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The Effect of Spironolactone on Exercise Tolerance and Arterial Function in Older Patients with HEpEF

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Abstract

OBJECTIVES—To evaluate the effects of aldosterone antagonism on exercise intolerance in older patients with heart failure (HF) and preserved ejection fraction (HFpEF).

DESIGN—Randomized, placebo-controlled, double-blind trial.

SETTINGS—Academic medical center, Winston Salem, NC, USA.

PARTICIPANTS—Eighty stable compensated HFpEF patients (age 71±1 years; 80% women) with controlled blood pressure (BP).

MEASUREMENTS—Participants were randomized into a 9 month follow-up double-blind trial of spironolactone 25 mg/d versus placebo. Assessments were peak exercise oxygen consumption (VO₂); 6-minute walk test; Minnesota Living with HF Questionnaire (MLHF); cardiac magnetic resonance imaging; Doppler-echocardiography; and vascular ultrasound.

RESULTS—Seventy-one patients completed the trial: 37 spironolactone group and 34 placebo group. Compliance by pill count was excellent (spironolactone 95%, placebo 97%). Mean spironolactone dose was 24.3±2.9 mg/day and was well tolerated. Spironolactone significantly reduced systolic and diastolic BP at rest and peak exercise. At 9-month follow-up, baseline-adjusted peak VO₂, the primary outcome, was 13.5±0.3 in the spironolactone group versus

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13.9±0.3 in placebo; adjusted mean difference: -0.4ml/kg/min; 95% CI, -1.1 to 0.4 ml/kg/min; $p = 0.38$). The 95% confidence intervals of spironolactone's effect on peak VO_2 (-8.2% to 3.2%) excluded a clinically significant beneficial effect. There were also no significant differences in six-minute walk distance, arterial stiffness, left ventricular (LV) mass, LV mass/end-diastolic volume, or MLHF score.

CONCLUSION—In stable, compensated older HFpEF patients, 9 months of spironolactone 25 mg/day was well-tolerated and reduced BP, but did not improve exercise capacity, quality-of-life, LV mass or arterial stiffness.

Keywords

Heart failure; exercise tolerance; aging; aldosterone antagonism; arterial function

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is nearly exclusively found in older persons, particularly older women, in whom 90% of new HF cases are HFpEF.¹ In contrast to HF with reduced EF (HFrEF), the prevalence of HFpEF is increasing and its prognosis is worsening.¹

Exercise intolerance, manifested by dyspnea and fatigue during exertion, is the primary chronic symptom experienced by HF patients^{1,2} and can be quantified objectively and reliably by measurement of peak exercise oxygen consumption (VO_2).^{2,3} We have shown that the reduction in peak VO_2 in HFpEF is similar in severity to HFrEF.² However, this clinically meaningful outcome has received much less attention than clinical endpoints in the quest for HFpEF treatments.

Several lines of evidence suggest that aldosterone excess could contribute to exercise intolerance in HFpEF. Serum aldosterone is increased in patients with HFpEF and is known to promote vascular inflammation and increased arterial stiffness and left ventricular hypertrophy (LVH), fibrosis, and stiffness.^{4,5} Arterial stiffness increases with age and inversely correlates with age-related decline in exercise capacity, and is further accelerated by hypertension, a common precursor to HFpEF.⁶ We have shown that aortic and carotid stiffness are severely increased in elderly HFpEF patients and are strongly correlated with their reduced peak VO_2 .⁷

Aldosterone antagonism with spironolactone improves exercise intolerance and aortic stiffness in patients with HFrEF.⁸ In hypertensive rats, aldosterone antagonism decreases myocardial collagen volume and improves LV concentric remodeling and diastolic stiffness.⁹ In our published open-label pilot study with HFpEF, spironolactone therapy was associated with improvements in peak VO_2 , echo-Doppler measures of diastolic function, and New York Heart Association (NYHA) class.¹⁰

We hypothesized that the severe exercise intolerance experienced by older patients with HFpEF can be improved with aldosterone antagonism and that this improvement would be mediated at least partly by improvements in arterial distensibility. To test this hypothesis, we

performed a 9-month prospective, randomized, double-blind, placebo-controlled trial with detailed measurements of exercise performance, health-related quality of life, and cardiac and vascular structure and function.

METHODS

Study Design

The study protocol was approved by the Wake Forest School of Medicine Institutional Review Board. Written informed consent was obtained. All tests were performed in a post-absorptive state with medications held for 12 hours prior to testing, except for the study medication. Testing was performed at baseline and was repeated after 4 and 9 months except cardiac magnetic resonance imaging (CMRI), which was repeated only at 9 months. Placebo and active drug were prepared and distributed by the research pharmacy using secure methodology. All investigators, staff, and patients were fully blinded to treatment group assignment throughout the entire study period, during data abstraction, clean-up, and image analyses, and until the database had been locked. Eligible patients were randomly assigned to receive either spironolactone (25 mg/d) or matching placebo. Compliance was assessed by actual pill count. The starting dose of spironolactone was 12.5 mg once daily in patients with baseline creatinine ≤ 2.0 mg/dL or potassium >4.5 meq/L; in all other patients the starting dose was 25 mg once daily. Among patients who initiated therapy with the 12.5-mg dose, the dose was increased to 25 mg daily as long as the creatinine remained <2.5 mg/dL and potassium remained ≤ 5.0 meq/L. Spironolactone was discontinued if 1-week creatinine was ≥ 2.5 mg/dL or potassium ≥ 5.5 meq/L. To assure patient safety, adherence, and retention in the study, patients were seen by clinic visit or contacted by telephone regularly.

