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Atrial Fibrillation-based Electrical Remodeling in a Computer Model of the Human Atrium

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Abstract

Atrial fibrillation (AF) is a common pathology. AF modifies the electrophysiological properties of cells (remodeling) promoting the occurrence and maintenance of AF.

Electrical remodeling includes changes in $I_{Ca,L}$, I_{to}, I_{K1} and $I_{K,ACh}$. These effects were integrated in a human atrial computer model. Gap junction remodeling was considered in the conductivity of the monodomain equation calculating excitation. Specific features were calculated to determine the risk of AF initiation and perpetuation.

ERP was reduced from 330ms to 103ms. CV was lowered from 755mm/s to 608mm/s. The WL reduction was even higher (from 249mm to 63mm) leading to a higher probability of occurrence and maintenance of AF. A maximum of 7 spirals waves were initiated leading to a peak in the power spectrum at 10.32Hz.

The computer model underlines the relevance of remodeling in AF chronification. The results add to the knowledge of AF maintenance. Our model might prove to be a tool for the development of novel therapeutic strategies.

1. Introduction

Cardiac arryhtmias and cardiovascular diseases are a major health problem, displaying the cause of death number one in western societies. The most common arrhythmia is atrial fibrillation (AF), which affects more than 10% of the population older than 70 and more than 1% of the population in general with an upward trend [1].

AF is characterized by an abnormal chaotic, rapid and irregular activation of the atria leading to electrical remodeling. In this case, the electrophysiological properties of the atrial myocardium are changed. Although AF is usually not life threatening itself, subjects suffering from this disease often suffer a reduced quality of life. AF frequently results in disorders like palpitations, fainting, chest pain or congestive heart failure. Additionally, people suffering from AF have a significantly increased risk of stroke.

Wijffels et al. [2] observed that the occurrence of AF modified the atrial electrophysiology in a way that increases the probability to develop a chronic form of AF. The underlying mechanism is called electrical remodeling and is based on changes in different ionic currents, mostly $I_{Ca,L}$, I_{to}, I_{K1} and $I_{K,ACh}$. By this, the effective refractory period (ERP) and the conduction velocity (CV) are decreased. These factors have an impact on the wavelength (WL) of the electrical impulse, which is its distance traveled within one refractory period. Electrical remodeling yields to a reduction of WL, thus increasing the predisposition for the occurrence and maintenance of AF.

The higher atrial rate present under AF supports a progressive Ca^{2+} loading that threatens cell viability. The cell reacts with a reduction of the Ca^{2+} conductance to reduce Ca^{2+} influx. A long term response decreases the expression of the $I_{Ca,L}$ forming α-subunit mRNA. The result is a decreased $I_{Ca,L}$ by 65% [3] leading to a shorter ERP.

I_{to} is also decreased by 65% due a strong reduction in mRNA and pore forming protein expression [4]. In contrast, the expression levels of the α-subunit mRNA of I_{K1} are increased [4]. $I_{K,ACh}$ is activated vagally during AF [5]. However, the expression and activation of $I_{K,ACh}$ is found to be lower under remodeling [6]. Due to spontaneous activity, $I_{K,ACh}$ might contribute to the total inward rectifying current independent of vagal tone [7]. The combination of both I_{K1} and $I_{K,ACh}$ builds a total current (I_{basal}) that is increased by 110% [6].

A gap junctional remodeling has been reported, which may cause a decreased CV. In a goat AF model, a reduction of connexin Cx40 was described, while the expression of Cx43 remained unaffected [8]. Cx40 is represented more in atrial myocardium than in the ventricles [9] leading to a total reduction of the tissue conductivity of around 30%.

The aim of this work is to implement these changes in a computer model of human tissue and to investigate the properties of remodeling. Therefore, the ERP, CV, WL and their restitution curves were investigated and the power spectrum of the pseudo ECG was analyzed.

