ORIGINAL RESEARCH

# Myocardial Effects of Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction

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***Background*—**Spironolactone may have prognostic benefit in selected patients with heart failure with preserved ejection fraction. This study assessed the myocardial tissue effects of spironolactone in heart failure with preserved ejection fraction.

***Methods and Results*—**A 1:1 randomized controlled study of 6 months of spironolactone versus control in heart failure with preserved ejection fraction. The primary outcome was change in myocardial extracellular volume fraction by cardiovascular magnetic resonance as a surrogate of diffuse fibrosis. Of 55 randomized patients, 40 (20 women; age, 75.2±5.9 years) completed follow-up (19 treatment, 21 control). A significant change in extracellular volume over the study period was not seen (treatment, 28.7±3.7% versus 27.7±3.4% [*P*=0.14]; controls, 27.6±3.4% versus 28.3±4.4% [*P*=0.14]); however, the rate of extracellular volume expansion was decreased by spironolactone (−1.0±2.4% versus 0.8±2.2%). Indexed left ventricular mass decreased with treatment (104.4±26.6 versus 94.0±20.6 g/m$^2$; *P*=0.001) but not in controls (101.4±29.4 versus 104.0±32.8 g/m$^2$; *P*=0.111). Extracellular mass decreased by 13.8% (15.1±4.8 versus 13.0±3.4 g/m$^2$; *P*=0.003), and cellular mass decreased by 8.3% (37.6±10.0 versus 34.3±7.9 g/m$^2$; *P*=0.001) with spironolactone, but was static in controls.

***Conclusions*—**Spironolactone did not lead to significant change in extracellular volume. However, spironolactone did decrease rate of extracellular expansion, with a decrease in the mass of both cellular and extracellular myocardial compartments. These data point to the mechanism of action of spironolactone in heart failure with preserved ejection fraction, including a direct tissue effect with a reduction in rate of myocardial fibrosis. **(*J Am Heart Assoc.* 2020;9:e011521. DOI: 10.1161/JAHA.118.011521.)**

**Key Words:** cardiovascular magnetic resonance • extracellular volume • heart failure • heart failure with preserved ejection fraction



In contrast to heart failure with reduced ejection fraction, 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 neurohormonal activation,[2] medications with clear benefit in heart failure with reduced ejection fraction, including angiotensin-converting enzyme inhibition,[3] angiotensin receptor blockade,[4] and β 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 TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function)[6] trial. In the TOPCAT trial, 3445 patients with symptomatic heart failure and a left ventricular (LV) ejection fraction of ≥45% 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, subgroup 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 randomized controlled studies have demonstrated that MRA administration in HF-PEF leads

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## Clinical Perspective

### What Is New?

- In a randomized controlled study of 6 months of spironolactone versus control in heart failure with preserved ejection fraction, spironolactone did not lead to a significant change in extracellular volume.
- Spironolactone did, however, change rate of extracellular expansion, with a decrease in the mass of both cellular and extracellular myocardial compartments.
- This study, using a noninvasive assessment of myocardial fibrosis, suggests that spironolactone administration in heart failure with preserved ejection fraction may lead to a relative decrease in diffuse myocardial fibrosis, a key pathophysiological feature of the disease.

### What Are the Clinical Implications?

- Cardiovascular magnetic resonance fibrosis quantification, as part of a comprehensive noninvasive assessment, has potential as a new outcome measure in clinical studies where both conventional outcomes and the mode of action of an agent are to be established.
- This study adds to the literature about the use of aldosterone antagonists in heart failure with preserved ejection fraction, suggesting it has potential as a true disease-modifying agent in selected patients.

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 heart failure with reduced ejection fraction,[10,11] and they improve both survival and quality of life, caused, in part, by modulation of myocardial fibrosis.[12] Myocardial fibrosis is a key mediator of myocardial stiffness and diastolic dysfunction in HF-PEF,[13,14] and it has been demonstrated both invasively and noninvasively. Furthermore, noninvasively 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 the TOPCAT trial has suggested a benefit of spironolactone in certain patients with HF-PEF, 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 characterized by expansion of the myocardial interstitium.[20]

In this randomized trial, we used CMR to determine if spironolactone has an antifibrotic effect on myocardium in a well-phenotyped population of patients with HF-PEF. For the first time, we were using a CMR-derived measure of diffuse myocardial fibrosis as a primary end point.

