Published in final edited form as:
Curr Cardiovasc Risk Rep. 2013 December ; 7(6): 495–502. doi:10.1007/s12170-013-0350-9.

Update on heart failure with preserved ejection fraction

Scott L. Hummel, M.D., M.S.[a,b] and **Dalane W. Kitzman, M.D.**[c]

[a]Department of Internal Medicine, Section of Cardiovascular Medicine, University of Michigan School of Medicine

[b]Ann Arbor Veterans Affairs Health System, Ann Arbor, MI

[c]Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine

Abstract

Heart failure with preserved ejection fraction (HFPEF) is the most common form of heart failure (HF) in older adults, and is increasing in prevalence as the population ages. Morbidity and long-term mortality in HFPEF are substantial and can be similar to HF with reduced ejection fraction (HFREF), yet HFPEF therapy remains empirical and treatment guidelines are based primarily on expert consensus. Neurohormonal blockade has revolutionized the management of HFREF, but trials in HFPEF based on this strategy have been disappointing to date. However, many recent studies have increased knowledge about HFPEF. The concept of HFPEF has evolved from a 'cardio-centric' model to a syndrome that may involve multiple cardiovascular and non-cardiovascular mechanisms. Emerging data highlight the importance of non-pharmacological management strategies and assessment of non-cardiovascular comorbidities. Animal models, epidemiological cohorts, and small human studies suggest that oxidative stress and inflammation contribute to HFPEF, potentially leading to development of new therapeutic targets.

Keywords

diastolic heart failure; treatment; mechanisms; hypertension

Introduction: prevalence, outcomes, and definition of HFPEF

Current estimates suggest that over five million Americans have heart failure (HF); of these, approximately 50% have heart failure with preserved ejection fraction (HFPEF). [1] HFPEF is the predominant form of HF in older adults, and accordingly is increasing in prevalence as the overall population ages. [2] Long-term mortality in HFPEF is similar to heart failure with reduced ejection fraction (HFREF), with less than 50% five-year survival in community HFPEF cohorts. [2, 3] Outcomes following hospitalization for decompensated

Corresponding author: Dalane W. Kitzman, M.D., Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC. 27157-1045, dkitzman@wakehealth.edu.

Compliance with Ethics Guidelines

Conflict of Interest

Scott L. Hummel and Dalane W. Kitzman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

HFPEF are quite poor, with over 1/3 of patients dead or rehospitalized within 60–90 days of discharge. [4]

The diagnosis of HFPEF remains challenging due to the advanced age and frequent multiple concomitant illnesses. In fact, multiple comorbidities are the rule in HFPEF rather than the exception, [5] and significantly influence cardiovascular structure and function as well as long-term prognosis. [6] Many of these conditions (e.g. advanced age, obesity, atrial fibrillation, anemia) [7, 8] can mimic HF signs and symptoms, and some have questioned the concept of HFPEF as a distinct disorder. [9] Non-cardiovascular hospital readmissions and mortality are more frequent in HFPEF than in HFREF, [11] and while cardiovascular mortality in HFPEF is also lower than in HFREF, it is still substantial, accounting for 50% or more of all deaths. [10,12]

The European Society of Cardiology, the Heart Failure Society of America, and the American Heart Association/American College of Cardiology guidelines agree that HFPEF patients should have symptoms and/or signs of HF and a left ventricular ejection fraction of ≥ 50%, with exclusion of other primary causes of the symptom pattern. Previous diagnostic algorithms mandated the presence of left ventricular diastolic dysfunction, which remains an important and validating criterion. However, recognizing that many other mechanisms may also contribute, current guidelines support the diagnosis of HFPEF if the clinical picture is consistent and diastolic dysfunction is indeterminate, but other evidence of HFPEF-associated adverse cardiovascular remodeling (e.g. left ventricular hypertrophy, left atrial enlargement, atrial fibrillation) is present. [13–15] Diagnostic criteria for HFPEF will likely continue to evolve along with our understanding of the disorder.

Mechanisms of HFPEF

Hemodynamic/cardiovascular mechanisms

The classic paradigm for HFPEF implicates impaired diastolic ventricular filling due to delayed active relaxation, intrinsic ventricular stiffness, or a combination of these factors. [16, 17] Worsening left ventricular diastolic dysfunction is an important risk factor for developing HFPEF, [18] and strongly predicts mortality in unselected community cohorts and in patients with prevalent HFPEF. [19, 20] In comparison to age- and gender-matched controls, HFPEF patients had increased baseline ventricular stiffness, lower stroke volume during rapid atrial pacing, and exaggerated rise in end-diastolic pressures during handgrip exercise. [21] Borlaug et al. recently studied diastolic function in HFPEF patients undergoing cycle ergometry and confirmed an upward and leftward shift of the end-diastolic pressure-volume relationship, attributing increased filling pressures to intrinsic ventricular stiffness and reduced diastolic filling time at higher heart rates. [22]

