

Computational Investigation of Pro-arrhythmogenesis of Heart Failure Induced Electrical Remodelling in Ventricles

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Abstract

Heart failure (HF) is one of the most common cardiac diseases that are associated with increased susceptibility of ventricular arrhythmia causing morbidity and mortality. Previous studies have found that HF causes a series of electrical and structural remodeling in the heart. The aim of this study was to determine the predominant factor of HF-induced remodeling responsible for ventricular arrhythmias.

We developed a new family of cellular electrical models of canine ventricular and Purkinje fiber (PF) myocytes in control and HF condition based on experimental data. These models were validated by reproducing experimentally observed AP prolongation in HF condition. Single cell models were then incorporated into a 3D anatomical model with detailed electrical heterogeneity and structural anisotropy, as well as PF network. Re-entrant excitation waves were initiated using the phase distribution method. Role of each individual HF-induced electrical and structural remodeling on lifespan of re-entry was investigated.

Among HF-induced remodeling, the reduction of intercellular conductivity plays an important role in sustaining ventricular arrhythmia. The ion channel remodeling though prolongs APD leading to increased vulnerability, it however reduces sustainability of re-entry.

1. Introduction

According to the reports, there are estimated to be 14.9 million patients across the EU [1] and 5.7 million in the US living with HF [2]. 25% of HF patients die within one year of diagnosis [3] and 50% die within five years [4]. Sudden death normally caused by cardiac arrhythmias accounts for up to 50% of deaths among patients with HF.

Previous studies have found that HF causes a series of electrical and structural remodelling in the heart, which may be responsible for arrhythmogenesis. Firstly, action potential duration (APD) prolongation is the most commonly observed feature in animal HF models.

Secondly, connexin43, which reflects intercellular electrical coupling, can be reduced by up to 50% in HF conditions. Thirdly, in the case of HF induced by dilated cardiomyopathy (DCM), the ventricle is dilated and has a thinner wall thickness and an enlarged chamber volume.

In this study, we developed a biophysically detailed 3D model of canine ventricles. Using the model, we investigated the pro-arrhythmic effects of HF-induced remodelling. The role of each individual HF-induced electrical and structural remodeling on the lifespan of re-entrant excitation waves is investigated.

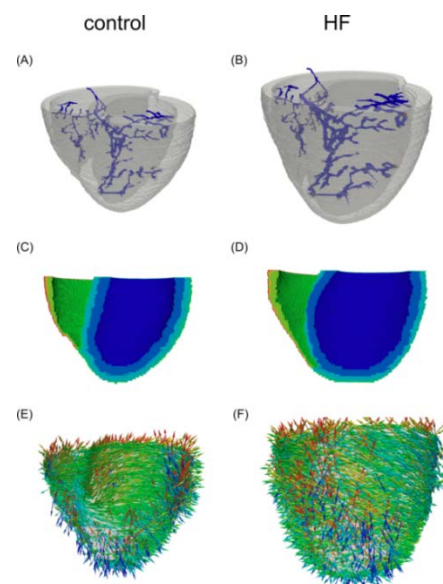


Figure 1. Anatomical geometries of the normal and the failing ventricles. A-B: Incorporation of the His-Purkinje system into the ventricles. C-D: Segmentation of the ventricular wall. E-F: Map of fiber orientations.

2. Methods

2.1. Single cell simulations

In order to determine the predominant factor of the HF-induced remodelling that is responsible for ventricular arrhythmias, we developed two families of canine single

cell models: one is for canine ventricular cells, which was developed by modifying the Benson et al. [5] models. These single cell models take into account of the transmural heterogeneity of the ventricle wall, forming three different ventricular cell types, i.e., the endocardium, the mid-myocardium and the epicardium cell. The other is the canine Purkinje Fibre cell model which was developed by modifying the Aslanidi et al. [6] model.

HF-induced ionic remodelling were simulated based on comprehensive experimental data. These modifications include the update of the original Benson et al. [5] and Aslanidi et al. [6] models as well as incorporation of the HF-induced ionic channel remodelling on I_{Na} , I_{K1} , I_{to1} , I_{Kr} , I_{Ks} , I_{CaL} , I_{CaT} , $[Ca^{2+}]_i$, I_{NaK} and Na^+-Ca^{2+} exchange current (NCX).

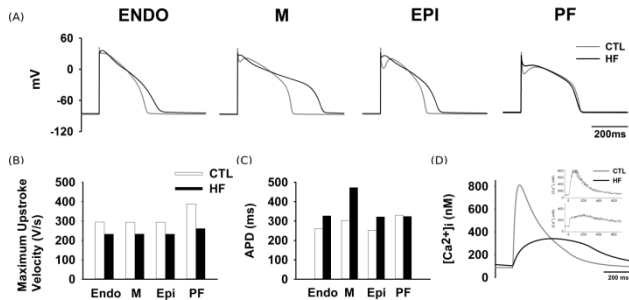


Figure 2. Time courses of action potentials (A), maximum upstroke velocity (B), APD (C) and intracellular calcium with experimental data [7] shown in insets (D).

