The main objective of this project is to verify a hypothesis that iron deficiency in heart failure (HF) results in exacerbation of abnormalities of intracellular Ca^{2+} handling typical for heart failure (HF) and worsens cardiomyocyte function, leading to deterioration of the left ventricular function, exacerbating its detrimental remodeling and increasing mortality, while correction of iron deficiency will have the opposite effect in the model of post-myocardial infarction HF in the rat.

A specific aim of this project is to clarify mechanisms and nature of disturbances of iron turnover in HF as well as mechanisms of potentially beneficial correction of these disturbances.

This may contribute to preparation of more effective methods of therapy of HF patients.

In the developed countries HF is considered as 21st century epidemics. Along with ageing of society and reduced peri-infarction mortality, the number of HF patients will increase, constituting a serious burden for economy and health care systems. Despite recent advances, long term prognosis for HF patients is poor (approximately 50% of patients die within 4 years of the HF diagnosis). Search for new supplementary methods of HF therapy is thus one of the challenges of modern medicine. Correction of abnormalities of iron turnover in HF can improve prognosis of HF patients. Despite the fact that iron deficiency is found in as many as 30% of HF patients, mechanism of development of abnormalities of myocardial iron turnover and their effect on HF remains poorly understood.

In particular no data is available on the effects of iron deficiency on cardiomyocyte function and intracellular Ca^{2+} handling and on the left ventricular remodeling and function as well as mortality. On the other hand, safety of long term iron supplementation in HF needs to be considered. Excessive iron supply, in particular in the long-term, can exacerbate myocardial oxidative stress and exacerbate preexisting cardiomyocyte dysfunction. Currently there are no clear recommendations on iron supplementation in HF in relation to subpopulations with systemic iron deficiency and anemia and iron deficiency limited to myocardial tissue. Preparation of clear recommendations on iron supplementation in HF requires understanding of cellular and molecular mechanisms responsible for development of abnormalities of iron turnover in HF and their effect on the disease progression.

Thus in the proposed project we attempt to undertake investigations aimed at better understanding of the mechanism of post-myocardial infarction left ventricular remodeling. These investigations will be conducted in a rat model. We will study cardiac remodeling at the whole organ level, using echocardiography to determine left ventricular dimensions, its wall thickness and its function. Furthermore, cardiac catheterization will provide left ventricular and aortic pressures. Subsequently we will investigate remodeling at the cellular level: morphology of the myocardial contractile cells and their function through examination of potency and kinetics of their contraction as well as intracellular Ca^{2+} handling that determines cellular contractility. These are unique studies utilizing sophisticated equipment.

Furthermore we plan to investigate in detail the nature of iron turnover abnormalities after myocardial infarction through measurement iron turnover parameters in serum (iron, ferritin, soluble transferrin receptor, hepcidin concentration and transferrin saturation) as well as in myocardial tissue and cardiomyoctes (iron and ferritin, hepcidin, transferrin receptor (TfR-1)) and in the liver (iron as a marker of systemic iron stores).

We will conduct our studies in rats fed with chow containing conventional amount of iron, with reduced iron content and iron-free chow to investigate development of post-myocardial infarction HF in animals without iron deficiency, with moderate iron deficiency and with iron deficiency anemia, respectively.

Moreover, post-infarction rats will be given an iron formulation to investigate effect of such therapy on development of heart failure and to verify safety of such therapy.

Results of our project may contribute to better understanding of mechanisms of iron deficiency in HF. Furthermore they may indicate specific mechanisms of detrimental effects of iron deficiency on cardiomyocytes and if its correction improves cardiomyocyte function and whether it is safe. Thus our project has not only scientific relevance, but may also contribute to development of new prophylactic and therapeutic treatments for post-myocardial infarction HF.