

Modelling Effect of Heart Failure on the Electrical Activity of Sheep Atria

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Abstract

Heart failure (HF) is associated with cardiac arrhythmias, which impairs cardiac electromechanics that causes dysfunction of cardiac muscle contraction leading to increased risks of morbidity and mortality. Previous studies have revealed that HF causes alteration to the electrophysiological and structural properties of the atria.

The aim of this study was to investigate the primary factor of HF-induced remodelling on the dynamical behaviours of electrical excitation waves in sheep atria.

*The biophysically detailed model of sheep atrial action potentials developed by Butters *et al* was modified to incorporate experimental data of HF-induced remodelling on ion channels. The developed atrial cell models in HF were then incorporated into the 3D anatomical sheep atria model developed in our previous study. The 3D model considered both electrical heterogeneity and tissue anisotropy.*

At the cellular level, HF shortened the action potential duration at 90% of repolarisation (APD_{90}). At 3D organ level, activation time of the whole atria was prolonged due to the downregulation of expression of gap junction proteins (Cx43). Consequently, the wavelength of excitation waves was abbreviated, which may help to sustain re-entrant excitation waves in the atria.

This study provides mechanistic insights into the pro-arrhythmic effect of HF-induced remodeling on ion channels, Ca^{2+} handling and intercellular coupling in the sheep atria.

and maintenance of AF [2]. For example, ectopic activity in pulmonary veins has been found to be a possible trigger that may initiate AF [3]. Although the chaotic activities were observed in many experimental and computational models of AF, mapping studies demonstrate that AF is mainly driven by organised and high frequency re-entrant circuits [4]. Moreover, the anatomical structure plays an important role in determining the fibrillatory behaviour and dominant frequency of re-entrant activities.

Heart failure (HF) is associated with increased risks of cardiac arrhythmias, including AF. Previous studies have revealed that HF causes alteration to the electrophysiological and structural properties of the atria. However, the mechanism underlying the proarrhythmic effect of HF is incompletely understood yet.

The aim of this study was to use the biophysical detailed computer model of the sheep atria to investigate the effects of HF-induced remodelling on ion channels at cellular and 3D organ levels with considered electrical heterogeneity and tissue anisotropy. Specifically, the effect of HF-induced remodelling on ion channels in morphology of action potential and its duration at 90% of repolarisation (APD_{90}), AP characteristics and activation time in the 3D model was studied by simulations.

To achieve that, the sheep atria model developed in our previous study was modified to incorporate experimental data of HF-induced remodelling on ion channels and Ca^{2+} handling. Then, the developed atria cell models of HF were incorporated into the 3D anatomical model of the sheep atria.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with features of chaotic and disorganised excitation activity in different regions of the atria, leading to increased mortality rates [1]. Genesis of AF may be attributable to the altered electrical physiological properties of atrial cells, including changes in action potential duration (APD) and effective refractory period (ERP). Since 1959 when Moe *et al* started studying re-entrant circuits associated with AF, several theories been proposed for the mechanisms underlying the initiation

2. Methods

2.1. Single cell simulations

At the single cell level, the biophysically detailed model of sheep atrial action potentials for different cell types developed by Butters *et al* [5] including the left atrium (LA), crista terminalis (CT), pectinate muscles (PMs), right atrial appendage (APG), pulmonary veins (PVs) and Bachmann's bundle (BB) was modified to incorporate comprehensive experimental data of HF-

induced remodeling on ion channels and Ca^{2+} handling. These ion channels remodelling include downregulation of the L-type calcium current (I_{CaL}), the slow delayed rectifier potassium current (I_{Ks}), and the transient outward potassium current (I_{to}), and upregulation of the inward rectifier potassium current (I_{K1}) and the exchanger $Na^+ - Ca^{2+}$ current (I_{NaCa}).

The equation governing the time (t) course of cell membrane potential (V) was given by the formulation [6]:

$$-C_m \frac{dV_m}{dt} = I_{tot} + I_{stim} \quad (1)$$

Where, C_m is the membrane capacitance, I_{tot} is the total ionic current and I_{stim} is the external applied simulation current.

