

# Simulation Study of the Electrophysiological Mechanisms for Heart Failure Phenotype

K Cardona, JF Gomez, JM Ferrero\*, J Saiz, S Rajamani, L Belardinelli and B Trenor

Prolongation of action potential duration (APD) and altered calcium ( $\text{Ca}^{2+}$ ) handling in ventricular myocytes are commonly observed in heart failure (HF). Abnormalities in repolarization can predispose to dispersion of repolarization, leading to nonexcitable gap reentry. Moreover action potential (AP) prolongation also favors the development of early afterdepolarizations (EADs), which can induce triggered arrhythmias. So, patients with congestive HF are prone to develop complex ventricular tachyarrhythmias and some die suddenly.

The main goal of this study is to build a mathematical model of human HF, using Grandi et al. model for human ventricular AP, and perform a sensitivity analysis to investigate how the reported variability in HF remodeling might modulate the main electrophysiological (EP) characteristic in HF. To reproduce the experimentally observed HF EP phenotype, the late  $\text{Na}^+$  current ( $\text{I}_{\text{NaL}}$ ) was included,  $\text{Ca}^{2+}$  handling was modified and the transient outward  $\text{K}^+$  current ( $\text{I}_{\text{to}}$ ) and the inward rectifier  $\text{K}^+$  current ( $\text{I}_{\text{K1}}$ ) were reduced.

Our simulations showed that the  $\text{APD}_{90}$  was increased in 24% in failing myocytes versus normal ones, diastolic  $[\text{Ca}^{2+}]_i$  was slightly increased, whereas peak systolic  $[\text{Ca}^{2+}]_i$  was reduced to 41% of its normal value. These values are within the physiological ranges observed in HF. From the sensitivity analysis it could be extracted that APD is particularly sensitive to  $\text{I}_{\text{NaL}}$  and  $\text{I}_{\text{NaK}}$ . Furthermore,  $\text{I}_{\text{K1}}$ ,  $\text{I}_{\text{NCX}}$  and  $\text{I}_{\text{NaK}}$  have an important effect on AP shape. The most impactful parameters on  $\text{Ca}^{2+}$  handling are the SERCA function,  $\text{I}_{\text{NaL}}$ ,  $\text{I}_{\text{NaK}}$ ,  $\text{I}_{\text{leak}}$ ,  $\text{I}_{\text{Ca,b}}$  and  $\text{I}_{\text{NCX}}$ , which condition diastolic  $[\text{Ca}^{2+}]_i$  and systolic  $[\text{Ca}^{2+}]_i$  decay. Finally, peak systolic  $[\text{Ca}^{2+}]_i$  was mainly influenced by  $\text{I}_{\text{NaL}}$ ,  $\text{I}_{\text{NaK}}$ ,  $\text{I}_{\text{leak}}$ ,  $\text{I}_{\text{Ca,b}}$  and  $\text{I}_{\text{NCX}}$ .

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