## Methods

### Monitoring and 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 (13/NE/0292), sponsor institution, and Medicines and Health Regulatory Authority was given. The data that form the findings of this study are available from the corresponding author on reasonable request. All subjects gave informed written consent.

### Participants

Adults, aged 18 to 90 years, with a clinical diagnosis of HF-PEF, according to 2012 European Society of Cardiology[1] criteria, under the care of the local heart failure service (Leeds Teaching Hospitals NHS Trust, Leeds, UK) were eligible to participate in the study. Study inclusion criteria were as follows: New York Heart Association heart failure symptoms class II to IV, physical signs consistent with heart failure, LV ejection fraction on clinical echocardiography of >50%, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) >400 pg/L at routine clinic attendance. Study exclusion criteria were as follows: renal impairment with estimated glomerular filtration rate <30 mL/min per 1.73 $m^2$, serum potassium >5.0 mmol/L at enrollment, allergy to spironolactone, inability to comply with study drug monitoring, diabetes mellitus, uncontrolled hypertension (>140 mm Hg systolic blood pressure despite medical therapy), pregnancy, breastfeeding, Addison disease, and any relative or absolute contraindication 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. After written informed consent was obtained, patients underwent a baseline assessment, including the following: study echocardiography, CMR, blood sampling, and 24-hour blood pressure, all of which were repeated at study completion (Figure 1). On completion of baseline assessment, patients underwent 1:1 randomization without stratification, using a randomized permuted block strategy, with a standard block size of 20 provided by a commercial online system (https://www.sealedenvelope.com). Patients were randomized to nonblinded spironolactone, 25 mg orally once daily, for 6 months or no intervention (control group) without up titration. The study drug was commenced in accordance with National Institute for Health and Care Excellence[22] and British National Formulary[23] guidance, as per use in heart failure with reduced ejection fraction. Serum potassium and renal function were measured at 1 week, 1 month, 2 months, 3 months, and 6 months after commencement. Dose adjustment and study drug withdrawal were performed in accordance with British National Formulary 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 1 month after study completion.

## Assessments

### *Cardiovascular magnetic resonance*

All studies were performed on a 3-T Achieva TX system equipped with a 32-channel cardiac phased array receiver coil and multitransmit technology (Philips Healthcare, Best, the