2. Methods

We used the Courtemanche, Ramirez, Nattel (CRN) model which is a mathematical model of the AP based on ionic current data obtained from human atrial cells [10]. The electrophysiological changes under AF conditions were integrated in the CRN model by modifying the corresponding currents. The maximum conductance of $I_{Ca,L}$ and I_{to} were both decreased by 65%. The CRN model does not present a description of $I_{K,ACh}$. As I_{K1} and $I_{K,ACh}$ show similar behavior between -80mV and 20mV [6], I_{K1} can be represented as I_{basal} in this physiological range. Therefore, an increase of I_{K1} by 110% was chosen. Electrical remodeling further includes a decrease in connexin Cx40 expression. This was considered in the conductivity for the monodomain equation calculating excitation propagation. The conductance σ of the monodomain equation (initially 0.076S/m) was reduced by 30%.

For the determination of ERP, CV and WL, a 1D tissue model was used. This patch contained 200 voxel with a resolution of 0.1mm. At voxel 50 and 150 the maximum upstroke was measured. Beginning with a basic cycle length (BCL) of 1000ms, the patch was stimulated until a steady state was reached. CV and ERP were calculated and the BCL was reduced by 10ms until again a steady state was reached. The procedure was repeated until a BCL of 200ms in control and 100ms under AF was accomplished.

In order to investigate fibrillation and its power spectrum density, a 2D rectangle was used. It consisted of 1000 x 1000 voxel with a resolution of 0.1mm. The area was 10cm x 10cm representing approximately the surface of the atria. Both 1D and 2D simulations were integrated with a forward Euler method and a time step of 10μs.

The pseudo ECG (pECG) was calculated as the potential difference between two points P_1 and P_2, positioned in the center with a distance of 10mm between each other:

$$pECG = \Phi(P_1, t) - \Phi(P_2, t). \quad (1)$$

The electric potential $\Phi(P, t)$ within an infinite and homogeneous medium can be calculated as:

$$\Phi(P, t) = \frac{1}{4\pi\sigma} \int_{vol} \frac{I(t)}{r} dV, \quad (2)$$

with $I(t)$ being the electric source current and r the distance of the current source to the position P. σ is the electrical conductivity.

Finally, in order to quantify the gained pseudo ECG, a fast Fourier transform (FFT) was performed and the dominant frequency was extracted. Jason and colleagues described that the dominant frequency is a good method to quantify the persistency of AF. The higher the measured dominant frequency is, the lower is the probability of AF to terminate on its own [11].

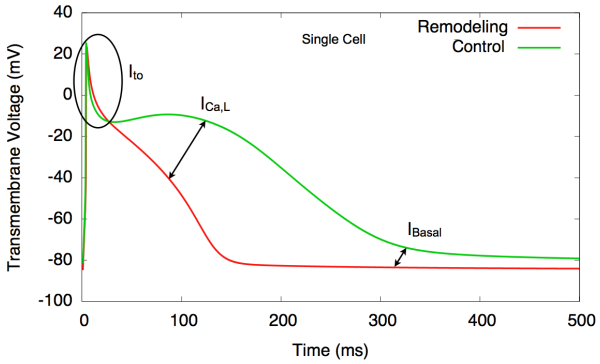

Figure 1. Action potential under physiological (green) and remodeling AF (red) conditions. Modifications of I_{to}, $I_{Ca,L}$, and I_{K1} resulted in a shorter APD, mainly due to a shorter plateau phase, and a more negative resting voltage (BCL = 1000ms). Picture from [12].

3. Results

The action potential duration (APD_{90}) in tissue was reduced from 322ms in the physiological case to 144ms for remodeling (see fig. 1). The ERP was reduced from 330ms to 103ms. ERP in remodeling showed a lower capacity to adapt to higher pacing rates (see fig 2). CV was lowered from 755mm/s to 608mm/s for slow rates. The CV restitution of remodeling showed similar but shifted characteristics in contrast to the normal cell (see fig 2). As the WL is the product of ERP and CV, its reduction was even higher (from 249mm to 63mm for slow rates) leading to a higher chance of occurrence and maintenance of AF. Also here, the rate adaptivity was much lower (see fig 2).

