Review Article

Particularities of Heart Failure with Preserved Ejection Fraction in Women – Pathways to Better Care

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Abstract

While heart failure with reduced ejection fraction (HFrEF) is more prevalent in males, female predominance is a striking feature in heart failure with preserved ejection fraction (HFpEF).

The incidence of HFpEF has been gaining alarming proportions. It has exceeded HFrEF as the primary form of heart failure, especially in the female sex. Women tend to have smaller cardiac chambers with higher left ventricular ejection fraction; however, they have more severe symptoms and signs. Until now, there is no consensus about the exact mechanisms of these differences related to sex. Understanding these mechanisms is essential to mitigate the risks for HFpEF and direct efforts towards identifying novel preventive and disease-modifying treatments. Lifestyle, pharmacologic, and device-based approaches to reduce the medical and societal impact of HFpEF could improve patients' quality of life.

The purpose of this review is to outline known biological sex differences in women with HFpEF with a specific focus on pathways to better care for the diagnosis and treatment of women with HFpEF.

Introduction

Heart failure (HF) is a complex clinical syndrome of systemic nature, defined as cardiac dysfunction that causes inadequate blood supply to meet tissue metabolic needs. Heart failure is the third leading cause of cardiovascular death in developed countries and a significant cause of morbidity and hospitalization.[1] The major causes of HF are ischemia in men and hypertension and diabetes in women.[1]

Keywords

Women; Heart Failure; Left Ventricular Function; Diagnosis; Therapeutics

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The clinical syndrome of HF is the sum of multiple anatomical, functional, and biological changes that interact with each other and can be characterized according to left ventricular ejection fraction (LVEF). Heart failure with preserved ejection fraction (HFpEF - LVEF >50%) is the most common condition in women over 65 years of age, associated with smaller cardiac chambers, higher LVEF, and high morbidity and mortality. Risk factors differ between heart failure with reduced ejection fraction (HFrEF) and HFpEF, whose patients are older, mostly women, and more often have hypertension, obesity, and anemia.[2]

Breathlessness and edema are common in both sexes, but, in general, women have orthopnea and paroxysmal nocturnal dyspnea more frequently than men. Women more often tend to have advanced symptoms and congestion, and lower quality of life. Despite having similar rates of HF hospitalization compared to men, women less often are properly treated and more frequently have depression.[1-3]

In the Framingham Study, median survival was 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving for 5 years. The 5-year survival rate for all patients with HF, regardless of the ejection fraction, is lower than 50%. Although survival of patients with HFrEF has improved over time, the same has not happened to patients with HFpEF.[4] A recent publication has shown that approximately 50% of hospitalizations for HF were due to HFpEF, and 50%, to HFrEF.[5,6]

