Popular science summary

Right ventricular dysfunction is a major problem in heart failure. It is the main cause of death in pulmonary arterial hypertension and makes outcomes much worse in pulmonary hypertension caused by left heart disease. Right ventricular dysfunction and pulmonary hypertension are crucial factors that affect treatment options and patient outcomes in advanced heart failure. Therefore, keeping the right ventricle functioning well is essential for effective patient care, making patients more eligible for advanced heart support, and improving survival rates. Understanding why right ventricular heart failure happens, especially in the case of pulmonary arterial hypertension, is crucial for developing targeted treatments to improve patient outcomes.

In our research, we are examining right ventricular tissues from end-stage heart failure patients who have undergone heart transplantation, as well as non-failing control hearts, to uncover the molecular mechanisms of right ventricular dysfunction. Some of these transplanted hearts still have relatively intact right ventricular structure and function, allowing us to study molecular changes from early to advanced stages of failure. However, our findings could be affected by factors such as medications, other health conditions, and end-stage left ventricular heart failure. To address this, we also use precision-cut right ventricular slices and animal models. The precision-cut slices allow us to culture human heart tissue under controlled conditions for long periods, while animal models help us study disease mechanisms with fewer genetic and environmental variables.

Our project aims to identify new molecular targets for right ventricular dysfunction by using three models: 1) Native right ventricular tissues from 40 heart transplant patients and 10 matched controls, 2) Precision-cut slices of human right ventricular exposed to immune and fibrotic signaling and mechanical stress, and 3) Right ventricular dysfunction in rat model induced by pulmonary artery banding. In the initial phase, we will use ribosomal profiling and high-plex proteomics to identify affected molecular pathways in human right ventricular tissue. For native right ventricular tissues from transplanted hearts, we will identify molecular targets linked to right ventricular function, pulmonary artery pressure, tissue fibrosis, cardiomyocyte size, and other relevant factors. In the ex vivo model, we will study how pro-fibrotic agents, inflammatory factors, and mechanical stress affect right ventricular tissue. The rat model will help us validate molecular pathways primarily triggered by pulmonary arterial hypertension. Ultimately, we aim to develop a therapeutic strategy using existing agents, such as small molecule inhibitors, to target newly discovered disease pathways. We will test these treatments in both the ex vivo heart slice culture model and the in vivo model, focusing on their protective effects on the heart and potential side effects.

This project aims to improve our understanding of heart failure by studying how the right side of the heart responds under various conditions. We want to find out what causes severe heart failure so we can develop precise treatments for it. By understanding right ventricular dysfunction better, we can create better treatments and improve patient care. This will help fill current gaps in how we diagnose, predict, and treat heart failure.