Review Article

Novel paradigms in the therapeutic management of heart failure with preserved ejection fraction: clinical perspectives

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Abstract: Heart failure with preserved ejection fraction (HfPbEF) is a pathological complexity that decreases cardiac output and elevates the ventricular filling pressure. HfPbEF is usually misdiagnosed and maltreated. HfPbEF is usually correlated with excessive morbidity and mortality. The prevalence of HfPbEF is growing, and there is a deficiency of evidence-based therapy, creating challenges for the physician with no effective management guidelines. Moreover, HfPbEF is not equivalent to diastolic heart failure as previously thought, as diastolic dysfunction is not the only underlying mechanism related to HfPbEF and sometimes may be absent. Several other mechanisms may work in concert to produce HfPbEF syndrome, either cardiac related (chronotropic incompetence, a longitudinal left ventricular (LV) systolic dysfunction despite a normal ejection fraction) or extracardiac related (pulmonary hypertension, abnormal ventricular-arterial coupling, abnormal exercise-induced vasodilation, extracardiac volume overload). These complex pathophysiologic mechanisms indicate that HfPbEF is heterogeneous and that this syndrome might be related to a vascular or an endothelial dysfunction or might be considered a cardiac manifestation of one or more systemic illnesses. The heterogeneity of HfPbEF necessitates excluding many differential diagnoses. In addition, the multiple comorbidities that are inherent to this condition need to be controlled in order to achieve effective management. Taken together, these key mechanisms might contribute to the multiple difficulties in the management of HfPbEF patients; these mechanisms also explain why medications used in patients with other heart conditions may or may not be successful in these patients. Novel therapies and clinical trials including paradigm shifts in therapeutic management are needed to effectively manage HfPbEF. The current review article sheds light on novel paradigms related to pathologies, diagnoses, and strategies, along with some proposed recommendations and clinical options for effective management of HfPbEF.

Keywords: Heart failure, new paradigm, clinical, management, HfPbEF

Introduction

Heart failure is a clinical constellation of symptoms of dyspnea, fatigue, and fluid retention. Patients with diastolic dysfunction might progress to diastolic heart failure leading to unexplained dyspnea or exercise intolerance in elderly patients, who usually have isolated left atrial dilatation resulting from elevated left ventricular filling pressure. Heart failure with preserved ejection fraction (HfPbEF) is discrete heart failure with a clinical constellation of symptoms, after exclusion of valvular, infiltrative and pulmonary disease [1]. Comorbidities including hypertension, coronary artery disease (CAD), diabetes, chronic kidney disease (CKD), anemia, obesity, and metabolic syndrome are contributing reasons for HfPbEF. HfPbEF was initially termed diastolic HF [2] or HF due to diastolic dysfunction. However, the condition is not synonymous with diastolic dysfunction, as other contributing mechanisms for this syndrome include endothelial dysfunction, chronotropic incompetence, impaired heart rate recovery, impaired vascular coupling, abnormal ventricular-vascular recovery, impaired vasodilator reserve, post capillary pulmonary hypertension, autonomic dysfunction, renin angiotensin aldosterone system (RAAS) and sympathetic systems up regulation [3]. In addition, at a
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molecular level, decreased activity of nitric oxide-cyclic guanosine monophosphate cGMP-protein kinase G (NO-cGMP-PKG), endothelial dysfunction, oxidative stress, and cardiac inflammation are often observed [4]. Clinically, HFpEF is defined as normal left ventricular (LV) systolic function, EF > 50%, left ventricular end-diastolic volume (LVEDV) < 97 ml/m², left ventricular mass index (LVMI) ≥ 115 g/m² in males and ≥ 95 g/m² in females, diastolic dysfunction, mean tissue Doppler (e) < 9, elevated E/e ratio using the lateral wall > 13, left atrial (LA) volume index > 34 ml/m², elevated N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) biomarker, and elevated pulmonary artery pressure. Elevated pulmonary artery systolic pressure on echocardiography in the presence of a normal ejection fraction should bring prompt consideration of HFpEF [4].

Clinically, HFpEF is defined as normal left ventricular (LV) systolic function, EF > 50%, left ventricular end-diastolic volume (LVEDV) < 97 ml/m², left ventricular mass index (LVMI) ≥ 115 g/m² in males and ≥ 95 g/m² in females, diastolic dysfunction, mean tissue Doppler (e) < 9, elevated E/e ratio using the lateral wall > 13, left atrial (LA) volume index > 34 ml/m², elevated N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) biomarker, and elevated pulmonary artery pressure. Elevated pulmonary artery systolic pressure on echocardiography in the presence of a normal ejection fraction should bring prompt consideration of HFpEF [4].

The incidence of new cases of HFpEF in US is approximately 600,000-700,000 annually; HFpEF occurs in 40-60% of newly diagnosed heart failure (HF) cases and involves healthcare expenditures of $40 billion on HF according to a 2010 Center for Medicare and Medicaid Services reimbursement report. The annual mortality range is 5-30% [4].

HFpEF is a comorbidity driven by a systemic disease, manifested by cumulative risk factors that cause a loss of adaptation of both heart and vessels. HFpEF is associated with almost equivalent prevalence and clinical outcomes compared to heart failure with reduced ejection fraction (HFrEF), yet there is a different response to therapeutic drugs. This may be due to different pathophysiology, multiple comorbidities, and high non-cardiac causes [5]. Apart from the fact that while HFrEF starts from the heart and leads to the periphery, HFpEF has evolved from a ‘cardiocentric’ model which starts peripherally and ends with cardiac manifestation [6].

