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Effect of Aldosterone Antagonism on Exercise Tolerance, Doppler Diastolic Function, and Quality of Life in Older Women With Diastolic Heart Failure

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Abstract

Optimal therapy for diastolic heart failure (DHF), the most common form of heart failure in older persons, is unclear. To determine the effect of aldosterone antagonism in DHF, we conducted an open-label preliminary trial of spironolactone 25mg/day in 11 women with DHF.

Cardiopulmonary exercise testing, Doppler-echocardiography, and a quality of life (QOL) survey were administered at baseline and after 4-months. Peak exercise VO_2 increased by 8.3% ($p=0.001$), the ratio of Doppler diastolic early filling velocity to mitral annulus velocity decreased by 25% ($p=0.02$), QOL score improved by 21% ($p=0.16$ for trend), and median NYHA class improved from class III to class II ($p=0.004$). Findings from this preliminary study confirm the role of aldosterone in the pathophysiology of DHF and suggest that aldosterone antagonism may benefit such patients. These hypotheses are currently being tested in two separated NIH-funded, randomized trials, the Spironolactone For Failure in the Elderly (SPIFFIE) and the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone antagonist (TOPCAT) trials.

INTRODUCTION

Heart failure is the most frequent cause of hospitalization and most costly medical illness in adults over 65 years of age.(1) Greater than 50% of patients in this age group develop heart failure symptoms in the presence of normal left ventricular systolic function, often termed diastolic heart failure (DHF).(2–4) Exercise intolerance is the hallmark symptom of chronic heart failure. Maximal oxygen consumption during exercise (VO_2) is an objective measure of exercise tolerance and has been shown to strongly correlate with survival rates and quality of life in heart failure patients with depressed left ventricular systolic function.(5;6) We have previously shown that elderly patients with DHF have markedly reduced exercise tolerance, measured by VO_2 , and to a similar extent as those with systolic heart failure.(7) Furthermore, measures of morbidity, including rehospitalization rates are similar when comparing the two heart failure groups.(8) Despite the increasing incidence and prevalence

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of this disorder, there have been relatively few studies testing the effects of specific pharmacologic agents for treating DHF.(9–12)

Several lines of evidence suggest that aldosterone may play a role in the pathophysiology of DHF. Similar to patients with systolic heart failure, patients with DHF have significant activation of the renin-angiotensin-aldosterone system.(7;13–17) Aldosterone is a major promoter of excess collagen deposition and fibrosis in the myocardium(18–20) and this is prevented by aldosterone antagonism with spironolactone in animal models.(21) Furthermore, in patients with systolic heart failure, spironolactone added to standard therapy, has been shown to improve exercise capacity,(22) and reduce symptoms, hospitalizations, and mortality.(23) These improvements appear to be related to reductions in myocardial fibrosis, a pathological characteristic that DHF appears to share with systolic heart failure.(24) Spironolactone may thus be a potential candidate for the treatment of DHF. Therefore, the purpose of this trial was to evaluate the potential effects of spironolactone on exercise tolerance, diastolic LV filling, and quality of life in older subjects with heart failure and a normal left ventricular ejection fraction.

METHODS

Study overview

This study was a single-center, prospective, open-label trial of spironolactone in addition to standard therapy for DHF. The study was approved by the Institutional Review Board and written informed consent was obtained from each participant. Outcome assessments were performed at baseline and at 4 months. Outcome measures included peak exercise oxygen consumption (VO_2), exercise ventilatory anaerobic threshold, six-minute walk distance, a quality of life questionnaire, New York Heart Association (NYHA) classification, and evaluation of left ventricular diastolic function by echocardiography.

Subjects

Eleven women aged ≥ 60 years of age with DHF were enrolled in the trial. All patients had at least one prior hospitalization for heart failure. As previously described,(25) isolated diastolic heart failure was defined as symptoms of heart failure with normal systolic function (LV ejection fraction $\geq 50\%$, no segmental wall motion abnormalities) and no evidence of significant coronary, valvular, infiltrative, or pericardial, or pulmonary disease(7;26). The clinical diagnosis of heart failure, based on criteria from Rich, *et al*, included a history of acute pulmonary edema, or the occurrence of at least 2 of the following with no other identifiable cause and with improvement following diuresis: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema, or exertional fatigue.(27) At the beginning of the study, patients had chronic, stable NYHA class II or III symptoms. Patients were excluded if they had a baseline serum potassium > 5.0 meq/L, or serum creatinine ≥ 2.5 mg/dl.

