Simulation Study of the Electrophysiological Mechanisms for Heart Failure Phenotype

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Abstract

Prolongation of action potential duration (APD) and altered calcium (Ca²⁺) handling in ventricular myocytes are commonly observed in heart failure (HF). This study describes a mathematical model of human HF, using a modified version of the Grandi et al. formulation for human ventricular action potential, which includes the late Na⁺ current (I_{NaL}). A sensitivity analysis is performed to investigate how the reported variability in HF remodeling might modulate the main electrophysiological (EP) characteristics in HF. Our simulations reproduced experimental observations in failing myocytes and the APDₙₐₜ was increased in 24% in HF versus normal ones, diastolic [Ca²⁺], was slightly increased, whereas peak systolic [Ca²⁺], was reduced to 41% of its normal value. From the sensitivity analysis it could be extracted that APD is particularly sensitive to I_{NaL} and I_{NaK}. The most impactful parameters on Ca²⁺ handling are the SERCA function, I_{NaL}, I_{NaK}, I_{leak}, I_{Ca,h} and I_{NCX}.

1. Introduction

Heart failure (HF) is a clinical syndrome caused by the inability of the heart to supply blood to the tissues, and has a high variability in its etiology. The most frequent causes for HF failure are myocardial infarction, pressure overload, volume overload, viral myocarditis, toxic cardiomyopathy and mutations in genes encoding for sarcomeric or cytoskeletal proteins.

Abnormalities of atrial and ventricular electrophysiology in diseased human hearts have been recognized for more than four decades. Remodeling of ventricular myocyte electrophysiology in both human and animal models of HF is well described. Prolongation of the action potential (AP) is a hallmark of cells and tissues isolated from failing hearts regardless of the etiology, and has been observed in isolated myocytes and intact ventricular preparations (1-3). The AP prolongation is heterogeneous, resulting in exaggeration of the physiological inhomogeneity of electrical properties in the failing heart.

In the setting of HF, altered calcium (Ca²⁺) homeostasis underlies abnormalities in excitation-contraction coupling (4,5). These changes include reduced Ca²⁺ transient amplitude, increased Ca²⁺ transient duration, prolonged Ca²⁺ transient decay time, as well as reduced sarcoplasmic reticulum (SR) Ca²⁺ load.

Furthermore, in myocytes from failing hearts intracellular sodium concentration ([Na⁺]), and Ca²⁺ handling are closely linked; [Na⁺], is increased in failing ventricular myocytes and a prominent increase of the late Na⁺ current (I_{NaL}) has been documented, which has been proposed as a therapeutic target (6). The increase of I_{NaL} contributes to cell Ca²⁺ accumulation in HF. Abnormal cell Ca²⁺ accumulation, worsens both contractility (via diastolic function) and rhythm (via spontaneous Ca²⁺ releases triggered delayed afterdepolarizations) (7).

The main goal of this study is to build a mathematical model of human HF, using Grandi et al. model (GPB model)(8) for human ventricular AP, and perform a sensitivity analysis to investigate how the reported variability in HF remodeling might modulate the main electrophysiological (EP) characteristics in HF.

2. Methods

In this study, the AP model formulated by Grandi et al. (8) was used to simulate the electrical activity of human ventricular myocytes. This model provides a powerful tool to explore repolarization abnormalities taking place in failing hearts.

We modified the formulation of I_{NaL} proposed by Hund et al. (9) for dog ventricular cells, using Hodgkin Huxley formalism (see equations 1 to 4).

\[ I_{NaL} = \bar{g}_{NaL} \cdot m^3 \cdot h \cdot (V - E_{NaL}) \]  
\[ \alpha_{m} = \frac{0.32 \cdot (V_m + 47.13)}{1 - e^{-0.1(V_m+47.13)}} \]  
\[ \beta_m = 0.08 e^{-\frac{V_m}{27}} \]  
\[ h_{leak} = \frac{1}{1 - e^{-\frac{(V_m+90)}{6.1}}} \]
The maximum conductance \( g_{\text{NaL}} \) and the time constant of inactivation \( \tau_{\text{NaL}} \) were modified to reproduce \( I_{\text{NaL}} \) data taken from human myocytes by Maltsev et al. (10). Maltsev et al. (10) measured a \( I_{\text{NaL}} / I_{\text{NaT}} \) ratio of 0.1% approximately, using a voltage clamp protocol at room temperature. We simulated their experiments to fit \( g_{\text{NaL}} \), which yielded 0.015 mS/µF. We also included the temperature effect in ion channel dynamics, as reported experimentally by Maltsev et al. (12) for human ventricular myocyte multiplying \( \tau_{\text{NaL}} \) by a \( Q_{10} \) factor of 2.2 (11), yielding 233 ms at 37°C.

Once the formulation of \( I_{\text{NaL}} \) was introduced in GPB model, changes in the main ion channels were applied to simulate HF. In the present work, we propose specific changes in the formulation of several ionic currents of GPB model, based on experimental observations (12;13-15) and previous simulation studies (16-18), to reproduce the experimental reported changes in AP and Ca\(^{2+}\) handling in failing human myocytes.

