Mechanical Consequences of Electrical Remodeling due to Persistent Atrial Fibrillation: a Cellular Level Sensitivity Analysis

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Abstract

During atrial fibrillation, the tissue undergoes electrical remodeling that alters myocyte electrophysiology. These changes in electrophysiology affect the contraction of the cells. While electrical remodeling has been characterized extensively, data on tension development are scarce. In silico experiments help to understand the link between electrophysiology and the tension development of the human atrial myocyte. We systematically vary electrophysiological parameters from their baseline value toward atrial fibrillation remodeling. From single-cell electro-mechanical simulations, we obtained action potential duration, peak intracellular calcium concentration, and maximum tension. A total of 280 model variants were studied, of which 94 models reproduced the experimentally reported reduction of action potential duration. 11 models reproduced the reduction of the peak calcium concentration, and 4 models reproduced the reduction of peak tension observed in patients with atrial fibrillation. We conclude that electrical remodeling has a marked impact on tension development, mainly affected by reducing the L-type Ca^{2+} channel.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, and while it is mostly characterized as an electrical disorder, atrial mechanical contraction is also affected by electrophysiological changes due to AF. During persistent atrial fibrillation (peAF), different ion channels located in the membrane of the cardiomyocytes are remodeled [1, 2]. One effect of these remodeling processes is a shortening of the action potential. On the contrary, very little has been described regarding the effects of AF remodeling of electrophysiology on tension development in cardiac myocytes.

Under peAF, the action potential duration (APD) has been reported to decrease by between 32% and 49% [3–5]. APD reduction is a result of a combination of different changes in the ionic currents. The most affected ion channel is the L-type Ca^{2+}, which has a great impact on intracellular calcium dynamics [6]. The reported values for the peak $[Ca^{2+}]_i$ during peAF range between 0.26 µM and 0.5 µM [4, 5]. For the tension development, Schotten et al. reported a reduction by approximately 75% in patients with peAF [7].

Mathematical descriptions of the cardiac myocyte can be used to advance the understanding of the nonlinear relationship between input and output variables. Here we use in silico experiments to investigate not only the direct effects of the electrical remodeling of the cardiac myocytes during peAF but also the the effects on tension development in a controlled environment.

In this study, using single-cell in silico experiments, we explore the tension development in electrically remodeled human atrial myocytes due to peAF.

2. Methods

2.1. Atrial myocyte electrophysiology model

The human atrial action potential (AP) model proposed by Skybsbye et al. [1] was used to simulate atrial electrophysiology. This model features a detailed formulation of the intracellular calcium dynamics and an up-to-date sodium current formulation that faithfully reproduces human atrial myocyte electrophysiology.

During peAF, the atrial myocytes undergo electrical remodeling that changes, among other aspects, the duration of the action potential. Skibsbye et al. proposed an electrically remodeled variant that reproduces experimental observations. Briefly, the cell is dilated by 10%, the maximum conductance of sodium channel (GNa) is decreased by 18%, the L-type calcium maximum conductance ($GCaL$) is reduced by 55%, the maximum conductance of the transient outward potassium channel (Gto) is decreased by 62%, the sustained potassium channel ($Gsus$) is decreased by 38%, the slow delayed rectifier potassium current (GKs) is increased by 145%, the maximum conductance of the inward potassium rectifier ($GK1$) is increased by 68%, the sodium-calcium ex-

changer ($kNaCa$) is increased by 50%, the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) pump ($cpumps$) is decreased by 16%, phospholamban (PLB) is increased by 18%, sarcolipin (SLN) is decreased by 40%, the baseline phosphorylation ($phos$) is increased by 100%, the ryanodine receptor Ca^{2+} sensitivity (RyR) is increased by 100%, and the Ca^{2+} activated potassium channel ($GKCa$) is decreased by 50%.