Exercise Performance

Exercise testing was performed with subjects in the upright position on an electronically braked bicycle with expired gas analysis and continuous electrocardiographic and blood pressure monitoring as previously described.(7;25;26) Expired gas analysis was carried out using a metabolic cart (CPX-2000 Medgraphics, Inc., Minneapolis, MN) which was calibrated with a standard gas of known concentration before each test. The initial workload was 12.5 watts for 2 minutes, followed by 25 watts for 3 minutes, and advanced thereafter by 25 watt increments in 3 minute stages. Metabolic gas exchanged was measured continuously during exercise and averaged over 15 second intervals. Peak values were averaged from the final 30 seconds of the exercise test. All exercise studies were presented

in a random, blinded fashion to an experienced observer for determination of ventilatory anaerobic threshold (VAT) using methods described previously.(7;25) The six minute walk test was performed as described by Guyatt et al.(28)

Echocardiography

Echo-Doppler examinations were performed as previously described using a Hewlett-Packard model Sonos 5500 ultrasound imaging system with a multiple frequency transducer. (7;29;30) Standard 2-Dimensional images were obtained in the parasternal long and short axes, and in the apical 4 and 2 chamber views. Pulsed-wave Doppler tracings of mitral valve inflow were recorded at the mitral leaflet tips.(7;29) Tissue Doppler tracings were obtained from the lateral mitral valve annulus.(31) Left ventricular size, wall thickness, volumes and Doppler tracings were analyzed using a commercially available, quantitative digital echocardiography workstation (ImageVue, Eastman Kodak, Rochester, NY).(7;29)

Quality of Life

At each visit, subjects completed the Minnesota Living with Heart Failure (MLHF) questionnaire.(32) The MLHF questionnaire assesses the patient's perception of the effect heart failure is having on the patient's life. Each of the 21 questions is rated from 0 to 5, resulting in a maximum possible score of 105. NYHA class was assessed by interview by a cardiologist at each visit.

Drug administration and follow-up

After completing the baseline assessments, open-label spironolactone therapy was initiated in addition to each subject's usual medications. The starting dose of spironolactone was 12.5 mg once daily in subjects with baseline creatinine ≥ 2.0 mg/dl or potassium > 4.5 meq/L; in all other subjects the starting dose was 25 mg once daily. One week after initiating treatment repeat creatinine and potassium levels were obtained. Among subjects who initiated therapy with the 12.5 mg dose, the dose was increased to 25 mg daily as long as the creatinine remains < 2.5 mg/dl and the potassium remains ≤ 5.0 meq/L. Spironolactone was discontinued in all patients with a 1-week creatinine ≥ 2.5 mg/dl or potassium ≥ 5.5 meq/L.

Data Analysis

For comparison of the means of repeated measures, paired Student's T-tests were used for data that conformed to a normal distribution and the Wilcoxon signed ranks test was used for non-parametric data. SPSS version 10.0 software was used for all statistical analyses. All reported p-values are 2-sided with $p \leq 0.05$ considered statistically significant.

RESULTS

Subjects (Table 1)

Mean age of the 11 subjects was 72 ± 8 year. There were 8 Caucasians and 3 African-Americans. Ten patients had a history of hypertension, 5 had a history of diabetes mellitus, 6 had hyperlipidemia, 5 had prior history of cigarette use (none current) and 2 had a history of prior myocardial infarction. Medications at baseline included ACE inhibitors or angiotensin II antagonists (9 subjects), beta-blockers (6 subjects), and diuretics (10 subjects) and were unchanged throughout the study. Patient weights did not change over the course of the study (89.3 ± 22.3 kg to 88.9 ± 21.7 kg, $p=0.38$).

Tolerability and Safety

One subject developed asymptomatic hyperkalemia (5.7 mEq/L) after one week of spironolactone with no other sequelae and by protocol was withdrawn from the study. The

remaining 10 subjects tolerated spironolactone well and there were no other side effects or adverse events reported. There were no heart failure exacerbations or hospitalizations during the study.

