Heart Failure with Preserved Ejection Fraction
An Ongoing Enigma

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KEYWORDS

• Heart failure • Preserved ejection fraction • Diastolic dysfunction • HFpEF • Review

KEY POINTS

- Heart failure with preserved ejection fraction (HFpEF) is an increasing epidemic with mortality and morbidity similar to heart failure with reduced ejection fraction, but is more multifactorial in cause and has limited evidence-based therapies.
- Its pathophysiology may be induced by a systemic proinflammatory state, resulting in combined ventricular and arterial stiffness and impaired chronotropic and cardiac output reserve.
- At present, recommended therapy for patients with HFpEF includes symptom relief and management of related comorbidities such as hypertension, atrial fibrillation, and coronary artery disease.
- Medications endorsed by the most recent American College of Cardiology Foundation/American Heart Association guidelines for HFpEF include only diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and omega-3 fatty acids.
- Ongoing investigations of potential HFpEF therapies include aldosterone antagonists, phosphodiesterase-5 inhibitors, advanced glycation end product crosslink breakers, physical exercise, and rate-adaptive pacing from implantable cardiac devices.

INTRODUCTION

With an estimated 50% (range 40%–71%) of all patients with clinical symptoms of heart failure (HF) having normal or near normal left ventricular (LV) ejection fractions (LVEF),[1–5] there has been an increasing need to understand and treat the complex syndrome of HF with preserved ejection fraction (HFpEF). The diagnosis of HFpEF requires a patient to have the typical symptoms of HF, such as dyspnea and fatigue, with normal LV volumes and contractility but increased LV filling pressure. HFpEF used to be called diastolic HF[6]; however, the terminology was controversial and has been updated over the past 8 years, initially to HF with normal ejection fraction (HFnEF),[7–11] then to HFpEF because the pathogenesis of HFpEF is not exclusively based on diastolic dysfunction. It is imperative to isolate the terminology diastolic dysfunction to describe an abnormality in LV relaxation or chamber compliance.[12] Diastolic dysfunction can be present regardless of the LVEF or symptoms. The threshold for defining preserved LVEF varies greatly, from LVEF greater than 40% to greater than or equal to 55%, with greater than or equal to 50% becoming more widely accepted.[1,11] Patients with LVEF of 40% to 49% represent an intermediate or borderline HFpEF group and may also be considered as HF with improved or recovered LVEF. In practice, the diagnosis of HFpEF is often established after echocardiography reveals preserved LV systolic function

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with signs of HF on examination and without valvular disease, pericardial disease, or other noncardiac causes accounting for dyspnea, edema, and fatigue.

EPIDEMIOLOGY

Over time, the proportion of patients with HFpEF has increased.[3,13] Although HF symptoms unify patients with HFpEF, there is marked heterogeneity in the clinical characteristics that potentially confer risk for this syndrome. Patients with HFpEF are typically older, more likely to be female, with higher body mass index and prevalence rates of hypertension and atrial fibrillation, and lower rates of coronary artery disease (CAD) and valve disease.[13,14] Hypertension (chronic pressure overload) remains the single most important predictor of HFpEF across multiple HF registries, epidemiologic trials, and large controlled trials.[15] Because patients with HFpEF have important comorbidities that strongly influence outcomes, the focus of HFpEF therapy is often on comorbid conditions (eg, hypertension, atrial fibrillation, diabetes, chronic kidney disease).

PATHOPHYSIOLOGY

Substantial attention has been devoted to better define the pathogenesis that leads to HFpEF in order to potentially target more effective treatment. Patients with HFpEF, even when well compensated, are characterized as having chronically increased left-sided filling pressures, reduced LV chamber distensibility (compliance), and increased diastolic wall stress. The classic paradigm is based on chronic LV afterload or pressure overload resulting in decreased LV compliance. Although impaired LV relaxation is usually present in patients with HFpEF, it is also considered part of the normal aging process, present in otherwise healthy seniors. What the HF community has not understood is why abnormal myocardial relaxation does not always indicate HFpEF.

