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ORIGINAL ARTICLE

Determinants of the beneficial effect of mineralocorticoid receptor antagonism on exercise capacity in heart failure with reduced ejection fraction

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Abstract

Background: The determinants of the impact of mineralocorticoid receptor antagonism (MRA) on exercise tolerance in heart failure with reduced ejection fraction (HFrEF) have not been sufficiently characterised.

Aim: We sought to investigate the factors associated with improvement in exercise capacity following the introduction of spironolactone to therapy in HFrEF patients, as well as to assess the association between improvement in exercise capacity and changes in cardiac functional characteristics with treatment.

Methods: In 120 patients (age 62 ± 11 years) with stable chronic HFrEF, remaining on optimal pharmacotherapy, spironolactone 25 mg/d was added to treatment. Echocardiographic assessment, including myocardial deformation, and treadmill exercise tests were performed at baseline and at six-month follow-up.

Results: According to the functional improvement at follow-up, patients were stratified into two groups: with increase in exercise capacity > 20% (IMPRpos, n = 68) and < 20% (IMPRneg, n = 52) of the baseline value. The IMPRpos subset demonstrated significantly larger improvement in left ventricular systolic and diastolic functions at follow-up, as assessed by global longitudinal deformation (GLS), ejection fraction, and tissue e' velocity. Functional improvement > 20% was independently predicted by diabetes (odds ratio [OR] 5.62, p = 0.011), estimated glomerular filtration rate (OR 0.95, p = 0.008), and B-type natriuretic peptide (BNP) at baseline (OR 0.54, p = 0.027), and associated with increase in GLS at follow-up (OR 1.40, p = 0.019).

Conclusions: In patients with HFrEF, improvement in exercise capacity in response to the addition of spironolactone to treatment is more evident in the presence of diabetes, decreased renal function and lower BNP, and improvement in GLS is a contributor to this beneficial effect of MRA.

Key words: exercise capacity, heart failure with reduced ejection fraction, left ventricular longitudinal deformation, mineralocorticoid receptor antagonism

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INTRODUCTION

Mineralocorticoid receptor antagonism (MRA) has been extensively shown to decrease mortality and morbidity in heart failure (HF) with reduced ejection fraction (HFrEF), with a number of pathophysiological mechanisms mediating its treatment effects [1–4]. The HF guidelines endorse the addition of MRA as the next step in pharmacotherapy for HFrEF patients not responding satisfactorily to treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, and diuretics [5, 6]. The translation of evidence-based therapy to routine clinical practice is, however, suboptimal, because in some

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registries the proportion of eligible patients not receiving MRA exceeds 60% [7]. The major reason discouraging physicians from prescribing MRA is the risk of renal dysfunction and hyperkalaemia as potential side effects.

Despite the increasing use of MRA in HF, the factors influencing the impact of this treatment on exercise tolerance have not been sufficiently studied. Better recognition of this issue may aid decision-making, especially in patients with renal disorders and/or the propensity to develop hyperkalaemia, who require a careful weighing of the benefits and risks associated with this therapy. Both hyperkalaemia and decreased renal function may coexist in HF patients and are frequently linked with older age, hypotension, and diabetes mellitus [8].

The improvement in left ventricular (LV) performance is a major component of the favourable impact of MRA on exercise tolerance in HF patients [9, 10]. Global longitudinal deformation (GLS) is a well-validated parameter of LV systolic function, which has been demonstrated as a sensitive and specific marker outperforming other measures of LV contractility, especially in early stages of HF and subclinical myocardial disease [11, 12]. Nonetheless, the diagnostic role of GLS in advanced cardiac impairment in HFrEF is less well established. Some evidence suggests that GLS is more closely associated with alterations in exercise capacity than LV ejection fraction (LVEF) [13, 14].

In this study, we sought to investigate the factors associated with improvement in exercise capacity following the introduction of spironolactone to therapy in patients with HFrEF to better characterise the subset with a high probability of functional benefit. We also sought the association between the improvement in exercise capacity and changes in cardiac functional characteristics with treatment, with special focus on GLS, which is assumed to be superior in this aspect to other echocardiographic metrics.

METHODS

Patients

The study population encompassed 120 patients with stable symptomatic heart failure in New York Heart Association (NYHA) functional class ≥ II and LVEF < 45%, remaining on treatment with ACEI or ARB and β-blockers (if not contraindicated) at the recommended dose or maximal tolerated dose, who were enrolled from hospital clinics at two tertiary cardiology centres (University Hospital in Wroclaw and St. John Paul II Hospital in Poznan). We initially planned to recruit patients with LVEF < 35% as per the guidelines [6], but because this threshold was too restrictive to ensure a sufficient sample size it was increased to < 45%. Finally, patients with LVEF > 35% represented 55% of the studied population. Exclusion criteria comprised permanent arrhythmias, including atrial fibrillation (because of the confounding effect of heart rhythm irregularities on the accuracy of GLS measurement), significant valvular and congenital heart disease, primary hepatic dysfunction, a serum potassium level exceeding 5.0 mmol/L, an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 of body-surface area, a history of side-effects with spironolactone, and treatment with MRA or acute coronary syndromes within the preceding six months.

