

The challenge of treating a stiff heart

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.

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 HFpEF. 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.

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Dr Nazha Hamdani's recent research, based at Ruhr University, Germany, has been uncovering the mechanisms that contribute to HFpEF – the most common form of HF which makes up more than 50% of cases in Western societies.

ONE SIZE DOES NOT FIT ALL

Current treatments for HFpEF elicit a poor rate of response, and previous attempts to develop new therapeutics have yielded little success. Indeed, thus far, all large scale clinical trials of potential treatments for HFpEF, including those effective for HFrEF, have failed to produce positive results. This indicates that a "one size fits all" approach to the treatment of HFpEF may not be an appropriate way of tackling the problem. Dr Hamdani suspects that this could be due to a lack of understanding of the molecular mechanisms that are unique to each form of the disease. She thinks that therapeutic strategies which employ specific treatments for distinct subtypes of HFpEF may prove key in developing new therapies for patients.

The need to find effective solutions is increasingly pressing, as the incidence of HFpEF continues to rise. This increase is correlated with increased age and rates of

hypertension, obesity, metabolic syndrome and type 2 diabetes. The annual mortality rate is approximately 22% – a worse prognosis than for many cancer diagnoses. Therefore, Dr Hamdani and her team also plan to assess treatment strategies for a range of these co-morbidities. Investigating the different effects of a range of factors on heart cells and the extracellular matrix will provide them with new insights into the development of therapeutic interventions.

TITIN PHOSPHORYLATION REGULATES HEART CELL STIFFNESS

Dr Hamdani and her team's recent research has focused on comorbidities that are common in HFpEF for treatment of HFpEF. Dr Hamdani thinks that the syndrome of HFpEF goes above and beyond the comorbidities. She thinks it is not just a collection of comorbidities but that those comorbidities play an integral role in driving an inflammatory process so each comorbidity creates inflammation in the body which is driving the syndrome. The team found in their recent elegant study using biopsies from HFpEF patients and animal models of HFpEF that inflammation drives coronary endothelial dysfunction through a nitric oxide pathway that decreases cyclic guanosine monophosphate (cGMP)-dependent protein kinase G (PKG). What does this do to the heart? It leads to decreased compliance of and increased stiffness of the ventricles creating diastolic dysfunction.

The diastolic stiffness that causes the decreased relaxation capacity of the ventricle in these cases is associated with the giant protein titin. Titin forms a network of filaments in heart cells known as cardiomyocytes. In recent years, it has become apparent that titin elasticity is highly variable within the heart during development and can become altered in heart disease. *TTN*, the gene encoding titin, has also been identified as a major human disease gene. Variations in titin elasticity due to changes in genetic expression play a major role in the stiffness of cardiomyocytes, as do the modifications that occur after protein synthesis.

The team's work has revealed that the phosphorylation of titin by cGMP-PKG decreases cardiomyocyte stiffness. Furthermore, they have been able to demonstrate that this process is impaired in HFpEF patients and animal models. They have identified that the co-morbid

elements common in HFpEF 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 HFpEF. 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 the nature 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 elasticity. 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.

