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Original Article

Effects of Mineralocorticoid Receptor Antagonists in Early-Stage Heart Failure With Preserved Ejection Fraction

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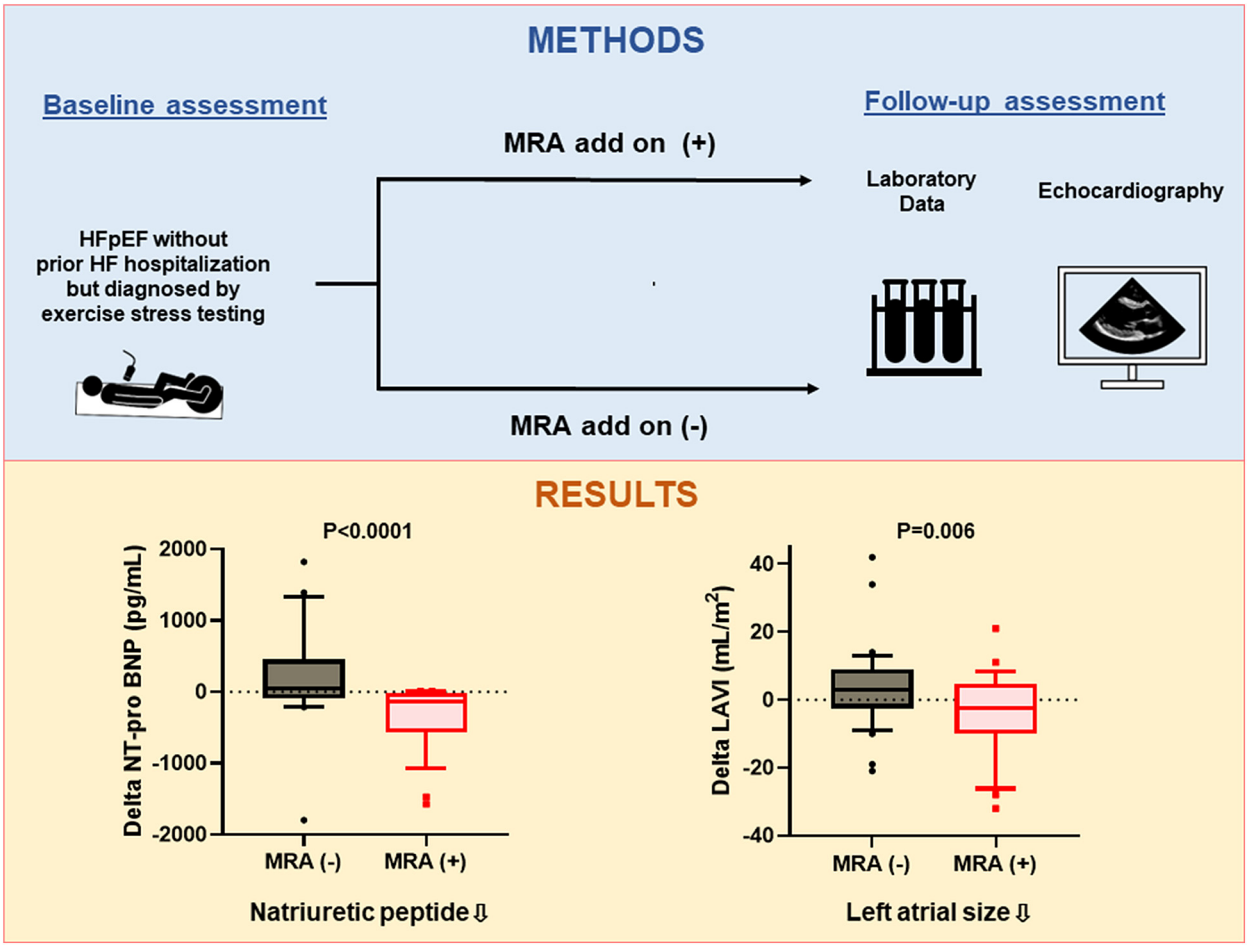

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ABSTRACT

Background: Hospitalization with a first episode of heart failure (HF) is a serious event associated with poor clinical outcomes in HF with preserved ejection fraction (HFpEF). Identification of HFpEF via detection of elevated left ventricular filling pressure at rest or during exercise may allow early intervention. Benefits of treatment with mineralocorticoid receptor antagonists (MRAs) in established HFpEF have been reported, but use of MRAs is not well studied in early HFpEF without prior HF hospitalization.

Methods: We retrospectively studied 197 patients with HFpEF who did not have prior hospitalization but had been diagnosed by exercise stress echocardiography or catheterization. We examined changes in natriuretic peptide levels and echocardiographic parameters reflecting diastolic function following MRA initiation.

Results: Of the 197 patients with HFpEF, MRA treatment was initiated for 47 patients. After a median 3-month follow-up, reduction in N-terminal pro-B-type natriuretic peptide levels from baseline to follow-up was greater in patients treated with MRA than in those who were not (median, -200 pg/mL [interquartile range, -544 to -31] vs 67 pg/mL [interquartile range, -95 to 456], $P < 0.0001$ in 50 patients with paired data). Similar results were observed for the changes in B-type natriuretic peptide levels. Reduction in the left atrial volume index was also greater in the MRA-treated group than in the non-MRA-treated group after a median 7-month follow-up (77 patients with paired echocardiographic data). Patients with lower left ventricular global longitudinal strain experienced a greater reduction in N-terminal pro-B-type natriuretic peptide levels following MRA treatment. In the safety assessment, MRA modestly decreased renal function but did not change potassium levels.

Conclusions: Our results suggest that MRA treatment has potential benefits for early-stage HFpEF.

RÉSUMÉ

Contexte : L'hospitalisation consécutive à un premier épisode d'insuffisance cardiaque (IC) est un événement grave associé à des résultats cliniques médiocres dans l'IC à fraction d'éjection préservée (ICFEP). Or, la détection d'une pression de remplissage ventriculaire gauche élevée au repos ou à l'effort peut permettre de déceler une ICFEP et d'intervenir de façon précoce. Par ailleurs, le recours à des antagonistes des récepteurs minéralocorticoïdes (ARM) serait bénéfique dans les cas d'ICFEP, mais leur utilisation n'a pas été bien étudiée dans l'ICFEP précoce sans hospitalisation préalable pour cause d'insuffisance cardiaque.

