‘Myocardial Effects of Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction’

Adam K McDiarmid MD[1,2], Peter P Swoboda PhD[1], Bara Erhayiem BMBS[1], Katrina A Bounford BSc[3], Petra Bijsterveld MA[1], Keith Tyndall RN[3], Graham J Fent MBChB [1], Pankaj Garg MD[1], Laura E Dobson MD[1], Tarique A Musa PhD[1], James RJ Foley MBChB[1], Klaus K Witte MD[1], Mark T Kearney MD[1], John P Greenwood PhD[1], Sven Plein PhD[1].

[1]Multidisciplinary Cardiovascular Research Centre (MCRC) & Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Clarendon Way, Leeds, UK.

[2] Department of Cardiology, Freeman Hospital, Newcastle-upon-Tyne, UK

[3] Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds, UK

Corresponding Author: A K McDiarmid, Multidisciplinary Cardiovascular Research Centre (MCRC) & Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Clarendon Way, Leeds, UK and Division of Imaging Sciences and Biomedical Engineering

Email: adam.mcdiarmid@nuth.nhs.uk

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Abstract

Background: Spironolactone may have prognostic benefit in selected patients with Heart Failure with Preserved Ejection Fraction (HF-PEF). This study assessed the myocardial tissue effects of spironolactone in HF-PEF.

Methods and Results: 1:1 randomised controlled study of six months of spironolactone versus control in HF-PEF. The primary outcome was change in myocardial extracellular volume (ECV) fraction by cardiovascular magnetic resonance (CMR) as a surrogate of diffuse fibrosis. Of 55 randomised patients, 40 (20 female, age 75.2 ± 5.9yrs) completed follow-up (19 treatment, 21 control). A significant change in ECV over the study period was not seen (treatment 28.7 ± 3.7 vs 27.7 ± 3.4%, P=0.14; controls 27.6 ± 3.4 vs 28.3 ± 4.4%, P=0.14), however the rate of extracellular volume expansion was decreased by spironolactone (-1.0 ± 2.4 vs +0.8 ± 2.2%). Indexed LV mass (LVMi) fell (104.4 ± 26.6 vs 94.0 ± 20.6g/m2, P=0.001) but not in controls (101.4 ± 29.4 vs 104.0 ± 32.8g/m2, P=0.111). Extracellular mass decreased by 13.8% (15.1 ± 4.8 vs 13.0 ± 3.4g/m2, P=0.003), and cellular mass decreased by 8.3% (37.6 ± 10.0 vs 34.3 ± 7.9g/m2, P=0.001), but was static in controls.

Conclusions: Spironolactone did not lead to significant change in extra-cellular volume. However, spironolactone did change rate of extracellular expansion, with a decrease in the mass of both cellular and extra-cellular myocardial compartments. These data point to the mechanism of action spironolactone in HF-PEF, including a direct tissue effect with a reduction in rate of myocardial fibrosis.

Key Words: Heart Failure, HF-PEF, cardiovascular magnetic resonance, extracellular volume, ECV

Clinical Perspective

What is new?

- This study helps explain the basis of the positive effects of aldosterone antagonism in heart failure with preserved ejection fraction (HF-PEF), as seen in sub-group analysis of the large multi-centre TOPCAT study.
- This study is the first to use non-invasive assessment of myocardial fibrosis as a primary outcome measure in a therapeutic heart failure study.
- Cardiovascular magnetic resonance fibrosis quantification, as part of a comprehensive non-invasive assessment, has potential as new outcome measure in clinical studies where both conventional outcomes and the mode of action of an agent are to be established.

What are the clinical implications?

- Spironolactone administration in HF-PEF leads to a relative decrease in diffuse myocardial fibrosis, a key pathophysiological feature of the disease.
- This study adds to the literature regarding the use of aldosterone antagonists in HF-PEF, suggesting it has potential as a true disease modifying agent in selected patients.

