Sex differences in heart failure with preserved ejection fraction

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Abstract
This narrative review aims to collect and assess the available knowledge about sex differences in heart failure with preserved ejection fraction (HFpEF). HFpEF is more common in women. The differences between men and women in the development of HFpEF will be discussed including cardiovascular differences, hormonal differences, inflammatory differences and differences in body composition. Current treatments of HFpEF are not effective, the subdivision of HFpEF into subgroups based on the prevalence of co-morbidities is proposed in several papers and aims to lead to more effective treatments. There is a need for further research in order to establish subgroups and achieve effective treatments.

Introduction
Heart failure is a major public health issue worldwide (1). Heart failure is clinically defined as a syndrome that can occur in patients with preserved ejection fraction or in patients with reduced left ventricular ejection fraction. Heart failure with preserved ejection fraction (HFpEF) is outnumbered by women with a ratio of 2:1 (2). Sex differences in the prevalence and development of HFpEF may be related to differences in cardiovascular structure, hormones and inflammation, as well as sex differences in risk factors for HFpEF. The different risk factors for the development of HFpEF including diabetes, hypertension, smoking, non-cardiovascular co-morbidities including chronic lung disease, anaemia, cancer, liver disease and obesity among HFpEF patients play an important role in this disorder. Often HFpEF is not diagnosed because the co-morbidities disguise the presence of HFpEF (3). It will become clear that there is a diversity of HFpEF phenotypes. Most current treatments for HFpEF are not effective (3, 4). This is due to the large heterogeneity of this disorder. Among HFpEF patients there are large differences in underlying causes and co-morbidities resulting in different needs of treatments. Thus, it may be necessary to divide HFpEF into subgroups based on the prevalence of different co-morbidities in order to effectively treat this disease. Dividing HFpEF into subgroups with specific treatments per subgroup will hopefully have future advances in the treatment and in the prevention of this disorder.

Risk factors for heart failure with reduced ejection fraction (HFrEF), also known as systolic heart failure, are similar to those of HFpEF (5). HFrEF is not the same as HFpEF since HFrEF causes the heart muscle to contract inadequately. Coronary heart diseases commonly result in HFrEF and are more prevalent in men. This narrative review, however, focuses on HFpEF.
This narrative review will discuss the physiology of the heart, the prevalence and pathophysiology of HFpEF and risk factors for HFpEF. Because HFpEF is more common in women, sex differences in several mechanisms will be discussed. These sex differences include differences in cardiovascular structure and hormonal influences on the cardiovascular functions, sex differences in CVD and sex differences in inflammation. The renin angiotensin system, and inflammation in CVD and HFpEF inflammation in HFpEF, as well as, the association between fat and inflammation will also be discussed. Finally, sex differences in body composition will be discussed, this is followed by the conclusion. Many terms, including diastolic heart failure and diastolic dysfunction, can be used to describe HFpEF. In this review the term HFpEF will be used to refer to this specific type of heart failure.

**Physiology of the heart**

Before discussing the pathophysiology of HFpEF, the heart’s physiology will be discussed. Blood enters the right and left atria during ventricular systole (6). The atrium-ventricle (A-V) valves are closed at that moment. Whenever pressure falls to the lower diastolic values, the pressure developed inside the atria pushes the A-V valves open allowing a rapid flow of blood into the ventricles. This period is called the period of rapid filling of the ventricles. When the ventricles are filled with blood the ventricular pressure rises, thereby causing the A-V valves to close again. When enough pressure is built within the ventricle, the semilunar valves open against the pressures in the aorta and pulmonary artery. The semilunar valves are the aortic and pulmonary valves. This period is called the isovolumic or isometric contraction. The semilunar valves open, caused by ventricular pressure, when the left ventricular pressure is above 80 mm Hg and right ventricular pressure is above 8 mm Hg. Then blood is ejected out of the ventricles. Ventricular relaxation begins at the end of systole, the intraventricular pressures decrease back to low diastolic levels. A new cycle of ventricular pumping will begin whenever the pressure rises causing the A-V valves to open again. The end diastolic volume is the volume of blood filling the ventricles, which is about 110 to 120 ml. The stroke volume output is the amount of blood leaving the ventricles during systole. The amount of blood left behind in the ventricles after systolic emptying is called the end-systolic volume. The ejection fraction is the end-diastolic volume that is ejected. A schematic image of the heart’s anatomy is given in figure 1. Women, in general, have lower stroke volumes in comparison with men, this is because of their relatively smaller hearts (7). Women also have less blood volume than men. These may be a few reasons explaining why women are at greater risk for the development of HFpEF. More risk factors will be discussed within this review.

