Advances in the treatment of heart failure with preserved systolic function

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Abstract

Heart failure with preserved ejection fraction (HFpEF) comprises 40% of the heart failure (HF) population. The morbidity and mortality of HFpEF is similar to HF with reduced ejection fraction (HFrEF), but unlike this latter population, the prognosis of HFpEF has not changed over the past 30 years. Therapies that are the mainstay of treatment in HFrEF have not been found to be effective in HFpEF, while others have not been fully studied. At present, there are no effective therapies available for the HFpEF population. This paper reviews the current knowledge of HFpEF treatment, as well as the novel therapies that may be coming in the future.

Keywords: Diastolic; drug therapy; heart failure; randomized controlled trials as topic

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Main Clinical Article

Introduction

Heart failure (HF) is a common cause of morbidity and mortality with a prevalence of 6–10% in those over 65 years of age [1]. It is a leading cause of acute care hospitalizations and more Medicare dollars are spent for this diagnosis than any other [1]. It is well recognized that approximately half of all HF patients have a preserved left ventricular ejection fraction (LVEF). Despite a normal LVEF, they have similar hospital readmission and mortality rates as patients with a reduced LVEF [2]. Over the past three decades, medical advances have improved patient outcomes in those with HF with reduced left ventricular ejection fraction (HFrEF). The same cannot be said for patients with HF with preserved left ventricular ejection fraction (HFpEF) as the prognosis of this population has remained unchanged despite the use of the same advances [2]. Few randomized control trials (RCT) have been performed in HFpEF and most with disappointing results. Past therapies and novel agents are reviewed below.

A definition of heart failure with preserved ejection fraction

HFpEF is defined by the presence of symptoms and/or signs of HF and a preserved LVEF greater than 40–50%, usually measured by echocardiography. There is no agreement on the exact LVEF that corresponds to a preserved LVEF, which varies between guidelines [1, 3–5]. In addition, one guideline recommends demonstration of an increased filling pressure, measured invasively in the coronary catheterization laboratory, by echocardiography using tissue Doppler techniques or by finding elevated brain natriuretic peptide levels on laboratory testing [5].

Regardless of the definition used, HFpEF is of growing interest, an important public health issue and a target for therapy.

Treatment of comorbidities

Hypertension

Hypertension is the most common medical comorbidity in HFpEF and is seen in up to 60% of patients [2]. Hypertension-related left ventricular hypertrophy (LVH) plays an important role in the development of HF potentially due to changes in diastolic filling parameters [6]. Regression of LVH may result in improvements in diastolic function, as demonstrated in a recent meta-analysis evaluating the differential effects of antihypertensive therapies on LVH [7]. This found that angiotensin II receptor blockers (ARB), angiotensin converting enzyme (ACE) inhibitors, calcium-channel blockers and diuretics are significantly better than β-blockers at improving LVH. Consistently, RCT of antihypertensive agents reduce the clinical endpoint of HF of which an uncertain percentage of this is related to systolic or diastolic dysfunction [8]. HF guidelines recommend control of systolic and diastolic hypertension in HFpEF and these patients should have their blood pressure managed to targets established by hypertension guidelines [1, 3–5].

Atrial fibrillation

Atrial fibrillation is the most common arrhythmia in HF and has a prevalence of 40% in HFpEF patients [2]. Selby et al [9] illustrated that tachycardia associated with atrial fibrillation can induce diastolic dysfunction associated with increased left ventricular mass, left atrial volumes, and resting tone in patients with normal LVEF. Atrial fibrillation also has prognostic value in HFpEF and was an independent predictor of HF death or hospitalization in HFpEF patients, but not in HFrEF patients [10]. While there is currently no evidence that strict rate control of atrial fibrillation is beneficial in HFpEF, it is strongly recommended by HF guidelines [1, 3–5].

Coronary artery disease

Although coronary artery disease is not as prevalent in HFpEF patients as in those with reduced LVEF, it is present in up to 50% of patients [2]. This high prevalence is probably due to the fact that HFpEF patients often have multiple risk factors for coronary artery disease such as hypertension, diabetes and older age [2]. Furthermore, myocardial ischemia can impair ventricular relaxation inducing diastolic dysfunction. Guidelines recommend consideration of coronary revascularization in HFpEF patients with symptomatic coronary disease or in those with demonstrable myocardial ischemia that is judged to be having an adverse effect on cardiac function [1, 3–5].

