

REVIEW

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Heart failure with preserved ejection fraction based on aging and comorbidities

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) is a leading cause of hospitalizations and mortality when diagnosed at the age of ≥ 65 years. HFpEF represents multifactorial and multisystemic syndrome and has different pathophysiology and phenotypes. Its diagnosis is difficult to be established based on left ventricular ejection fraction and may benefit from individually tailored approaches, underlying age-related changes and frequent comorbidities. Compared with the rapid development in the treatment of heart failure with reduced ejection fraction, HFpEF presents a great challenge and needs to be addressed considering the failure of HF drugs to improve its outcomes. Further extensive studies on the relationships between HFpEF, aging, and comorbidities in carefully phenotyped HFpEF subgroups may help understand the biology, diagnosis, and treatment of HFpEF. The current review summarized the diagnostic and therapeutic development of HFpEF based on the complex relationships between aging, comorbidities, and HFpEF.

Keywords: Aging, Comorbidities, Diagnosis, Heart failure with preserved ejection fraction, Treatment

Introduction

Heart failure (HF) is divided into three forms based on left ventricular (LV) ejection fraction (LVEF): heart failure with preserved ejection fraction (HFpEF, LVEF $\geq 50\%$), heart failure with reduced ejection fraction (HFrEF, LVEF $< 40\%$), and heart failure with mid-range ejection fraction (HFmEF, LVEF ≥ 40 and $< 50\%$) [1]. HFpEF has a global prevalence of 2% and will increase by 50% by 2035 in aging populations [2]. Patients suffering from HFpEF are older, mostly female and obese, and exhibit a lower prevalence of coronary artery disease (CAD) than patients with HFrEF [3, 4]. Nearly all patients

with HF have preserved EF in the elderly ≥ 90 years [5, 6]. Atrial fibrillation (AF) increases subsequent HF risk five-fold during the following ten years [7]. Patients with AF and underlying HFpEF have reduced exercise tolerance and worsened ventricular function than those with AF alone [8–11]. HFpEF is a leading cause of hospitalizations and mortality when diagnosed at the age of ≥ 65 years. Patients with HFpEF have higher morbidity, mortality, and rehospitalization as those with HFrEF, and life quality in patients with HFpEF is worse than in those with HFrEF [12]. The complex interaction between aging and comorbidities makes HFpEF a significant burden to public health. The current review summarized the diagnostic and therapeutic development of HFpEF based on the complex relationships between aging, comorbidities, and HFpEF.

Pathophysiology

HFpEF is a systemic syndrome involving multiple organs [13]. Diastolic factors affecting HFpEF are the pulmonary vein (preload), vascular resistance (afterload), and contractility relaxation (cardiac). Contractility is disturbed by

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atrial function, ventricular dyssynchrony, and atrioventricular maladjustment [14]. Relaxation of myocardial tissue is achieved through energy-dependence myofilament dissociation and passive relaxation of noncardiomyocyte matrix in the cardiac chambers and pericardium [15–17].

HFpEF is triggered by the cumulative expression of various risk factors and comorbidities, including age, sex (female), physical inactivity, obesity, AF, CAD, diabetes, dyslipidemia, hypertension, metabolic syndrome, chronic kidney disease, anemia, chronic obstructive pulmonary disease and sleep-disordered breathing [18]. However, there are no specific diseases demonstrated to be etiologic of HFpEF. HFpEF is a systemic inflammatory or metabolic disorder [19]. First, HFpEF is associated with endothelial inflammation, leading to coronary microvascular dysfunction [20, 21]. Endothelial dysfunction is a significant factor linking cardiac and extracardiac effectors [22]. Second, the changed composition and structure of both cardiomyocytes and noncardiomyocytes can increase diastolic stiffness and promote HFpEF development [23–25]. Third, both obesity and diabetes are accompanied by increased epicardial adipose tissue volume, which transduces the effects of these diseases on cardiac function and structure [26]. HFpEF is a microcirculation defect following the obesity and diabetes. Both obesity and diabetes lead to an inflammatory and fibrotic atrial and ventricular myopathy, the two major elements of HFpEF [27]. Obesity and diabetes increase the risk of exercise intolerance and promote rapid progression of HFpEF due to multimorbidity, impaired chronotropic reserve, left ventricular hypertrophy, and activation of inflammatory, pro-oxidative, vasoconstrictor, and profibrotic pathways [28].