![Figure 1: Schematic image of the anatomy of the heart, retrieved from Guyton and Hall textbook (6)](image)

**Prevalence and pathophysiology of HFpEF**

Heart failure is described as a syndrome with the impaired ability of the heart to fill with and/or to eject blood resulting in pulmonary and systemic venous congestion (8). Systemic venous congestion is the accumulation of fluid outside of the lungs (9). This induces a rise in venous pressure and organ perfusion is decreased. Systemic venous congestion is associated with the progression of heart failure. 2% of the western population is affected by heart failure, the prevalence increases with age and is around 10% in people aged 75 years and older (8). In heart failure with preserved ejection fraction (HFpEF) left ventricular systolic function is normal and ejection fraction is preserved. Also, left ventricular diastolic function is disturbed.
HFpEF guidelines and characteristics

According to the guidelines by the Echocardiography and Heart Failure Associations of the European Society of Cardiology there are three diagnostic criteria features: clinical signs or symptoms of HF, evidence of normal LV systolic function and evidence of abnormal LV diastolic dysfunction. These pathophysiological features were also described in an article by Borlaug and Paulus (10). One of these features is diastolic left ventricular dysfunction which results from myocardial stiffness. Myocardial stiffness is determined by several parameters including titin status in cardiomyocytes, the energy levels in cardiomyocytes, and fibrosis. Stiffness of extracellular matrix is regulated by collagen, relative abundance of collagen type 1 and the degree of collagen cross-linking. In HFpEF these 3 features are disrupted leading to stiffness of extracellular matrix.

Slow LV relaxation is another characteristic feature of HFpEF (10). LV relaxation is dependent on nitric oxide signalling, cross-bridge detachment within cardiomyocytes and calcium reuptake. Disturbances in these features are described in patients with HFpEF. It must be mentioned that ventricular and vascular stiffening increases with age, hypertension and diabetes. However, in HFpEF ventricular and vascular stiffening are abnormally elevated. Arterial elastance is elevated in HFpEF as well, which explains the blood pressure swings in HFpEF patients. The arterial elastance reflects the vascular load/ resistance (11). Which is the end-systolic pressure. HFpEF is diagnosed by coupling dyspnoea and a normal LVEF with objective measures of left atrial enlargement, LV hypertrophy, diastolic LV dysfunction or plasma levels of natriuretic peptides as recommended by all guidelines for the diagnosis of HFpEF (10). Thus, the presence of evidence of normal systolic function and evidence of diastolic LV dysfunction such as LV hypertrophy, LA enlargement, atrial fibrillation or elevated NP plasma levels are required to be present in order to diagnose HFpEF. HFpEF is a diverse phenotypic condition (12). Patients with HFpEF tend to be older, more often female and generally have a higher burden of comorbidities.