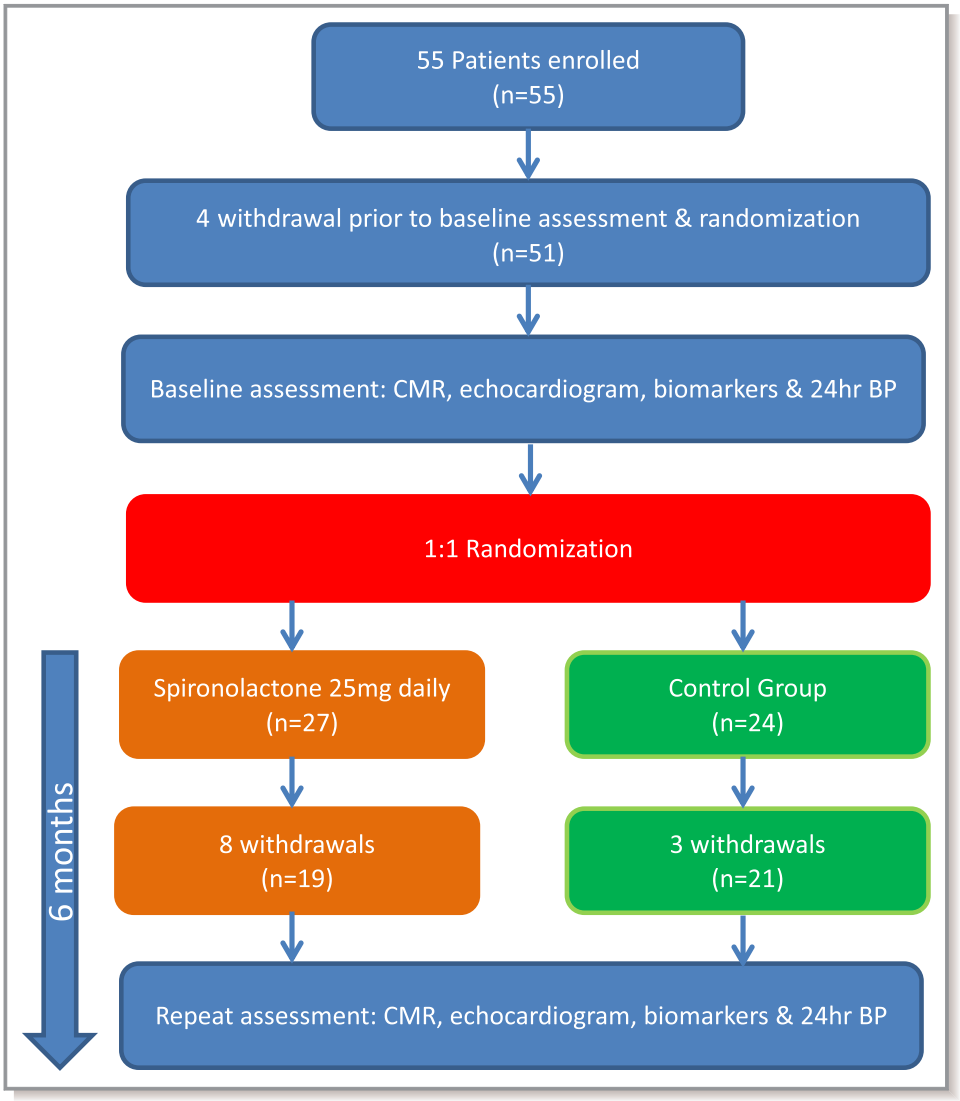


**Figure 1.** Study flowchart. BP indicates blood pressure; CMR, cardiovascular magnetic resonance.

Netherlands). The cardiac long and short axes were determined using standard scout views. Mid LV native (precontrast) T1 maps were generated using a previously described modified look locker inversion recovery sequence,[24] briefly comprising the following: ECG (electrocardiogram)-triggered 5b(3s)3b modified look locker inversion recovery, flip angle of 35°, and voxel size of $1.98\times1.98\times10$ mm$^3$. LV mass and volumes were obtained from cine imaging covering the entire LV in the short axis. Right ventricular and atrial volumes were obtained from a transaxial cine stack covering the entire heart. A total of 0.15 mmol/kg gadobutrol (Gadovist; Bayer) was delivered by power injector (Medrad Inc, Warrendale, PA) as a single bolus via a venous cannula placed in the antecubital fossa, followed by a 20-mL saline flush at 5 mL/s. Late gadolinium enhancement imaging was performed to image the entire LV 7 to 10 minutes after contrast administration. Postcontrast T1 maps were acquired using the same modified look locker inversion recovery scheme 15 minutes after contrast administration.

### *Image Analysis*

All image analysis was performed using cmr[42] software (Circle Cardiovascular Imaging Inc, Calgary, AB, 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 (right ventricle). T1 values were calculated from source images using manual motion correction with a region of interest in the mid inferoseptum, ensuring avoidance of the blood pool.[25] ECV was calculated, as previously described, with offline analysis of source images to avoid mistriggering and partial volume artefact.[26] The masses of the cellular and extracellular myocardial compartments were derived as follows: indexed extracellular mass=indexed LV mass×ECV; indexed cellular mass=indexed LV mass×(1−ECV). CMR analysis was performed by 2 observers (A.K.M. and P.P.S.) blinded to subject data.

### *Echocardiography*

All patients underwent echocardiography (Vivid e9; GE Medical Systems, Milwaukee, WI), including Doppler measurements of mitral inflow and tissue Doppler imaging 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–accredited echocardiographers, blinded to study information.

### *24 Hour Blood Pressure*

Ambulatory blood pressure at 24 hours 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*

Blood (20 mL) was drawn from each subject while 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 NT-proBNP, procollagen type I N-terminal peptide, procollagen type III N-terminal peptide, high-sensitivity CRP (C-reactive protein), and matrix metallopeptidase 3.

