Defining the signs

Professor Eva Gerdts from the University of Bergen, Norway leads the Female Heart project which focuses on gaining knowledge of hypertensive heart disease in women. Here, she explains the importance of her novel, gendered approach and why she sought inter-institutional collaborations

To begin, what led to your interest in sex differences in cardiac hypertrophy? How did your current research project come about?

My interest in sex differences in cardiac hypertrophy came from my clinical practice as a cardiologist in the 1990s. I got the impression that, among patients with chronic pressure overload conditions like hypertension, cardiac adaptation differed between women and men. There was not much known about this at that time and, being a female cardiologist, I was interested in heart disease in women and wanted to examine whether my clinical notion was true.

What do you hope to achieve through the Female Heart project? What makes it unique from other investigations into heart disease?

In the experimental part of the project we hope to gain a better understanding of the underlying cellular and molecular changes in the heart that may explain the sex differences that we see in structure and function with ultrasound. By conducting serial echocardiograms in our experimental studies, we aim to identify an ultrasound pattern that is associated with the development of heart failure with preserved ejection fraction. This type of heart failure is particularly common in women, and less well understood. In the clinical part of the project we will determine the prevalence of such an ultrasound pattern in groups of patients at high risk of heart failure.

Why is using echocardiography beneficial for this study? Do you use any other methods?

Echocardiography is the core of this project. Using this, we can identify an echocardiographic pattern which reflects changes in the heart muscle cells that precede the development of heart failure with preserved ejection fraction, and test the prevalence of this pattern in echocardiograms from patients at high risk of heart failure.

While cardiac magnetic resonance imaging (cMRI) could have been used, we chose echocardiography because we did not possess large enough MRI databases to apply the experimental findings in humans. Furthermore, unlike echocardiography, cMRI is not widely available in clinical patient management.

The project is a joint effort between Norwegian and Italian universities. How does the study benefit from collaboration?

There has been vital collaboration between our research group and Professor Giovanni de Simone's team at Federico II University in Napoli, Italy. Advantageously, de Simone is an expert in metabolic heart disease and a pioneer in echocardiography in rats – experience that our research group did not have. Their echocardiography laboratory also became the core laboratory in many larger clinical trials. Digital image databases have subsequently been built up from these projects and are available for the human studies in the Female Heart project.

We also work with the Cardiovascular Research Group at the University of Tromsø – a partner in the Female Heart project. Tromsø is geographically as far away from Bergen as Napoli. However, the benefits from this collaboration are numerous: the Tromsø team is the only experimental research group in Norway interested in sex differences in cardiac hypertrophy and they possess modern equipment for echocardiography in rodents and have vast experience in experimental techniques needed for the project. Therefore, they are a perfect partner.

Given that cardiovascular diseases are the leading causes of death in all Western societies, do you think enough is being done to prevent heart diseases and promote heart health?

Although many fantastic new treatments have been developed over the past 20-30 years, cardiovascular diseases remain a leading cause of death. However, we need to focus the research more upon unsolved questions relating to the world's leading health problems. For example, I believe that less is known about the treatment of cardiovascular diseases in women, simply because women have been less frequently studied. We lack important information about heart disease in women, and not enough is done to fund or promote this much needed research.

Although I believe risk factors are well-recognised, due to information and campaigns from private organisations such as the European Society of Cardiology, not enough is being done to prevent cardiovascular disease. Governmental strategies for healthy foods and prevention of childhood obesity are badly needed.

The way to a **woman's heart**

Cardiovascular diseases affect males and females in strikingly different ways. While coronary artery disease is the most common cause of heart failure in men, uncontrolled high blood pressure is the predominant cause in women. Better understanding of such sex differences is vital for future treatment and prevention

CARDIOVASCULAR DISEASE (CVD) is caused by disorders of the heart and blood vessels and is the number one cause of death globally, responsible for an estimated 30 per cent of all annual global deaths. Alarmingly, the World Health Organization (WHO) estimates that the number of annual CVD-related deaths is likely to reach 23.3 million by 2030. High blood pressure, or hypertension, is a fundamental contributor to these worrying statistics. Found in around 20 per cent of the adult population, hypertension predisposes sufferers to other cardiovascular diseases such as heart attacks, strokes and heart failure.

Most cardiovascular diseases, including hypertension, can be prevented by addressing their risk factors such as smoking, unhealthy diet and physical inactivity. Yet, notwithstanding such precautions, there are a number of factors which are in desperate need of scientific attention. One such area of much needed research is the differences between male and female sufferers of CVD. For example, it has been demonstrated that male and female hearts respond differently to high blood pressure over time, with women being particularly prone to blood pressure-related cardiac damage. Despite this knowledge, drastic improvements in our understanding of why and how such phenomena occur are crucial.

Fortunately, the Female Heart project – led by Professor Eva Gerdts at the University of Bergen, Norway – is dedicated to exploring these issues, in an attempt to restore the knowledge balance. Gerdts' team hopes to better understand why hypertension is the leading cause of heart failure in women, why women predominantly develop a special type of heart failure (heart failure with preserved ejection fraction) and how the development of this type of heart failure can be detected at an early stage, before the presentation of symptoms. Excitingly, their results could soon form the basis for treating and even preventing this disease amongst female populations.

WHY WOMEN?