Patients

As previously described, and in accord with the 2013 American College of Cardiology Guideline for Evaluation and Management of HF, HFpEF was defined as history, symptoms, and signs of HF, a preserved LVEF ($\geq 50\%$), and no evidence of other medical condition that could mimic HF symptoms.^{2;11–17} Coronary disease was excluded by history, medical records, electrocardiogram, and rest and exercise echocardiogram. The diagnosis of HF was based on clinical criteria as previously described that included a HF clinical score from the National Health and Nutrition Examination Survey-I (NHANES) of ≥ 3 ,¹⁸ and those used by Rich et al.¹⁹ and verified by a board certified cardiologist.^{14;16} The NHANES-1 criteria have been shown to have 94% specificity for HF, similar to the traditional Framingham criteria.²⁰ Exclusions included prior aldosterone antagonism use within the past 3 months, a known contra-indication, concomitant therapy with a potassium sparing diuretic or potassium supplementation, a baseline serum potassium >5.0 meq/L, or serum creatinine ≥ 2.5 mg/dL.

Outcome measures

Exercise Performance—Exercise testing was performed as previously described, with participants in the upright position on an electronically braked bicycle.^{2;12;13;17;17} Expired gas analysis was carried out using a metabolic cart calibrated with a standard gas of known concentration and volume. Metabolic gas exchange was measured continuously during exercise and averaged over 15-second intervals. Peak values were averaged from the final 30

seconds of the exercise test. A 6-minute walk test was performed as described by Guyatt et al.²¹

Aortic distensibility and LV structure and function—CMRI scans were performed on a 1.5T General Electric CVi scanner with a phased-array surface coil applied to optimize signal to noise. Multi-slice coronal, gradient-echo sequences was used to obtain scout images of the chest and thus locate the heart and aorta. After locating the aorta, a series of sagittal and axial images in both standard and oblique planes was obtained. Assessment of aortic distensibility was then defined and calculated according to previously published techniques.^{7;22}

As previously described, LV volumes and LV mass were assessed from a series of multi-slice, multi-phase gradient-echo sequences positioned perpendicular to the long axis of the LV (short-axis), spanning apex to base.^{13;22} For LV volume and mass determinations, the epi- and endocardial borders of each slice were traced manually at end diastole and end systole, and volumes were calculated by summation (Simpson's rule).^{13;22} LV stroke volume and EF were calculated from standard formulas.

Carotid Artery Stiffness—As described previously,²³ standardized longitudinal B-mode images of the left common carotid artery (LCA) were recorded with the subject in the supine position. The following data were then computed from each image: mean, maximum, and minimum values of the arterial diameter, the lumen diameter, and wall thickness. Carotid artery stiffness indexes were then calculated using standard equations.

Pulse Wave Velocity (PWV)—We analyzed PWV measured by the Doppler method with 2D guidance where regional Doppler PWV was defined as the distance between the extremities of a given segment divided by the transit time calculated by Doppler.²⁴ The examination began with the patient in a supine position after locating the LCA with B-mode at the supraclavicular level. We then identified the Doppler wave flow simultaneously with ECG. The process was repeated on the left femoral artery in the groin.

LV diastolic filling—Mitral annulus tissue and blood flow Doppler were performed using an ultrasound imaging system with a multiple frequency transducer. Doppler tracings were then analyzed using a digital echocardiography workstation as previously described.^{2;22;25}

Quality of Life—The Minnesota Living with HF Questionnaire (MLHF), a HF specific measure, was administered to assess the impact of the intervention on quality-of- life.^{2;26}

Statistical Analysis

The study was designed to test for an effect of spironolactone on two primary outcome measures, peak VO₂ and total score of the MLHF questionnaire. The sample size was derived from a formal power analysis using data from our previously published studies and from our pilot study conducted specifically to inform the design of the present trial.¹⁰ These data indicated that a final sample size of 60 evaluable patients at the end of the study (72 patients randomized at the beginning of the study and assuming up to 15% dropout during 9-

month follow-up) would provide 94% power to detect a 5% change in peak exercise VO_2 and 90% power to detect a 20% change in the total MLFH score.

Group comparisons of outcome measures between intervention groups were made by repeated measures analysis of covariance procedures. For the CMRI outcome measures, comparisons between intervention groups were made by analysis of covariance. By prospective study design in order to reduce bias and increase precision, the analyses adjusted for pre-randomization values of the outcome measure being considered as well as other factors (age, gender) significantly associated with the outcome variable after adjusting for the other terms in the model.²⁷ The values of the non-CMRI outcome measures taken at 4 and 9 months were considered the repeated measures. A test of the group by time interaction was used to check the consistency of any intervention effect at each of the two endpoint evaluations (4, 9 months). If the interaction was non-significant at the 0.10 level of significance, then the overall effect of the intervention over the experimental period was estimated. Data are presented as raw, unadjusted mean $\pm$ standard deviation at each visit for each group, along with the P-value corresponding to the adjusted least squares outcomes means from the analysis of covariance procedures accounting for all data at all follow-up visits. Significance was set at $p < 0.05$.