## Study End Points

The prespecified primary outcome was difference in final myocardial ECV (%) after 6 months of treatment with spironolactone between treatment groups. Prespecified 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±SD. Normality of distribution was determined with Kolmogorov-Smirnov testing. Differences between groups were assessed using the $\chi^2$ test and paired or independent $t$ test, where appropriate. Correlation was assessed with Spearman correlation coefficient. Analysis was conducted as a complete case analysis. To detect a change in ECV of 1.5% on treatment with spironolactone (interstudy SD, 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

A total of 55 subjects were recruited, with 40 completing the follow-up period (19 in the treatment group and 21 in the control group). Of those who did not complete follow-up, 8 (5 women and 3 men) were in the treatment group, 3 (2 women and 1 man) were in the monitoring group, and 4 dropped out before randomization (3 women and 1 man). Reasons for study dropout were as follows: deterioration in renal function (n=3), inability to tolerate CMR (n=1), protocol breach (n=3), and withdrawal of consent (n=8).

Of those who completed follow-up, the mean age was 75.1±7.3 years, and 20 were women (50%). Subject demographics in the active treatment and monitoring groups were similar between the 2 groups and can be seen in Table 1. Baseline characteristics were similar between groups, with atrial fibrillation (89% spironolactone versus 71% control group; *P*=0.15) and hypertension (79% spironolactone versus 62% control group; *P*=0.15) common in both groups. Prerandomization medical therapy did not differ significantly between groups, with widespread prescription of angiotensin-converting enzyme inhibitors, β blockers, and diuretics. NT-proBNP was elevated as mandated by study protocol and not significantly different between groups (spironolactone versus control, 1737.2±1238.7 versus 1699±1548.0 pg/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 with controls (1229±52.3 versus 1266.7±59.4 ms; *P*=0.041), although ECV did not differ (28.7±3.7% versus 27.3±3.1%; *P*=0.31) (Table 2).

**Table 1.** Baseline Characteristics

| Characteristics | Spironolactone (n=19) | Control (n=21) | *P* Value |
|---|---|---|---|
| Sex (male/female ratio) | 10:9 | 10:11 | 0.75 |
| Age, y | 76.4±5.4 | 74.0±8.8 | 0.295 |
| BMI, kg/m$^2$ | 29.8±5.3 | 29.1±7.1 | 0.71 |
| Comorbidities | | | |
| Hypertension | 15 (79) | 13 (62) | 0.240 |
| Atrial fibrillation | 17 (89) | 15 (71) | 0.154 |
| Heart rate/min (sinus) | 77±10.6 | 74.5±12.5 | 0.541 |
| Heart rate/min (atrial fibrillation) | 77±19.8 | 73.8±7.5 | 0.745 |
| Ischemic heart disease | 0 (0) | 1 (5) | 0.335 |
| Cerebrovascular disease | 3 (16) | 0 (0) | 0.058 |
| Medications | | | |
| ACE inhibitor/ARB | 11 (58) | 12 (57) | 0.962 |
| β Blocker | 10 (53) | 14 (67) | 0.366 |
| Calcium channel blocker | 11 (58) | 12 (57) | 0.962 |
| Digoxin | 3 (16) | 9 (43) | 0.062 |
| Diuretic | 12 (63) | 12 (57) | 0.698 |
| NYHA status | | | |
| II | 14 | 17 | 0.583 |
| III | 5 | 4 | |
| IV | 0 | 0 | |

Data are given as mean±SD, number (percentage), or number. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; NYHA, New York Heart Association.

## Intervention Effect

A significant change in absolute ECV was not seen over the study period in either the treatment group (28.7±3.7% versus 27.7±3.4%; *P*=0.14) or controls (27.6±3.4% versus 28.3±4.4%; *P*=0.14). However, a significant difference was seen in rate of ECV (ΔECV) expansion between treatment and control groups (−1.0±2.4% versus 0.8±2.2%) (Figure 2). In addition, over the study period, significant changes were seen after intervention in indexed LV mass (52.7±14.1 versus 47.3±10.8 g/m$^2$; *P*<0.01) and LV volume (71.8±14.0 versus 65.4±11.2 mL/m$^2$; *P*<0.01) but not in the control group (52.1±14.0 versus 53.3±15.1 g/m$^2$ [*P*=0.15]; and 71.8±18.5 versus 70.7±19.5 mL/m$^2$ [*P*=0.43], respectively) (Table 2).