Medical therapy

ACE inhibitors and ARB

ACE inhibitor therapy is firmly entrenched in the treatment of HFrEF, but the same cannot be said for HFpEF. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study, 850 patients aged 70 years or older with evidence of diastolic dysfunction and a LVEF greater than 40% were randomly assigned to either perindopril or placebo [11]. Overall, no conclusion can be drawn with respect to the primary outcome (all-cause mortality and HF hospitalization) as the study was underpowered and had a high treatment withdrawal rate after 1 year. However, a secondary analysis highlights improvements in 6-minute walk time and symptoms as well as a significant reduction in cardiovascular death and HF-related hospitalization at 1 year [11].

Two major RCT have been performed looking at the use of ARB in HFpEF. In the Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (CHARM-P) trial, 3023 patients with New York Heart Association class II–IV symptoms and LVEF greater than 40% were assigned to receive either candesartan or placebo [12]. At a median follow up of 37 months, there was no difference in the primary outcome of cardiovascular death or HF admission, but there was an 18% reduction in the secondary endpoint of HF hospitalizations. The more recently published Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (I-PRESERVE) trial randomly assigned 4128 patients who were at least 60 years or older with New York Heart Association class II–IV HF and a LVEF of 45% or greater to irbesartan or placebo [13]. At a mean follow-up of 50 months, there was no difference in the primary outcome of death from any cause or hospitalization for cardiovascular causes, or any of the other secondary endpoints [13].

There continues to be no strong RCT data supporting the use of ACE inhibitors/ARB in HFpEF. In the

absence of other indications, guidelines weakly support ACE inhibitor therapy in HFpEF for the reduction of symptoms, and no other large RCT are planned at this time to address this indication better. Similarly, ARB may be considered in HFpEF to reduce hospitalization [4] or symptoms [1, 3], but should not be used in conjunction with ACE inhibitors.

β-Blockers

Much like ACE inhibitors and ARB, β-blockers are important in the treatment of HFrEF, but their use in HFpEF is not established. Small observational studies have shown a morbidity, symptom and mortality benefit with β-blockers in HFpEF [14, 15]. Conversely, larger registry data from OPTIMIZE-HF (4153 patients) with HFpEF showed that discharge use of β-blockers had no association with 1-year mortality or hospitalization rate [16]. In the 752 HF patients with a LVEF greater than 35% in the SENIORS trial (comparing nebivolol versus placebo), there was no statistical difference in the primary outcome of all-cause mortality or cardiovascular admission [17]. At present, there is limited RCT evidence supporting β-blockers for use in HFpEF, and assuming there is not another indication for their use, guidelines give them a weak recommendation.

Diuretics

There are no clinical trial data prospectively evaluating the overall impact of thiazide or loop diuretics on mortality in HF probably because few symptomatic patients can be managed without them. Current guidelines strongly recommend diuretic therapy to control pulmonary congestion and peripheral edema in HFpEF, with caution advised against excessive diuresis as it can lead to volume depletion with subsequent decreased cardiac output and worsening of renal function [1, 3–5].

Aldosterone blockade

Aldosterone is known to promote hypertension, ventricular hypertrophy and progressive myocardial fibrosis – all of which are implicated in the pathogenesis of HFpEF and therefore aldosterone synthesis or receptor blockade may be useful in the treatment of HFpEF. In a small RCT of patients with HFpEF, 6 months of treatment with the aldosterone receptor blocker eplerenone appeared to improve echocardiographic measures of diastolic function, but not 6-minute walk time [18]. HF guidelines do not refer to the use of aldosterone blockers in the treatment of HFpEF, but this may change as there are currently two large randomized outcome studies being carried out to explore the use of spironolactone in HFpEF. The Aldosterone Receptor Blockade in Diastolic Heart Failure–ISRCTN94726526 (ALDO-DHF) trial has been completed, but results have yet to be released while the larger Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function–NCT00094302 (TOPCAT) study is expected to have results available in 2013. Their results are highly anticipated and will shed light on the clinical application of aldosterone blockers in HFpEF.

Other agents

Several other agents commonly used in HFrEF have undergone limited study in HFpEF. The DIG trial had similar results in the 988 patients with LVEF greater than 45% as it did for those with an LVEF of 45% or less, with no difference in all-cause or HF-related mortality [19]. Current guidelines either do not or only weakly recommend the use of digoxin in HFpEF, but it can be a useful adjunct for patients with atrial fibrillation.

Calcium channel blockers may improve passive ventricular filling by reducing left ventricular end-diastolic pressure. In a small RCT, verapamil improved exercise capacity and ventricular filling in HF patients with a LVEF greater than 45% [20]; however, this has yet to be corroborated and therefore some guidelines weakly recommend calcium channel blockers for the reduction of symptoms for HFpEF [1, 4] while others recommend it only if there is another indication [3].