2.2. 3D organ level simulation

The developed atrial cell models with HF were then incorporated into the 3D anatomical sheep atria model in our previous study. The 3D model considered both electrical heterogeneity and tissue anisotropy. The propagation of action potential (AP) in 3D organ level was described using monodomain equation [7]:

$$\frac{\partial V_m}{\partial t} = \nabla \cdot (D \nabla V) - \frac{I_{ion} + I_{stim}}{C_m} \quad (2)$$

Where, C_m is the membrane capacitance, ∇ is the gradient operator, I_{ion} is the total ionic current, I_{stim} is the external applied simulation current and D is the tensor of diffusion coefficient that describe the AP propagation in relation to the myofibre orientations:

$$D = D_{\parallel} a a^T + D_{\perp} b b^T + D_{*} c c^T \quad (3)$$

Where, D_{\parallel} is the diffusion coefficient along the fibres, D_{\perp} is the diffusion coefficient orthogonal to the fibres in sheet plan, D_{*} is the diffusion coefficient orthogonal to fibres and sheet plan, and a, b and c are fibre vectors in the corresponding directions.

3. Results

3.1. Single cell simulation

Figure 1 shows the simulated AP in control (CTL) and HF conditions by using the LA cell model. It was shown that the AP morphology of the left atrium was triangular and less plateau in phase 2 than in the CTL condition. This is attributable to the HF-induced alteration in some ionic channel currents and Ca^{2+} handling. The observed changes in AP morphology in simulation were in consistence with experimental measurements [8].

Further analysis showed that, APD_{90} in the LA was

significantly shortened by 22.74% in HF condition as compared to CTL. Moreover, the AP characteristics were altered, resulting in a decrease in the overshoot (OS) by 10.32%, a slight reduction of the action potential amplitude (APA) by 1.01%. The resting potential was more hyperpolarised from -76.51 mV (CTL) to -77.63 mV (HF). The maximum upstroke velocity dV/dt_{MAX} was decreased by 1.98% (Figure 1).

The action potential duration restitution curve (APDR) that describe the rate-dependence of the APD_{90} was flattened by HF as compared to CTL condition. The computed maximum slope of the $APDR_{50}$ and $APDR_{90}$ were decreased by 40.84% and 24.24%, respectively in the HF condition (Figure 2).

For more detailed analysis, the inclusive and exclusive methods [9] were used to investigate the relative contribution of I_{CaL} and I_{K1} currents in the predominant effect of APD shortening in sheep atrium (Figure 3).

3.2. 3D organ level simulation

Figure 4 shows simulated excitation pattern in the 3D anatomical model of the sheep atria that considered the electrical heterogeneity and tissue anisotropy in both CTL and HF conditions.

In CTL condition the total activation time (the time when each point reach the maximum upstroke velocity) of the propagation of the electrical wave from the sinus node (SA) to the whole atria was 93 ms. Although there was a reduction of the conduction velocity in HF condition (data not shown here), the activation time was less than that in CTL condition (63 ms). However, in the 3D simulation in HF condition with a consideration of decreased gap junctional coupling (Cx43) by 30%, the total activation time was increased to 174 ms. With a consideration of reduction of Cx43 by 50%, the total activation time became 169 ms, but with regions being not activated in the LA and the Right atrium (RA). These results highlighted the importance of gap junction remodelling in impairing atrial excitation (Figure 4), supporting the hypothesis the deficiency of gap junctions in cardiac myocytes may contribute to arrhythmogenesis with unhealthy human heart [10].

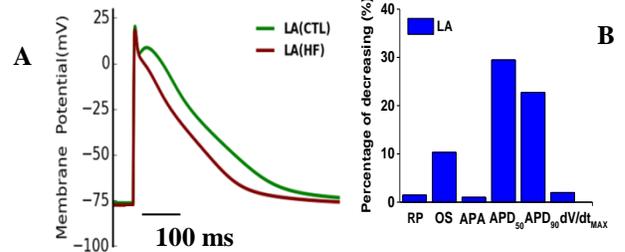


Figure 1. Time course of action potential (AP) of the left atria (LA) in CTL (green) and HF (red) conditions with BCL=1000 ms (A). Percentage of decrease in AP characteristics of the LA in CTL and HF conditions

includes: resting potential (RP), overshoot (OS), action potential amplitude (APA), APD_{50} and APD_{90} , respectively, and maximum upstroke velocity dV/dt_{MAX} .