Interventions

Effective interventions in HFpEF have yet to be found, probably because of the diverse phenotypes of this condition. Not all HFpEF patients have diastolic abnormalities for example. Several authors emphasize the importance of identifying the different phenotypes of HFpEF and to divide HFpEF into subgroups in order to effectively treat patients (10, 12). Shah, Kitzman et al. later on propose that subgroups involve clinical presentation phenotypes like lung congestion, chronotropic incompetence, pulmonary hypertension, skeletal muscle weakness and atrial fibrillation (4). This

<table>
<thead>
<tr>
<th>Table 1: Subdivision phenotype specific HFpEF treatment matrix, abstracted from Shah et al. (4)</th>
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<tbody>
<tr>
<td>Lung congestion</td>
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<td>overweight, obesity, metabolic syndrome, type 2 DM</td>
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<td>Atrial hypertension</td>
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matrix, which is abstracted from the paper of Shah et al. is given in table 1. In addition, predisposition phenotypes including overweight, obesity, metabolic syndrome, type 2 diabetes mellitus, atrial hypertension, renal dysfunction and coronary artery disease are suggested to affect the type of treatment needed. Proposed medications include ACE-I, ARB, diuretics, statins, inorganic nitrite/nitrate, sacubitril, spironolactone and pulmonary vasodilators, which are all drugs that are already applied in the setting of HF (rEF). Unfortunately, ACE-I, ARBs and beta blockers have not been found to prevent the decline in ejection fraction that happens over time in HFpEF patients (1). More longitudinal studies are required to confirm these observations and to establish more efficient treatments. Several risk factors for the development of HFpEF will be discussed in the following section.

Risk factors for the development of HFpEF
HFpEF is more common in women, and female gender is considered an independent risk factor for HFpEF (8),(13), (14). Other risk factors, including diabetes, smoking and hypertension, commonly proceed the onset of both HFrEF and HFpEF (5). Women are more likely to have hypertension, diabetes mellitus and the metabolic syndrome, increasing their odds of developing HFpEF (13). Risk factors for the development of HFpEF are often non-cardiovascular, and highly prevalent in HFpEF. These co-morbidities include renal impairments, chronic lung disease, anaemia, cancer, liver disease, peptic ulcer disease, hypothyroidism, diabetes, hypertension and obesity. The differences between co-morbidities and risk factors are not always that clear, especially in HFpEF patients. Co-morbidities can be risk factors for developing a certain disease. Several co-morbidities are indeed risk factors for developing HFpEF.

Coronary heart diseases and HFpEF
HFpEF is also more likely in people without pathogenesis of coronary heart disease, people with higher systolic blood pressure and in people with atrial fibrillation. People without pathogenesis of coronary heart disease more often develop HFrEF. Diastolic dysfunction can also play a role in these patients, but this is disguised by systolic dysfunction. Atrial fibrillation may trigger HFpEF via loss of LV filling and shortening of diastolic filling time. The presence of atrial fibrillation in HFpEF patients varies between 15% and 41% (15). In comparison with HFrEF patients, HFpEF patients have a 10% higher prevalence of atrial fibrillation.

Diabetes and HFpEF
30-40% of patients with HFpEF have diabetes mellitus (DM) (16). This shows that DM is an important risk factor for HFpEF. Moreover, DM patients with HFpEF are more often female and obese. It is known that diabetes promotes myocardial deposition of collagen and the formation of advanced glycation end products which promote myocardial cross-linking, impairing LV compliance. Haemoglobin levels are even lower in HFpEF patients with DM. Low haemoglobin and low diastolic wall stress are both associated with the prevalence of HFpEF. HFpEF mostly occurs in older women with a history of hypertension (8). Like in many other articles, the female gender is again found to be a risk factor for the development of HFpEF. Age is another important risk factor, HFpEF patients are consistently found to be of advanced age.

Preeclampsia and HFpEF
Another risk factor for HFpEF specifically for women is preeclampsia. Women are at greater risk for the development of HFpEF when having preeclampsia (14). Preeclampsia is the occurrence of hypertension and proteinuria during pregnancy, and is associated with the development of hypertension, diabetes type 2 and obesity later in life. Proteinuria is the excessive secretion of proteins in urine. In healthy people urine contains only a small amount of protein. Proteinuria is a symptom of preeclampsia. The exact pathophysiology of preeclampsia is yet unclear; known is that preeclampsia causes endothelial and diastolic dysfunction during pregnancy. Diastolic dysfunction can even occur until 1 year after pregnancy.
**Co-morbidities and HFpEF**

While co-morbidities alone cannot explain why people develop HFpEF, the effect of co-morbidities can explain the higher susceptibility of women. However, no studies have investigated the effects of co-morbidities in relation to HFpEF. Lund et al. even suggested that HFpEF previously was undetected or misdiagnosed because it is disguised by co-morbidities (3). Therefore, co-morbidities form an important topic of future research in HFpEF. The next section will discuss the different cardiovascular sex differences, since the pathophysiology and the risk factors for HFpEF have now been discussed.