Introduction

In contrast to heart failure with reduced ejection fraction (HF-REF) treatment of heart failure with preserved ejection fraction (HF-PEF) lacks strong evidence for any specific disease modifying therapies(1). Despite several shared clinical and pathophysiological abnormalities including myocardial fibrosis and neuro-hormonal activation(2), medications with clear benefit in HF-REF, including ACE inhibition(3), angiotensin receptor blockade(4) and beta-blockade(5), have failed to demonstrate prognostic benefit in HF-PEF. Treatment with mineralocorticoid antagonist (MRA) has been tested in the recent randomized, double-blind 'Aldosterone Antagonist Therapy for Adults with Heart Failure and Preserved Systolic Function'(6) (TOPCAT) trial. In TOPCAT 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more were assigned to receive either spironolactone or placebo. In the primary analysis treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. However, sub-group analysis of the study demonstrated a clinical benefit of MRA administration in selected patients(7). These patients tended to be an older group, many with atrial fibrillation and elevated heart failure biomarkers(7). Further randomised controlled studies have demonstrated that MRA administration in HF-PEF leads to improved tissue relaxation(8) and positive changes in markers of collagen turnover(9), suggesting MRAs may have disease modifying properties in this group.

MRAs are established in the treatment of HF-REF(10,11), and improve both survival and quality of life, due in part to modulation of myocardial fibrosis(12). Myocardial fibrosis is a key mediator of myocardial stiffness and diastolic dysfunction in HF-PEF(13,14), and has

been demonstrated both invasively and non-invasively. Furthermore, non-invasively measured myocardial fibrosis has been associated with increasing myocardial stiffness and adverse prognosis(15). Prior mechanistic and clinical studies in HF-PEF have demonstrated that cardiac relaxation improves with MRA administration, and these changes are associated with changes in circulating biomarkers of collagen turnover(8,9). In addition, MRAs also have a potent blood pressure lowering effect(16). Although the subgroup analysis of TOPCAT has suggested a benefit of spironolactone in certain patients with HFPEF it is unclear whether this is mediated by changes in blood pressure, fibrosis or both.

Cardiovascular magnetic resonance (CMR) provides accurate and reproducible assessment of cardiac structure, function(17) and scar. CMR T1 and extracellular volume (ECV) mapping are histologically validated techniques(18) that allow quantification of expansion of the extracellular space and diffuse fibrosis and thus allow investigation of the mode of action and mechanisms of MRAs in HF-PEF. ECV is now becoming established as an important prognostic marker in heart failure with both reduced and preserved ejection fraction(19). In addition, the use of ECV quantification to measure the tissue effects of therapeutic interventions will allow assessment of interventions in disease characterised by expansion of the myocardial interstitium(20).

In this randomised trial we used CMR to determine if spironolactone has an anti-fibrotic effect on myocardium in a well-phenotyped population of HF-PEF patients. Whilst for the first time using a CMR derived measure of diffuse myocardial fibrosis as a primary end-point.

Methods

Monitoring & Ethics: The study was conducted in accordance with the Declaration of Helsinki and registered with EudraCT (2013-000867-10). Approval by the National Research Ethics Service (NRES) (13/NE/0292), sponsor institution and Medicines and Health Regulatory Authority (MHRA) was given. The data that the findings of this study are available from the corresponding author upon reasonable request. All subjects gave informed written consent.

Participants: Adults aged 18-90 with a clinical diagnosis of HF-PEF according to 2012 European Society of Cardiology (ESC)(1) criteria under the care of the local heart failure service (Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom) were eligible to participate in the study. Study inclusion criteria were: New York Heart Association (NYHA) heart failure symptoms class II-IV, physical signs consistent with heart failure, left ventricular ejection fraction (LVEF) on clinical echocardiography of >50% and N-terminal prohormone brain natriuetic peptide (NT-proBNP) >400pg/L at routine clinic attendance. Study exclusion criteria were: renal impairment with eGFR <30ml/min/1.73m^2, serum potassium >5.0mmol/L at enrolment, allergy to spironolactone, inability to comply with study drug monitoring, diabetes mellitus, uncontrolled hypertension (>140mmHg systolic blood pressure despite medical therapy), pregnancy, breast-feeding, Addison's disease and any relative or absolute contra-indication to CMR. Patients with diabetes mellitus were specifically excluded as this has been shown independently to be associated with extracellular fibrosis by CMR(21).

