Simulation Study of the Electrophysiological Mechanisms for Heart Failure Phenotype

K Cardona[1], JF Gómez[1], JM Ferrero[1], J Saiz[1], S Rajamani[2], L Belardinelli[2], B Trénor[1]

[1]I3BH, Universitat Politècnica de València, Valencia, Spain
[2]Department of Biology in Gilead Sciences, Palo Alto, CA, USA

Abstract

Prolongation of action potential duration (APD) and altered calcium (Ca^{2+}) 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 APD_{90} was increased in 24% in HF versus normal ones, diastolic $[Ca^{2+}]_i$ was slightly increased, whereas peak systolic $[Ca^{2+}]_i$ 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 Ca^{2+} handling are the SERCA function, I_{NaL}, I_{NaK}, I_{leak}, $I_{Ca,b}$ 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 exageration of the physiological inhomogeneity of electrical properties in the failing heart.

In the setting of HF, altered calcium (Ca^{2+}) homeostasis underlies abnormalities in excitation-contraction coupling (4;5). These changes include reduced Ca^{2+} transient amplitude, increased Ca^{2+} transient duration, prolonged Ca^{2+} transient decay time, as well as reduced sarcoplasmic reticulum (SR) Ca^{2+} load.

Furthermore, in myocytes from failing hearts intracellular sodium concentration ($[Na^+]_i$) and Ca^{2+} handling are closely linked; $[Na^+]_i$ 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 Ca^{2+} accumulation in HF. Abnormal cell Ca^{2+} accumulation, worsens both contractility (via diastolic function) and rhythm (via spontaneous Ca^{2+} 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).

$$I_{NaL} = \bar{g}_{NaL} \cdot m_L^3 \cdot h_L \cdot (V - E_{NaL}) \quad (1)$$

$$\alpha_{m,L} = \frac{0.32 \cdot (V_m + 47.13)}{1 - e^{(-0.1 \cdot (V_m + 47.13))}} \quad (2)$$

$$\beta_{m,L} = 0.08 e^{\left(-V_m / 11\right)} \quad (3)$$

$$h_{L,\infty} = \frac{1}{1 - e^{\left((V_m + 91) / 6.1\right)}} \quad (4)$$

The maximum conductance (g_{NaL}) and the time constant of inactivation (τ_{hL}) were modified to reproduce I_{NaL} data taken from human myocytes by Maltsev et al. (10). Maltsev et al. (10) measured a I_{NaL} /I_{NaT} ratio of 0.1% approximately, using a voltage clamp protocol at room temperature. We simulated their experiments to fit g_{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 τ_{hL} by a Q_{10} factor of 2.2 (11), yielding 233 ms at 37ºC.

Once the formulation of I_{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 (1;2;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_{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_{K1}) and the transient outward current (I_{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_{NaK}). The changes in intracellular and sarcoplasmic (SR) Ca^{2+} homeostasis were achieved by increasing the Na^+/ Ca^{2+} exchanger (I_{NCX}) (16), and decreasing the SR Ca^{2+}-ATPase activity (22) (J_{SERCA}). To reproduce the experimentally observed changes in Ca^{2+} sensitivity of the ryanodine receptor (23), SR leak current (I_{leak}) was increased and EC_{50}SR (see Grandi (8) supplementary data) was reduced. Finally, to balance the Ca^{2+} extrusion through I_{NCX}, the Ca^{2+} background current (I_{Cab}) was changed as in (18). Likewise, the Na^+ background current (I_{Nab}) was reduced until cero, because I_{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 (APD_{90}) prolongation of 24% in HF versus normal conditions, as well as a 18% prolongation in APD_{50}, so that triangulation (APD_{90}-APD_{50}) was increased in 43% under conditions of HF. Similar experimental observations taken from (2) are shown in Figure 1 panel B. Simulated and experimental $[Ca^{2+}]_i$ transients under HF and normal conditions are shown in Panels C and D, respectively. Diastolic $[Ca^{2+}]_i$ is slightly increased, whereas peak systolic $[Ca^{2+}]_i$ is reduced to 41% of the normal value. Furthermore, our model reproduces the slowed decay of failing $[Ca^{2+}]_i$ transient. In our simulations τ_{Ca} 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.