2.2. Atrial contraction model

Land et al. [8] proposed a model for the tension development in cardiac myocytes. The Skibsbye et al. model was extended by incorporating this contraction model to study the link between intracellular calcium dynamics and tension development. The contraction model was adjusted to represent atrial myocytes as proposed by Land et al. [9] but not further modified to represent for example peAF remodeling processes directly affecting the tension development.

2.3. Sensitivity analysis

A sensitivity analysis was performed for each individual parameter of the electrophysiological model. They were varied from their physiological value to the fully remodeled values mentioned above in 10 equally spaced steps. The 14 parameters were varied one at a time while keeping the others at their physiological value to evaluate their individual contribution on electrophysiology and tension development. In a second series of experiments, the full peAF remodeling setup was considered as a starting point and one parameter at a time was changed towards the physiological range.

Isolated myocytes were stimulated at a basic cycle length of 1000 ms for 100 pulses to reach a limit cycle. The electrophysiology models were simulated using openCARP [10]. Biomarkers, such as action potential duration at 90% of repolarization (APD_{90}), peak calcium concentration ($[Ca^{2+}]_{i,max}$), and peak tension (Ta_{max}) were measured for the last AP. To calibrate the set of models, literature ranges for APD_{90}, $[Ca^{2+}]_{i,max}$, and Ta_{max} were used. We considered all models that had a reduction of APD_{90} between 41.65% and 48.77%, a reduction of $[Ca^{2+}]_{i,max}$ between 0.26 µM and 0.5 µM, and a reduction of peak tension between 65.75% and 78.05%.

3. Results

Figure 1 (top row) depicts the 280 models and the traces for a human atrial myocyte under physiological conditions (control) and after peAF electrical remodeling. The control myocyte had an APD_{90} of 262.10 ms, a $[Ca^{2+}]_{i,max}$ of 0.83 µM, and a Ta_{max} of 44.85 kPa. Under full electrical remodeling due to peAF, APD_{90} was 152.94 ms (–41.65%), $[Ca^{2+}]_{i,max}$ was 0.43 µM (–48.19%), and peak tension was 6.54 kPa (–85.42%).

The change of parameters and their effect on the APD_{90}, $[Ca^{2+}]_{i,max}$, and Ta_{max} are depicted in Figure 2. Variation of $GK1$ had a big impact on the electrophysiology of the cardiac myocyte up to rendering it inexcitable.

$GCaL$, Gto and $Gsus$ affected APD_{90} and $[Ca^{2+}]_{i,max}$ in a wider range compared to the other 11 parameters. However, only $GCaL$ had the strongest impact on tension development. Fully remodeled $GCaL$ led to a break-down of tension development while the myocyte still exhibited an AP.

From the 280 models, only a subset reproduced the APD_{90}, the $[Ca^{2+}]_{i,max}$, or the Ta_{max} reported in literature (Figure 1). A total of 94 models were in the range of the APD_{90} criterion. They had a mean APD_{90} of 137.52 ms±14.95 ms, a mean $[Ca^{2+}]_{i,max}$ of 0.29 µM±0.06 mM, and a mean Ta_{max} of 1.81 kPa±4.26 kPa. A total of 11 models were in the range of the $[Ca^{2+}]_{i,max}$ criterion. These 11 models had a mean $[Ca^{2+}]_{i,max}$ 0.40 µM±0.05 mM, a mean APD_{90} of 155.03±9.45 ms, and a mean Ta_{max} of 6.15±5.29 kPa. Lastly, four models developed a tension within the Ta_{max} criterion. The four models had a mean Ta_{max} of 11.05±3.10 kPa, mean APD of 165.94± 2.66 ms and a mean $[Ca^{2+}]_{i,max}$ 0.45 µM± 0.02 µM. These four models that fulfilled all three criteria were the full peAF remodeled parameter set as proposed by Skibsbye et al. with the exception that $GCaL$ was reduced only to between 75.56% and 81.67%.

4. Discussion

In this study, we showed how differential electrical remodeling due to peAF affects the tension development. At full electrical remodeling as proposed by Skibsbye et al., APD_{90} and $[Ca^{2+}]_{i,max}$ were in the reported ranges [5, 6]. However, Ta_{max} was decreased (–85.42%) below the reported values [7, 11].