Study Procedure: Patients meeting entry criteria under the care of the local heart failure service were approached. Following written informed consent patients underwent a

baseline assessment including: study echocardiography, CMR, blood sampling, 24hr blood pressure – all of which were repeated at study completion (figure 1). On completion of baseline assessment patients underwent 1:1 randomisation without stratification, employing a randomised permuted block strategy, with a standard block size of twenty provided by a commercial online system (sealedenvelope.com). Patients were randomised to non-blinded spironolactone 25mg orally once daily for six months or no intervention (control group) without up-titration. The study drug was commenced in accordance with National Institute for Health and Care Excellence (NICE)(22) and British National Formulary (BNF)(23). guidance as per use in HF-REF. Serum potassium and renal function were measured at one week, one month, two months, three months and six months following commencement. Dose adjustment and study drug withdrawal were performed in accordance with BNF guidance. Patients who failed to attend safety monitoring in accordance with the study protocol were withdrawn from the study by investigators. Safety follow-up was continued for one month after study completion.

Assessments: CMR: All studies were performed on a 3 Tesla Achieva TX system equipped with a 32-channel cardiac phased array receiver coil and multi-transmit technology (Philips Healthcare, Best, The Netherlands). The cardiac long and short axes were determined using standard scout views. Mid LV native (pre-contrast) T1 maps were generated using a previously described Modified Look Locker Inversion Recovery (MOLLI) sequence (24) briefly comprising: ECG triggered 5b(3s)3b MOLLI, flip angle 35^{o}, voxel size of 1.98x1.98x10 mm^3. Left ventricular (LV) mass and volumes were obtained from cine imaging covering the entire LV in the short axis. Right ventricular (RV) and atrial volumes were obtained from a transaxial cine stack covering the entire heart. 0.15mmol/kg Gadovist (Bayer) was delivered

by power injector (Medrad Inc, Warrendale, Pennsylvania, USA) as a single bolus via a venous cannula placed in the ante-cubital fossa, followed by a 20ml saline flush at 5ml/second. Late gadolinium enhancement (LGE) imaging was performed to image the entire LV seven to ten minutes following contrast administration. Post-contrast T1 maps were acquired using the same MOLLI scheme fifteen minutes after contrast administration.

Image Analysis: All image analysis was performed using cmr^{42} software (Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada) by operators blinded to treatment allocation. Volumetric and mass analysis was performed in the standard manner from the short axis stack (LV) or long axis cine images (RV). T1 values were calculated from source images using manual motion correction with a region of interest (ROI) in the mid infero-septum ensuring avoidance of the blood pool (25). ECV was calculated as previously described, with offline analysis of source images to avoid mis-triggering and partial volume artefact (26) . The mass of the cellular and extracellular myocardial compartments were derived as follows: indexed extracellular mass = indexed LV mass x ECV; indexed cellular mass = indexed LV mass x (1-ECV). CMR analysis was performed by two observers (AKM, PPS) blinded to subject data.

Echocardiography: All patients underwent echocardiography (Vivid e9, GE Medical Systems, Milwaukee, WI, USA) including Doppler measurements of mitral inflow and tissue Doppler imaging (TDI) of the lateral and medial mitral annulus for the assessment of diastolic function in accordance with national guidelines. Studies were performed by British Society of Echocardiography (BSE) accredited echocardiographers, blinded to study information.

24 hour blood pressure: 24hr ambulatory blood pressure was performed on standard clinical equipment (DelMar Reynolds NIBP, Sentinel Space Lab 7.0.0737), with analysis performed by institute physiologists, blinded to study information.

Biomarkers: 20mL of blood was drawn from each subject whilst supine at the time of CMR. Full blood count was measured at that time. Serum was stored at -70°C and tested in one batch for N-terminal prohormone brain natriuetic peptide (NTpro-BNP), procollagen type I N-terminal peptide (P1NP), procollagen type III N-terminal peptide (P3NP), high sensitivity CRP (HsCRP) and matrix metallopeptidase 3 (MMP3).

Study End-points: The pre-specified primary outcome was difference in final myocardial ECV (%) following six months of treatment with spironolactone between treatment groups. Pre-specified secondary outcomes included the relationship between change in myocardial tissue composition and echocardiographic measures of myocardial tissue relaxation, LV geometry, blood pressure and circulating biomarkers.