Figure 1.

Figure 1. Phenotypes of diastolic dysfunction. HFpEF is a systemic syndrome with multiple phenotypes and contributing to diverse clinical representation, along with the degree of diastolic dysfunction and not necessarily the presence of right heart disease and pulmonary hypertension. Phenotype A is very common and is linked with few symptoms at rest including exercise induced left ventricle filling impairment and initial diastolic dysfunction. Phenotype B shows evident symptoms of heart failure, whereas phenotype C is related to overnight heart failure with severe pH. *HF: Heart Failure; LV: Left Ventricle; HFpEF: Heart Failure with preserved Ejection Fraction.

Phenotypes of heart failure with preserved ejection fraction and clinical implications (Figure 1)

Patients with HFpEF are mostly older females [7]. Moreover, these patients have more obesity, anemia mostly related to iron deficiency, hypertension, atrial fibrillation (AF), and have less coronary artery disease compared with patients with HFrEF [8]. Since HFpEF patients are most likely to be older, the new endpoints, defined as functional class and quality of life, should be prioritized over the traditional end points [9]. It is important to note that the Boodoo effect, which is a physiological tachycardia leading to an increased force of contraction in a normal heart, but not in a failing heart, is manifested as exercise intolerance in patients with HFpEF. This results from tachycardia; thus, lowering heart rate in HFpEF is desirable to maintain an adequate force of contraction at an impaired relaxation level, but not in stiffer ventricles with higher grades of diastolic dysfunction [10]. Data from the I PRESERVE study suggested that the ideal hemodynamic parameters include a heart rate approximately 70 b/m (especially with advanced diastolic dysfunction), an ideal systolic blood pressure of 130-140 mmHg and an ideal diastolic blood pressure of 70-80 mmHg, an ideal central venous pressure (CVP) 12-15 cmH₂O, along with the maintenance of an adequate renal blood flow by adequate mean perfusion pressure and cardiac output [11].

HFpEF is a diverse syndrome consisting of multiple pathophysiological mechanisms such as...
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Chronic volume overload phenotype (combined systolic and diastolic). Other phenotypes include associated right HF, and/or pulmonary hypertension, or the less commonly exercise-induced diastolic dysfunction phenotype [12].

Failure of clinical trials in HFpEF was mainly due to consideration of the one-size-fits-all concept, which turned out not to be true and confirmed that differentiation into different phenotypes is a must.

Based on phenotypic classifications, it is important to treat HFpEF patients by treating their comorbidities. Excessive reduction in the heart rate in HFpEF is not constantly preferable (although it is desirable in mild grades of diastolic dysfunction, but not in higher grades). It is crucial to consider uncommon diseases (“zebras”) as infrequent causes or risk factors for HFpEF during management [12].

Proposed mechanisms of diastolic dysfunction (Figure 2)

LV relaxation is an active process that consumes energy. It begins during the ejection phase of the systole and continues through IVR (isovolumic relaxation) and rapid filling phase. Calcium ions fluxes regulate the contraction and relaxation phases. Depolarization releases large amount of Ca into the cytosol to initiate contraction. A decrease in cytosolic Ca initiates relaxation through calmodulin mediated closure of L-type Ca channels and sarcoplasmic reuptake of Ca by SERCA (sarcoplasmic/endoplasmic reticulum calcium ATPase). Phosphorylation of phospholamban enhances calcium uptake. Phospholamban responds to B adrenergic stimulation mediated by protein kinase A (PKA). That is explained by the fact that impaired beta adrenergic signaling and inadequate ATP levels impair ventricular relaxation. The major factors influencing the relaxation process are calcium levels, which should fall to initiate relaxation (requires ATP and phosphorylation of phospholamban) and the inherent viscoelastic properties of myocardium, as in a hypertrophied heart there is an increase in fibrosis that leads to slower relaxation together with systolic load (the higher the systolic load, the faster the relaxation, and the poorer the compliance) [7]. The mechanism of the underly-
Diastolic dysfunction of the left ventricle is an important abnormality that usually appears ahead of abnormal systolic function. The fundamental problems in HFrEF are abnormal relaxation, impaired LV filling and/or increased stiffness. These changes will lead to a higher level of diastolic pressure-volume relation with increased left ventricular end diastolic pressure (LVEDP), left atrial pressure (LAP), and pulmonary arterial wedge pressure (PAWP), manifested as congestive symptoms [17].

Symptomatology in HFrEF may be due to chronotropic incompetence, impaired vasodilation during exercise, and metabolic derangement [18].

HFrEF is not just a disease, it is a multiplex of clinical conditions, involving not just diastolic dysfunction but also other contributing pathophysiological mechanisms that will lead to uneasiness of management [19].

The *sine qua non* of HFrEF is abnormal relaxation and abnormal diastolic function. Diastolic dysfunction is considered not only a preclinical disorder but also stage-B of heart failure.

No single drug has proper lusitropic (relaxation) properties, with selective enhancement of relaxation, without affecting contractility and function. The optimal treatment of HFrEF might exacerbate HFrEF [20].

**Proposed causes of HFrEF (Figure 3)**

There are plenty of causative dilemmas for patients with HFrEF including misdiagnosis, incorrect assessment of ejection fraction, episodic LV systolic dysfunction, primary valvular disease, atrial myxoma, restrictive cardiomyopathies, pericardial constriction, obesity, diastolic dysfunction of uncertain origin, severe hypertension, myocardial ischemia, high-output failure, cor pulmonale, and pulmonary hypertension due to abnormal pulmonary vasculature [21].

