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MEDICAL MANAGEMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION: A CONCISE REVIEW

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ABSTRACT

Heart failure (HF) is segregated into subtypes based on the left ventricular ejection fraction. Heart failure with preserved ejection fraction (HFpEF) accounts for up to 50% of all HF patients, and is linked to high morbidity and mortality. Lately it is becoming clearer that HFpEF is a heterogeneous syndrome that is probably caused by a combination of genetic predisposition, environmental factors, and a great burden of associated comorbidities, each of which contributes to a range of pathophysiologic abnormalities that are still not comprehended. In this review, we discuss the current explanations on HFpEF etiology, diagnosis, current guideline recommendations and management of HFpEF.

KEYWORDS

Heart failure, HFpEF, Heart failure with preserved ejection fraction, ejection fraction, medical management, AHA/ACC/HFSA guideline recommendations.

INTRODUCTION

Heart failure (HF) is a clinical syndrome having multifaceted pathophysiology with high rates of hospitalisations and poor quality of life. Thus it is a major reason of morbidity and mortality[1–3].

HF has been classified into various subtypes based on the left ventricular ejection fraction (LVEF), [4]. This includes HF with reduced ejection fraction (HFrEF; LVEF ≤40%), HF with mildly reduced ejection fraction (HFmrEF; LVEF 41% to 49%), HF with preserved ejection fraction (HFpEF; LVEF ≥50%) and HF with improved ejection fraction (HFimpEF; HF with a baseline LVEF of ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF of >40%) [5].

Currently, HFpEF account for half of all HF cases [6]. Compared to HFrEF, annual prevalence of HFpEF is rising by ~1%, thus making HFpEF as most common type of HF [7]. HFpEF is more common in women, which may be due to longer life expectancy and the age distribution of the population at risk noted in women's [8–10]. The rising prevalence of

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HFpEF can be attributed to various factors viz: increased longevity, exponential rise in cardiac and non-cardiac comorbidities such as atrial fibrillation (AF), diabetes mellitus, chronic renal disease, and obesity, and greater clinical awareness towards HFpEF [6,11].

HF patients continue to have a very high rate of re-hospitalisation rate and which is similar for both HFpEF and HFrEF patients [12]. A 29% re-hospitalisation rate has been noted for the HFpEF patients within 60-90 days' of hospital discharge [13]. Absolute mortality rate of HFpEF remains higher than HFrEF, regardless of age, gender, or etiology [14].

HFpEF is a relatively newly classified condition [14]. With increasing prevalence and clinical relevance, it is critical to have a better understanding of HFpEF for better disease management and outcome. This article reviews and summarises available information on the etiology, diagnosis, phenotypes, and potential treatment options of HFpEF.