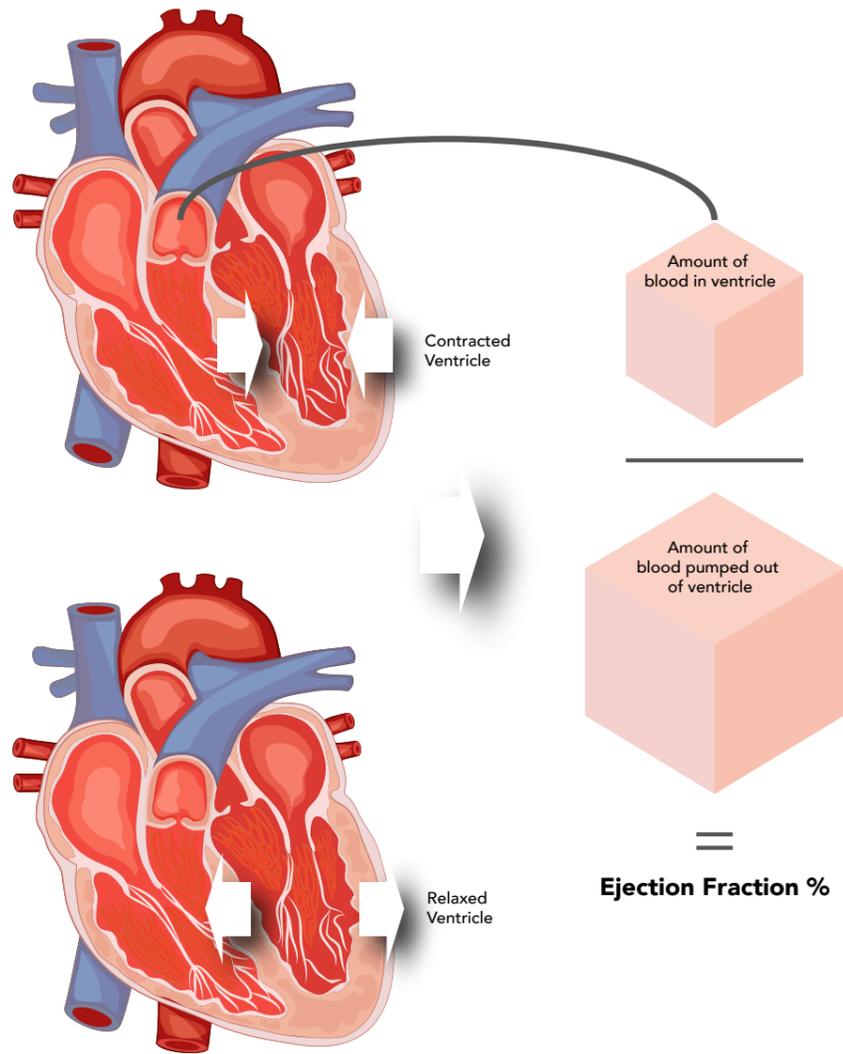
HOW CO-MORBIDITIES AND COLLAGEN CONTRIBUTE TO HFpEF

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, or form, of 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 HFpEF.



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GENDER ROLES

Dr Hamdani and her research team hope to develop HFpEF therapy specifically designed for men or women based on the physiology and co-morbidities involved in their case of HFpEF. Obesity and a history of hypertension or renal impairment have a higher correlation in females with HFpEF than males. Women generally exhibit smaller left ventricular volumes, higher EF values and greater ventricular and arterial stiffness. In men, HFpEF is more likely to be associated with atrial fibrillation and chronic obstructive pulmonary disease.

Now, armed with an understanding of the mechanisms that underpin the heterogeneity of the condition, Dr Hamdani plans to focus on working towards developing these specialised therapeutic approaches.

Q&A

What inspired you to begin working on the biology of HFpEF in particular?

This is a growing clinical problem for health care and services. However, our understanding of this condition is very limited and therefore so are our treatment options. It is the predominant form of heart failure in women, the elderly and with a lot of comorbid conditions, such as diabetes, obesity, and lung diseases and unfortunately there is no effective therapy. So there is a strong rationality to try something different to treat these patients in hope of prolonging their lives.

Why is so little currently known about HFpEF and how to treat it, in comparison to HFrEF?

We have collected information about the mechanisms of the disease over the past years, but I personally believe there are lots of subtypes of this condition. With HFrEF we were very effective in treating this condition and we were successful in reducing mortality and morbidity rates by 40% using some common treatment irrespective of the etiology. Unfortunately, moving to HFpEF, we haven't been successful with that strategy and therefore we need to put more effort into understanding the pathophysiology of this type of disease. I strongly believe that understanding this disease depends largely on subdividing it into subgroups of patients based on co-morbidities, age and sex differences and trying to understand the pathophysiology of every subtype. Accordingly, we will be able to personalise the treatment approaches. Taking this approach, I am sure we will be in a good position to manage the patients of tomorrow.

How is HFpEF currently diagnosed? Do you think these methods could be improved upon and if so how?

Clinicians are often confronted with these patients and yet have little guidance on how to effectively diagnose and manage them. In my opinion, the diagnosis of HFpEF is challenging, because the symptoms are non-specific and can be explained by several alternative non-cardiac conditions. I believe the right

diagnosis requires: determination of left ventricular ejection fraction (>50%), wall thickness (hypertrophy) and estimated pressure (increased E/e'), and diastolic dysfunction by echocardiography (e.g. decreased E/A); left atrial diameter (dilation); NT-proBNP levels; AND fatigue, dyspnoea, physical intolerance, chronotropic incompetence, with the main goal being treatment for subclasses of HFpEF according to etiology and pathomechanism.

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 thinking 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 intermesh 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 very long-standing mystery, but there have been some incredible leaps forward in HFpEF research over the last 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 of new life to HFpEF patients. Therefore, I can say with great confidence, we will crack the mystery of HFpEF very soon.

Detail

RESEARCH OBJECTIVES

Dr Hamdani's research looks at the biological mechanisms and potential treatment options within heart disease, particularly focused on the connections between diastolic stiffness and heart failure with preserved ejection fraction.

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BIO

Dr Hamdani studied Medicine and Pharmaceutical Sciences at Free University of Brussels and Amsterdam before doing her PhD at Cardiovascular Research (ICAR-VU), VU University Medical Center. Since then, she has worked in different centres of Cardiovascular Research in Europe, Germany, The Netherlands, and UK.

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