The mass of both myocardial compartments decreased significantly after MRA administration, with an 8.3% (74.5±19.4 versus 68.3±15.9 g/m$^2$; *P*<0.01) reduction in cellular mass and a 13.8% (29.8±8.4 versus 25.7±5.9 g/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 versus 74.3±22.0 g/m$^2$; *P*=0.390) or extracellular mass (14.4±4.8 versus 15.0±5.9 g/m$^2$; *P*=0.091) over the study period.

In the treatment group, significant change was seen in systolic (130.8±19.1 versus 120.2±13.5 mm Hg; *P*<0.01) and diastolic blood pressure (76.8±8.0 versus 72.1±6.8 mm Hg; *P*=0.013), mean arterial pressure (94.2±10.4 versus 79.7±5.9 mm Hg; *P*<0.01), and serum creatinine (97.4±27.2 versus 109.6±37.0 mmol/L; *P*<0.01), whereas 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 indexed LV mass (*r*=0.442; *P*<0.01), LVEDVi (indexed Left Ventricular End Diastolic Volume) (*r*=0.401; *P*=0.011), and tissue relaxation (mean E′; *r*=0.348; *P*=0.03), although not with change in blood pressure. Change in indexed LV mass correlated with change in all systolic, diastolic, and mean arterial blood pressure (*r*=0.468 [*P*=0.004], *r*=0.357 [*P*=0.032], and *r*=0.367 [*P*=0.03], respectively) (Table 4).

## Discussion

Although 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 ECV

**Table 2.** Baseline and Intervention Effect (Multimodality Imaging)

| | Spironolactone | | | Control | | | Change Over Study Period | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Baseline | Completion | *P* Value | Baseline | Completion | *P* Value | Intervention | Control | *P* Value |
| CMR volumetric | | | | | | | | | |
| LVEDV, mL | 142.5±26.5 | 129.8±21.6 | 0.001 | 138.9±35.3 | 136.9±38.2 | 0.44 | −12.6±14.3 | −2.00±11.7 | 0.014 |
| Indexed LVEDV, mL/m$^2$ | 71.8±14.0 | 65.4±11.2 | 0.001 | 71.8±18.5 | 70.7±19.5 | 0.43 | −6.4±7.4 | −3.40±11.3 | 0.33 |
| LV mass, g | 104.4±26.2 | 94.0±20.6 | 0.001 | 101.4±29.4 | 104.0±32.8 | 0.11 | −10.5±10.9 | 2.6±6.9 | 0.00 |
| Indexed LV mass, g/m$^2$ | 52.7±14.1 | 47.3±10.8 | >0.001 | 52.1±14.0 | 53.3±15.1 | 0.15 | −5.4±5.5 | 1.1±3.7 | 0.00 |
| LVEF, % | 53.5±5.5 | 53.8±6.6 | 0.85 | 54.8±5.2 | 58.2±6.4 | 0.001 | 0.3±6.7 | 3.5±4.0 | 0.084 |
| RVEDV, mL | 140.0±26.6 | 137.7±19.4 | 0.60 | 153.0±43.4 | 155.5±43.7 | 0.49 | −2.22±17.5 | 2.50±15.9 | 0.39 |
| Indexed RVEDV, mL/m$^2$ | 74.4±14.6 | 73.31±11.3 | 0.64 | 76.3±20.1 | 78.9±18.9 | 0.45 | −1.07±9.6 | 1.46±8.5 | 0.39 |
| RVEF, % | 48.4±5.7 | 47.1±7.0 | 0.26 | 46.5±6.6 | 44.8±15.8 | 0.64 | −1.3±4.8 | −1.8±16.4 | 0.91 |
| Left atrial volume, mL | 145.6±32.2 | 142.4±30.7 | 0.44 | 133.7±36.8 | 135.0±36.8 | 0.70 | −3.3±17.4 | 1.4±14.9 | 0.39 |
| Indexed left atrial volume, mL/m$^2$ | 73.6±16.7 | 72.0±15.7 | 0.45 | 69.1±18.5 | 69.9±18.4 | 0.67 | −1.6±8.9 | 0.8±7.6 | 0.38 |
| Right atrial volume, mL | 157.6±40.3 | 148.5±35.2 | 0.11 | 153.1±49.9 | 146.6±45.2 | 0.17 | −9.1±23.1 | −6.5±20.0 | 0.72 |
| Indexed right atrial volume, mL/m$^2$ | 79.6±20.3 | 74.6±15.8 | 0.080 | 79.0±24.8 | 75.6±21.9 | 0.19 | −5.0±11.4 | −3.4±10.6 | 0.65 |
| Echo tissue relaxation | | | | | | | | | |
| Lateral E′ | 11.22±2.42 | 11.09±2.59 | 0.87 | 10.21±3.39 | 10.99±4.48 | 0.24 | −0.12±3.043 | 0.83±3.07 | 0.34 |
| Septal E′ | 8.65±2.00 | 8.14±1.72 | 0.21 | 8.09±3.24 | 7.89±2.80 | 0.71 | −0.51±1.72 | −0.24±2.48 | 0.70 |
| Mean E′ | 9.89±1.87 | 9.15±2.81 | 0.22 | 9.15±3.36 | 9.44±3.49 | 0.58 | −0.32±1.86 | 0.29±2.43 | 0.39 |
| CMR tissue characterization | | | | | | | | | |
| Native T1, ms | 1229±52 | 1207±87 | 0.31 | 1266±59 | 1241±71 | 0.018 | 1±107 | −22±2 | 0.39 |
| ECV, % | 28.7±3.7 | 27.7±3.4 | 0.14 | 27.6±3.4 | 28.3±4.4 | 0.14 | −1.0±2.43 | 0.8±2.2 | 0.019 |
| Indexed cellular mass, g | 37.6±10.0 | 34.3±7.9 | 0.001 | 37.5±9.6 | 37.8±9.8 | 0.54 | −3.3±3.7 | 1.1±5.3 | 0.001 |
| Indexed extracellular mass, g | 15.1±4.8 | 13.0±3.4 | 0.002 | 14.4±4.8 | 15.0±5.9 | 0.091 | −2.1±2.6 | 0.8±1.7 | <0.001 |

