Heart failure is one of the most common diseases of the cardiovascular system in developing countries. The number of hospitalizations of cardiac patients is still increasing, however mortality rates have been reduced. This is due to the efficacy of the currently used pharmacology of heart failure, which is largely based on both: the inhibition of the angiotensin converting enzyme (ACE) enzyme by using its inhibitors, as well as the blocking of angiotensin II receptor (AT1R). Angiotensin II (Ang II) is the main product of ACE activity and its overproduction is considered to be a key factor enhancing fibrosis and inflammation of the myocardium. As a result, it is conducive to the impairment of not only cardiac function, but the entire cardiovascular system. Unfortunately, therapy to reduce Ang II plasma concentration reduces patient mortality and relieves the disease symptoms only in some cases (no efficacy in patients with preserved ejection fraction. In many patients, despite the initial Ang II decrease, we observed its re-growth after a certain duration of therapy in so-called "**Ang II escape".** Therefore, it seems necessary to develop a more effective therapy, and above all a better understanding of the mechanisms responsible for the adverse effects of accessively activated RAAS system (Renin-Angiotensin-Aldosterone System -especially the role of enzymes involved in the transformation of subsequent angiotensins in the production of Ang II.

The main goal of this project is to evaluate the alternative routes of Ang II synthesis in the development of peripheral endothelial dysfunction in the model of heart failure (Tgαq * 44). Tgαq * 44 mice are a unique model due to the fact that they mimic the pathophysiology of heart failure in humans at the biochemical, molecular and functional level [5,6]. This model, apart from early diastolic disorders, develops dilatility of the left ventricular dilatation typical of dilated cardiomyopathy. There are studies that confirm the development of **peripheral vascular endothelial dysfunction** parallel to heart disorders, which may be an element that connects the pathology of the heart with disorders of other organs that are observed in cardiac patients. The mechanisms that play a role in heart failure with non-ischemic etiology are still not well understood. Analysis of peripheral endothelial dysfunction, especially in terms of its mechanisms, is important because of its prognostic and therapeutic significance in cardiovascular disorders.

The first step of the project aims to characterize endothelial dysfunction and impaired NO synthesis in the mouse model of heart failure with non-ischemic etiology (Tgαq*44) based on functional and biochemical tests in peripheral vessels. The next step will be to examine the substrates used for the synthesis of Ang II regardless of the RAAS plasma system. This will determine the main source of Ang II production in peripheral vessels. The final stage will be the identification of enzymes responsible for the conversion of the above-mentioned peptides to Ang II using functional tests.

This project is a precise combination of pharmacological, analytical and biochemical techniques that will allow the study of alternative ways of Ang II production to search for new therapies for heart failure.