RESULTS

Participants were recruited using a staged screening process: 4,035 patient charts were selected by electronic search criteria and reviewed; 546 of those patients were contacted and screened by telephone; and 142 of those were scheduled for a screening clinic visit. A total of 80 patients were enrolled in the trial; 42 patients randomized to receive spironolactone and 38 randomized to receive placebo. There were no significant differences between the treatment groups with regard to age, sex, race, and weight, EF, or NYHA class. (Table 1)

Compliance, adverse events, and retention

Compliance was excellent in both groups (spironolactone, 95%; placebo, 97%). Eight patients (10%) received less than full dose or were down-titrated (6 for spironolactone; 2 for placebo). Of the 6 down-titrated patients in the spironolactone group, 2 patients were increased back to full dose within one week, 2 patients eventually dropped the study, and 2 patients finished at less than full dose. The total daily final dose was 12.5 mg in both cases. The mean daily dose of spironolactone was 24.3 ± 2.9 mg/day. The most common reasons for not achieving full dose were increased potassium levels and a decrease in resting BP. Thirty-seven patients randomized to spironolactone and 35 patients randomized to placebo completed 4 months of follow-up, and 37 patients randomized to spironolactone and 34 patients randomized to placebo completed 9 months of follow-up. The 9 patients not represented in the 9 month follow-up data were due to 8 dropouts and 1 death (car accident in the placebo group). The dropouts were due to: patient request (7); and increased potassium (1). By the blinded investigators, only the latter was judged to be possibly related to study medication, which occurred in the spironolactone group

Twenty-three minor adverse events occurred during the study period (12, spironolactone and 11, placebo). By the blinded investigators, 1 event that occurred was judged possibly related

to study medication: increased potassium. In addition, there were 16 hospitalizations during the study: 3 for chest pain [all ruled out for myocardial infarction (MI)], (2, spironolactone and 1, placebo); 5 for shortness of breath (placebo); 2 for syncopal episodes (spironolactone); 1 for hypotension (spironolactone); 1 for self-limited angioedema (spironolactone); and 4 for elective surgery (2 for broken bones, 1 for torn rotator cuff, and 1 for gall bladder surgery), (1, spironolactone and 3, placebo).

Exercise performance—Patients gave an exhaustive effort at baseline and follow-up testing as evidenced by a mean respiratory exchange ratio (RER) greater than 1.10, and there was equal effort between the groups as shown by no significant difference in RER values (Table 2). At baseline, peak exercise VO_2 was severely reduced in both groups compared to expected for age (Table 2). There was also no significant difference in the baseline-adjusted 9-month follow-up mean peak VO_2 values: 13.5 ± 0.3 spironolactone vs. 13.9 ± 0.3 placebo, mean difference -0.4 ml/kg/min ; 95% CI, -1.1 to 0.4 ml/kg/min ; $p = 0.38$) (Table 2). The estimated treatment effect size on peak exercise VO_2 was $-0.4 \pm 0.4 \text{ ml/kg/min}$ (-2.5% ; 95% CI, -1.1 to 0.4 ml/kg/min [-8.2% to 3.2%]), essentially excluding potential for a clinically meaningful effect. There were also no significant differences between the groups in any other measure of peak exercise capacity or in any measure of sub-maximal exercise performance.

Quality-of-life—No significant difference seen with total score on the MLHF questionnaire between spironolactone and placebo group ($p=0.81$; Table 2).

LV structure and function—There were no significant differences in any Doppler LV diastolic function variables (Table 3) between two groups. By CMRI, there were no differences during follow-up in LV mass, LV volumes, EF, or the ratio of LV mass to end-diastolic volume, a measure of concentric LV remodeling (Table 4).

Arterial function—Aortic distensibility by CMRI, the primary mechanistic outcome, was not significantly different between groups during follow-up. Similarly neither carotid distensibility nor PWV by ultrasound were significantly different between groups during follow-up. (Table 4)

Neurohormones—Serum aldosterone was significantly increased in spironolactone compared to placebo (17.2 ± 8.6 vs. 9.7 ± 5.3 ; $p=0.0001$), but B-type natriuretic peptide (BNP) was unchanged. (Table 2)

Discussion

This randomized, placebo-controlled, double-blinded study examined the potential benefit of 9 months treatment with the aldosterone antagonist spironolactone to improve exercise tolerance and quality-of-life in HFpEF as well as measures of arterial stiffness that are thought to contribute to the pathophysiology of this important disorder. Patients at baseline were stable and compensated, had controlled BP, and had severely reduced exercise capacity. Contrary to our primary hypothesis, there was no difference in peak or sub-maximal exercise

capacity, nor in quality-of-life by the MLHF questionnaire, arterial function, or LV mass/volume.