2.2. Anatomical geometries manipulation

Two anatomical geometries were implemented which were downloaded from the CardioVascular Research Grid (CVRG): one for normal canine ventricles and the other for failing canine ventricles that were reconstructed based on the DT-MRI data [7–9]. Both ventricles were then interpolated and segmented into the endocardium, the mid-myocardium and the epicardium with a constitutional portion of 60%, 30% and 10% respectively [11]. The His-Purkinje network created by Panfilov [12] was rescaled and incorporated into the ventricles.

2.3. 3D electrophysiological simulations

Action potential propagation is described using the monodomain equation in this study:

$$\frac{\partial V_m}{\partial t} = \nabla \cdot \mathbf{D}(\nabla V_m) - \frac{I_{ion}}{C_m}$$

where V_m is the membrane potential, ∇ is the 3D spatial Laplacian defined within the tissue, C_m is the cell

capacitance per unit surface area, I_{ion} is the sum of all transmembrane ionic currents and \mathbf{D} is the tensor of diffusion coefficient given by:

$$\mathbf{D} = fD_{\parallel}f^T + sD_{\perp 1}s^T + nD_{\perp 2}n^T$$

where f , s and n represent the vectors in the direction along fibre, in the direction perpendicular to fibre in sheet, and in the direction perpendicular to sheet respectively. D_{\parallel} , $D_{\perp 1}$ and $D_{\perp 2}$ represent the diffusion coefficients in these directions. The diffusion coefficients were determined based on experimental data [13] and resulted in 40% reduction of the electrical conduction velocity in the HF condition.

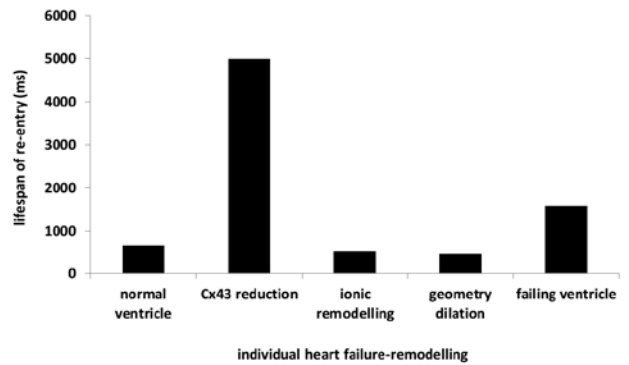


Figure 3. Bar chart of the lifespan of re-entry in the normal ventricle, the ventricle with Cx43 remodeling, the ventricle with ion channel remodeling, the ventricle with geometry remodeling and the failing ventricle.

3. Results

3.1. Single cell simulations

In the HF condition, the simulated APs present a similar morphology compared to the CTL condition. However, the characteristics of the APs are altered (Figure 2). The overshoot (OS) and the AP amplitude (APA) are dramatically decreased, along with reduction of the maximum upstroke velocity in the ENDO (by 21.2%), M (by 20.9%) and EPI (by 20.9%), and followed by a less prominent phase 1 repolarisation. Most importantly, APDs are significantly prolonged in the ENDO (by 25.6%), M (by 55.9%) and EPI (by 27.1%). On the other hand, simulation results show a slight shortened APD in PF cells, with increased maximum upstroke velocity under the HF condition.

In all ventricular and the Purkinje fiber cells, the modifications result in a dramatic reduction in the systole $[Ca^{2+}]_i$ and an increase in the $[Ca^{2+}]_i$ diastole concentration in the HF condition.

These simulated results are in consistence with experimental observations [11, 13-14].

3.2. Individual role of heart failure-induced remodeling on sustainability of the ventricular arrhythmias

In this section, role of each individual HF-induced electrical and structural remodeling on lifespan of re-entry is investigated. Evolution of the re-entry mapped in Figure 4 and corresponding lifespan of the re-entry is shown in Figure 3.

The initiated re-entry lasted for 620ms in control condition and 1500ms in HF condition. When the HF-reduced conductivity alone was considered, the re-entry lasted for the whole period of simulation of 5000ms, whilst either ion channel or anatomical remodeling did not alter the sustainability of re-entry compared to control

condition.

3.3. Individual role of revising each heart failure-induced remodeling on sustainability of the ventricular arrhythmias

In this section, role of individually revising HF-induced remodeling back to normal condition is investigated on lifespan of re-entry initialized by the phase distribution method (shown in Figure 5).

In the absence of intercellular conductivity or geometry remodeling, the re-entry broke up and only lasted for around 500ms in HF condition. However, in absence of ion channel remodeling, the re-entry sustained for more than 5000ms.