Méthodologie : Nous avons étudié rétrospectivement 197 patients atteints d'ICFEP qui n'avaient pas été hospitalisés auparavant, mais dont la maladie avait été diagnostiquée par une échocardiographie de stress ou un cathétérisme. Après l'instauration des ARM, nous avons examiné les variations des taux de peptides natriurétiques et des paramètres échocardiographiques reflétant la fonction diastolique.

Résultats : Sur les 197 patients atteints d'ICFEP, 47 ont entamé un traitement par des ARM. Après un suivi médian de trois mois, la réduction des taux de propeptides natriurétiques de type B N-terminal (NT-proBNP) entre la valeur initiale et le suivi était plus importante chez les patients traités par des ARM que chez ceux qui ne l'étaient pas (médiane : -200 pg/ml [écart interquartile : -544 à -31] contre 67 pg/ml [écart interquartile : -95 à 456], $p < 0{,}0001$ chez 50 patients ayant des données appariées). Des résultats similaires ont été observés pour la variation des taux de peptides natriurétiques de type B. La réduction du volume de l'oreillette gauche était également plus importante dans le groupe traité par des ARM que dans le groupe témoin après un suivi médian de sept mois (données échocardiographiques appariées pour 77 patients). Les patients présentant une déformation longitudinale globale du ventricule gauche plus faible ont connu une réduction plus importante des taux de NT-proBNP après le traitement par des ARM. Enfin, lors de l'évaluation de l'innocuité, les ARM ont légèrement altéré la fonction rénale, mais sans modifier les taux de potassium.

Conclusions : Ces résultats semblent indiquer que le traitement par des ARM présente des avantages potentiels dans les cas d'ICFEP au stade précoce.

Heart failure (HF) with preserved ejection fraction (HFpEF) is a major healthcare problem, with a high incidence of morbidity and mortality.[1] The first hospitalization for HF is a serious event in the progression of the disease and is associated with poor clinical outcomes.[2,3] One potential reason for the poor prognosis in HFpEF may be related to delays in diagnosis and therapeutic intervention.[2-4] Early identification of the disease, prior to the first HF hospitalization, may improve outcomes. Detection of elevated left ventricular (LV) filling pressure at rest or during physiological stress, such as exercise, is emphasized as the key objective evidence that can be used to identify HFpEF at an earlier disease stage.[5-11] Recent large clinical trials have demonstrated effective treatments to improve clinical outcomes in HFpEF,[12-15] but very little is known about how to treat patients with early HFpEF, especially those who do not have prior HF hospitalization but have been diagnosed by the presence of elevated LV filling pressure during exercise testing.[3,16]

Activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of HFpEF.[17] Mineralocorticoid receptor antagonists (MRAs) may mitigate LV diastolic dysfunction and improve clinical outcomes in patients with HFpEF, possibly by suppressing RAAS-mediated cardiac fibrosis and hypertrophy.[12,18-20] The American College of Cardiology, American Heart Association, and Heart Failure Society of America guidelines now recommend that patients with HFpEF be treated with an MRA (class IIb).[11] Although some therapeutic effects of RAAS inhibitors may be attenuated in early HFpEF,[3] findings from the **T**reatment **o**f **P**reserved **C**ardiac Function Heart Failure With an **A**ldosterone An**t**agonist (TOPCAT) trial and others

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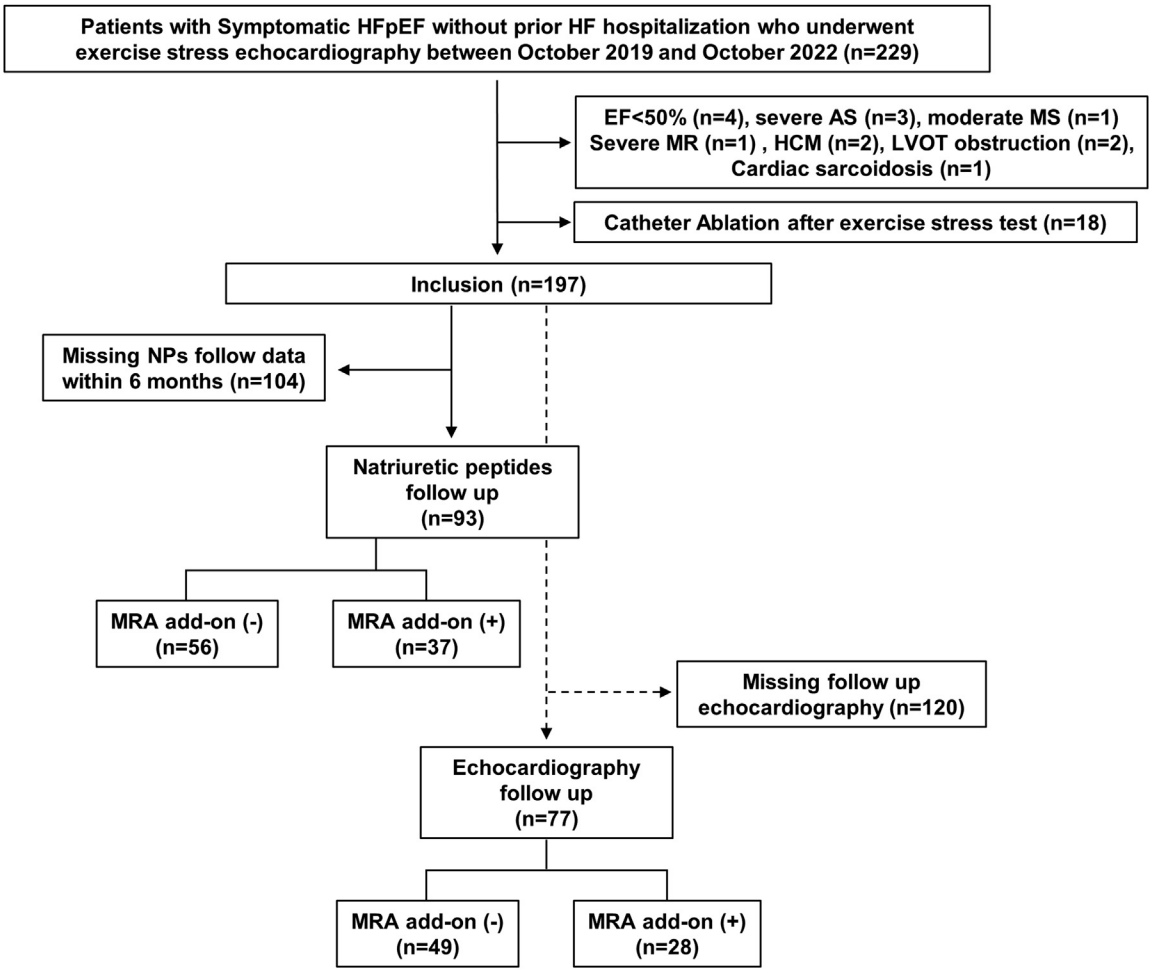