**Sex differences in cardiovascular structure**

Thus, several studies have shown that HFpEF is more common in women. Several factors that may cause women to be more at risk for HFpEF are described in more detail below. Arterial differences between men and women are important factors increasing the susceptibility for HFpEF in women (2). Postmenopausal women show greater aortic stiffening than men because of greater proximal aortic stiffness, even after adjusting for ascending aorta diameter. This finding suggests differences in material properties of the aorta between men and women. Women also show lower total arterial compliance than men. The efficiency of the cardiovascular system is decreased in women because of the greater aortic stiffness and pulsatile load during early systole, indicating the predispositional risk for HFpEF. Thus, aortic stiffness and arterial pulsatility are greater in older women than in men. The increased arterial stiffness is associated with left ventricular diastolic dysfunction in older women, increasing their chances of developing HFpEF.

**Additional cardiac sex differences**

Additional differences in cardiovascular structure and function between men and women exist (17). Sex differences in cardiac structure were investigated among 279 HFpEF patients, consisting for 57% out of postmenopausal women. It was concluded that women have higher indexed LV wall thicknesses. The average age in this study was 71 years. This is a reasonable population, since women of this age are indeed in their menopause. Furthermore, the population consists for 57% out of women, and for 43% out of men which is quite an equal sex division. In women, of this relatively advanced age, there was a trend towards more abnormal LV geometry. Indicating the influence of menopause on cardiovascular structure. Remodelling or hypertrophy was significantly associated with only the female sex. Left ventricular diastolic function was more impaired in women than in men. This means that LV relaxation was more impaired, LV filling pressure was higher and LV diastolic stiffness was greater in women. Women also showed a steeper increase of LV mass with aging. Arterial stiffness was higher in women. Diastolic function is therefore worse in women as compared to men in normal aging. However, overall pump function was similar between men and women.

**Elastin and Collagen**

Extracellular matrix components such as elastin and collagen play an important role in cardiac stiffening. With aging, elastin and collagen fatigue (18). There is an excessive degradation of the elastic component elastin. This is replaced by tensile collagen fibres, causing stiffened arterial walls. Estrogen increases elastin production and decreases collagen deposition in arteries of premenopausal women. Women have higher arterial estrogen receptor levels than men. Another difference between men and women is that levels of nitric oxide (NO) are higher in premenopausal women than in men. The effects of nitric oxide will be discussed in more detail in the following section. The stiffening of the aorta and arterial walls causes an increase in cardiac workload and wall stress. The optimal stroke volume will be maintained by adaptive mechanisms including increasing the left ventricular systolic stiffness and wall thickness. Left ventricular relaxation is impaired because of this coping mechanism. Resulting in concentric remodelling and hypertrophy, which are associated with cardiovascular problems. The effects of aging on cardiovascular structure will be discussed in more detail in the section of “sex differences in normal cardiovascular aging”. The following section will discuss the hormonal influences on cardiovascular functions.

**Hormonal influences on cardiovascular functions**

Sex hormones have been linked to differences in HFpEF among men and women. Reduced levels of estrogens in post-menopausal women seem to inhibit nitric oxide and natriuretic peptides which are needed for cGMP production (17). Inhibited cGMP production causes...
increased cardiac hypertrophy explaining the greater LV diastolic dysfunction in women. Also, in general women have smaller body sizes as compared to men, which leads to shorter arterial length. This causes lower vascular compliance in women. Lower estrogen levels have also been linked to the activation of the renin-angiotensin system and alterations in renal sodium handling. The renin-angiotensin system will be discussed in more detail in the section of “The Renin-Angiotensin system”.