Over the past decade, the pathogenesis of HFpEF has been shown to be related to ventricular stiffness combined with arterial or vascular stiffness.[16,17] Ventricular and arterial stiffness increases with advancing age[18] and is further amplified by comorbidities such as hypertension, diabetes, and chronic kidney disease.[19] However, increased end-diastolic static ventricular stiffness may not be a universal finding in patients with HFpEF compared with healthy, sedentary, age-matched controls.[20] In addition, left atrial stiffness has been reported as a predictor of discriminating patients with HFpEF from those with LV hypertrophy without HF symptoms.[19,21] It has been hypothesized that titan, the third myofilament of cardiac muscle, also plays an important role in diastolic function by defining cardiomyocyte passive stiffness.[22] Although there is ongoing debate regarding the degree and prevalence of primary myocardial stiffness in this syndrome, it seems that additional contributive mechanisms must be present in order for HF to manifest.

The cardiac interstitium has been of increasing interest in this conundrum. In particular, fibroblasts and changes in the extracellular matrix (ECM) can cause myocardial fibrosis and thus myocardial remodeling. In a cohort of symptomatic patients with HFpEF, compared with patients with asymptomatic LV hypertrophy, plasma biomarkers that indicate ongoing ECM collagen changes were present, suggesting that a disruption of collagen homeostasis may be related to the pressure overload–LV remodeling phenomenon.[23] The panel of biomarkers (matrix metalloproteinases [MMPs]) was a more powerful predictor of HFpEF than N-terminal-pro-B-type natriuretic peptide, and a few of these biomarkers (MMP-2, MMP-7, MMP-8) showed patterns that were specific to patients with HFpEF compared with patients with only LV hypertrophy. Endomyocardial biopsy samples of patients with HFpEF have shown increased cardiac inflammatory cells that expressed profibrotic transforming growth factor beta, resulting in substantially more cardiac collagen production (type I and III).[24] These findings suggest that inflammation may be a key trigger in the accumulation of ECM that leads to fibrosis and HFpEF.

Other cardiovascular abnormalities, namely impaired chronotropic and cardiac output reserve, have been observed and likely contribute to the pathogenesis and presentation of HFpEF.[16] Chronotropic incompetence, defined as an inadequate heart rate response to exercise, is exaggerated in patients with HFpEF compared with healthy or hypertensive controls.[25,26] Patients with HFpEF also had significantly delayed heart rate recovery, more impaired exercise tolerance and systemic vasodilation, and lower increase in cardiac output with exercise.[25,26] Although diastolic dysfunction promotes congestion and pulmonary hypertension with stress in HFpEF, reduction in exercise capacity is predominantly related to inadequate cardiac output relative to metabolic needs.[27]

As in HF with reduced ejection fraction (HFrEF), neurohormonal imbalances have also been implicated in HFpEF. The renin-angiotensin-aldosterone system (RAAS) is considered an important contributor to the development of HFpEF.[28] The neurohormones angiotensin II and aldosterone have effects on vascular tone, water

retention, and renal tubular sodium retention. These instigators lead to hypertensive remodeling with extensive ECM turnover and eventual ventricular fibrosis.[29] Recent data suggest that patients with HFpEF may also have a deficit of cyclic guanosine monophosphate (cGMP)–dependent protein kinase (PKG) activity.[30]