Figure 1. Study flow chart. AS, aortic stenosis; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, HF with preserved EF; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; MS, mitral stenosis; and NP, natriuretic peptide.

suggest potential benefits of MRA treatment in early-stage HFpEF.[19,21-23]

Accordingly, we hypothesized that MRA treatment could have potential benefits among patients with early HFpEF who have no history of hospitalization for HF. To test this hypothesis, we examined changes in natriuretic peptide (NP) levels and echocardiographic parameters reflecting diastolic function, following MRA initiation in HFpEF patients without prior HF hospitalization but diagnosed by elevated LV filling pressure at rest or during exercise stress testing.

Methods

Study population

Consecutive patients who were referred to our echocardiographic laboratory for exercise stress echocardiography for evaluation of exertional dyspnea between October 2019 and October 2022 were retrospectively screened. The participants were required to have no history of hospitalization for HF. The diagnosis of HFpEF was determined using the Heart Failure Association **P**re-test Assessment, **E**chocardiography and Natriuretic Peptide, **F**unctional Testing, **F**inal Etiology (HFA-PEFF) algorithm proposed by the HFA of the European Society of Cardiology.[9] Briefly, the HFA-PEFF score was calculated as the sum of echocardiographic functional (maximum: 2 points), morphologic (maximum: 2 points), and NP (maximum: 2 points) domains. Points were added to the HFA-PEFF score depending on the findings of the exercise stress echocardiography (2 points were added if the ratio of early diastolic mitral annular velocity to early diastolic transmitral inflow velocity [E/e' ratio] during exercise was $\geq$ 15, and 3 points were added if the E/e' ratio during exercise $\geq$ 15 with tricuspid regurgitant velocity [TRV] during exercise $>$ 3.4 m/s). A diagnosis of HFpEF was confirmed if the total HFA-PEFF score was $\geq$ 5 points. Patients with elevated invasively measured LV filling pressures (pulmonary capillary wedge pressure $>$ 15 mm Hg at rest and/or $\geq$ 25 mm Hg during exercise) on exercise right heart catheterization also were classified as having HFpEF.

Patients with an ejection fraction (EF) $<$ 50%, significant left-sided valvular heart disease ($>$ moderate regurgitation, $>$ mild stenosis), infiltrative, restrictive, or hypertrophic cardiomyopathy, non-group II pulmonary

Table 1. Baseline characteristics among patients with paired natriuretic peptide data

Characteristic	MRA (−) (n = 56)	MRA (+) (n = 37)	*P*
Age, y	74 ± 8	75 ± 9	0.71
Male	34 (50)	13 (34)	0.11
Body mass index, kg/m^2	24.1 ± 5.7	24.2 ± 4.1	0.84
HFA-PEFF score	6 (5, 7)	6 (5, 8)	0.39
Comorbidities			
Diabetes mellitus	18 (26)	11 (29)	0.78
Hypertension	51 (75)	33 (87)	0.14
Sinus rhythm/ paroxysmal AF/ persistent AF, %	71/12/18	66/16/18	0.83
Coronary artery disease	17 (25)	4 (11)	0.06
Medications			
ACEI or ARB	27 (40)	15 (39)	0.98
Beta-blocker	25 (37)	13 (34)	0.79
Loop diuretic	24 (35)	13 (34)	0.91
SGLT2i	5 (7)	3 (8)	0.92
Vital signs			
Heart rate, bpm	74 ± 15	72 ± 12	0.59
Systolic BP, mm Hg	126 ± 17	131 ± 23	0.26
Saturation, %	97 ± 2	97 ± 2	0.44
Laboratories			
BNP, pg/mL	94 (45, 205)	110 (32, 218)	0.84
NT-proBNP, pg/mL	399 (190, 859)	413 (153, 981)	0.84
eGFR, mL/min per 1.73 m^2	54.3 ± 16.4	63.3 ± 19.1	0.01
Potassium, mEq/L	4.4 ± 0.4	4.2 ± 0.4	0.06
Assessments of congestion			
Peripheral edema (no/1+/2+), %	75/23/2	67/27/6	0.52
Pulmonary congestion on chest X-ray	0 (0)	0 (0)	—
Pleural effusion on chest X-ray	6 (9)	2 (6)	0.50
Echocardiographic measures at rest			
LV mass index, g/m^2	88 ± 21	89 ± 23	0.90
LA volume index, mL/m^2	34 (27, 45)	39 (28, 56)	0.34
LV end-diastolic volume, mL	73 ± 33	68 ± 26	0.42
LV ejection fraction, %	65 ± 8	63 ± 7	0.30
E-wave, cm/s	74 ± 27	84 ± 31	0.08
A-wave, cm/s	87 ± 23	90 ± 24	0.48
Mitral e', cm/s	5.8 ± 1.7	5.9 ± 1.6	0.59
E/e' ratio	13 (10, 17)	14 (10, 17)	0.47
TR velocity, cm/s	2.2 ± 0.4	2.3 ± 0.4	0.87
PASP, mm Hg	26 ± 10	25 ± 8	0.81
RAP, mm Hg	3 (3, 3)	3 (3, 3)	0.49
TV s', cm/s	11.8 ± 3.0	11.3 ± 2.9	0.38
Exercise tolerance and symptoms			
Peak watts, W	46 ± 20	51 ± 20	0.22
Exercise time, s	454 ± 186	479 ± 183	0.51
Peak VO_2, mL/min per kg	10.6 ± 3.3	10.7 ± 3.3	0.88
Echocardiographic measures during exercise			
E/e' ratio	16 (12, 20)	16 (13, 20)	0.85
TR velocity, cm/s	3.0 ± 0.5	3.1 ± 0.5	0.30
Invasive hemodynamics at rest*			
PCWP, mm Hg	15 ± 7	15 ± 3	0.69
PA mean pressure, mm Hg	21 ± 8	21 ± 3	0.94
RA pressure, mm Hg	8 ± 7	8 ± 3	0.82
Cardiac output, L/min	5.1 ± 1.9	4.5 ± 0.8	0.25
Invasive hemodynamics during exercise*			
PCWP, mm Hg	33 ± 8	34 ± 7	0.88
PA mean pressure, mm Hg	40 ± 6	46 ± 10	0.08
RA pressure, mm Hg	15 ± 4	16 ± 5	0.60
Cardiac output, L/min	6.7 ± 1.6	7.1 ± 1.5	0.53

Data are mean ± standard deviation, median (interquartile range), or n (%), unless otherwise indicated. HFA-PEFF score is expressed as median and IQR. Peripheral edema is expressed as %.