**Nitric oxide and cGMP production**

NO is a potent vasodilator with effects on inflammation and endothelial function (19). When NO concentrations are reduced, impairments in vasodilatation will follow. Estrogens cause vasodilatation by increasing NO concentrations (20). After menopause NO levels therefore decrease. Nitric oxide plays a role in the synthesis of cGMP, since cGMP pools are generated by cytosolic NO-stimulated guanine cyclise. Because NO is inhibited in post-menopausal women, cGMP production is inhibited which potentially leads to the high percentage of women having HFpEF. Increased cGMP levels in cardiomyocytes are associated with a reverse effect on cardiac hypertrophy thereby protecting against reperfusion injury (21). When cGMP levels decrease, due to menopause, this protective effect is decreased as well. Hypertrophied hearts show a decrease in chamber size of both ventricles. This causes limitations in vascular perfusion. Hypertension commonly causes cardiomyocyte hypertrophy. With menopause, there is not only a change in NO and cGMP values. LDL and triglyceride levels rise and HDL levels also fall. Accumulation of LDL causes atherosclerosis. Atherosclerosis is a progressive inflammatory process in which vascular protective mechanisms are lost. The susceptibility to plaque and ruptures increases, thus increasing the risk of heart failure. This indicates that besides the increased risk for developing HFpEF, postmenopausal women are also at greater risk for the development of heart failure because of the increased risk for developing atherosclerosis.

In both men and women testosterone levels decline with age, however this decline is more steep in women following menopause. Circulating estrogen levels are low in men, but estrogen deficiencies increase testosterone levels. In a mouse model the conversion of testosterone to estrogen by aromatase was found to aid in maintaining a normal vascular tone in male mice. Greater values of total cholesterol measurements are higher in men until in their fifties, then women show greater values (22). Men have lower HDL levels than women. Women do experience a relatively mild decline in HDL level at menopause. This decline in HDL levels in women explains the higher risk of coronary heart diseases in post-menopausal women. Women also show less atherogenic lipoprotein subclasses than men. Atherogenic lipoproteins protect against atherosclerosis. Women are therefore at greater risk of coronary heart disease as well. The administration of hormones, hormone replacement therapy (HRT), in postmenopausal women showed no overall cardioprotective effects (23). Estrogen administration is therefore not effective in preventing cardiovascular problems in postmenopausal women. This indicates a more complex mechanism beyond the lower estrogen levels in postmenopausal women underlying HFpEF.

**The renin-angiotensin system**

The renin-angiotensin system (RAAS) is an important regulator of blood pressure and fluid and electrolyte homeostasis (24). Angiotensinogen, renin, angiotensin converting enzyme (ACE), angiotensin 1 and angiotensin 2 receptor are the components of the renin-angiotensin system. Angiotensin serves as the substrate for renin. The kidneys secrete renin, renin converts angiotensinogen to angiotensin 1. Angiotensin I is converted to angiotensin II by the angiotensin converting enzyme. Angiotensin 2 binds to its receptor which mediates vasoconstriction and aldosterone and catecholamine release which can in turn cause an elevated blood pressure. ACE-1 inhibitors inhibit the ACE molecule thereby preventing the increase in angiotensin 2 molecules which inhibits an increase in blood pressure (4). Estrogen stimulates angiotensinogen synthesis (25). Postmenopausal women have slightly lower angiotensinogen levels than premenopausal women. Oral administration of estrogen causes angiotensinogen stimulation. However, administration of estrogen to premenopausal and postmenopausal women causes lower renin levels as compared to men or postmenopausal women without estrogen replacement therapy. The mechanism of this renin down-regulation is unknown. The chronic activation of angiotensin 2 is associated with vascular dysfunction, vascular inflammation, arterial wall thickening,
myocardial fibrosis, atherosclerosis, hypertension and heart failure (26). Estrogen influences the RAAS favouring vasodilation. Menopause upregulates the vasoconstricting arm of the RAAS, causing elevated blood pressure in postmenopausal women. The RAAS explains how menopause affects blood pressure in postmenopausal women. Thus, there is an increased risk of developing HFrEF in postmenopausal women due to the up regulation of the vasoconstricting arm of the RAAS. Sex differences in cardiovascular aging will be discussed in the next section.