All participants were informed of the purpose of the study and provided written informed consent. Investigations conformed with the Declaration of Helsinki and were approved by the Institutional Ethics Committee.

Study protocol

At baseline, the enrollees underwent physical examination, blood specimen collection, echocardiography, and treadmill exercise testing. A 25-mg dose of spironolactone once daily was added to the treatment regimen in each participant. Previous pharmacotherapy was maintained unchanged. To standardise the comparisons between the treatment regimens using different drugs, medication quantity was determined by a daily defined dose calculated as per World Health Organisation standards [15]. Patients' status, compliance with the treatment, and serum electrolytes and creatinine were monitored at fortnightly visits during the first two months and then monthly, with more frequent controls in case of clinical indications. After six months, the baseline investigations were repeated.

Echocardiography

Echocardiographic imaging was performed using standard equipment (Vivid e9, General Electric Medical Systems, Milwaukee, WI, USA) with a phased array 2.5 MHz multifrequency transducer. Cardiac dimensions, volumes, and wall thicknesses were measured according to standard recommendations. Peak early (E) and late diastolic flow velocity (A), and deceleration time of early diastolic flow wave (DT) were obtained from the apical four-chamber view by pulsed-wave Doppler. The ratio of mitral inflow early diastolic velocity to peak early diastolic tissue velocity (e') averaged from the septal and lateral sides of the mitral annulus (E/e') was calculated to approximate LV filling pressure.

Myocardial deformation was assessed by a semi-automated two-dimensional speckle tracking technique (Echopac, GE Medical Systems, Horten, Norway) from the three apical views with temporal resolution of 60 to 90 frames/s. All echocardiographic indices were averaged over three consecutive cardiac cycles.

Exercise testing

Each participant underwent symptom-limited exercise testing on a treadmill using a modified Bruce protocol. Exercise capacity was evaluated in metabolic equivalents (METs) on the basis of the peak exercise intensity from treadmill speed and grade.

Laboratory assays

Peripheral venous blood samples were drawn between 08:00 and 09:00 h, after a 30-min rest in the supine position, and were subsequently frozen at –70°C until assayed. A commercially available fluorescence immunoassay (Triage BNP Test, Biosite Diagnostics Inc., San Diego, CA, USA) was used to assess circulating B-type natriuretic peptide (BNP).

Estimated GFR was computed according to the Modification of Diet in Renal Disease (MDRD) four-variable formula.

Statistical analysis

Data are presented as mean ± standard deviation. Intergroup comparisons were carried out using an unpaired two-sided Student t test for continuous variables and by χ^2 test for categorical variables. Homogeneity of variances was assessed by the Levene test. Longitudinal analyses were performed by a paired two-sided Student t test. Skewed variables were log-transformed before analysis. Logistic regression analysis was used to determine predictors and assess associations of improvement in exercise capacity at follow-up. The c-statistic was used to evaluate model performance. A receiver operator characteristic analysis was used to examine the ability of particular variables to predict improvement in exercise capacity at follow-up. Changes in particular parameters with intervention (Δ) were calculated by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. All calculations were performed with standard statistical software (Statistica for Windows 12; StatSoft Inc., Tulsa, OK, USA). A p-value of 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

According to the degree of improvement in exercise capacity at six months, the study sample was divided into two groups including subjects demonstrating an arbitrary increase in METs > 20% (IMPRpos) and ≤ 20% (IMPRneg) of the baseline value. The two subsets did not differ in terms of age, sex proportions, body mass index (BMI), prevalence of hypertension and ischaemic aetiology of HF, NYHA class distribution, HF duration, blood pressure, heart rate, lipidogram, diabetes control, drugs prescriptions and quantities, baseline exercise capacity and exercise time, or sodium, potassium, and haemoglobin levels. The IMPRpos group was characterised by a higher prevalence of diabetes, more impaired renal function, and lower baseline BNP level (Tables 1, 2). A larger increase in METs after a six-month treatment with spironolactone in the IMPRpos group was accompanied by a more pronounced beneficial change in NYHA classification (Table 2). No significant intergroup differences were noted in BNP-level dynamics with treatment; however, the percentage of patients with improvement (decrease) of this biomarker was higher in the IMPRpos group (51 [75%] vs. 30 [58%]; p = 0.04).

In agreement with previous studies employing aldosterone blockade, there was a slight but significant increase in serum potassium (p < 0.001 in both subgroups) and a slight reduction in renal function (p for the decline in eGFR 0.05 in the IMPRpos group and 0.02 in the IMPRneg group; Table 2).

Cardiac morphology and function

The two groups formed on the basis of clinical response to treatment did not differ with respect to baseline values of cardiac functional and structural characteristics. At follow-up, patients from the IMPRpos group demonstrated significantly greater improvements in LV end-diastolic, LV end-systolic, and stroke volumes, left atrial volume, LVEF, GLS, and septal e' velocity as compared with their peers from the IMPRneg subset (Table 3).

