Redox Modification of the Arrhythmic Substrate in Heart Failure

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Recent evidence indicates that alterations in reduction-oxidation (redox) potential of the cytoplasm, sarcoplasmic reticulum, and mitochondria of the heart may be key factors involved in progression of cardiac hypertrophy and failure. Redox biology encompasses redox couples central to energy metabolism (e.g. $NADH/NAD_+$, $FADH_2/FAD$, etc), biosynthesis, and antioxidant pathways (e.g. $NADPH/NADP_+$, GSH/GSSG, etc). In heart failure (HF), there is evidence that oxidative stress may contribute to impaired function. Moreover, a large number of ion channels, transporters, and signaling pathways have been shown to be modulated either directly by reactive oxygen species (ROS), or by changes in the thiol status or redox carrier concentration (e.g. NAD_+, $NADP_+$). Some, or many of these targets could contribute to an enhanced susceptibility of the failing heart to arrhythmia and sudden cardiac death (SCD). A comprehensive view of how shifts in metabolism and redox balance influence the electrophysiological substrate requires a systems biology approach to the problem, involving deconstruction of how individual ion channels, transporters and signaling pathways are affected by redox modulators, and how the performance of the integrated system (from metabolic pathways to whole-heart) is changed. Accordingly, our objective is to examine how enhanced oxidative stress alters electrophysiology, calcium (Ca) regulatory processes, and arrhythmia susceptibility in HF.

Our approach involves close coupling between experiments, theory and computation. In previous work, we have developed highly integrative models of the cardiac myocyte describing sarcolemmal ion channel and membrane transporter function, as well as mitochondrial generation of ATP, it's control by intracellular Ca and sodium levels, and production and release of ROS from mitochondria. Very importantly, we have developed a model of Ca-induced Ca-release that captures a fundamentally important property of the cardiac myocyte – tightly controlled high gain and graded release of Ca from the sarcoplasmic reticulum. To do this we have developed mathematical approaches by which stochastic, molecular models of Ca release formulated at nanometer length scales and nsec time scales in structures known as dyads may be reduced to low dimensional systems of ordinary differential equations and incorporated into whole cell models. We have developed computationally efficient methods for using these ionic models to simulate electrical conduction in the cardiac ventricles. These models enable us to investigate the link between ROS production and release by mitochondria and increased risk of arrhythmia in heart failure.

Numerous types of experimental data are used to formulate and validate these multi-scale models. Patch-clamp and whole-cell electrophysiological experiments provide information on the ways in which ROS modulates ion channel function and Ca-induced Ca-release. Fluorescence imaging data from single cells and the epicardial surface of whole hearts provides information on cellular and regional metabolic function (mitochondrial membrane potential, Ca levels, NADH concentration, etc). We have also developed an automated imaging and microtome system for high-resolution ($\sim$ 300 nm) anatomic reconstruction of whole small mammalian hearts. The microscope is configured with an automated moveable stage and microtome to perform optical sectioning followed by sequential tissue slicing of large tissue samples. Image processing and reconstruction techniques are used to stack and align successive images to obtain volume reconstructions of whole hearts. This approach enables us to visualize local regions of depolarized mitochondria that can render cells electrically inactive, creating functional non-conducting dead zones that may be a substrate for reentry. These data-driven multi-scale modeling approaches are enabling us to investigate the fundamental mechanisms of ROS-induced arrhythmia in the setting of heart failure.