Statistical Analysis: Statistical analysis was performed using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY). Unless otherwise stated the results are presented as mean ± standard deviation (SD). Normality of distribution was determined with Kolmogarov-Smirnov testing. Differences between groups were assessed using the Chi-squared test, paired or independent t-test where appropriate. Correlation was assessed with Spearman correlation co-efficient. Analysis was conducted as a complete case analysis. To detect a change in ECV of 1.5% on treatment with spironolactone (inter-study standard deviation 1.95%(24), significance 5%, power 90%) a sample size of 20 was required in each arm. Significance for all tests was defined as $P<0.05$.

Results

Study Participant Demographics and Baseline Characteristics: 55 subjects were recruited with 40 completing the follow-up period (19 in the treatment group and 21 in the control group). Of those that did not complete follow-up 8 (5 female, 3 male) were in the treatment group, 3 (2 female, 1 male) were in the monitoring group and 4 dropped out prior to randomisation (3 female, 1 male). Reasons for study drop out were as follows: deterioration in renal function (3), inability to tolerate CMR (1), protocol breach (3), withdrawal of consent (8).

Of those who completed follow-up, the mean age was 75.1 ± 7.3 years and 20 were female (50%). Subject demographics in the active treatment and monitoring groups were similar between the two groups and can be seen in table 1. Baseline characteristics were similar between groups with atrial fibrillation (89% spironolactone vs 71% control group, P = 0.15) and hypertension (79% vs 62%, P=0.15) common in both groups. Pre-randomisation medical therapy did not differ significantly between groups with widespread prescription of ACE inhibitors, beta-blockers and diuretics. NT-proBNP was elevated as mandated by study protocol, and not significantly different between groups (1737.2 ± 1238.7 vs 1699 ± 1548.0pg/L, P=0.932). Cardiac geometry by CMR was similar between groups and no differences were seen in measures of echocardiographic tissue relaxation. Native T1 at baseline was lower in the treatment group compared to controls (1229 ± 52.3 vs 1266.7 ± 59.4ms, P=0.041) though ECV did not differ (28.7 ± 3.7 vs 27.3 ± 3.1%, P=0.31). (table 2)

Intervention Effect: A significant change in absolute ECV was not seen over the study period in either the treatment group (28.7 ± 3.7 vs 27.7 ± 3.4%, P=0.14) or controls (27.6 ± 3.4 vs 28.3 ± 4.4%, P=0.14). However significant difference was seen in rate of extracellular volume (ΔECV) expansion between treatment and control groups (-1.0 ± 2.4 vs 0.8 ± 2.2%) (figure 2). Additionally, over the study period significant changes were seen following intervention in indexed LV mass (52.7 ± 14.1 vs 47.3 ± 10.8g/m^2, P <0.01) and LV volume (71.8 ± 14.0 vs 65.4 ± 11.2ml/m^2, P=<0.01) but not in the control group (52.1 ± 14.0 vs 53.3 ± 15.1g/m^2, P=0.15; 71.8 ± 18.5 vs 70.7 ± 19.5ml/m^2, P=0.43 respectively) (table 2).

The mass of both myocardial compartments decreased significantly following MRA administration, with an 8.3% (74.5 ± 19.4 vs 68.3 ± 15.9g/m^2, P<0.01) reduction in cellular mass, and a 13.8% (29.8 ± 8.4 vs 25.7 ± 5.9g/m^2, P<0.01) reduction in the extracellular mass seen. In the control group no significant change was seen in either indexed cellular (73.3 ± 20.5 vs 74.3 ± 22.0g/m^2, P=0.390) or extracellular mass (14.4 ± 4.8 vs 15.0 ± 5.9g/m2, P=0.091) over the study period

Following In the treatment group significant change was seen in systolic (130.8 ± 19.1 vs 120.2 ± 13.5mmHg, P<0.01) and diastolic blood pressure (76.8 ± 72.1 ± 6.8mmHg, P=0.013), mean arterial pressure (94.2 ± 10.4 vs 79.7 ± 5.9mmHg, P<0.01) and serum creatinine (97.4 ± 27.2 vs 109.6 ± 37.0mmol/L, P<0.01), whilst no significant changes were seen in the control group.

No changes were seen in echocardiographic measures of cardiac relaxation, circulating markers of collagen turnover or heart failure severity. (Table 3).