Prediction of functional improvement with spironolactone

Logistic regression analysis revealed that the independent determinants of > 20% increase in exercise capacity at follow-up were as follows: presence of diabetes, baseline BNP, and eGFR. Each subsequent parameter added to a previous model improved the predictive power for improvement in exercise capacity at six months; namely, adding baseline eGFR improved the model based on diabetes mellitus, and adding baseline BNP improved the model based on diabetes and eGFR (Fig. 1A). Other variables tested in the model were selected on the basis of anticipated association and included age, sex, blood pressure, BMI, baseline values of LVEF, GLS, E/e', and tricuspid annular plane systolic excursion. No significant association with changes in exercise capacity was found for a decrease in renal function with treatment.

To relate our findings to the symptomatic improvement in exercise tolerance, an analogical sequential logistic regression analysis was performed, in which the dichotomous dependent variable was defined as a post-treatment improvement in NYHA class vs. no improvement. Similarly to the exercise capacity-based analysis, the presence of diabetes and baseline BNP level were independent predictors of symptomatic treatment benefit, whereas eGFR was of borderline significance in the final model (Fig. 1B). Seventy-five per cent of patients in the symptomatic improvement group demonstrated an increase in METs > 20%. The subsets with and without a positive symptomatic response to spironolactone did not differ in BNP-level dynamics at follow-up (–60 [–209; –13] pg/mL vs. –44 [–128; 18] pg/mL, p = 0.25); however, the former group exhibited a significantly greater increase in GLS (3.7% ± 2.2% vs. 1.6% ± 2.7%, p < 0.001).

Receiver operator characteristic analysis showed that the utility of particular variables in predicting improvement in exercise capacity at six months increased progressively in the following order: BNP (area under the curve [AUC] 0.61), presence of diabetes (AUC 0.64), and eGFR (AUC 0.69; Fig. 2). However, it should be noted that the AUC values for the predictors were low.

Table 1. Demographic and clinical characteristics of the patients with an increase in baseline exercise capacity > 20% (IMPRpos) and < 20% (IMPRneg)

	IMPRpos (n = 68)	IMPRneg (n = 52)	p IMPRpos vs. IMPRneg
Age [years]	63.4 ± 11.9	60.4 ± 8.5	0.14
Male sex	50 (74)	38 (73)	0.96
Ischaemic aetiology of HF	54 (79)	42 (81)	0.89
LVEF > 35%	38 (56)	28 (54)	0.82
Heart failure duration [years]	3.70 ± 3.76	3.50 ± 2.95	0.75
Body mass index [kg/m^2]	29.3 ± 5.2	28.0 ± 4.0	0.15
Hypertension	55 (81)	38 (73)	0.31
Diabetes mellitus	29 (43)	8 (15)	0.002
Renal dysfunction	24 (35)	7 (13)	0.007
CABG	3 (4)	3 (6)	0.74
Total cholesterol [mg/dL]	170.0 ± 35.3	164.0 ± 31.6	0.34
LDL-cholesterol [mg/dL]	99.7 ± 32.1	94.1 ± 28.3	0.32
HDL-cholesterol [mg/dL]	41.9 ± 7.1	40.6 ± 12.4	0.47
Triglycerides [mg/dL]	142.0 ± 51.9	146.4 ± 81.4	0.71
Haemoglobin A1c [%]*	5.85 ± 0.93	6.09 ± 1.29	0.56
Pharmacological treatment:			
ACEIs/ARBs	68 (100)	51 (98)	0.26
β-blockers	67 (99)	51 (98)	0.85
Ivabradine	1 (1)	1 (2)	0.85
Diuretic agents	51 (75)	36 (69)	0.60
Daily defined dose:			
ACEIs/ARBs	1.21 ± 0.52	1.31 ± 0.54	0.31
β-blockers	0.83 ± 0.28	0.76 ± 0.24	0.15
Loop diuretics	2.34 ± 1.26	2.40 ± 0.45	0.74

Data are shown as number (percentage) or mean ± standard deviation. Renal dysfunction was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. *Comparison of haemoglobin A1c only in diabetic patients. ACEI/ARBs — angiotensin converting enzyme inhibitors/ /angiotensin receptor blockers; CABG — coronary artery bypass grafting; HDL — high-density lipoprotein; HF — heart failure; LDL — low-density lipoprotein; LVEF — left ventricular ejection fraction; Conversion to SI units are as follows: for cholesterol — multiply by 0.02586, for triglicerydes — multiply by 0.01129

Table 2. Baseline values and change during follow-up in blood pressure, laboratory, and exercise testing characteristics of the patients with an increase in baseline exercise capacity > 20% (IMPRpos) and < 20% (IMPRneg)