**Sex differences in normal cardiovascular aging**

There are also gender differences in the aging process of a normal functioning heart. Myocardial mass is better preserved in aging women than in aging men (27). Aging has declining effects on growth reserve capacity of myocytes and thereby limiting the ventricular responding ability. Ventricular myocytes are lost with aging. Myocyte cell loss may induce coronary artery disease and hypertension, which are common in the elderly. Heart weight is related to body weight, in general men are bigger and taller than women therefore heart weight is generally higher in men. In a study, by the authors Olivetti, Giordano et al., the average heart weight of women was 280gr, and 320gr for men in a population consisting out of 53 women and 53 men. The different sexes in this relatively small population are equally divided. The ages of the hearts in this study ranged between 20-95 years for women and 17-89 years for men. Which is a large range. Wall thickness was measured as well. Bigger left ventricle wall thickness was observed in women. Preservation of cardiac muscle mass occurs in aging women, in aging men there is a reduction in left and right ventricular weight. The total number of myocyte nuclei does not change in aging women, however in male hearts there is a significant loss of myocyte nuclei. The dimensional properties of myocytes are not altered in aging female hearts, however in men myocyte alterations lead to hypertrophied cells.

**Fat mass and cardiovascular aging**

More differences between men and women were mentioned in another study, in which increased waist circumference was associated with left ventricular diastolic dysfunction (28). Both aspects are common in HFrEF patients. A big risk factor for the development of cardiovascular disease is a large visceral fat mass, while peripheral fat seems to protect against CVD. Increases in left ventricular stiffness at end systole were found in women with central obesity and insulin resistance, not in men. This indicates a sex difference in age related ventricular systolic stiffening (27)(28). Obesity produces hemodynamic alterations which cause changes in cardiac morphology and ventricular function. Diastolic function is impaired by limiting energetic availability or increasing myocardial lipid content in obese subjects, which is in turn correlated with increased left ventricular diastolic stiffness. Healthy weight loss might prevent increases in ventricular stiffening with aging. Losing too much weight is associated with adverse outcomes for HFrEF development. The correlation between body composition and HFrEF will further be discussed in the section of “Sex differences in body composition”.

**Sex differences in cardiovascular diseases**

CVD is the leading killer of both men and women in the United States, there are however substantial differences between men and women in the prevalence and burden of different CVD (29). CVD risk factors in women increase at menopause (30). Women are at greater risk for the development of obstructive coronary artery disease at times of low estrogens levels. This explains the high number of postmenopausal women with HF. Women have a higher incidence of endothelial dysfunction than men and a higher prevalence of micro-vascular dysfunction. Endothelial dysfunction is associated with the development of atherosclerosis. Atherosclerosis is different in men and women, women show more plaque erosion and more diffuse plaque than men. There is however no clear understanding of these sex-specific mechanisms in atherosclerosis.

Other CVD like the acute coronary syndrome also show differences between men and women. Women were found to have higher rates of angina pectoris, heart failure, diabetes and hypertension in a study with 7638 women and 19117 men with acute coronary syndromes (ACS) (13). Angina pectoris is the medical term for chest pain due to ischemia, which is the narrowing of the heart’s arteries (31). In acute coronary syndromes women show different symptoms than men, indicating sex differences in this syndrome (13). For example, women are more likely to have minimal coronary artery
disease (CAD) as compared to men. Different treatment choices are favourable for this syndrome. This approach is similar to the proposed approach of treatment in HFpEF. However, the understanding of acute coronary syndrome in women is not complete yet. Coronary dysfunction is a precursor for atherosclerosis, which is linked to the progression of CAD (32). CAD causes cardiovascular-related events such as angina, myocardial infarction (MI) and death. This explains the higher rates of angina in women with ACS. Myocardial infarction is strangely considered a disease of men (33). But it is a cause of death for almost as many women as men, women experience MI later than men because of their longer life period than men. Differences between men and women are not only described in HFpEF, they are described in a range of CVD. In the following section inflammatory influences in cardiovascular diseases will be discussed.

