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Impact of Spironolactone on Vascular, Myocardial and Functional Parameters in Untreated Patients with a Hypertensive Response to Exercise.

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ABSTRACT

Background: A hypertensive response to exercise (HRE) is associated with cardiac risk and masked hypertension (MHT), but the mechanisms of a HRE and treatment recommendations remain unclear. This study investigated spironolactone as a treatment for abnormal vascular and myocardial stiffness in patients with a HRE.

Methods: This was a randomized, double-blind, placebo-controlled study of 115 patients (54±9 years, 57% men) with a HRE (≥210/105mmHg in men; ≥190/105mmHg in women) but no prior history of hypertension or myocardial ischemia. MHT prevalence was 40%. Patients were randomized to spironolactone 25mg daily (n=58) or placebo (n=57) and underwent evaluation at baseline and 3 months with exercise echocardiography, $VO_{2max,}$ aortic stiffness, exercise and central blood pressure (BP), and 24-hour ambulatory BP. Changes in left ventricular mass index (LVMI), Doppler-derived E/e_m ratio (LV filling pressure) and myocardial strain were assessed.

Results: Baseline 24-hour systolic BP (SBP) was 133±10mmHg and peak-exercise SBP was 219±16mmHg. Peak systolic strain (0.3±3.6% vs -0.1±3.2, p=0.56), E/e_m (-1.1±2.3 vs -0.6±1.7, p=0.30), exercise E/e_m (-0.3±2.4 vs 0.8±2.8, p=0.06) or VO_{2max} (0.4±4.9 vs -0.9±4.1 ml/kg/min, p=0.15) did not significantly change with treatment, despite reduction in exercise SBP, 24-hour SBP, aortic stiffness and LVMI. However, patients with higher LVMI significantly increased VO_{2max} (1.1±5.6 vs -2.4±4.4 ml/kg/min, $p<0.05$) and reduced exercise E/e_m (-0.7±2.7 vs 1.9±2.8, $p<0.05$).

Conclusions: In HRE patients without a previous diagnosis of hypertension, short-term spironolactone reduced exercise BP, 24hr ambulatory BP and LVMI, but did not significantly alter exercise capacity, myocardial strain or E/e_m. Larger studies are required to confirm these findings.

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INTRODUCTION

The presence of a hypertensive response to exercise (HRE) has been associated with the future onset of hypertension,[1,2] cardiovascular events and mortality.[3-5] Furthermore, in hypertensive patients, a HRE is associated with decreased exercise tolerance and diastolic dysfunction, while subtle systolic dysfunction has been demonstrated in HRE patients without documented hypertension.[6] We have previously published cross sectional data demonstrating a high prevalence of masked hypertension (MHT), together with increased left ventricular (LV) mass, in patients with a HRE.[7] Very few therapeutic trials have been conducted in patients with HRE and current hypertension management guidelines do not make specific treatment recommendations regarding exercise-induced hypertension or indeed MHT[8].

Although the mechanism of a HRE is incompletely understood, disordered ventricular-vascular coupling may play an important role, with increased arterial stiffness and central vascular loading contributing to the development of early hypertensive heart disease and subsequent functional impairment.[9,10] Aldosterone has been implicated as an important mediator of dynamic myocardial and vascular fibrosis, and there is evidence that aldosterone antagonism may have beneficial effects as a treatment for hypertensive heart disease.[11,12] Exercise blood pressure (BP) independently correlates with measures of inappropriate serum aldosterone activity[13] and in animal studies, short-term spironolactone has been shown to markedly reduce aortic fibrosis.[14] In this randomized, double-blind clinical study, we investigated the role of aldosterone antagonism with spironolactone in HRE patients. We hypothesized that treatment with spironolactone would be associated with improvement in markers of myocardial and vascular function as well as exercise capacity.

METHODS

Patient selection. Patients with no prior clinical diagnosis of hypertension but who were noted to have a HRE on treadmill testing were eligible for this study. A HRE was defined as a peak systolic (SBP) and/or diastolic BP (DBP) ≥210/110 mmHg for men, ≥190/105 mmHg for women.[15] Patients were excluded if they were >70 years of age, had a history of known coronary artery disease or had evidence of renal dysfunction (serum creatinine >180 μmol/L). Patients were also excluded if they were receiving anti-hypertensive medication, had a history of gynecomastia, required regular non-steroidal inflammatory medication, or were pregnant. Patients were identified from hospital and community cardiology clinic stress testing records between 2004 and 2008 and then retested for assessment of suitability. These were patients who were referred initially for conventional treadmill screening for ischemic heart disease, with negative results. Baseline data on MHT derived from this study has been previously published.[7] The local institutional ethics committee approved the study and informed consent was obtained.