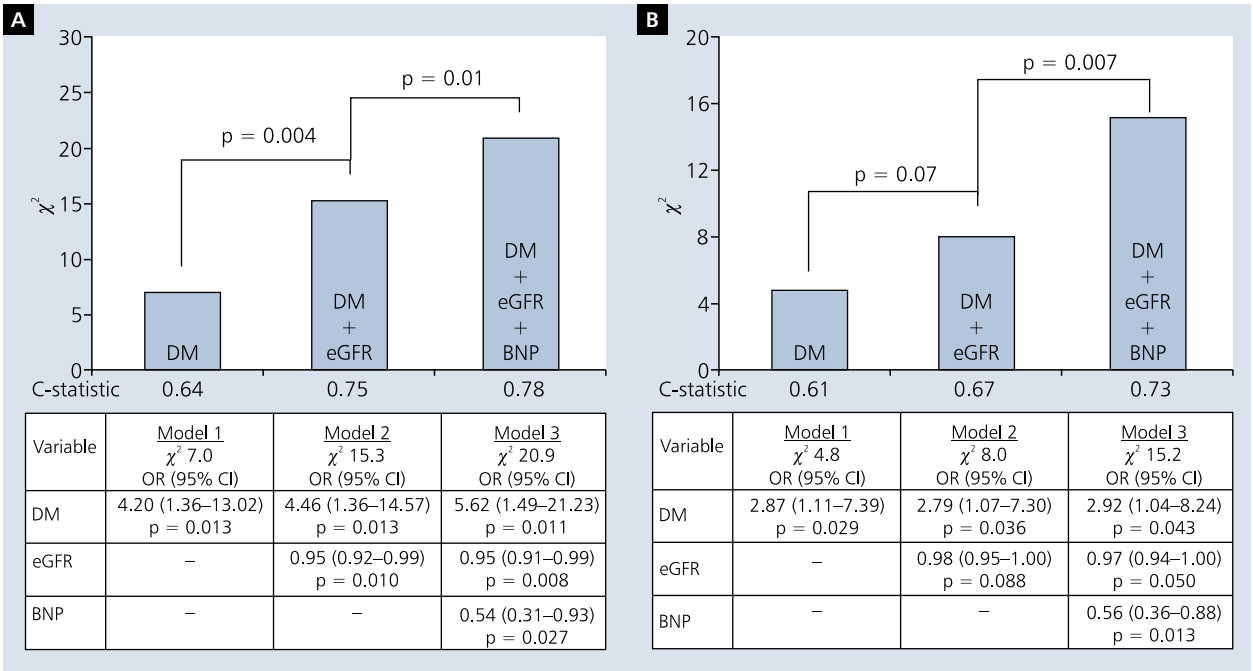
	Baseline			Change from baseline to follow-up		
	IMPRpos (n = 68)	IMPRneg (n = 52)	p IMPRpos vs. IMPRneg	IMPRpos	IMPRneg	p IMPRpos vs. IMPRneg
Systolic BP [mmHg]	115.0 ± 15.2	114.6 ± 15.1	0.89	0.5 ± 11.2	–0.7 ± 8.7	0.53
Diastolic BP [mmHg]	73.0 ± 8.1	71.7 ± 8.1	0.40	–3.0 ± 9.5	–1.1 ± 7.6	0.25
Heart rate [bpm]	73.2 ± 8.7	74.3 ± 8.3	0.48	–2.5 ± 8.4	–1.4 ± 6.6	0.43
NYHA class I/II/III	0/46/22 (0/68/32)	0/33/19 (0/64/36)	0.64	16/44/8 (24/64/12)	8/27/17 (15/52/33)	0.02
BNP [pg/mL]	132 (79–341)	279 (121–474)	0.04	–51 (–158 – 1)	–47 (–96 – 17)	0.71
Creatinine [mg/dL]	1.10 ± 0.25	1.01 ± 0.21	0.04	0.04 ± 0.20	0.07 ± 0.18	0.40
eGFR [mL/min/1.73 m^2]	68.1 ± 14.8	78.0 ± 17.9	0.002	–3.1 ± 10.4	–5.6 ± 16.0	0.31
Haemoglobin [g/dL]	11.6 ± 2.9	10.9 ± 2.6	0.18	0.1 ± 0.7	0.1 ± 0.6	0.68
Sodium [mmol/L]	138.9 ± 2.4	138.7 ± 2.2	0.64	0.7 ± 2.6	0.3 ± 2.2	0.43
Potassium [mmol/L]	4.2 ± 0.3	4.3 ± 0.3	0.21	0.3 ± 0.4	0.3 ± 0.3	0.40
METs	5.3 ± 2.5	6.1 ± 2.5	0.09	3.0 ± 1.4	0.0 ± 0.8	< 0.001
METs [% predicted]	67.6 ± 31.0	74.5 ± 17.4	0.18	39.4 ± 20.1	0.1 ± 9.3	< 0.001
Exercise time [s]	251 ± 144	292 ± 103	0.09	163.0 ± 112	6 ± 54	< 0.001

Data are shown as number (percentage), mean ± standard deviation or median (interquartile range); BP — blood pressure; BNP — B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; METs — metabolic equivalents; NYHA — New York Heart Association

Table 3. Baseline values and change during follow-up in cardiac structural and functional characteristics of the patients with an increase in baseline exercise capacity > 20% (IMPRpos) and < 20% (IMPRneg)