Firstly, the current density and the time constant of inactivation of \( I_{\text{NaL}} \) were increased as described in several models of heart failure (14;19). Secondly, downregulation of potassium (K\(^+\)) currents has also been observed in animal and human models of HF, mainly, the inward rectifier potassium current \( (I_{\text{Kr}}) \) and the transient outward current \( (I_{\text{to}}) \) currents (2;20). As reported in experimental studies, the expression and function of the Na\(^+/K^-\)-ATPase are reduced in HF (3;15;21), and we reduced accordingly Na\(^+/K^-\) pump activity \( (I_{\text{NaK}}) \). The changes in intracellular and sarcoplasmic (SR) Ca\(^{2+}\) homeostasis were achieved by increasing the Na\(^+/\) Ca\(^{2+}\) exchanger \( (I_{\text{NCX}}) \) (16), and decreasing the SR Ca\(^{2+}\)-ATPase activity \( (I_{\text{SERCA}}) \). To reproduce the experimentally observed changes in Ca\(^{2+}\) sensitivity of the ryanodine receptor (23), SR leak current \( (I_{\text{leak}}) \) was increased and EC\(_{50}\)-SR (see Grandi (8) supplementary data) was reduced. Finally, to balance the Ca\(^{2+}\) extrusion through \( I_{\text{NCX}} \), the Ca\(^{2+}\)background current \( (I_{\text{cb}}) \) was changed as in (18). Likewise, the Na\(^+\)background current \( (I_{\text{nb}}) \) was reduced until cero, because \( I_{\text{NaK}} \) balances extrusion of Na\(^+\) ion.

In order to reproduce the phenotype of HF and develop the sensitivity analysis we paced the cell with a BCL of 1000 ms until the steady-state was achieved.

3. Results and discussion

Our results showed an AP duration at 90% of repolarization \( (\text{APD}_{90}) \) prolongation of 24% in HF versus normal conditions, as well as a 18% prolongation in \( \text{APD}_{50} \). However, it was observed that the slow decay of failing \( \text{APD}_{50} \) was increased in 43% under conditions of HF. Similar experimental observations taken from (2) are shown in Figure 1 panel C. Simulated and experimental \( \text{APD}_{90} \), transients under HF and normal conditions are shown in Panels C and D, respectively. Diastolic \( \text{APD}_{90} \) is slightly increased, whereas peak systolic \( \text{APD}_{50} \), is reduced to 41% of the normal value. Furthermore, our model reproduces the slowed decay of failing \( \text{APD}_{50} \), transient. In our simulation \( \tau_{\text{NaL}} \) yielded 630 ms and 380 ms in the failing and nonfailing myocyte, respectively. The slow decay simulated and experimentally recorded in (13) can be observed in Figure 1 panels C and D, respectively.

![Figure 1. Panel A: Simulated APs for myocytes from normal (dark line) and failing hearts (light line). Panel B: Experimental APs taken from Li et al. 2004 (2). Panel C: Simulated [Ca\(^{2+}\)]\(_i\) transients. Panel D: Experimental [Ca\(^{2+}\)]\(_i\) transients taken from Weber et al. (13).](image-url)
Panels B and C highlight the roles of the currents (conductances) that affect APD₉₀ and triangulation under conditions of HF. In panel B, Iₐₙ and Iₐₖ are represented. When Iₐₙ undergoes a double change with respect to the control HF two-fold increase, APD is prolonged 22% and no change at all (GPB model conditions) in this current leads to a decrease of APD₉₀ of 10% with respect to control HF conditions. In panel B, simulations show that Iₖ₁ produces the most important variation in triangulation, in agreement with Romero et al. (24) in a non pathological model.

Figure 2. Panel A: Relative sensitivities of the EP properties (1st column) to changes in ionic current properties (1st row). A gray color scale is used. White indicates maximum relative sensitivity of a particular electrophysiological property among all parameters, whereas black indicates property and parameter are independent. Panel B: Changes in APD₉₀ and Panel C: triangulation with changes in Iₐₙ, Iₐₖ, IₙCX, Iₖ₁ and Iₙcab as indicated in the legend. The x-axis indicates the simulation conditions; for “HF Conditions” the remodeling of the control HF model is considered, for “No Change” the labeled current is unchanged as it is in GPB model, for “Double Change” the indicated current undergoes a double change with respect to the change exerted in “HF conditions”.

Figure 3, panel A shows the sensitivity analysis related with the EP characteristics that might modulate the Ca²⁺ transient. These characteristics are peak systolic and diastolic [Ca²⁺] transient, [Ca²⁺] transient decay quantified as the time needed from the peak value to reach 10% of the transient amplitude (τCa decay), and the time of the reversal point for the NCX (tNCXRP). From this sensitivity analysis it could be extracted that the main features of [Ca²⁺] transient in HF (3 top rows) were mainly influenced by Iₐₙ, Iₐₖ, SERCA function, IₙCX, Iₙleak and, Iₙcab. The time to reversal point of IₙCX (medium row) is mainly regulated by IₙSERCA.

As observed in panel B, when IₙSERCA undergoes a double change with respect to the control HF 50% decrease, diastolic [Ca²⁺] level is decreased in 14% and no change at all (GPB model conditions) in this current leads to an increase of diastolic [Ca²⁺] level of 30% with respect to control HF conditions. In panel C, IₙCX modifies slightly diastolic [Ca²⁺] level but a considerable effect is produced in peak systolic [Ca²⁺]; (panel C) when IₙCX activity is unaltered as in GPB model conditions. The behavior of Iₐₖ is similar to IₙCX but this current exerts an important effect on τCa decay as well. Last but not least, Iₐₙ and Iₙcab strongly modified peak systolic [Ca²⁺].

4. Conclusions

In conclusion, this simulation study provides new insights into the ionic basis of the EP changes occurring during HF. The sensitivity analysis is a useful tool to improve the understanding of the HF phenotype observed in experimental studies.

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