Consistent with previous studies of low dose spironolactone, serum potassium increased from 4.0 ± 0.4 to 4.4 ± 0.5 meq/L ($p=0.03$). Serum potassium exceeded 5.0 meq/L in 6/30 measurements in 5/11 subjects. There was a mild increase in blood urea nitrogen from 22.1 ± 4.6 to 25.8 ± 4.2 (p=0.04). Serum sodium (138 meq/L) and creatinine (1.3 mg/dl) were unchanged.

Exercise Performance

At baseline, the patients had severe exercise intolerance, with a mean peak exercise VO_2 of 1103 ± 272 ml/min. After 4 months of spironolactone, subjects experienced an 8.3% increase in peak exercise VO_2 to 1194 ± 274 ml/min ($p=0.001$). The peak exercise VO_2 , indexed for body weight increased from 12.8 ± 3.1 ml/kg/min to 13.6 ± 3.2 ml/kg/min ($p=0.004$). Exercise time increased 14% from 8.0 ± 3.2 to 9.1 ± 2.9 minutes ($p=0.027$, Table 2). Importantly, there was no difference in the respiratory exchange ratio, an objective measure used to determine maximal exertion. The ventilatory anaerobic threshold, a relatively effort independent measure of exercise performance, increased 21% from 599 ± 118 to 722 ± 113 ml/min ($p=0.015$). Six-minute walk distance did not change (1266 ± 345 to 1271 ± 310 , $p=0.496$).

Doppler-echocardiography (Table 3)

Peak early mitral annulus velocity (E') increased from 7.3 ± 1.9 to 8.3 ± 2.2 cm/s ($p=0.07$, Figure 1). Early mitral filling peak velocity (E) did not change significantly (73 ± 27 to 66 ± 23 cm/s, $p=0.36$). The E/E' ratio, a measure that is reflective of left atrial pressure and diastolic stiffness, decreased significantly from 10.8 ± 5.6 to 8.1 ± 1.5 ($p=0.020$). Late mitral annulus peak velocity (A') increased from 10.2 ± 3.0 to 11.2 ± 3.2 cm/s ($p=0.046$). LV posterior wall thickness tended to decrease (13.0 ± 3.3 to 11.9 ± 2.1 mm, $p=0.076$), while LV diastolic dimension was unchanged, suggesting improvement in concentric LV remodeling. Isovolumic relaxation time (IVRT) demonstrated a trend towards improvement, increasing from 69 ± 14 to 76 ± 12 ms ($p=0.063$).

Quality of Life (Table 4)

The total Minnesota Living with Heart Failure (MLHF) Questionnaire score improved 21%, from 38 ± 33 to 30 ± 26 , but this trend did not reach statistical significance ($p=0.16$). The emotional component (9 ± 6) showed a similar trend ($p=0.16$), and the improvement in the physical component (19 ± 13 to 17 ± 12) was not significant ($p=0.24$).

Symptoms

At baseline, 7 subjects had NYHA class III symptoms [III_m(4), III_s(3)], and 3 had class II symptoms [II_m(2), II_s(1)]. After 4 months of spironolactone therapy, all of the subjects improved by at least one-half of a NYHA functional class, from a median of III_m at baseline to II_m at follow up ($p=0.004$). All of the subjects with NYHA class III symptoms had improved to class II, and 2 of the subjects with class II symptoms had become asymptomatic (class I).

DISCUSSION

In this 4 month prospective trial of spironolactone added to usual therapy, treatment was associated with improvements in exercise capacity, echocardiographic measures of diastolic function, and NYHA class in older women with isolated DHF. Peak exercise oxygen

consumption and the anaerobic threshold, objective measures of exercise capacity that are also predictors of mortality in heart failure,(33;34) improved significantly. This was paralleled by improvements in heart failure symptoms as assessed by NYHA class. Minnesota Living with Heart Failure Questionnaire scores demonstrated a trend towards improvement in quality of life as well. A sub-diuretic dose of spironolactone was used, with no change in patient weight or blood pressure over the course of the study such that the observed improvements were not likely due to diuresis, but rather to improvement in the underlying pathophysiology. These findings are important because DHF is the most common form of heart failure among the older population, and exercise intolerance is the primary chronic symptom and primary determinant of poor quality of life in this disorder.