	Baseline			Change from baseline to follow-up		
	IMPRpos (n = 68)	IMPRneg (n = 52)	p IMPRpos vs. IMPRneg	IMPRpos	IMPRneg	p IMPRpos vs. IMPRneg
LV end-diastolic dimension [mm]	61.1 ± 8.2	60.4 ± 7.3	0.62	–0.8 ± 8.7	–0.6 ± 4.6	0.88
Septal wall [mm]	11.7 ± 2.1	11.2 ± 2.0	0.20	–0.5 ± 1.8	0.0 ± 1.5	0.14
Posterior wall [mm]	10.2 ± 2.2	9.7 ± 1.9	0.21	–0.2 ± 1.7	0.1 ± 1.3	0.31
LV mass index [g/m^2]	135.4 ± 32.6	126.9 ± 33.4	0.18	–5.6 ± 22.3	–1.8 ± 16.0	0.30
Basal RV dimension [mm]	38.6 ± 4.8	37.7 ± 5.1	0.33	–0.1 ± 2.6	0.5 ± 2.5	0.22
LV end-diastolic volume [mL/m^2]	68.4 ± 21.6	71.9 ± 27.7	0.44	–3.8 ± 13.4	0.4 ± 17.3	0.15
LV end-systolic volume [mL/m^2]	43.3 ± 17.7	44.8 ± 20.5	0.66	–8.7 ± 13.4	–1.4 ± 14.4	0.005
Stroke volume index [mL/m^2]	25.1 ± 8.2	27.1 ± 9.3	0.32	5.0 ± 6.5	1.8 ± 5.5	0.006
LA volume index [mL/m^2]	37.7 ± 15.0	34.0 ± 16.0	0.21	–3.0 ± 7.9	1.6 ± 10.4	0.007
LV ejection fraction [%]	37.7 ± 6.8	37.2 ± 7.1	0.70	5.7 ± 7.4	3.0 ± 5.8	0.03
LV global longitudinal strain [%]	11.3 ± 3.2	12.2 ± 3.2	0.15	3.6 ± 2.6	1.6 ± 2.3	< 0.001
E/A ratio	0.98 ± 0.50	0.93 ± 0.44	0.58	0.00 ± 0.52	0.03 ± 0.39	0.74
E-wave deceleration time [ms]	207 ± 68	222 ± 82	0.30	10 ± 81	–7 ± 52	0.20
Septal e' velocity [cm/s]	5.3 ± 1.5	5.0 ± 2.2	0.39	0.3 ± 1.2	–0.3 ± 1.3	0.008
E/e'	14.6 ± 6.1	13.9 ± 5.9	0.52	–1.9 ± 7.3	–0.3 ± 4.6	0.18
TAPSE [mm]	20.3 ± 4.4	20.9 ± 3.9	0.43	0.6 ± 3.9	–0.2 ± 3.0	0.21

Data are shown as mean ± standard deviation. LA — left atrial; LV — left ventricular; RV — right ventricular; TAPSE — tricuspid annular plane systolic excursion



Variable	Model 1 χ^2 7.0 OR (95% CI)	Model 2 χ^2 15.3 OR (95% CI)	Model 3 χ^2 20.9 OR (95% CI)
DM	4.20 (1.36–13.02) p = 0.013	4.46 (1.36–14.57) p = 0.013	5.62 (1.49–21.23) p = 0.011
eGFR	–	0.95 (0.92–0.99) p = 0.010	0.95 (0.91–0.99) p = 0.008
BNP	–	–	0.54 (0.31–0.93) p = 0.027

Variable	Model 1 χ^2 4.8 OR (95% CI)	Model 2 χ^2 8.0 OR (95% CI)	Model 3 χ^2 15.2 OR (95% CI)
DM	2.87 (1.11–7.39) p = 0.029	2.79 (1.07–7.30) p = 0.036	2.92 (1.04–8.24) p = 0.043
eGFR	–	0.98 (0.95–1.00) p = 0.088	0.97 (0.94–1.00) p = 0.050
BNP	–	–	0.56 (0.36–0.88) p = 0.013

Figure 1. Predictive value of diabetes, renal function, and B-type natriuretic peptide (BNP) for > 20% improvement in exercise capacity at six months (**A**) and for improvement in New York Heart Association class at six months (**B**) by logistic regression models; CI — confidence interval; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; OR — odds ratio