**The role of inflammation in cardiovascular diseases**

Inflammatory mechanisms are associated with CVD development. The development of atherosclerosis is promoted by different factors including smoking, hypertension, atherogenic lipoproteins and hyperglycemia (34). These risk factors cause injury to the vascular system. All stages of atherosclerosis may actually be an inflammatory response to this injury. In response to the vascular injury leukocytes are secreted, the attachment of monocytes to endothelial cells is facilitated by this response. The monocytes migrate into the subintimal space transforming into macrophages. The uptake of cholesterol lipoproteins and the accumulation of macrophages are thought to initiate the plaque formation in atherosclerosis. Within the atherosclerotic region more macrophages, mast cells and activated T cells are attracted. Macrophages and T lymphocytes accumulate in the atherosclerotic lesions (35). Activated macrophages break down collagen which weakens the vascular embedment, making it more prone to rupture (34). Thus, inflammatory cells play an important role in the development of atherosclerosis. Elevated levels of these inflammatory cells can be measured in order to identify plaque formation in atherosclerosis.

**C-reactive protein and cytokines**

C-reactive protein (CRP) is an acute-phase reactant secreted by the liver in response to inflammation. High sensitivity CRP measurements in particular can detect low grade inflammatory reactions which seem to have predictive abilities for future CVD events. Elevated CRP levels are related to the metabolic syndrome (MetS) (36). The metabolic syndrome predisposes individuals with elevated chances of developing CVD and type 2 diabetes. CRP levels are more often elevated in women in comparison to men (30).

The hepatic synthesis of CRP is regulated by the proinflammatory cytokine interleukine-6 (IL-6) (37). IL-6 is a circulating cytokine which can be secreted by activated macrophages and lymphocytes. The production of IL-6 increases with increasing adiposity. Approximately one third of the circulating concentrations of IL-6 originate from adipose tissue. Obesity therefore resembles a low-grade inflammatory state. IL-6 is thought to be the major regulator of the hepatic acute phase response. The acute phase reaction is associated with elevated levels of fibrinogen which is in turn associated with coronary heart disease (CHD). Fibrinogen is an essential protein for blood clotting. Fibrinogen and fibrin 1 are present in plaques (38). Fibrin 2 is detected in luminal thrombus. Fibrin 1 and fibrin 2 can be formed from fibrinogen cleavage. Atherosclerotic lesions are well known for choosing endothelial regions with previous thrombus formation (39). Atherosclerotic plaque can easily be formed at healed, by thrombotic deposition, vascular regions.

**Inflammation in HFpEF**

Inflammation plays an important role in HFpEF as well. Patients with HFpEF show increased circulating IL-6 and other inflammatory proteins like TNF-alpha, IL-8 and MCP1 (40). Fibrotic signals are also increased in HFpEF patients, this can be measured by measuring PIIINP and CITP levels. Chronic pressure overload (e.g. hypertension) regulates pro-inflammatory mechanisms (41). Endothelial adhesion molecules, inflammatory cytokines and chemokines are elevated in inflammation. This is why hypertension is a major risk factor for the development of HFpEF. Cytokines and chemokines activate infiltration of inflammatory cells into cardiac tissue. Inside cardiac tissue monocytes differentiate into macrophages. Macrophages promote cardiac inflammation, tissue injury and myocardial fibrosis. Structural and mechanical remodelling of the heart occurs, primarily due to excessive deposition of collagens. HFpEF patients show altered cGMP-PKG
signalling. Endothelial inflammation alters paracrine signalling from endothelial cells to surrounding cardiomyocytes (42). The fall in NO-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) signalling causes hypertrophy and high diastolic resting tension in cardiomyocytes. Which results in increased stiffness of the myocardium (43). The expression of vascular adhesion molecules (VCAM) and E-selectin is increased in HFpEF patients. The activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is also increased, causing a rise in reactive oxygen species (ROS) production. Oxidative stress increases, causing damage to cardiomyocytes. Oxidative stress also increases due to myocardial nitric oxide synthase (NOS) uncoupling. Oxidative stress and inflammation play an important role in the pathogenesis of HFpEF because they increase LV diastolic dysfunction.