The overarching objective of the Female Heart project is to analyse and interpret the sex differences presented in heart function within a group of patients with high blood pressure and a predisposition to heart failure, specifically that with preserved ejection fraction. The project will shed light upon the underlying molecular and cellular processes which, in turn, will explain the sex differences in heart failure phenotype.

In the past, the Bergen team demonstrated key cardiac function differences according

Ultrasound image of a woman's heart. Thickening of the heart muscle due to longstanding hypertension is present in the left ventricle both in long-axis (Left panel) and in short-axis (Right panel) views. From such images cardiac structure and dynamics can be evaluated.

SEX-DIFFERENCES IN CARDIAC HYPERTROPHY IN PRESSURE OVERLOAD – LINK TO HEART FAILURE WITH PRESERVED EJECTION FRACTION

OBJECTIVES

- To identify molecular and cellular mechanisms explaining the sex differences in left ventricular structure and function found by echocardiography in patients with high blood pressure
- To assess the impact of loss of oestrogen, obesity and Type II diabetes on these mechanisms
- To identify new echocardiographic predictors of transition from adaptive hypertensive hypertrophy to heart failure with preserved ejection fraction

KEY COLLABORATORS

Professor Kirsti Ytrehus, Cardiovascular Research Group, University of Tromsø, Norway

Professor Giovanni de Simone, Federico II University Hospital, Napoli, Italy

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EVA GERDTS, MD, PhD was appointed Professor of Medicine (Cardiology) at the University of Bergen in 2006. She has been a licensed Cardiologist since 1994 and Head of the Non-invasive Cardiac Imaging Unit at Haukeland University Hospital, Bergen, Norway since 1997. Her research focus is primarily hypertensive heart disease.

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to gender in patients with chronic pressure overload like hypertension or aortic valve stenosis. Their work proved that the heart's collagen structure and the amount of its fibrous tissue differed significantly between women and men. However, it is the current Female Heart project which seeks to uncover the underlying cellular and molecular mechanisms for these observed sex differences in cardiac hypertrophy. Furthermore, the project will evaluate the impacts that loss of oestrogen, obesity and Type II diabetes have on these mechanisms.

EJECTION FRACTION

They have also dedicated much of their attention to preserved ejection fraction. Heart failure can be divided into two types, based on whether the left ventricular pump function is reduced or normal. Pump function can be measured from ejection fraction (the percentage of the returned blood that is ejected in the next heartbeat) and is usually over 50 per cent. Thus, preserved ejection fraction refers to a type of heart failure which occurs despite normal ejection fraction. This type of heart failure is most commonly caused by hypertension and is more prevalent among women. In light of this, another crucial aim of the Bergen team is to identify new echocardiographic predictors of transition from adaptive hypertensive hypertrophy to heart failure with preserved ejection fraction.

USING RATS

One of the key features of the research will be to undertake experimental rat studies. A pilot investigation to fine-tune the imaging protocol was completed in December 2012, and the ongoing, first experimental rat study started in February 2013. Due for completion in July this year, the study is focusing upon the role of oestrogen in the sex differences of cardiac response to hypertension and the subsequent development of heart failure. The team expects that this will provide new knowledge on cardiac response to hypertension in the heart muscle and its cells.

From a wider perspective, the experiment could improve general understanding of the sex differences in cardiac hypertrophy and function that are observed among patients with hypertension. This work could then be extended to a series of experimental studies, addressing a different research question at a time, such as: how is cardiac hypertrophy modified by the presence of obesity or Type II diabetes?

Yet despite this positive start, the use of rats has not been wholly straightforward. Indeed, Gerdts has pointed to this as one of the most challenging parts of their study, requiring optimal echocardiography in the rats. Indeed, dedicated rat ultrasound scanners had to be developed and, because the team uses state-of-the-art echocardiographic equipment, the operators had to be highly trained. Even though the group managed to overcome these challenges, bone formation in the rat chest could still render imaging of the heart very difficult. As the project is dependent upon optimal imaging, the team has been forced to work tirelessly on these techniques.

FROM RATS TO HUMANS

While it is not possible to apply results from experimental rat studies directly into clinics, the results form a crucial stepping stone towards the treatment of humans. Gerdts and her colleagues hope to describe the echocardiographic signs that best identify the cardiac response type to hypertension, which subsequently develops into heart failure in spite of normal pump function (heart failure with preserved ejection fraction). Thus, when moving to human studies, the team will identify whether this pattern is present among different patient groups at high risk of developing heart failure.

The research will then be used to identify the clinical characteristics of patients in which the pattern is found – it is anticipated that female gender will be among these characteristics. The results from the Female Heart study will not be ready for translation into clinical practice without further testing in epidemiologic and clinical prospective studies, but the project is certainly moving in the right direction.

LOOKING TO THE FUTURE

After identifying the high risk echocardiographic pattern for heart failure with preserved ejection fraction in hypertension, the Female Heart project will be extended to include epidemiological and clinical studies. Subsequently, the question as to whether this identified pattern accurately predicts the development of this type of heart failure will be asked.

On achieving better cellular and molecular understanding of hypertensive heart failure, the findings could lead to improved ideas about how this condition can better be treated and prevented. Moreover, Gerdts hopes that her team's results will inspire other leading research groups to join the quest to solve the puzzle of heart failure with preserved ejection fraction in women. "In my opinion, the ultimate achievement will be to have contributed to such a process," she concludes.