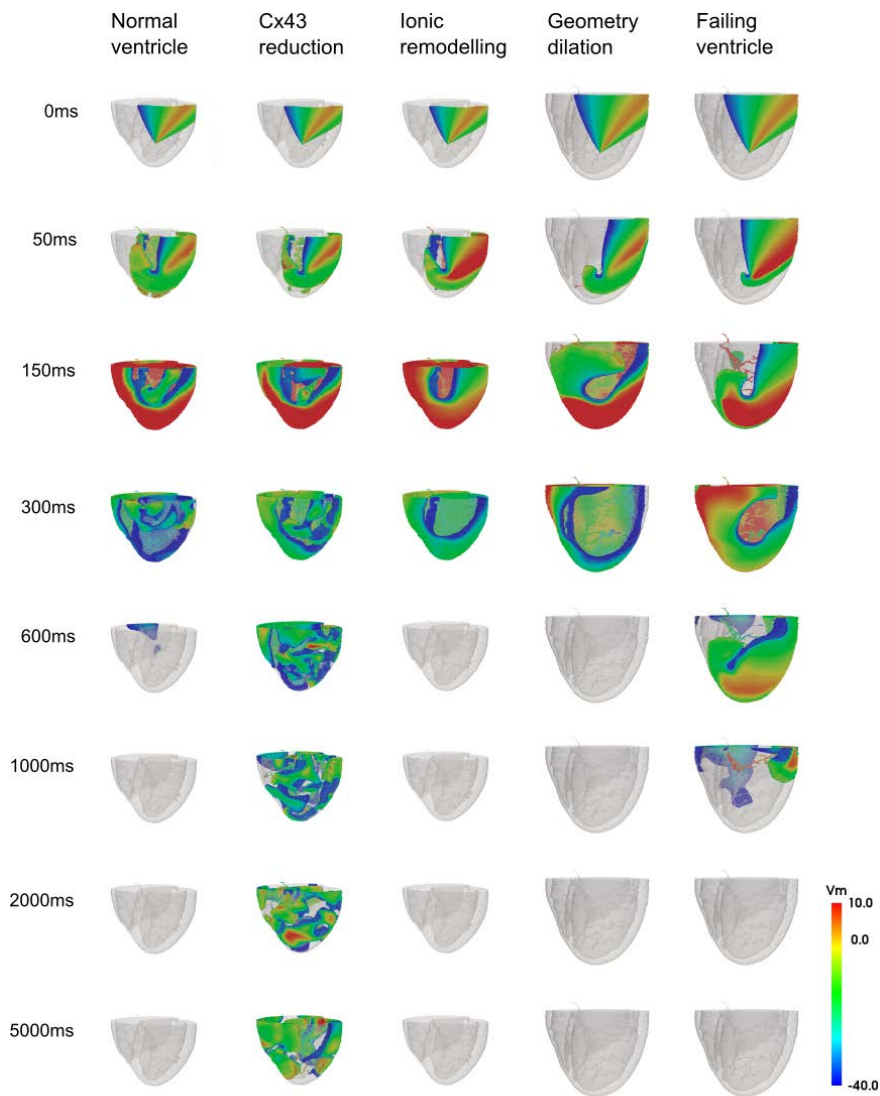


Figure 4. Snapshot of the evolution of re-entry in the normal ventricle, the ventricle with Cx43 remodeling, the ventricle with ion channel remodeling, the ventricle with geometry remodeling and the failing ventricle.

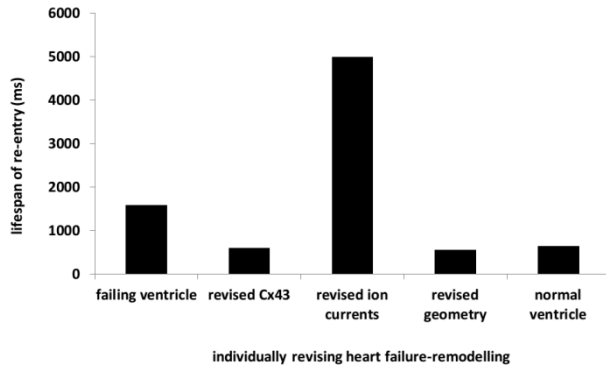


Figure 5. Bar chart of the lifespan of re-entry in the failing ventricle, the ventricle with Cx43 revised, the ventricle with ion channel revised, the ventricle with geometry revised and the normal ventricle.

4. Conclusion

Reduced intercellular coupling increases the excitable gap between the repolarising tail and depolarizing head of successive excitation waves, thus increases sustainability of the re-entry.

APD prolongation is a key factor that is responsible for genesis of ventricular arrhythmias. However, prolongation of APD increases wavelength of the electrical conduction thus reduces sustainability of re-entry.

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