Along with improvements in exercise capacity and heart failure symptoms, diastolic filling of the left ventricle (LV) as assessed by Doppler echocardiography also improved. Tissue Doppler peak velocity of the mitral valve annulus during early diastole, E' (also called E_m , or E_a) declines with worsening diastolic function.(35) At baseline, the patients had Doppler indices of impaired relaxation and had an abnormally reduced E' . With treatment, multiple indices of diastolic function improved or tended to improve, including E' , isovolumic relaxation time, and the ratio E/E' , which is related to LV filling pressure.(31) This was accompanied by a strong trend toward reduced thickness of the posterior LV wall with maintenance of LV diastolic size, suggesting improvement in the concentric hypertrophic LV remodeling that appears characteristic of older patients with DHF.(7;26)

The results from the present study are supported by those of Mottram et al who conducted a placebo controlled study of 30 patients with hypertension, dyspnea on exertion, and delayed relaxation LV filling patterns by Doppler. Their data showed that strain rate and peak strain improved with spironolactone therapy.(36) Though the study by Mottram addressed an LV function outcome relevant to potential mechanisms of DHF, there have previously been no data assessing outcomes that directly impact patient well-being, such as exercise capacity and quality of life.

DHF is a major public health problem associated with substantial morbidity and mortality in older adults, yet treatment of this condition remains largely empiric due to the relative lack of large, randomized clinical outcomes trials.(37) While promising, these preliminary results regarding spironolactone, a generic aldosterone antagonist which has been in use for many years for other conditions, should be confirmed in larger, definitive randomized controlled trials.

In addition to the present study results, there are multiple lines of evidence to suggest the potential benefit from antagonism of aldosterone in patients with DHF.(38;39) We previously showed that exercise intolerance in DHF is related to increased LV diastolic stiffness, and this has been confirmed by several others.(40–43) Aldosterone is a potent promoter of myocardial hypertrophy and fibrosis, both of which are known to increase LV diastolic stiffness.(18–20;38;39;44–47) In the 4E study of patients with hypertension, eplerenone independently improved LV concentric remodeling.(48) Lopez et al showed that in hypertensive rats, spironolactone resulted in a histologically documented decrease in collagen volume in the myocardium and this was accompanied by improved LV concentric remodeling and diastolic stiffness.(49;50) Notably, the decline in collagen volume was highly correlated with a decrease in the circulating collagen type 1 c-terminal propeptide (CICP).(51;52) Ciciora et al reported that the strongest predictor of exercise intolerance in systolic heart failure was the degree of aldosterone “escape” during ACEI therapy.(53) Ciciora et al also showed that in patients with systolic heart failure, 12 month treatment with spironolactone resulted in significant improvements in exercise intolerance associated with improved LV remodeling and diastolic function.(54)

Furthermore, in 2 large trials in systolic heart failure patients, RALES and EPHESUS, aldosterone antagonism significantly reduced mortality.(23;55) In a subset analysis of the RALES trial, most of the survival improvement imparted by spironolactone appeared to occur in patients with the highest baseline concentrations of pro-collagen biomarkers of fibrosis, and these were reduced with chronic therapy.(24) Finally, prevention and even reversal of the sequence from aldosterone excess to myocardial fibrosis, LV remodeling, and increased LV diastolic stiffness by agents that antagonize aldosterone have now been documented in a number of animal models and in human cardiovascular diseases, including hypertension, hypertrophic cardiomyopathy, aortic stenosis, and the most stark example, Conn's syndrome (primary hyperaldosteronism).(18–20;24;38;47;52;56) All of these disorders share common features with the phenotype associated with DHF.

The dose of spironolactone and the safety monitoring protocol in the present study was identical to that used in the RALES trial, which was associated with very good tolerability and safety.(23) As in the present study, in RALES there was no evidence of diuretic effect from low dose spironolactone.(23) Further, as in the present study, in RALES most (95%) of patients were already taking angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers. Several studies indicate that long-term treatment with these agents may not completely block aldosterone or its adverse effects on LV and arterial function. (18;21;57;58)

This study has limitations inherent in the open-label, uncontrolled study design, including potential for participant and investigator bias. In order to minimize bias, assessments of exercise function, echocardiography, and quality of life were performed by personnel who were not involved with patient management, and they were not allowed to review baseline findings prior to completion of follow up visits. In addition, the ventilatory anaerobic threshold and echo-Doppler outcomes, both of which are effort-independent and cannot be altered volitionally by the patient, were analyzed in random, blinded, unpaired fashion by individuals unaware of patient identity or of whether they were viewing baseline or follow-up studies. Another important limitation is the small sample size, which raises the possibility that effects may be missed due to insufficient statistical power, or that effects could be magnified if there was a non-homogenous sample. However, even with the small sample size, improvements were observed in multiple, objective, clinically relevant outcomes. A final limitation is that, although we did not systematically exclude men during recruitment, all participants in this study were women. Thus, it is uncertain whether the study results apply to men with HFNEF. However, the present results should apply to the majority of persons with HFNEF since population-based studies have shown that approximately two-thirds or more of persons with this disorder are older women.(2;3)