PATHOPHYSIOLOGY

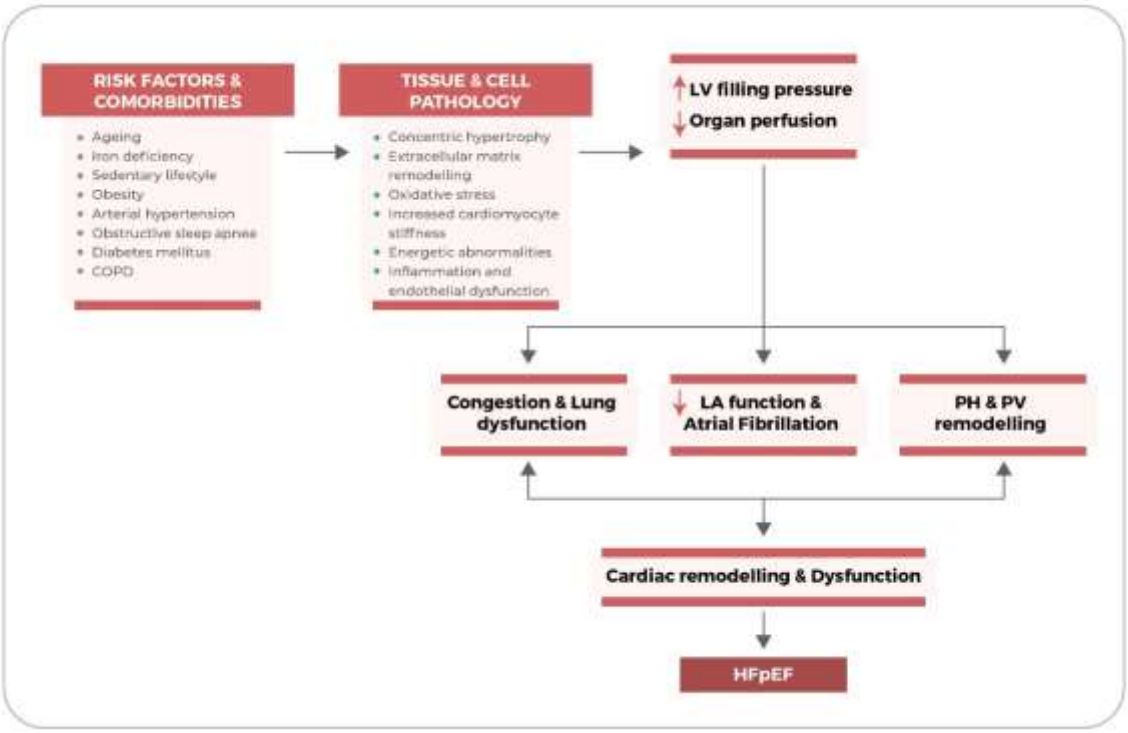

Figure 1: Pathophysiology of HFpEF.

COPD Chronic obstructive pulmonary disease, LV Left ventricle, LA Left atrium, PH Pulmonary hypertension, PV Pulmonary vasculature, HFpEF heart failure with preserved ejection fraction.

The exact pathophysiology of HFpEF is not well established. Microvascular dysfunction mediated by microRNAs, systemic low-grade inflammation, myocardial fibrosis and hypertrophy are key involved factors [14]. Comorbidities plays an important part in the development of HFpEF (Figure 1) and HFrEF, however there is a considerable difference between the two [11,14–18]. Table 1 summarises the broad differences between HFpEF and HFrEF [14–16].

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Table 1: Differences between HFpEF and HFrEF

HFpEF	HFrEF
More common in older population and women	More common in men
Valvular heart disease, hypertension, atrial fibrillation and anemia are more prominent	More commonly have an ischemic etiology and left bundle branch block presentation
Increase in Ca^{2+} availability leads to enhanced cardiac contractility	Supressed Ca^{2+} activity and diminished contractility

DIAGNOSIS

Diagnostic algorithms of HFpEF published by AHA/ACC/HFSA and ESC recommend history and detailed clinical examination, followed by investigations which includes: natriuretic peptide evaluation and echocardiography. Based on this HF can be divided into either HFrEF, HFpEF or HFmrEF [19,20]. In case of uncertainty, exercise stress echocardiography, cardiac MRI, biopsy, CT or PET can be deployed to confirm the diagnosis and aetiology [20].

A recent approach for risk assessment of subclinical heart failure is determination of H_2FPEF score (Table 2) [21]. Similar scoring system namely HFA-PEFF score has been reported by ESC guidelines [18]. These scores are clinically meaningful in identifying the patients at high risk of HF however around one-fourth of the patients with poor scores meeting invasive HFpEF criteria are incorrectly classified [22].

Table 2: H_2FPEF score

SCORE COMPONENT	DESCRIPTION	ALLOTTED POINTS
H	BMI >30 kg/m2	2
H	Use of ≥2 antihypertensive medications	1
F	Presence of atrial fibrillation	3
P	PH defined as pulmonary artery systolic pressure >35 mm Hg	1
E	Elderly with an age >60 years	1
P	Elevated filling pressures evident from E/e' >9	1

<2 – Low likelihood, 3-4 – Intermediate likelihood, ≥5 – High likelihood of HFpEF. BMI- Body mass index, PH- Pulmonary hypertension, E- mitral valve inflow E velocity; e'- mitral annular tissue Doppler velocity.