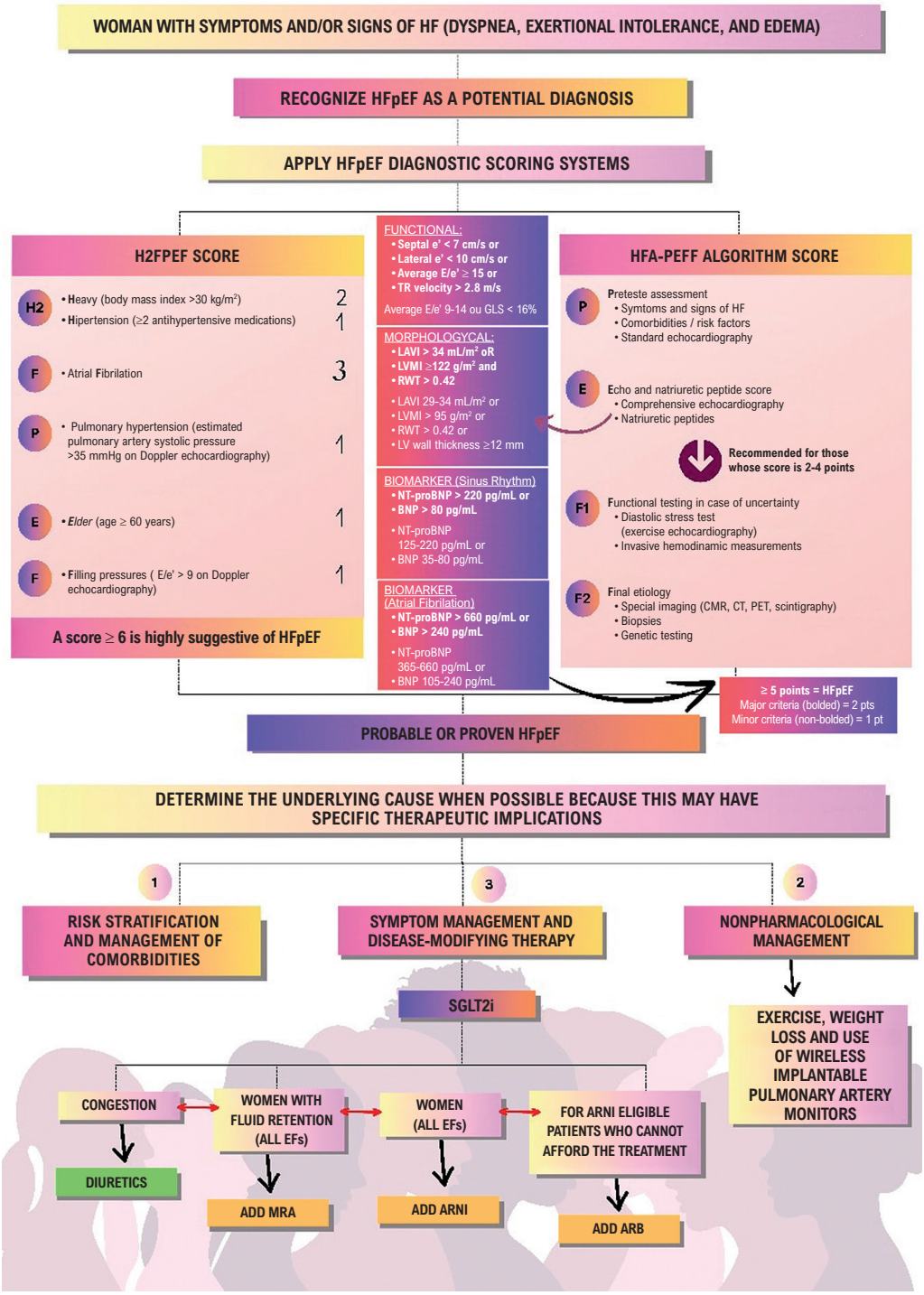
The purpose of this review is to outline known biological sex differences in women with HFpEF with a specific focus on pathways to better care for the diagnosis and treatment of these patients.

Epidemiology and risk factors

In the community, approximately 50% of the patients with HF have HFpEF. Although the age-specific incidence of HF is decreasing, this trend is less dramatic for HFpEF than for HFrEF. The risk of HFpEF increases sharply with age, but hypertension, obesity, and coronary artery disease are additional risk factors. Multimorbidity is common in HFpEF, with nearly 50% of patients having 5 or more significant comorbidities. It is essential to note that most deaths in patients with HFpEF are cardiovascular, but the proportion of noncardiovascular deaths is higher in HFpEF than in HFrEF.[7]

With regards to sex distribution, women are ≈2 times more likely than men to develop HFpEF. Black women with HFpEF

Central Illustration: Particularities of Heart Failure with Preserved Ejection Fraction in Women – Pathways to Better Care



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Algorithm for better diagnosis and care of women with heart failure with preserved ejection fraction (HFpEF).[47,48] ARB: angiotensin-receptor blocker; ARNI: Angiotensin Receptor - Neprilysin Inhibitor; CMR: cardiac magnetic resonance imaging; CT: computed tomography; E/e': ratio between E wave and e' wave velocities; EF: ejection fraction; GLS: global longitudinal strain; HF: heart failure; LAVI: left atrial volume index; LV: left ventricular; LVMI: left ventricular mass index; MRA: mineralocorticoid receptor antagonist; PET: positron emission tomography; RWT: relative wall thickness; SGLT2i: sodium-glucose cotransporter-2 inhibitor; TR: tricuspid regurgitation.

experience a disproportionately higher excess prevalence of disability.[8] Community-based cohort studies have reported higher proportions of women in HFpEF populations, leading to the general idea that women may be more susceptible to HFpEF than men. Women with type 2 diabetes show more pronounced adverse left ventricular (LV) remodeling (concentric hypertrophy) and worse outcomes and quality of life compared to men with type 2 diabetes, even when they have a mean body mass index and glucose levels in the prediabetes range. A recent study suggests that obesity and obesity-related cardiometabolic traits (including insulin resistance) are more strongly associated with the risk of incident HFpEF than HFrEF, especially in women.[9,10]

A systematic review of Brazilian studies has demonstrated that the prevalence of HFpEF in patients with confirmed HF ranged from 28.2% to 59.0% in the outpatient setting and from 20.0% to 53.1% in the hospital environment. The most frequently reported comorbidities were systemic arterial hypertension and diabetes, with a prevalence of 57.4% to 100.0%. The proportion of women in the samples ranged from 44% to 74%.[11]

The main comorbidities of women with HFpEF are illustrated in Figure 1.