Independent predictors for mortality in HFrEF include age, gender, NYHA (New York Heart Association) class, lower LVEF, the extent of CAD, peripheral arterial disease (PAD), diabetes mellitus (DM), renal dysfunction, stage of diastolic dysfunction, anemia, and increased red cell distribution width [22].
Precipitating factors for HFpEF include tachycardia, ischemia, hypertension (HTN), exercise, systemic stress (thyrotoxicosis, anemia, infection, and fever), arrhythmias (atrial fibrillation (AF)), atrioventricular block (AVB)), increased salt intake, and nonsteroidal anti-inflammatory drugs (NSAIDs) [18].

Some risk factors such as smoking, obesity, and AF precede and are more prevalent in the diagnosis of new HFpEF compared to HFrEF [22].

Patients with HFpEF poorly withstand atrial fibrillation, as a loss of atrial contraction leads to a significant reduction in left ventricular filling due to a lack of atrial emptying with reduction in stroke volume and cardiac output. Tachycardia is poorly tolerated in HFpEF as it worsens the diastolic function via decreased relaxation time and time for fiber recoil, leading to elevated filling pressure.

Sudden or persistent elevation of blood pressure as in cases of renovascular disease will cause abnormal diastolic relaxation and increase wall stress. Ischemic heart disease will lead to abnormal diastolic function, a rise in left atrial pressure and pulmonary venous congestion which results into respiratory congestion (angina equivalent) [2, 3]. HFpEF patients are a heterogeneous group, as has been reported in a metaanalysis. The group includes valvular heart disease in 11-22% of patients; pulmonary disease in 31-33%; left ventricular dilatation in 19%; and no LV hypertrophy, LA enlargement, or diastolic dysfunction (DD) in 30%; moreover, less than 2/3 of the patients did not have diagnostic criteria of DHF (diastolic heart failure) [23]. HFpEF is a disease of non-cardiac comorbidities including obesity, diabetes, anemia, chronic obstructive airway disease, peptic ulcer, cancer, and psychiatric disorders [24]. HFpEF is a substantial heterogeneous group of patients with a mixture of diagnoses including valvular, pulmonary, renal, myocardial and pericardial disease. There are many confounders with no purity [25].

**HFpEF scores**

The initial step of calculating an ESC HFA-PEF score is to detect pretest probability followed by performing a sophisticated echocardiographic assessment and natriuretic peptide level together with the presence or absence of atrial fibrillation. (Score < 2: likelihood of non-cardiac origin; 5-6: high likelihood of cardiac origin; 2-4: need further testing, consisting exercise testing in combination with echocardiography or invasive hemodynamics). The last step is to assess the underlying etiology and pathophysiology with cardiac magnetic resonance, laboratory measures and/or myocardial scintigraphy or myocardial biopsy [26].

The risk assessment tool using information from atherosclerotic risk assessment in community (ARIC), heart failure community surveillance for patients with acute heart failure admitted to the hospital included the following factors: white or black patient, more than 55 years old, and ejection fraction of more than 50%. It predicted risk of death within 28 days and one year from hospital admission, including the following variables: age, systolic blood pressure, BUN (mg/ml), Na (mEq/L), Hb (g/dL), HR (bpm), either BNP (pg/mL) or NT-pro-BNP.

**Figure 3.** Proposed causes of HFpEF. The figure shows the schematic representation of the cardiac and non-cardiac causes of HFpEF. Cardiac causes basically represent the cellular and biological changes within the heart in the following years of the disease; lead to the left ventricular hypertrophy and left atrial enlargement leading to atrial fibrillation and mitral regurgitation. *CRF: Chronic Renal Failure; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; IDA: Iron Deficiency Anemia; LVH: Left Ventricular Hypertrophy; LAE: Left Atrial Enlargement; AF: Atrial Fibrillation; MR: Mitral Regurgitation.*
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**(Table 1. Heart failure with preserved ejection fraction (H2FPEF) score**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Parameters</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>H*</td>
<td>Heavy</td>
<td>Body mass index more than 30 KG/M²</td>
<td>2</td>
</tr>
<tr>
<td>H*</td>
<td>Hypertensive</td>
<td>2 or more antihypertensive medication</td>
<td>1</td>
</tr>
<tr>
<td>F*</td>
<td>Atrial Fibrillation</td>
<td>Paroxysmal or persistent</td>
<td>3</td>
</tr>
<tr>
<td>P*</td>
<td>Pulmonary hypertension</td>
<td>sPAP more than 35 mmHg by ECHO Doppler</td>
<td>1</td>
</tr>
<tr>
<td>E*</td>
<td>Elder</td>
<td>More than 60 years old</td>
<td>1</td>
</tr>
<tr>
<td>F*</td>
<td>Filling pressure</td>
<td>Doppler ECHO E/e more than 9</td>
<td>1</td>
</tr>
</tbody>
</table>

*H2FPEF is used to diagnose heart failure with non-cardiac causes in patients with dyspnea, ranging from 0-9. ‘H = heart; F = failure; P = preserved; E = ejection; F = fraction.*

(pg/mL), white race, BMI less than 18.5 (kg/m²), hypoxia (O₂ sat less than 90), cerebrovascular stroke (TIA or stroke), COPD (chronic obstructive pulmonary disease), and atrial fibrillation or flutter [26].

An evidence based approach for diagnosis of HFpEF was developed by Reddy et al. [27], who created a composite score (H2FPEF score) ranging from 0-9 based on a range of predictive variables. The H2FPEF score simplified differentiating different causalities of HFpEF, in comparison to the ESC HFA-PEF score, which is a sophisticated score depending upon many variables [26]. The use of NT-pro-BNP levels did not incrementally add diagnostic ability to the H2FPEF score. Shown in **Table 1**.