COMORBIDITIES IN HFpEF

Cardiac and non-cardiac comorbidities are more common in HFpEF patients as compared to HFrEF patients [23]. In a large observational study involving ~0.1 million patients, the common comorbidities noted were hypertension (80%), chronic kidney disease (52%),

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coronary artery disease (44%), atrial fibrillation (34%), pulmonary disease (33%), diabetes (21-24%) and anemia (22%) [24]. Present evidence highlighted that number of comorbidities is directly proportional to mortality rate and HF hospitalisations in HFpEF patients [24]. Based on the predominant symptoms and comorbidities and application of analytical tools like machine learning, HFpEF patients have now been classified into various subgroups referred to as phenotypes [25]. Classification based on phenotypes may provide more specific and effective management of HFpEF patients [26].

MANAGEMENT

Lifestyle management therapy

Majority of HFpEF patients are with advanced age with reduced exercise tolerance leading to a low quality of life [27,28]. Exercise training (ET) for people with HF is now being emphasised due to several advantages [14]. According to a recent meta-analysis, quality of life after ET is significantly improved in HFpEF patients [29]. HFpEF and commonly associated comorbidities like AF and CAD which responds favourably to ET [22]. Diet modifications such as calorie restriction and low-sodium diet has also shown to positively affect HFpEF outcome [22,30]. Diet modification and exercise produced cumulative benefits [30]. The Mediterranean, whole-grain, plant-based food, and DASH diets are examples of healthy eating habits that may provide some protection against the development of HF [31].

Medical therapy

No pharmacotherapy has yet reported reduction in all-cause or CV mortality associated with HFpEF [4]. Despite limited data, diuretics have been the cornerstone of HFpEF care [4]. write year AHA/ACC/HFSA released their guidelines for the management of heart failure, the key highlights along with recommended medications are mentioned in Box 1 and Table 3 [9].

Table 3: Medication recommendation for management of HFpEF

SYMPTOMATIC HF WITH LVEF ≥ 50%		
CLASS 1 (STRONG) Benefit >>> Risk	**CLASS 2a (MODERATE)** Benefit >> Risk	**CLASS 2b (WEAK)** Benefit ≥ Risk
Diuretics, as needed.	SGLT2i	ARNi* MRA* ARB*

* Greater benefit in patients with LVEF closer to 50%. LVEF left ventricular ejection fraction, SGLT2i sodium SGLT2i glucose cotransporter 2 inhibitor, ARNI angiotensin receptor-neprilysin inhibitors, MRA Mineralocorticoid receptor antagonist, ARB Angiotensin receptor blocker.

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Box 1: AHA/ACC/HFSA guideline recommendations for management of HFpEF

1. Blood pressure needs to titrated to attain targets in accordance with published clinical practice guidelines to prevent morbidity.
2. SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.
3. Management of AF can be useful to improve symptoms.
4. In selected patients, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.
5. In selected patients, ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.
6. In selected patients, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.
7. Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.

HFpEF is complex disease and multidisciplinary approach is needed. Clinical trials which studied the various therapeutic methods are summarised in Table 4.