HFPEF patients display combined ventricular and arterial stiffness, which increases in stress-induced blood pressure, cardiac metabolic demand, and the energy cost for cardiac output. [23] Aortic distensibility [24] and carotid artery distensibility [25] are severely reduced in elderly HFPEF patients. While resting values of arterial and end-systolic ventricular elastance are similar to age-matched hypertensive controls, [18] chamber-level and myocardial contractility in HFPEF are decreased. [26, 27] Moderate-intensity cycle

ergometry exercise in HFPEF patients shows a disproportionate impact of proximal arterial stiffness on ventricular afterload. [28] Part of the mechanism of exercise intolerance, particularly in hypertensive HFPEF, may be an inability to augment contractile function to match arterial load. [23, 29, 28, 25]

Peripheral vasodilation may also be abnormal in HFPEF, particularly during exercise. [29] However, in HFPEF compared to age-matched controls, flow-mediated arterial dilation, measured in the femoral artery by phase-contrast MRI [30] and in the brachial artery by high-resolution ultrasound, [31] was found to be preserved.

A subset of HFPEF patients have normal ventricular stiffness and increased ventricular capacitance, particularly in the setting of comorbidities that are associated with increased plasma volume such as obesity, anemia, and renal insufficiency. [32, 33] Patients with ‘pre-clinical’ HFPEF have impaired natriuretic function, [34] and even seemingly well-compensated HFPEF patients often have demonstrably elevated plasma volume. [33] Some view volume overload and congestion as key contributors to HF development and progression. [35] Chronotropic incompetence is frequently present in HFPEF and contributes significantly to exercise intolerance, the primary manifestation of HFPEF. [36, 29] Consequently, chronotropic incompetence, which can easily be measured, [37] should be considered before agents that slow the heart rate are used. Echocardiographic strain studies indicate that left atrial stiffness and contractile dysfunction, particularly evident during preload changes induced by leg lifts, can help identify HFPEF. [38, 39]

Noncardiovascular mechanisms of HFPEF

The Cardiovascular Health Study cohort showed that frailty, as evidenced by slow gait speed and muscular weakness, strongly predicts hospital admission in older adults newly diagnosed with HF. [40] Rather than being simply a result of deconditioning, recent data suggest that frailty and muscular abnormalities may directly contribute to the HFPEF syndrome, a finding similar to HFREF, where skeletal muscle abnormalities can be independent of physical activity and deconditioning. [41, 42] Exercise training improves physical functioning and peak oxygen consumption in HFPEF patients, [43, 44] but has largely neutral effects on cardiac filling pressures, ventricular diastolic function, conduit artery endothelial function, and large-arterial stiffness. [45, 44, 46] Improvements in peak oxygen consumption following training in HFPEF patients relate more strongly to increased peak arterial-venous oxygen difference rather than increased cardiac output. [47] Analysis of lean body mass with dual-energy X-ray absorptiometry shows that sarcopenia (degenerative skeletal muscle loss) is common in HFPEF patients. Moreover, the increase in peak oxygen consumption per unit of lean body mass in HFPEF is markedly reduced compared with sedentary age-matched controls. [48] Taken together, these data suggest that impaired oxygen utilization by skeletal muscle contributes to the severe exercise intolerance in HFPEF and may represent a potential novel therapeutic target.

Cellular/metabolic mechanisms of HFPEF

With the increasing prevalence of associated factors such as advanced age, hypertension, diabetes mellitus, obesity, and chronic kidney disease in the U.S. population, the incidence

of HFPEF is expected to rise in the years ahead. [2] The specific mechanisms that promote the development of HFPEF in patients with these risk factors have previously been unclear. However, hints come from two large and well-characterized U.S. cohorts of community-dwelling older adults, in which markers of systemic inflammation strongly predicted incident HF (in particular HFPEF) even following extensive adjustment for other known risk factors. [49, 50]

Several small-animal models of HFPEF have been studied, among them the Dahl S (salt-sensitive) rat, the obese spontaneously hypertensive rat, and the deoxycorticosterone/salt uninephrectomized mouse, [51–53] and the dog cellophane renal wrap model has been proposed as a large-animal example of HFPEF. [54] These and other similar experimental models share the common pathways of increased oxidative stress and perivascular inflammation. These factors are important driving mechanisms for HFPEF, as antioxidant supplementation and modulation of immune cell function in these or similar models greatly diminish vascular and cardiorenal damage and dysfunction. [55–57, 51, 58]