**General strategies and directives (Figure 4)**

HFpEF patients have clusters of comorbidities, which all will conspire in such a complex multifaceted condition that needs multiple drug therapy with its negative impact on renal function. Quality of life estimation is a very important end point in such a complex syndrome, which therefore needs to be included in the studies, together with proper selection of similar phenotypes to avoid underpowered clinical trials [28].

HFpEF management is difficult. Any minor variation from normal hemodynamic parameters could lead to low cardiac output and lowering of blood pressure or pulmonary venous congestion [2]. As the left ventricle operates at barely adequate volume, if the volume is reduced, this will directly translate into significant hypotension. It is important to realize that it is difficult to achieve normal volume in HFpEF due to impaired relaxation. In spite of left ventricular volume, the left atrial pressure is high [4].

In a paradoxical phenomenon, patients with HFpEF are sensitive to hypovolemia (diuretic paradox), and insensitive to fluid infusion when the LAP (left atrial pressure) is already high. Acute renal failure leads to fluid retention and can trigger DHF [8]. Excessive fluid infusion can be a contributing factor for postoperative diastolic heart failure. Vasodilators are appropriate in cases of combined systolic and diastolic heart failure, and in cases of secondary diastolic dysfunction due to right ventricular dysfunction, unloading of RV (right ventricle) will reduce the effect of left ventricle compression. However, in cases of pure diastolic dysfunction vasodilator use can lead to hypotension (vasodilator paradox) [8]. Inodilators improve diastolic dysfunction in systolic and diastolic dysfunction, and biventricular failure to maintain stroke volume at lower left ventricular end diastolic volume and pressure, while this is not true in patients with HFpEF (Inotropic paradox) [7].

Therefore, the management of HFpEF is a fine tuning technique, requiring the maintenance of a euvolemic status and a fluid balance, together with controlling the triggering factors that can be tolerated in a normal heart but will not be in a heart with HFpEF, such as reduction of preload due to bleeding or vasodilatation [6]. The strategy of maintaining adequate cardiac output, while avoiding pulmonary congestion (warm the patient up while drying the patient out) [5], and correcting any predisposing factors, should be implemented. Close monitoring is mandatory to guide therapy and its response [1]. Proactive management by anticipating the problem before its occurrence is a better strategy. It is of utmost importance to target the ideal hemodynamic parameters together with the management of the reversible causes [3].

**Managing common comorbidities**

Hypertension heralds the diagnosis of HFpEF in 75-85% of cases, and shares its adverse outcomes as well as its acute and chronic symp-
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Figure 4. Proposed strategies in the management of HFP EF. The schematic representation of treatment options for HFP EF depicts that treatment for acute HFP EF is same as that of HFr EF. On the other hand, for chronic treatment options can be either pharmacologic or non-pharmacologic or may be both. In pharmacologic, treatment of precipitating factors to decrease the complications of the condition and diuretics are given to reduce the congestive symptoms associated with hypervolemia, whereas physical activity and frequent visits to HFC are recommended in non-pharmacologic management of HFP EF. HFr EF: Heart Failure with Low Ejection Fraction; AF: Atrial Fibrillation; HTN: Hypertension; HFC: Heart Failure Consultant.

Symptoms [29]. Intensive diastolic BP reduction could reduce myocardial perfusion and promote myocardial ischemia, LV dilation, and subsequent HF. In HFP EF patients, there is an increase in both ventricular and vascular stiffness in excess due to associated aging or hypertension [30]. Therefore, excessive reduction in BP with vasodilation in HFP EF could potentially offset any benefit from the antagonism of pathological neuro-hormonal activation [31]. However, in spite of the potentially adverse effects of intensive BP lowering, the recent SPRINT (systolic blood pressure intervention trial) demonstrated that intensive BP lowering can significantly reduce the rate of development of acute decompensated HF [30]. While it is uncertain what proportion of these HF events were HFP EF versus HFr EF, it is likely that HFP EF was well-represented [32]. Both HFP EF and AF are related to adverse cardiovascular outcomes [33]. ACC/AHA (American College of cardiology/American Heart Association) guidelines recommend rate control for atrial fibrillation management; ESC guidelines, however, supported restoring rhythm control although strong evidence lacked [34]. Further studies are required to determine whether different rate control strategies or, indeed, rhythm control, will improve outcomes in management of HFP EF. Approximately 85% of elderly HFP EF patients are overweight or obese, and the HFP EF epidemic has largely paralleled the obesity outbreak [35]. Unfortunately, obesity has been overlooked as a factor in HFP EF pathophysiology and treatment [36].

Management of acute HFP EF

Patients with acute HFP EF, like patients of HFr EF, should be treated with intravenous short-acting beta blocker, esmolol [37] as well as verapamil, a calcium channel blocker [38], and control atrial fibrillation in case of acute HFP EF [39]. Calcium channel blockers had a more beneficial effect on patients with hypertrophic cardiomyopathy [31] compared to other causes of diastolic dysfunction [20]. Up to date, there is no specific drug designed for diastolic dysfunction. Inodilators used in cases of combined systolic and diastolic heart failure and in cases of biventricular failure will improve the stroke volume without significant rise in left ventricular end diastolic volume and pressure [7]. Amiodarone reduces preoperative ventricular and supra-ventricular tachyarrhythmia’s (atrial fibrillation) when used after cardiac surgery [3, 4].