Table 4: Summary of clinical studies investigating treatments for HFpEF

SR. NO.	CLINICAL TRIAL	DRUG CLASS TARGETED	INTERVENTIONS	INCLUSION CRITERIA	ENDPOINTS	CONCLUSION
1	CHARM-Preserved (51)	ACEI/ARB	Candesartan	Age ≥ 18 years, NYHA II-IV, EF > 40%	CV death, HF hospitalization	No mortality benefit; moderate impact in preventing HF hospitalisation.
2	PEP-CHF (33)		Perindopril	Age ≥ 70 years, clinical diagnosis of chronic HF, EF ≥ 40%, hospitalised for a cardiac problem, able to walk without the aid of another person	Composite of all-cause mortality and unplanned HF hospitalization	Improved HFpEF symptoms and exercise capacity; fewer HF hospitalisations; no reduction in

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SR. NO.	CLINICAL TRIAL	DRUG CLASS TARGETED	INTERVENTIONS	INCLUSION CRITERIA	ENDPOINTS	CONCLUSION
						mortality.
3	PARAMOUNT(52)	ARNI	Sacubitril/ valsartan	Aged ≥ 40 years, EF ≥ 45%, HF signs or symptoms, NT-proBNP ≥ 400 pg/mL, eGFR ≥ 30 mL/min/1.73m2, potassium ≤ 5.2 mmol/L	NT-proBNP	Significant reduction of NT-proBNP with S/V.
4	PARALLAX(53)			Age ≥ 45 years, EF > 40%, LAE or LVH on echocardiography, NYHA II–IV, NT-proBNP > 220 pg/mL for patients with no AF or > 600 pg/mL for those with AF	NT-proBNP, 6MWD	Significant reduction in NT-proBNP with S/V; S/V had no additional benefits on 6MWD
5	VITALITY (54)	sGC stimulator and activator	Vericiguat	Age ≥ 45 years, EF ≥ 45%, NYHA II–III, H/O chronic HF and HF decompensation within 6 months, NT-proBNP ≥ 300 or BNP ≥ 100 pg/mL in sinus rhythm, or NT-proBNP ≥ 600 or BNP ≥ 200 pg/mL in AF, Echocardiographic evidence of LVEF ≥45% and either LVH or LAE.	Change in the KCCQ PLS.	No improvement in physical limitation score of KCCQ
6	SOCRATES-PRESERVED (55)			NYHA II-IV, EF ≥ 45%, BNP ≥ 100 pg/mL or NT- proBNP ≥ 300 pg/mL(or BNP ≥ 200 pg/mL or NTproBNP ≥ 600 pg/mL in AF), LAE determined by	Change in NT-proBNP and LAV.	No change in NT-proBNP and LAV; improvement in QOL

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SR. NO.	CLINICAL TRIAL	DRUG CLASS TARGETED	INTERVENTIONS	INCLUSION CRITERIA	ENDPOINTS	CONCLUSION
				echocardiography		
7	EMPEROR-PRESERVED (40)	SGLT-2 inhibitor	Empagliflozin	NYHA II-IV, EF > 40%, NTproBNP > 300 pg/mL in patients without AF and > 900 pg/mL in AF, structural changes in the heart (left atrial size or LVM) on echocardiography, HF hospitalization	CV death, HF hospitalization	Reduced risk of CV death and HF hospitalisation.
8	SOLOIST-WHF(41)		Sotaglifozin	Type 2 diabetes mellitus, HF hospitalization	CV death, HF hospitalization	Significant reduction in CV deaths, HF urgent visits and HF hospitalisations.
9	TOPCAT (39)	MRA	Spironolactone	Age ≥ , EF ≥ 45%, potassium < 5.0 mmol/L, HF hospitalization, BNP ≥ 100 pg/ml, NTproBNP ≥ 360 pg/ml	Composite of CV death, aborted cardiac arrest, or HF	No change in composite of primary outcome.
10	Aldo-DHF(38)			Age ≥ 50 years, NYHA II-III, EF 50%, diastolic dysfunction	LV diastolic function (E/e') and peak O_2 consumption.	Improved diastolic function and LV remodelling; no change in maximal exercise capacity.

