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Treatment of Heart Failure With Normal Ejection Fraction

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Opinion Statement

Heart failure (HF) is a major cause of mortality and morbidity and one of the most frequent reasons for hospital admission in the United States and Europe. Currently, more than 50% of HF patients have a normal (N) left ventricular (LV) ejection fraction (EF) (LVEF >50%). The main pathophysiologic processes involved in HFNEF are increased LV stiffness and abnormal relaxation, resulting in impaired LV filling. Hypertension and myocardial ischemia are the most common causes of HFNEF. Precipitating factors include volume overload, tachycardia, physical exercise, systemic stressors (such as fever and infection), arrhythmia, increased salt intake, and use of nonsteroidal anti-inflammatory drugs. There is little evidence to guide treatment, as previously HFNEF patients have been excluded from clinical trials on the basis of a normal LVEF. Survival improved over time in patients with reduced (R) EF (HFREF) (LVEF <40%), reflecting the beneficial effects of treatment in this phenotype. However, survival did not improve for HFNEF patients. The approach to the treatment of HFNEF patients should focus on reducing LV filling pressure, controlling hypertension, modifying ischemia, and improving LV relaxation. Therefore, diuretics are suitable for HFNEF patients to reduce ventricular filling pressure. Hypertension can be treated by using multiple agents if necessary. Drugs of particular interest and recommended to treat hypertension are calcium channel blockers (CCBs) and antagonists of the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists. Ischemic heart disease can be treated with antiplatelet therapy, anticoagulants, and β-blockers. Heart rate control in atrial fibrillation can be achieved with β-blockers and digoxin. Finally, ACE inhibitors and ARBs could potentially decrease LV hypertrophy in hypertensive patients with HFNEF.

Introduction

Heart failure (HF) with normal (N) ejection fraction (EF) constitutes nearly half of all HF patients and is associated with high morbidity and mortality [1]. This phenotype is the predominant form of HF among

the elderly, in women, and those with a history of hypertension or diabetes. HFNEF patients have concentric left ventricular (LV) remodeling with a normal LV end diastolic volume, abnormalities of active relaxation, and increased passive ventricular stiffness [2–4]. The European Society of Cardiology (ESC) issued new criteria for the diagnosis of HFNEF based on clinical signs and/or symptoms of HF in the presence of an LVEF >50% in a non-dilated LV (LV end-diastolic volume <97 mL/m^2) and of abnormalities in LV diastolic function/filling [5, 6••]. The American College of Cardiology (ACC) and the American Heart Association (AHA) joint guidelines [7, 8] so far only recommended blood pressure control, heart rate control, central blood volume reduction, and alleviation of myocardial ischemia as useful measures to treat HFNEF patients.

However, despite the importance of HFNEF, the pathophysiology and treatment of this phenotype remain poorly understood. Until now, large-scale clinical trials in HFNEF patients (Irbesartan in HF with Preserved EF [I-Preserve] [9••, Class I], Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF] [10, Class I], Candesartan in Heart Failure-Assessment of Reduction of Mortality and Morbidity [CHARM]-Preserved [11, Class I], and Digitalis Investigation Group Congestive Heart Failure [DIG-CHF] [12, Class I]) failed to demonstrate effectiveness of any specific therapy on mortality (Table 1). However, because HFNEF patients are usually elderly, often with other co-morbidities, quality of life and exercise capacity may be more relevant endpoints than mortality.

In many studies, the effects of angiotensin-converting enzyme (ACE) inhibitors [13], β-blockers [14], and angiotensin receptor blockers (ARBs) [15] have been assessed in HF patients with reduced (R) EF, but few studies specifically evaluated the same compounds in HFNEF patients. Pharmacologic treatment of HFNEF patients is aimed to decrease blood pressure, promote regression of LV hypertrophy, prevent tachycardia, treat symptoms of congestion, and maintain atrial contraction as recommended by the ACC and the AHA joint guidelines [7, 16 Class III]. These guidelines target underlying HFNEF causes and are estimated to improve LV function and optimize hemodynamics. β-blockers are usually used to improve LV function, however they do not directly affect myocardial relaxation. HFNEF patients may benefit from the use of β-blockers, with reduction in heart rate, which would reduce myocardial oxygen demand, increase coronary perfusion time, and lengthen diastole [16]. In addition, β-blockers have been shown to reduce blood pressure, to promote regression of LV hypertrophy, and to antagonize the excessive adrenergic stimulation present in HF. Optimizing hemodynamics is primarily achieved through reduction of cardiac preload and afterload. ACE inhibitors and ARBs directly affect myocardial relaxation and compliance by blocking angiotensin II receptors, thereby reducing interstitial collagen deposition and fibrosis [17, 18]. ACE inhibitors have shown to cause regression of LV hypertrophy, decrease blood pressure, and prevent or modify cardiac remodeling; these findings support the use of ACE inhibitors in HFNEF patients [19, Class III]. Moreover, in the CHARM trial using the ARB candesartan, beneficial effects were observed in HFNEF [11] with reduction in the incidence of hospitalization for CHF exacerbation (Table 1). However, in HFNEF patients the ARB candesartan did not show a significant mortality benefit [11].

