OPINION

Heart mitochondrial sex differences control diastolic dysfunction

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Fatima S. Heart mitochondrial sex differences control diastolic dysfunction. Clin Cardiol J. 2022; 6(4):47-49.

ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) has a sex bias because it affects more women than men. We propose that this bias may be due to sex differences in the mitochondria. We find that heart mitochondrial DNA levels and function are typically lower in females than in males in genetic studies of heart failure in mice. In human cohorts, we also notice that males express more genes for mitochondrial proteins than females do. We test our theory using a panel of mice with a variety of genetic inbred strains, known as the Hybrid Mouse Diversity Panel (HMDP). Indeed, we discover a strong correlation between diastolic function, a crucial characteristic of HFpEF, and mitochondrial gene expression. Studies using a "two-hit" mouse model of HFpEF support this by showing that mitochondrial function varies between sexes and is closely linked to a variety of HFpEF characteristics. We identified the mitochondrial gene *Acsl6* as a genetic predictor of diastolic function by combining data from human heart failure and the mouse HMDP cohort. We use adenoviral overexpression in the heart to confirm its function in HFpEF. We come to the conclusion that the sex bias in diastolic function is partially explained by sex differences in mitochondrial activity.

INTRODUCTION

Diastolic dysfunction and maintained ejection fraction characterise the increasingly common syndrome known as HFpEF HFpEF. In terms of pathophysiology and successful therapeutic therapy, it differs from Heart Failure with Reduced Ejection Fraction (HFrEF). Epidemiologic statistics show that restrictive cardiomyopathies, diabetes, and hypertension make up half of all instances of Heart Failure (HF) with multiple comorbidities. Diastolic dysfunction is highlighted as a significant contributor to the morbidity of heart failure by the fact that people with systolic heart failure also exhibit symptoms of diastolic dysfunction. The morbidity and mortality in HFpEF are not improved by medications that are effective in HFrEF. We have employed genetic methods in animal models to assist discover genes and pathways that contribute to the illness because the molecular mechanisms behind HFpEF are poorly understood. The part played by sex differences in HFpEF is one of the questions we have examined. Consistent epidemiological data show that women have a roughly twofold higher risk of developing HFpEF than men do, and that they also tend to present with a greater number of symptoms, including markedly increased diastolic dysfunction and enhanced left ventricular stiffness. The idea of sex differences in HFpEF has been challenged since HFpEF is so varied. Women's hearts differ structurally and physiologically from men's hearts in a number of ways, such as smaller Left Ventricle (LV) chambers, lower stroke volumes, more pronounced concentric remodelling upon pressure overload, higher systolic and diastolic LV stiffness at a given age, and a more pronounced response to hypertension and obesity. Examining mouse models, where genetic and environmental factors can be manipulated, is one strategy for resolving the problem. A sex bias in mitochondrial DNA content and function, with men exhibiting larger amounts of cardiomyocytes, was discovered by our genetic analyses of heart failure features in a heterogeneous cohort of mice. We predicted that sex variations in mitochondria may partially explain why women are more susceptible to heart failure given the substantial data supporting this theory. We've looked at this idea rom a variety of angles, and using genetics, we found a mitochondrial protein called ACSL6 that appears to guard

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Received: 09-July-2022, Manuscript No. PULCJ-22-5246; Editor assigned: 11-July-2022, PreQC No. PULCJ-22-5246(PQ); Reviewed: 18-July-2022, QC No. PULCJ-22-5246 (Q); Revised: 23-July-2022, Manuscript No. PULCJ-22-5246 (R); Published: 30-July-2022, doi: 10.37532/pulcj.22.6(4).47-49

against a variety of HFpEF features, including diastolic dysfunction, in a "two-hit" mouse model of the condition.

RESULTS

Study design

We looked into the genetic components—including sex disparities—that may be responsible for characteristics like diastolic and metabolic dysfunction in HFpEF. Due to genetic variation, the inability to access important organs, and complicated environmental influences, this is challenging to directly address in human populations. We chose the HMDP for our research because it offers high-resolution genetic mapping, replication, and multi-omics analysis in the context of genetics. The HMDP is a cohort of more than 100 genetically distinct inbred mouse strains. Through the analysis of publicly accessible human data, we also aimed to determine how applicable our findings were to human disease.

Sex differences in diastolic dysfunction in HFpEF

We replicated the "two-hit" HFpEF mouse model in C57BL/6 J male and female mice to determine if females are more prone to diastolic dysfunction in the course of HFpEF. The model replicates the clinical characteristics of HFpEF following a High-Fat Diet (HFD) and L-NAME feeding for seven weeks. A significant rise in body weight, fat mass, left ventricle mass, and adipose weight, as well as a decline in exercise tolerance, was seen in both male and female mice. Both male and female mice developed glucose intolerance after receiving HFD+ L-NAME diet. Additionally, HFpEF hearts had higher levels of Fatty-Acid-Binding Protein 3 (*Fabp3*) than chow diet controls, demonstrating the dysregulation in the heart. *Fabp3* is an early indicator of cardiac injury.

Diastolic function is associated with mitochondrial DNA levels in an isoproterenol model of heart failure

We used data from a previously published investigation of isoproterenol-induced cardiomyopathy in 105 inbred strains of female HMDP mice (ISO-HMDP), concentrating on the trait of diastolic function, to discover genetic variables implicated in diastolic function. In that study, adult female mice had an ISO infusion for 21 days, and every week, echocardiography was used to assess their heart health. Global transcriptome profiling of the left ventricles was carried out after 21 days of ISO treatment. As proxies for cardiac diastolic function, we used heart weight, lung weight, and E/A ratio (the ratio of peak velocity blood flow in early diastole to peak velocity flow in late diastole). We measured the amount of mitochondrial copy number in the ventricles of the female ISO-HMDP mice and carried out trait-by-trait correlations in order to directly investigate the association between mitochondrial levels and cardiovascular features. A number of cardiac features, including lung mass/body weight, left atrium mass/body weight, IVS at end-diastole (day 0), and IVS to PW ratio at end-diastole, were inversely linked with mtDNA concentration, which raises the possibility that mitochondria play a role in diastolic qualities. Following the exclusion of samples with an exceptionally high mtDNA content, we also reanalyzed the data. The relationships remained substantial with the exception of mitral inflow E velocity.