Data are given as mean±SD. CMR indicates cardiovascular magnetic resonance; ECV, extracellular volume; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction.



expansion in HF-PEF. Thereby, our results suggest potential mechanisms for the disease-modifying effect of spironolactone seen in larger randomized trials.[7,8]

## Therapeutic Effect

We have demonstrated that MRA administration in HF-PEF leads to a decrease in LV mass, a further antihypertensive effect in a well-treated cohort, relative regression of myocardial fibrosis, and significant mass reduction of both the cellular and, possibly more important, 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 noninvasive 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 caused by increased myocardial fibrosis leads to elevation of left atrial pressure, in turn leading to elevation of pulmonary pressures and progressive right ventricular 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 subgroup analysis of the TOPCAT trial, spironolactone was demonstrated to lead to a reduction in morbidity and mortality in selected patients.[6] In our study, ΔECV was significantly correlated with change in indexed LV mass and change in mean E′. This association suggests that the previously observed beneficial effects of spironolactone are likely related to improved passive stiffness because of regression of diffuse myocardial fibrosis and decrease in LV mass.

## Blood Pressure Effect

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

We are unable to determine if the difference in rate of change in myocardial fibrosis accumulation observed is caused by improved blood pressure control with a decrease in afterload, a direct antifibrotic effect of spironolactone, or a combination of the 2. Alternatively, it has been previously reported that the diuretic effect of some nonneurohormonal antihypertensive 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 caused by decrease in afterload and that spironolactone is exerting a direct tissue effect in HF-PEF.

Despite normal blood pressure at enrollment, 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 remodeling. 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 (Systolic Blood Pressure Intervention Trial)[29] may, in part, be explained by such an effect.