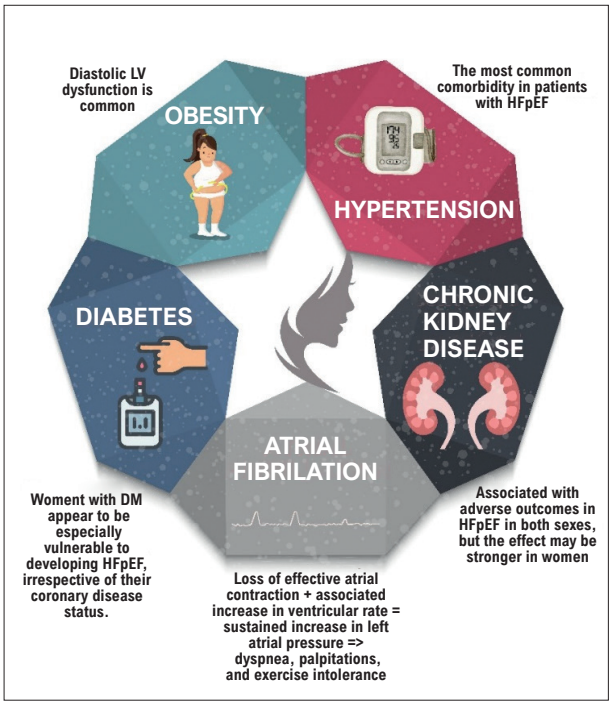

Figure 1 – *Main comorbidities in women with HFpEF. DM: diabetes mellitus; HFpEF: heart failure with preserved ejection fraction; LV: left ventricular.*

Pathophysiological mechanisms related to HFpEF in women

Until now, no consensus exists about the exact pathophysiological mechanisms involved in the HFpEF differences between sexes. What we know is that despite the heterogeneity in pathophysiology, all patients show signs of 'pump failure' reflected in the pathognomonic pathological increases in exertional left atrial (LA) pressures, which represent an increase in pulmonary capillary wedge pressure (PCWP). This abnormality is related to pulmonary edema, dyspnea, reduced exercise capacity, and prognosis.[12,13]

It is undeniable that the inflammatory paradigm plays a central role in the pathophysiology of HFpEF, especially in women, who experience more significant inflammation and chronic microvascular dysfunction.[14,15] Diseases such as diabetes, hypertension, and obesity are among the main drivers of systemic microvascular inflammation. But other noncardiac conditions, such as physical inactivity, estrogen deprivation, chronic kidney disease, iron deficiency, eclampsia and preeclampsia, and chronic pulmonary disease, also stimulate overexpression of vascular adhesion molecules, facilitating leukocyte migration through the endothelium, leading to oxidative stress, increasing reactive oxygen species (ROS), reducing nitric oxide (NO) bioavailability and cyclic guanosine monophosphate (cGMP) levels in cardiomyocytes, and altering the titin phosphorylation. The final path comprises cardiomyocyte hypertrophy, leading to concentric hypertrophy, diastolic dysfunction, and, finally, HFpEF.[16]

In addition, autoimmune diseases, more prevalent in women, with a heightened immune response (e.g., lupus, rheumatoid arthritis, thyroiditis), may be associated with HFpEF.[16]

Estrogen may mediate signaling pathways attenuating ROS, leading to downstream anti-inflammatory effects. So, the loss of estrogen protection can contribute to systemic inflammation. Moreover, in women after menopause, there is an activation of the renin-angiotensin-aldosterone system (RASS) in response to low estrogen levels, which increases oxidative stress, resulting in an additional decline in NO and increasing collagen synthesis.[15]

Women with HFpEF have more severe disturbances of arterial hemodynamics than men and female controls, showing a reduced aortic capacitance and a less compliant arterial system, which results in higher LV afterload and reinforces the idea of vascular dysfunction as one of the pathophysiological mechanisms of the disease.[17] It is important to remember that coronary flow reserve (CFR) and arterial resistance are also impaired, resulting in coronary microvascular dysfunction.