Table 1. Completed large trials for HFNEF

	DIG-PEF [12]	CHARM-Preserved [11]	I-PRESERVE [9••]	PEP-CHF [10]
Drug	Digoxin	Candesartan	Irbesartan	Perindopril
HFNEF patients, *n*	988	3023	3600	850
LVEF,%	>45	>40	>40	>45
Follow-up, *mo*	37	36.6	49.5	26.6
Outcome results				
No effect on	Mortality	Mortality	Mortality	Mortality
Reduced	Hospitalizations	Hospitalizations	Hospitalizations	Hospitalizations

HFNEF heart failure with normal ejection fraction, *LVEF* left ventricular ejection fraction

HF trials in HFNEF Patients

Overview The first large study that assessed the clinical outcomes in HFNEF patients was the CHARM-Preserved trial [11], aimed at evaluating the effect of candesartan in patients with LVEF >40%. The median duration of follow-up was 37.7 months. There was no overall difference in the primary outcome of all-cause death between the candesartan and the placebo group. The number of HF hospitalizations was however significantly lower. The latter effect was of similar magnitude to the one observed with enalapril in HFREF patients in the Studies of Left Ventricular Dysfunction (SOLVD) study [20]. However, more patients in the candesartan group developed hypotension, hyperkalemia, or renal insufficiency. The HFNEF patients treated with candesartan also showed a decreased incidence of diabetes mellitus. Blockade of the renin-angiotensin system with an ARB could therefore be beneficial for HFNEF patients.

The PEP-CHF study [10] was a randomized double-blind trial comparing placebo with perindopril. The study included patients ≥70 years of age and 55% were women. Median follow-up was 26.6 months and all patients had a LVEF >45%. The trial showed no decrease in mortality with the prolonged use of perindopril. Patients who had a previous myocardial infarction or with elevated systolic blood pressure however appeared to benefit from perindopril. Nevertheless, the effects of perindopril on long-term morbidity and mortality in HFNEF remain dubious as the trial had inadequate power for its primary endpoint.

The I-PRESERVE trial [9••] recruited elderly patients, predominantly female (60%), with an average age of 72 years and an LVEF >60%. The patients also frequently had a history of hypertension (88%) and electrocardiographic evidence of LV hypertrophy. The prevalence of previous myocardial infarction was low. The I-PRESERVE trial assigned HFNEF patients to irbesartan or placebo and demonstrated no decrease in mortality or hospitalizations for cardiovascular causes.

DIG-PEF [12] was a randomized, double-blind, placebo-controlled trial that evaluated the effects of digoxin on all-cause mortality and on hospitalizations in patients with LVEF >45% and with normal sinus rhythm. Average follow-up was 37 months. The trial revealed that 23.4% of HFNEF patients died during follow-up because of cardiovascular causes (70%) and non-cardiovascular causes (30%). The study suggested that digoxin reduced hospitalization over the first 24 months of treatment but that it had no effect on mortality.

Characteristics of patients recruited in I-PRESERVE and PEP-CHF were similar. Characteristics of patients recruited in DIG-PEF and CHARM-Preserved were however different, especially in terms of HF etiology, age and gender. In addition, patients from DIG-PEF and CHARM-Preserved had a lower LVEF compared to patients from I-PRESERVE and PEP-CHF. Furthermore, in all these studies diastolic LV dysfunction was poorly characterized and this could have led to inclusion of numerous patients whose exercise intolerance was unrelated to HF but caused by deconditioning because of co-morbidities such as arthrosis deformans, chronic obstructive pulmonary disease, and obesity.