Although LVEF is not reduced, increased LV-filling pressure results in exertional dyspnea and exercise intolerance. If dysfunctional epicardial adipose tissue is adjacent to LV, it impairs LV distensibility and promotes HFpEF development. However, if it is adjacent to left atrium (LA), atrial myopathy is caused by electro-anatomical fragmentation and structural remodeling of LA [29]. AF may be the first indicator of an inflammatory or metabolic LA myopathy causing HFpEF [30]. Patients with HFpEF and AF, especially patients at increased risk of adverse outcomes, have increased epicardial adipose tissue volume [31]. AF reflects the development of myocardial inflammation, fibrosis, and hypertrophy in parallel with atrial and ventricular myopathy that results in HFpEF. Myocardial inflammation, fibrosis, and hypertrophy are identified in LA and LV of both patients with AF and those with HFpEF. Atrium and ventricle may be adversely affected by inflammation, and myocardial fibrosis and hypertrophy may contribute to exercise intolerance [32]. Cardiometabolic abnormalities, such as

abnormal mitochondrial function, changed substrate utilization, and intracellular calcium overload, are also considered pathophysiological mechanisms in HFpEF [33].

Aging affects pathophysiological process of HFpEF. Structural and functional changes related to aging are generally believed to be significant risk factors of HFpEF [34]. Aging results in changed body composition, missed muscle mass, and increased sarcopenic adiposity [35]. Both aging and HFpEF are associated with changed epicardial adipose and its secretory adipocytokines. The elderly with HFpEF have 5.5 noncardiac comorbidities on average [36]. Aging, frailty, and comorbidities have cumulative and synergistic effects on cardiac function and outcomes [37]. Aging promotes coronary microvascular endothelial abnormalities and myocardial remodeling and dysfunction in HFpEF [38–40].

A key obstacle for exploring new pathophysiological mechanisms and testing new pharmaceutical substances is the availability of suitable animal models for HFpEF, which realistically reflect the research and clinical picture. A variety of animal models are developed with the signs of HFpEF ranging from murine models to a pig model. Most of these animal models develop HFpEF triggered by a single factor like hypertension (Dahl salt-sensitive rat, aldosterone-infused uninephrectomized mouse, and transverse aortic constriction-induced pressure overload in mouse), obesity/diabetes (db/db mouse), and aging (senescence-accelerated mouse). Schiattarella and colleagues recently formulated a ‘two-hit’ hypothesis, inducing HFpEF in mice by metabolic stress (feeding of a high fat diet) and mechanical stress (hypertension induced by blocking eNOS activity) as second stressor. However, another animal model, developing HFpEF owing to diabetes and hypertension, is the ZSF1 (Zucker fatty and spontaneously hypertensive) rat. This model was developed by crossing rat strains with two separate leptin receptor mutations (fa and facp), the lean female ZDF rat (+/fa) and the lean male SHHF rat (+/facp). Offspring being homozygous for both mutations (fa:facp) are obese and develop insulin resistance, hyperglycaemia, and mild hypertension (ZSF1-obese). The ZSF1-obese animals developed HFpEF signs, exercise intolerance, reduced skeletal muscle contractility and endothelial dysfunction. ZSF1 rat may serve as a suitable animal model to study pathophysiological mechanisms and pharmaceutical strategies for HFpEF.

Diagnosis

HFpEF presents a significant challenge in the diagnostic process, lacking a useful and objective one-method-fit-all approach [41]. Diagnosing HF in the elderly poses specific challenges to specialized physicians as false-positive and false-negative diagnosis are common in

clinical practice [42]. First, exercise intolerance often happens in the elderly or obese population and represents pathophysiologic changes associated with aging or noncardiac etiologies [43, 44]. Second, HFpEF may be difficult to be diagnosed in the elderly because of existing comorbidities, which mimic HFpEF clinical manifestation and further complicate its diagnosis [45]. Third, the elderly with HFpEF have no classic HF manifestations. Circulating B-type natriuretic peptide (BNP) levels may not represent LV-filling pressure in patients with HFpEF. Patients with increased LV-filling pressures related to HFpEF commonly have no elevated BNP levels, possibly because distensibility is impaired by myocardial fibrosis or due to coexistent obesity [46]. Patients with HFpEF often have BNP levels below typical diagnostic thresholds. Most studies have suggested that around 30% of HFpEF patients have a BNP < 100 pg/ml, challenging the common practice of using BNP levels to determine HF diagnosis [47]. Fourth, HFpEF cannot be diagnosed based on diastolic dysfunction by itself due to the lack of a universally agreed definition. Finally, the limited ability of echocardiographic variables in identifying diastolic dysfunction further challenges its diagnosis in clinical practice [48].