Among patients with HFrEF and those with MI complicated by LV dysfunction, aldosterone antagonists are effective in reducing overall mortality and hospitalizations for HF.^{28–30} This is in contrast with the trials of aldosterone antagonism performed in HFpEF patients to date.^{31–33} (Table 5) In the large TOPCAT, the overall effect of spironolactone was neutral on clinical endpoints (survival, cardiovascular events, hospitalizations), although there appeared to be a strong, divergent response depending on geography and disease severity.^{33;34} Additionally, they also noted that, in TOPCAT trial, the potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum.³⁵

Our results are consistent with those of two prior trials examining the effect of aldosterone antagonism on exercise function in HFpEF. In the RAAM-HF single-center trial, there were no significant treatment related differences in 6 minute walk distance (MWD), the primary outcome, or quality-of-life, despite improvements in procollagen type I amino terminal peptide, a fibrosis biomarker, and E/e', a Doppler measure of diastolic function.³¹ Similarly, in the ALDO-DHF multi-center trial, although E/e' and LV remodeling improved, there was no treatment-related difference in the peak VO₂, the co-primary outcome, or 6 MWD.³² Combining our study along with RAAM-HF and ALDO-DHF provides a total of 546 randomized HFpEF patients in three separate randomized, controlled, blinded trials, utilizing two different aldosterone antagonists, all showing no treatment-related improvement in the key outcome of exercise capacity (two measured peak VO₂ and all 3 measured with 6 MWD). Furthermore, the confidence limits of the effect size in our trial alone exclude the potential for a clinically meaningful impact on peak VO₂ (0.5 ml/kg/min), the most rigorous measure of exercise capacity in HF.³⁶

Kosmala and colleagues recently reported results that differ from the above three studies. In patients with exertional dyspnea, diastolic dysfunction, and an increase in non-invasively estimated diastolic LV diastolic filling pressure (measured as exercise E/e' ratio) during exercise, the addition of spironolactone to existing therapy for 6 months was associated with increased exercise capacity and this appeared to be associated with improved LV filling pressure.³⁷ It is possible that selection of patients on the basis of exercise-induced increase in E/e' might have helped to select the particular HFpEF phenotype that is most likely to be responsive to spironolactone.

Our study extends previously published data in several ways. Our patients were approximately 5 years older than previous studies, including Kosmala et al and ALDO-DHF, and had a larger proportion of women, and thus had demographics more similar to those reported in population-based studies.¹ In addition, we used a really robust and novel means of exercise testing that also included ventilatory anaerobic threshold (VAT), which is a measure of submaximal exercise capacity. This may be most relevant in older persons who infrequently undertake physical activity at the level of exhaustive exercise. We had shown before that submaximal and peak exercise test variables in our protocol exhibited good reliability and were not significantly altered by a learning effect or placebo administration. Furthermore, we utilized CMRI which has been shown to be much more sensitive to change

in LV mass than echocardiography.³⁸ We also examined aortic distensibility by CMRI and arterial stiffness by ultrasound. We have shown that arterial stiffness is markedly reduced in older HFpEF patients and is strongly correlated with their reduced peak VO_2 ,^{7;39} and others have shown that it is a key determinant of LV afterload and ventricular-vascular coupling.¹³ Spironolactone was previously shown to reduce aortic stiffness among patients with resistant hypertension,⁴⁰ diabetes⁴¹ and early-stage kidney disease.⁴² In previous trials, we showed that neither enalapril nor alagebrium were able to improve aortic distensibility or exercise capacity in older HFpEF patients.^{14;22} It is possible that the severely increased aortic and arterial stiffness in older HFpEF patients may have limited potential for reversibility given that it likely develops over many years and is likely caused by multiple factors.⁶

It is uncertain why aldosterone antagonism hasn't improved exercise capacity in most studies of HFpEF. However, it is notable that aldosterone antagonism may not substantially improve symptoms in patients with HFrEF, despite its ability to improve survival and HF hospitalizations in that disorder.^{30;43} As occurred in ALDO-DHF, we observed significant reductions in rest and exercise systolic and diastolic BP,³² which would have been expected to produce favorable effects on LV afterload, ventricular-vascular coupling, and LV relaxation. Mechanistic studies of exercise intolerance in patients with HFpEF (and HFrEF) indicate that exercise intolerance in HF is multi-factorial and a complex interaction of cardiac, peripheral vascular, and skeletal muscle factors, including abnormal skeletal muscle composition and function,^{44–47} the latter of which might not be expected to be influenced by aldosterone antagonism.^{45;48}

Limitations

By design, participants were stable, well-compensated outpatients who were able to participate in exhaustive exercise testing and long-term follow-up. As a result, the mean BNP level was less than in patients with acute, decompensated HF. However, the BNP levels are similar to other studies of stable HFpEF patients able to undergo maximal exercise testing,^{14;49–52} including the Kosmala study (which were slightly lower than ours),³⁷ and are several-fold increased compared with healthy, age-matched, normal subjects.² Our patients had abnormalities in ventilatory efficiency (V_E/VCO_2), a measure of disease severity and prognosis, and in peak VO_2 at baseline that were similar in degree compared to other studies of aldosterone antagonism in HFpEF.^{31;32} However, our results may not apply to patients with more severe disease and more comorbidities. We cannot exclude the possibility that an even longer duration of treatment or higher aldosterone antagonist dose would improve exercise capacity, although the ALDO-DHF trial treatment duration was 12-months. Our study utilized the ACC/AHA criteria for HFpEF, with confirmation of HF using the NHANES-1 criteria and the Rich et al criteria. Other studies of spironolactone that utilized the European HFpEF criteria, which have specific thresholds for measures from echocardiography and blood tests, have also had neutral outcomes.³² Since we did not assess post-exercise Doppler measures of LV filling in the fashion of Kosamala, et al, we cannot be certain whether selection of similar patients would have shown more favorable results for spironolactone. Indeed, the HFpEF syndrome is heterogeneous and some have speculated that this may have contributed to challenges in the quest for successful therapy. We acknowledge that we observed increase standard error of the mean of the CMRI measures in

our study due to small sample size and might have affected overall results. In addition, the applicability of our results to subjects with different HFpEF phenotype is uncertain. Acknowledging these factors and the resulting key phenotypes in designing HFpEF trials could help achieve more homogenous study populations, and thereby better match underlying pathophysiology with proposed therapeutic mechanisms.