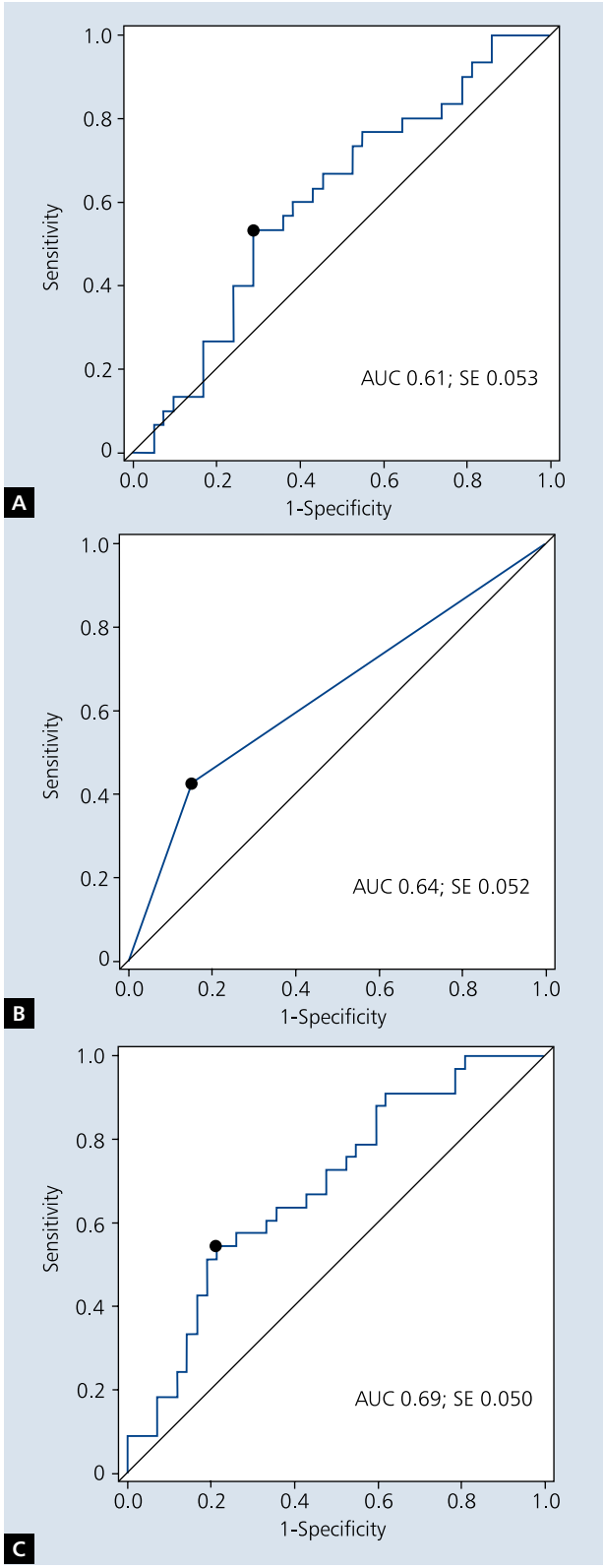


Figure 2. Receiver operating characteristic curves of B-type natriuretic peptide (**A**), diabetes (**B**), and estimated glomerular filtration rate (**C**) in predicting > 20% improvement in exercise capacity at six months; AUC — area under the curve; SE — standard error

Associations of changes in LV functional characteristics with improvement in exercise capacity

Logistic regression analysis demonstrated that among LV systolic and diastolic parameters, only improvement in GLS was independently associated with an > 20% increase in exercise capacity at follow-up (Table 4).

Adherence and side effects

All enrolled patients completed the study. In four participants (two in each subgroup), the dose of spironolactone had to be reduced to 25 mg every other day due to hyperkalaemia > 5.5 mmol/L. Mild gynaecomastia developed in one male patient but did not lead to drug discontinuation. No other adverse effects or complications were reported.

DISCUSSION

This study demonstrates that improvement in exercise capacity in a clinically stable population with HFrEF in response to the addition of spironolactone to standard treatment is more evident in the presence of diabetes, decreased renal function and lower BNP level, and improvement in GLS may be an indicator of this beneficial effect of MRA. Accordingly, symptomatic HFrEF patients with diabetes and kidney disease, despite being at increased risk for the development of hyperkalaemia and worsening renal performance, should be considered for this therapeutic strategy.

Clinical determinants of response to aldosterone blockade

The mechanisms behind the clinical benefit imparted by MRA in HF are not entirely clear. Previous large, randomised trials demonstrated that the prognostic benefits of MRA were achievable over a wide spectrum of clinical and pathophysiological derangements; however, the magnitude of the effect of this treatment might differ between some subsets [1–3]. The current study identified factors promoting improvement in exercise tolerance with a six-month spironolactone therapy in the HF population with LVEF < 45%.

Diabetes mellitus is recognised as a major risk factor for adverse outcomes, as well as the development of hyperkalaemia and renal insufficiency in HF [8]. However, patients with diabetes in the present study were more likely to exhibit a greater post-treatment increase in exercise capacity than their non-diabetic counterparts. In the pathophysiological milieu of metabolic disturbances, the cardiovascular system may be more prone to the detrimental influence of aldosterone and thereby respond more positively to aldosterone blockade. The finding of the amplification of the MRA effect in diabetes is in line with the post hoc analysis from the EPHESUS trial reporting a higher absolute risk reduction of the composite of cardiovascular death and hospitalisation in the diabetic cohort [16].

