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Management Heart Failure with Preserved Ejection Fraction: A Mini Review

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Abstract

BACKGROUND: Heart failure (HF) is a complex clinical syndrome that results when heart's ability to contract or fill is impaired structurally or functionally. Current guideline has been classified HF according to level of left ventricular ejection fraction (EF). 1) Heart failure with reduced ejection fraction (HRrEF): EF ≤ 40%; 2) Heart failure with mildy ejection fraction (HRmrEF): EF 41 - 49%; 3) Heart failure with preserved ejection fraction (HRpEF): EF ≥50%.

AIM: We aimed to analyse the management of heart failure with preserved ejection fraction.

METHODS: We conducted a literature search of relevant articles in various databases (Pubmed & Google Scholar). Articles to include in the review was based on agreement of the authors.

RESULTS: Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of all heart failure cases. HFpEF remains a challenging condition to diagnose given its unclear and often heterogenous etiology with numerous clinical mimics and complex systemic pathophysiology.

CONCLUSION: Additionally, effective treatment modalities are limited with numerous negative clinical trials over the past few decades. In this review, we updated the last knowledge of management HFpEF by reviewing recent guideline and studies.

Introduction

Heart failure (HF) is a complex clinical syndrome that results when heart's ability to contract or fill is impaired structurally or functionally [1]. Current guideline has been classified HF according to the level of the left ventricular ejection fraction (EF). (1) HF with reduced EF: EF ≤40% (2) HF with mildly EF: EF 41–49% (3) HF with preserved EF: EF ≥50% [2]. HF with preserved EF (HFpEF) accounts for 50% of all HF cases and is characterized by typical signs and symptoms of HF, a left ventricular EF of ≥50%, and the presence of cardiac structural and/or functional abnormalities [3].

Those with reduced and preserved EF have similar signs and symptoms, but there are differences in pathophysiology and treatment. Patients who have HF with reduced EF (HFrEF) frequently experience LV contraction problems but in patients with HF and preserved EF (HFpEF), LV EF is normal, although contractile dysfunction is frequently present and only detected with advanced imaging techniques. Elevated end-diastolic pressure and congestion are as severe as in HFrEF [4]. Patients who have HFpEF with normal resting but abnormal exercise and atrial pressures have a higher risk for the combined outcome of mortality or hospitalization for HF compared with people without HFpEF [5].

HFpEF remains a challenging condition to diagnose given its unclear and often heterogeneous etiology with numerous clinical mimics and complex systemic pathophysiology. In addition, effective treatment modalities are limited with numerous negative clinical trials over the past few decades [6]. Treatment guidelines have accordingly emphasized symptomatic management through congestion reduction and treatment of comorbidities [7]. Although the overall incidence of HF in the United States appears to be stable or even decreasing, the incidence of HFpEF specifically continues to rise [8].

The management of HFpEF is based on the following guiding principles; (1) confirm the diagnosis of HF and rule out potentially treatable alternatives; (2) manage congestion and comorbidities (3) evidence-based medical therapy [9].

Confirm the Diagnosis of HF

The diagnosis of HFpEF begins with the identification of key symptoms and signs from bedside examination or early diagnostic assessment, such as exertional dyspnea, orthopnea, paroxysmal nocturnal

dyspnea, fatigue, and edema [9], [10]. In HFpEF presenting as “unexplained dyspnea” where LVEF is normal, physical examination and chest radiography do not suggest congestion, and natriuretic peptide levels are low [9], [11]. Differentiation of dyspnea may be challenging because overlapping symptom presentations comorbid are common in HFpEF, such as obesity, chronic obstructive pulmonary disease (COPD), anemia, chronic kidney disease (CKD), degenerative, and frailty. The diagnosis may be easier in patients who present with overt signs of congestion on physical examination, markedly elevated natriuretic peptides, or radiographic evidence of congestion or elevated filling pressures [9].

The diagnosis of HFpEF is established not only based on a general clinical impression but through a systematic, objective assessment of the medical history, bedside evaluation, imaging, and laboratory profile for typical features. There’s required evidence of increased cardiac filling pressures (right atrial pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure) at rest or with exercise [7], [9]. Increased cardiac filling pressures can be an inference from physical examination, chest radiography, echocardiography, natriuretic peptide assays, the H2FPEF score (Figure 1), or by direct measurement at the right heart catheterization (RHC) [7], [12], [13].