Finally, the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure (SENIORS) trial should be mentioned as it is the first large HF outcome trial restricted to a population over 70 years of age and as it specifically looked at a subgroup of patients with a LVEF >35% [21]. The SENIORS trial showed that treatment with the β-blocker nebivolol decreased cardiovascular morbidity and that this effect did not differ between patients with a LVEF <35% and a LVEF >35%. Favorable effects of nebivolol treatment on LV remodeling such as a decrease in LV end-systolic volume and an increase in LVEF were however limited to patients presenting with a LVEF >35%. Beneficial effects of β-blocker treatment in older HF patients are in line with previous trials on the use of β-blockers in HF such as the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (patients ≥ 65 years) [22], the Cardiac Insufficiency Bisoprolol Study (CIBIS II) trial (patients ≥71 years) [23], and the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) trial (patients >69 years) [24], which all showed a reduction in all-cause mortality or cardiovascular hospitalization in elderly patients [21, 25].

Unequal Outcome of Trials in HFNEF and HFREF

There are LV structural and functional similarities and differences between HFNEF and HFREF patients. The similarities include an increased LV mass and an increased LV end-diastolic pressure [5, 26]. The differences between the two phenotypes involve both LV geometry and LV function and could account for the unequal outcome of trials in HFNEF and HFREF de-

spite use of similar pharmacologic agents. HFREF is characterized by LV dilatation, eccentric LV remodeling, and abnormal systolic and diastolic function, whereas HFNEF is characterized by a normal LVEF and concentric LV remodeling with increased LV wall thickness and decreased LV volume/mass ratio [27, 28]. These structural and functional differences were also evident at the ultrastructural level. LV myocardium of HFNEF patients has larger cardiomyocytes, less interstitial fibrosis, and preserved myofilamentary density. When cardiomyocytes were isolated from LV biopsies, cardiomyocyte resting tension ($F_{passive}$) was also higher in HFNEF compared to HFREF [27, 29]. Because of these anatomic and histologic differences between LV myocardium in HFNEF and HFREF, LV remodeling also follows a distinct course in both phenotypes. In HFREF, LV remodeling mainly evolves to progressive LV dilatation and further reduction of LV systolic function. In HFNEF, this evolution is absent as disease progression is characterized by further development of concentric LV hypertrophy and exacerbation of abnormal diastolic function. Unequal outcome of trials using similar pharmacologic compounds is therefore again no surprise as the ultimate goal of treatment in terms of preventing unfavorable myocardial remodeling is vastly different in both conditions.

This concept was nicely illustrated by a study that looked at the myocardial effects of β-blocker treatment in HFNEF and HFREF patients. This study investigated the effects of β-blocker therapy on myofilamentary function of cardiomyocytes isolated from endomyocardial biopsies of HFNEF or HFREF patients. The study observed a significantly higher $F_{passive}$ in HFNEF patients treated with β-blockers compared to HFNEF patients without β-blockers and failed to report a similar finding in HFREF patients. Even after in vitro administration of protein kinase A (PKA), $F_{passive}$ remained significantly higher in HFNEF patients treated with β-blockers compared to HFNEF patients without β-blockers, indicating that β-blocker therapy had distinct effects on myofilamentary function in HFNEF and HFREF patients [29].

Treatment

Diet and Lifestyle

- According to the ESC guidelines, lifestyle modifications [6••, Class III] are recommended to reduce the risk of all forms of cardiovascular disease. These lifestyle modifications include the following:
- Weight loss: exercise helps to achieve and maintain a healthy weight and control diabetes, elevated cholesterol, and high blood pressure [30].
- Optimal blood pressure control.
- Diet and nutrition: eating a low-fat, low-sodium diet. Randomized clinical trials with low-salt and fluid-restricted diet showed that following a 6-month period of an individually prescribed salt- and fluid restricted-diet, patients with mild to moderate HF showed clinical improvements with an absence of edema and fatigue, leading to an improvement in New York Heart Association (NYHA) class and quality of life [30].
- Smoking cessation: smoking is a major risk factor for HF. No prospective studies have assessed the effects of smoking cessation in patients with HF. Observational data support the association between continued smoking and increased HF mortality and rates of hospitalizations as compared to non-smokers, recent ex-smokers, and longer ex-smokers [31, 32].
- Alcohol may have a negative inotropic effect, and may be associated with an increase in blood pressure [31]. Alcohol intake should be limited to 10 to 20 g/d (1–2 glasses of wine/day).

- Identification and treatment of other associated co-morbidities that directly or indirectly worsen the diastolic function, such as high blood pressure, diabetes, and hypercholesterolemia, are important in reducing the risk of subsequent HFNEF [7, 30 Class III].