One recent human study examined inflammation in HFPEF using endomyocardial biopsies showed activated macrophages, staining TGF-β, increased vascular adhesion markers when compared with controls. Primary fibroblasts cultured from the HFPEF samples and stimulated with TGF-β transdifferentiated into myofibroblasts,. [59] In the Dahl S rat model of HFPEF, neutralizing antibodies to IL-16 greatly reduce cardiac macrophage infiltration and TGF-β production, myocardial fibrosis, and lung weight. An observational study linked serum levels of IL-16 to ventricular diastolic dysfunction and left atrial enlargement in HFPEF patients. [60] A cross-sectional study showed that older HFPEF patients have increased biomoarkers for inflammation. [61]

Elevated oxidative stress is present in endomyocardial biopsies from HFPEF patients showing increased DHE-positive nuclei [59] and nitrotyrosine content. [62] A new paradigm for HFPEF has recently been proposed, [63] focusing on comorbidity-induced oxidative stress as a central causative mechanism. In this construct, low nitric oxide bioavailability and reactive oxygen species lead to decreased cyclic GMP and protein kinase G activity. In strong support of this model, in comparison to patients with aortic stenosis or HFREF, patients with HFPEF have markedly reduced myocardial protein kinase G activity and cyclic GMP levels that are inversely proportional to myocardial nitrotyrosine residues. [62] The adverse effects of oxidative stress in HFPEF patients may not be confined to the heart and vasculature. Preliminary findings from ^{31}phosphate magnetic resonance spectroscopy suggest that HFPEF patients have impaired skeletal muscle oxidative metabolism independent of vascular function or oxygen delivery. [64]

Treatment of HFPEF

Neurohormonal antagonists

Several studies have investigated angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blocker (ARB) therapy, [65–67] a concept strongly grounded in data from animal models [68–71] as well as human hypertensives without heart failure. However,

a 12-month, randomized controlled trial of the ACEI enalapril in elderly patients with established HFPEF showed no improvement in exercise capacity or quality of life. [72]

Of the three large randomized trials of ACEI/ARB performed to date in HFPEF, only the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity – Preserved (CHARM-Preserved) study found nominal benefit for candesartan in reducing HF hospitalizations [HR 0.86 (95% CI 0.74–1.0), p=.051] over three years of follow-up, [65] and none showed benefit for their primary endpoints. Recently, Lund and colleagues explored community ACEI/ARB use in 16,216 HFPEF patients. They found a modest reduction in one-year mortality for ACEI/ARB therapy [propensity score–adjusted HR 0.90 (95% CI, 0.85–0.96), p<.001] with evidence for increased benefit at higher doses. However, mortality reduction was mainly observed in patients with LVEF 40–49%. [73]

The Phase II Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) study randomized 301 HFPEF patients to valsartan vs. LCZ696, a combination ARB/neprilysin inhibitor (intended to inhibit the breakdown of natriuretic peptides). Compared to valsartan alone, the LCZ696 group had significantly lower nt-pro BNP levels and at 36 weeks, decreased left atrial size and a trend towards improved functional class. [74]

The Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction (RAAM-PEF) trial randomized 44 HFPEF patients to six months of eplerenone vs. placebo, and showed reductions in circulating markers of collagen turnover and modest improvements in diastolic function. [75] The larger Aldosterone Receptor Blockade in Diastolic Heart Failure (Aldo-DHF) randomized HFPEF patients to spironolactone or placebo for 12 months. Spironolactone reduced left ventricular mass and the mitral E/e′ ratio, although these findings were partially attenuated by adjustment for blood pressure reduction. [76] Despite these favorable signals, neither study demonstrated improvement in its primary outcome of six-minute walk distance, and Aldo-DHF participants reported no improvement in quality of life. Moreover, in a propensity-matched analysis of hospitalized older HFPEF patients from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study, aldosterone antagonists had no effect on all-cause mortality or hospitalization. [77] The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist (TOPCAT) study has randomized HFPEF patients to spironolactone or placebo [78] TOPCAT is powered for the composite outcome of cardiovascular mortality, aborted cardiac arrest, and/or HF hospitalization, and should further define the role of aldosterone blockade in HFPEF.

Other pharmacological interventions

Pulmonary hypertension is common in HFPEF and predicts a poor prognosis. [79] Phosphodiesterase-5 inhibitors vasodilate the pulmonary vascular bed and improve functional capacity in pulmonary arterial hypertension. One study randomized 44 HFPEF patients with documented pulmonary hypertension to 12 months of sildenafil vs. placebo. Sildenafil markedly reduced pulmonary vascular resistance while significantly improving quality of life. [80] However, in a recent PhosphodiesteRasE-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) study, sildenafil

did not improve six-minute walk distance or quality of life, and was associated with modest worsening of renal function and increases in neurohormone levels. [81] In a seven-day study, 61 HFPEF patients were randomized to placebo or ivabradine, a selective sinus node I_f sodium channel inhibitor that reduces heart rate without affecting contractility or lusitropy. Patients in the ivabradine group increased peak oxygen consumption and reduced exercise E/e′ ratio, and in this short-term study ivabradine was well-tolerated. [82]