Cardiac magnetic resonance imaging provides structural evidence of HFpEF, such as increased epicardial adipose tissue volume and myocardial fibrosis. Cardiac catheterization is the best method to confirm increased LV-filling pressure, but being an invasive method, its application in the elderly is limited. Electrocardiography showing AF may be an available and sensitive marker of HFpEF in the elderly. Diastolic stress testing is of essential significance for diagnosing HFpEF [49–53]. HFpEF with diastolic dysfunction results in increased LV end-diastolic pressure (LVEDP) to generate sufficient cardiac output for the peripheral tissue's needs. Elevated LVEDP or reduced end-organ perfusion is the most significant indicator for HFpEF diagnosis [54, 55]. Genetic analysis, imaging, and biopsy have been recommended to determine the etiologies of HFpEF.

HFpEF may be represented by different pathophysiological phenotypes, which require differential

identification and management [56]. Diagnostic algorithms with a series of measures include clinical, laboratory, and instrumental characteristics; sophisticated imaging modalities; and invasive hemodynamic measurements. As shown in Fig. 1, Heart Failure Association Pretest assessment, Echocardiography, and natriuretic peptide, Functional testing, Final etiology (HFA-PEFF) has been suggested as a diagnostic procedure for HFpEF [57]. Additionally, a weighted score based on obesity, AF, age > 60 years, treatment with ≥ 2 antihypertensives, echocardiographic E/e' ratio > 9, and echocardiographic pulmonary artery systolic pressure > 35 mmHg was used to create a composite score (H₂FPEF score) ranging from 0 to 9. The odds of HFpEF doubled for each 1-unit score increase. H₂FPEF score relies on simple clinical characteristics, whereas cardiac catheterization is necessary in HFA-PEFF. H₂FPEF score enables the discrimination of HFpEF from noncardiac causes of dyspnea and determine further diagnostic testing in the evaluation of patients with unexplained dyspnea.

Prevention

The prevention of HF is hard and controlling risk factors may be feasible. Lifestyle modifications, such as dietary control, nutrient management, physical activity, weight loss, and cardiorespiratory fitness, have beneficial effects on the prevention of HFpEF [58]. Treating obesity or diabetes can affect the volume or function of epicardial adipose tissue. Both caloric restriction and physical activity are effective methods to improve cardiac outcomes in patients with HFpEF. Caloric restriction and weight loss significantly improve exercise tolerance and life quality in the elderly with HFpEF and obesity [59–61]. Weight loss reduces the risk of HFpEF, lowers elevated diastolic filling pressure, and alleviates epicardial adipose inflammation [62–64]. Exercise protocols mainly include aerobic exercise, such as walking or cycling, in the elderly. Exercise training at home can be achieved by remote monitoring, individualization programme, and fall prevention. Exercise training improves physical function, shows clear security, and reduces HFpEF rehospitalization in the elderly [65]. Moderate and regular physical activity is recommended in patients with HFpEF by the

(See figure on next page.)

Fig. 1 Heart Failure Association Pretest assessment, Echocardiography, and natriuretic peptide, Functional testing, Final etiology (HFA-PEFF): a diagnostic procedure for heart failure with preserved ejection fraction HFpEF. *HF* heart failure, *AF* atrial fibrillation, *CAD* coronary artery disease, *MetS* metabolic syndrome, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *SDB* sleep-disordered breathing, *NPs* natriuretic peptides, *Hb* hemoglobin, *HbA1C* hemoglobin A1C, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *ALT* alanine aminotransferase, *TSH* thyroid stimulating hormone, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *LAE* left atrial enlargement, *6MWT* 6 min walk test, *CPET* cardiopulmonary exercise testing, *TR* tricuspid regurgitation, *PASP* pulmonary artery systolic pressure, *GLS* global longitudinal strain, *LAVI* left atrial volume index, *LVMi* left ventricular mass index, *RWT* relative wall thickness, *LV* left ventricular, *SR* sinus rhythm, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *BNP* B-type natriuretic peptide, *LVEDP* left ventricular end-diastolic pressure, *PCWP* pulmonary capillary wedge pressure, *CT* computed tomography, *PET* positron emission tomography, *HCM* hypertrophic cardiomyopathy, *RCM* restrictive cardiomyopathy, *CHD* congenital heart disease, *VHD* valvular heart disease