Conclusion

Nine months treatment with spironolactone did not improve exercise capacity, quality-of-life, arterial stiffness, or LV mass, remodeling, or diastolic function in older patients with stable, compensated HFpEF and controlled BP.

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Reference List

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006; 355:251–259. [PubMed: 16855265]
2. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA*. 2002; 288:2144–2150. [PubMed: 12413374]
3. Scott JM, Haykowsky MJ, Eggebeen J, Morgan TM, Brubaker PH, Kitzman DW. Reliability of peak exercise testing in patients with heart failure with preserved ejection fraction. *Am J Cardiol*. 2012; 110:1809–1813. [PubMed: 22981266]
4. Brown NJ. Aldosterone and vascular inflammation. *Hypertension*. 2008; 51:161–167. [PubMed: 18172061]
5. Rocha R, Chander PN, Khanna K, Zuckerman A, Stier CT Jr. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. *Hypertension*. 1998; 31:451–458. [PubMed: 9453344]
6. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a “set up” for vascular disease. *Circulation*. 2003; 107:139–146. [PubMed: 12515756]
7. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle-dependent changes in aortic area and aortic distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol*. 2001; 38:796–802. [PubMed: 11527636]
8. Vizzardi E, Pina PD, Caretta G, et al. The effect of aldosterone-antagonist therapy on aortic elastic properties in patients with nonischemic dilated cardiomyopathy. *J Cardiovasc Med (Hagerstown)*. 2015; 16:597–602. [PubMed: 24978872]
9. Querejeta R, Varo N, Lopez B, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation*. 2000; 101:1729–1735. [PubMed: 10758057]
10. Daniel KR, Wells G, Stewart K, Moore B, Kitzman DW. Effect of aldosterone antagonism on exercise tolerance, doppler diastolic function, and quality of life in older women with diastolic heart failure. *Congest Heart Fail*. 2009; 15:1–7. [PubMed: 19187399]

11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCR/AHA Guideline for the Management of Heart Failure. *Circulation*. 2013; 128:e240–e319. [PubMed: 23741058]
12. Marburger CT, Brubaker PH, Pollock WE, Morgan TM, Kitzman DW. Reproducibility of cardiopulmonary exercise testing in elderly heart failure patients. *Am J Cardiol*. 1998; 82:905–909. [PubMed: 9781977]
13. Hundley W, Kitzman D, Morgan T, et al. Cardiac cycle-dependent changes in aortic area and aortic distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol*. 2001; 38:796–802. [PubMed: 11527636]
14. Kitzman DW, Hundley WG, Brubaker P, Stewart K, Little WC. A randomized, controlled, double-blinded trial of enalapril in older patients with heart failure and preserved ejection fraction; effects on exercise tolerance, and arterial distensibility. *Circ Heart Fail*. 2010; 3:477–485. [PubMed: 20516425]
15. Kitzman D, Brubaker P, Morgan T, Stewart K, Little W. Exercise training in older patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2010; 3:659–667. [PubMed: 20852060]
16. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomised clinical trial. *JAMA*. 2016; 315:36–46. [PubMed: 26746456]
17. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan M. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol*. 1991; 17:1065–1072. [PubMed: 2007704]
18. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol*. 1992; 20:301–306. [PubMed: 1634664]
19. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney R. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med*. 1995; 333:1190–1195. [PubMed: 7565975]
20. Fonseca C, Oliveira AG, Mota T, et al. Evaluation of the performance and concordance of clinical questionnaires for the diagnosis of heart failure in primary care. *Eur J Heart Fail*. 2004; 6:813–822. [PubMed: 15542422]
21. Guyatt GH, Sullivan M, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J*. 1985; 132:919–923. [PubMed: 3978515]
22. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, deGroof RC. The Effect of Alagebrium Chloride (ALT-711), a Novel Glucose Cross-Link Breaker, in the Treatment of Elderly Patients with Diastolic Heart Failure. *J Card Fail*. 2005; 11:191–195. [PubMed: 15812746]
23. Liao D, Arnett DK, Tyroler HA, et al. Arterial stiffness and the development of hypertension. The ARIC study. *Hypertension*. 1999; 34:201–206. [PubMed: 10454441]
24. Kass DA, Shapiro EP, Kawaguchi M, et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation*. 2001; 104:1464–1470. [PubMed: 11571237]
25. Kitzman DW, Sheikh KH, Beere PA, Philips JL, Higginbotham MB. Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility, and loading conditions. *J Am Coll Cardiol*. 1991; 18:1243–1250. [PubMed: 1918701]
26. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol*. 1993; 71:1106–1107. [PubMed: 8475878]
27. Crager MR. Analysis of covariance in parallel-group clinical trials with pretreatment baselines. *Biometrics*. 1987; 43:895–901. [PubMed: 3427174]
28. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999; 341:709–717. [PubMed: 10471456]
29. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003; 348:1309–1321. [PubMed: 12668699]