Study design. Eligible patients were examined at baseline with cardiopulmonary testing, comprehensive assessment of peripheral and central hemodynamics, echocardiographic assessment of myocardial function, and biochemistry. Participants were then randomized to spironolactone 25mg daily or matching placebo for 3 months, after which all testing was repeated. Treatment was independently randomized by the pharmacy trials department with both patients and investigators blinded to treatment allocation.

Echocardiography. Conventional two-dimensional echocardiography at rest was performed at baseline and at the end of three months. Evaluation of LV volumes and ejection fraction (EF) was performed using the Simpson's biplane method. LV mass index (LVMI) was assessed

according to the method of Devereux and indexed to body surface area, with LV hypertrophy (LVH) categorized according to American Society of Echocardiography guidelines.[16] Diastolic function was assessed using Doppler interrogation of the early (E wave) and late (A wave) diastolic filling profile across the mitral valve. Pulsed-wave tissue Doppler was used to measure the early diastolic relaxation velocity (Em) at the septal mitral annulus. The E/e_m ratio was used as validated estimate of LV filling pressure at rest and after maximal exercise.[17] Myocardial tissue deformation was assessed off-line with Doppler measurement of peak longitudinal strain and strain rate (SR) using specialized software (Echopac BT 2008, GE Medical Systems). The instantaneous difference between velocities within a 11mm region of interest were used to calculate SR and strain. Results are reported as the average of 6 basal segments from 3 standard apical views. All repeated measures were made with the observer blinded to previous results.

Cardiopulmonary Testing. Exercise capacity was assessed at baseline and after three months of treatment with spironolactone. Patients underwent a maximal (symptom-limited) graded treadmill stress test with assessment of peak oxygen consumption (VO_{2max}) at exhaustion by indirect calorimetry (Vmax29c, Sensormedics, Yorba Linda, CA). Regular assessment of BP every one to two minutes with electrocardiographic monitoring was performed (CASE 14, General Electric Medical Systems, Milwaukee, WI). Careful attention was paid to assessing the peak BP at the moment of maximal exhaustion. To exclude the presence of inducible ischemia, stress echocardiography was performed in all patients immediately post-exercise (Vivid 7, General Electric Medical Systems, Milwaukee, WI).

Blood pressure and vascular stiffness. Brachial BP was assessed by mercury sphygmomanometer after at least 5 minutes rest in the supine position. The average of two readings were used for analysis as per recommendations.[18] Supine central BP was estimated by

radial applanation tonometry and customized software (SphygmoCor 7.1, AtCor Medical, Sydney, NSW) incorporating a generalized transfer function that we have previously shown to be valid and reproducible.[19,20] The radial waveform was calibrated using brachial BP. Ambulatory BP monitoring was performed over 24 hours (TM2430, A&D Mercury, A&D Medical, Thebarton, South Australia) with measures recorded each 30 minutes during the day (6am to 10pm) and each 60 minutes over night (10pm to 6am). The 24-hour mean arterial pressure (MAP) was calculated as (2*DBP+SBP)/3, and the pulse pressure (PP) calculated as the difference between SBP and DBP. Aortic stiffness was determined using ECG-gated pulse wave velocity (PWV) from the carotid to femoral arteries (using SphygmoCor 7.1 apparatus) as per recommendations.[21] The presence of MHT was defined by a resting brachial BP <140/90 mmHg and daytime ambulatory BP ≥135/85 mmHg[22]

Biochemistry. Patients underwent biochemical assessment at baseline and at the end of 3 months. Parameters assessed included fasting glucose, glycosylated hemoglobin (HbA_{1c}), fasting lipids, electrolytes, serum urea and creatinine (repeated at weeks 2 and 6).

Statistical analysis. The study was powered to show a reduction in strain markers, which have been shown to correlate with markers of fibrosis.[23-25] In a previous study of aldosterone blockade, we saw a 30% improvement in strain and an 18% improvement in SR.[7] We planned to recruit 60 patients/group in order to have 80% power to show a significant difference (p=0.05) at the end of follow-up, assuming a treatment effect of 18%.