Correlations were determined between ΔECV, LV geometry and relaxation, systolic and diastolic blood pressure, mean arterial pressure, markers of collagen turnover and heart failure severity across the whole study group. Significant correlations were seen between ΔECV and LVMi (r=0.442, P<0.01), LVEDVi (r=0.401, P=0.011) and tissue relaxation (mean E', r=0.348, P=0.03) though not with change in blood pressure. ΔLVMi correlated with change in all of systolic, diastolic and mean arterial blood pressure (r=0.468, P=0.004; r=0.357, P=0.032; r=0.367, P=0.03 respectively) (table 4).

Discussion

Whilst this study failed to demonstrate a change in absolute ECV over the study period we have demonstrated that MRA administration significantly affects the rate of extracellular volume expansion in HF-PEF. Thereby our results suggest potential mechanisms for the disease modifying effect of spironolactone seen in larger randomised trials(7,8).

Therapeutic Effect: We have demonstrated that MRA administration in HF-PEF leads to a decrease in LV mass, a further anti-hypertensive effect in a well-treated cohort, relative regression of myocardial fibrosis and significant mass reduction of both the cellular and, possibly more importantly, the extracellular compartments. These data provide important insights into the mode of action of MRAs in HF-PEF and help explain the potential disease modifying effects of spironolactone previously reported(7-9).

Previous invasive and non-invasive studies have demonstrated that abnormalities of cardiac relaxation in HF-PEF are associated with increased myocardial fibrosis(14,15). Progressive fibrosis is promoted by elevation of circulating aldosterone levels(27). In addition, aldosterone antagonism has previously been demonstrated to lead to positive changes in

cardiac relaxation which are associated with change in circulating levels of markers of collagen turnover(9,28). It is likely that the absence of change in biomarkers seen in this study was related to sample size, as the effect of MRAs on markers of collagen turnover are well established(9).

Impaired cardiac relaxation due to increased myocardial fibrosis leads to elevation of left atrial pressure, in turn leading to elevation of pulmonary pressures and progressive RV dysfunction. Recent studies have demonstrated that myocardial fibrosis and expansion of the extracellular matrix are associated with both poor outcomes and the presence of pulmonary hypertension in HF-PEF(14,15). In a retrospective sub-group analysis of the TOPCAT study spironolactone was demonstrated to lead to a reduction in morbidity and mortality in selected patients(6). In our study ΔECV was significantly correlated with ΔLVMi and Δmean E'. This association suggests that the previously observed beneficial effects of spironolactone are likely related to improved passive stiffness, due to regression of diffuse myocardial fibrosis and fall in LV mass.

Blood Pressure Effect: Patients in this study underwent 24-hour blood pressure monitoring on enrolment and at completion of the study. Treatment with spironolactone led to a significant decrease in blood pressure versus controls with an associated drop in LV mass, despite appropriate blood pressure control at enrolment.

We are unable to determine if the difference in rate of change in myocardial fibrosis accumulation observed is due to improved blood pressure control with a decrease in afterload, a direct anti-fibrotic effect of spironolactone or a combination of the two. Alternatively, it has been previously reported that the diuretic effect of some non-neurohormonal anti-hypertensive agents results in significant change in LV geometry

independent of mean blood pressure. However, the relative mass change of the extracellular compartment was greater than the change in myocyte mass, suggesting that the change is not purely due to drop in afterload and that spironolactone is exerting a direct tissue effect in HF-PEF.

Despite normal blood pressure at enrolment significant regression in LV mass was seen in this study. This suggests that despite blood pressure being within the normal range, further reduction of systolic blood pressure leads to positive cardiac reverse remodelling. Elevated LV mass has previously been shown to be associated with adverse prognosis in hypertension. The benefits of enhanced blood pressure control seen in the SPRINT study(29) may in part be explained by such an effect.

Future Directions: Neuro-hormonal activation, myocardial fibrosis, salt/water retention and hypertension are all key features of HF-PEF pathophysiology and are modified by MRAs. We have shown that MRAs lead to demonstrable change in blood pressure and myocardial tissue composition. A decrease in the mass of the extra cellular compartment, and fibrosis, is likely to lead to an improvement in passive stiffness. However, this only addresses one aspect of a complex syndrome: active stiffness, abnormalities of ventricular-aortic coupling and complex systemic abnormalities are not necessarily affected. The HF-PEF cohort is heterogeneous and probably includes multiple pathologies and disease manifestations. Further characterisation and phenotyping to identify the sub-groups that make up the population is essential. Future studies are likely to focus on identifying agents to target impairment of active stiffness and address additional factors specific to the abnormalities underlying different HF-PEF subgroups. Additionally, myocardial ECV assessment has now been used to help differentiate between patients with hypertension and HF-PEF, and

identify those with significant functional limitation.(30) It is possible in future studies that an ECV threshold may be used for study enrolment.