The RHC directly measures atrial pressures and is considered the criterion standard (100% sensitivity and specificity; C statistic, 1.0) for HFpEF diagnosis [14]. Clinicians should formally integrate historical features, evidence of structural heart disease from 2-dimensional echocardiography, Doppler assessment of diastolic function and intracardiac filling pressures, and laboratory assessment of cardiac biomarkers to estimate the likelihood of HFpEF and identify those in whom additional exercise hemodynamic evaluation or diastolic stress testing would be helpful [10], [13].

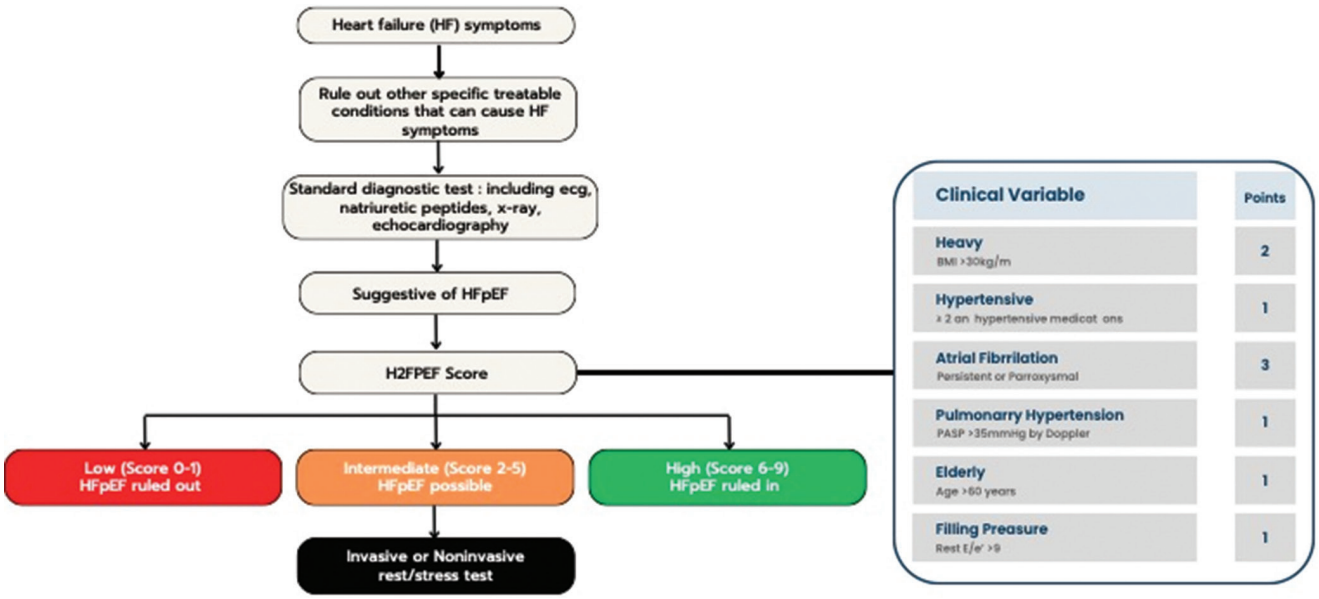
Clinicians should be considered invasive diagnostics where noninvasive diagnostics are inconclusive.

Rule Out Potentially Treatable Alternatives

Patients with the syndrome of HF symptoms and normal or nearly normal EF should be separated from other conditions that specifically causes HF symptoms but have different causes and treatments.

The differential diagnosis is lengthy and includes pericardial disease (constrictive pericarditis), myocardial disease (hypertrophic cardiomyopathy), infiltrative heart disease (amyloidosis, hemochromatosis, and sarcoidosis), storage disease (Fabry disease), valvular heart disease (aortic stenosis, aortic insufficiency, rheumatic heart disease, and degenerative mitral or tricuspid valve disease), pulmonary hypertension, high-output HF, primary right ventricular failure (arrhythmogenic right ventricular cardiomyopathy and RV infarction), and even non-cardiac illness (particularly renal/hepatic failure in those presenting with edema/anasarca) [10].