Redfield et al.[18] have demonstrated that both increasing age and female sex were associated with increases in arterial stiffness and load. Furthermore, in population-based studies, arterial stiffness increased more steeply with age in females than in males. As the aorta stiffens, cardiac workload and wall stress increase, LV contractility raises, and concentric remodeling develops to maintain cardiac performance, predisposing to HFpEF.[9,19]

Obesity contributes in a multifactorial way: insulin resistance and the adipose tissue may exacerbate metabolic inefficiency,[3] leading to systemic inflammation (increasing the secretion of inflammatory cytokines), endothelial dysfunction, and subsequent myocyte remodeling.[16]

Schulz et al.[20] have found a dynamic LA filling impairment with worse LA functional reserve only in women with HFpEF. Based on these findings, LA dysfunction appears to be a

critical mediator of the elevation in PCWP during exertion in HFpEF, suggesting that loss of LA functional reserve may be a preferential driver of elevation in exercise PCWP in female HFpEF.

Multiple mechanisms can explain the pathophysiology of HFpEF and are detailed in Figure 2.

Sex differences and risk factors of HFpEF in women

In the HF's background, there are significant sex differences, particularly when considering HFpEF, such as epidemiologic, phenotypic, and outcome factors.

Ischemia is the major cause of HF in men, especially HFrEF, whereas women are at greater risk attributable to the traditional risk factors.[21] Hypertension confers a more significant risk of HF in women (a 3-fold increase in risk *versus* a 2-fold increase in men). Diabetes mellitus also has a more significant effect on HF in women, with an associated 5-fold increase in risk in women *versus* a 2-fold increase in risk in men. Obesity carries a higher risk for HF in women, not just because it is more prevalent in women, but the association of obesity with HF risk is more significant for women, with an increased propensity for HFpEF, being a more potent risk factor. Tobacco use is reported as less prevalent in women. However, the independent risk association of smoking with HF among women is almost double that of men. Lifestyle also influences the risk of HF; in this context, dietary patterns may be of particular importance. It should be noted that heavy alcohol consumption is related to HF risk with no documented sex difference.[16,21,22]

Haykowsky et al.[23] have found that intra-abdominal fat was significantly higher in patients with HFpEF compared to healthy controls and was the strongest predictor of peak oxygen consumption (a marker of exercise performance).

It is worth keeping in mind the sex-specific risk factors for HF, with some of them being risk factors for HFpEF. An example of this is radiation therapy for breast cancer, which can be associated with an increased risk for HF due to potential cardiac radiation exposure (especially in cases of left breast cancer), resulting in microvascular endothelial inflammation.[2]

A range of sex-related differences in risk factors still need to be better studied. Women need to be better represented in studies so that we can finally understand the mechanisms involved, from pathophysiology to therapeutic response, focusing on knowledge gaps that still need to be filled.

Figure 3 summarizes the impact of risk factors for HFpEF in women.

Diagnosis of HFpEF in women

Pretest probability algorithms for HFpEF have been used to evaluate patients with suspected diagnosis, and echocardiogram plays an essential role in this investigation. However, non-invasive methods for the diagnosis or exclusion of HFpEF depend on many parameters, always in combination with others derived from clinical and laboratory tests, which together provide a probability for the diagnosis.

Sex-neutral thresholds are used to define HF syndromes. However, these thresholds may result in underestimating LV