The factors that mostly impacted APD_{90} and $[Ca^{2+}]_{i,max}$ were $GK1$, $Gsus$, Gto, and $GCaL$ as reported in a previous study [3]. However, $GCaL$ plays the major role for the reduction of peak tension (Ta_{max}).

The proposed approach aimed at exploring a wide range of possible electrical remodeling due to peAF. 94 different models reproduced the APD_{90} reduction observed during peAF. These models had an average reduction of the peak tension of 97.48%. Following the $[Ca^{2+}]_{i,max}$ criterion, the Ta_{max} was reduced by 86.29%, which is closer to the range of the reported values (75% [7] and 82% [11]). The four models fulfilling the Ta_{max} criterion had an average peak tension reduction of 75.37%. These four models in which $GCaL$ was reduced to between 75.56% and 81.67% also exhibited an APD_{90} and $[Ca^{2+}]_{i,max}$ reduction

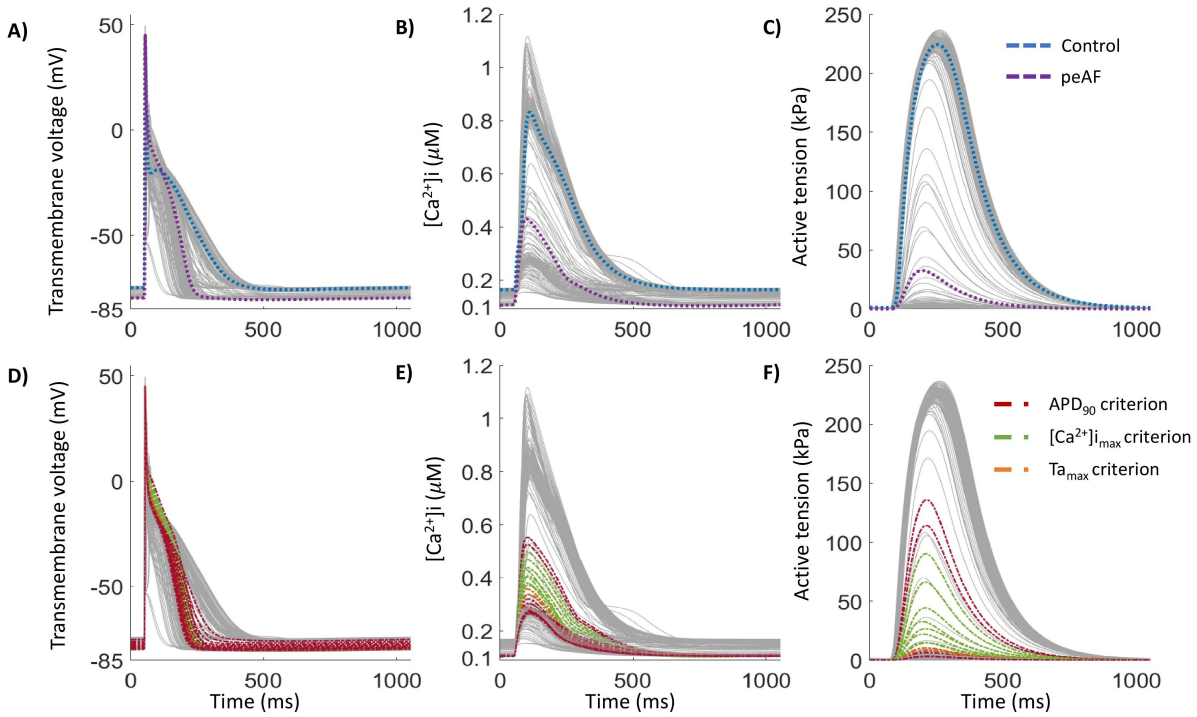

Figure 1. Human atrial myocyte electrophysiology and tension development. Top row shows control (blue trace), full peAF remodeled (purple trace) and the 280 models variants in between (grey traces). Bottom row indicates which traces fulfilled the APD_{90} (red traces), $[Ca^{2+}]_i$ (green traces), and Ta_{max} (orange traces) criteria. A) Action potential variation when changing one parameter at a time from its baseline value to fully AF remodeled; B) $[Ca^{2+}]_i$; C) Tension development. D) Action potentials for all three criteria. E) $[Ca^{2+}]_i$ for all three criteria. F) Ta_{max} resulting for each criterion based on reported values.