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin-receptor blockers; BP, blood pressure; BNP, B-type natriuretic peptide; bpm, beats per minute; E/e' ratio, ratio of early diastolic mitral inflow to mitral annular tissue velocities; eGFR, estimated glomerular filtration rate; HFA-PEFF, Heart Failure Association pretest assessment, echocardiography & natriuretic peptide, functional testing, final etiology; LA, left atrial; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-BNP; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; Peak VO_2, oxygen consumption at peak exercise; RA, right atrial; RAP, right atrial pressure; TR, tricuspid regurgitant; TV, tricuspid valve; SGLT2i, sodium-glucose co-transporter-2 inhibitors.

*Data were available in 34 participants.

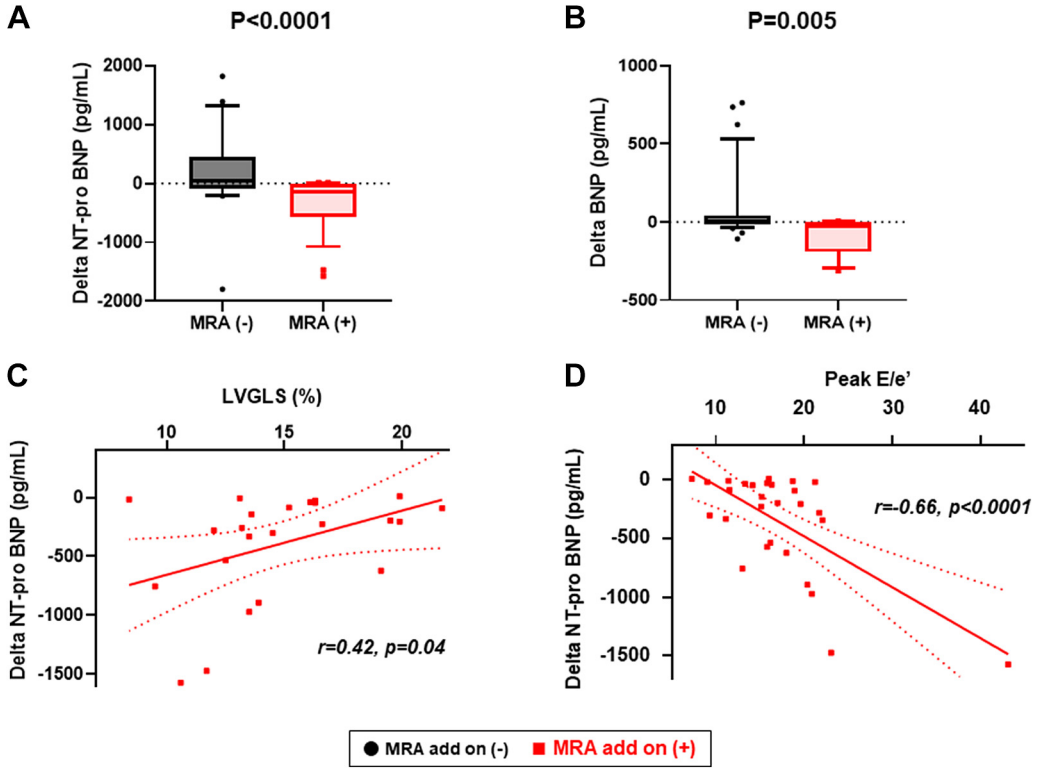

Figure 2. Changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP). (**A**) Change in NT-proBNP from baseline to follow-up was significantly lower in patients with mineralocorticoid receptor antagonist (MRA) treatment than in those without. (**B**) Similarly, change in BNP levels was lower in the MRA group than in the non-MRA group. (**C, D**) Following initiation of MRA, patients with a lower left ventricular global longitudinal strain (LVGLS) at rest or higher ratio of early diastolic mitral inflow to mitral annular tissue velocities (E/e' ratio) during peak exercise demonstrated greater reduction in NT-proBNP levels. **Boxes** represent medians and interquartile ranges, and **whiskers** represent 10th and 90th percentiles.

artery hypertension, and exercise-induced pulmonary hypertension without elevation in the E/e' ratio were excluded. Patients who underwent catheter ablation for atrial fibrillation (AF) after indexed exercise stress echocardiography were also excluded because restoration of sinus rhythm may affect NP levels.[24]

From this HFpEF group, patients with at least one follow-up NP assessment or resting echocardiographic evaluation in a compensated (outpatient) state (that was performed a minimum of >1 month from baseline assessment) were identified (Fig. 1). When patients had multiple follow-up NP data, the measures taken within 6 months and at the most distant point from the baseline assessment were used. Participants were required to have the pair of either B-type NP (BNP) or N-terminal pro-B-type NP (NT-proBNP) level measurements. This study was approved by our institutional review board, as was the waiver for obtaining informed consent. The article's data may be shared upon reasonable request to the corresponding author.

Assessments of cardiac structure and function at baseline and follow-up

Two-dimensional and Doppler echocardiography were performed by experienced sonographers according to current guidelines.[25] All studies were interpreted by well-trained sonographers who were blinded to medication and NP data. LV systolic function was assessed by EF and global longitudinal strain (GLS). GLS was obtained by averaging peak longitudinal strains from 4-, 2-, and 3-chamber apical views (EchoPAC, GE, Milwaukee, WI) and was reported as absolute values. Early diastolic mitral inflow velocity (E-wave) was measured at the mitral leaflet tips, and early diastolic mitral tissue velocity (e') at the septal annulus was recorded to obtain the septal E/e' ratio. The left atrial (LA) volume was calculated using the disk method. LA volume and LV mass were then indexed to the body surface area. Right atrial pressure at rest was estimated from the diameter of the inferior vena cava and its respiratory change.[25] Pulmonary artery systolic pressure at rest was then calculated as $4 \times$ peak TRV^2 + estimated right atrial pressure. The most recent study (distant from the baseline assessment) was used for follow-up echocardiography.