Measures of grouped data are reported as mean±SD. Patients lost to follow-up with missing data had their last measure (baseline) carried forward to their final visit (n=6). The Shapiro-Wilk test was used to test normality of data distribution. Analysis of differences between groups was performed using *t*-tests and analysis of variance (ANOVA), with the Mann-Whitney U Test used

for non-normally distributed data. Levene's test of equality of variance was performed before all *t*-tests. Analysis of covariance (ANCOVA) was used to assess influence of covariates. Chi-squared tests were used for categorical comparisons. Statistical significance was defined as $p<.05$. Analysis was performed using standard statistical software (SPSS 17, SPSS Inc., Chicago, IL).

RESULTS

Baseline patient characteristics. Flow of participants through the study is shown in Figure 1. After completing baseline assessment, 6 patients (4 in placebo, 2 in spironolactone arm) were lost to follow-up. These patients were included in the final analysis (baseline measure carried forward). The baseline characteristics of the study population are shown in Table 1. Despite no previously documented history of hypertension, at baseline retesting the prevalence of hypertension (defined by resting brachial BP ≥140/90mmHg) was found to be 22% (n=24). The prevalence of MHT in all subjects was 40%. There was a non-significant trend to higher exercise BP in the spironolactone group and to higher smoking prevalence in the placebo group. Those patients with MHT had significantly higher LVMI (96±19 g/m^2 vs 81±18 g/m^2, p=0.001) and a higher peak exercise SBP (223±17mmHg vs 212±13mmHg, p=0.003) and peak exercise DBP (96±13mmHg vs 89±11mmHg, p=.006), compared to those with no hypertension. There was no inducible myocardial ischemia in accordance with the selection criteria. There were no significant baseline differences between randomization groups.

Myocardial and vascular effects of spironolactone. The primary endpoint of the trial - peak systolic strain (p=0.56), and the secondary endpoints E/e_m and exercise E/e_m, were not significantly reduced by treatment with spironolactone (Table 2), although there was a trend to reduced exercise E/e_m (p=0.06). Although there was no statistically difference in baseline

smoking history, the difference in exercise E/e_m was significant after adjustment for the lower prevalence of smoking in the spironolactone group (p=0.012). Aortic PWV (a measure of arterial stiffness) was reduced, with this difference still borderline significant after adjustment for 24-hour MAP (p=0.05), but not when adjusted for change in 24-hour ambulatory SBP (p=0.08). Sample size may not have been sufficient to detect a significant difference.

LVMI was significantly reduced by treatment with spironolactone, with this difference persisting after accounting for changes in peak exercise BP, rest peripheral and central BP and 24-hour ambulatory SBP, MAP and PP (p=0.013). There was no significant relationship between change in LVMI and quantitative BP parameters. There was a significantly higher prevalence of LVH in the placebo group at follow-up. Although there was a trend to higher baseline prevalence of LVH, the placebo group increased LVH prevalence from 22 to 30% with no change in prevalence within the spironolactone group. There was no significant effect of spironolactone upon exercise capacity as assessed by VO_{2max} (p=0.15) (Table 2).

Effects of spironolactone in patients with masked hypertension.

In those patients with MHT at baseline who were treated with spironolactone, compared with placebo, there were significant differences in regards to change in exercise BP (-10.0±12.9mmHg vs 0.3±8.7mmHg, p<0.01) and 24hr ambulatory PP (-2.4±4.7mmHg vs 2.1±8.4mmHg, <0.05) and a trend to reduced LVMI (-8.3±17.4g/m^2 vs 1.5±16.6g/m^2, p=0.07), but no significant differences in regards to any other vascular, myocardial markers or exercise capacity. There was no difference in the prevalence of MHT between the treatment and control groups at 3 months and no difference in change within individuals in regards to MHT status (MHT status between treatment and placebo group was resolved in 21% vs 18%, newly present

in 15% vs 15% and unchanged in 67% vs 62% , p=0.84). However, caution must be taken in interpretation of these sub-group analyses due to the limited sample size.

