The Importance of Controlling Comorbidities in HFpEF and How They Influence Disease Evolution

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Heart failure (HF) is a disease with high morbidity and mortality in Brazil and in the world, and HF with preserved ejection fraction (HFpEF) accounts for more than half of cases. Effective pharmacological treatment options for HFpEF are scarce, with poor outcomes and an annual mortality of 10 to 30%. Mortality from noncardiovascular causes is high, which is to be expected given the high number of comorbidities[1] (Figure 1). The syndromic diagnosis is composed of several etiologies and diseases, each one with a specific treatment but with common aspects regarding clinical presentation.

An approach based on the different phenotypes of the disease was proposed, which comprises multiple situations experienced by the group of patients with HFpEF. Each phenotype is dependent on the different presentations of comorbidity severity, which constitutes a challenge for the definitive clinical diagnosis of HFpEF by a clinical cardiologist. Diagnostic scores with probabilistic models were developed to facilitate HFpEF diagnosis, using clinical, echocardiographic, and biomarker variables, such as B-type natriuretic peptide (BNP) and N-terminal portion of BNP. A more detailed description of the diagnosis is beyond the scope of this article.

The main comorbidities in HFpEF include systemic arterial hypertension (SAH), obesity, diabetes, atrial fibrillation (AF), chronic kidney disease (CKD), anemia, macro and microvascular coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea (OSA), among others. This population is composed of older patients with an elevated frailty index. Although comorbidities are similar between older patients with and without HFpEF, those with the disease have more symptoms, such as reduced cardiorespiratory fitness and higher rates of obesity. One of the most common symptoms of HFpEF is dyspnea during effort. However, symptoms of poor exercise tolerance are common among older patients and may reflect normal physiological changes related to aging or may be correlated with noncardiac etiologies. Patients with HFpEF commonly have poor quality of life, increased frequency of hospitalizations, and increased mortality, mostly from cardiovascular causes. Regarding drug treatment, the priority is to try to treat current comorbidities with effective therapies, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers, aldosterone inhibitors, diuretics to reduce congestion, and, more recently, sodium glucose cotransporter 2 (SGLT2) inhibitors. Despite the available treatments, hospital readmission rates can reach 20% in 30 days and up to 50% in 1 year.

When treating specific comorbidities, the way they interact with HFpEF and with the treatment should be taken into consideration. SAH is one of the most common comorbidities in HFpEF and is closely involved in HFpEF development and progression. Changes in the ventricular wall, passive stiffness, ventricular-arterial coupling, systolic reserve, and chronotropic response occur.[2] SAH treatment is a cornerstone of HFpEF treatment and is associated with regression of left ventricular hypertrophy and improvement of diastolic function. Unfortunately, none of the therapies used to lower blood pressure resulted in reduced mortality in HFpEF.

Patients with HFpEF are 4.5 times more likely to develop COPD than age-matched controls. Patients with COPD have worse symptoms and a greater number of fatal and nonfatal outcomes independently.[3] Approximately 20% of patients with HF also have COPD and vice-versa. Importantly, the adequate treatment of one disease reduces the morbidity and mortality of the other.

Myocardial ischemia causes systolic and diastolic dysfunction and is part of the pathophysiology of HFpEF. A study with patients with HFpEF identified that most of them had chronic epicardial coronary disease, whereas more than 80% of the remaining patients had microcirculatory dysfunction, highlighting the high burden of unrecognized CAD in HFpEF. Results from the Prevalence of Microvascular Dysfunction in Heart Failure with Preserved Ejection Fraction (PROMIS-HFpEF) study showed a high prevalence of microvascular dysfunction in patients with HFpEF.[4] Myocardial ischemia without obstructive CAD in women increases the risk of major cardiovascular events.[5] Observational studies with patients with microvascular dysfunction have shown that long-term outcomes are marked by hospitalizations due to HFpEF.