Exercise stress echocardiography

All participants underwent supine ergometry exercise stress echocardiography, starting at 20 W for 5 minutes, increasing in 20-W increments in 3-minute stages until the subject reported exhaustion, as previously reported.[7,26,27] Mitral E-wave, septal e' velocity, E/e' ratio, and TRV were recorded at rest and during each stage of exercise. Doppler measurements represent the mean of 2 beats in sinus rhythm and ≥ 3 beats in AF.

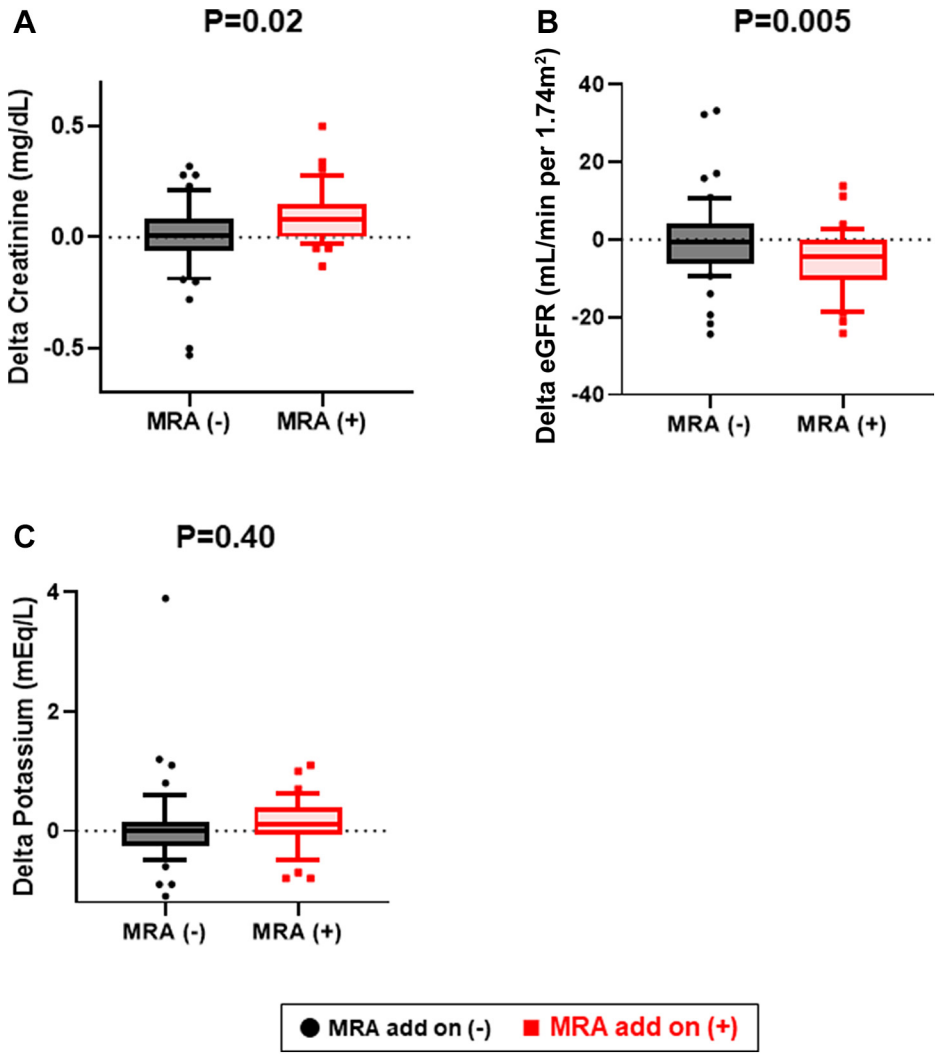

Figure 3. Changes in laboratory data. (**A, B**) Change in creatinine levels was higher, and change in the estimated glomerular filtration rate (eGFR) was lower, in the mineralocorticoid receptor antagonist (MRA)-treated group than in the non-MRA-treated group. (**C**) The change in potassium level was similar between the groups. **Boxes** represent medians and interquartile ranges, and **whiskers** represent 10th and 90th percentiles.

Outcome assessments

Patients with HFpEF were divided based on MRA use (spironolactone, eplerenone, or esaxerenone) or non-use after indexed exercise stress echocardiography. Treatment was determined by the attending cardiologists' clinical judgment based on their evaluation, including exercise stress echocardiography results. The primary outcome was to compare changes in NP levels from baseline to follow-up evaluation between the groups. The secondary outcomes were echocardiographic parameters reflecting diastolic function, including LV mass index, E/e' ratio, and LA volume index (LAVI).

Statistical analysis

Data are reported as the mean (standard deviation), median (interquartile range [IQR]), or number (%), unless otherwise specified. Between-group differences were compared using the unpaired *t*-test, Wilcoxon's rank-sum test, or the χ^2 test, as appropriate. All tests were 2-sided, with a significance level of $P < 0.05$. All statistical analyses were performed using JMP 15.2.0 (SAS Institute, Cary, NC).

Results

Baseline demographics

A total of 215 patients met the inclusion criteria of HFpEF (Fig. 1). Of the 215 patients, 18 were excluded because they had undergone catheter ablation after indexed exercise stress echocardiography, resulting in 197 patients for the final analysis. Overall, 122 patients (62%) were diagnosed with HFpEF based solely on the resting evaluation, and the remaining 75 (38%) were diagnosed after exercise stress testing. Of the 197 patients, 47 were diagnosed based on right heart catheterization at rest or during exercise. Comparisons of the baseline clinical characteristics according to MRA status are presented in Supplemental Table S1.

Of the 197 patients with HFpEF, paired NP data were available for 93 patients (NT-proBNP, n = 50; BNP, n = 47), of which MRA was initiated for 37 patients (40%). Sensitivity analysis comparing baseline characteristics between the patients with paired NP data (n = 93) and those without (n = 104) showed similar results (Supplemental Table S2).