For the initialization of rotating waves, a cross-field stimulation protocol was used. After that, further stimuli were chosen to cause continuing wave breaks. In the physiological case, no spirals could be initiated with any kind of stimulation protocol because of the long WL (not shown). For remodeling, a maximum of up to 7 spirals were initiated for different stimulation protocols (see fig 3). Most of these spirals have been stable and therefore a sustained AF was initiated. Figure 4 depicts the pECG and the power spectrum density of the 7 spiral case. After 5s of fibrillation, the pECG showed stable characteristics leading to a peak in the power spectrum at 10.32Hz.

4. Discussion and conclusions

In this work, measurement data of electrical remodeling was inserted in the electrophysiological model of a human atrial myocyte. ERP, CV, WL and their restitution curves were investigated. The power spectrum of the pseudo ECG was analyzed. All these measures show a tendency towards a higher risk of initiation and maintenance of AF.

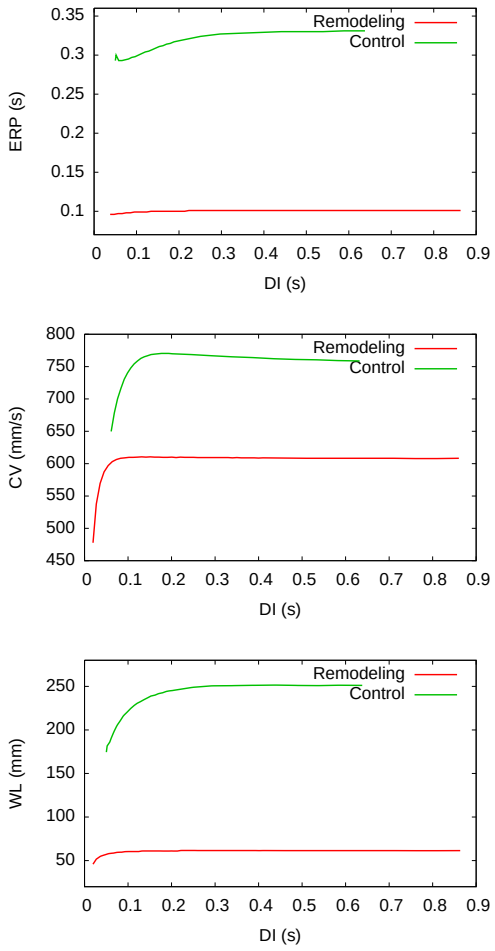

Figure 2. Effective refractory period (ERP), conduction velocity (CV) and wave length (WL) restitution for the physiological and the remodeling case.

Bosch et al. reported an APD reduction from 319ms to 134ms [3] which is in good agreement to the simulated reduction from 322ms to 144ms. The ERP changes due to remodeling were in detail described by Yu et al. [14]. They measured a reduction from 264ms to 217ms at a rate of 0.7s (-18%). Our results of 330ms versus 103ms (-69%) correlate more with the APD reduction data of Bosch et al. (-58%). The discrepancy between measured and simulated ERP might be due to the tissue probes Yu et al. worked with. Both probes were taken from AF patients after succesful and unsuccesful cardioversion, respectively. APD and ERP are based on the same effects, namely due to the ion channel changes, mainly the reduction in $I_{Ca,L}$.

Raitt et al. measured a CV change from 930mm/s in physiology to 750mm/s in chronic AF (-20%) [15]. In the simulation, CV was also lowered by -20% from 755mm/s to 608mm/s for low rates. This effect is mainly based on the conductivity reduction due to the decrease in Cx40.