## Future Directions

Neurohormonal activation, myocardial fibrosis, salt/water retention, and hypertension are all key features of HF-PEF pathophysiological characteristics 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 extracellular 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 pathological conditions and disease manifestations. Further characterization and

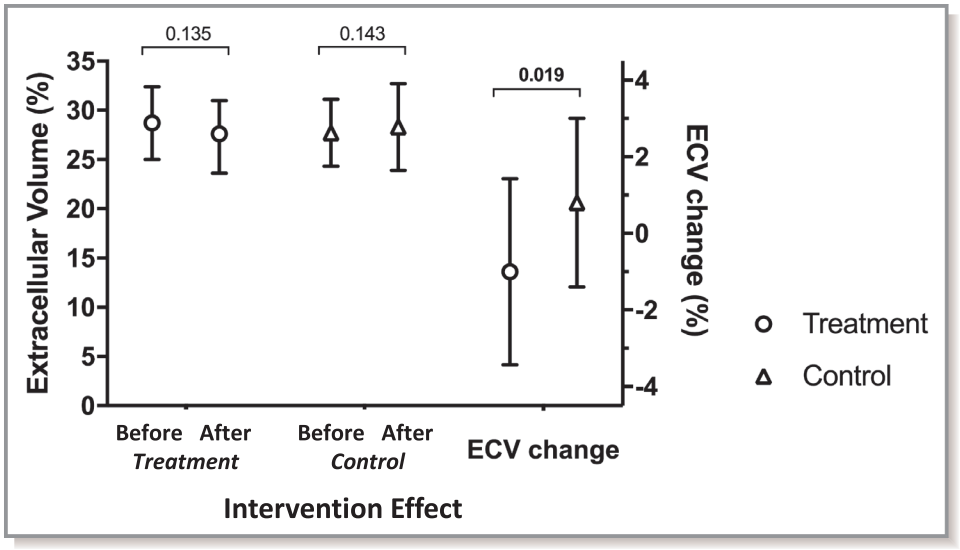


**Figure 2.** Effect on myocardial fibrosis of spironolactone vs controls in heart failure with preserved ejection fraction. Significant change was not seen on intragroup analysis (*P*=0.135 and *P*=0.143, respectively); however, rate of change in extracellular volume (ECV) differed significantly, with a relative decrease seen in extracellular volume after treatment (*P*=0.019).

**Table 3.** Baseline and Intervention Effect (Blood Pressure and Serum)

| | Spironolactone | | | Control | | | Change Over Study Period | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Baseline | Completion | *P* Value | Baseline | Completion | *P* Value | Intervention | Control | *P* Value |
| Blood pressure | | | | | | | | | |
| Systolic, mm Hg | 130.8±19.1 | 120.2±13.5 | <0.01 | 129.6±9.9 | 130.5±13.1 | 0.625 | −9.94±13.2 | 1.00±13.3 | 0.017 |
| Diastolic, mm Hg | 76.8±8.0 | 72.1±6.8 | 0.013 | 75.4±11.4 | 79.1±12.6 | 0.195 | −4.33±6.7 | 2.84±11.1 | 0.023 |
| MABP, mm Hg | 94.2±10.4 | 79.7±5.9 | <0.01 | 94.6±8.9 | 89.2±8.8 | 0.045 | −5.47±6.9 | 0.89±10.0 | 0.035 |
| Pulse pressure, mm Hg | 52.1±19.0 | 38.7±18.6 | 0.004 | 54.2±11.2 | 50.2±21.1 | 0.353 | −5.61±9.4 | −1.84±10.2 | 0.252 |
| Laboratory | | | | | | | | | |
| Creatinine, mmol/L | 97.4±27.2 | 109.6±37.0 | <0.01 | 101.33±38.1 | 96.3±29.0 | 0.460 | 12.7±14.7 | −5.1±30.7 | 0.027 |
| Potassium, mmol/L | 4.11±0.4 | 4.31±0.4 | 0.056 | 4.06±0.22 | 4.10±0.43 | 0.673 | 0.26±0.35 | 0.04±0.46 | 0.097 |
| Serum biomarkers | | | | | | | | | |
| NT-proBNP, pg/mL | 1667±1246 | 1619±1169 | 0.753 | 1706±1588 | 1599±1496 | 0.494 | −78±676 | −107±685 | 0.895 |
| P1NP | 52.32±18.83 | 51.47±19.94 | 0.733 | 57.15±31.47 | 50.25±26.06 | 0.130 | −1.72±10.16 | −6.90±19.52 | 0.307 |
| P3NP | 9.816±3.22 | 9.02±2.94 | 0.223 | 10.0±3.70 | 8.39±2.93 | 0.013 | −0.53±2.57 | −1.61±2.70 | 0.208 |
| HS-CRP | 4.55±3.33 | 4.09±3.13 | 0.560 | 5.30±3.91 | 5.06±3.60 | 0.629 | −0.79±3.1 | −0.25±2.29 | 0.536 |
| MMP3 | 228.29±50.04 | 224.65±57.65 | 0.762 | 237.63±72.59 | 243.85±54.20 | 0.663 | −3.64±51.64 | 6.21±64.28 | 0.599 |