With evolving understanding of the potential mechanisms for HFpEF, based on myocardial structure, endothelial function, and cell signaling, a novel paradigm for the development of HFpEF has been suggested that is based on a systemic proinflammatory state induced by comorbidities. In this new paradigm, HFpEF occurs after the following sequence of events: (1) a high prevalence of comorbidities (such as hypertension, obesity, diabetes mellitus, and chronic obstructive pulmonary disease) induce a systemic proinflammatory state; (2) a systemic proinflammatory state causes coronary microvascular endothelial inflammation; (3) coronary microvascular endothelial inflammation reduces nitric oxide bioavailability, cGMP content, and PKG activity in adjacent cardiomyocytes; (4) low PKG activity favors hypertrophy development and raises resting tension because of hypophosphorylation of titin; and (5) both stiff cardiomyocytes and interstitial fibrosis contribute to high diastolic LV stiffness and development of HF.[31]

DIFFERENTIAL DIAGNOSIS

Dyspnea, reduced exertional tolerance, edema, and orthopnea are classic symptoms of HF. When present in the setting of a preserved LVEF and absence of valvular abnormalities on noninvasive imaging, HFpEF is presumed. However, other common conditions share some of these complaints. Pulmonary disease (including obstructive sleep apnea), obesity, and myocardial ischemia need to be excluded as the cause of symptoms. Documentation of increased B-type natriuretic peptide can be helpful in determining whether increased LV diastolic pressures are contributing to the symptoms.[32] Perhaps newer biomarkers such as MMP[23] will become more commonly used in the future.

Multiple diagnostic algorithms exist for the workup of HFpEF. In the simplest strategy, after noncardiac causes are ruled out, causes of HF can be divided into high output, nonmyocardial, and myocardial (**Fig. 1**).[11] Chronic anemia, chronic liver disease, thyrotoxicosis, or arteriovenous shunts (such as fistulas for hemodialysis) may all lead to LV volume overload and high-output HF. Pericardial diseases from constriction or tamponade and valvular diseases comprise the nonmyocardial causes that are important to distinguish. The myocardial category contains the broadest differential.