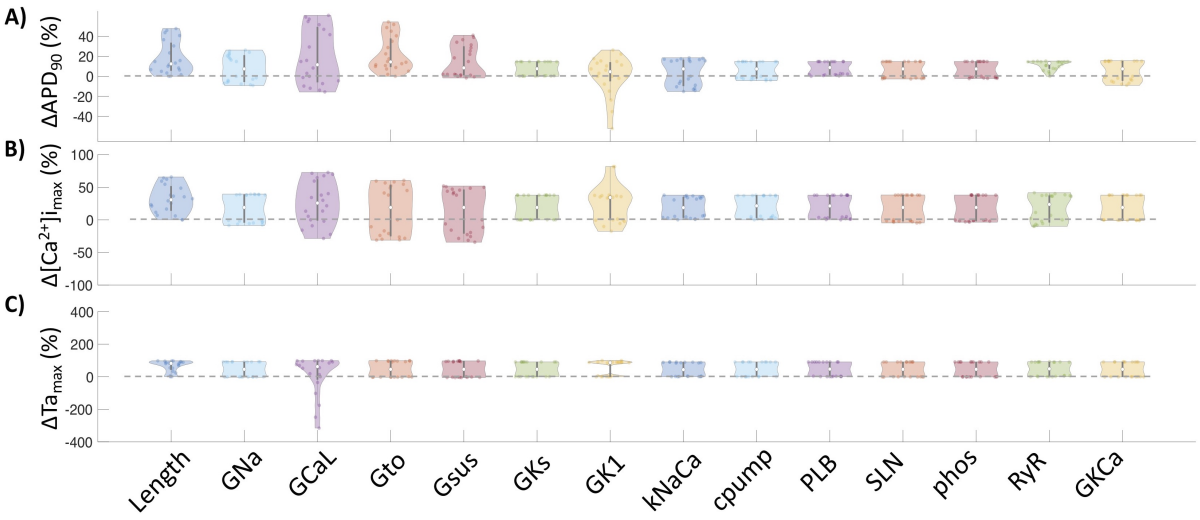

Figure 2. Human atrial myocyte electrophysiology and tension development parameter sensitivity. A) APD_{90} variation when varying one parameter at a time from its physiological value; B) peak calcium variation; C) peak tension variation.

in accordance with the reported literature values [4, 5].

The presented approach gives a first insight into the link between the electrical remodeling due to peAF and tension development. However, additional measurements from human atrial myocytes would help to understand the validity of the model parameters. We did not explore any potential

direct peAF-induced remodeling of tension development in the Land et al. [8] model. As the mechanical function during AF is severely impaired anyway, we investigated the behavior at a cycle length of 1 s to investigate how effective tension development would be after acute termination of peAF. Additionally, the sensitivity analysis is limited to one parameter at a time starting from both ends of the spectrum (control and full peAF remodeling). This approach could be extended to latin hypercube sampling of the full space or scaling of a remodeling vector affecting all currents uniformly [12] in future work. It would also be interesting to simulate the electrical coupling between myocytes and fibroblasts to study the effect on tension development. As myofibroblasts act as a current source and can prolong the APD [13], one could hypothesize that also the tension transient will be prolonged.

5. Conclusions

Atrial myocyte electrical remodeling due to AF has pronounced effects on tension development also during sinus rhythm. Further experimental and computational research is required to elucidate the interplay between electrical and mechanical remodeling and their effect on atrial hemodynamic function.

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