30. Zannad F, McMurray J, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2010 In print.
31. Deswal A, Richardson P, Bozkurt B, Mann D. Results of the Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction Trial (RAAM-PEF). *J Card Fail*. 2011; 17:634–642. [PubMed: 21807324]
32. Edelmann F. Aldo-DHF investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The aldo-dhf randomized controlled trial. *JAMA*. 2013; 309:781–791. [PubMed: 23443441]
33. Pitt B, Pfeffer M, Assmann S, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014; 370:1383–1392. [PubMed: 24716680]
34. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circulation*. 2015; 131:34–42. [PubMed: 25406305]
35. Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016; 37:455–462. [PubMed: 26374849]
36. Guazzi M, Adams V, Conraads V, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012; 126:2261–2274. [PubMed: 22952317]
37. Kosmala W, Rojek A, Przewlocka-Kosmala M, Wright L, Mysiak A, Marwick TH. Effect of Aldosterone Antagonism on Exercise Tolerance in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol*. 2016; 68:1823–1834. [PubMed: 27765184]
38. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2000; 2:271–278. [PubMed: 11545126]
39. 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; 68:161–167. [PubMed: 22522508]
40. de SF, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension*. 2010; 55:147–152. [PubMed: 19858405]
41. Davies J, Gavin A, Band M, Morris A, Struthers A. Spironolactone reduces brachial pulse wave velocity and PIIINP levels in hypertensive diabetic patients. *Br J Clin Pharmacol*. 2005; 59:520–523. [PubMed: 15842549]
42. Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol*. 2009; 54:505–512. [PubMed: 19643310]
43. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *PG - J Am Coll Cardiol*. 2001; 37:1228–1233.
44. Middlekauff HR. Making the Case for Skeletal Myopathy as the Major Limitation of Exercise Capacity in Heart Failure. *Circ Heart Fail*. 2010; 3:537–546. [PubMed: 20647489]
45. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of Exercise Intolerance in Elderly Heart Failure Patients With Preserved Ejection Fraction. *J Am Coll Cardiol*. 2011; 58:265–274. [PubMed: 21737017]
46. Haykowsky MJ, Tomczak CR, Scott JM, Patterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol*. 2015:739. [PubMed: 25911681]
47. Houstis N, Lewis G. Causes of Exercise Intolerance in Heart Failure with Preserved Ejection Fraction: Searching for Consensus. *J Card Fail*. 2014; 20:762–778. [PubMed: 25108084]
48. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail*. 2015; 8:286–294. [PubMed: 25344549]

49. Borlaug BA, Olson TP, Lam CSP, et al. Global Cardiovascular Reserve Dysfunction in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol*. 2010; 56:845–854. [PubMed: 20813282]
50. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure with Preserved Ejection Fraction. *Circ Heart Fail*. 2010; 3:588–595. [PubMed: 20543134]
51. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation*. 2004; 110:558–565. [PubMed: 15277317]
52. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, Clinical Phenotype, and Outcomes Associated With Normal B-Type Natriuretic Peptide Levels in Heart Failure With Preserved Ejection Fraction. *Am J Cardiol*. 2012; 110:870–876. [PubMed: 22681864]

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Table 1

Baseline Characteristics of the Study Population

Characteristic	Spironolactone (n=42)	Placebo (n=38)	p-value
Age (years)	70 ± 1.1	72 ± 1.2	0.31
Women	34 (81%)	30 (79%)	0.83
African American	9 (21%)	14 (37%)	0.37
Body weight (kg)	85 ± 2.9	88 ± 3.4	0.57
Body surface area (m ²)	1.96 ± 0.04	1.99 ± 0.04	0.61
Body mass index (kg/m ²)	31.5 ± 0.8	32.4 ± 1.2	0.52
Body fat (%)	39 ± 1.1	39 ± 1.0	0.83
Left ventricular ejection fraction (%)	62.6 ± 1.1	62.0 ± 1.1	0.69
Sinus rhythm	39 (93%)	38 (100%)	0.54
New York Heart Association class			
II	12 (29%)	10 (26%)	0.30
III	27 (64%)	24 (63%)	0.31
History of pulmonary edema	5 (12%)	10 (26%)	0.10
Diabetes mellitus	7 (17%)	11 (29%)	0.19
History of hypertension	35 (83%)	35 (92%)	0.24
Systolic blood pressure (mmHg)	139 ± 2.7	143 ± 3.2	0.34
Diastolic blood pressure (mmHg)	78 ± 1.7	80 ± 1.5	0.43
Diastolic Function			
Normal	3 (8%)	1 (3%)	0.62
Delayed	31 (78%)	29 (78%)	1.0
Pseudonormal	6 (15%)	7 (19%)	0.76
Peak oxygen consumption (ml/kg/min)	13.5 ± 0.5	13.3 ± 0.5	0.76
Respiratory exchange ratio	1.11 ± 0.01	1.12 ± 0.02	0.67
Workload	63 ± 4.0	60 ± 4.2	0.51
Exercise time (min)	8.1 ± 0.5	7.9 ± 0.5	0.83
Current Medication			
Beta-blockers	13 (31%)	12 (32%)	0.95
CA channel blockers	15 (36%)	13 (34%)	0.89
Digoxin	1 (2%)	0 (0%)	0.35
Diuretics	31 (74%)	27 (71%)	0.79
Nitrates	3 (7%)	3 (8%)	0.90

Data are presented as mean ± SD or count (%).