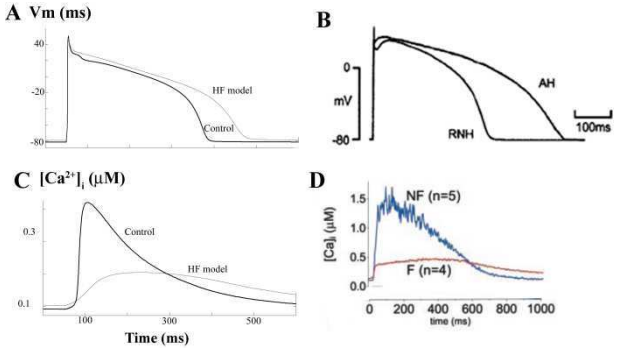

Figure 1. Panel A: Simulated APs for myocytes from normal (dark line) and failing hearts (light line). Panel B: experimental APs taken from Li et al. 2004 (2). Panel C: Simulated $[Ca^{2+}]_i$ transients. Panel D: Experimental $[Ca^{2+}]_i$ transients taken from Weber et al. (13).

To further understand the ionic mechanisms leading to HF phenotype, we performed a sensitivity analysis of the proposed HF model. This study provides understanding of how the reported variability in HF remodeling might modulate the main EP characteristics in HF. The properties of the ionic currents considered in the sensitivity study were the maximal conductances and some time constants of the main transmembrane ionic currents, namely, the maximal conductance of the I_{NaL}, the inactivation gate time constant τ_{hL}, the maximal conductance of some of the currents involved in calcium dynamics (I_{Cab}, I_{leak}, J_{SERCA}), the maximal conductance of I_{K1} and I_{to}, I_{NaK}, and the maximal activity of I_{NCX}.

The parameters corresponding to the different properties of the ionic currents were varied from their remodeled value in the basic HF model to their normal value in the GPB or to a double change with respect to the remodeled value. The indexes of percentage of change and sensitivities were calculated as in Romero et al. (24).

To summarize the sensitivity of the considered EP characteristics (1st column) during HF to the altered ionic parameters (1st row), Figure 2 panel A indicates the relative sensitivity normalized to the maximum sensitivity for that particular characteristic. The positive and negative signs indicate whether the change of the ionic current and the HF EP characteristic follow the same or inverse tendency, respectively. It can be observed that APD_{90} is particularly sensitive to the maximum conductance of I_{NaK} and triangulation (APD_{90}-APD_{50}) however, seems more dependent on I_{K1}.

Panels B and C highlight the roles of the currents (conductances) that affect APD_{90} and triangulation under conditions of HF. In panel B, I_{NaL} and I_{NaK} are represented. When I_{NaL} 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 APD_{90} of 10% with respect to control HF conditions. In panel B, simulations show that I_{K1} produces the most important variation in triangulation, in agreement with Romero et al. (24) in a non pathological model.