Observational data have shown a mortality benefit for the use of statins in HFpEF and HFrEF, but no benefits were found in the GISSI-HF RCT, which included patients with HFpEF [21]. Statins are currently not recommended in HFpEF unless there is another indication.

Exercise therapy

Exercise intolerance is a primary symptom of chronic HF, a predictor of HF mortality and a key therapeutic target [22]. Studies of exercise therapy in HFrEF have shown improvements in exercise performance, and this has recently also been shown in HFpEF. In a single blind study, Kitzman et al [22] randomly assign 53 HFpEF patients to 3 days a week of medically supervised exercise therapy for 16 weeks. Measures of exercise tolerance including peak exercise oxygen uptake and 6-minute walk time increased significantly

in the therapy group compared to the control group. Another small RCT showed similar improvements in peak oxygen uptake with 3 months of exercise therapy, and also demonstrated improvements in measures of left ventricular diastolic function and left atrial size [23]. Exercise therapy that is initially supervised is recommended for all HF patients, and it may exert beneficial effects on myocardial and skeletal muscle function that are yet to be fully understood.

Novel agents

A rational approach to the treatment of HFpEF is to target regression of LVH. Animal and human studies have revealed that inhibition of phosphodiesterase-5 leads to cardiac antihypertrophic and antifibrotic effects resulting in improved cardiomyocte relaxation and increased left ventricular distensibility [24]. In a RCT, Guazzi et al [24] assigned 44 patients with HFpEF and pulmonary hypertension (pulmonary artery systolic pressure >40 mmHg) to placebo or sildenafil. At 6 months and 1 year, the sildenafil group had improvements in mean pulmonary artery pressure and right ventricular function, and a reduction in wedge pressure and isovolumetric relaxation time. There was, however, no difference in quality of life measures or symptoms between the two groups. The ongoing Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People with Diastolic Heart Failure–NCT00763867 (RELAX) trial, expected to be complete in January 2013, will offer further enlightenment on the clinical use of phosphodiesterase-5 inhibitors in HFpEF.

Diastolic filling and myocardial relaxation is impaired in HFpEF and therefore heart rate slowing may improve diastolic parameters in these patients. While β-blockers and calcium channel blockers do not appear particularly useful in this population, use of the “funny” current (I_f)-channel blocking agent ivabradine may be of benefit [25]. Because there are no I_f channels in the myocardium, it selectively reduces heart rate without a negative effect on myocardial contractility or cardiac output. Trials investigating the use of this agent are ongoing in patients with HFpEF both on (NCT01373619) and off (NCT00757055) dialysis.

The increased left ventricular stiffness often seen in elderly people with HFpEF is partly due to non-enzymatic crosslinks that develop between advanced glycation end products on collagen and elastin [26]. Alagebrium chloride (ALT-711) is a novel compound that breaks these crosslinks and was associated with reduced left ventricular mass and improved diastolic filling in an open label trial of elderly HFpEF patients [27]. This compound has not been shown to be of benefit in a RCT enrolling HFrEF patients [26], but has yet to be adequately tested in patients with HFpEF.

See table « Prior, current and future trials in heart failure with preserved ejection fraction » in online-only data supplement [28-40]

Conclusion

Significant advances in understanding HFpEF have occurred in the past decade, and it is likely that there will be a treatment that reduces morbidity and mortality for these patients by the end of this decade. The heterogeneity of causal diseases, complexity of cardiac and skeletal muscle derangements, chronic metabolic and fibrosis changes and vascular dysfunction that occurs in HFpEF make this a very complex puzzle to solve. Which cellular pathway or combination of therapies will correct the underlying pathophysiology remains to be seen. •

References

1. Hunt SA, Abraham WT, Chin MH, et al (2009) Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation J Am Coll Cardiol 53:e1–e90
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction N Engl J Med 355:251–259
3. Lindenfeld J, Albert NM, Boehmer JP, et al; Heart Failure Society of America (2010) Comprehensive heart failure practice guideline J Cardiac Fail 16: e1–194
4. Arnold JM, Liu P, Demers C, et al (2006) Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management Can J Cardiol 22: 23–45
5. McMurray JJ, Adamopoulos S, Anker SD, et al (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC Eur Heart J 33:1787–1847
6. Wachtell K, Bella JN, Rokkedal J, et al (2002) Change in diastolic left ventricular filling after one year of antihypertensive treatment: the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study Circulation 105:1071–107
7. Fagard RH, Celis H, Thijs L, Wouters S (2009) Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies Hypertension 54:1084–1091

8. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M (2011) Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk Arch Intern Med 171:384–394
9. Selby DE, Palmer BM, LeWinter MM, Meyer M (2011) Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction J Am Coll Cardiol 58:147–154
10. Linssen GCM, Rienstra M, Jaarsma T, et al (2011) Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction Eur J Heart Fail 13:1111–1120
11. Cleland JGF (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study Eur Heart J 27:2338–2345
12. Yusuf S, Pfeffer MA, Swedberg K, et al (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial Lancet 362:777–781
13. Massie BM, Carson PE, McMurray JJ, et al (2008) Irbesartan in patients with heart failure and preserved ejection fraction N Engl J Med 359:2456–2467
14. Dobre D, Van Veldhuisen DJ, DeJongste MJL, et al (2007) Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival Eur J Heart Fail 9:280–286
15. Massie BM, Nelson JJ, Lukas MA, et al (2007) Comparison of outcomes and usefulness of carvedilol across a spectrum of left ventricular ejection fractions in patients with heart failure in clinical practice Am J Cardiol 99:1263–1268
16. Hernandez AF, Hammill BG, O'Connor CM, et al (2009) Clinical effectiveness of beta-blockers in heart failure J Am Coll Cardiol Am Coll Cardiol Found 53:184–192
17. Van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al (2009) Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) J Am Coll Cardiol 53:2150–2158
18. Deswal A, Richardson P, Bozkurt B, Mann DL. (2011) Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF) J Cardiac Fail 17:634–642
19. Ahmed A, Rich MW, Fleg JL, et al (2006) Effects of digoxin on morbidity and mortality in diastolic heart failure: the Ancillary Digitalis Investigation Group Trial Circulation 114:397–403
20. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R (1990) Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance Am J Cardiol 66:981–986
21. Tavazzi L, Maggioni AP, Marchioli R, et al; Gissi-HF Investigators (2008) Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial Lancet 372:1231–1239
22. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC (2010) Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial Circ Heart Fail 3:659–667
23. Edelmann F, Gelbrich G, Düngen H-D, et al (2011) Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study J Am Coll Cardiol 58:1780–1791
24. Guazzi M, Vicenzi M, Arena R, Guazzi MD (2011) Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study Circulation 124:164–174
25. Reil J-C, Reil G-H, Böhm M (2009) Heart rate reduction by I(f)-channel inhibition and its potential role in heart failure with reduced and preserved ejection fraction Trends Cardiovasc Med 19:152–157
26. Hartog JWL, Willemsen S, Van Veldhuisen DJ, et al (2012) Effects of alagebrium, an advanced glycation endproduct breaker, on exercise tolerance and cardiac function in patients with chronic heart failure Eur J Heart Fail 13:899–908
27. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC (2005) The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure J Cardiac Fail 11:191–195
28. Aronow WS, Kronzon I (1993) Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction Am J Cardiol 71:602–604
29. Zi M, Carmichael N, Lye M (2003) The effect of quinapril on functional status of elderly patients with diastolic heart failure.Cardiovasc Drugs Ther 17:133–139
30. Solomon SD, Janardhanan R, Verma A, et al (2007) Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial Lancet 369:2079–2087
31. Mottram PM (2004) Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure Circulation 110:558–565
32. Roongsritong C, Sutthiwan P, Bradley J, Simoni J, Power S, Meyerrose GE (2005) Spironolactone improves diastolic function in the elderly Clin Cardiol 28:484–487
33. Bergström A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U (2004) Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC) Eur J Heart Fail 6:453–461
34. Takeda Y, Fukutomi T, Suzuki S, et al (2004) Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction Am J Cardiol 94:448–453
35. Conraads VM, Metra M, Kamp O, et al (2012) Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study Eur J Heart Fail 14:219–225
36. Aronow WS, Ahn C, Kronzon I (1997) Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors Am J Cardiol 80:207–209
37. Hung MJ, Cherng WJ, Kuo LT, Wang CH (2002) Effect of verapamil in elderly patients with left ventricular diastolic dysfunction as a cause of congestive heart failure Int J Clin Pract 56:57–62
38. Maier L, Wachter R, Edelmann F, et al (2012) Ranolazine for the treatment of diastolic heart failure in patients with preserved ejection fraction: results from the RALI-DHF study J Am Coll Cardiol 59:E865
39. Little WC, Zile MR, Klein A, Appleton CP, Kitzman DW, Wesley-Farrington DJ (2006) Effect of losartan and hydrochlorothiazide on exercise tolerance in exertional hypertension and left ventricular diastolic dysfunction Am J Cardiol 98:383–385
40. Yip GWK, Wang M, Wang T, et al (2008) The Hong Kong Diastolic Heart Failure Study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction Heart 94:573–580