Table 2. Baseline characteristics among patients with paired echocardiographic data

Characteristic	MRA (−) (n = 49)	MRA (+) (n = 28)	*P*
Age, y	73 ± 7	73 ± 9	0.82
Male	15 (31)	10 (36)	0.65
Body mass index, kg/m^2	23.4 ± 3.6	23.6 ± 4.2	0.81
HFA-PEFF score	6 (5, 7)	7 (5, 8)	0.02
Comorbidities			
Diabetes mellitus	8 (16)	8 (29)	0.21
Hypertension	38 (76)	27 (96)	0.02
Sinus rhythm/ paroxysmal AF/ persistent AF, %	82/10/8	79/7/14	0.66
Coronary artery disease	9 (18)	1 (4)	0.04
Medications			
ACEI or ARB	17 (35)	12 (43)	0.48
Beta-blocker	16 (33)	8 (29)	0.71
Loop diuretic	14 (29)	8 (29)	1.00
SGLT-2i	0 (0)	1 (4)	0.15
Vital signs			
Heart rate, bpm	75 ± 13	71 ± 11	0.14
Systolic BP, mm Hg	125 ± 19	133 ± 24	0.09
Saturation, %	97 ± 2	97 ± 2	0.72
Laboratories			
BNP, pg/mL	69 (39, 192)	135 (52, 226)	0.35
NT-proBNP, pg/mL	289 (148, 1489)	528 (211, 1002)	0.69
eGFR, mL/min per 1.73 m^2	54.0 ± 23.3	62.9 ± 20.5	0.10
Potassium, mEq/L	4.3 ± 0.4	4.3 ± 0.4	0.76
Assessments of congestion			
Peripheral edema, no/1+/2+, %	71/26/3	65/31/4	0.88
Pulmonary congestion on chest X-ray	0 (0)	0 (0)	-
Pleural effusion on chest X-ray	3 (7)	1 (4)	0.61
Echocardiographic measures at rest			
LV mass index, g/m^2	87 ± 24	90 ± 24	0.49
LA volume index, mL/m^2	34 (25, 47)	39 (30, 53)	0.11
LV end-diastolic volume, mL	66 ± 24	67 ± 20	0.99
LV ejection fraction, %	64 ± 7	64 ± 7	0.79
E-wave, cm/s	77 ± 27	86 ± 33	0.20
A-wave, cm/s	94 ± 27	93 ± 26	0.81
Mitral e', cm/s	5.5 ± 1.6	6.0 ± 1.7	0.29
E/e' ratio	13 (10, 18)	14 (10, 17)	0.99
TR velocity, cm/s	2.2 ± 0.4	2.4 ± 0.4	0.10
PASP, mm Hg	24 ± 9	26 ± 8	0.34
RAP, mm Hg	3 (3, 3)	3 (3, 7)	0.72
TV s', cm/s	12.7 ± 3.3	12.1 ± 3.4	0.43
Exercise tolerance and symptoms			
Peak watts, W	42 ± 18	52 ± 22	0.03
Exercise time, s	445 ± 174	508 ± 202	0.16
Peak VO_2, mL/min per kg	10.6 ± 3.7	11.4 ± 3.7	0.42
Echocardiographic measures during exercise			
E/e' ratio	17 (14, 21)	17 (13, 20)	0.55
TR velocity, cm/s	2.9 ± 0.5	3.3 ± 0.5	0.003
Invasive hemodynamics at rest*			
PCWP, mm Hg	17 ± 8	17 ± 5	0.92
PA mean pressure, mm Hg	22 ± 9	20 ± 4	0.53
RA pressure, mm Hg	9 ± 7	9 ± 4	0.98
Cardiac output, L/min	5.0 ± 2.2	4.1 ± 0.9	0.30
Invasive hemodynamics during exercise*			
PCWP, mm Hg	35 ± 6	37 ± 13	0.76
PA mean pressure, mm Hg	42 ± 6	45 ± 14	0.54
RA pressure, mm Hg	16 ± 5	18 ± 8	0.64
Cardiac output, L/min	6.6 ± 2.1	7.0 ± 1.2	0.65

Data are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated. HFA-PEFF score is expressed as median and IQR. Peripheral edema is expressed as %.

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin-receptor blockers; BP, blood pressure; BNP, B-type natriuretic peptide; E/e' ratio, ratio of early diastolic mitral inflow to mitral annular tissue velocities; eGFR, estimated glomerular filtration rate; HFA-PEFF, Heart Failure Association pretest assessment, echocardiography & natriuretic peptide, functional testing, final etiology; LA, left atrial; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-BNP; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; Peak VO_2, oxygen consumption at peak exercise; RA, right atrial; RAP, RA pressure; TR, tricuspid regurgitant; TV, tricuspid valve; and SGLT2i, sodium-glucose co-transporter-2 inhibitors.

*Data were available in 19 participants.

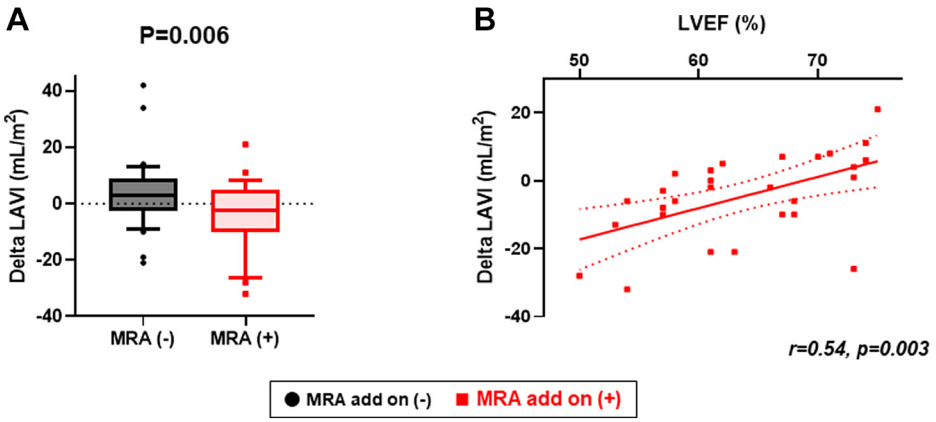

Figure 4. Changes in left atrial volume. (**A**) Change in left atrial volume index (LAVI) was lower in patients in the mineralocorticoid receptor antagonist (MRA)-treated group than those in the non-MRA-treated group. (**B**) Patients with a lower left ventricular ejection fraction (LVEF) at baseline experienced greater reduction in LAVI at follow-up. **Boxes** represent medians and interquartile ranges, and **whiskers** represent 10th and 90th percentiles.

