Heart failure, when the heart fails to pump blood properly around the body, hospitalises more people in the Western world than any other condition. Dr Nazha Hamdani from Ruhr University aims to unravel the biological mechanisms underlying the stiffening of heart tissue that can lead to heart failure. She plans to use the knowledge gained from her recent discoveries to investigate novel treatment options for the condition.

Her work will employ a more refined approach than has ever been trialled before, based on an understanding of the variable factors involved in each case of heart failure.

The challenge of treating a stiff heart

When the heart beats, it contracts to push blood out of chambers known as ventricles, and then relaxes to allow the ventricles to refill with blood. The measure of how much blood a ventricle in the heart pumps with each heartbeat is known as ejection fraction (EF) and is usually measured as a percentage (normally > 50%). This value represents the proportion of blood inside the ventricle that is pumped out with each contraction. Most commonly, EF is used to refer specifically to the amount of blood that is expelled from the left ventricle – the main chamber within the heart that is responsible for pumping oxygenated blood around the body.

Heart failure (HF) can occur either with reduced or preserved EF. In cases of heart failure with reduced EF (HFrEF), the heart is not able to send the normal amount of blood out and around the body. Patients with normal ventricular EF are diagnosed as having heart failure with preserved EF, referred to as HFP EF. This means that, although the heart contracts normally to push blood out, the left ventricle is unable to relax completely, thus limiting its ability to refill with blood to full capacity.

In heart failure with preserved ejection fraction, although the heart contracts normally to push blood out, the left ventricle is unable to relax completely, thus limiting its ability to refill with blood to full capacity.
elements common in HFrEF contribute to inflammation and oxidative stress that drive cell dysfunction. These in turn lead to a reduction in the level of cGMP and the activity of PKG. Dr Hamdani and her team hypothesise that the impact of comorbidities, combined with other factors, including gender, affects the pathophysiology of HFrEF. They suspect that the result of the changes they have found in the cGMP-PKG pathway is one key mechanism through which this occurs.

Next, the researchers plan to analyse the phosphorylation sites along the entire titin molecule. They aim to discover how many of the components of the cGMP-PKG signalling cascade involved in titin phosphorylation, and therefore cellular stiffness. Dr Hamdani hopes to discover through this research a way to artificially increase cGMP concentration within cardiomyocytes, thus increasing their plasticity. She thinks this can be done through either increasing the pool of cGMP or through targeting the upstream pathway by reducing inflammation and thereby oxidative stress, which then may improve endothelial function, cardiomyocytes and extracellular activities all in one. This could prove an effective mechanism for the design of a new treatment.

HOW CO-MORBIDITIES AND COLLAGEN CONTRIBUTE TO HFpEF

In addition to Dr Hamdani’s recent discoveries about the involvement of the titin protein, she also suspects that oxidative stress and inflammation lead to hypertrophy and fibrosis of the left ventricle. The co-morbidities present with the condition raise levels of pro-inflammatory proteins in the blood and drive inflammation of cardiac vasculature. This disrupts signalling between the endothelial cells that line the small blood vessels within the heart muscle, cardiomyocytes and fibroblasts (cells responsible for the synthesis of collagen and the extracellular matrix). Immune system cells called macrophages infiltrate the inflamed tissues and secrete growth factors that drive fibroblasts to differentiate into myofibroblasts. These cells alter the amount, form, or collagen deposition in the region, further contributing to ventricular stiffness.

Myocardial collagen is composed primarily of two types of fibres, and their ratio affects ventricular elasticity. Other mechanical factors related to collagen, including fibre geometry and cross linking, are also involved. Changes to any of these properties can be altered in heart disease and contribute to the diastolic stiffness characteristic of HFrEF.

GENDER ROLES

Dr Hamdani and her research team hope to develop HFrEF therapy specifically designed for men or women based on the condition of the titin protein, sex, and collagen deposition in the region, further contributing to ventricular stiffness. Obesity and a history of hypertension or renal impairment have a higher correlation in females with HFpEF. In men, HFpEF is more likely to be associated with atrial fibrillation and chronic obstructive pulmonary disease.

What inspired you to begin working on the biology of HFpEF in particular? This is a growing clinical problem for both men and women.

Dr Hamdani: A number of variables would contribute to the research on HFpEF. It is a poorly understood disease, and therefore there is a lot of room for improvement.

What do you think will be the most difficult aspects to accomplish in your proposed research? I would put this in a very simple and positive way, the aim of the proposed research is to deepen our basic understanding of HFpEF pathophysiology associated with comorbidities, age and sex differences, in order to provide firm foundations for clinical innovation. This will never be accomplished by just one group—it requires a range of expertise that is far beyond the capacity of any one group, but is provided by teamwork and collaborations based on shared knowledge and a range of professional skills. The knowledge and skills intermingle perfectly to resolve the complex structural, functional, molecular, and biological interactions underlying diastolic dysfunction to achieve one goal providing a novel HFpEF treatment and giving HFpEF patients a new lease on life.

How do you see your research progressing over the following years? HFpEF is a longstanding mystery, but there have been some incredible leaps forward in HFpEF research over the last few years. Looking back at our achievements and our understanding even if it’s still limited, I am extremely positive that we will have more amazing scientific discoveries in HFpEF within the next few years. These will change our conception of how we see the disease and guide us to the missing puzzle piece in HFpEF that will give a boost to new life to HFpEF patients. Therefore, I can say with great confidence, we will crack the mystery of HFpEF very soon.