Effects of spironolactone according to LVMI. In a post hoc analysis of the overall population, patients in the highest tertile of LVMI (mean 110±10 g/m^2) showed that exercise E/e_m (but not resting E/e_m) decreased with spironolactone and increased in the placebo group, with this difference significant between the treatment groups (-0.7±2.7 versus 1.9±2.8, p<0.05) (Figure 2). This difference was independent of changes in resting and exercise BP, change in LVMI, or the presence of MHT at baseline (p<0.03). Furthermore, in the higher LVMI tertile, VO_2max increased in those randomized to spironolactone and decreased in the placebo group, with this difference significant between the treatment groups (1.1±5.6 versus -2.4±4.4, p<0.05). This difference in exercise capacity was independent of change in 24-hour ambulatory SBP and MAP (p<0.05), but not 24-hour PP (p=0.07), exercise SBP (p=0.15) or the presence of MHT at baseline (p=0.058).

Safety. Treatment with spironolactone was well tolerated with no hyperkalemia or adverse renal effects (see online Supplementary Data for details). There were no significant differences between groups in regards to serum potassium (p=0.50), urea (p=0.25) or creatinine (p=0.82). In the placebo group, one patient complained of self-limiting mastalgia and one was withdrawn following an admission with acute nephritis in the setting of a recent gastrointestinal illness.

DISCUSSION

This study showed that in patients with a HRE, short-term treatment with spironolactone did not significantly improve exercise capacity or myocardial markers such as strain or E/e_m. As expected, spironolactone reduced 24hr SBP. Furthermore, spironolactone improved aortic

stiffness (but not independent of 24hr SBP), exercise BP, and LVMI (the latter independent of change in BP), but did not influence prevalence of MHT. Interestingly, after adjustment for non-significant differences in baseline smoking status, exercise E/e_m was significantly reduced in the spironolactone group, suggesting a beneficial effect on LV filling pressure with exercise concomitant with the hemodynamic effects of reduced exercise BP.

Significance of a hypertensive response to exercise. HRE is often considered an incidental finding during exercise testing. However, it may be important as a correlate of markers of adverse cardiac risk, including increased mortality and cardiovascular events.[3,5,26]. Furthermore, we have previously shown a high prevalence of MHT in this population, with this factor being one of the strongest predictors of LVMI. Importantly, treatment recommendations of both exercise hypertension and MHT are inadequately addressed in current guidelines. An exaggerated BP response has also been associated with reduced exercise capacity in patients with subtle systolic and/or diastolic myocardial dysfunction. [6,10,27] From a therapeutic standpoint, the treatment of HRE without resting hypertension may be considered to avoid LVH, an established prognostic marker that is independent and incremental to clinical evaluation.

Mechanisms of a HRE. The potential mechanisms by which an exaggerated BP response to exercise occurs are many and remain to be fully elucidated. It seems likely that increased vascular/myocardial stiffness and abnormal vascular reactivity are important factors. Increased systolic loading is associated with delayed LV relaxation and subsequent elevation in LV filling pressures, which may in turn limit exercise capacity.[10] LV hypertrophy is a common correlate of impaired myocardial relaxation (due to a combination of myocyte hypertrophy and increased interstitial fibrosis), and is now included as a criteria used in the diagnosis of diastolic heart failure. Patients with diastolic heart failure have both an exaggerated exercise SBP response and

reduced exercise capacity.[27] In the current study, LV filling pressure (E/e_m) and central pulse pressure (closely related to aortic stiffness)[32] were independent correlates of exercise capacity, supporting the association of a HRE with both disordered ventricular and vascular function.

Spironolactone as a treatment for hypertensive heart disease. Aldosterone has been implicated as a mediator of end-organ damage in hypertensive heart disease, probably by both BP-dependent and independent effects. Extra-renal effects of aldosterone include development of fibrosis and inflammation in the myocardium and vasculature.[33] Treatment with spironolactone has been demonstrated to result in BP-independent reductions in aortic stiffness and fibrosis.[14,34] Myocardial strain has been shown to correlate with serum markers of collagen turnover and myocardial fibrosis.[23-25] In previous work by our group looking at hypertensive patients with diastolic heart failure, we showed that spironolactone had beneficial effects on strain, independent of BP.[11] These observations support the hypothesis that treatment of patients with early hypertensive heart disease with an aldosterone antagonist may improve disordered vascular and myocardial structure and function with subsequent improvements in exercise capacity. In our study, patients with higher LVMI who received spironolactone had associated improvements in exercise capacity, suggesting that LVMI may identify a group of patients with more advanced disease who may benefit from aldosterone blockade. These findings are consistent with those by Warner et al, who showed that losartan improved exercise BP and exercise duration in a small study of 20 patients with HRE and diastolic dysfunction. [10] The higher tertile of LVMI in our study had a range of 96-139 g/m^2. Interestingly, the threshold for a diagnosis of LVH also starts for women at $96g/m^2$.[16] The results of this study suggest a potential sub-group of patients that may benefit from treatment with spironolactone may be those with an HRE who have evidence of LV hypertrophy or a higher LVMI identified by a LVMI $>95g/m^2$.

