

# Mechano-Electric Feedback Effects in a Ventricular Myocyte Model Subjected to Dynamic Changes in Mechanical Load

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The effect of mechano-electric coupling on myocytes action potential (AP) has been largely studied considering constant stretches. This study examined the role of mechano-electric feedback (MEF) in a more physiologic setting, in which sarcomere length varies following cardiac work loops (WLs) and affects the stretch-modulated currents ( $I_{sm}$ ) in real time. A model of mammalian myocyte contraction was incorporated into a complete mathematical description of AP, ionic currents and  $Ca^{2+}$  transient of the guinea pig ventricular cell. In addition, the effect of myocytes strain on stretch-modulated channels was implemented by integrating a modified version of the MEF model proposed by Gurev et al. This new coupled model simulates the four phases of the cardiac cycle as a sequence of isometric and isotonic contractions/relaxations. Intracellular  $Ca^{2+}$  controls contraction and half sarcomere length ( $L_m$ ) is used as input to MEF, that in turn affects the AP through  $I_{sm}$ . Simulations were conducted to investigate the role of MEF in modulating electrical activity during WL for different length preloads and force afterloads. Results were in agreement with experimental WL and MEF studies. Moreover, considering varying resting half sarcomere length ( $L_{mo}$ ), our simulations showed that under basal conditions ( $L_{mo}=0.855$  micrometers),  $I_{sm}$  activation during the WL has a limited impact on AP. However a progressive increase in the strain sensed by  $I_{sm}$ , induced by decreasing  $L_{mo}$ , results in DADs during WL phase 4 ( $L_{mo}=0.75$  micrometers), ectopic activations ( $L_{mo}=0.70$  micrometers) and triggered activity ( $L_{mo}=0.68$  micrometers). To our knowledge, our model is the first to integrate cardiac cell electrophysiology and mechanics with physiological details such as ionic membrane currents, intracellular  $Ca^{2+}$  handling, cross-bridge formation and WL implementation. On the base of simulation results, it can be asserted that the generation of arrhythmogenic phenomena could arise when the strength of the MEF is increased, as under heavy myocardium stress conditions.