These conditions should be separated from cardiac conditions that frequently occur with HFpEF (such as coronary artery disease, atrial fibrillation, functional mitral or tricuspid regurgitation, post-capillary pulmonary hypertension, and chronotropic incompetence) and may be targeted for therapy [10].



HFpEF diagnostic algorithm.[9,11] ECG = Electrocardiogram; BMI = Body mass index; PASP = pulmonary arterial systolic pressure; E/e'= ratio of early diastolic mitral inflow blood velocity to mitral annular tissue velocity

Figure 1: Diagnostic algorithm for heart failure preserved ejection fraction

Accordingly, excluding specific cardiac conditions is an early step in the diagnosis of HFpEF [10].

Manage Congestion and Comorbid

Patients HF and presented congestion or volume overload should be offered diuretic therapy, type, and dose depending on the severity of volume overload. Loop diuretic agents have been the first choice of decongestion in patients with HF, and are used in more than 80–90% of patients enrolled in clinical trials despite concerns that these agents may worsen neurohormonal activation, electrolyte derangements, and renal dysfunction, particularly at higher dose [15] because the majority of medication changes made by clinicians in response to hemodynamic monitoring data were adjustment in loop diuretic dose, these data give reassurance that targeted use of diuretic agents to relieve congestion may improve, rather than worsen, long-term outcomes [16].

Treatment of HFpEF also includes the management of comorbid causes of HFpEF. Patients HFpEF have highly prevalent cardiovascular and non-cardiovascular comorbidities including hypertension, obesity, diabetes, atrial fibrillation, COPD, CKD [9], [16].

Prevalence hypertension in HFpEF patients is between 55% and 90% [16]. The role of hypertension is to make the left ventricular hypertrophy, LV diastolic dysfunction, LV fibrosis, left atrial dilatation, and microvascular and macrovascular stiffness [17]. A meta-analysis of 10 randomized controlled trials suggested that SBP <130 mmHg may reduce hospitalization in patients HFpEF but also increased the risk of renal dysfunction [18]. Similarly, in 2022, the American College of Cardiology (ACC)/American Heart Association (AHA)/ HFSA Guideline for the management of HF recommend target blood pressure for hypertension patient with HFpEF is <130/80 mmHg [7].

The prevalence of diabetes in HFpEF patients is 40% [19]. Oxidative stress is believed to have a role in resulting vascular inflammation and endothelial dysfunction in diabetes patients which will cause endothelial dysfunction in HFpEF more widely [20]. Previous studies suggest that the administration of SGLT2 inhibitor in diabetic patients with HFpEF reduced cardiovascular death and HF hospitalization by 31% [21].

Overweight or obesity in HFpEF patients is more than 80% [22]. Previous studies have shown caloric restriction and routine aerobic exercise may improve overall functional capacity and quality of life in patients with HFpEF, especially those with obesity [22, 23].

Atrial fibrillation and HFpEF are also risk factors for each other, prevalence of AF in HFpEF, between 15% and 40% [24]. Administration of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/ atrial flutter) suggested a reduction in cardiovascular events in HFpEF patients with paroxysmal atrial fibrillation or flutter randomized to treatment with the antiarrhythmic drug dronedarone [25]. Another study comparing of antiarrhythmic drugs versus ablation in HF patients with AF suggests that catheter ablation is associated with improved clinical outcomes, quality of life, and possibly lower rates of mortality [26].

Evidence-Based Therapy

Exercise

Exercise training in HFpEF has shown consistent benefits on exercise performance and quality of life in HFpEF and, as earlier, these benefits are observed even in frail, elderly hospitalized patients with HFpEF [27]. Current HF guidelines establish that exercise training (or regular physical activity) is recommended to improve functional status, exercise performance, and quality of life with a Class I level of recommendation.