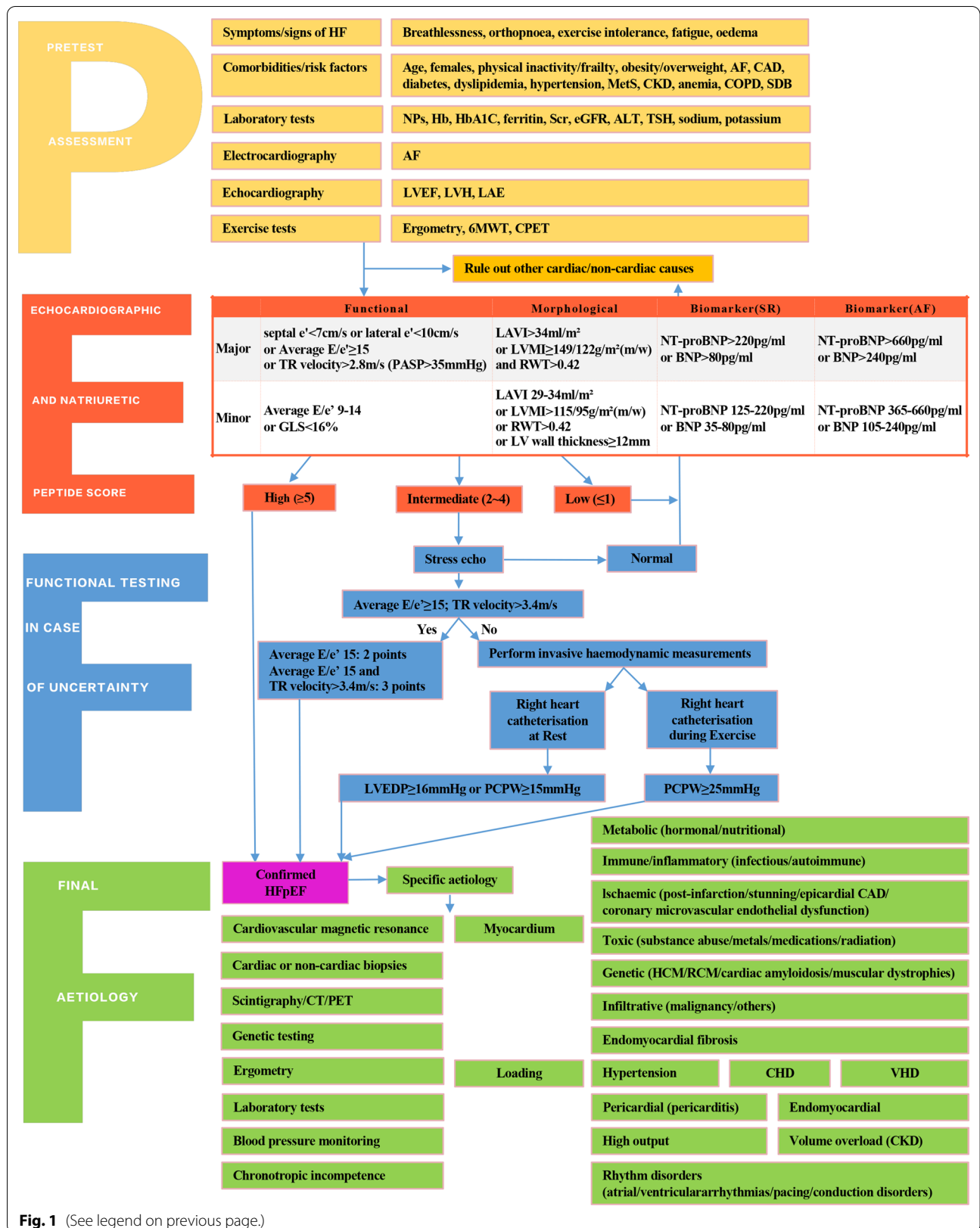


Fig. 1 (See legend on previous page.)

American College of Cardiology/American Heart Association (ACC/AHA).

Addressing the risk factors and comorbidities is a significant way of preventing the development of HFpEF [66, 67]. First, hypertension can obviously increase prevalence, rehospitalization and mortality of patients with HFpEF; thus, treating hypertension may be the most effective prevention method for HFpEF [68, 69]. Second, CAD deteriorates ventricular function and outcomes and increases the occurrence of HFpEF, and patients with CAD patients should receive systemic treatment, such as coronary revascularization [70, 71]. Third, because of increased longevity, AF has increasing prevalence and coexists with HFpEF [72]. AF is closely related to abnormal atrial and ventricle function, neurohumoral activation, and exercise intolerance [73]. Tachycardia is also deleterious by shortening diastole time and impairing diastolic filling. Rate or rhythm control of AF may prevent the development of an underlying HFpEF. Rate control and permanent anticoagulation are recommended in patients with AF [74, 75]. Finally, anemia is related to elevated prevalence, hospitalization and mortality of HFpEF [76, 77]. Enhancing mitochondrial energy by iron supplementation prevents the development of HFpEF, and iron supplementation rather than erythropoietin is recommended by the ACC/AHA [78].