Anemia is highly prevalent in HFPEF and carries a poor prognosis; leading to the hypothesis that epoeitin-alfa would improve submaximal exercise capacity and ventricular remodeling. However, after 24 weeks of therapy there was no change in 6-minute walk distance or left ventricular end-diastolic volume. [83] The ongoing RAnoLazIne for the Treatment of Diastolic Heart Failure (RALI-DHF) study, based on pre-clinical models, randomized HFPEF patients with invasively confirmed diastolic dysfunction to intravenous followed by oral ranolazine vs. placebo. [84] In acutely decompensated HF patients, intravenous serelaxin was highly effective in relieving dyspnea and was associated with encouraging trends for end-organ function and 6-month mortality in both HFPEF and HFREF; however, rehospitalization rates were not affected. [85].

Nonpharamacological strategies

Given that symptoms in HFPEF are most prominent during physical activity, interest has recently focused on exercise training as a potential treatment modality. In a single-blind, single-center study, 53 HFPEF patients were randomized to moderate-intensity aerobic exercise training vs. intention control. The intervention group exercised in a medically supervised environment three times weekly for 16 weeks, and the intervention increased peak exercise oxygen uptake, 6-minute walk distance, and physical quality-of-life scores. [44] Similar results for these endpoints were seen in a multicenter study of 40 HFPEF patients randomized to a 32-session, 3-month exercise protocol including both aerobic and resistance exercise training. [43] To date, positive effects on exercise intolerance from exercise training has been reported in 5 studies involving over 200 HFPEF patients. [86] The effect of exercise training on survival in HFPEF is unknown, but will be examined in the Ejection-HF trial. [87]

Patients with HFPEF are often advised to limit dietary sodium intake, [13] and those who receive this recommendation at hospital discharge have a lower risk of hospital readmission. [7] In multiple ‘salt-sensitive’ experimental models of HFPEF, high sodium consumption exacerbates oxidative stress and adverse cardiovascular remodeling. [53, 52, 51]. The sodium-restricted Dietary Approaches to Stop Hypertension (DASH/SRD) reduces oxidative stress and in a cohort of postmenopausal women the incidence of HF was inversely proportional to DASH diet adherence. [88–89] In a recent proof-of-concept study, 13 hypertensive HFPEF patients consumed the sodium-restricted DASH diet for 21 days. Clinic and 24-hour ambulatory blood pressure were significantly reduced, and urinary F2-isoprostanes, a measure of systemic oxidative stress, declined by 31%. [90] In addition, relaxation- and stiffness based measures of diastolic function improved, arterial elastance decreased, and the ventricular-vascular coupling ratio improved. [91] These hypothesis-generating findings remain to be confirmed in a larger randomized study.

Conclusions

In summary, recent work illustrates that HFPEF patients frequently have functional abnormalities in multiple cardiovascular and noncardiovascular domains. In any given patient, one mechanism may predominate or several may contribute simultaneously to the HFPEF syndrome. Structural and functional phenotyping of HFPEF patients may have important implications for clinical trial patient selection and individualized treatment plans. Animal models, epidemiological cohorts, and small mechanism-focused studies in humans suggest that oxidative stress and chronic inflammation are important underlying contributors to the development and progression of HFPEF. Considering phenotypic heterogeneity and novel mechanisms may lead to new therapeutic and prevention-focused strategies for HFPEF.

Acknowledgments

Supported in part by: NIH grant R3718915, NIH grant K23HL109176

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127(1):e6–e245.10.1161/CIR.0b013e31828124ad [PubMed: 23239837]
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. [see comment]. N Engl J Med. 2006; 355(3):251–9. [PubMed: 16855265]
3. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J. 2008; 29(3):339–47.10.1093/eurheartj/ehm554 [PubMed: 18156618]
4. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007; 50(8):768–77. [PubMed: 17707182]
5. Lam CSP, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, et al. Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community/Clinical Perspective. Circulation. 2011; 124(1):24–30.10.1161/circulationaha.110.979203 [PubMed: 21670229]
6. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, et al. Comorbidity and Ventricular and Vascular Structure and Function in Heart Failure With Preserved Ejection Fraction: A Community-Based Study. Circ Heart Fail. 2012; 5(6):710–9.10.1161/circheartfailure.112.968594 [PubMed: 23076838]
7. Hummel SL, DeFranco AC, Skorcz S, Montoye CK, Koelling TM. Recommendation of Low-Salt Diet and Short-term Outcomes in Heart Failure with Preserved Systolic Function. Am J Med. 2009; 122(11):1029–36. [PubMed: 19854331]
8. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Adhere Scientific Advisory Committee and I. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database.erratum appears in J Am Coll Cardiol. 2006 Apr 7;47(7):1502. J Am Coll Cardiol. 2006; 47(1):76–84. [PubMed: 16386668]
9. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. Circ Heart Fail. 2011; 4(5):538–40.10.1161/circheartfailure.111.963710 [PubMed: 21934089]

10. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJV. What Have We Learned About Patients With Heart Failure and Preserved Ejection Fraction From DIG-PEF, CHARM-Preserved, and I-PRESERVE? J Am Coll Cardiol. 2012; 60(23):2349–56.10.1016/j.jacc.2012.04.064 [PubMed: 23141494]
11. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of Noncardiac Comorbidities on Morbidity and Mortality in a Predominantly Male Population With Heart Failure and Preserved Versus Reduced Ejection Fraction. J Am Coll Cardiol. 2012; 59(11):998–1005.10.1016/j.jacc.2011.11.040 [PubMed: 22402071]
12. Chan MMY, Lam CSP. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail. 2013; 15(6):604–13.10.1093/eurjhf/hft062 [PubMed: 23610137]
13. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, et al. 2013 ACCF/AHA Guideline for the Management of Heart FailureA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 201310.1016/j.jacc.2013.05.019
14. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J. 2012
15. Lindenfeld J, Albert N, Boehmer J, Collins S, Ezekowitz J, Givertz M, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010; 16(6):e1–194. [PubMed: 20610207]
16. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. [see comment]. J Am Coll Cardiol. 1991; 17(5):1065–72. [PubMed: 2007704]
17. Zile MR, Baicu CF, Gaasch WH. Diastolic Heart Failure -- Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle. N Engl J Med. 2004; 350(19):1953–9. [PubMed: 15128895]
18. Lam CSP, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, et al. Cardiac Structure and Ventricular-Vascular Function in Persons With Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota. Circulation. 2007; 115(15):1982–90. [PubMed: 17404159]
19. AlJaroudi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, et al. Impact of Progression of Diastolic Dysfunction on Mortality in Patients With Normal Ejection Fraction/Clinical Perspective. Circulation. 2012; 125(6):782–8.10.1161/circulationaha.111.066423 [PubMed: 22261198]
20. Persson H, Lonn E, Edner M, Baruch L, Lang CC, Morton JJ, et al. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence:results from the CHARM Echocardiographic Substudy-CHARMES. J Am Coll Cardiol. 2007; 49(6):687–94. [PubMed: 17291934]
21. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of Left Ventricular Stiffness in Heart Failure With Normal Ejection Fraction. Circulation. 2008; 117(16):2051–60.10.1161/circulationaha.107.716886 [PubMed: 18413502]
22. Borlaug BA, Jaber WA, Ommen SR, Lam CSP, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart. 2011; 97(12):964–9.10.1136/hrt.2010.212787 [PubMed: 21478380]
23. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003; 107(5):714–20. [PubMed: 12578874]
24. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, et al. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol. 2001; 38(3):796–802. [PubMed: 11527636]
25. Kitzman DW, Herrington DM, Brubaker PH, Moore JB, Eggebeen J, Haykowsky MJ. Carotid arterial stiffness and its relationship to exercise intolerance in older patients with heart failure and preserved ejection fraction. Hypertension. 2013; 61(1):112–9.10.1161/hypertensionaha.111.00163 [PubMed: 23150511]