SGLT2 Inhibitor

First-line therapy for HFpEF includes SGLT2 inhibitor. In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic HFpEF) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With EFpHF) trial suggest that treatment SGLT2 inhibitor Empagliflozin in HFpEF patient can reduce both cardiovascular death and hospitalization for HF [27]. More recently, treatment with dapagliflozin compared to placebo in patients with chronic HF, LVEF >40% NYHA functional Class II–IV HF symptoms, and evidence of structural heart disease by echocardiography suggest that administration of dapagliflozin can reduce 18% in the primary composite outcome such as unplanned hospitalization or urgent ambulatory visits for HF management or cardiovascular death with a significant reduction in worsening HF event (21%) [28]. Based on these data ACC/AHA guidelines 2022 suggest that SGLT2 inhibitor to treat patients with HF and LVEF ≥50% is reasonable (Class of Recommendation IIa).

Angiotensin receptor-neprilysin inhibitor (ARNI)

PARAGON-HF (Prospective Comparison of ARNI with Angiotensin-converting-enzyme inhibitor [ACEI] to Determine Impact on Global Mortality and

Morbidity in HF) trial of patients with NYHA functional class II to IV HF, LVEF ≥45%, and elevated natriuretic peptide levels randomly assigned to treatment with sacubitril/valsartan or valsartan suggests that use of composite angiotensin receptor-neprilysin inhibition may be a superior approach to angiotensin receptor blocker (ARB) monotherapy for the selected patient with HFpEF. Treatment with sacubitril/valsartan was associated with a modest reduction in the primary composite of total hospitalizations for HF and cardiovascular death, including quality of life, NYHA functional class, and composite renal events [29].

Data from the PARADIGM-HF (prospective comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in HF) suggest effect of sacubitril/valsartan on HF hospitalization depending on level LVEF, greatest effect seen for those with LVEF below the normal than supranormal LVEF. But benefits do appear to extend too many patients with an EF ≥50% and to a higher LVEF in women than in men [30]. The 2022 ACC/AHA treatment guidelines suggest that the use of ARNI may be considered to reduce HF hospitalization in patients with HFpEF (class of recommendation IIb). However, the 2022 ACC/AHA guidelines still recommended to use of ARB in patients HFpEF to reduce hospitalization (Class of Recommendation IIb). However, considering previous studies, these agents may be most appropriate as a second-line alternative for those who cannot tolerate or afford treatment with ARNIs [9].

Mineralocorticoid Receptor Antagonist (MRA)

Data from the TOPCAT (Aldosterone Antagonist Therapy for Adults With HF and Preserved Systolic Function) trials compared the treatment of spironalactone with placebo in patient HFpEF showed that it did not significantly improve the combined rate of cardiovascular death, HF hospitalization, or cardiac arrest at 3.3 years of follow-up [31]. Treatment benefits appear to be greatest in those with LVEF near the lower end of the range of eligibility [32]. The ACC/AHA 2022 guidelines recommend that spironolactone can be considered to reduce HF hospitalization in appropriately selected HFpEF patients. According to a study from TOPCAT trials suggest greater benefit in those with LVEF closer to 50% (Class of Recommendation IIb).” is revised to “TOPCAT trials suggests using spironolactone in patients with LVEF of 44% to 49% to reduce cardiovascular death, HF hospitalization, or resuscitated sudden death.

A main reason consideration the use of MRAs in patients HFpEF is the risk of hypercalcemia and worsening renal function. However, spironolactone efficacy appears consistent in patients with CKD but less safety and efficacy in patients with lower eGFR (eg, <45 mL/min/1.73 m^2). Similarly, the guidelines suggest the avoidance of spironolactone in patients with severe renal dysfunction (eGFR <30 mL/min/1.73 m^2) [32].

Conclusions

Management in patients with HFpEF begins with confirmation the diagnosed and exclusion of differentially diagnosed, treatment in HFpEF should focus on congestion (if present) and optimalization management of comorbidities such as hypertension, diabetes mellitus, CKD, atrial fibrillation, and obesity. Loop diuretic agents have been the first choice of decongestion in patients with HF and presented volume overload. Based on the cumulative evidence of efficacy, First-line therapy for HFpEF includes a sodium-glucose cotransporter type 2 (SGLT2) without contraindications. In some patients who remain symptomatic despite SGLT2 inhibition consider the addition of ARNI or ARB/angiotensin-converting enzyme (ACE-I), but we recommend ARNI rather than ARB/ACE-I. Furthermore, in patients with normal renal function and level of potassium 3-drug regimen with further addition of MRA may also be appropriate.

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