Although our findings are consistent with prior mechanistic studies, we did not demonstrate a correlation between change in circulating biomarkers of collagen turnover and fibrosis regression or cardiac relaxation. However prior studies have separately shown that aldosterone antagonism in HF-PEF leads to both; the lack of such an association seen here may be related to limitation of sample size.

Limitations

Whilst the findings of this study are novel and in line with prior mechanistic studies there are some important limitations. Firstly, despite the analysis being performed in a blinded manner this was a non-blinded study without placebo control, consequently the results need to be confirmed in a larger blinded placebo controlled randomised trial.

The dropout rate of 27% was higher than anticipated, and as a result only 41 participants completed the study. The majority of dropouts were due to withdrawal of consent, due in part to the demanding nature of study protocol. Withdrawal was asymmetric, with 8 in the active treatment group, and 3 in the control group. Only 3 withdrawals were directly related to adverse events due to medication administration, which is in line with prior studies examining the effect of aldosterone antagonists. This suggests that with appropriate monitoring this class of medication can be used safely in this patient group. Furthermore, though pre-specified it must be recognised that the secondary outcome findings may have occurred by chance.

The study population included a high percentage of patients with atrial fibrillation when compared to other HF-PEF studies. The reasons for this in our study are not clear however, though this differs from previously published data it should be noted that sub-group analysis of TOPCAT suggest that these patients may benefit from spironolactone administration. In addition, the presence of atrial fibrillation may theoretically affect CMR ECV calculation due to variable cycle length. This was not corrected for in this study, and ideally all CMR examinations would be performed in sinus rhythm.

We excluded patients with diabetes mellitus as a response to initial data from our centre suggesting the presence of ECV expansion in diabetes with microalbuminaemia (21). This step was taken in an attempt to minimise heterogeneity in the study population as a response to problems with previous HF-PEF studies, however we recognise this too may limit application of the findings as DM is a frequently encountered co-morbidity in HF-PEF populations.

Conclusions

In this study, we have demonstrated that spironolactone decreases the rate of accumulation of myocardial fibrosis in HF-PEF, an abnormality increasingly linked to both its pathophysiology and prognosis. The masses of both the extracellular and cellular myocardial compartments fell significantly over the study period and occurred in association with a fall in blood pressure. Our data and prior studies support that spironolactone has a direct tissue effect on myocardium in HF-PEF, as well as secondary effects due to further blood pressure modification.