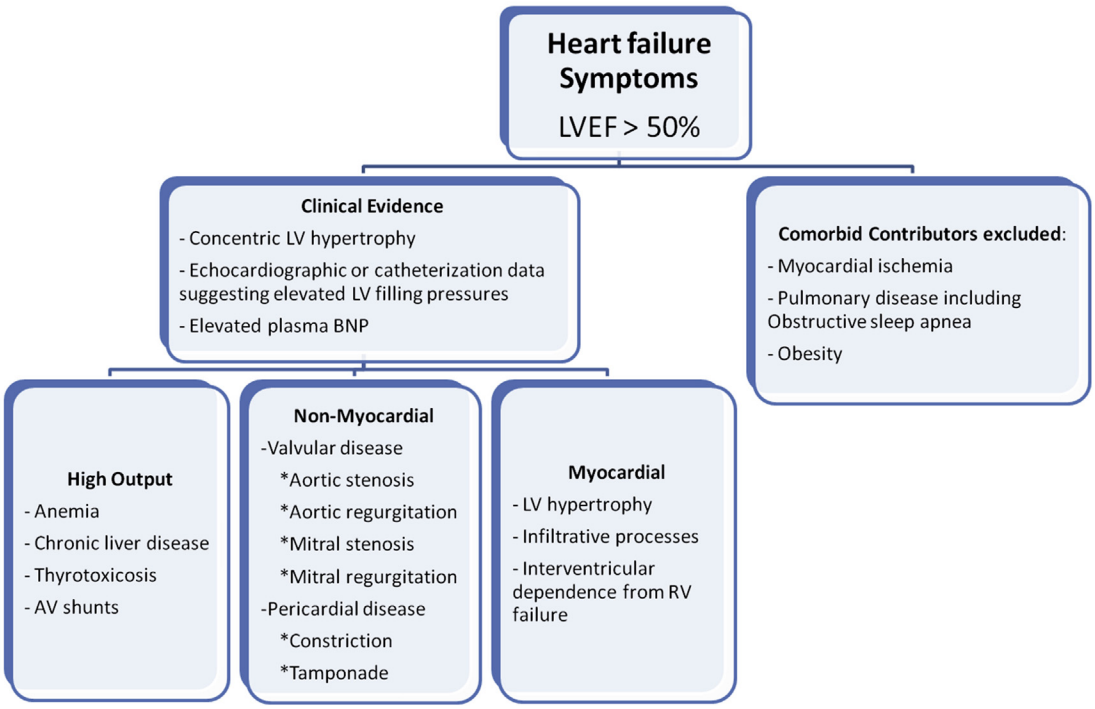

Fig. 1. Diagnostic algorithm for working up HF symptoms (dyspnea, fatigue, edema) in patients with documented LVEF greater than 50%. AV, arteriovenous; BNP, B-type natriuretic peptide; RV, right ventricular.

Although hypertensive LV hypertrophy is the most common cause of HFpEF, CAD is also common. Infiltrative disorders such as cardiac amyloidosis, sarcoidosis, and associated storage disorders like hemachromatosis all need to be considered. In addition, interventricular dependence, from right ventricular enlargement and dysfunction, must be excluded. Careful history and physical examination coupled with a thorough diagnostic evaluation are important to eliminate other conditions that may present in a similar manner. In some cases, invasive hemodynamic evaluation can be useful for diagnosis and to guide therapy.[33]

OUTCOMES

Although it is often reassuring to have an LVEF reported as normal, substantial morbidity and mortality still exist in HFpEF. Patients with preserved ejection fraction presenting with an acute HF decompensation may have a 50% chance of rehospitalization within 6 months.[34] Functional decline, as measured by an activities of daily living scale, occurred in more than a quarter of survivors. Both readmission and functional decline were statistically similar compared with those patients with reduced LVEF.

Survival with HFpEF may or may not be different than that of HFrEF. There are varying survival rates reported for patients with HFpEF depending on the population studied, how HFpEF was defined, and severity of disease.[35] The Veterans Administration Heart Failure Trial showed an annual mortality of 8% for HFpEF compared with 19% among those with HFrEF.[36] Over a mean follow-up of about 3 years, the Digitalis Intervention Group (DIG) study revealed a mortality approaching 23% for HFpEF versus 35% for HFrEF.[37] Other studies have shown similar survival rates between patients with HFpEF and patients with HFrEF.[3,13,38]

The varying prognoses reported among patients with HFpEF underscore the marked heterogeneity of these patients. Studies not controlling for a history of HF or the wide variety of comorbidities likely account for some of the observed discrepancies. Despite the differences, there has been much insight gained into the natural history of the HFpEF syndrome.

TREATMENT

Unlike the overwhelming evidence for guideline-based HFrEF therapy, there has been less direction on the best treatment of HFpEF. In part, this is because of the recent recognition of the HFpEF epidemic and consequently the limited number of studies over the past decade. Most of the recommendations for treating HFpEF are extracted from smaller studies and expert opinion.[1,7,10,11] The newly released 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) recommendations continue to focus on therapies directed at symptoms and comorbidities that can worsen HFpEF.[1] No current therapy recommendation was given a level of evidence A (data derived from multiple randomized controlled trials or meta-analyses). The few large-scale trials on HFpEF treatment have been neutral. The current treatment options that have been evaluated for HFpEF are summarized later.

Controlling Comorbid Conditions

In the latest versions of the 2013 ACCF/AHA guidelines and the 2010 HFSA guidelines on treatment of HFpEF, managing comorbid conditions remains a top priority.[1,11] These conditions include managing hypertension, atrial fibrillation, and CAD. **Table 1** summarizes the recommended approach and rationale for the management of the related comorbidities. Although no set blood pressure goal has been established in the most recent HF guidelines,[1] the 2009 ACC/AHA guidelines suggest a goal systolic pressure less than 130 mm Hg and diastolic pressure less than 80 mm Hg with potentially multiple agents with different mechanisms of action.[10] Because atrial fibrillation decreases LV filling and diastolic relaxation, rate control is highly recommended. Although some experts have suggested that restoring sinus rhythm might also improve patients, because of the reliance of LV filling on atrial contraction[7] there are no randomized controlled trials evaluating the benefits of sinus rhythm in patients with HFpEF; thus the 2013 ACCF/AHA guidelines do not comment on rhythm control strategies. Treatment of CAD in this population is similar to treatment in the general population, although no specific study addresses CAD management in HFpEF. However, care must be taken in using nitrates because patients with HFpEF tend to be more dependent on preload and can become hypotensive.

