Redox Modification of the Arrhythmic Substrate in Heart Failure

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Recent evidence indicates that alterations in the reduction-oxidation (redox) potential of the cytoplasm, endo/sarcoplasmic reticulum, and the mitochondria of the heart may be key factors involved in the 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.) and communication among these moiety-conserved cycles is emerging as an important paradigm. In heart failure (HF), there is evidence that oxidative stress may contribute to impaired function, and this may arise as a consequence of altered ion homeostasis, energetic deficiencies, and post-translational modification of protein targets. 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). In order to obtain a comprehensive view of how shifts in metabolism and redox balance influence the cardiac electrophysiological substrate, we are taking a systems biology approach that involves deconstruction of how individual ion channels, transporters, and signaling pathways are affected by redox modulators, and how the performance of the integrated system is changed. *Specifically, our objective is to examine how enhanced oxidative stress alters electrophysiology, calcium (Ca) regulatory processes, and arrhythmia susceptibility in HF.* In HF, elevated intracellular sodium (Na) levels lead to ROS production and release, and collapse of mitochondrial membrane potential. The resulting oxidative stress can result in regions of reduced excitability, leading to increased risk of arrhythmia and SCD. We refer to this as the "metabolic sink hypothesis". We are using a multi-scale systems biology approach, with close coupling of experiments, theory, and computation, to examine how enhanced oxidative stress alters electrophysiology, mitochondrial function, and arrhythmia susceptibility in HF from the level of cellular pathways to whole heart.

Here we present recent advances in our work toward these goals. We have developed a new model of the normal and failing ventricular myocyte incorporating excitation-contraction (EC) coupling, membrane electrophysiology, and mitochondrial function. The model has provided mechanistic insights regarding the experimentally observed causal relationship between action potential shape and timing of Ca and force transients. We have experimentally characterized the actions of redox couples and antioxidant pathways on the I_{K1} and I_{Kr} potassium currents, the L-Type Ca current, and the Na-Ca exchanger. We have developed a model of redox regulation describing mitochondrial ROS production by the electron transport chain and have experimentally characterized and modeled ROS scavenging by the glutathione and thioredoxin antioxidant systems. Results demonstrate how these two mechanisms work cooperatively to minimize ROS levels in the cell. We have developed an initial two-dimensional tissue model of how redox status effects electrical conduction. Finally, we have developed an imaging system for anatomic reconstruction of small mammalian hearts. We will present the first high spatial-resolution reconstructions (800 nm in-plane, 10 um out of plane) of whole murine hearts. This technique will enable us to capture a "snapshot" of the metabolic state of the heart and thus reconstruct, in 3D, the location and size of the putative metabolic sinks resulting from oxidative stress, and will enable quantitative modeling of how the metabolic state of the heart effects its electrical activity.