In both mice and humans, there is a sex bias in the amount and gene expression of mitochondrial DNA, with men typically exhibiting a higher expression than females

We counted the copies of cardiac mitochondrial DNA (mtDNA) in 100 strains of male and female HMDP mice fed a Western diet heavy in fat and sugar. We measured the number of copies of mitochondria in each cell using PCR.

We noticed that, across the HMDP, the mtDNA content (copies per cell) in female hearts was considerably lower than that in male hearts. Additionally, we looked at the expression of nuclear or mitochondrial genes that encode proteins for the mitochondria in the heart.

Heart mitochondrial DNA and functions are regulated by sex hormones

We removed the gonads from male and female C57BL/6 J strain mice in order to ascertain if the sex differences are brought about by chromosomal or hormonal influences. Notably, gonadectomy boosted mtDNA in females while decreasing mtDNA in men' hearts. Hormone replacement therapy revealed that testosterone raised the number of mitochondrial copies in males while oestrogen decreased the number of copies in females. We replicated a "two-hit" HFpEF mouse paradigm in C57BL/6 J male and female mice after gonadectomy to further assess heart mitochondrial function. Male mouse gonadectomy decreased lean mass and body weight.

DISCUSSION

To comprehend the genetic and technological underpinnings of HFpEF characteristics, such as diastolic dysfunction, we have applied systems genetics techniques. The higher frequency of HFpEF in women compared to males was one feature of this study that was of special relevance. We found that males typically have higher levels of mitochondrial gene expression than females using both mouse models and data from human heart failure research. We also discovered that male mice had larger quantities of mitochondrial DNA and that both gene expression and mitochondrial DNA levels were controlled by both male and female sex hormones in mice. Furthermore, we found that in a panel of several strains, diastolic function—a crucial component of HFpEF—was substantially correlated with mitochondrial DNA level. We identified putative causative genes for diastolic function based on the connection between the cis component of gene expression and echocardiographic parameters representing diastolic function in order to better understand the role of mitochondrial function in HFpEF. As a result, a gene's expression might be connected with a trait either because the trait controls the gene's expression (a process known as trans-regulation) or because the gene's expression controls the trait, a relationship known as cis-regulation. For validation and follow-up, we selected the gene Acsl6, which codes for a mitochondrial protein implicated in lipid metabolism. Below, we go over each of these principles individually. With the rise in obesity and diabetes, HFpEF has become more prevalent and now makes up roughly half of all heart failure cases. There has been an urgent need for a deeper understanding of the mechanisms underlying HFpEF and for the development of novel therapies to treat it because the medications that are helpful in treating HfrEF have been useless for HFpEF. Recent research has demonstrated that SGLT2 inhibitors, which were initially created to treat diabetes, are also useful in lowering cardiovascular mortality and hospitalizations in patients with HFpEF. Additionally, studies using human and mouse models indicate that nicotinamide and medications that encourage NAD+ synthesis are promising. Metainflammation, the result of the interaction between metabolic abnormalities and systemic inflammatory load, is being considered as a potential therapeutic target in HFpEF. The pathogenesis of HFpEF appears to be extremely complex and heterogeneous, having both metabolic and inflammatory components. Because of this, it has been difficult to conduct human investigations, hence mice models that mimic many of the characteristics of HFpEF have been created. Studies in the "two-hit" animal model of HFpEF indicate that lipid accumulation and contractile function are controlled by the Unfolded Protein Response (UPR).

Imeglimin's targeting of UPR shields the animal from metabolic and cardiac problems. Sex bias is one of the hallmarks of HFpEF because women make up roughly two-thirds of the patient population and because they frequently experience more severe symptoms than men. We remark that the idea of female inclination has been contested and may partly be explained by the fact that women often have smaller statures than men. Studying animal models, where treatments like gonadectomy may be used and genetic and environmental factors can be controlled, is one method of exploring sex differences. We discovered that males often contain more mitochondrial DNA and higher expression of genes encoding mitochondrial proteins than females during the course of our study of various mouse strains. These results were supported by functional investigations that used Seahorse assessments of oxygen utilisation. As testosterone increased in gonadectomized males and oestrogen declined in gonadectomized females, we also saw that sex hormones controlled both mitochondrial DNA levels and function. By employing an adeno-associated viral vector to overexpress the Acsl6 gene in the heart, which encodes a mit-

-ochondrial protein involved in fatty-acid metabolism, the gene's validity was established. Increased running distance, decreased left ventricular mass, improved glucose clearance, and enhanced diastolic function were all benefits of overexpression. The oxygen consumption rate of isolated mitochondria in males, but not in females, indicated that it also improved some aspects of mitochondrial function. As Acsl6 exhibits some overexpression in other organs, particularly the liver, additional research will be needed to ascertain its methods of action, which is one limitation of our study. Clinical ramifications could result from the discovery that sex hormones control mitochondrial levels. In older males, testosterone levels fall, while in women after menopause, oestrogen levels fall. However, testosterone therapy has a variety of side effects that make it less effective as a treatment. Additionally, a meta-analysis of eight minor heart failure studies involving a combined total of 170 participants failed to find any appreciable benefit after testosterone therapy.