Pharmacologic Treatment: Review of the Evidence

The currently recommended pharmacologic therapy, according to the 2013 ACCF/AHA guidelines,[1] includes diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and omega-3 fatty acid supplementation (see **Table 1**). Although other HF medications, such as calcium channel blockers, digoxin, aldosterone antagonists, and phosphodiesterase-5 (PDE5) inhibitors, are not

Table 1
Management of HFpEF by comorbidity and pharmacologic therapy

Strategy	Recommendation[a]	Class[a]	Level of Evidence[a]	Rationale/Evidence
Hypertension	Blood pressure should be controlled according to published clinical practice guidelines	I	B	↓ LV hypertrophy[44,70] ↓ Hospitalizations[71] ↑ Exercise tolerance[72]
Atrial fibrillation	Managing atrial fibrillation according to published clinical practice guidelines is reasonable to improve HF symptoms	IIa	C	Patients with HFpEF rely more heavily on the atria's contribution to stroke volume
CAD	Coronary revascularization for patients with CAD is reasonable if documented myocardial ischemia or anginal symptoms is present despite guideline-directed medical therapy	IIa	C	Ischemia impedes LV relaxation
Diuretics	Should be used to treat symptoms caused by volume overload	I	C	Hong Kong Diastolic HF study (n = 150, LVEF >45%): ↑ QoL[39]
β-Blockers	Reasonable for controlling hypertension and atrial fibrillation	IIa	C	SENIORS trial: HFpEF subgroup (n = 1359, LVEF >35%); nebivolol vs placebo, ↓ mortality/CV hospitalizations[45]
ACE inhibitors	Reasonable for controlling hypertension	IIa	C	PEP-CHF (n = 850, LVEF >40%), perindopril vs placebo: no difference on combined outcome mortality/HF hospitalization; ↑ functional status and 6MWT[40]
ARBs	Reasonable for controlling hypertension	IIa	C	I-PRESERVE (n = 4128, LVEF >45%), irbesartan vs placebo: no difference on mortality, hospitalization, or QoL[41]
	Might be considered for decreased hospitalizations	IIb	B	CHARM-PRESERVED (n = 3023, LVEF >40%), candesartan vs placebo: no difference on CV mortality/hospitalization; ↓ hospitalization[42]
Omega-3 fatty acid	Reasonable to use as adjunctive therapy	IIa	B	GISSI-HF (n = 6975), omega-3 fatty acid vs placebo: ↓ mortality and CV hospitalization regardless of whether LVEF > or ≤40%[56]
Other nutritional supplements	Routine use of other nutritional supplements is not recommended	III	C	—

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Table 1
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Strategy	Recommendation[a]	Class[a]	Level of Evidence[a]	Rationale/Evidence
Calcium channel blockers	—	—	—	Verapamil (n = 15–20, LVEF >45%): ↓ HF symptoms, ↑ exercise capacity[47,48]
Digoxin	—	—	—	DIG Ancillary study (n = 988, LVEF >45%); digoxin vs placebo, no difference in mortality/ hospitalization[53]
Aldosterone antagonist	—	—	—	RAAM-PEF (n = 44, LVEF ≥50%) eplerenone vs placebo: improved diastolic function by echo, ↓ biomarkers; no difference in 6MWT[49] ALDO-DHF (n = 422, LVEF >50%), spironolactone vs placebo: improved diastolic function by echo; no difference in exercise tolerance, symptoms, or QoL[50] TOPCAT (n = 3445, LVEF >45%), spironolactone vs placebo: ongoing[52]
PDE5 inhibitors	—	—	—	RELAX (n = 216, LVEF ≥50%), sildenafil vs placebo: ↓ mPA, ↑ QoL, no difference in peak Vo_2 or 6MWT[55]