These results should be viewed as preliminary, requiring verification by definitive randomized, controlled clinical trials. Indeed, the study results presented in this report served as the pilot data for a trial that was recently funded by the National Institute on Aging (project #R37-AG18915), and has the acronym SPIFFIE (Spironolactone For Failure In the Elderly). SPIFFIE is a randomized, placebo controlled, 9-month double-blinded trial of 25 mg spironolactone in 80 patients ≥ 60 years who have DHF. The primary outcomes are exercise tolerance measured as peak VO_2 during cardiopulmonary exercise testing and quality of life measured as the total score on the MLHF questionnaire. The study is also assessing potential mechanistic outcomes, including improvement in diastolic LV function by tissue Doppler, reversal of concentric hypertrophic LV remodeling measured by magnetic resonance imaging, and amelioration of myocardial fibrosis measured by circulating procollagen markers. In addition, a large, multi-center, international randomized, controlled trial of 30 mg/day spironolactone named TOPCAT (Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist) funded by the National

Heart, Lung, and Blood Institute has been launched. TOPCAT will enroll 4500 patients aged ≥ 50 yrs with heart failure and $EF > 45\%$ and follow them for an average of 3.25 years. The primary outcome of the trial is a composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure,

Conclusion

Although DHF is a common disorder among older Americans, therapy remains largely empiric. In this study, 4 months treatment with 25 mg per day of generic spironolactone was well tolerated and was associated with improvements in symptoms, exercise performance, echo-Doppler measures of diastolic function, and quality of life. These preliminary results lend support to the hypothesis that aldosterone may play a role in the pathophysiology of DHF. Two larger randomized clinical trials of aldosterone antagonism in DHF are currently underway in order to definitively test this hypothesis.

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References

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics - 2006 update - A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006; 113(6):E85–E151. [PubMed: 16407573]
2. Kitzman DW, Gardin JM, Gottdiener JS, Arnold AM, Boineau R, Aurigemma GP, et al. Importance of heart failure with preserved systolic function in patients ≥ 65 Years of Age. CHS Research Group. *Cardiovascular Health Study*. *Am J Cardiol*. 2001; 87(4):413–419. [PubMed: 11179524]
3. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. *Circulation*. 1998; 98(21):2282–2289. [PubMed: 9826315]
4. 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):1628–1637. [PubMed: 10807470]
5. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol*. 1987; 59:634–638. [PubMed: 3825904]
6. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991; 83:778–786. [PubMed: 1999029]
7. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA*. 2002; 288(17):2144–2150. [PubMed: 12413374]
8. 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(3):251–259. [PubMed: 16855265]
9. Redfield MM, Kitzman DW. Heart Failure: A rose by another name? *Congest Heart Fail*. 2006; 12(3):166–168. [PubMed: 16760703]
10. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure: The Ancillary Digitalis Investigation Group Trial. *Circulation*. 2006; 114(5):397–403. [PubMed: 16864724]
11. Flather MD, Shibata MC, Coats AJ, van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital

- admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005; 26(3):215–225. [PubMed: 15642700]
12. 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. *Lancet*. 2003; 362(9386):777–781. [PubMed: 13678871]
 13. Lang CC, Prasad N, McAlpine HM, Macleod C, Lipworth BJ, MacDonald TM, et al. Increased plasma levels of brain natriuretic peptide in patients with isolated diastolic dysfunction. *Am Heart J*. 1994; 127:1635–1636. [PubMed: 8197998]
 14. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. 2002; 105(5):595–601. [PubMed: 11827925]
 15. Clarkson PBM, Wheeldon NM, MacFadyen RJ, Pringle SD, MacDonald TM. Effects of brain natriuretic peptide on exercise hemodynamics and neurohormones in isolated diastolic heart failure. *Circulation*. 1996; 93:2037–2042. [PubMed: 8640980]
 16. Bettencourt P, Ferreira A, Dias P, Castro A, Martins L, Cerqueira-Gomes M. Evaluation of brain natriuretic peptide in the diagnosis of heart failure. *Cardiology*. 2000; 93(1–2):19–25. [PubMed: 10894902]
 17. Daniel KR, Brosnihan B, Fray B, Stewart KP, Kitzman DW. Renin-Angiotensin-Aldosterone System Activation in Diastolic Heart Failure: Comparison with Systolic Heart Failure and Age-Matched Normal Subjects. *J Am Coll Cardiol*. 2004; 45(3A):1017–167. 130A.
 18. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. *J Mol Cell Cardiol*. 1994; 26(7):809–820. [PubMed: 7966349]
 19. Weber KT, Janicki JS, Pick R, Capasso J, Anversa P. Myocardial fibrosis and pathologic hypertrophy in the rat with renovascular hypertension. *Am J Cardiol*. 1990; 65(14):1G–7G. [PubMed: 2294675]
 20. Robert V, Silvestre JS, Charlemagne D, Sabri A, Trouve P, Wassef M, et al. Biological determinants of aldosterone-induced cardiac fibrosis in rats. *Hypertension*. 1995; 26(6 Pt 1):971–978. [PubMed: 7490157]
 21. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol*. 1993; 25(5):563–575. [PubMed: 8377216]
 22. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *PG J Am Coll Cardiol*. 2002; 40(2):304–310.
 23. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999; 341(10):709–717. [PubMed: 10471456]
 24. Zannad F, Dousset B, Alla F. Treatment of congestive heart failure: interfering the aldosterone-cardiac extracellular matrix relationship. *Hypertension*. 2001; 38(5):1227–1232. [PubMed: 11711528]
 25. 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(7):905–909. [PubMed: 9781977]
 26. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, 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(3):796–802. [PubMed: 11527636]
 27. 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]
 28. Guyatt GH, Sullivan M, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, 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]

29. Gandhi SK, Powers JE, Fowle KM, Rankin KM, Nomeir AM, Kitzman DW, et al. The Pathogenesis of Acute Pulmonary Edema Associated with Hypertension. *N Engl J Med.* 2000; 344(1):17–22. [PubMed: 11136955]
30. 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]
31. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol.* 1997; 30(6):1527–1533. [PubMed: 9362412]
32. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure: content, reliability and validity of a new measure—the Minnesota Living with Heart Failure questionnaire. *Heart Failure.* 1987; 3:198–209.
33. Francis DP, Shamin W, Davies LC, Piepoli M, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO₂ slope and peak VO₂. *Eur Heart J.* 2000; 21:154–161. [PubMed: 10637089]
34. Bol E, de Vries WR, Mosterd WL, Wielenga RP, Coats A. Cardiopulmonary exercise parameters in relation to all-cause mortality in patients with chronic heart failure. *Int J Cardiol.* 2000; 72:255–263. [PubMed: 10716136]
35. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation.* 2002; 105(11):1387–1393. [PubMed: 11901053]
36. 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(5):558–565. [PubMed: 15277317]
37. Kitzman DW. Therapy for diastolic heart failure: on the road from myths to multicenter trials. *J Card Fail.* 2001; 7(3):229–231. [PubMed: 11561222]
38. Rajagopalan S, Pitt B. Aldosterone as a target in congestive heart failure. *Med Clin North Am.* 2003; 87(2):441–457. [PubMed: 12693733]
39. Pitt B, Stier CT Jr, Rajagopalan S. Mineralocorticoid receptor blockade: new insights into the mechanism of action in patients with cardiovascular disease. *J Renin Angiotensin Aldosterone Syst.* 2003; 4(3):164–168. [PubMed: 14608520]
40. 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]
41. Bonow RO. Determinants of exercise capacity in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1992; 19:513–515. [PubMed: 1538002]
42. Lele SS, Thomson HL, Seo H, Belenkie I, McKenna WJ, Frenneaux MP. Exercise capacity in hypertrophic cardiomyopathy. Role of stroke volume limitation, heart rate, and diastolic filling characteristics. *Circulation.* 1995; 92(10):2886–2894. [PubMed: 7586256]
43. Briguori C, Betocchi S, Romano M, Manganelli F, Angela LM, Ciampi Q, et al. Exercise capacity in hypertrophic cardiomyopathy depends on left ventricular diastolic function. *Am J Cardiol.* 1999; 84(3):309–315. [PubMed: 10496441]
44. Weber KT. Cardiac interstitium in health and disease: the fibrillar collagen network. *J Am Coll Cardiol.* 1989; 13:1637–1652. [PubMed: 2656824]
45. Gonzalez A, Lopez B, Diez J. Fibrosis in hypertensive heart disease: role of the renin-angiotensin-aldosterone system. *Med Clin North Am.* 2004; 88(1):83–97. [PubMed: 14871052]
46. Burlew BS, Weber KT. Cardiac fibrosis as a cause of diastolic dysfunction. *Herz.* 2002; 27(2):92–98. [PubMed: 12025467]
47. Suzuki G, Morita H, Mishima T, Sharov VG, Todor A, Tanhehco EJ, et al. Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodeling in dogs with heart failure. *Circulation.* 2002; 106(23):2967–2972. [PubMed: 12460880]

48. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation*. 2003; 108(15):1831–1838. [PubMed: 14517164]
49. Lopez B, Gonzalez A, Varo N, Laviades C, Querejeta R, Diez J. Biochemical assessment of myocardial fibrosis in hypertensive heart disease. *Hypertension*. 2001; 38(5):1222–1226. [PubMed: 11711527]
50. Querejeta R, Varo N, Lopez B, Larman M, Artinano E, Etayo JC, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation*. 2000; 101(14):1729–1735. [PubMed: 10758057]
51. Poulsen SH, Host NB, Egstrup K. Long-term changes in collagen formation expressed by serum carboxyterminal propeptide of type-I procollagen and relation to left ventricular function after acute myocardial infarction. *Cardiology*. 2001; 96(1):45–50. [PubMed: 11701940]
52. Lopez B, Gonzalez A, Varo N, Laviades C, Querejeta R, Diez J. Biochemical assessment of myocardial fibrosis in hypertensive heart disease. *Hypertension*. 2001; 38(5):1222–1226. [PubMed: 11711527]
53. Ciccoira M, Zanolla L, Franceschini L, Rossi A, Golia G, Zeni P, et al. Relation of aldosterone "escape" despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2002; 89(4):403–407. [PubMed: 11835920]
54. Ciccoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 2002; 40(2):304–310. [PubMed: 12106936]
55. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003; 348(14):1309–1321. [PubMed: 12668699]
56. Stowasser M. New perspectives on the role of aldosterone excess in cardiovascular disease. *Clin Exp Pharmacol Physiol*. 2001; 28(10):783–791. [PubMed: 11553016]
57. Cleland JG, Dargie HJ, Hodsman GP, Ball SG, Robertson JL, Morton JJ, et al. Captopril in heart failure. A double blind controlled trial. *Br Heart J*. 1984; 52(5):530–535. [PubMed: 6388612]
58. Staessen J, Lijnen P, Fagard R, Verschueren LJ, Amery A. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol*. 1981; 91(3):457–465. [PubMed: 7035596]

Figure 1. Tissue Doppler images from a representative patient demonstrating the motion of the mitral annulus in diastole. E' is the early mitral annulus motion and A' is the late annulus motion. Notice the improvement (increase) in E' after treatment with spironolactone.

Table I

Baseline Characteristics

Demographics	
Age (years)	72 ± 8
Race (Caucasian)	8 (73)
Hypertension (%)	10 (91)
Systolic BP (mmHg)	138 ± 6
Diastolic BP (mmHg)	82 ± 3
Diabetes Mellitus (%)	5 (45)
Hyperlipidemia (%)	6 (55)
Smoking (%)	5 (45)
Previous MI (%)	2 (18)
Medications	
ACE/ARB (%)	9 (82)
Beta Blocker (%)	6 (55)
Diuretic (%)	10 (91)

Blood pressure was from supine rest. Values are mean±SD or count (%).