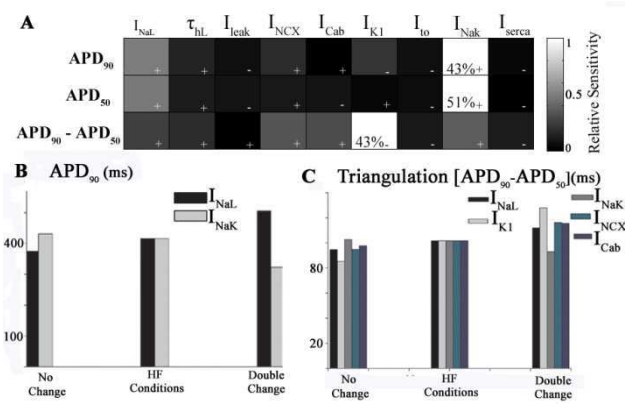

Figure 2. Panel A: Relative sensitivities of the EP properties (1st column) to changes in ionic current properties (1st row). A gray color scale is used. White indicates maximum relative sensitivity of a particular electrophysiological property among all parameters, whereas black indicates property and parameter are independent. Panel B: Changes in APD_{90} and Panel C: triangulation with changes in I_{NaL}, I_{NaK}, I_{NCX}, I_{K1} and I_{Cab}, 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 Ca^{2+} transient. These characteristics are peak systolic and diastolic $[Ca^{2+}]_i$ transient, $[Ca^{2+}]_i$ transient decay quantified as the time needed from the peak value to reach 10% of the transient amplitude (τ_{Ca} decay), and the time of the reversal point for the NCX (t_{NCXRP}). From this sensitivity analysis it could be extracted that the main features of $[Ca^{2+}]_i$ transient in HF (3 top rows) were mainly influenced by I_{NaL}, I_{NaK}, SERCA function, I_{NCX}, I_{leak}, and, I_{Cab}. The time to reversal point of I_{NCX} (medium row) is mainly regulated by I_{SERCA}

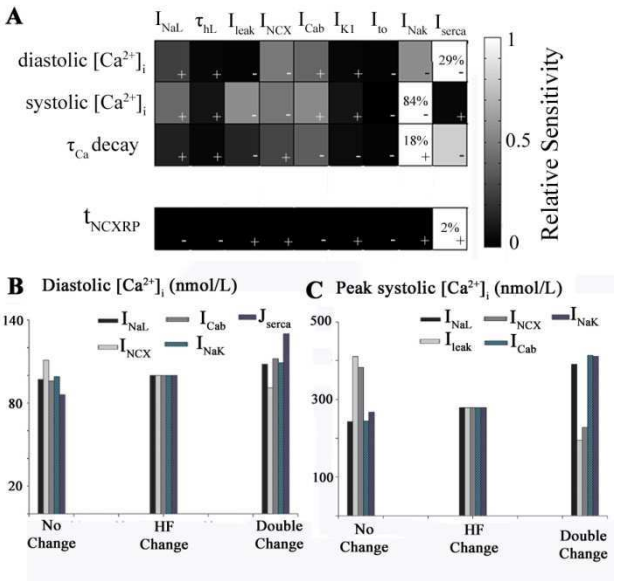

Figure 3. Panel A: Relative sensitivities of the EP properties (1st column) to changes in ionic current properties (1st row). Panels B and C: Changes in diastolic $[Ca^{2+}]_i$ and peak systolic $[Ca^{2+}]_i$, respectively, with changes in the most influent ionic properties, as indicated in the legend.

As observed in panel B, when I_{SERCA} undergoes a double change with respect to the control HF 50% decrease, diastolic $[Ca^{2+}]_i$ level is decreased in 14% and no change at all (GPB model conditions) in this current leads to an increase of diastolic $[Ca^{2+}]_i$ level of 30% with respect to control HF conditions. In panel C, I_{NCX} modifies slightly diastolic $[Ca^{2+}]_i$ level but a considerable effect is produced in peak systolic $[Ca^{2+}]_i$ (panel C) when I_{NCX} activity is unaltered as in GPB model conditions. The behavior of I_{NaK} is similar to I_{NCX} but this current exerts an important effect on τ_{Ca} decay as well. Last but not least, I_{NaL} and I_{Cab} strongly modified peak systolic $[Ca^{2+}]_i$.

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.

Acknowledgements

This work was partially supported by the European Commission preDiCT grant (DG-INFSO-224381), by the Plan Nacional de Investigación Científica, Desarrollo e

Innovación Tecnológica del Ministerio de Ciencia e Innovación of Spain (TEC2008-02090), by the Programa de Apoyo a la Investigación y Desarrollo (PAID-06-09-2843) de la Universidad Politécnica de Valencia, and by the Dirección General de Política Científica de la Generalitat Valenciana (GV/2010/078).

References

[1] Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation 1992 Mar;85(3):1046-55.

[2] Li GR, Lau CP, Leung TK, Nattel S. Ionic current abnormalities associated with prolonged action potentials in cardiomyocytes from diseased human right ventricles. Heart Rhythm 2004 Oct;1(4):460-8.

[3] Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004 Oct 15;95(8):754-63.

[4] del MF, Johnson CM, Stepanek AC, Doye AA, Gwathmey JK. Defects in calcium control. J Card Fail 2002 Dec;8(6 Suppl):S421-S431.