Abbreviations: 6MWT, 6-minute walk test; ACE, angiotensin-converting enzyme; ALDO-DHF, Aldosterone Receptor Blockade in Diastolic Heart Failure; ARB, angiotensin receptor blocker; CHARM-Preserved, Candesartan in Heart Failure - Assessment of Reduction in Mortality and Morbidity; CV, cardiovascular; DIG, Digitalis Intervention Group; echo, echocardiography; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; mPA, mean pulmonary artery pressure; PDE5, phosphodiesterase-5; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; QoL, Quality of life; RAAM-PEF, Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; SENIORS, Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure; TOPCAT, Treatment of Preserved Cardiac Function with an Aldosterone Antagonist; Vo_2, oxygen consumption.

[a] Based on the 2013 ACCF/AHA Heart Failure Guidelines (Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013. pii:S0735-1097(13)02114-1. http://dx.doi.org/10.1016/j.jacc.2013.05.019).

recommended in the most recent ACCF/AHA guidelines, there have been mixed data and ongoing investigations regarding their effectiveness. Nevertheless, the evidence supporting these different medications is based mostly on a limited number of clinical trials, which are summarized in **Table 1**, many of which are of modest size.

Although loop and thiazide diuretics remain widely accepted therapy for decongesting patients with HFpEF, there are no randomized controlled trials comparing diuretics with placebo. Only 1 study, the Hong Kong Diastolic HF study, revealed significant improvement in quality of life at 52 weeks in patients treated with diuretic therapy that did not improve further with addition of an ACE inhibitor or ARB.[39]

Although ACE inhibitors have not been shown to improve mortality in HFpEF compared with placebo, the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial did show that perindopril improved functional class and 6-minute walk distances in patients with HFpEF more than the age of 70 years.[40] ARBs have been the most studied in the HFpEF population. Although the large trials (I-PRESERVE [Irbesartan in Heart Failure with Preserved Ejection][41] and CHARM-Preserved [Candesartan in Heart Failure - Assessment of Reduction in Mortality and Morbidity][42]) failed to show significant survival benefits for patients with HFpEF taking ARBs, candesartan was associated with a significant decrease in hospitalizations.[42]

β-Blockers have been shown to improve diastolic function in patients with HFpEF,[43] induce left ventricular hypertrophy regression[44] and are standard therapy for hypertension, atrial

fibrillation, and CAD. However, the evidence for β-blockers in patients with HFpEF has been mixed and is based on comparative data from combined populations of patients with HFpEF and HFrEF: the SENIORS trial (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) showed some benefit,[45] but the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry showed no benefit.[46]

Calcium channel blockers have been mentioned in previous treatment guidelines as treatment of hypertension, symptom-limit angina, and rate control of atrial fibrillation,[7,10,11] but are not specifically addressed in the 2013 ACCF/AHA guidelines.[1] Data supporting calcium channel blockers in this population remain limited to small patient samples (n = 20 or less) but they were associated with symptomatic improvement.[47,48]

Aldosterone antagonists are also not currently recommended in the 2013 ACCF/AHA guidelines but are actively being investigated as therapy for HFpEF. Although spironolactone may improve diastolic function and LV mass index by echocardiographic measures,[49,50] improved clinical outcomes have not been observed.[49–51] TOPCAT (Treatment of Preserved Cardiac Function with an Aldosterone Antagonist) is currently underway, comparing spironolactone versus placebo in 3445 patients with HFpEF with LVEF greater than 45% and controlled blood pressure.[52]

Digoxin has not been specifically recommended for HFpEF. An ancillary study of the DIG trial enrolled HF patients with LVEF greater than 45% but showed no statistical difference in mortality or hospitalization.[53] Although there was a trend toward decreased HF hospitalizations for patients with HFpEF on digoxin, this was offset by an increase in hospitalizations for unstable angina.