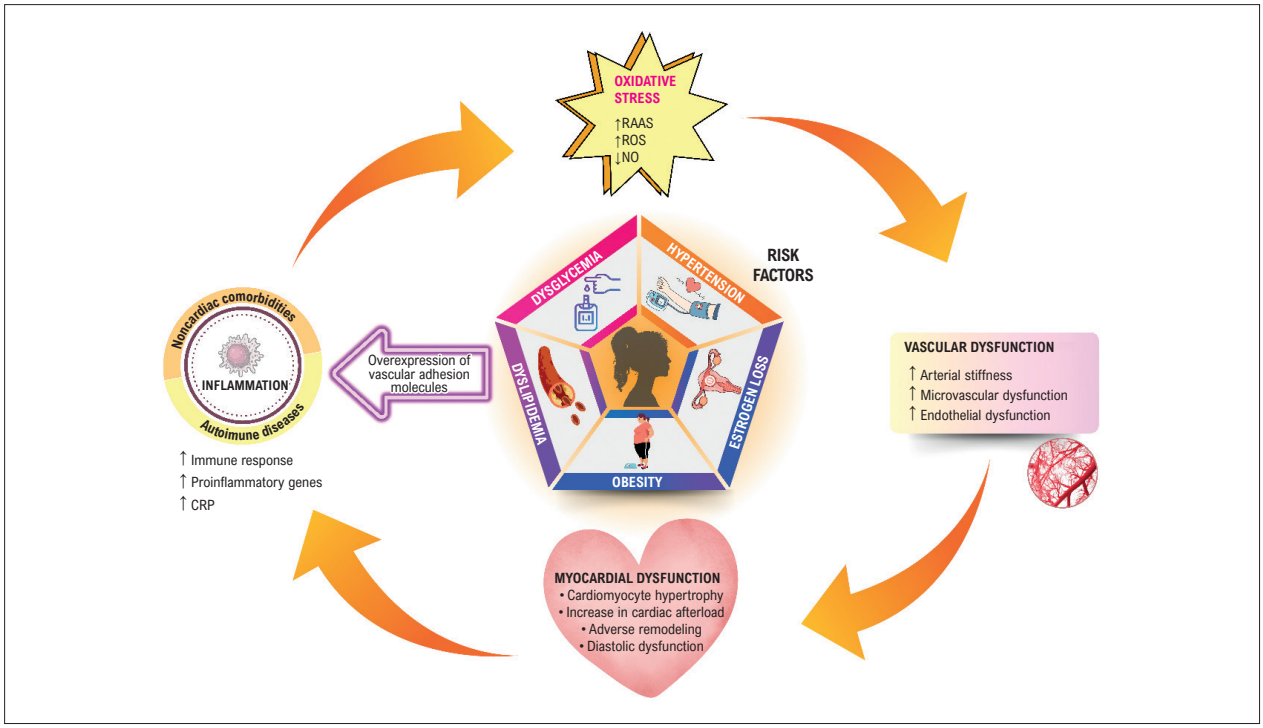

Figure 2 – *Pathophysiological mechanisms involved in heart failure with preserved ejection fraction in women. CRP: C-reactive protein; NO: nitric oxide; RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species.*

Figure 3 – *Sex differences in risk factors for heart failure with preserved ejection fraction (HFpEF) in women. DM: diabetes mellitus; HF: heart failure; PPCM: peripartum cardiomyopathy*

dysfunction in women. An ejection fraction of about 50%, especially in the presence of HF symptoms, may reflect a relatively more significant reduction in systolic function compared to men with the same LVEF. It is important to remember that LVEF is one systolic function parameter, but not the only one. In this context and keeping in mind the hallmark feature of the HFpEF, we should improve the understanding that other measures of LV systolic dysfunction are of particular relevance to women and can be found in specific literature.[2,24]

Women with HFpEF more frequently have some echocardiographic signs, such as concentric remodeling, smaller LV diameters, a greater propensity to elevated ejection fraction, and the trend toward a more preserved global longitudinal strain (GLS).[25] Concentric remodeling in women predisposes to more pronounced changes in diastolic relaxation and LV stiffness when compared to those of men with HFpEF.[25] An Asian cohort with 55% female participants, PURSUIT-HFpEF, has shown that women had more pronounced parameters of diastolic dysfunction on echocardiography than men (septal e' < 7 cm/s, lateral e' < 10 cm/s, E/e' > 14, LA volume > 34 mL/m^2, and tricuspid regurgitation velocity > 2.8 m/s) and that the female sex alone was a factor associated with diastolic dysfunction.[3,26]

One of the most specific stress tests in diagnosing HFpEF is the cardiopulmonary exercise test (CPET), which assesses cardiorespiratory fitness during exertion, aerobic capacity, and gas exchange efficiency by measuring maximum oxygen

consumption (VO2 peak).[27-29] The relationship between ventilation (VE) and carbon dioxide production (VCO2) during exercise is represented by VE/VCO2 slope, and the higher it is, the worse the gas exchange efficiency is during exercise, which may be an early marker of cardiovascular dysfunction and indicates a worse prognosis in HF.[30] Women with HFpEF have worse effort capacity and gas exchange efficiency than men, which can be demonstrated by the parameters analyzed in CPET: lower VO2 peak and VO2 at ventilatory threshold and anaerobic threshold, and a higher VE/VCO2 slope. These CPET parameters are essential in guiding the management of HFpEF.[30] Studies evaluating hemodynamic criteria for HFpEF based on invasive CPET have shown that, after multivariate analysis, women had lower systolic and diastolic reserve and that the latter correlated with diastolic dysfunction found on echocardiography. In addition, they have shown higher capillary pressure, higher pulmonary pressure at peak effort, and lower pulmonary and systemic arterial compliance during exercise.[27,28] On exertion, there were also more significant increase in elastance and lower chronotropic and contractile reserve than in men, contributing to considerable effort intolerance associated with substantial increase in heart rate, exacerbated by the smaller LV dimension.[29]