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SR. NO.	CLINICAL TRIAL	DRUG CLASS TARGETED	INTERVENTIONS	INCLUSION CRITERIA	ENDPOINTS	CONCLUSION
11	DELIVER (56)	SGLT-2 inhibitor	Dapagliflozin	Age >40 years, stabilised HF, with or without T2D, LVEF >40%, evidence of structural heart disease and elevated natriuretic peptide level.	Composite of unplanned hospitalisation for HF or an urgent visit for HF or CV death.	Reduced the combined risk of worsening HF or CV death.

HFpEF heart failure with preserved ejection fraction, NYHA New York Heart Assocation, AF atrial fibrillation, QOL quality of life, 6MWD 6-min walk distance, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, ARNI angiotensin receptor-neprilysin inhibitor, eGFR estimated glomerular filtration rate, CV cardiovascular, BNP B-type natriuretic peptide, NT-proBNP N-terminal pro-B-type natriuretic peptide, sGC soluble guanylyl cyclase, LAE left atrial enlargement, CO cardiac output, PCWP pulmonary capillary wedge pressure, SGLT-2 sodium glucose cotransporter-2, HF heart failure, PAP pulmonary artery pressure, LVH left ventricular hypertrophy, PDE-5 phosphodiesterase-5, MRA mineralocorticoid receptor antagonist, ECV extracellular volume fraction, MRI magnetic resonance imaging, E/e′ mitral early diastolic velocity/mitral annular velocity, LVMI left ventricular mass index, IASD interatrial shunt device, ASV adaptive servo-ventilation, HFrEF heart failure with reduced ejection fraction, AHI apnea–hypopnea index, EF ejection fraction, S/V Sacubitril/Valsartan, KCCQ Kansas City Cardiomyopathy Questionnaire, PLS physical limitation score, LAV left atrial volume, T2D typre 2 diabetes mellitus, LVEF left ventricular ejection fraction

Role of diuretics

The primary goal of diuretics treatment in HFpEF is to reduce the oedema and dyspnea [32] . Diuretics reduce LV filling pressure, decreases pulmonary artery pressure and improves RV loading [25]. Thiazide and thiazide-like diuretics are known to reduce the incidence of new-onset HF and events of HF exacerbations, and therefore has a role in patients of HFpEF with hypertension [25]. Loop diuretics are preferred over thiazide/thiazide-like diuretics in view of powerful diuresis [25]. They can be considered as first line drugs in HFpEF patients with DM [25].

Role of ACEi/ARBs/ARNI

ACEi and ARBs reduces the risk of HF hospitalisation but have failed to demonstrate a significant decrease in all-cause or CV mortality [22]. Currently, these drugs are used to manage patients of HFpEF having CKD with proteinuria [32]. ACEi can be recommended in patients with coexistence of hypertension and DM for renal protection [25]. The PEP-CHEF trial involving patients with LVEF ≥40% receiving perindopril reported no significant reduction in all-cause mortality and/or heart failure-related hospitalizations in patients [33].

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However, Swedish Heart Failure registry has shown a significant reduction of all-cause mortality with the use of ACEi or ARBs in HF patients with EF>40% [34]. ARBs can be preferred over ACEi in the management of hypertension to decrease the hospitalisation frequency in patients HFpEF [25]. Studies have shown that individuals with increased troponin levels or recent hospitalisation for HF were more likely to experience CV events and may benefit from ARNI, and this effect may be further enhanced in patients who were prescribed MRA in the past [22]. In PARAGON-HF trial, compared to valsartan, sacubitril-valsartan reduced HF hospitalizations but not the composite outcome of CV mortality and total HF hospitalizations [35].

Role of β-blockers

β-blockers can be considered in HFpEF patients with coexistence of atrial fibrillation and CAD with history of MI [22,25]. Exercise testing should be done to check for chronotropic incompetence before starting a β-blocker as this can make the patient's symptoms worse from the medication [25]. J-DHF and ELANDD are the two major RCTs performed to evaluate the role of beta blocker in HFpEF [36,37]. None of these two studies showed a positive outcome, although J-DHF trial inferred that a higher dose of drug might prove beneficial than those tested in the trial.