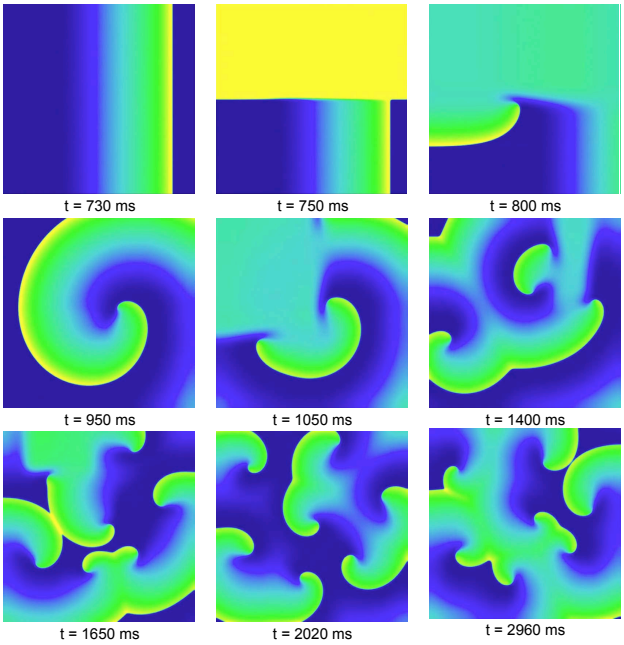

Figure 3. Initiation of fibrillation. At first, a stimulus crosswise to the direction of the wave propagation was set (three figures at the top). Afterwards, further stimuli initialized more rotating waves. A maximum of 7 stable rotors could be initiated. Picture from [13].

Additionally, the lower resting membrane voltage is reducing the CV since the cell needs more time to reach the threshold.

A short wavelength and its low adaptation to heart rate are viewed as the electrophysiological milieu for AF recurrence. This allows more multiple circuits coexisting in the given tissue, thus the vulnerability for AF increases. The performed simulations showed a reduction in WL from 249mm to 63mm. The WL was not yet measured but the simulations showed the tendency of the WL changes that predispose atrial tissue to AF.

In the 2D tissue model, sustained atrial fibrillation was able to be initiated. Different stimulation protocols were used in order to initiate between 1 and 7 rotors in the tissue patch. In the case of 7 rotors, the maximum in the pECG signal spectrum was at 10.32Hz. Jason and Goldberger investigated the dominant frequency of ECGs of AF patients and found a maximum of 10.7 Hz [11].

Kharche and Zhang found similar results in a computational study [16] although they included different remodeling measurement data and did not consider gap junction remodeling. Their WL was shorter because of the lower CV they chose. Tsujimae et al. investigated with their model of remodeling the effects of different I_{Kur} blocker [17]. They also found similar APD reductions but did not investigate ERP, CV, WL nor 2D excitation.

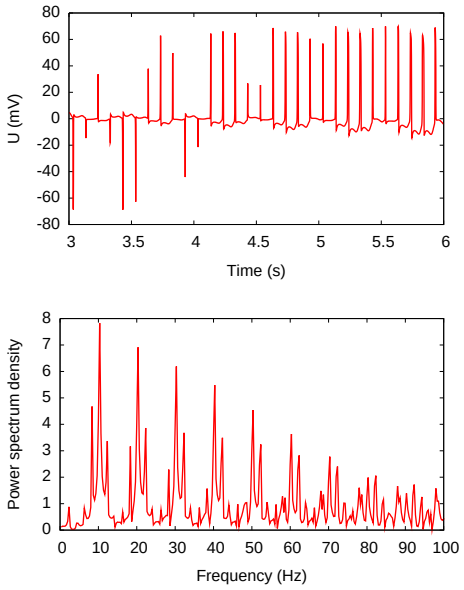

Figure 4. Pseudo ECG and resulting Fourier transform. In case of AF, the rotors remained stable, which was evidenced by the unaltered dominant frequency of 10.32Hz.

In summary, the model reconstructed mechanisms of electrophysiological remodeling caused by AF and showed the potential risk of the remodeling. In future, effects of other pathologies like mutations in atrial cells on the behavior of the atrium will be investigated. The model will be used to verify the mechanisms of AF initiation and perpetuation. It will be enhanced by considering realistic atrial shape and heterogeneity in order to understand the influence of individual geometry and electrophysiology on atrial activity. A further patient-specific adaptation has to be performed to use such a model in computational studies of AF treatment planning like RF ablation or drug design.

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