26. Borlaug BA, Lam CSP, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease: Insights Into the Pathogenesis of Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2009; 54(5):410–8. http://dx.doi.org/10.1016/j.jacc.2009.05.013. [PubMed: 19628115]
27. Zhong L. Attenuation of stress-based ventricular contractility in patients with heart failure and normal ejection fraction. Ann Acad Med Singapore. 2011; 40(4):179–85. [PubMed: 21678003]
28. Tartière-Kesri L, Tartière J-M, Logeart D, Beauvais F, Cohen Solal A. Increased Proximal Arterial Stiffness and Cardiac Response With Moderate Exercise in Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2012; 59(5):455–61.10.1016/j.jacc.2011.10.873 [PubMed: 22281248]
29. Borlaug BA, Olson TP, Lam CSP, Flood KS, Lerman A, Johnson BD, et al. Global Cardiovascular Reserve Dysfunction in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2010; 56(11):845–54. [PubMed: 20813282]
30. Hundley WG, Bayram E, Hamilton CA, Hamilton EA, Morgan TM, Darty SN, et al. Leg flow-mediated arterial dilation in elderly patients with heart failure and normal left ventricular ejection fraction. Am J Physiol Heart Circ Physiol. 2007; 292(3):H1427–34.10.1152/ajpheart.00567.2006 [PubMed: 17085542]
31. Haykowsky MJ, Herrington DM, Brubaker PH, Morgan TM, Hundley WG, Kitzman DW. Relationship of flow-mediated arterial dilation and exercise capacity in older patients with heart failure and preserved ejection fraction. J Gerontol A Biol Sci Med Sci. 2013; 68(2):161–7.10.1093/gerona/gls099 [PubMed: 22522508]
32. Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW. Ventricular Structure and Function in Hypertensive Participants With Heart Failure and a Normal Ejection Fraction: The Cardiovascular Health Study. J Am Coll Cardiol. 2007; 49(9):972–81. [PubMed: 17336721]
33. Noumi B, Teruya S, Salomon S, Helmke S, Maurer MS. Blood Volume Measurements in Patients With Heart Failure and a Preserved Ejection Fraction: Implications for Diagnosing Anemia. Congest Heart Fail. 2011; 17(1):14–8.10.1111/j.1751-7133.2010.00208.x [PubMed: 21272222]
34. McKie PM, Schirger JA, Costello-Boerrigter LC, Benike SL, Harstad LK, Bailey KR, et al. Impaired Natriuretic and Renal Endocrine Response to Acute Volume Expansion in Pre-Clinical Systolic and Diastolic Dysfunction. J Am Coll Cardiol. 2011; 58(20):2095–103.10.1016/j.jacc.2011.07.042 [PubMed: 22051332]
35. Colombo PC, Ganda A, Lin J, Onat D, Harxhi A, Iyasere JE, et al. Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. Heart Fail Rev. 2012; 17(2):177–90.10.1007/s10741-011-9261-3 [PubMed: 21688186]
36. Brubaker PH, Joo KC, Stewart KP, Fray B, Moore B, Kitzman DW. Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. J Cardiopulm Rehabil. 2006; 26(2):86–9. [PubMed: 16569976]
37. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation. 2011; 123(9):1010–20.10.1161/circulationaha.110.940577 [PubMed: 21382903]
38. Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left Atrial Function in Diastolic Heart Failure. Circ Cardiovasc Imag. 2009; 2(1):10–5.10.1161/circimaging.108.813071
39. Obokata M, Negishi K, Kurosawa K, Arima H, Tateno R, Ui G, et al. Incremental Diagnostic Value of LA Strain With Leg Lifts in Heart Failure With Preserved Ejection Fraction. JACC Cardiovasc Imaging. 2013; 6(7):749–58. http://dx.doi.org/10.1016/j.jcmg.2013.04.006. [PubMed: 23747067]
40. Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, et al. Risk Factors for Hospital Admission Among Older Persons With Newly Diagnosed Heart Failure: Findings From the Cardiovascular Health Study. J Am Coll Cardiol. 2013; 61(6):635–42. http://dx.doi.org/10.1016/j.jacc.2012.11.027. [PubMed: 23391194]
41. Duscha BD, Annex BH, Green HJ, Pippen AM, Kraus WE. Deconditioning fails to explain peripheral skeletal muscle alterations in men with chronic heart failure. J Am Coll Cardiol. 2002; 39(7):1170–4. [PubMed: 11923042]

42. Simonini A, Long CS, Dudley GA, Yue P, McElhinny J, Massie BM. Heart failure in rats causes changes in skeletal muscle morphology and gene expression that are not explained by reduced activity. Circ Res. 1996; 79(1):128–36. [PubMed: 8925560]
43. Edelmann F, Gelbrich G, Düngen H-D, Fröhling S, Wachter R, Stahrenberg R, et al. 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. 2011; 58(17):1780–91.10.1016/j.jacc.2011.06.054 [PubMed: 21996391]
44. Kitzman D, Brubaker P, Morgan T, Stewart K, Little W. Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction: A Randomized, Controlled, Single-Blind Trial. Circ Heart Fail. 2010; 3(6):659–67. [PubMed: 20852060]
45. Kitzman, DW.; Brubaker, PH.; Herrington, DM.; Morgan, TM.; Stewart, KP.; Hundley, WG., et al. Effect of Endurance Exercise Training on Endothelial function and Arterial Stiffness in Older Patients with Heart Failure and Preserved Ejection Fraction: A Randomized, Controlled, Single-Blind Trial. J Am Coll Cardiol. http://dx.doi.org/10.1016/j.jacc.2013.04.033
46. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. Am Heart J. 2012; 164(6):869–77. http://dx.doi.org/10.1016/j.ahj.2012.06.028. [PubMed: 23194487]
47. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of Endurance Training on the Determinants of Peak Exercise Oxygen Consumption in Elderly Patients With Stable Compensated Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol. 2012; 60(2):120–8.10.1016/j.jacc.2012.02.055 [PubMed: 22766338]
48. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired Aerobic Capacity and Physical Functional Performance in Older Heart Failure Patients With Preserved Ejection Fraction: Role of Lean Body Mass. J Gerontol A Biol Sci Med Sci. 2013; 68(8):968–75.10.1093/gerona/glt011 [PubMed: 23525477]
49. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol. 2000; 35(6):1628–37. [PubMed: 10807470]
50. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, et al. Inflammatory Markers and Incident Heart Failure Risk in Older Adults: The Health ABC (Health, Aging, and Body Composition) Study. J Am Coll Cardiol. 2010; 55(19):2129–37. [PubMed: 20447537]
51. Rickard A, Morgan J, Tesch G, Funder J, Fuller P, Young M. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. Hypertension. 2009; 54(3):537–43. [PubMed: 19635989]
52. Klotz S, Hay I, Zhang G, Maurer M, Wang J, Burkhoff D. Development of heart failure in chronic hypertensive Dahl rats: focus on heart failure with preserved ejection fraction.see comment. Hypertension. 2006; 47(5):901–11. [PubMed: 16585423]
53. Matsui H, Ando K, Kawarazaki H, Nagae A, Fujita M, Shimosawa T, et al. Salt excess causes left ventricular diastolic dysfunction in rats with metabolic disorder. Hypertension. 2008; 52(2):287–94. [PubMed: 18606904]
54. Munagala VK, Hart CY, Burnett JC Jr, Meyer DM, Redfield MM. Ventricular structure and function in aged dogs with renal hypertension: a model of experimental diastolic heart failure. Circulation. 2005; 111(9):1128–35. [PubMed: 15723971]
55. Tian N, Moore RS, Phillips WE, Lin L, Braddy S, Pryor JS, et al. NADPH oxidase contributes to renal damage and dysfunction in Dahl salt-sensitive hypertension. Am J Physiol Regul Integr Comp Physiol. 2008; 295(6):R1858–65.10.1152/ajpregu.90650.2008 [PubMed: 18922960]
56. Usher MG, Duan SZ, Ivaschenko CY, Frieler RA, Berger S, Schütz G, et al. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. J Clin Invest. 2010; 120(9):3350–64. [PubMed: 20697155]
57. Bayorh MA, Mann G, Walton M, Eatman D. Effects of Enalapril, Tempol, and Eplerenone on Salt-Induced Hypertension in Dahl Salt-Sensitive Rats. Clin Exp Hypertens. 2006; 28(2):121–32. [PubMed: 16546838]