[5] Hasenfuss G, Maier LS, Hermann HP, Luers C, Hunlich M, Zeitz O, et al. Influence of pyruvate on contractile performance and Ca(2+) cycling in isolated failing human myocardium. Circulation 2002 Jan 15;105(2):194-9.

[6] Undrovinas NA, Maltsev VA, Belardinelli L, Sabbah HN, Undrovinas A. Late sodium current contributes to diastolic cell Ca2+ accumulation in chronic heart failure. J Physiol Sci 2010 Jul;60(4):245-57.

[7] Pogwizd SM, Schlotthauer K, Li L, Yuan W, Bers DM. Arrhythmogenesis and contractile dysfunction in heart failure: Roles of sodium-calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. Circ Res 2001 Jun 8;88(11):1159-67.

[8] Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. J Mol Cell Cardiol 2010 Jan;48(1):112-21.

[9] Hund TJ, Rudy Y. Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. Circulation 2004 Nov 16;110(20):3168-74.

[10] Maltsev VA, Undrovinas AI. A multi-modal composition of the late Na+ current in human ventricular cardiomyocytes. Cardiovasc Res 2006 Jan;69(1):116-27.

[11] Nagatomo T, Fan Z, Ye B, Tonkovich GS, January CT, Kyle JW, et al. Temperature dependence of early and late currents in human cardiac wild-type and long Q-T DeltaKPQ Na+ channels. Am J Physiol 1998 Dec;275(6 Pt 2):H2016-H2024.

Address for correspondence.

Name: Karen Cardona
E-mail: kcardona@gbio.i3bh.es

[12] Maltsev VA, Sabbah HN, Higgins RS, Silverman N, Lesch M, Undrovinas AI. Novel, ultraslow inactivating sodium current in human ventricular cardiomyocytes. Circulation 1998 Dec 8;98(23):2545-52.

[13] Weber CR, Piacentino V, III, Houser SR, Bers DM. Dynamic regulation of sodium/calcium exchange function in human heart failure. Circulation 2003 Nov 4;108(18):2224-9.

[14] Maltsev VA, Silverman N, Sabbah HN, Undrovinas AI. Chronic heart failure slows late sodium current in human and canine ventricular myocytes: implications for repolarization variability. Eur J Heart Fail 2007 Mar;9(3):219-27.

[15] Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 1999 May;42(2):270-83.

[16] Winslow RL, Rice J, Jafri S, Marban E, O'Rourke B. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, II: model studies. Circ Res 1999 Mar 19;84(5):571-86.

[17] Zhang Y, Shou G, Xia L. Simulation study of transmural cellular electrical properties in failed human heart. Conf Proc IEEE Eng Med Biol Soc 2005;1:337-40.

[18] Priebe L, Beuckelmann DJ. Simulation study of cellular electric properties in heart failure. Circ Res 1998 Jun 15;82(11):1206-23.

[19] Undrovinas AI, Maltsev VA, Sabbah HN. Repolarization abnormalities in cardiomyocytes of dogs with chronic heart failure: role of sustained inward current. Cell Mol Life Sci 1999 Mar;55(3):494-505.

[20] Li GR, Lau CP, Ducharme A, Tardif JC, Nattel S. Transmural action potential and ionic current remodeling in ventricles of failing canine hearts. Am J Physiol Heart Circ Physiol 2002 Sep;283(3):H1031-H1041.

[21] Bundgaard H, Kjeldsen K. Human myocardial Na,K-ATPase concentration in heart failure. Mol Cell Biochem 1996 Oct;163-164:277-83.

[22] Piacentino V, III, Weber CR, Chen X, Weisser-Thomas J, Margulies KB, Bers DM, et al. Cellular basis of abnormal calcium transients of failing human ventricular myocytes. Circ Res 2003 Apr 4;92(6):651-8.

[23] Antoons G, Oros A, Bito V, Sipido KR, Vos MA. Cellular basis for triggered ventricular arrhythmias that occur in the setting of compensated hypertrophy and heart failure: considerations for diagnosis and treatment. J Electrocardiol 2007 Nov;40(6 Suppl):S8-14.

[24] Romero L, Pueyo E, Fink M, Rodriguez B. Impact of ionic current variability on human ventricular cellular electrophysiology. Am J Physiol Heart Circ Physiol 2009 Jul 31.