Classic pharmacological therapy (Figure 5)

Diuretics

Diuretic therapy will lead to hypovolemia and result in a reduction in the filling of a stiff ventricle, resulting in low cardiac output and hypo-
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**Figure 5. Proposed therapies in HFpEF.** The schematic representation depicts the current and future approach towards the therapeutic options of HFpEF. Future approaches can be either pharmacologic or non-pharmacologic. Pharmacologically promising drugs are Statin (lower cholesterol levels), PDE15 (Inhibitor of Cyclic GMP in blood vessel lining) and NTG (blood vessels relaxation), however, the treatment options for HFpEF are now shifting towards new paradigm in which drugs are mainly anti-anginal. But, in future the focus will be mainly on treatment of comorbidities and precipitating factors. On the other hand, non-pharmacologic options include healthy diet, treatment of comorbidities and skilled persons for early diagnosis. "HFpEF: Heart Failure with Reduced Ejection Fraction; ACE1: Angiotensin Converting Enzymes 1; ARB: Angiotensin II Receptor Blockers; BB: Beta Blockers; HTN: Hypertension; AF: Atrial Fibrillation; MMP-1: Matrix Metalloproteinase-1; EPO alfa: Epoetin alfa.

In addition to its diuretic effect, as part of the renin angiotensin-aldosterone system that is activated in heart failure, mineralocorticoid antagonists (aldosterone antagonists) reduce insulin resistance and the prevalence of atrial fibrillation [40]. The Aldo HF trial had a positive result while the TOPCAT trial (double blind randomized, multicenter) showed no significant difference in cardiovascular mortality, sudden cardiac death, or heart failure re-hospitalization. These ambiguous results may be related to geographical differences in patient enrollment, with some countries contributing comparatively healthier patients with fewer cardiovascular events resulting in dilution of the overall results [41].

**Traditional pharmacological agents**

Although drugs affecting myocardial remodeling, such as angiotensin converting enzymes inhibitors, angiotensin blockers, and beta blockers, are considered disease modifying agents in patients with HFrEF [42], there is a lack of evidence of effective use in patients with HFpEF, and the data from clinical trials are ambivalent [43]. Ad hoc trials were done in ACE-I (PEPCHF) [44] and angiotensin receptor antagonists (CHARM-Preserved Trial) [34], and the I-PRESEVE Trial with irbesartan was done in patients with heart failure and preserved systolic function ejection fraction where more than 45% showed that every 12.4 b/m increase in heart rate resulted in 13% higher risk of cardiovascular death and heart failure re-hospitalization [45].

The effect of non-dihydropyridine calcium channel blockers (verapamil) is still not clear [46]. Some trials showed improvement in diastolic function [47]. A sub study of the ASCOT trial (Anglo-Scandinavian cardiac outcome trial) demonstrated that patients getting an amlodipine-perindopril regimen had improved diastolic function as compared to atenolol-thiazide therapy [48]. Similarly, nifedipine and isosorbide dinitrate/hydralazine showed an improvement
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in diastolic function and exercise tolerance together with a reduction in soluble vascular cell adhesion Molecule-I with no reduction in left ventricular hypertrophy and pulmonary congestion [49].

Beta blockers work by reducing heart rate and prolonging the diastolic filling time, which improves filling of stiffed ventricles, however, the evidence still lacks [30]. Although a small, early study of propranolol suggested a reduction in total mortality, the patient group was atypical in that all were selected to have prior MI (myocardial infarction) and were mostly men, and the ejection fraction (EF) was as low as 40% [48]. In addition, there was no significant difference in cardiac deaths between these groups. Both carvedilol (the J-DHF study) and nebivolol (ELANDD study) had equivalent effects on the outcome in HFpEF patients [49]. Discharging HFpEF patients with beta blockers had no effect on one-year mortality or re-hospitalization as shown in the OPTIMIZE-HF registry [49].

Digoxin at a serum concentration of 0-0.9 ng/ml reduces heart failure re-hospitalization but has no effect on mortality or all cause re-hospitalization in patients with diastolic heart failure [50]. Digoxin when compared with placebo in the digitalis investigation group (DIG) trial, showed neutral results on mortality among patients with HFpEF [32]. A recent study showed a statistically significant effect of mortality and re-hospitalization in heart failure patients with either HFpEF or HFrEF treated with digoxin for two years as compared to placebo, however, at the end (3.2 year period) there was no difference between digoxin and placebo in both groups which may be due to higher digoxin dose or higher crossover as shown by Meyer and his coworkers. Recommendations suggest that the results of the DIG trial may provide support for the use of digoxin in patients who have HFpEF, because a trend towards reduction in hospitalizations for heart failure was observed with digoxin in the ancillary trial [50]. The DIG trial provided support of a beneficial effect of digoxin in patients with HFpEF, however, the current guideline does not support the usage as the main mechanism is defective relaxation not contraction [50].

Contemporary therapies with promise

Statins as anti-inflammatory agents

Statins, while important in management of CAD, still had a minimal role in patients with HFrEF [34]. In patients with HFpEF there are multiple studies showing that using statins in patients with HFpEF had a beneficial clinical effect. Fukuta et al. [51], reported that patients with heart failure and ejection fraction of more than 50% when treated with statins and followed for 21 months showed a significant reduction in mortality [52]. Another study showed that using statins is associated with improved survival [51]. In the EuroHeart Failure Survey analysis of 6800 heart failure patients of whom 46% had HFpEF, those using statins had a lower all-cause mortality over 12 weeks [50]. A meta-analysis of nearly 18,000 patients supported the use of statins for better survival in patients with HFpEF, although it is worth mentioning that statins did not show any significant effect in two mega trials in patients with HFrEF [53].

