

DESCRIPTION FOR THE GENERAL PUBLIC

Arterial pulmonary hypertension is a rare disease, with little knowledge regarding its etiology, and high mortality. Development of right and later on also left ventricular heart insufficiency, secondary to pulmonary hypertension, is a negative predictive factor. Clinical trials show that over the course of arterial pulmonary hypertension, opposing changes occur in both heart ventricles. Volume of the right ventricle increases, whereas the left ventricle reduces its volume. The most prominent findings are reductions in left ventricular end-diastolic volume, stroke volume, and ejection fraction. Individual pieces of data from clinical trials and those conducted on animal models also indicate decrease in left ventricle mass. Genetic and molecular processes underlying left heart ventricle remodeling over the course of pulmonary hypertension remain unknown. In particular, there is no knowledge regarding the mechanisms of left heart ventricle atrophy which was completely avoided by researchers until recently.

One of proposed mechanisms of left ventricle atrophy includes decrease in initial load of the left heart part (hemodynamic stress). Another possible mechanism of left ventricle mass loss over the course of pulmonary hypertension includes hypoxia and ischemia of the myocardium, resulting from right ventricle heart failure (metabolic stress). It is assumed that the left ventricle mass loss over the course of pulmonary hypertension results more from mass decrease and reduction in size of cardiomyocytes themselves (atrophy), than the decrease in their number (apoptosis).

The aim of our project is to find molecular mechanisms responsible for loss of left ventricular heart mass over the course of pulmonary hypertension. Particular attention will be placed on detection autophagy and ubiquitinated proteolysis pathway, which may be responsible for this process.

Our study will be conducted on 66 rats with pulmonary hypertension. The animals will be subjected to regular transthoracic echocardiographic examination and invasive measurements of blood pressure in the heart. The intensity of the autophagy and ubiquitinated proteolysis in the left ventricle will be assessed by analyzing changes in the expression of 169 genes involved in the ubiquitination and autophagy path using next generation sequencing techniques (RNA-seq) and analysis of changes in the levels of proteins characteristic for those processes.

The proposed approach is second to none, both due to its plurality and quality of used research techniques (imaging, morphological, morphometric, genomic and proteomic techniques), as well as the fact of analyzing different pathways involved in the process of cells' or its elements' death. We expect proving the role of autophagy and ubiquitination in gradual loss of left heart ventricle mass over the course of pulmonary hypertension. Learning the mechanisms of left ventricle mass loss may constitute an anchor point for new therapies in patients with pulmonary hypertension and significantly expand the knowledge regarding cooperation of various metabolic pathways in myocardium plasticity.