Role of MRAs

In individuals with HFpEF, MRAs enhance diastolic function [38]. All patients with increased BNP, past-history of HF hospitalisation, or indications of volume overload should be given spirolactone, which is a cornerstone of therapy for HFpEF [25]. The TOPCAT study with spironolactone in patients with HFpEF was unable to demonstrate an overall improvement in the key composite endpoint of CV mortality or HF hospitalisation [39]. It is suggested that spironolactone may have antifibrotic actions on individuals with extensive collagen deposition and cardiac remodelling in addition to its diuretic and antihypertensive effects [25].

Role of SGLT2i

2022 AHA/ACC/HFSA guideline for management of HF recommended beneficial role of SGLT2i in reducing HF hospitalizations and cardiovascular death in people with HFpEF [19]. In EMPEROR-PRESERVED trial, regardless of comorbidity of diabetes, empagliflozin decreased the overall risk of CV mortality or hospitalisation for HF in individuals with HFpEF [40]. Additionally, in the SOLOIST-WHF trial, sotagliflozin decreased the primary outcome of CV death and HF hospitalizations in patients with diabetes and worsening HF (both HFrEF and HFpEF) [41].

Role of Ivabradine

Ivabradine, a funny current inhibitor, causes a decrease in heart rate without influencing inotropy [42]. In the EDIFY trial, treatment with ivabradine for 8 months in HFpEF patients did result in HR decrease, but did not reported a positive outcome on cardiac filling pressures (E/e′), exercise capacity (6MWT) and plasma NT-proBNP concentrations [43]. In further investigations, selective HR lowering effects of ivabradine in HFpEF patients were assessed, however the results were contrasting [44,45]. In the first, functional capacity improved in the

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HFpEF patients, whereas in the later, exercise capacity had decreased [44,45]. Other than reducing HR, ivabradine has few cardiovascular effects [46]. Ivabradine-based HR reduction hence does not seem to consistently help HFpEF patients.

Drugs to avoid

Due to an increased risk of angioedema, sacubitril/valsartan shouldn't be given to patients who have had an ACE- during the previous 36 hours [47]. In an RCT, isosorbide mononitrate showed no improvement in submaximal exercise capacity, quality-of-life scores, or NT-proBNP levels and moreover decreased daily activity levels [48]. Non-dihydropyridine calcium channel blockers appear safe to use in HFpEF patients, although they are not always advantageous [49]. Glitazones are contraindicated in HF patients due to the risk of salt and water retention which may lead to worsening of the condition [50]. NSAIDs must also be avoided as it is linked with sodium and water retention and elevated risk of renal impairment and HF hospitalisations [50].

Device therapy

For the treatment of the HFpEF patients, various innovative device-based therapy techniques can also be utilised. The most frequently utilised ones are Interatrial shunt device (IASD) and implantable pulmonary arterial pressure monitoring. The former has reported to reduce the elevated left atrium pressure in HFpEF patients, whereas the later one continuously monitors hemodynamics which enables evaluation of diastolic left ventricular pressures and prompt, effective delivery of diuretics [50].

CONCLUSION

The complexity and variability of the HFpEF phenotypes makes it clinically challenging to apply standard treatment methods to HFpEF patients. With increasing prevalence and worsening prognosis, HFpEF is nearly unique to the elderly. Drugs and interventions applied to treat HFpEF have been principally based on central hemodynamic and neurohormonal abnormalities. Individually tailored approaches may promote effective identification of HFpEF through underlying age-related changes and various comorbidities. Further extensive studies aimed to investigate HFpEF, aging, and comorbidities in carefully phenotyped HFpEF subgroups may elucidate the diagnosis, and treatment of HFpEF. While there are many ongoing clinical trials, there are no disease-modifying agents available for the treatment of HFpEF. Instead, clinicians should thoroughly look for an underlying aetiology and target any potentially reversible causes.

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