In older people, the main clinical manifestation of HFpEF is exercise intolerance, usually of multifactorial cause, in which several comorbidities act together to trigger the clinical condition.[6]

Keywords

Comorbidity; Heart Failure; Hypertension

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Pulmonary hypertension is a very prevalent condition in HFpEF that remains without adequate treatment. Pulmonary vascular remodeling in advanced HFpEF was found to be very similar to vascular remodeling in pulmonary arterial hypertension.[7] Both diseases seem to arise at the peripheral level at the systemic and pulmonary vascular beds. At the vascular bed, remodeling is induced by reduced nitric oxide availability, whereas at the pulmonary level, the increased pressure results in vasoconstriction and reduced compliance, mediated by cyclic guanosine monophosphate reduction.[8]

Anemia occurs in approximately 50% of patients with HF, and lower hemoglobin levels are independently associated with decreased physical capacity, with consequent worsening of quality of life and increased adverse outcomes. In the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial, patients with anemia and HFpEF had higher levels of biomarkers (NT-proBNP), increased oxidative stress, and increased markers of necrosis. Iron deficiency and low ferritin values were associated with more severe left ventricular systolic dysfunction.[9]

Hypoxia-induced OSA stimulates the sympathetic nervous system and the RAAS as a result of alteration and oxidative stress, maintaining a systemic inflammatory state.[10] The final process pathway consists of alterations in collagen and cardiac titin, with the development of myocardial fibrosis and stiffening, leading to HFpEF progression. OSA treatment improved some surrogate outcomes, but there were no improvements in hard outcomes.[11]

Approximately 65% of patients with HFpEF have AF, and both conditions share similar risk factors. The worsening of left ventricular dysfunction is followed by remodeling and fibrosis of the left atrium, increasing the arrhythmogenic substrate.[12] Interestingly, the risk factors for HFpEF are identical to triggers of arrhythmia substrate. Atrial fibrillation increases the risk of readmission due to HFpEF.[13]

Obesity is very prevalent among patients with HFpEF. In the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study, approximately 83% of patients were overweight or had obesity. The mechanisms proposed for patients with obesity include systemic inflammation, sodium retention, neurohormonal changes, and pulmonary hypertension. Proper diagnosis of HFpEF in euvolemic patients with obesity and unexplained dyspnea is difficult, especially because natriuretic peptides levels may be low and the echocardiographic window may be of poor technical quality in this group.

The paradox of obesity leading to a reduced risk of adverse events is debatable[14] and could be better assessed if waist circumference, which is a more direct marker of central adiposity, was used instead of body mass index in HFpEF with obesity.

Diabetes is a highly prevalent comorbidity, affecting 45% of patients with HFpEF. This group of patients often has more congestion and worse renal function, with an inadequate response to diuretics, elevated inflammatory markers, and an increased readmission rate within 30 days. New studies of diabetes and HFpEF have shown important results in hard outcomes, especially with the use of SGLT2 inhibitors.[15]

Renal dysfunction may trigger HFpEF. Approximately 50% of patients with HFpEF have CKD. Patients with CKD have impaired levels of diastolic function compared with those without CKD. A meta-analysis of more than 1 million patients with established HF reported higher rates of mortality among patients with HFpEF and CKD than among patients with HF with reduced ejection fraction and CKD. The opposite is also true: increased filling pressures and reduced cardiac output increase central venous pressure, leading to reduced renal flow and consequent worsening of renal function.[16] The good outcomes of SGLT2 studies, with improvement of renal function and HF, promote the possibility of a joint treatment for these conditions for the populations in question.

The lack of a HFpEF diagnosis is related to poor knowledge, uncertainty about pathophysiology and treatment, and more specific diagnostic criteria. Understanding the actual pathophysiological aspects of the disease, with a focus on optimizing the treatment of comorbidities, should significantly improve disease outcomes.

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 important intellectual content: Hoffmann Filho CR, Duraes AR, Erzinger GS.

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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.