* p<0.05,

+ p 0.01,

* p 0.001 spironolactone vs. placebo

Table 2

Exercise Performance, Quality of Life and Neurohormones

	Spironolactone			Placebo			P-value
	Baseline	4 mo.	Final	Baseline	4 mo.	Final	
Peak Exercise (Bike)							
VO ₂ (ml/min)	1141 ± 308	1146 ± 385	1167 ± 384	1152 ± 338	1180 ± 369	1202 ± 383	0.37
Indexed VO ₂ (ml/kg/min)	13.5 ± 2.9	13.6 ± 3.5	13.8 ± 3.2	13.3 ± 2.9	13.5 ± 3.4	13.9 ± 3.7	0.38
Time (min)	8.1 ± 3.0	8.5 ± 2.9	8.4 ± 3.1	7.9 ± 3.1	8.2 ± 3.1	8.3 ± 3.0	0.76
Workload (Watts)	63 ± 26	67 ± 26	68 ± 26	60 ± 26	64 ± 27	66 ± 25	0.85
Heart rate (bpm)	122 ± 23	121 ± 25	124 ± 27	119 ± 17	118 ± 20	118 ± 19	0.68
Systolic blood pressure (mmHg)	181 ± 25	169 ± 20	176 ± 22	185 ± 26	181 ± 26	183 ± 28	0.04
Diastolic blood pressure (mmHg)	83 ± 12	76 ± 9	78 ± 9	81 ± 9	80 ± 12	82 ± 10	<.001
Pulse pressure	98 ± 19	94 ± 15	98 ± 17	104 ± 21	101 ± 20	101 ± 23	0.62
Respiratory rate (bpm)	32 ± 7	32 ± 6	33 ± 7	35 ± 8	35 ± 6	35 ± 9	0.94
Oxygen pulse (ml/beat)	9.4 ± 2.1	9.5 ± 2.5	9.6 ± 3.0	9.8 ± 3.0	10.2 ± 3.5	10.4 ± 3.8	0.22
VC0 ₂ (ml/min)	1278 ± 394	1338 ± 471	1381 ± 485	1281 ± 402	1383 ± 454	1363 ± 423	0.81
VE (l/min)	41 ± 13	44 ± 17	46 ± 17	41 ± 12	43 ± 13	43 ± 13	0.40
RER	1.11 ± .10	1.16 ± .12	1.17 ± .12	1.12 ± .10	1.17 ± .09	1.15 ± .10	0.48
VE/VC0 ₂ slope	31 ± 6	31 ± 5	32 ± 7	31 ± 5	30 ± 4	30 ± 4	0.04
VAT (ml/min)	683 ± 167	703 ± 206	669 ± 162	719 ± 175	725 ± 205	708 ± 182	0.47
6 Minute walk (feet)	1377 ± 247	1508 ± 204	1430 ± 263	1361 ± 261	1419 ± 276	1426 ± 284	0.96
MLHFQ							
Emotional	5 ± 5	4 ± 4	4 ± 4	4 ± 4	4 ± 5	3 ± 4	0.60
Physical	16 ± 11	15 ± 10	14 ± 9	13 ± 10	14 ± 11	11 ± 9	0.88
Total	32 ± 21	29 ± 20	29 ± 18	28 ± 19	29 ± 23	25 ± 18	0.81
Neurohormones							
Aldosterone	9.1 ± 6.0	17.6 ± 9.1	17.2 ± 8.6	10.0 ± 9.0	10.1 ± 7.5	9.7 ± 5.3	<.0001
B-type natriuretic peptide	55 ± 46	55 ± 42	58 ± 44	61 ± 50	54 ± 38	55 ± 46	0.20

Data represent means ± SD; p-value represents comparison of least square means at combined follow-up visits following adjustment for baseline values, age and gender.

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Logarithmic transformation was used for non-normally distributed variables that were highly skewed.

Abbreviations: VO₂: oxygen consumption; VCO₂: carbon dioxide production; VE: minute ventilation; RER: respiratory exchange ratio; VAT: ventilatory anaerobic threshold; MLHFQ: Minnesota Living with Heart Failure Questionnaire;