PDE-5 inhibitors: phosphodiesterase-5 (PDEI-5)

Phosphodiesterase-5 (PDE5) is highly explicit in pulmonary artery smooth muscle cells and involved in breakdown of cGMP leading to vasconstriction. PDEI-5 sildenafil might have some benefits in patients with HFpEF [54]. As of now, end points in studies of PDE-5 inhibition in HFpEF are mainly improvement of symptoms and functional class [55] which still reflect on quality of life. The dilemma of end point selection is still ambiguous, such as in patients with HFrEF. For example, using inotropes improves symptoms but worsens survival, while using beta blockers worsens symptoms acutely but reduces mortality [55]. A small trial showed symptomatic improvements, however, the relax trial in patients with HFpEF reported no significant improvement in exercise capacity, quality of life or diastolic function, but the clinical benefits still need to be evaluated [54].

Isosorbide mononitrate

In the NEAT-HFpEF trial, isosorbide mononitrate did not improve 6-min walk distance (MWD), quality of life, or NT-pro B type natriuretic pep-
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tide (BNP) levels as compared to placebo [56]. Even though, this result is disappointing about nitric oxide deficiency in patients with endothelial dysfunction, this is because of continuous release of nitric oxide by the effect of therapeutic nitrate and there is no targeted release when needed together with occurrence of nitrate tolerance. Randomized studies revealed that inhaled or intravenous sodium nitrite increases stroke volume and cardiac output, and reduces ventricular filling and pulmonary artery pressure at rest and with exercise [56]. Beneficial effects are thought to be related to enhanced production of nitric oxide by nitrite in the setting of tissue hypoxia and acidosis [57].

Paradigm shifts in management

There is a huge requirement for management of HFpEF due to its increasing prevalence. Additionally, there is a need for new strategies aimed towards specific phenotypes and mechanisms of HFpEF.

The current therapeutic approach for management of HFrEF was not successful in management of patients with HFpEF, which is the main stimulus for targeting other pathophysiological mechanisms in the molecular structure [25] such as anti-fibrotic, anti-hypertrophic and anti-inflammatory drugs [58].

According to the PROMIS study, coronary microvascular dysfunction (CMD) was frequently found in patients with HFpEF despite no significant macrovascular coronary artery disease [25] which indicates that microvascular dysfunction may be a promising therapeutic target in HFpEF.

There is a new paradigm shift away from the traditional emphasis on afterload excess pathway (RAAS) and towards inflammation as the primary stimulus for hypertrophy and diastolic dysfunction [59]. Declining protein kinase G (PKG) pathway activity accelerates pro-hypertrophic signaling and increases myocyte stiffness by promoting hypophosphorylation of titin, enhancing diastolic dysfunction and ventricular stiffening (NO-cGMP-PKG signaling pathway) [60].

Verciguat

This molecule was found to stimulate the soluble cGMP pathway in patients with HFpEF and is currently being studied in the SOCRATES trial (Soluble Guanylate Cyclase Stimulator Heart Failure Study). In a prespecified secondary analysis, a dose-related effect on the primary endpoint change in NT-proBNP levels was observed. Moreover, vericiguat was not associated with any deleterious effects on heart rate, blood pressure, renal function, or troponin release [61]. Reduction in NT-proBNP in the highest dose arm was associated with improved LVEF and trended towards fewer clinical events at 12 weeks [62].

LCZ696

LCZ696 is a first-in-class ARNI (angiotensin receptor neprilysin inhibitors) that is a complex molecule derived from the combination of the neprilysin inhibitor (neprilysin degrades biologically active natriuretic peptides that reduce the production of cGMP) and the angiotensin receptor blocker valsartan. LCZ696 additionally stimulates natriuretic peptide signals through transmembrane receptor guanylyl cyclase, which acts as an antihypertrophic and antifibrotic, and improves diastolic function (lusitropic effect) by stimulating the activity of PKG [63].

LCZ696 has been demonstrated to decrease NT-proBNP in a phase II trial in patients with HFpEF (LVEF ≥ 45%) [55]. LCZ696 is currently being tested on a large scale in a phase III trial PARAGON-HF [64].

Ranolazine

Ranolazine causes late sodium current inhibition, and a verification of a study (Ranolazine for the Treatment of Diastolic Heart Failure [RALI-DHF]) in 20 patients with HFpEF indicated an improvement in hemodynamic parameters but no effect on diastolic function. Further clinical studies are needed to address the efficacy of ranolazine in patients with HFpEF [65].

Ivabradine

Inhibitor ivabradine, when used for heart rate reduction in HFpEF, was found to have an effect as an anti-hypertrophic, anti-fibrotic, anti-inflammatory and anti-apoptotic agent as compared to metoprolol (a selective B1 receptor blocker) as shown in a preliminary and experimental study [65].
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These results testify that the addition of ivabradine to conventional therapy in patients with HFpEF can improve LV diastolic function, as evaluated by 2D and tissue Doppler-echocardiographic patterns. These Doppler-echocardiographic results match with the clinical improvement of patients evaluated [66]. Ivabradine improves diastolic function and decreases aortic stiffness and fibrosis in a diabetic mouse model with HFpEF [67].