Table 4. Associations of changes from baseline to follow-up in left ventricular systolic and diastolic parameters with > 20% improvement in exercise capacity at six months

Parameter	Unadjusted			Model with diabetes, eGFR, and BNP		
	OR	95% CI	p	OR	95% CI	p
Δ GLS	1.40	1.10–1.37	0.005	1.40	1.06–1.84	0.019
Δ LVEF	1.06	0.99–1.15	0.10	1.03	0.93–1.14	0.53
Δ E/e'	0.96	0.88–1.04	0.31	0.97	0.88–1.06	0.45

Δ — value at follow-up minus value at baseline; CI — confidence interval; BNP — B-type natriuretic peptide; GLS — global longitudinal deformation; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; OR — odds ratio

Renal dysfunction, both present at baseline and developing during treatment, contributes to increased risk in HF [8]. Despite a potential GFR-depressing effect of MRA, HF patients with mild to moderate renal insufficiency (eGFR 30–60 mL/min/1.73 m^2) are beneficiaries of therapy with aldosterone blockade [8, 17]. Our analysis revealed that decreased pre-treatment renal function was associated with a greater functional improvement at six months. This is consistent with the absolute clinical risk reduction in the RALES trial, which was most pronounced in patients with reduced GFR [17], as well as with the results of a small study showing improvements in LV structural and functional characteristics with MRA in chronic kidney disease [18, 19]. The explanation for the favourable effects of MRA in the context of reduced renal function might be that specific pathophysiological features promote a positive response to aldosterone-antagonising therapy in this setting. Up-regulation of the renin–angiotensin–aldosterone system and a subsequent aldosterone-mediated cardiac and renal injuries might provide a substrate for MRA to induce beneficial alterations resulting in clinical improvements [17, 20].

The larger post-treatment increment in exercise capacity in the current study was linked with lower BNP levels at a baseline assessment. BNP and N-terminal pro–BNP (NT-proBNP) have been shown to be major prognosticators in HFrEF, as well as markers mirroring the treatment effects, also with MRA [5, 21, 22]. We did not demonstrate a higher average decline in BNP levels in the subset that benefited more from taking spironolactone, but on an individual basis, a higher proportion of patients from this group experienced the decrease in BNP as compared with their peers who had a lower degree of functional improvement. It can be hypothesised that lower pre-treatment BNP levels might reflect a higher potential for reversibility of cardiovascular abnormalities. The reasons for this are speculative, and the amount of myocardial fibrosis, which has been shown to be associated with the level of natriuretic peptides even in the subclinical disease, should be considered [23]. This notion is not discrepant with the finding that the groups of better and poorer responders to treatment did not differ significantly in the baseline LV impairment, because the degree of cardiac fibrosis may not correlate with LV functional indices in HFrEF [24]. From a practical point of view, the obtained results encourage the early implementation of spironolactone therapy in patients with stable HF and relatively low BNP values, especially if they have diabetes, because in this group of patients one can expect the greatest functional improvement after using this drug.

LV remodelling and contribution from GLS

The addition of MRA to therapy generated favourable changes in LV structural and functional remodelling, which were more pronounced in the subset with a greater increase in exercise capacity. Both LV volumetric improvement (with an increase in ejection fraction as a consequence) and myocardial deformation improvement were demonstrated, but only the augmentation of GLS was significantly associated with a more apparent regression of exercise intolerance. Despite strong pathophysiological underpinnings, the direct relationship between improvements in cardiac function and clinical benefits has not been convincingly shown in previous interventions with MRA in HFrEF [4]. One of the reasons for this might be the use of echo-derived LVEF having a number of limitations that decrease the sensitivity and appropriateness of assessment [11]. This study showed that GLS, characterised by avoidance of geometric assumptions, less variability and load-dependence, and higher sensitivity to subtle changes, might be a better tool to provide incremental information on the translation of myocardial improvements into clinical gains.

Limitation of the study

The results of this study should be interpreted in view of several limitations. First, the study population does not satisfy the newly-proposed definition of HFrEF because of the inclusion of a number of individuals currently classified as having HF with mid-range ejection fraction. Therefore, the extrapolation of our findings to patients with a more severely depressed ejection fraction should be made cautiously. Second, the estimated GFR was calculated on the basis of the MDRD formula, which may be less accurate for eGFR > 60 mL/min/1.73 m^2. Third, the exclusion of patients with atrial fibrillation might restrict the external validity of our investigations. Fourth, we did not use a core-lab for

echocardiographic analyses; however, a high reproducibility of measurements between the two participating centres (**Supplementary material — see journal website**) suggests that this could not have been a reason for data misinterpretation. Finally, because all the study participants were of Caucasian race, the applicability of our findings to other ethnic groups is uncertain.

In conclusion, the coexistence of diabetes mellitus and/or impaired renal function — conditions associated with an increased risk of adverse clinical outcomes and detrimental side-effects of MRA — favours greater post-treatment increments in exercise capacity in response to aldosterone blockade added on top of optimal medical therapy in clinically stable HFrEF patients. These high-risk subgroups require, however, very strict biochemical control and reconsideration of MRA that are more selective than spironolactone and possess a better safety profile in terms of undesirable metabolic and potassium-increasing effects. GLS reflects the changes in cardiac mechanics closely associated with the regression of exercise limitation and might be suitable to monitor the improvements in LV function with treatment.