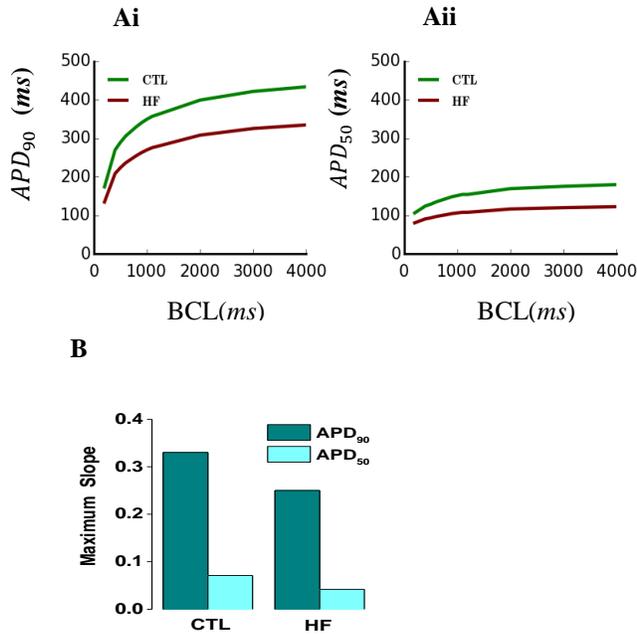


Figure 2. Action potential duration at 90% and 50% of repolarisation and their restitution curves ($APDR_{90}$) and ($APDR_{50}$) in CTL (green) and HF conditions (red) (Ai, Aii). Maximum slope of $APDR_{90}$ and $APDR_{50}$ (B) restitution curves.

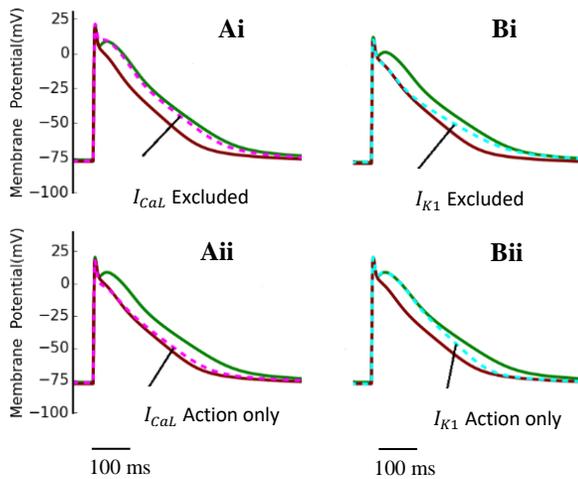


Figure 3. The role of individual remodeled of ionic channels in HF condition. Action potential (AP) was computed in CTL (green), and HF-induced remodelling with all changes in ionic current considered (I_{CaL} , I_{Ks} , I_{to} , I_{K1} and I_{NaCa}) (red). HF remodelling of I_{CaL} was omitted, and HF action of I_{CaL} was only considered (Ai, Aii, pink). HF remodelling of I_{K1} was omitted, and HF action of I_{K1} was only considered (Bi, Bii, cyan). BCL = 1000 ms