While healthy women have modestly higher natriuretic peptide levels than men, women with HFpEF have natriuretic peptide levels lower than or similar to those of men. Men have higher markers of cardiac injury, both in the general population and among patients with HF.[2]

In addition to echocardiography, cardiac magnetic resonance imaging (CMR) has been increasingly used in diagnosing heart disease, providing information on cardiac structure, myocardial mass, chamber volume, and ejection fraction. In women with HFpEF, CMR shows smaller LV volume and mass, and ejection fraction equal to or greater than that of men.[30] Stress CMR is an effective method to evaluate microcirculation dysfunction through the analysis of CFR, which is correlated with diastolic function, as well as to evaluate the presence of ischemic coronary artery disease, helping understand HFpEF pathophysiology. In addition, CFR can be assessed using methods, such as myocardial perfusion scintigraphy with PET, which is still rarely available.[31]

In conclusion, imaging methods are essential in diagnosing and understanding the pathophysiology of HFpEF and its peculiarities in females, helping the better management and analyses of its prognosis.

Particularities of the treatment of HFpEF in women

The treatment of HFrEF has an arsenal of medications with proven efficacy in reducing unfavorable outcomes and mortality, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BB), and, more recently, the new hypoglycemic drugs, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors. However, the treatment of HFpEF is still controversial, and the drugs used to treat HFrEF do not always show the same results.[32]

The effectiveness of medications to treat HFrEF has been proven by large randomized controlled trials. Still, in most of them, women are underrepresented, generally corresponding to around 20% to 25% of the studied population. One of the explanations for the exclusion of women, especially those of childbearing age, might be the potential teratogenic effects of some drugs and the predominance of HFpEF in women.[32]

Studies have shown that around 72% of studies still do not conduct a differentiated analysis about sex, which may be a treatment bias because the doses used in women are the same as in men, therefore without adjustment for body weight. These data may be related to the more significant adverse effect of drugs (AED) in women.[32]

Women have specific characteristics regarding the pharmacokinetics and pharmacodynamics of drugs, the first being related to intrinsic factors, such as genetic predisposition, weight, liver and kidney function, and associated diseases, as well as to external factors, such as interaction with other drugs, smoking, and alcohol consumption. Other factors, such as women's anatomical, biochemical, physiological, and hormonal characteristics, which influence the response to the drug's effect, must be mentioned. Sexual differences in drug absorption are related to higher gastric pH and longer gastrointestinal transit in women, differences about the intestinal metabolism of cytochrome P-450 and the active transporter p-glycoprotein (GLp), with its hepatic expression 2.4 times lower in women. Furthermore, associated with a smaller body surface, lead to greater exposure to medications which are used in the same dosage as for men.[3,33,34] There are particularities in the safety and efficacy of pharmacotherapy, such as the fact that AEDs are 1.5 to 1.7 times more frequent in women, and, therefore, more hospitalizations secondary to these effects occur.[34]

Drug clearance is also influenced by sexual factors, such as the expression of sex-linked metabolic enzymes, reduced renal clearance in women due to a lower glomerular filtration rate, lower body mass index, and differences in blood volume, plasma volume, and body water percentage. In addition, other physiological hormonal changes, such as higher percentage of body fat in women and hormonal changes in the menstrual cycle and pregnancy, are related, as many of these particularities depend on estrogen and progesterone. All these factors can alter the distribution of drugs.[34]

Despite these relevant data, sexual differences in the pharmacokinetics and pharmacodynamics of drugs are not usually taken into consideration in guidelines.[35] Studies have shown that, when parameters are corrected for body weight, there is a 15% reduction in statistical difference in the drug's pharmacokinetics. At the same time, non-correction leads to a difference greater than 20%.[36]