Table 1 summarizes the baseline clinical demographics according to the MRA status in patients with paired NP levels. No significant differences were present in age, sex, body mass index, major comorbidities, medication use, vital signs, or NP levels between patients with vs without MRA treatment. As expected, renal function was impaired in patients without MRA treatment compared to those who received MRA treatment, but potassium levels were similar between the groups. The LV mass, size, EF, LV diastolic function, and right heart parameters at rest were similar between the groups. Exercise capacity, as assessed by exercise intensity, exercise time, and peak oxygen consumption, did not differ between patients who did vs did not receive MRA treatment, with similar E/e' ratios and TRV during peak exercise (Table 1).

Changes in NP levels according to MRA status

The median follow-up duration between baseline and follow-up NP assessments did not differ between patients who did vs did not receive MRA treatment (median 3.3 months [IQR, 2.1-5.1] vs 3.4 months [IQR, 2.7-5.1], $P = 0.78$). No differences occurred in the rate of initiation or the increase in use of non-MRA agents between the baseline and follow-up assessments (Supplemental Table S3). The reduction in NT-proBNP levels from baseline to follow-up was greater in patients who were treated with MRA than in those who were not (median, -200 pg/mL [IQR, -544 to -31] vs 67 pg/mL [IQR, -95 to 456], $P < 0.0001$; Fig. 2A). Similar results were observed for the changes in BNP levels (median, -25 pg/mL [IQR, -191 to 1] vs 7 pg/mL [IQR, -18 to 44], $P = 0.005$; Fig. 2B). When NT-proBNP and BNP were combined, percent decreases in NP levels were consistently greater in patients who received MRA treatment than in those who did not receive MRA treatment (median, -39% [IQR, -56% to -21%] vs 28% [IQR, -20% to 73%], $P < 0.0001$). Patients with a lower GLS at rest or higher E/e' ratio during peak exercise demonstrated a greater reduction in NT-proBNP levels following MRA initiation (Fig. 2, C and D). Although a reduction in renal function was greater in the MRA-treated group than in the non-MRA-treated group (Fig. 3, A and B), it was modest (median changes in creatinine level and estimated glomerular filtration rate were +0.08 mg/dL and -4.5 ml/min per 1.74 m^2, respectively). Changes in potassium levels were similar between the groups (Fig. 3C). Details of the changes in laboratory data from the baseline to follow-up evaluations are presented in Supplemental Table S4.

Changes in echocardiographic measures

Paired echocardiographic data at baseline and follow-up were available for 77 patients with HFpEF for whom MRA treatment was initiated after indexed exercise stress echocardiography (Fig. 1). Sensitivity analysis comparing baseline demographics between the patients with paired echocardiographic data and those without (n = 120) showed that patients with paired echocardiographic data were younger, were predominantly female, and had a lower prevalence of AF and a higher E/e' ratio during exercise than those without (Supplemental Table S5). Table 2 demonstrates no differences in clinical and echocardiographic characteristics according to MRA status, except for peak exercise TRV. The median duration between the baseline and follow-up assessments was similar between patients who received vs did not receive MRA treatment (median, 7.3 months [IQR, 5.3-11.8] vs 8.6 months [IQR, 6.1-12.9], $P = 0.23$). No differences were present in the rate of initiation or increase of non-MRA drugs between the assessments (Supplemental Table S6). The reduction in LAVI was greater in patients who received MRA treatment than in those who did not receive MRA treatment (Fig. 4A). Consistently, the percent reduction in LAVI was also greater in the MRA group than in the non-MRA group (median, -6.7% [IQR, -27.7% to 12.2%] vs 9.5% [IQR, -8.0% to 28.0%], $P = 0.01$). After MRA initiation, patients with HFpEF and lower LV ejection fraction demonstrated greater decreases in LAVI ($r = 0.54$, $P = 0.03$; Fig. 4B).

Table 3. Comparisons of clinical characteristics in the present study vs those in previous studies examining MRA treatment

Study (year)	Design	Subjects	N (MRA group)	Age, y	Female, %	BMI, kg/m^2	HTN, %	Diuretics, %	Prior HF hospitalization, %	BNP NT-proBNP, pg/mL
Present study	Observational	HFpEF without HF hospitalization	197 (47)	75	66	23.6	89	32	0	BNP: 115 NT-proBNP: 429
Kosmalaet al.[34] (2011)	RCT	Metabolic syndrome	79 (40)	58	52	32.8	100	48	NR	NR
Mottram et al.[35] (2004)	RCT	HTN with LVDD	29 (14)	61	60	29.8	100	43	NR	BNP: 29.3 —
Gu et al.[23] (2016)	Observational	HTN with LVH	195 (65)	67	54	25.3	100	11	0	NR
Cleland et al. [19] (2021)	RCT (HOMAGE)	CAD or high-risk of CAD with raised NP	527 (265)	73	23	28.4	81	17	0	— NT-proBNP: 172
Kosmala et al.[36] (2016)	RCT (STRUCTURE)	HFpEF	131 (67)	68	81	29.7	91	64	21[†]	BNP: 54 —
Edelmann et al.[18] (2013)	RCT (Aldo-DHF)	HFpEF	422 (213)	67	52	28.9	92	55	38[†]	— NT-proBNP: 179
Kurrelmeyer et al.[38] (2014)	RCT	HFpEF	48 (24)	66	100	29.4	88	83	58[†]	BNP: 139 —
Deswal et al.[37] (2011)	RCT[*] (RAAM-PEF)	HFpEF	44 (21)	72	5	30.1	100	95	43	BNP: 255 —
Pitt et al.[21] (2014)	RCT (TOPCAT)	HFpEF	3445 (1722)	69	52	31	91	82	71.5[†]	BNP: 235 NT-proBNP: 1017

Values are mean, median, or %. Aldo-DHF, **Aldo**sterone Receptor Blockade in **D**iastolic **H**eart **F**ailure; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; HF, heart failure; HFpEF, HF with preserved ejection fraction; HOMAGE, **H**eart '**Om**ics' in **Age**ing; HTN, hypertension; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; NP, natriuretic peptide; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAM-PEF, **R**andomized **A**ldosterone **A**ntagonis**m** in Heart Failure With **P**reserved **E**jection **F**raction; RCT, randomized control trial; STRUCTURE, **S**pironolac**t**one in Myoca**r**dial Dysf**unct**ion With Red**u**ced Exer**cis**e Capacity; TOPCAT, **T**reatment **o**f **P**reserved **C**ardiac Function Heart Failure With an **A**ldosterone An**t**agonist.