Anakinra

Pro-inflammatory cytokines IL-1 and IL-1B (Interleukin-1) contribute to ventricular and vascular remodeling in cases of pressure overload induced cardiac hypertrophy. Anakinra, an IL-1 antagonist used in management of rheumatoid arthritis, was shown in the D-HART Pilot Study in HFpEF patients to have led to a significant reduction in C-reactive protein (CRP) and resulted in significant improvement in oxygen consumption [23].

In response to chronic cardiac stress as in heart failure, there is higher level of ST2 (interleukin 1 receptor-like), and the receptor for IL-33 (IL-33 is a member of IL-1 family) together with upregulation of IL-33/ST2 pathway which causes hypertrophy and fibrosis [24]. Aging is associated with increased metallo-proteinase-9 (MMP-9) levels that precedes the development of diastolic dysfunction, this lead to use MMP-9 inhibitor in experimental mice study, transcription factor STAT3 (Signal transducer and activator of transcription 3) had a cardiac protection and anti-remolding, decreased the effect of angiotensin and improved endothelial function and antioxidant. Further studies are warranted for evidence based medicine [25].

Advanced glycation end-products (AGEs) breaker

Advanced glycation end-products (AGEs) are formed when glucose interacts non-enzymatically with proteins. AGEs cause myocardial stiffness through either direct cross linking of collagen and elastin fibers or indirectly stimulating oxidative stress via promoting production of stiffer collagen together with reduction of nitric oxide [68]. Advanced glycation end-products breaker (Algebrium) may have a beneficial effect in the management of HFpEF [69]. Algebrium reduces left ventricular mass with reducing left ventricular filling pressure with improvement in quality of life [70]. In spite of failure in a proof of concept in patients HFrEF further studies are needed in patients with HFpEF [69].

SGLT2

Studies are underway to test the efficacy of inhibitors of sodium-glucose cotransporter type 2 (SGLT2) in HFpEF patients. Recently, empagliflozin resulted in reduction of hospitalization and cardiovascular mortality together with a reduction in blood pressure and body weight in heart failure patients mostly due to glucosuria and osmotic diuresis. Empagliflozin, which showed a valuable effect in patients with and without heart failure, is currently being evaluated in the EMPEROR-Preserved study while the HF-PRESERVED trial, will evaluate the effect of dapagliflozin on biomarkers, symptoms, and functional status in HFpEF patients with type-2 diabetes or prediabetes [71].

Sitaxsentan

Sitaxsentan, a selective endothelin type-A (ETA) receptor antagonist, provides a modest increase in treadmill exercise time [62] in HFpEF patients, but did not improve any of the secondary endpoints such as left ventricular mass or diastolic function. Further studies will be necessary to determine the effect of ETA receptor antagonists on HFpEF.

Other strategies that can be used include myostatin-blocking antibodies and MicroRNAs. However, well designed proof of conceptual studies is still needed for further confirmation. A Phase-I trial evaluating the safety and tolerability of MTP-131 (elamipretide, a novel mitochondria-targeting peptide) in mild to moderate HF patients is currently under investigation [25].

Device therapy

CardioMEMS

CardioMEMS is a wireless device using a radio frequency transmitter inserted in the distal pulmonary artery during right heart catheteriza-
tion to monitor daily hemodynamic parameters [72]. In the single-blind randomized CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, 119 HFpEF patients were implanted with a microelectromechanical pressure sensor during right heart catheterization [55]. Patients were randomized to sensor guided treatment or regular clinical guided treatment and were followed for up to 18 months. Those with sensor guided treatment had a 50% reduction in hospitalization for heart failure. Further studies are warranted [73].

**Interatrial shunt**

Heart failure symptoms in HFpEF are usually preceded by a rise in LA pressure and pulmonary venous congestion, so creating a controlled or unidirectional shunt between atria to allow left atrial decompression will relieve symptoms in patients with HFpEF. Hemodynamic modeling based on clinical measurements suggests that an appropriately sized iatrogenic atrial septal defect could reduce exercise-induced increase in LA pressure in patients with HFpEF. Subsequently, an open-label study (REDUCE LAP heart failure trial) showed an exercise reduction in left atrial pressure with symptomatic improvement in functional tolerance and quality of life during a 6 month follow up period [74]. During one year of follow up, device patency was maintained and there was an improvement in functional class and exercise tolerance together with an improvement in quality of life and in pulmonary arterial wedge pressure.

**Microventricular assist device**

A device implanted via mini-thoracotomy in the right subclavian area to drain the blood from the left atrium to the right subclavian artery had a significant value on hemodynamics, increased cardiac output, provided mild increase in blood pressure, and reduced left atrial and pulmonary artery pressure in patients with HFrEF, however, in HFpEF, it still needs to be evaluated [75].

**Baroreflex activation therapy**

Carotid sinus stimulation will intensify the parasympathetic tone in patients with HFpEF for their autonomic dysfunction [76]. BAT (baroreflex activation therapy) was studied in HOP4HF (a randomized outcome trial to evaluate the clinical safety and efficacy of BAT in HFpEF patients) for HFpEF (NYHA III) in addition to guideline medical therapy. It was found to be safe, with improvement in exercise tolerance, quality of life and reduction of heart failure hospitalization [77].

**Rate-adaptive pacing (RAP)**

Rate-adaptive pacemakers showed considerable benefits to patients with mild to moderate HFpEF for treatment of chronotropic incompetence, as shown in the RESET trial [75].

**Left atrial (LA) pacing therapy**

Pacing of the left atrium had a valuable effect, demonstrating improvement of left ventricular filling and reduction of left atrial pressure, which will have a clinical effect in patients with HFpEF due to the presence of interatrial dysynchrony [74]. Cardiac resynchronization therapy might be beneficial in HFpEF and is currently under investigation [78].