Beta-blockers have more significant effects on women, with a more significant reduction in heart rate and blood pressure, compared to men at the same doses.[37,38] The European, prospective, multicenter cohort study, *BIOlogy Study to Tailored Treatment in Chronic Heart Failure*, and the Asian prospective, multicenter, cohort study, *Asian Sudden Cardiac Death in Heart Failure* registry, have evaluated the ideal dose for treating HFpEF in men and women and have concluded that women who used BB associated with ACEIs

or ARBs, at half the dose recommended in the guidelines, had a lower risk of hospitalization and death, without further risk reduction when the drugs were used at full dose. These data must be evaluated carefully, as they can lead to valuable information regarding specific doses for women in the treatment of HFpEF.[39]

The pathophysiology of HFpEF is directly related to obesity, increased insulin resistance, and metabolic syndrome. Thus, weight reduction and encouragement of physical activity are essential to prevent HFpEF, especially in women (Figures 2 and 3). Regarding pharmacological treatment, the evidence is not so robust, and, even until recently, no pharmacological therapy has been recommended.[32] Randomized studies have shown a neutral effect of the major drugs used for HF.[32] Sub-analyses of two of those studies, one involving spironolactone, TOPCAT, and another involving angiotensin receptor II blocker - neprilysin inhibitor (ARNI), PARAGON-HF, have suggested different responses to therapy according to sex. In addition, SGLT2 inhibitors have shown benefits in HFpEF with similar results in men and women.[10] Thus, current evidence points to the benefit of SGLT2 inhibitors for both sexes and the potential benefit of spironolactone and sacubitril-valsartan for women.[32,40-42] In the PARAGON-HF study, a sub-analysis of sex differences in the treatment of HFpEF with sacubitril-valsartan compared to valsartan alone has shown that women had a more significant reduction in hospitalization and mortality with sacubitril-valsartan, whereas men did not had this benefit.[42] This finding emphasizes the need for further studies to understand the interaction between sexual characteristics and the therapeutic response to drugs in the HFpEF treatment, aimed at better results at lower doses. Prospective studies to assess differences between sexes are necessary. Figure 4 highlights the the main differences between sexes in HF.

Women have nonobstructive ischemic heart diseases as the etiology of HFpEF, and, as a remodeling response, less fibrosis and a lower rate of ventricular arrhythmias, resulting in fewer sudden cardiac deaths. However, even after adjusting for age and comorbidities, the female sex had a lower probability of receiving an implantable cardiac device as compared to the male sex. It is worth noting that women have higher rates of complications related to device implantation, such as pneumothorax, infection, bleeding, and tamponade. However, because of the less fibrotic profile and even structural and anatomical characteristics, studies have suggested that women respond more favorably to cardiac resynchronization therapy, which improves symptoms, quality of life, LVEF, and mortality.[43]

With population aging, higher incidence of HFpEF in women, and few therapeutic options of proven efficacy to date, adequate treatment must be carried out for the comorbidities with most significant risk, such as obesity, diabetes, and hypertension.[43]

Further studies are needed to better understand the female-sex characteristics that impact the HFpEF treatment. In addition, prospective multicenter registries could provide more accurate evidence in the female population.[32]

Prognosis of women with HFpEF

In addition to mortality and hospitalization, patients with HFpEF experience significantly reduced quality of life, similar to that in HFrEF.[32]

The HFpEF is associated with multimorbidity, with up to 50% of patients experiencing 5 or more significant comorbidities. Atrial fibrillation and chronic kidney disease are factors that worsen the prognosis of women.[16,44]

Approximately 60% of deaths in HFpEF are due to cardiovascular conditions, such as sudden death, right ventricular failure, and stroke but women are at lower risk of sudden death. One study has shown that pulmonary hypertension is present in 73% of patients, predominantly in women, leading to right ventricular dysfunction in 20-50%, which worsens the prognosis and increases mortality.[16,45] A high NYHA functional class is also associated with shorter survival, previous hospitalization, higher levels of natriuretic peptides, and high-sensitivity troponin.[16]

Early diagnosis, treatment, and prophylactic measures, such as control of risk factors in HFpEF, are essential to provide a better prognosis for this severe and prevalent pathology. In addition to reducing mortality, it is necessary to recognize that reducing hospitalization and improving symptoms and functional capacity are critical patient-centered goals in treating HFpEF.[46]

The best way to prevent progression to advanced HFpEF is the institution of adequate cardiovascular prevention strategies and proper treatment.[32,43]

Perspectives for women with HFPEF

Knowledge about HFpEF in women has evolved in recent years. Understanding the pathophysiology has helped understand the behavior of the disease. However, our knowledge is still scarce, and more research is needed, including the contributions of sex hormones and their deficiency, to identify new preventive and modifying treatments for HFpEF.[32,43]