Data are given as mean±SD. HS-CRP indicates high-sensitivity C-reactive protein; MABP, mean arterial blood pressure; MMP3, matrix metallopeptidase 3; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P1NP, procollagen type I N-terminal peptide; P3NP, procollagen type III N-terminal peptide.



phenotyping to identify the subgroups 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. In addition, 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 enrollment.

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 herein may be related to limitation of sample size.

## Limitations

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

The dropout rate of 27% was higher than anticipated, and, as a result, only 41 participants completed the study. Most dropouts were because of withdrawal of consent, caused, in part, by 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 caused by 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, although prespecified, it must be recognized that the secondary outcome findings may have occurred by chance.

The study population included a high percentage of patients with atrial fibrillation when compared with other HF-PEF studies. The reasons for this in our study are not clear; however, although this differs from previously published data, subgroup analysis of the TOPCAT trial suggests that these patients may benefit from spironolactone administration. In addition, the presence of atrial fibrillation may theoretically

**Table 4.** Correlation of Selected Imaging and Physiological Changes

| Change ECV | *R* | *P* Value | Change Indexed LV Mass | *R* | *P* Value |
|---|---|---|---|---|---|
| ECV, % | … | … | ECV | 0.442 | <0.01 |
| Indexed LV mass, g/m$^2$ | 0.442 | <0.01 | Indexed LV mass, g/m$^2$ | … | … |
| Indexed LVEDV, mL/m$^2$ | 0.401 | 0.011 | Indexed LVEDV, mL/m$^2$ | 0.610 | <0.01 |
| Indexed LA volume, mL/m$^2$ | 0.307 | 0.065 | Indexed LA volume, mL/m$^2$ | 0.273 | 0.107 |
| Indexed RVEDV, mL/m$^2$ | 0.196 | 0.238 | Indexed RVEDV, mL/m$^2$ | 0.305 | 0.062 |
| RVEF, % | 0.464 | <0.01 | RVEF, % | 0.074 | 0.663 |
| Lateral E′, cm/s | 0.279 | 0.086 | Lateral E′, cm/s | 0.069 | 0.685 |
| Septal E′, cm/s | 0.240 | 0.141 | Septal E′, cm/s | 0.103 | 0.543 |
| Mean E′, cm/s | 0.348 | 0.030 | Mean E′, cm/s | 0.097 | 0.568 |
| Systolic BP, mm Hg | 0.236 | 0.160 | Systolic BP, mm Hg | 0.468 | <0.01 |
| Diastolic BP, mm Hg | 0.163 | 0.336 | Diastolic BP, mm Hg | 0.357 | 0.032 |
| MABP, mm Hg | 0.153 | 0.374 | MABP, mm Hg | 0.367 | 0.030 |

BP indicates blood pressure; ECV, extracellular volume; LA, left atrial; LV, left ventricular; LVEDV, LV end-diastolic volume; MABP, mean arterial blood pressure; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction.

affect CMR ECV calculation because of 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 center, suggesting the presence of ECV expansion in diabetes mellitus with microalbuminemia.[21] This step was taken in an attempt to minimize heterogeneity in the study population as a response to problems with previous HF-PEF studies; however, we recognize this too may limit application of the findings as diabetes mellitus is a frequently encountered comorbidity in populations with HF-PEF.

## 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 pathophysiological characteristics and prognosis. The masses of both the extracellular and cellular myocardial compartments decreased significantly over the study period and occurred in association with a decrease 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 caused by further blood pressure modification.

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