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Figures

Figure 1. Study Flow Chart

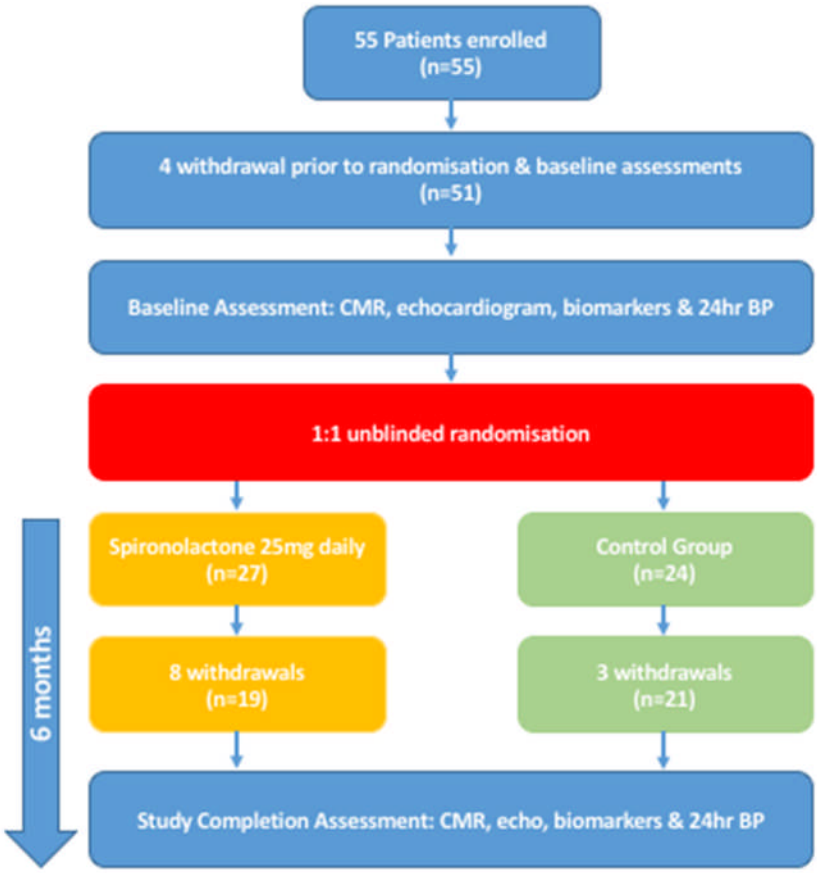
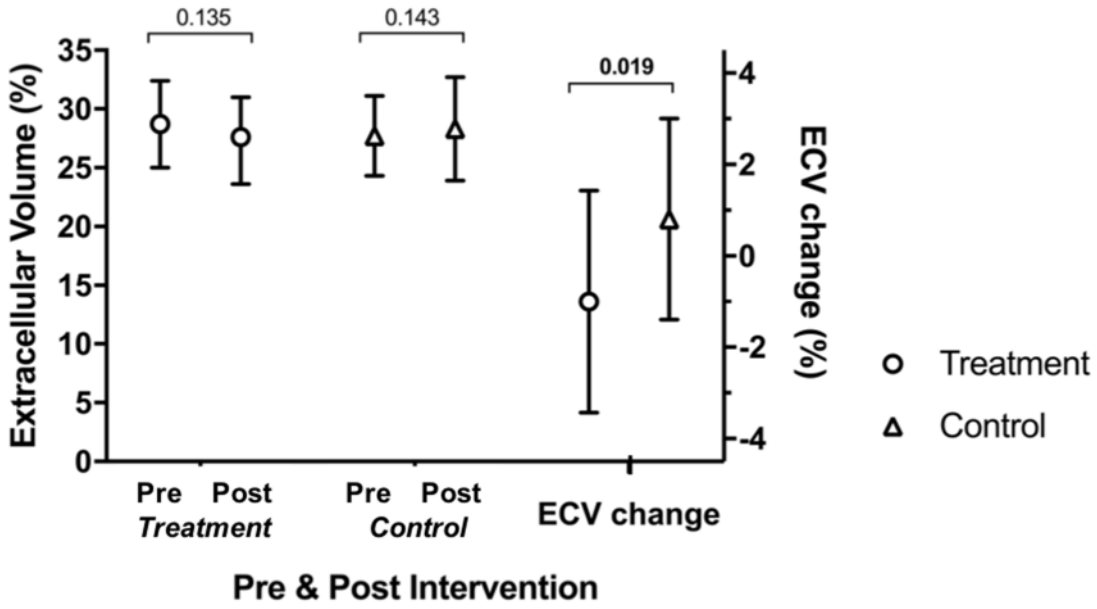


Figure 2. Effect on myocardial fibrosis of Spironolactone versus controls in HF-PEF.

Significant change was not seen on intra-group analysis (P=0.135 and 0.143 respectively), however rate of change in ECV differed significantly, with a relative drop seen in extracellular volume following treatment (P=0.019). (ECV, extracellular volume)



References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JF, Coayts AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis BP, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal 2016;37:2129-200.
2. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. European heart journal 2011;32:670-9.
3. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. European heart journal 2006;27:2338-45.
4. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile M, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. The New England journal of medicine 2008;359:2456-67.
5. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. PloS one 2014;9:e90555.
6. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. 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.
7. Pfeffer MA, Pitt B, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. The New England journal of medicine 2014;371:181-2.
8. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krain E, Colantonio C, Kamke W, Duvainage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschopem C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. 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;309:781-91.
9. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). Journal of cardiac failure 2011;17:634-42.
10. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England journal of medicine 1999;341:709-17.
11. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B . Eplerenone in patients with systolic heart failure and mild symptoms. The New England journal of medicine 2011;364:11-21.
12. Coelho-Filho OR, Shah RV, Neilan TG, Mitchell R, Moreno H, Kwong R, Jerosch-Herold M. Cardiac magnetic resonance assessment of interstitial myocardial fibrosis and cardiomyocyte hypertrophy in hypertensive mice treated with spironolactone. Journal of the American Heart Association 2014;3:e000790.
13. Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lucke C, Gutberlet, Linke A, Schuler G, Lurz P. Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology 2016;67:1815-1825.
14. Su MY, Lin LY, Chang CC, Wu CK, Lin JL Tseng YH. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. JACC Cardiovascular imaging 2014;7:991-7.