Table 3**Doppler LV Diastolic Function**

	Spironolactone			Placebo			P-Value
	Baseline	4 mo.	Final	Baseline	4 mo.	Final	
Early mitral annulus velocity (lateral) (Ea: cm/s)	7.0 ± 2.1	7.0 ± 2.1	7.4 ± 2.2	6.8 ± 1.4	6.8 ± 1.4	6.6 ± 1.6	0.36
Early mitral annulus velocity (septal) (Ea: cm/s)	6.3 ± 1.2	5.9 ± 1.4	6.3 ± 1.6	6.2 ± 1.5	6.1 ± 1.1	6.0 ± 1.4	0.91
Early deceleration time (ms)	235 ± 57	242 ± 59	258 ± 76	240 ± 55	238 ± 55	249 ± 62	0.32
Early mitral flow velocity (E: cm/s)	80 ± 19	78 ± 21	78 ± 21	81 ± 22	83 ± 21	80 ± 22	0.45
Atrial mitral flow velocity (cm/s)	88 ± 20	87 ± 19	89 ± 19	90 ± 19	90 ± 18	89 ± 17	0.90
Early/Atrial mitral flow velocity ratio	.91 ± .2	.89 ± .2	.86 ± .2	.92 ± .3	.95 ± .3	.90 ± .3	0.16
E/Ea (lateral)	12.2 ± 4.5	12.1 ± 4.9	11.2 ± 4.6	12.5 ± 4.3	12.5 ± 3.7	12.6 ± 4.2	0.17
E/Ea (septal)	13.3 ± 4.2	14.0 ± 5.2	13.3 ± 5.6	13.9 ± 5.4	14.0 ± 4.5	13.8 ± 5.0	0.76

Data represent means ± SD; p-value represents comparison of least square means at final visit following adjustment for baseline values, age and gender.

Table 4

Left Ventricular and Arterial Function

	Spironolactone		Placebo		P-Value
	Baseline	Final	Baseline	Final	
Left Ventricular Function (CMRI)					
Mass (grams)	126 ± 45	124 ± 39	131 ± 34	129 ± 35	0.66
Mass/end diastolic volume ratio	1.8 ± 0.4	1.7 ± 0.4	1.7 ± 0.5	1.6 ± 0.4	0.23
End diastolic volume (ml)	73 ± 21	73 ± 20	78 ± 20	81 ± 22	0.15
End systolic volume (ml)	29 ± 10	28 ± 8	28 ± 7	29 ± 8	0.28
Stroke volume (ml)	45 ± 14	45 ± 15	50 ± 17	52 ± 18	0.14
Ejection fraction (%)	61 ± 7	62 ± 8	63 ± 8	64 ± 7	0.43
Aortic function (CMRI)					
Phasic area change (mm ²)	44 ± 28	59 ± 45	44 ± 31	54 ± 31	0.77
Distensibility (10 ⁻³ /mmHg)	0.88 ± .45	1.20 ± .86	0.82 ± .48	1.02 ± .67	0.39
Aortic compliance (mm ²)	0.72 ± .42	1.03 ± .95	0.73 ± .53	0.91 ± .71	0.54
Systolic blood pressure (mmHg)	139 ± 18	134 ± 15	141 ± 20	143 ± 19	0.05
Diastolic blood pressure (mmHg)	76 ± 11	74 ± 8	79 ± 10	80 ± 10	0.03
Pulse pressure (mmHg)	62 ± 12	60 ± 12	62 ± 16	63 ± 14	0.24
Pulse pressure/stroke volume	1.46 ± .43	1.44 ± .43	1.34 ± .48	1.29 ± .36	0.29
Arterial Function (Ultrasound)					
Carotid arterial compliance (10 ⁻³ /mmHg)	0.49 ± 0.05	0.44 ± 0.05	0.48 ± 0.06	0.47 ± 0.05	0.68
Carotid arterial distensibility (10 ⁻³ /mmHg)	1.81 ± 0.20	1.64 ± 0.19	1.80 ± 0.25	1.84 ± 0.18	0.45
Carotid-Femoral Pulse wave velocity (mm/sec)	1142 ± 118	1137 ± 123	1195 ± 68	1216 ± 142	0.68

Data represent means ± SD; p-value represents comparison of least square means at final visit following adjustment for baseline values, age and gender.

Abbreviations: CMRI= cardiac magnetic resonance imaging

Table 5

Summary of aldosterone antagonism in HFpEF

First Author/Trial (Ref.#)	Intervention	HFpEF Patient Type	Primary Endpoint	Trial Result
TOPCAT ³³	Spironolactone	50 ys (median 68.7 years), 3445 patients (52% female) with symptomatic HF. Patients had a h/o HF hospitalization within previous 12 months and elevated BNP within 60 days before randomization	CV death or aborted cardiac arrest, HF hospitalization	Neutral
Aldo-DHF ³²	Spironolactone	50 ys, 422 ambulatory patients/NYHA class II-III symptoms (mean age:67±8 years; 52% female), grade I DD and normal or near-normal BNP levels	Peak VO ₂ , change in E/e'	Neutral
RAAM-PEF ³¹	Eplerenone	Elderly 44 patients (mean age 71±10 years; 7% female) symptomatic NYHA class II/III, increased BNP within 60 days	6MWD	Neutral
Kosmala, et al ³⁷	Spironolactone	Elderly 150 patients (mean age 67 ± 9 years; 85% female), symptomatic NYHA class II/III, DD, and baseline increased exercise E/e' ratio	Peak VO ₂ and exertional E/e' ratio	Positive
Kitzman, et al (Current study)	Spironolactone	80, elderly (mean age:71±1 years), predominant female (80%) with compensated HF	Peak VO ₂ , 6 MWD and arterial function	Neutral

HFpEF = heart failure with preserved ejection fraction; CV=cardiovascular; HF=heart failure; DD=diastolic dysfunction; VO₂= oxygen consumption; MWD=minute walk distance; BNP=B-type natriuretic peptide; E= Mitral early diastolic velocity; e' =mitral annular velocity.