**Cardiac contractility modulation (CCM)**

CCM used in patients with HFrEF with reduced EF less than 35% and with normal or slightly wider QRS complex did not fulfill the indication of cardiac synchronization therapy. CCM emits biphasic high voltage bipolar signal to the right ventricular septum during the absolute refractory period resulting in improvement in myocardial contraction with subsequent improvement in quality of life and exercise capacity [79].

CCM was used experimentally in 2 patients with HFpEF and resulted in improvement of functional class, exercise capacity, quality of life, and diastolic function. In HFpEF, there is low phosphorylation of titin resulting in stiffness and fibrosis. CCM improves phosphorylation of titin with subsequent reduction in fibrosis and collagen expression [79].

**Exercise training**

Exercise rehabilitation programs in patients with HFpEF had a valuable effect, either due to a cardiac effect through reversing atrial remodeling and reducing diastolic dysfunction or due to peripheral mechanisms through improving endothelial dysfunction in skeletal vasculature
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[80]. Making lifestyle changes to incorporate more activity is recommended in stable patients with HFrEF. In patient with HFpEF, Ex-DHF (exercise training in diastolic heart failure) showed an improvement in quality of life mainly by improving cardiac function [81], while on the other hand Haykosky et al. [82], showed that the improvement in exercise capacity was mainly due to improvement in skeletal muscle vasculature. Kitzman et al. [83], showed that after 16 weeks of exercise there is an increase in peak VO2 (Volume of Oxygen) that was dissociated from endothelial dependent arterial dilatation [73]. In contrast, Fujimoto et al. [84], found that one year of exercise training failed to improve cardiac output. Overall, exercise training improves exercise tolerance and quality of life in patients with HFpEF. Cardiac rehabilitation programs are warranted and need further evaluation [42].

Nutritional strategies

Dietary modifications have a valuable effect, such as the DASH (sodium restricted dietary approach to stop hypertension) diet for treatment of hypertensive HFpEF, which showed an improvement in diastolic function along with reduced ventricular and arterial stiffness [85]. Beetroot juice (rich in inorganic nitrate) daily for one week significantly improved submaximal aerobic endurance and blood pressure in elderly HFpEF patients [86]. Zamani et al. [86], found that a single dose of inorganic nitrate (beetroot juice) given to the patients with HFpEF improves peak oxygen consumption via reduction of systemic vascular resistance. Inorganic nitrate converts to nitrite by the effect of oral flora, which in turn converts into nitrate by the effect of hypoxia that will cause vasodilation and increase blood flow with increase in oxygen delivery to the skeletal muscle [83]. Kitzman et al. [83], showed that caloric restriction in addition to exercise training in elderly HFpEF patients significantly improves exercise tolerance and quality of life [87].

Current guidelines

ACC/AHA and the European Society of Cardiology (ESC) guidelines have similar recommendations. The guidelines for the management of HFpEF advocate controlling of blood pressure, management of comorbidities, and adjustment of volume status with a fitting diuretic dose to relieve hypervolemia without causing hypotension [18].

Perspectives in management

No treatment has yet been shown to reduce morbidity and mortality in patients with HFpEF. There is a deficiency of evidence in management of HFpEF, in contrast to the evidences in management of HFrEF [88].

This could be due to variation in patient selection, dropout rates, phenotypes/stages of the disease, etc. (The absence of evidence from clinical trials does not mean evidence of absence) [89].

HFpEF syndrome is a superimposition of HF over a systemic disease which needs proper phenotypic differentiation and control of the associated comorbidities [90]. Molecular structural changes, left atrial hypertension and elevated pulmonary artery pressure contribute in a majority of the symptoms. Therefore, the main strategy should be pulmonary decongestion and control pulmonary artery pressure [16]. There is an intense need to control comorbidities, improve reserve through exercise rehabilitation programs and restore the balance of oxidative stress due to various factors [91]. It is important to avoid inotropic constraint, achieve euvolemic status and control heart rate (ivabradine). There is therapeutic potential in soluble cyclic guanylyl cyclase activators, tetrahydrobiopterin (BH4) cofactor essential for production of nitric oxide, PKG modulators, nitric oxide (nNOS) activators, and NADPH oxidase 2 (NOX2) inhibitors. (NOX2 stimulation will lead to cardiomyopathy and oxidative stress in case of sepsis) [92]. Patients with chronic HFpEF should not be treated as though they have chronic HFrEF (however, acute HFpEF and HFrEF are treated similarly). It is advisable to avoid drugs that do not have benefit especially those which are considered for the treatment of HFrEF [89]. When there is pulmonary hypertension, functional NYHA classification is necessary along with a 6 minute walk test, at the start of the treatment and on follow up, to detect the hemodynamic response [93].

Conclusion

HFpEF is a clinical syndrome of multiple pathophysiological mechanisms, differential diagnoses, comorbidities, misdiagnoses, and mal-
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treatments are associated with clinical outcomes similar to HFrEF. It is challenging to deal with such patients, their frequent emergency room visits and hospital readmissions. Diagnostic modalities such as hemodynamic assessment, elevated pulmonary artery pressure, and assessment for coronary artery disease are significant addition to the usual diagnostic modalities, where B-type natriuretic peptide is less specific. There are few evidence-based therapies with no stringent guidelines. Management of comorbidities and phenotypic consideration will help in improving clinical outcomes. It is also essential that further trials regarding therapeutic innovations be conducted to benefit patients with HFpEF.

Disclosure of conflict of interest

None.

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