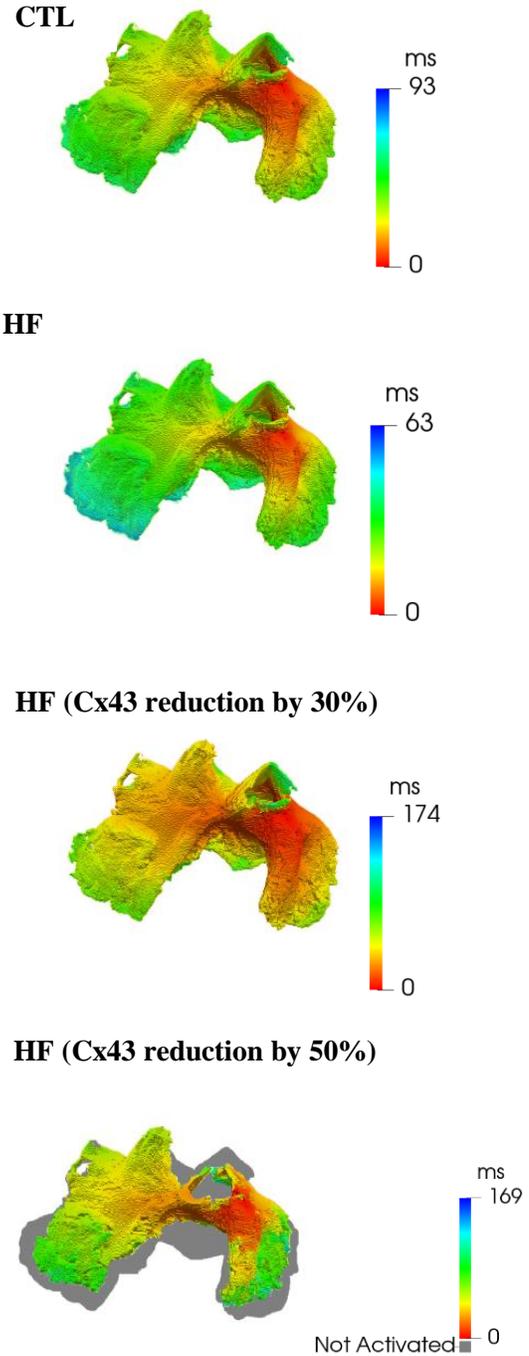


Figure 4. Anterior view of the activation time sequence on the whole sheep atria under control condition (CTL), heart failure (HF), HF condition with downregulation of Connexin (Cx43) expression by 30%, and 50%. The colour bar is an indication of running time from red to blue. Gray colour indicates inactivated region.

4. Discussion and conclusion

In this study, we modified sheep atria model from our pervious study to incorporate experimental measurements of HF-induced remodeling of ion channels, intracellular Ca^{2+} handling and intercellular coupling for investigating the consequences of heart failure on action potential characteristics at cellular level and activation time at the organ level. These findings were consistent with experimental results. At cellular level, Our simulation results showed that the downregulation of I_{CaL} , I_{Ks} , I_{to} currents and the upregulation of the I_{K1} and I_{NaCa} currents caused significant shortening of the action potential duration APD. This is consistent with findings from Clarke *et al* [8]. To identify the primary factor that produce the reduction of APD_{90} , we applied the inclusive and exclusive methods [9] for more detailed analysis. It has been found that the downregulation of I_{CaL} has the most influence on the shortening of APD in sheep atrial myocytes as shown in figure 3. Furthermore, the AP restitution curve in HF condition was flattened. It was shown APD was shortened across all BCLs in HF condition compared to CTL condition, with least rate adaptation in HF condition as there was a decrease in the maximal slope of APDR in HF condition. The loss of rate adaptation of atrial excitation at the cellular level may facilitate high frequency re-entrant circuits at 3D simulation results [11].

Our 3D simulation results showed that the activation time in HF condition was decreased despite of the reduction of the conduction velocity (data are not shown here). However, HF-induced remodelling with a downregulation Cx43 expression by 30%, activation time was prolonged by 176%. Furthermore, with a downregulation of Cx43 expression by 50%, there was a 168% increase in the activation time, but with inactivated regions in the LA and the RA. These results emphasis the changes in gap junctions may contribute to the development pro-arrhythmic effects in diseased heart.

In conclusion, an investigation into the effects of HF-induced ionic channel remodelling and Ca^{2+} handling on electrophysiological function of sheep atrial cells and tissue has revealed shortened atrial APD and prolonged activation time as potential mechanisms for the pro-arrhythmic of HF in the sheep atria.

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