Multiscale Computational Modeling of Myocardial Energetics, Mechanics, and Whole-Body Cardiovascular Function in Heart Failure

Abstract

Heart failure is known to be associated with changes in metabolite pools, and theoretical modeling studies have revealed that these changes result in a loss in the available free energy of ATP hydrolysis. Since a variety of cellular processes in the heart depend critically on ATP, it is hypothesized that alterations in ATP hydrolysis potential could result in mechanical dysfunction at the level of the cardiac myocyte resulting in impaired contractile performance of the heart and, ultimately, heart failure. However, heart failure is almost always accompanied by tissue and organ level structural remodeling that may be a consequence or a cause of energetic failure, or may occur independently from it. Moreover, heart failure is a whole-body disease, with clinical presentation influenced by cardiac, pulmonary, renal, and neurohumoral function. To probe if and how energetic failure influences loss of cardiac mechanical function and its role the pathogenesis of heart failure, we have developed a multiscale model of heart disease spanning molecular/metabolic function to whole-body cardiovascular dynamics. The model for myocardial metabolism is constructed based on in vitro experiments informing kinetic models at the levels of individual enzymes, transporters, and purified mitochondria. Experiments are conducted on isolated cells to identify models of cross-bridge mechanics, cellular electrophysiology, and calcium dynamics. The developed cell-level model is integrated into a whole-organ model of cardiac mechanics, which is in turn integrated into a whole-body model of cardiovascular dynamics. Simulations of the model reveal the extent to which the key clinical features (e.g., systolic dysfunction, pulmonary venous congestion) emerge as consequences of metabolic dysfunction at the cellular level.

Heart Failure

Clinical presentation arises from interactions between:
- Heart
- Circulation
- Autonomic System
- Endocrine System
- Kidney

Influence of Energetics on Muscle Mechanics

Simulation of metabolite levels on sliding velocity and force development. Decreasing ATP, increasing ADP, and increasing inorganic phosphate (Pi) all cause a reduction in velocity of contraction and peak isometric force generation.

Whole-Body Consequences of Energetic Dysfunction

Simulation of influence of cardiac energetics on whole-body cardiovascular phenotype. At time = 5 min, metabolite pools in left-ventricular free wall are instantaneously depleted to mimic the end-stage heart failure metabolic state. The metabolic perturbation impairs mechanical function, causing a rapid small drop in cardiac output. Pressure is maintained by autonomic and endocrine systems. Over the long term, increases in sympathetic tone and renin/angiotensin lead to volume retention and pulmonary congestion.

References