Biomarkers and inflammatory sex differences

CRP can be used as a biomarker to predict the chance of developing HFpEF (44). Since CRP proves to be a strong prognostic marker for risk assessment in patients with HFpEF. Elevated CRP levels are associated with cardiac and vascular events in healthy men and women (45). There are some significant race and sex differences in CRP levels. Women and black subjects show higher CRP levels than men and white subjects. It is, however, necessary to investigate this with a long-term follow-up. Besides CRP being a valuable biomarker for HFpEF, galectin-3 seems to be a valid biomarker as well. Galectin-3 is a biomarker for HF (46). Galectin-3 is secreted by activated macrophages and induces inflammation and fibrosis. Galectin-3 levels are associated with worse prognosis in patients with HFpEF. Galectin-3 proves to be a useful biomarker in HF patients with preserved LVEF.

The association between fat and inflammation

The role of adipose tissue in inflammation was already slightly described in this section. The role of inflammation in cardiovascular diseases. It is well understood that weight gain increases LV diastolic stiffness (28). Total and central obesity usually occurs in women, especially in postmenopausal women (47). IL-6 and TNF-alpha production in adipose tissue are elevated with overall and abdominal obesity. Circulating levels of CRP and IL-6 are higher in the metabolic syndrome. IL-6 concentrations correlated directly with CRP concentrations in obese subjects, suggesting that IL-6 delivery to the liver regulates CRP production (48). Visceral fat is thus involved in the regulation of the acute-phase inflammatory response. In vivo studies have proven that IL-6 release from subcutaneous abdominal fat is higher in obese subjects. Obesity is therefore an important risk factor for the development of HFpEF. The next section will discuss sex differences in body composition.

Sex differences in body composition

Men and women have different body compositions. Women generally have more body fat than men (49). Fat storage differs between men and women. Men tend to store fat around the waist and hips whereas men tend to store fat in the abdominal region (50). Fat oxidation is lower in women, which contributes to the higher ratio of fat storage in women. However, premenopausal women have a lower visceral adipose tissue volume than postmenopausal women (51). This proves that estrogen plays a role in the prevention of obesity in premenopausal women. Thus, women have more general adiposity than men and they have higher circulating IL-6 levels (37). Inflammation is therefore generally higher in women in comparison with men. The association between adiposity and CRP is also stronger in women (52). Thus, the greater adiposity in women increases their chances of developing inflammatory responses, which increases the risk of developing HFpEF.

Conclusion

Heart failure with preserved ejection fraction is more common in women. The numerous risk factors explaining the greater risk for the development of HFpEF in women, were described in this narrative review. The most important and prevalent female risk factors are hypertension, diabetes mellitus, renal insufficiency and obesity. The menopause plays a role as well, since postmenopausal estrogen levels are lower which increases the chances of developing cardiac hypertrophy. In addition, there are differences between men and women in cardiovascular structure and cardiovascular aging. Body composition is also important, women have greater general adiposity and circulating inflammatory cells. All these factors increase the risk for HFpEF development in women. Given the
differences in risk factors and mortality between men and women with HfPEF, it is necessary to develop sex-specific diagnostic criteria and treatments (53). These are necessary to efficiently treat HfPEF and to reduce its mortality. Therefore more research is necessary.

Literature

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