Limitations. The patients in this study population were relatively healthy: the potential benefit of spironolactone may have been more evident with more advanced disease. Furthermore, patients received spironolactone 25mg for only 3 months, and benefits (and/or adverse effects) may have been more apparent with longer duration of therapy and/or higher dose. The study population is selected, comprising patients referred for treadmill screening to rule out ischemia: these results may not apply to different populations. Nevertheless, the finding of a HRE is most commonly uncovered in this clinical setting. Finally, the sample size is below that calculated by our power analysis and that this may limit our conclusions of the neutral overall treatment effect of the intervention on the primary outcome. However, given that the sample size is only slightly below that estimated, it seems unlikely that a clinically significant effect was missed.

CONCLUSIONS

Myocardial and vascular fibrosis with disordered ventricular-vascular interaction is a potential mechanistic link between a HRE, impaired exercise capacity and adverse clinical outcome. Aldosterone has been implicated in the development of fibrosis, making antagonism of this hormone an attractive therapeutic target for patients with a HRE. This study showed that short-term treatment with spironolactone did not significantly impact sensitive markers of myocardial function (strain) or non-invasive measures of LV filling pressure. There were significant improvements in maximal exercise and ambulatory BP and LVMI, but no change in the prevalence of MHT. Future larger studies with longer duration and/or higher dose of spironolactone therapy are necessary to clarify the potential benefits of this treatment in patients with hypertensive heart disease.

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Disclosure: There are no conflicts of interest.

Ethics approval: This study was approved by the Princess Alexandra Hospital Human Research Ethics Committee, Queensland, Australia.

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Figure Titles:

Figure 1: Flow of participants through study. HRE, hypertensive response to exercise.

Figure 2: Change in peak exercise E/e_m ratio (filling pressure at peak exercise) (A) and change in exercise capacity (VO_{2max}) (B) according to tertiles of baseline LVMI and treatment group. LVMI, left ventricular mass index; VO_{2max}, maximal oxygen consumption.

Table 1

Table 1. Baseline characteristics.

	Overall (n=110)	Placebo (n=52)	Spironolactone (n=58)	p-value
Clinical				
Age (years)	54±9	55±8	54±9	0.54
Sex (% male)	56%	56%	57%	0.91
BMI (kg/m^2)	29±5	29±4	30±5	0.27
Type 2 diabetes mellitus (%)	13%	8%	18%	0.12
Smoker (%)	6%	10%	2%	0.08
Hemodynamic				
Office SBP (mmHg)	130±14	130±14	129±14	0.72
Office DBP (mmHg)	76±9	75±8	77±11	0.32
ABPM 24hr SBP (mmHg)	133±10	132±10	133±10	0.48
ABPM 24hr DBP (mmHg)	80±7	80±7	80±8	0.94
ABPM 24hr MAP (mmHg)	97±8	97±7	98±8	0.72
ABPM 24hr PP (mmHg)	53±7	53±7	54±7	0.34
ABPM Day SBP (mmHg)	136±11	136±11	137±11	0.64
ABPM Day DBP (mmHg)	82±8	82±7	83±9	0.79
ABPM Night SBP (mmHg)	117±12	116±12	119±13	0.32
ABPM Night DBP (mmHg)	69±8	69±8	69±9	0.72
Peak exercise SBP (mmHg)	219±16	216±16	222±16	0.06
Peak exercise DBP	93±12	94±12	92±13	0.45