Conflict of interest: *none declared*

References

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999; 341(10): 709–717, doi: 10.1056/NEJM199909023411001, indexed in Pubmed: 10471456.
2. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348(14): 1309–1321, doi: 10.1056/NEJMoa030207, indexed in Pubmed: 12668699.
3. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364(1): 11–21, doi: 10.1056/NEJMoa1009492, indexed in Pubmed: 21073363.
4. Jacob MS, Tang WH. Aldosterone-receptor antagonists in heart failure: insights after EMPHASIS-HF. Curr Heart Fail Rep. 2011; 8(1): 7–13, doi: 10.1007/s11897-010-0046-0, indexed in Pubmed: 21207206.
5. Ponikowski P, Voors AA, Anker SD, et al. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol. 2016; 74(10): 1037–1147.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62(16): e147–239.
7. Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J. 2011; 161(6): 1024–30.e3, doi: 10.1016/j.ahj.2011.01.027, indexed in Pubmed: 21641346.
8. Eschalier R, McMurray JJV, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure). J Am Coll Cardiol. 2013; 62(17): 1585–1593, doi: 10.1016/j.jacc.2013.04.086, indexed in Pubmed: 23810881.
9. Cicoira M, Zanolla L, Rossi A, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol. 2002; 40(2): 304–310, indexed in Pubmed: 12106936.
10. Macdonald JE, Kennedy N, Struthers AD. Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. Heart. 2004; 90(7): 765–770, doi: 10.1136/hrt.2003.017368, indexed in Pubmed: 15201246.
11. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart. 2014; 100(21): 1673–1680, doi: 10.1136/heartjnl-2014-305538, indexed in Pubmed: 24860005.
12. Sengeløv M, Jørgensen PG, Jensen JS, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging. 2015; 8(12): 1351–1359, doi: 10.1016/j.jcmg.2015.07.013, indexed in Pubmed: 26577264.
13. Hasselberg NE, Haugaa KH, Sarvari SI, et al. Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. Eur Heart J Cardiovasc Imaging. 2015; 16(2): 217–224, doi: 10.1093/ehjci/jeu277, indexed in Pubmed: 25552469.
14. Donal E, Coquerel N, Bodi S, et al. Importance of ventricular longitudinal function in chronic heart failure. Eur J Echocardiogr. 2011; 12(8): 619–627, doi: 10.1093/ejechocard/jer089, indexed in Pubmed: 21727079.
15. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2018. Oslo, 2017. https://www.whocc.no/atc_ddd_index/.
16. O'Keefe JH, Abuissa H, Pitt B. Eplerenone improves prognosis in postmyocardial infarction diabetic patients with heart failure: results from EPHESUS. Diabetes Obes Metab. 2008; 10(6): 492–497, doi: 10.1111/j.1463-1326.2007.00730.x, indexed in Pubmed: 17490427.
17. Vardeny O, Wu DH, Desai A, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol. 2012; 60(20): 2082–2089, doi: 10.1016/j.jacc.2012.07.048, indexed in Pubmed: 23083787.
18. Edwards NC, Steeds RP, Stewart PM, et al. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. J Am Coll Cardiol. 2009; 54(6): 505–512, doi: 10.1016/j.jacc.2009.03.066, indexed in Pubmed: 19643310.
19. Edwards NC, Ferro CJ, Kirkwood H, et al. Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. Am J Cardiol. 2010; 106(10): 1505–1511, doi: 10.1016/j.amjcard.2010.07.018, indexed in Pubmed: 21059444.
20. Di Zhang An, Nguyen Dinh Cat A, Soukaseum C, et al. Cross-talk between mineralocorticoid and angiotensin II signaling for cardiac remodeling. Hypertension. 2008; 52(6): 1060–1067, doi: 10.1161/HYPERTENSIONAHA.108.117531, indexed in Pubmed: 18981328.
21. Pitt B, Anker S, Böhm M, et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail. 2015; 17(2): 224–232, doi: 10.1002/ejhf.218.
22. Iraqi W, Rossignol P, Angioi M, et al. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction

complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. Circulation. 2009; 119(18): 2471–2479, doi: 10.1161/CIRCULATIONAHA.108.809194, indexed in Pubmed: 19398668.
23. Liu CY, Heckbert SR, Lai S, et al. Association of Elevated NT-proBNP With Myocardial Fibrosis in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2017; 70(25): 3102–3109, doi: 10.1016/j.jacc.2017.10.044, indexed in Pubmed: 29268924.
24. Su MYM, Lin LY, Tseng YHE, et al. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. JACC Cardiovasc Imaging. 2014; 7(10): 991–997, doi: 10.1016/j.jcmg.2014.04.022, indexed in Pubmed: 25240451.

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WHAT IS NEW?

Despite the increasing use of mineralocorticoid receptor antagonism (MRA) in heart failure, the factors influencing the effectiveness of this therapeutic option remain insufficiently defined. This issue may be important for decision-making especially in patients with renal disorders and/or the propensity to develop hyperkalaemia — conditions associated with an increased risk of adverse clinical outcomes and detrimental side-effects of MRA. Our study demonstrated that improvement in exercise capacity in a clinically stable population with heart failure with reduced ejection fraction (HFrEF) in response to the addition of spironolactone to standard treatment is more evident in the presence of diabetes and decreased renal function, and improvement in left ventricular longitudinal deformation is a contributor to this beneficial effect of MRA. Accordingly, symptomatic HFrEF patients with diabetes and kidney disease, despite being at higher risk for the development of hyperkalaemia and worsening renal performance, should be considered for this therapeutic strategy.