Myocardial energetics as a target for treatment of ischemic heart disease: A translational approach from patient to mitochondria

Ischemic heart disease (IHD) is the leading cause of morbidity and mortality in modern world. Its clinical representation ranges from angina pectoris and acute myocardial infarction to chronic heart failure, which is the end-point in pathological ischemia-induced cardiac remodeling. Moreover, IHD eventually becomes a systemic disease, with ischemic chronic heart failure (CHF) being also associated with skeletal muscle wasting as part of "cardiac cachexia" syndrome. Wasting of skeletal muscle is, in addition to cardiac inability to increase cardiac output during exertion, one of the main causes of extreme exercise intolerance in CHF.

There is a multitude of intracellular changes in ischemic heart including those associated with energy metabolism, ionic regulation, contractile machinery, cell death mechanisms, and mitochondrial function. In recent years, a metabolic therapy of ischemic myocardium has received a lot of attention[1,2]. It is based on pharmacological modulation of myocardial metabolism in IHD patients, whereby cardiac metabolism is shifted from fatty acid utilization towards more energetically favorable oxidation of glucose. When added to conventional therapy for IHD, metabolic therapy resulted in improvement of myocardial contractile performance and quality of life[3]. Although intracellular mechanisms of this beneficial pharmacological and genetic metabolic modulation have been studied in animal models, ***a comprehensive translational approach investigating the effects of metabolic therapy using patients' clinical assessment in combination with basic cellular research in human myocardium is almost non-existent***. Therefore, the main goal of this project is to use ***collaborative effort between clinicians and basic scientists*** to investigate the effects of metabolic therapy by trimetazidine, an antianginal drug and a partial inhibitor of fatty acid β-oxidation, on cardiac function in IHD patients and to correlate it with cellular changes in cardiac and skeletal muscle myocytes. Specifically, involvement of mitochondrial changes and the role of other energy-sensing mechanisms within the cell (such as ATP sensitive K^+ channels (KATP)) will be assessed, all of which are known to play a role in remodeling of diseased myocardium[1,4]. Furthermore, gathering of data from patients at different stages of the IHD, from ischemic hearts with preserved contractility to the failing hearts, with the purpose of identifying the crucial events in this pathological remodeling, might be used to develop novel therapeutic approaches.

Besides investigating an important clinical and scientific question, this project will enable formation of a ***strong translational research group consisting of clinicians-scientists (cardiologists and cardiac surgeons) and basic scientists (cell physiologists)***, which are all young faculty members at University of Split School of Medicine (USSM). The organizational approach that will help in realization of this interdisciplinary project will be modeled by a successful example from Norwegian University of Science and Technology, a main international partner on the project. Also, this project fits exactly to the strategy of the USSM, which promotes the collaboration of researchers with different expertise with the goal of investigating the major health issues.

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