Treatment

HFpEF, being one of the most challenging diseases to treat, does not respond to a one-method-fit-all approach; hence, several therapeutic methods are shown in Table 1 [79–82]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can alleviate the inflammation of adipose and attenuate myocardial fibrosis and remodeling [83]. They improve clinical symptoms and exercise tolerance rather than morbidity or mortality in patients with HFpEF [84]. Moreover, they do not cause further improved exercise tolerance or cardiac function after optimal diuretic treatment [85, 86]. Aldosterone mediates myocardial fibrosis, contributing to myocardial stiffness [87]. Mineralocorticoid receptor antagonists fail to improve clinical symptoms, exercise tolerance, and cardiac outcomes in patients with HFpEF [88].

Tachycardia predicts poor outcomes in patients with HFpEF [89]. Beta-blockers have no prognostic effect in patients with HFpEF but may have beneficial roles in some subgroup analyses [90]. Conventional beta-blockers mainly target beta1- and beta2-adrenoreceptors, which can mediate catecholamine effects. Beta3-adrenoreceptor prevents neurohormonal stimulation and myocardial hypertrophy [91]. Stimulating Beta3-adrenoreceptor with selective agonist mirabegron may be studied as a treatment method in HFpEF.

Although ivabradine reduces exercise-induced tachycardia and improves chronotropic incompetence, it cannot prolong diastole time to restore diastolic function in HFpEF [92]. HFpEF has overfilled LV but not impaired LV filling, thus invalidating traditional rationale for slowing heart rate [93, 94]. Cardiac glycosides, such as digoxin, cannot improve cardiac mortality but treat the tachyarrhythmia in HFpEF [95]. However, atrioventricular node blocking drugs, such as digoxin, can exert lethal proarrhythmic effects independent of slowing heart rate [96, 97]. A pacemaker is indispensable to treat conduction system disease in patients with HFpEF, particularly in those with AF [98, 99]. Rhythm control, such as cardioversion or catheter ablation, is considered when AF is associated with clinical symptoms of patients with HFpEF. Intensive application of membrane-active anti-arrhythmic drugs poses a risk to the development of arrhythmia and HFpEF [100, 101]. Catheter ablation restores sinus rhythm and improves LV function but is not effective in patients with myocardial fibrosis [102–106].

Statins can decrease epicardial adipose tissue volume and thereby prevent systemic inflammation and myocardium fibrosis [107, 108]. Statins reduce new-onset and recurrent AF and further prevent AF-related thromboembolic events [109]. Meanwhile, the application of statins is followed by improved diastolic dysfunction and reduced HFpEF risk [110].

Natriuretic peptides activate guanylyl cyclase, resulting in cyclic guanosine monophosphate (cGMP) formation and preventing myocardial fibrosis due to vasodilation and diuresis [111]. Endogenous natriuretic peptides by neprilysin inhibition may produce an antiadipogenic effect on the epicardium [112]. The addition of neprilysin inhibition to ARBs [sacubitril/valsartan; angiotensin receptor-neprilysin inhibitor (ARNI)] ameliorates atrial and ventricular myopathy in patients with HFpEF [113]. Although sacubitril/valsartan increases plasma natriuretic peptides levels by inhibiting neprilysin, it failed to reduce cardiac mortality in the PARADIGM-HF trial [114]. However, subgroup analyses have demonstrated its efficacy in female patients and those with HFmEF [115]. There is evidence from a meta-analysis that sacubitril/valsartan in HFpEF probably reduces HFpEF hospitalization but probably has little or no effect on cardiovascular mortality and life quality. There is a need for improved approaches to patient stratification to identify the subgroup of patients with HFpEF who are most likely to benefit from sacubitril/valsartan, as well as for an improved understanding of biology, and for new therapeutic approaches of HFpEF.