(mmHg)				
Rest central SBP (mmHg)	114±11	115±11	114±11	0.76
Rest central DBP (mmHg)	75±7	74±7	75±8	0.32
Rest central PP (mmHg)	40±9	41±10	39±8	0.23
Masked HT (%)	40%	39%	40%	0.90
Rest heart rate (bpm)	76±14	77±13	76±14	0.55
Aortic PWV (m/s)	8.3±1.8	8.2±1.7	8.4±1.9	0.68
Heart				
VO_{2max} (ml/kg/min)	31.2±7.5	30.8±7.3	31.4±7.8	0.68
LVH (%)	15%	22%	9%	0.057
LVMI (g/m^2)	87.5±19.1	89.6±20.9	85.7±17.5	0.29
LVEF (% EF units)	65±6	65±5	65±6	0.53
E wave (cm/s)	6.6±1.4	6.7±1.5	6.5±1.4	0.42
Em (cm/s)	- 6.7±1.5	-6.5±1.3	-6.8±1.6	0.33
E/e_m ratio	10.2±2.8	10.6±2.6	9.9±2.8	0.22
Exercise E wave (cm/s)	9.6±1.7	9.7±1.8	9.5±1.7	0.45
Exercise Em (cm/s)	-9.8±1.8	-9.9±1.9	-9.7±1.6	0.60
Exercise E/e_m ratio	10.0±2.1	10.1±2.5	9.8±1.7	0.45
Peak systolic strain (%)	-19.8±3.5	-20.1±3.4	-19.6±3.6	0.39
Peak systolic strain rate (1/s)	-1.26±0.42	-1.32±0.57	-1.22±0.22	0.22

P-value refers to unpaired t-test results of comparisons between treatment groups. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitor; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; VO_{2max}, maximal oxygen consumption; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.

Table 2

Table 2. Effect of spironolactone on hemodynamic, myocardial and vascular parameters.

	Placebo	Spironolactone 25mg	p-value
Hemodynamic			
Δ Peak exercise SBP (mmHg)	-0.4±10.2	-7.2±11.6	<0.01
Δ Peak exercise DBP (mmHg)	-1.9±8.8	-1.6±11.7	0.87
Δ 24hr SBP (mmHg)	0.7±8.3	-3.3±7.2	<0.01
Δ 24hr DBP (mmHg)	-1.3±8.1	-1.2±6.0	0.80
Δ 24hr MAP (mmHg)	- 0.7±7.6	-1.9±6.0	0.11
Δ 24hr PP (mmHg)	2.0±6.7	-2.1±4.7	<0.001
Δ Rest central SBP (mmHg)	-1.0±8.1	-3.8±7.7	0.06
Δ Rest central DBP (mmHg)	0.6±6.8	-1.6±6.1	0.09
Δ Rest central PP (mmHg)	-1.7±7.6	-2.4±5.3	0.18
Δ Office SBP (mmHg)	1.0±14.9	-1.2±14.7	0.15
Δ Office DBP (mmHg)	4.3±10.6	1.6±9.3	0.17
Masked HT (%)	38%	36%	0.84
Δ Rest heart rate (bpm)	1.1±10.9	1.7±12.7	0.81
Δ Aortic PWV (m/s)	0.37±1.67	-0.18±1.09	0.045
Heart			
Δ VO_{2max} (ml/kg/min)	-0.9±4.1	0.4±4.9	0.15
LVH (%)	30%	9%	<0.01
Δ LVMI (g/m^2)	2.6±14.9	-4.3±18.2	0.04
Δ E wave (cm/s)	-1.7±1.0	-3.2±1.1	0.44
Δ Em (cm/s)	0.4±1.1	0.4±1.4	0.71
Δ E/e_m	-0.6±1.7	-1.1±2.3	0.30
Δ Exercise E wave (cm/s)	0.3±1.3	-0.1±1.5	0.16
Δ Exercise Em (cm/s)	-0.4±2.3	0.3±2.0	0.15
Δ Exercise E/e_m	0.8±2.8	-0.3±2.4	0.06
Δ Peak systolic strain (%)	-0.1±3.2	0.3±3.6	0.56
Δ Peak systolic strain rate (1/s)	0.06±0.59	0.01±0.24	0.64
Δ LVEF (% EF units)	1.0±5.9	0.2±6.6	0.55

Δ Left atrial area (cm^2)	0.3±2.8	-0.1±2.0	0.39

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity. VO_{2max}, maximal oxygen consumption; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.

Supplementary Data (on-line only)

Biochemical markers according to treatment group.