Pharmacologic Treatment

- To date, no pharmacologic therapy was demonstrated to reduce mortality and morbidity in HFNEF patients. In many large, randomized, controlled clinical trials, researchers have assessed the beneficial effects of ACE inhibitors, β-blockers, and ARBs in HFREF patients, but these effects have not been established in HFNEF patients. Treatment recommendations are derived mainly from the large evidence-based trials that existed for management of HFREF [8, Class I] or are based largely on the results of small, non-randomized studies, clinical experience, and pathophysiologic reasoning [33, Class III]. Recently, two large-scale HFNEF trials have reported their disappointing results: in the CHARM-Preserved trial, the ARB candesartan produced a modest reduction in hospitalizations for HF but had no effect on mortality [11]; in PEP-CHF, the ACE-inhibitor perindopril had similar effects [10].
- Aldosterone antagonists reduce myocardial fibrosis [34]. In addition, aldosterone antagonists lower blood pressure and directly affect myocardial relaxation, which is also useful in the treatment of diastolic LV dysfunction in HFNEF patients.
- The reduction in heart rate and prevention of tachycardia with β-blocker treatment has several benefits on diastolic function, including a prolongation of diastole and the LV filling time and an improvement of ischemia. In addition, β-blockers have demonstrated benefits in reducing blood pressure and myocardial ischemia, promoting regression of LV hypertrophy, and antagonizing the excessive adrenergic stimulation during HF. β-blockers have been associated with decreased HF symptoms in HFNEF patients [35, Class II].
- Calcium channel blockers have been shown to accelerate ventricular relaxation in patients with hypertrophic cardiomyopathy and have been reported to directly improve diastolic LV function by decreasing cardiomyocyte cytoplasmic calcium concentration [36].
- Restriction of sodium intake and the administration of diuretics may be beneficial through reduction of LV ventricular filling pressures. They are also useful in treating hypertension, which is a common trigger for worsening HFNEF. In the Hong Kong Diastolic Heart Failure, diuretics alone appeared to be effective in reducing symptoms and improving quality of life in HFNEF patients [37]. The goals for pharmacologic treatment of HFNEF are summarized in Table 2.

Table 2. Goals for pharmacologic treatment of HFNEF

Drug class	Goal of treatment
ACE inhibitor	Hypertension
	LV blood pressure
	LV hypertrophy
	LV relaxation
	Myocardial fibrosis
	Myocardial ischemia
ARB	Hypertension
	LV hypertrophy
	LV filling pressures
	Myocardial fibrosis
CCB	Heart rate
	Hypertension
	LV hypertrophy
	Exercise capacity
	Myocardial ischemia
β-Blocker	Heart rate
	Hypertension
	LV hypertrophy
	Myocardial ischemia
	Tachycardia
Diuretic	Hypertension
	Myocardial ischemia
	LV filling pressure
	LV diastolic volume
Aldosterone antagonist	Myocardial fibrosis
	LV hypertrophy
Digoxin	Decrease heart rate in atrial fibrillation patients

ACE angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *HFNEF* heart failure with normal ejection fraction, *LV* left ventricular

Interventional Procedures

Percutaneous Coronary Intervention and Coronary Bypass Surgery

- When the cause of HFNEF is ischemic, standard pharmacologic treatment would be the use of nitrates, calcium channel blockers, and β-blockers. However, both a percutaneous coronary interventional technique and coronary artery bypass surgery should be considered in selected HF patients with coronary artery disease [38]. Their use will result in better outcome at lower cost (quality of life improvement) [39].

Valvular Replacement

- If the cause of HFNEF is valvular heart disease (usually aortic stenosis), aortic valve replacement is mandatory. Surgical replacement or repair of valves relieves symptoms and improves quality of life in HFNEF [40]. Relief may be gradual, in parallel with remodeling of

the heart and regression of LVH following the correction of the abnormal loading conditions imposed by the LV pressure overload.

Emerging Pharmacological Therapies

In the ongoing trials Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) and Aldosterone in Diastolic HF (ALDO-DHF), the role of spironolactone versus placebo is being studied to elucidate if an anti-fibrotic intervention strategy is adequate to improve the outcome in HFNEF. In the Japanese diastolic HF trial (J-DHF), the efficacy of β-blockers is being studied, and in the Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure (RELAX) trial, sildenafil (phosphodiesterase-5 inhibition) is being studied to improve clinical status and exercise capacity in HFNEF. In addition, smaller studies are investigating the effects of statins, ivabradine and cardiac resynchronization therapy (or biventricular pacing), which may also be beneficial for HFNEF patients.

Disclosure

Nazha Hamdani reports no potential conflict of interest relevant to this article. Walter J. Paulus reports no potential conflict of interest relevant to this article.

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