It would be interesting to review and create sex-specific diagnostic cutoff points in ejection fraction, as well as to identify new circulating biomarkers related to tissue remodeling, inflammation, and neurohormonal regulation to refine risk prediction in women with HFpEF, along with a better mechanistic understanding of sex-specific inflammatory cascades.[32,43,47]

Existing evidence suggests that sex-specific microRNA networks may mediate the relationship between comorbidity-induced inflammatory activation and the pathogenesis of HFpEF in women. Future research into microRNA-induced mechanisms may shed light on unique pathways that contribute to the development of HFpEF in women.[3,32,43,47]

Innovative approaches to treating HF, using artificial intelligence for proper diagnosis and optimized approach, still do not consider sex differences. This care needs to be considered to avoid erroneous behaviors and futile treatment. A preventive strategy must be adopted to reduce the growing incidence and prevalence of HFpEF in women.[32,43,47]

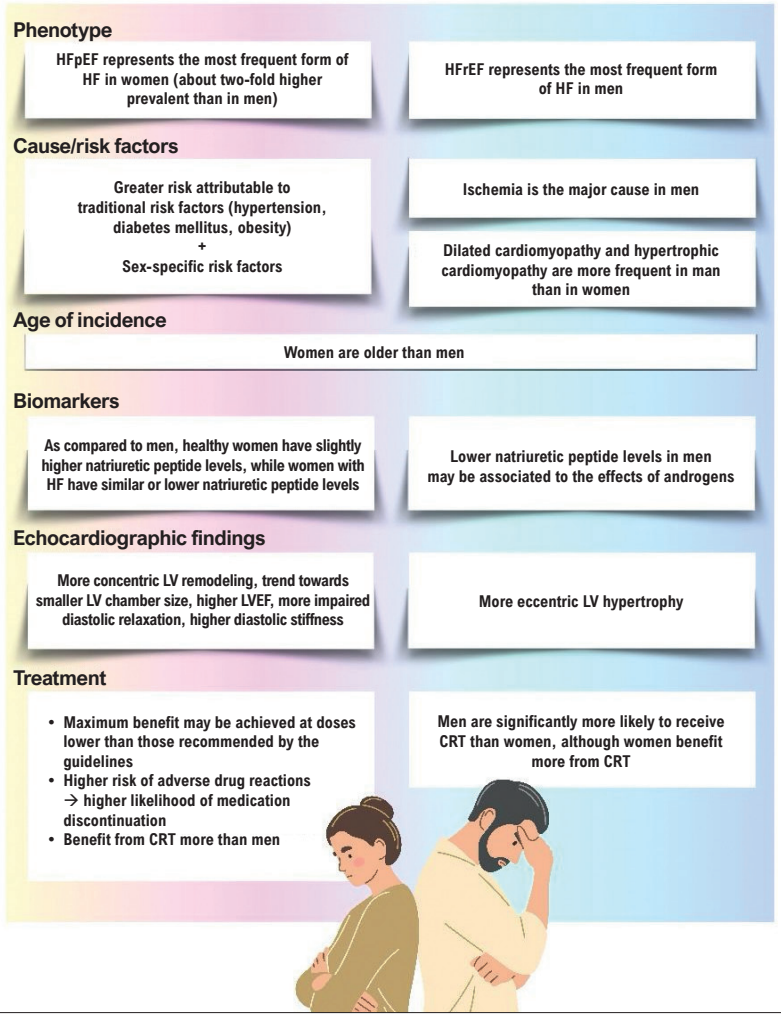

Figure 4 – *Main differences between sexes in heart failure. CRT: cardiac resynchronization therapy; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction.*

Proposed algorithm for better diagnosis and care of women with HFpEF

The most used algorithms for diagnosing HFpEF are the H2FPEF (proposed by Reddy *et al.*) and HFA-PEFF (proposed by the European Society of Cardiology), which include clinical, echocardiographic, and laboratory parameters. In 2023, the European Society of Cardiology suggested a simplified approach to HFpEF using 3 basic criteria: 1. presence of symptoms and/or signs of HF; 2. LVEF ≥ 50%; 3. objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides.[47,48]

In the Central Illustration, we propose an algorithm to facilitate the management of HFpEF, summarizing currently available literature data.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the manuscript for content: Espíndola LN, Almeida MCC, Castro ML, Freire CMV, Oliveira GMM.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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