Table II

Cardiopulmonary Exercise Function

Variable	Baseline	4 Months	p-value
Peak Bike	Mean $\pm$ SD	Mean $\pm$ SD	
VO ₂ (ml/min) *	1103 $\pm$ 272	1194 $\pm$ 275	<0.001
Indexed VO ₂ (ml/min/kg) *	12.8 $\pm$ 3.1	13.6 $\pm$ 3.2	<0.01
AT (ml/min*kg) *	7.1 $\pm$ 0.7	8.6 $\pm$ 1.6	<0.01
VCO ₂ (ml/min) *	1226 $\pm$ 350	1340 $\pm$ 364	<0.01
VE (l/min)	41.8 $\pm$ 10.0	46.1 $\pm$ 12.0	0.09
RER	1.12 $\pm$ 0.11	1.15 $\pm$ 0.10	0.18
Exercise Time (min) *	8.0 $\pm$ 3.2	9.1 $\pm$ 2.9	0.03
Workload (Watts)	57 $\pm$ 24	64 $\pm$ 26	0.07
Heart Rate (beats/min)	128 $\pm$ 23	136 $\pm$ 14	0.24
Systolic BP (mmHg)	190 $\pm$ 26	183 $\pm$ 14	0.27
Diastolic BP (mmHg)	84 $\pm$ 8	87 $\pm$ 20	0.48
Respiratory rate (min ⁻¹)	36 $\pm$ 9	38 $\pm$ 6	0.51
Oxygen pulse (ml/beat)	9.0 $\pm$ 3.3	8.8 $\pm$ 2.2	0.78
6 minute walk (feet)	1267 $\pm$ 345	1272 $\pm$ 310	0.68

Cardiopulmonary exercise testing results at baseline and after four months of treatment with spironolactone.

*
p<0.05;

VO₂: peak oxygen consumption, AT: oxygen consumption at the ventilatory anaerobic threshold, VCO₂: carbon dioxide production, VE: minute ventilation, RER: respiratory exchange ratio. Blood pressure values were recorded at maximal exercise workload.

Table III**Echo-Doppler Left Ventricular Function**

Variable	Baseline Mean $\pm$ SD	4 Month Mean $\pm$ SD	p-value
LVID-D (mm)	41 $\pm$ 5	40 $\pm$ 4	0.97
LVID-S (mm)	24 $\pm$ 7	26 $\pm$ 6	0.57
Fractional shortening	41 $\pm$ 13	39 $\pm$ 12	0.60
IVS (mm)	12.9 $\pm$ 4.0	12.8 $\pm$ 3.3	0.83
Posterior wall (mm)	13.0 $\pm$ 3.3	11.9 $\pm$ 2.1	0.08
E wave velocity (cm/s)	73 $\pm$ 27	66 $\pm$ 23	0.36
A wave velocity(cm/s)	77 $\pm$ 18	79 $\pm$ 19	0.30
E deceleration time (ms)	219 $\pm$ 68	226 $\pm$ 64	0.77
E deceleration rate (cm/s ²)	369 $\pm$ 257	299 $\pm$ 109	0.32
E/A ratio	0.95 $\pm$ 0.53	0.71 $\pm$ 0.16	0.52
IVRT (ms)	69 $\pm$ 14	76 $\pm$ 12	0.06
Diastolic filling period (ms)	400 $\pm$ 89	388 $\pm$ 102	0.69
S' (cm/s)	7.6 $\pm$ 2.0	7.9 $\pm$ 1.6	0.63
E' (cm/s)	7.3 $\pm$ 1.9	8.3 $\pm$ 2.2	0.07
A' (cm/s)*	10.2 $\pm$ 3.0	11.2 $\pm$ 3.2	0.04
E/E'*	10.8 $\pm$ 5.6	8.1 $\pm$ 1.5	0.02

Echo-Doppler measurements at baseline and after four months of treatment with spironolactone.

* p<0.05;

LVID-D: Left ventricular internal diameter at end-diastole; LVID-S: Left ventricular internal diameter at end-systole; IVS: Interventricular septum; IVRT: Isovolumic relaxation time.

Table IV

Quality of Life

Variable	Baseline Mean $\pm$ SD	4 Month Mean $\pm$ SD	p-value
MLWHF Questionnaire	38 $\pm$ 33	30 $\pm$ 26	0.16
Physical Component	19 $\pm$ 13	17 $\pm$ 12	0.24
Emotional Component	9 $\pm$ 10	6 $\pm$ 7	0.16
NYHA class (group median)	III _m	II _m	0.004
I (# of pts)	0	2	
II _m	2	4	
II _s	1	4	
III _m	4	0	
III _s	3	0	
IV	0	0	

Quality of Life scores by the Minnesota Living with Heart Failure Questionnaire (MLWHF) and functional class by the modified New York Heart Association (NYHA) scale.