Abnormal nitrogen monoxide-cGMP-protein kinase G (NO-cGMP-PKG) pathway may constitute a

Table 1 Trials of exercise, medications and devices in patients with HFpEF

Types	Interventions	Inclusion	Trials	Endpoints	Results
Exercise	Exercise training	NYHA II-III, EF \geq 50%, tissue Doppler-derived E/e' ratio	Ex-DHF	Exercise capacity, QOL	Positive
ACEI/ARB	Candesartan	Aged \geq 18 years, NYHA II-IV, EF > 40%	CHARM-Preserved	CV death, HF hospitalization	Neutral
	Perindopril	Aged \geq 70 years, clinical diagnosis of chronic HF, EF \geq 40%, hospitalised for a cardiac problem, able to walk without the aid of another person	PEP-CHF	CV death, HF hospitalization	Neutral
ARNI	Sacubitril/valsartan	Aged \geq 40 years, EF \geq 45%, HF signs or symptoms, NT-proBNP \geq 400 pg/mL, eGFR \geq 30 mL/min/1.73m ² , potassium \leq 5.2 mmol/L	PARAMOUNT	NT-proBNP	Positive
		Aged \geq 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	PARALLAX	NT-proBNP	Positive
sGC stimulator and activator	Vericiguat	Aged \geq 45 years, EF \geq 45%, NYHA II-III, HF decompensation, NT-proBNP \geq 300 or BNP \geq 100 pg/mL in sinus rhythm, or NT-proBNP \geq 600 or BNP \geq 200 pg/mL in AF, LVH (intraventricular septal or posterior wall thickness \geq 1.1 cm, and/or LVMI \geq 115 g/m ² in male and \geq 95 g/m ² in female), or LAE (LAV index \geq 29 mL/m ² , or LAV > 58 mL in male and > 52 mL in female patients, or LA area > 20 cm ² , or LA diameter > 40 mm in male and > 38 mm in female patients)	VITALITY	QOL	Positive
		NYHA II-IV, EF \geq 45%, BNP \geq 100 pg/mL or NT-proBNP \geq 300 pg/mL (or BNP \geq 200 pg/mL or NTproBNP \geq 600 pg/mL in AF), LAE determined by echocardiography	SOCRATES-PRESERVED	QOL	Neutral
SGLT-2 inhibitor	Riociguat	EF \leq 35%, NYHA Class III-IV	DYNAMIC	CO	Positive
	Empaglifozin	NYHA II-IV, EF > 40%, NT-proBNP > 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	EMPEROR-PRESERVED	CV death, HF hospitalization	Positive
	Sotaglifozin	EF > 40%, NYHA II-IV, 6MWD of \geq 100 m and \leq 350 m Type 2 diabetes mellitus, HF hospitalization	EMPERIAL-PRESERVED SOLOIST-WHF	6MWD CV death, HF hospitalization	Positive Positive

Table 1 (continued)

Types	Interventions	Inclusion	Trials	Endpoints	Results
Nitrate	Oral nitrate	Mean PAP \geq 35 mmHg and baseline PCWP \geq 20 mmHg, NYHA II-III, EF \geq 40%	PH-HFPEF	PAP at exercise	Positive
MRA	Spironolactone	Aged \geq 50 years, EF \geq 45%, potassium $<$ 5.0 mmol/L, HF hospitalization, BNP \geq 100 pg/ml, NT-proBNP \geq 360 pg/ml	TOPCAT	HF hospitalization	Neutral
		Aged \geq 50 years, NYHA II-III, EF 50%, diastolic dysfunction	Aldo-DHF	Neurohumoral activation, LVH	Positive
PDE-5 inhibitor	Sildenafil	Outpatients with HFpEF	RELAX	PAP, CO	Positive
Pirfenidone	Pirfenidone	Aged \geq 40 years, EF \geq 45%, symptoms and signs of HF, BNP \geq 100 pg/ml or NT-proBNP \geq 300 pg/ml (patients in AF are required to have BNP \geq 300 pg/ml or NT-proBNP \geq 900 pg/ml)	PIROUETTE	ECV	Positive
Cardiolipin peroxidase inhibitor	Elamipretide	Aged 40–80 years, EF \leq 40%, no hospitalization related to HF, at least 3 dysfunctional but viable segments (hyper-enhancement \leq 25%) by cardiac MRI examination	PROGRESS-HF	NT-pro-BNP	Positive
Beta3-adrenoreceptor selective agonist	Mirabegron	LVH (increased LVMI or LVWT \geq 13 mm in at least one wall segment), in the absence of genetic hypertrophic cardiomyopathy and significant valvular disease	BETA3-LVH	LVMI, E/e'	Positive
Device therapy	CardioMEMS	NYHA II-IV regardless of EF with and elevated natriuretic peptides	GUIDE-HF	All-cause death, HF hospitalization	Positive
	IASD	HF \geq 3 months, NYHA class III EF \geq 40% and NYHA III-IV HF, PCWP \geq 15 mmHg at rest or \geq 25 mmHg during supine bike exercise	CHAMPION REDUCE LAP-HF	HF hospitalization CV death, HF hospitalization	Positive Positive
	ASV	HFpEF or HFrEF, AHI \geq 15 events per hour	CAT HF	CV death, HF hospitalization, 6MWD	Positive