15. Duca F, Kammerlander AA, Zotter-Tufaro C, Aschauer S, Schwaiger ML, Marzluf BA, Bonderman D, Mascherbauer J. Interstitial Fibrosis, Functional Status, and Outcomes in Heart Failure With Preserved Ejection Fraction: Insights From a Prospective Cardiac Magnetic Resonance Imaging Study. Circulation Cardiovascular imaging 2016;9.
16. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, MacKenzie I, Padmanabhan S, Brown MJ. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059-2068.
17. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. The American journal of cardiology 2002;90:29-34.
18. Sado DM, Flett AS, Banypersad SM, White SK, Maestrini V, Quarta G, Lachmann RH, Murph E, Mehta A, Hughes DA, McKenna WJ, Taylor AM, Hausenloy DJ, Hawkins PN, Elliott PM, Moon JC. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart 2012;98:1436-41.
19. Schelbert EB, Fridman Y, Wong TC, Daya HA, Piehler KM, Kadakkal A, Miller CA, Ugander M, Maanja M, Kellman P, Shah D, Abebe KZ, Simon MA, Quarta G, Senni M, Butler J, Diez J, Redfield MM, Gheorghiade M. Temporal Relation Between Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction: Association With Baseline Disease Severity and Subsequent Outcome. JAMA cardiology 2017;2:995-1006.
20. Schelbert EB, Sabbah HN, Butler J, Gheorghiade M. Employing Extracellular Volume Cardiovascular Magnetic Resonance Measures of Myocardial Fibrosis to Foster Novel Therapeutics. Circulation Cardiovascular imaging 2017;10.
21. Swoboda PP, McDiarmid AK, Erhayiem B, Ripley DP, Dobson LE, Garag P, Musa TA, Witte KK, Kearney MT, Barth JH, Ajjan R, Greenwood JP, Plein S. Diabetes Mellitus, Microalbuminuria, and Subclinical Cardiac Disease: Identification and Monitoring of Individuals at Risk of Heart Failure. Journal of the American Heart Association 2017;6.
22. Excellence NIfHaC. Chronic heart failure in adults: management (CG108). 2010.
23. Britain BMAatRPSoG. British National Formulary: BMJ Publishing Group, 2012.
24. McDiarmid AK, Swoboda PP, Erhayiem B, Ripley DP, Kidambi A, Broadbent DA, Higgins DM, Greenwood JP, Plein S. Single bolus versus split dose gadolinium administration in extra-cellular volume calculation at 3 Tesla. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2015;17:6.
25. Rogers T, Dabir D, Mahmoud I, Voigt T, Schaeffter T, Nagel E, Puntmann VO. Standardization of T1 measurements with MOLLI in differentiation between health and disease--the ConSept study. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2013;15:78.
26. Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2012;14:63.
27. Weber KT. Aldosterone in congestive heart failure. The New England journal of medicine 2001;345:1689-97.
28. Edwards NC, Ferro CJ, Kirkwood H, Chue CD, Young AA, Stewart PM, Steeds RP, Townend JN. Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. The American journal of cardiology 2010;106:1505-11.
29. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Fine LJ, Cutler JA, Cushman

WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England journal of medicine 2015;373:2103-16.

30. Mordi IR, Singh S, Rudd A, Srinivasan J, Frenneaux M, Tzemos M, Dawson DK. Comprehensive Echocardiographic and Cardiac Magnetic Resonance Evaluation Differentiates Among Heart Failure With Preserved Ejection Fraction Patients, Hypertensive Patients, and Healthy Control Subjects. JACC Cardiovasc Imaging 2017.