	Placebo	Spironolactone 25mg	p-value
Δ Serum potassium (mmol/L)	0.0±0.2	0.1±0.3	0.50
Δ Serum urea (µmol/l)	-0.1±1.2	1.0±6.6	0.25
Δ Serum creatinine (µmol/l)	0.1±8.4	0.4±6.8	0.82
Δ HbA_{1c} (%)	-0.03±0.26	0.03±0.55	0.55
Δ Total cholesterol (mmol/L)	-0.05±0.52	-0.09±0.60	0.68
Δ LDL cholesterol (mmol/l)	-0.01±0.42	-0.11±0.59	0.38
Δ HDL cholesterol (mmol/l)	0.07±0.73	0.02±0.23	0.57
Δ Triglycerides (mmol/L)	0.00±0.64	-0.07±0.53	0.50

HbA_{1c}, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Figure 1

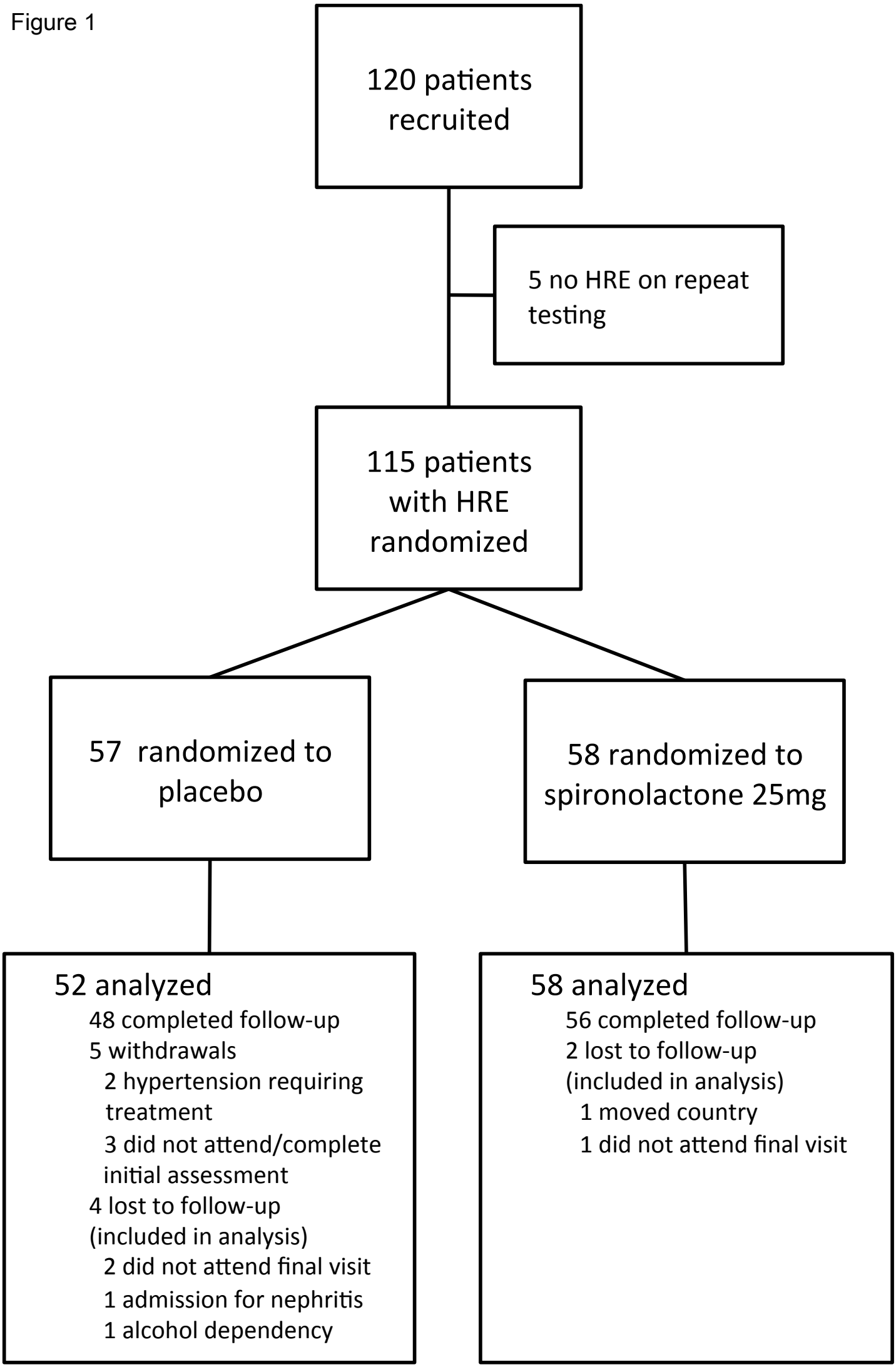
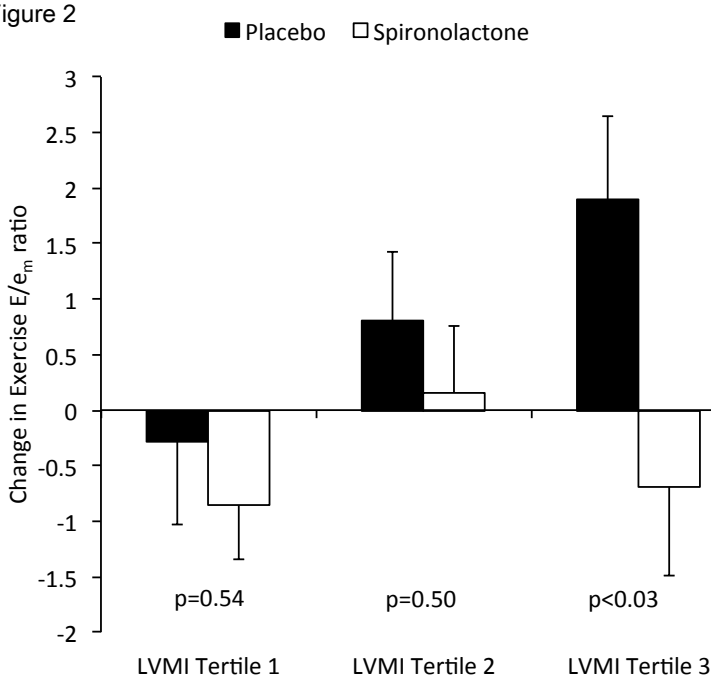
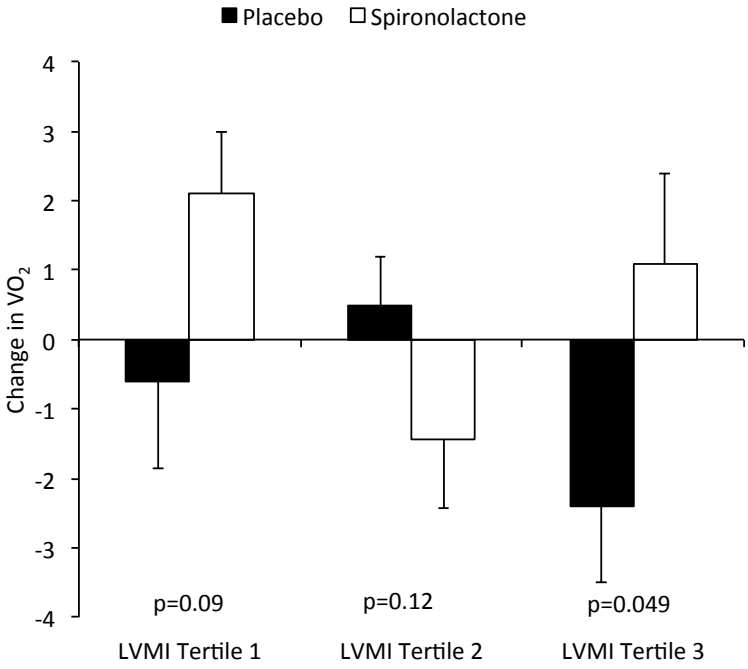

120 patients recruited
5 no HRE on repeat testing
115 patients with HRE randomized
57 randomized to placebo
58 randomized to spironolactone 25mg
52 analyzed
48 completed follow-up
5 withdrawals
2 hypertension requiring treatment
3 did not attend/complete initial assessment
4 lost to follow-up
(included in analysis)
2 did not attend final visit
1 admission for nephritis
1 alcohol dependency
58 analyzed
56 completed follow-up
2 lost to follow-up
(included in analysis)
1 moved country
1 did not attend final visit

Figure 2


Placebo
Spironolactone
Change in Exercise E/e'm ratio
3
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
p=0.54
p=0.50
p<0.03
LVMI Tertile 1
LVMI Tertile 2
LVMI Tertile 3


Placebo
Spironolactone
Change in VO2
4
3
2
1
0
-1
-2
-3
-4
p=0.09
p=0.12
p=0.049
LVMI Tertile 1
LVMI Tertile 2
LVMI Tertile 3