HFpEF heart failure with preserved ejection fraction, NYHA New York Heart Association, 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

pathophysiological mechanism promoting myocardial fibrosis and diastolic dysfunction in HFpEF [116, 117]. Direct nitric oxide (NO) donors, including organic nitrates (isosorbide-nitrate), are not recommended in patients with HFpEF, considering their disadvantages of vasodilatation and hypotension [118]. They also fail to increase exercise tolerance and improve diastolic function [119]. Enhancing endothelial nitric oxide synthase activity by the transcription amplifier AVE3085 increases

NO production and improves diastolic function [120]. However, this method is still pending clinical evaluation. Nitrosative stress is a major driver in HFpEF rather than the limited bioavailability of NO, with new strategies targeting nitrosative stress in the future [121].

Phosphodiesterase-5 inhibitors are applied to treat precapillary pulmonary arterial hypertension (PAH) and may be considered in combined precapillary and postcapillary PAH. Sildenafil fails to significantly lower pulmonary

artery pressure (PAP) in HFpEF patients without precapillary PAH and those with postcapillary PAH [122, 123]. However, sildenafil has positive effects in HFpEF patients with precapillary PAH or severe combined precapillary and postcapillary PAH [124]. Soluble guanylyl cyclase activators, such as vericiguat and riociguat, are administered in patients with PAH. Vericiguat has recently been demonstrated to reduce cardiac mortality in patients with HFrEF [125]. Further studies will assess its effects on cardiac function and outcomes in patients with HFpEF.

Insulin has hypoglycemic, antinatriuretic, and adipogenic effects and causes adverse outcomes in patients with HFpEF [126, 127]. Metformin reduces proinflammatory adipokines and has anti-inflammatory roles [128, 129]. It reduces the risk of AF and improves diastolic dysfunction in HFpEF [130]. Metabolic abnormalities and systemic inflammation impair the expression of peroxisome proliferator-activated receptor (PPAR), but co-stimulation of PPAR and adiponectin reverses epicardial adipose tissue dysfunction [131, 132]. Pioglitazone and rosiglitazone suppress atrial and ventricular inflammation and fibrosis and reduce the risk of AF and HFpEF [133, 134]. Thiazolidinediones have been associated with an improved diastolic filling abnormality in patients with diabetes [135]. However, they promote sodium retention, thereby increasing cardiac volume [136]. Sodium retention may aggravate cardiac fibrosis and hypertrophy and increases the risk of HFpEF [137]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as dapagliflozin and empagliflozin, achieve significantly decreased primary composite endpoint of worsened HF or cardiac mortality in patients with HFrEF, which is independent of diabetes [138, 139]. SGLT2 inhibitors reduce the volume of epicardial adipose and cardiac events caused by HFpEF [140]. A number of randomized trials are underway to explore the efficacy of SGLT-2 in patients with HFpEF [141, 142]. However, because the patients in these studies did not demonstrate any HF-related manifestations or the degree of HF was low at baseline, any recommendation of SGLT2is for the treatment of HFpEF should be cautious.

Regulation of incretin system includes mimicking glucagon-like peptide 1 (GLP-1) roles and inhibiting GLP-1-degrading enzyme dipeptidyl peptidase-4 (DPP-IV) [143]. GLP-1 analogues, such as semaglutide and liraglutide, improve cardiac outcomes in patients with diabetes [144]. LIVE trial determined that although liraglutide did not affect LV function compared with placebo in stable HF patients with and without diabetes, treatment with liraglutide was associated with more serious cardiac adverse events [142]. FIGHT trial revealed that the use of liraglutide did not lead to greater post-hospitalization clinical stability [143].

The results of existing evidence do not support the use of liraglutide or semaglutide in HF with diabetes, and LIVE points out the potential harmful effect of liraglutide in this population. The safety of these powerful GLP-1 analogues in patients with diabetes and HF remains uncertain, and further studies are needed to assess their risks and benefits especially in patients with HFpEF.

