 30 ms, and (D) 45 ms after the stimulation. White color indicates +10 mV, black color −80 mV.

4. Discussion and conclusion

The adjustment of the model parameters to mutant characteristics was based on measurement data of human atrial cells. The final differences between simulated and measured current-voltage relationship were not significant. There was no quantitative information about the temporal behavior of the mutant channel. But simulated current traces were in good agreement with measured ones. The main difference between physiological and mutant channel characteristics was a voltage shift in the rate constants of the gating variable. The measurement was done at room temperature. We considered the temperature drift of E_K, but had no data for the temperature variation of the rate constants.

The simulated APs show significant reduction of duration and ERP was reduced in the multi-cellular environment. This is the main reason why the mutation plays an important role in the initiation and maintenance of AF in the familial case. The APs could not be validated by experimental values due to missing data. Thus, the model might

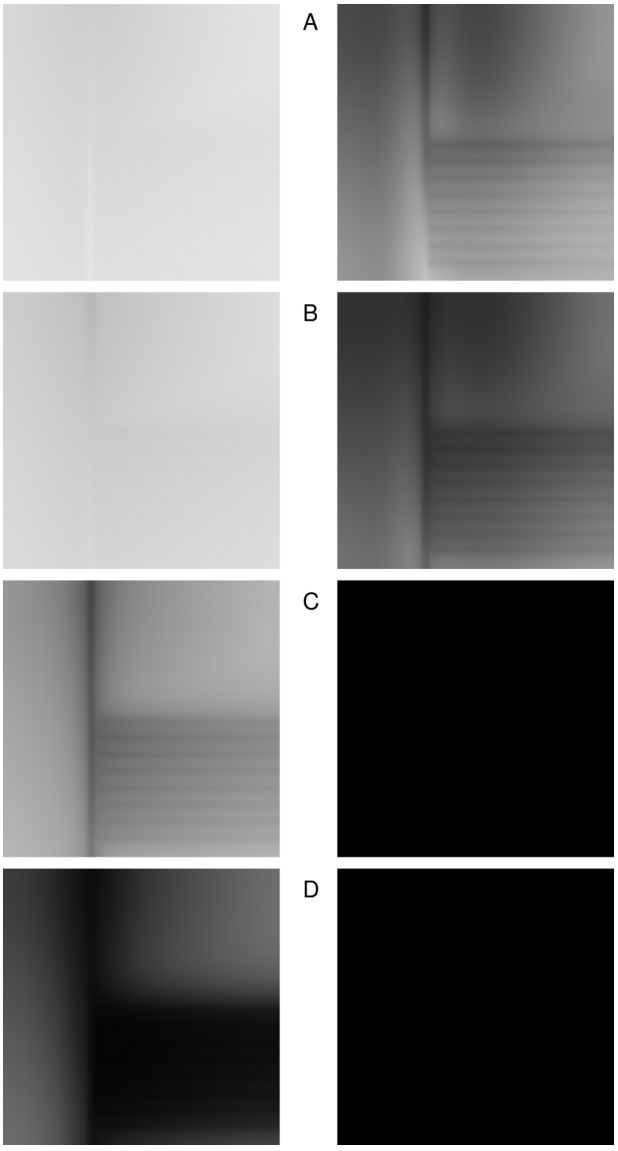

Figure 5. Transmembrane voltage distribution during repolarization in (left) the physiological and (right) the mutant model at time steps (A) 125 ms, (B) 150 ms, (C) 230 ms, and (D) 300 ms after the stimulation. White color indicates +10 mV, black color −80 mV.

not be able to reconstruct the changes in mutant APs absolute correctly. Up to now, it was not clarified if other mutations also cause familial atrial fibrillation. Brugada et al. identified a mutation linked to chromosome 10 that might also be able to effect familial atrial fibrillation [8].

With this model we will be able to transfer the electrophysiological findings to a complete anatomical model of the atria [5] and to investigate the initiation and perpetuation of AF based on different mechanisms, e.g. single and multiple wavelet re-entry. Also remodeling effects due to sustained AF can be incorporated and investigated [9]. Furthermore, the development of strategies of therapy and drug design for the treatment of AF could be supported.

In future we will integrate the mutant channel in a model of heterogeneous ventricular tissue [10]. We will investigate in this model why a large number of patients suffering from familial AF have no significant QT-interval changes [2].

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