ABSTRACT FOR THE GENERAL PUBLIC

The aim of this project is to explore the pathophysiology of the vessel wall in the development of heart failure on the cellular level.

Heart failure (HF) is currently a leading cause of mortality worldwide, moreover, in Poland, the morbidity and mortality of HF are one of the highest in Europe. It is a complex, multifactorial disorder leading to cardiac muscle overgrowth and eventually, decreased cardiac functionality. Endothelium, the single layer of cells lining the interior surface of blood vessels, plays a crucial role in maintaining healthy vessel function. Interestingly, systemic endothelial dysfunction is observed in patients even with mild HF and is an important factor predicting poor patient outcome and increased risk of cardiac death. Endothelial dysfunction is defined as an impairment of endothelial-dependent vascular relaxation, critical for cardiovascular health. To date, the mechanisms of endothelial dysfunction development in HF are not clear. We hypothesise that alterations in cellular energy production in the vessel wall may contribute to endothelial dysfunction in HF according to recent studies conducted in other cardiovascular diseases. With the activation of the endothelial cells, cellular respiration is weakened and there is a switch to anaerobic metabolism, consequently an increase in lactate production. Lactate is no longer considered merely a by-product of metabolism; it is now known that it is also a key energy source and a crucial regulatory factor. Studies in the context of other diseases indicate lactate regulation of certain cellular mechanisms that may be involved in blood vessel function.

Lactate dehydrogenase A (LDHA) is the main enzyme responsible for lactate production. **Therefore, this study is set out to understand the role of LDHA in endothelial dysfunction development during heart failure progression** in Tgαq*44 mice, a murine model of HF. In Tgαq*44 mice, HF develops gradually and mimics human pathophysiology, therefore it is considered a reliable model for studying the mechanisms of this condition.

To assess the role of LDHA in vascular metabolism and endothelial function, different approaches to inhibition of this enzyme will be used. Then, a comprehensive analysis of the vessel wall metabolism will be carried out using advanced biochemical and functional methods. Furthermore, the endothelial function will be assessed, both in isolated blood vessels and in mice *in vivo* using a non-invasive, unique magnetic resonance imaging method. In this project, an advantage will be taken of state-of-art physiological and biochemical methodologies of endothelial profiling and metabolic analysis.

In summary, this project is one of the first investigations aiming to evaluate the link between vascular metabolism and endothelial dysfunction during the development of heart failure. This study will shed a new light on vascular pathophysiology in HF and may contribute to novel therapeutic strategies improving patient prognosis.