As an anti-fibrotic drug, pirfenidone suppresses the development of ventricular fibrosis and diastolic dysfunction through targeting transforming growth factor β (TGF- β) signaling pathway in pressure-overload induced HF [145, 146]. Future studies would assess whether these effects account for patients with HFpEF [147, 148]. Lysyl oxidase-like 2 (Loxl2) promotes collagen's cross-linking and causes interstitial fibrosis [149]. Diastolic function may be improved by antibody-mediated inhibition of Loxl2 [150]. Inhibition of Loxl2 and new cross-linking strategies will be assessed in the future. Systemic inflammation is the main mediator in HFpEF, and cytokine inhibitors have been considered therapeutic options [151]. Although interleukin-1 (IL-1) blockade with anakinra cannot improve exercise tolerance, canakinumab, a monoclonal antibody targeting IL-1 β , decreases HF hospitalization and mortality [152].

Cardiolipin is a significant phospholipid in the inner mitochondrial membrane, and Szeto-Schiller (SS) peptide is an antioxidant peptide binding to cardiolipin [153]. Elamipretide (MTP-131, SS31) reduces LVEDP in patients with HFpEF and needs to be further assessed through clinical studies [154, 155]. Neladenoson bialanate, a partial adenosine A1 receptor agonist, may benefit both cardiac and skeletal muscles. It enhances SERCA2a activity and reverses ventricular remodeling through improving mitochondrial function but fails to significantly affect exercise tolerance in patients with HFpEF [156]. Levosimendan has positive inotropic and vasodilative effects through a combined effect on calcium sensitization and phosphodiesterase-3 inhibition. It improves inflammatory process and diastolic function in patients with HFrEF [157]. Meanwhile, inhaled iloprost causes an acute reduction of PAP in patients with HFpEF [158]. Further studies will assess levosimendan and prostacyclin analogs in patients with HFpEF. Fluid overload can aggravate clinical symptoms and exercise intolerance and increase cardiac decompensation and overall mortality in patients with HFpEF. Diuretics are established drugs to treat fluid overload and considered a cornerstone in the symptomatic therapy of HFpEF.

As small non-coding ribonucleic acid (RNA) molecules, micro-RNAs (miRNAs), such as miR-23, miR-24, miR-125, miR-195, miR-199, and miR-214, are observed to be increased in the heart tissue of patients with HF [159].

Hypertrophic growth was caused by overexpression of these miRNAs in cultured myocytes. There are different profiles of miRNAs between patients with HFpEF and HFrEF, and targeting miRNAs may initiate new treatment methods of HFpEF in the future [160]. However, mechanisms and application of treatment methods targeting miRNAs need to be better understood through further studies. Cell therapy targets myocardial inflammation and fibrosis in HFpEF and may be a promising treatment for HFpEF. It is still unclear which is the optimal cell type, dose, and delivery route in HFpEF [161].

CardioMEMS device, a radio frequency-based wireless pressure sensor, improves cardiac outcome through continuously monitoring PAP in patients with HF [162, 163]. LV mechanical dyssynchrony causes impaired LV function, higher LV-filling pressure, and worsened clinical symptoms in patients with HFpEF [164–166]. However, it may not be associated with cardiac outcomes of patients with HFpEF [167]. Further studies will assess the effects of both cardiac resynchronization therapy and cardiac contractility modulation on exercise tolerance in patients with HFpEF [168]. Renal sympathetic denervation cannot affect exercise tolerance in patients with HFpEF, although it lowers blood pressure, reduces LV mass, and improves diastolic function [169–172].

Conclusion

With its increasing prevalence and worsening prognosis, HFpEF is nearly unique to the elderly and considered a true geriatric syndrome. Compared with the tremendous progress in the diagnosis and treatment of HFrEF, HFpEF continues to be a great enigma and needs to be further studied considering the failure of HF drugs to improve its outcome [173]. There is a lack of precise indicators for diagnosing HFpEF and a high prevalence of comorbidities that may interfere with HFpEF diagnosis [174]. Clinical trials generally enroll all participants with HF symptoms and preserved LVEF [175]. However, HFpEF is a heterogeneous syndrome with multiple phenotypes, affected by aging, and involving many organs [176]. HFpEF represents multifactorial and multisystemic syndrome with different pathophysiologies and phenotypes. Treatment with a single target fails to significantly affect HFpEF outcomes; however, lifestyle modifications prove to be an effective way to approach HFpEF as a clinical syndrome. Drugs and interventions applied to treat HFpEF have been principally based on central hemodynamic and neurohormonal abnormalities, which appear to be less complete in HFpEF than in HFrEF [177]. 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 biology, diagnosis, and treatment of HFpEF.

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Authors' contributions

YL, SF, YY and YLL wrote the manuscript. YZ and LL revised the manuscript. All authors contributed to the article and approved the submitted version.

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The authors declare no competing interests.

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