58. Vanegas V, Ferrebuz A, Quiroz Y, Rodriguez-Iturbe B. Hypertension in Page (cellophane-wrapped) kidney is due to interstitial nephritis. Kidney Int. 2005; 68(3):1161–70. [PubMed: 16105047]
59. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, et al. Cardiac Inflammation Contributes to Changes in the Extracellular Matrix in Patients With Heart Failure and Normal Ejection Fraction/Clinical Perspective. Circ Heart Fail. 2011; 4(1):44–52.10.1161/circheartfailure.109.931451 [PubMed: 21075869]
60. Tamaki S, Mano T, Sakata Y, Ohtani T, Takeda Y, Kamimura D, et al. Interleukin-16 Promotes Cardiac Fibrosis and Myocardial Stiffening in Heart Failure with Preserved Ejection Fraction. PLoS ONE. 2013; 8(7):e68893.10.1371/journal.pone.0068893 [PubMed: 23894370]
61. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, et al. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci. 2009; 64(4):455–61.10.1093/gerona/gln038 [PubMed: 19196644]
62. van Heerebeek L, Hamdani N, Falcao-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, et al. Low myocardial protein kinase g activity in heart failure with preserved ejection fraction. Circulation. 2012; 126(7):830–9.10.1161/circulationaha.111.076075 [PubMed: 22806632]
63. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure With Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. 2013; 62(4):263–71. http://dx.doi.org/10.1016/j.jacc.2013.02.092. [PubMed: 23684677]
64. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, et al. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. Eur J Heart Fail. 2011; 13(12):1296–304.10.1093/eurjhf/hfr133 [PubMed: 21979991]
65. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. [see comment]. Lancet. 2003; 362(9386):777–81. [PubMed: 13678871]
66. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359(23):2456–67. [PubMed: 19001508]
67. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study.see comment. Eur Heart J. 2006; 27(19):2338–45. [PubMed: 16963472]
68. Groban L, Pailes NA, Bennett CD, Carter CS, Chappell MC, Kitzman DW, et al. Growth hormone replacement attenuates diastolic dysfunction and cardiac angiotensin II expression in senescent rats. J Gerontol A Biol Sci Med Sci. 2006; 61(1):28–35. [PubMed: 16456192]
69. Groban L, Yamaleyeva LM, Westwood BM, Houle TT, Lin M, Kitzman DW, et al. Progressive diastolic dysfunction in the female mRen(2). Lewis rat: influence of salt and ovarian hormones. J Gerontol A Biol Sci Med Sci. 2008; 63(1):3–11. [PubMed: 18245755]
70. Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol. 1999; 33(6):1567–72. http://dx.doi.org/10.1016/S0735-1097(99)00048-0. [PubMed: 10334425]
71. Little WC, Wesley-Farrington DJ, Hoyle J, Brucks S, Robertson S, Kitzman DW, et al. Effect of candesartan and verapamil on exercise tolerance in diastolic dysfunction. J Cardiovasc Pharmacol. 2004; 43(2):288–93. [PubMed: 14716219]
72. Kitzman DW, Hundley WG, Brubaker PH, Morgan TM, Moore JB, Stewart KP, et al. A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. Circ Heart Fail. 2010; 3(4):477–85.10.1161/circheartfailure.109.898916 [PubMed: 20516425]
73. Lund LH, Benson L, Dahlström U, Edner M. Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction. JAMA. 2012; 308(20):2108–17.10.1001/jama.2012.14785 [PubMed: 23188027]

74. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 380(9851):1387–95. http://dx.doi.org/10.1016/S0140-6736(12)61227-6. [PubMed: 22932717]
75. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction Trial (RAAM-PEF). J Card Fail. 2011; 17(8):634–42.10.1016/j.cardfail.2011.04.007 [PubMed: 21807324]
76. Edelmann FWRSAG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the ALDO-DHFrandomized controlled trial. JAMA. 2013; 309(8):781–91.10.1001/jama.2013.905 [PubMed: 23443441]
77. Patel K, Fonarow GC, Kitzman DW, Aban IB, Love TE, Allman RM, et al. Aldosterone Antagonists and Outcomes in Real-World Older Patients With Heart Failure and Preserved Ejection Fraction. JACC: Heart Failure. 2013; 1(1):40–7. http://dx.doi.org/10.1016/j.jchf.2012.08.001. [PubMed: 23814702]
78. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim H-Y, Harty B, et al. Baseline Characteristics of Patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circ Heart Fail. 201210.1161/circheartfailure.112.972794
79. Lam CSP, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Community-Based Study. J Am Coll Cardiol. 2009; 53(13):1119–26. [PubMed: 19324256]
80. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011; 124(2):164–74.10.1161/circulationaha.110.983866 [PubMed: 21709061]
81. Redfield MM, Chen HH. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: A randomized clinical trial. JAMA. 2013; 309(12):1268–77.10.1001/jama.2013.2024 [PubMed: 23478662]
82. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel Inhibition on Hemodynamics and Exercise Tolerance in Heart Failure with Preserved Ejection Fraction: A Randomized Trial. J Am Coll Cardiol. 201310.1016/j.jacc.2013.06.043
83. Maurer MS, Teruya S, Chakraborty B, Helmke S, Mancini D. Treating anemia in older adults with heart failure with a preserved ejection fraction with epoetin alfa: single-blind randomized clinical trial of safety and efficacy. Circ Heart Fail. 2013; 6(2):254–63.10.1161/circheartfailure.112.969717 [PubMed: 23258574]
84. Jacobshagen C, Belardinelli L, Hasenfuss G, Maier LS. Ranolazine for the treatment of heart failure with preserved ejection fraction: background, aims, and design of the RALI-DHF study. Clin Cardiol. 2011; 34(7):426–32.10.1002/clc.20897 [PubMed: 21538388]
85. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013; 381(9860):29–39.10.1016/s0140-6736(12)61855-8 [PubMed: 23141816]
86. Smart N, Haluska B, Jeffriess L, Marwick TH. Exercise training in systolic and diastolic dysfunction: effects on cardiac function, functional capacity, and quality of life. Am Heart J. 2007; 153(4):530–6.10.1016/j.ahj.2007.01.004 [PubMed: 17383289]
87. Mudge AM, Denaro CP, Scott AC, Atherton JJ, Meyers DE, Marwick TH, et al. Exercise training in recently hospitalized heart failure patients enrolled in a disease management programme: design of the EJECTION-HF randomized controlled trial. Eur J Heart Fail. 2011; 13(12):1370–5.10.1093/eurjhf/hfr139 [PubMed: 22065870]
88. Al-Solaiman Y, Jesri A, Zhao Y, Morrow JD, Egan BM. Low-sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. J Hum Hypertens. 2009
89. Levitan EB, Wolk A, Mittleman MA. Consistency With the DASH Diet and Incidence of Heart Failure. Arch Intern Med. 2009; 169(9):851–7.10.1001/archinternmed.2009.56 [PubMed: 19433696]
90. Hummel SL, Seymour EM, Brook RD, Kolias TJ, Sheth SS, Rosenblum HR, et al. Low-Sodium Dietary Approaches to Stop Hypertension Diet Reduces Blood Pressure, Arterial Stiffness, and

Oxidative Stress in Hypertensive Heart Failure With Preserved Ejection Fraction/Novelty and Significance. Hypertension. 2012; 60(5):1200–6.10.1161/hypertensionaha.112.202705 [PubMed: 23033371]

91. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, et al. Low-Sodium DASH Diet Improves Diastolic Function and Ventricular-Arterial Coupling in Hypertensive Heart Failure with Preserved Ejection Fraction. Circ Heart Fail. 2013 accepted for publication August 16, 2013.