[*] Eplerenone was used; otherwise spironolactone.

[†] History of HF hospitalization within previous 12 months.

Details for changes in echocardiographic parameters from baseline to follow-up evaluations are presented in Supplemental Table S7.

Discussion

To the best of our knowledge, this study is the first to investigate the changes in NP levels and echocardiographic parameters following MRA initiation for patients with early-stage HFpEF without prior HF hospitalization but diagnosed by evidence of elevated LV filling pressure. MRA initiation lowered NP levels and reduced LAVI in patients with early HFpEF. In safety assessments, MRA modestly decreased renal function but did not increase serum potassium levels. This study provides new insights into the potential benefits of MRA treatment for patients with early-stage HFpEF before their first HF hospitalization.

Clinical outcomes in patients with HFpEF remain poor. In addition to limited treatment options, the potential reason for the poor prognosis may be related to delays in diagnosis and therapeutic intervention.[2-4] This reasoning is based on previous observations showing that patients with even prior HF hospitalization experienced a higher risk of clinical events than those who had never been hospitalized.[2,4] Based on this background, a paradigm shift to early identification may allow for more timely intervention. Increases in LV filling pressure at rest or during exercise are fundamental abnormalities in HFpEF.[28,29] The identification of elevated LV filling pressure is an important step in diagnosing HFpEF, and exercise stress testing plays a central role in this process.[5-11] In this study, we examined patients presenting with dyspnea, and the presence of HFpEF was established based on the HFA-PEFF algorithm, including exercise stress testing. Participants had no pulmonary congestion on chest radiography, less peripheral edema, modestly elevated NP levels, and, according to our definition, no prior history of HF hospitalization, suggesting that they were in an early stage of the disease.[5,6]

Recent clinical trials have demonstrated positive results for patients with HFpEF.[12-15] However, evidence gaps exist regarding how patients with early HFpEF could be treated, especially those without prior HF hospitalization but diagnosed by evidence of elevated LV filling pressure during exercise testing.[3,16] Hypertension, diabetes, obesity, and chronic kidney disease are important risk factors for incident HFpEF.[2,30] These comorbidities can promote cardiac structural changes and diastolic dysfunction by inducing cardiac hypertrophy, fibrosis, and stiffening through activation of the RAAS.[17] The RAAS is closely associated with the pathogenesis of HFpEF and thus is likely to be the key therapeutic target.[31-33] To date, 9 studies have examined the efficacy of MRAs in patients with established HFpEF (5 studies) or pre-HFpEF (4 studies; Table 3),[18,19,21,23,34-38] but MRAs have not been well studied in early HFpEF without prior HF hospitalization. In the TOPCAT trial (history of HF hospitalization within 12 months: 71.5%), spironolactone reduced the rate of the primary outcomes among patients enrolled on the basis of an elevated NP level but not among those enrolled on the basis of a previous HF hospitalization.[21] Also, a greater benefit of spironolactone was seen in patients with lower NP levels.[22] Furthermore, previous studies demonstrated that MRA was associated with a reduction in NP levels or improvement in LV diastolic function in patients at high risk of HFpEF with raised NP levels (possibly pre-HFpEF).[19,23] Based on these findings, we examined the effects of MRA on LV diastolic function in patients with early HFpEF without prior HF hospitalization. The strength of our study is that all participants underwent exercise stress echocardiography and had evidence of elevated LV filling pressure at rest or during exercise. We demonstrated that NP levels and LA volume were decreased to a greater extent in patients who underwent MRA treatment than in those who did not. Treatment with MRA can improve water and sodium retention, which may lower LV filling pressures.[32] This change might lead to a reduction in NP levels and LA volume, as observed in this study. Although baseline characteristics were well balanced between the MRA and the non-MRA groups, renal function was better in the MRA group, which may have influenced the response to MRA. Despite the reduction in LA volume, we found no reduction in the E/e' ratio after MRA initiation. Although the reason remains unknown, this effect may be similar to that observed in the **P**rospective Comparison of **ARN**I With **A**RB on **M**anagement **o**f Heart Fail**u**re With Preserved Ejectio**n** Frac**t**ion (PARAMOUNT) trial, in which LA volume was decreased following ARNI treatment, but the E/e' ratio was not.[39]

We further demonstrated that HFpEF patients with relatively lower systolic function (LV ejection fraction and GLS) experienced a greater reduction in NT-proBNP levels and LA volume following MRA treatment. This finding is in accordance with the results of the TOPCAT trial showing a greater benefit from spironolactone treatment in patients with a lower EF.[40] A similar possible benefit has been seen with angiotensin receptor neprilysin inhibitor (ARNI), angiotensin receptors, and beta-blockers among patients with an EF below normal.[13,41,42] The results of this study and others suggest that patients with early HFpEF, and EF closer to 50%, have more significant benefits from MRA treatment. Elevated NP levels and larger LA volume are associated with an increased risk of outcomes.[22] Further studies are warranted to determine whether MRA treatment in early HFpEF can prevent initial hospitalization for HF and improve outcomes in this population.

Limitations

This study had a nonrandomized, retrospective observational design. All participants were referred for exercise stress echocardiography, introducing selection and referral bias. The sample size was modest. The current study included a subset of patients with either paired NP or echocardiographic data, limiting its generalizability.

Conclusions

MRA treatment lowered NP levels and LA volume in HFpEF patients who had no prior HF hospitalization but were diagnosed by the evidence of having elevated LV filling pressure during exercise testing. Our results suggest potential benefits of MRA treatment for early-stage HFpEF.

Ethics Statement

This study was approved by our institutional review board, as was the waiver for obtaining informed consent.

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Supplementary Material

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