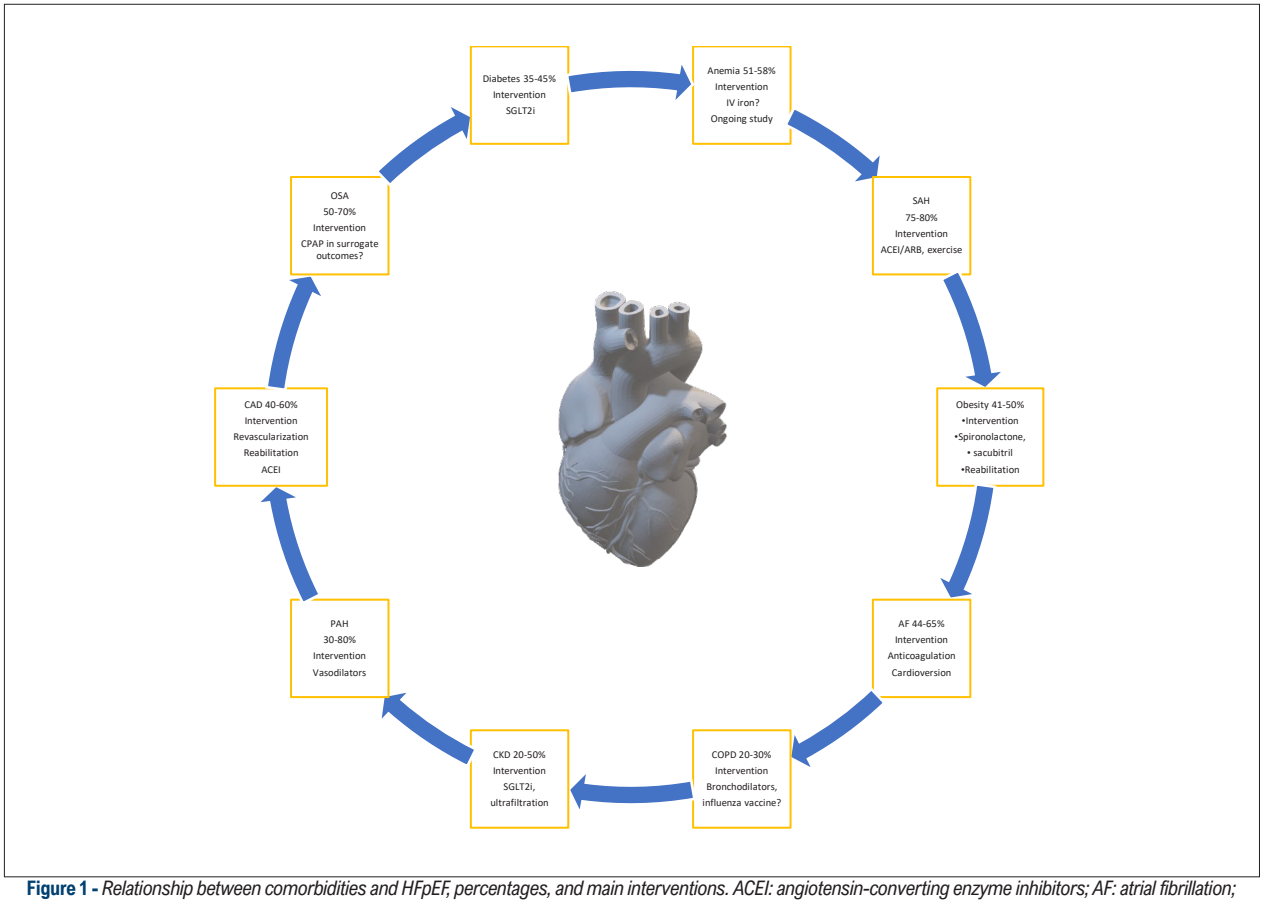

Figure 1 - *Relationship between comorbidities and HFpEF, percentages, and main interventions. ACEI: angiotensin-converting enzyme inhibitors; AF: atrial fibrillation; ARB: angiotensin receptor blockers; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; PAH: pulmonary arterial hypertension; SAH: systemic arterial hypertension; SGLT2i: sodium-glucose cotransporter 2 inhibitors.*

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