PDE5 inhibitors have emerged as a new class of medications for pulmonary hypertension and may be useful in patients with HFpEF with pulmonary hypertension. Although sildenafil effectively decreases pulmonary artery pressures and has been associated with improved quality of life in patients with HFpEF,[54] the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) study did not show any change in peak oxygen consumption during cardiopulmonary testing or in 6-minute walk distances at 24 weeks.[55] However, the short follow-up period may not have allowed enough time for differences to become apparent.

The only other medication endorsed by the ACCF/AHA guidelines for patients with HFpEF is omega-3 polyunsaturated fatty acids, based primarily on the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico – heart failure) trial.[56] However, other nutritional supplements are not recommended.

OTHER ONGOING INVESTIGATIONS

Reduced exercise tolerance in patients with HFpEF is generally attributed to inadequate chronotropic response. It is currently unknown whether rate-adaptive pacing from implantable cardiac devices may have a role in patients with HFpEF. Adjustment of pacemaker sensor parameters has been shown to improve chronotropic response in patients who do not have HF.[57] The RESET (Restoration of Chronotropic Competence in Heart Failure Patients with Normal Ejection Fraction) trial is currently investigating whether pacemaker implantation with rate-adaptive pacing may be beneficial in patients with symptomatic HFpEF with an impaired chronotropic response.[58]

Although physical exercise is encouraged, the largest exercise training trial in patients with chronic HF (HF-ACTION [Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training]) did not show significant reductions in clinical outcomes.[59] However, smaller studies of patients with HFpEF have at least confirmed improved exercise capacity after medically supervised exercise training,[60,61] and a randomized study of 64 patients with HFpEF additionally showed that exercise was associated with atrial reverse remodeling and improved LV diastolic function.[62]

Another area of active drug investigation involves advanced glycation end products (AGEs), which are formed by a reaction between reducing sugars and biologic amines, which accumulate slowly over time and can contribute to age-associated cardiovascular changes such as increased vascular and myocardial stiffness, endothelial dysfunction, altered vascular injury responses, and atherosclerotic plaque formation.[63] Early investigational studies in patients with HFpEF suggested that alagebrium, an AGE-crosslink breaker, can decrease LV mass and improve LV diastolic filling and quality of life in patients with HFpEF.[64]

Other potential novel pharmacologic agents in ongoing research include a dual angiotensin receptor and neprilysin inhibitor (LCZ696).[65,66] Future research, based on animal models, may evaluate the efficacy of and L-carnitine supplementation,[67] the I(f)-inhibitor ivabradine,[68] and MMP-9 inhibitors and nitroxyl donors.[69]

SUMMARY

HFpEF was initially thought to be a syndrome resulting from abnormalities of diastolic function from chronic pressure overload. However, further research suggests that there is much more at play. Its pathophysiology may be related to abnormalities of the endothelium, cardiomyocyte, and interstitium, and may be induced by a systemic proinflammatory state, resulting in combined ventricular and arterial stiffness, impaired chronotropic and cardiac output reserve, and increased filling pressures. This multifaceted syndrome is frequently encountered with an increasing prevalence and is associated with considerable mortality and morbidity, similarly to HFrEF. Although much effort has focused on establishing effective therapy, none of the evidence-based therapies for HFrEF have shown clear benefit in clinical outcomes for HFpEF. At present, management of volume overload with diuretics, control of hypertension, and therapy for comorbid conditions are the mainstay of therapy. With a projected 50% increase in the number of patients with HF by 2030, HFpEF will remain a focus of research for years to come.

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