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**ENERGETICS OF CARDIAC CELLS:  
FROM STARLING LAW TO SYSTEMS BIOENERGETICS**

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Studies of cardiac energy metabolism began almost hundred years ago with discovery of the Frank-Starling law and linear relationship between oxygen consumption and heart work. High energy demand of cardiac contraction is met by mitochondrial oxidation of fatty acids coupled to synthesis of ATP, which is used for phosphocreatine (PCr) synthesis for effective energy supply to contractile system and cell membranes. Another important discovery in the field of cardiac energetics was that of metabolic homeostasis – constant level of PCr and ATP during workload and respiration rate changes. Understanding cellular mechanisms behind these phenomena and thus regulation of energy fluxes in cardiac cells required the development of new approaches of studies of energy fluxes in living cells – Molecular System Bioenergetics. These studies revealed the connection between cell structural organization and effective regulation of cardiac energetics via phosphotransfer networks. Recent advancements of this new science show the important role of cellular cytoskeleton in regulation of mitochondrial activity. Changes in mitochondrial activity lead to pathogenic mechanisms such as increased free radical production, permeability pore opening, necrosis and apoptosis. These advancements help to better understand different mechanisms of development of heart failure and other pathologies, including cancer.

**ENERGETICS OF CARDIAC CELLS:  
FROM SYSTEMS BIOENERGETICS TO CARDIOPROTECTION**

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The heart is a strictly aerobic organ. Therefore adequate function and energy metabolism depends entirely on mitochondrial ATP synthesis. Energy metabolism of the heart is also characterized by high and highly variable oxygen demand. To face this challenge, energy supply to energy consuming sites is supported by energy transport system, namely the phosphocreatine / Creatine kinase system. Our work, conducted in collaboration with the research team of professor Valdur Saks has first focused on the implication of highly organized energy transfer networks in the control of contractile performance and relaxation of the heart. Our main conclusions emphasizes the fact that optimal intracellular compartmentation of energy transfer in cardiac cells is required to ensure appropriate energy supply to cytosolic ATPases and adequate heart function at constant intracellular ATP and PCr levels despite workload and respiration rate changes.

These concepts, developed from studies associating inputs from isolated perfused hearts, <sup>31</sup>P phosphorus Nuclear Magnetic Resonance, analysis of mitochondrial function permeabilized skinned fibers and isolated mitochondria and mathematical modeling of intracellular compartmentation of energy transfer, were then applied to the understanding of the mechanisms by which preconditioning and postconditioning protect the heart and reduce infarct size after lethal ischemia followed by reperfusion. We showed that preservation of intracellular compartmentation by these strategies is crucial for the preservation of intracellular ATP pool during ischemia, adequate PCr resynthesis upon reperfusion, improvement of recovery of heart function and decreased infarct size.