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Usefulness of myocardial work measurement in the assessment of left ventricular systolic reserve response to spironolactone in heart failure with preserved ejection fraction

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Aims Improvement in left ventricular (LV) systolic reserve, including exertional increase in global longitudinal strain (GLS), may contribute to the clinical benefit from therapeutic interventions in heart failure with preserved ejection fraction (HFpEF). However, GLS is an afterload-dependent parameter, and its measurements may not adequately reflect myocardial contractility recruitment with exercise. The estimation of myocardial work (MW) allows correction of GLS for changing afterload. We sought to investigate the associations of GLS and MW parameters with the response of exercise capacity to spironolactone in HFpEF.

Methods and results We analysed 114 patients (67 ± 8 years) participating in the STRUCTURE study (57 randomized to spironolactone and 57 to placebo). Resting and immediately post-exercise echocardiograms were performed at baseline and at 6-month follow-up. The following indices of MW were assessed: global work index (GWI), global constructive work (GCW), global wasted work, and global work efficiency. The amelioration of exercise intolerance at follow-up in the spironolactone group was accompanied by a significant improvement in exertional increase in GCW ($P = 0.002$) but not in GLS and other MW parameters. Increase in exercise capacity at 6 months was independently correlated with change in exertional increase in GCW from baseline to follow-up ($\beta = 0.24$; $P = 0.009$) but not with GLS ($P = 0.14$); however, no significant interaction with the use of spironolactone on peak VO_2 was found ($P = 0.97$).

Conclusion GCW as a measure of LV contractile response to exertion is a better determinant of exercise capacity in HFpEF than GLS. Improvement in functional capacity during follow-up is associated with improvement in exertional increment of GCW.

Keywords myocardial work • global longitudinal strain • HFpEF • Spironolactone

Introduction

Accumulating evidence indicates that disturbances of left ventricular (LV) systolic reserve, including blunted exertional increase in myocardial deformation, may contribute to the reduction of exercise capacity in heart failure with preserved ejection fraction (HFpEF).[1–4] The assessment of LV global longitudinal strain (GLS) response to exercise can be useful in the quantification of LV contractile response as well as provide relevant prognostic information in this disease condition.[1,4–6] However, GLS is an afterload-dependent parameter and its measurements may not adequately reflect myocardial contractility recruitment with exercise. This is likely to pose a problem especially in serial assessments, when different blood pressure responses to stress may affect visit-to-visit changes in LV deformation magnitude. Consequently, in the presence of changing afterload, the unrestricted reliance on strain may cause misinterpretation of LV contractile state

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and even lead to improper clinical conclusions. It has been proposed that the assessment of myocardial work (MW) adjusting myocardial deformation for LV pressure dynamics may provide a more accurate quantification of LV performance.[7–10]

The recently published STRUCTURE (SpironolacTone in myocaRdial dysfUnCTion with redUced exeRcisE capacity) study[11] showed an improvement of exercise intolerance over 6 months therapy with spironolactone. However, this improvement was not matched by an improvement in LV deformation reserve, perhaps because of the sensitivity of GLS to loading conditions. In this study, we sought to use a newly developed software approach for approximating LV pressure–strain loops to derive MW, to correct GLS for alterations in afterload. Specifically, we sought to investigate the associations of MW parameters with the response of exercise capacity to spironolactone in HFpEF patients participating in the STRUCTURE study. We hypothesized that MW might be superior to GLS in the assessment of LV contractile response to exercise in this context, irrespective of changing afterload.

Methods

Study design

The STRUCTURE trial (12614000088640) was a prospective, randomized, blinded, parallel-group, placebo-controlled study to test the hypothesis that therapy with spironolactone 25 mg/day for 6 months would improve functional capacity in patients with HFpEF and an abnormal LV diastolic response to exercise. Participants were enrolled and randomized between 2011 and 2015 in Wroclaw, Poland.

Patients and procedures

The study protocol, randomization procedure, and selection criteria have been presented in detail previously.[11] In brief, the basic features essential for patient inclusion were consistent with the diagnostic criteria for HFpEF available at the time of recruitment[12] and comprised: signs or symptoms of heart failure (dyspnoea, fatigue, and exercise intolerance) typical for New York Heart Association (NYHA) functional Class II or III, exercise capacity reduced from age- and sex-predicted normal ranges (according to the reference equation by Wasserman *et al.*[13]), and preserved LV ejection fraction (>50%). Candidate subjects underwent an exercise test and were enrolled in the presence of post-exercise *E*/e' >13 (reflecting elevation of LV filling pressure during exertion) and impaired exercise capacity. The major exclusion criteria encompassed heart rhythm other than stable sinus rhythm, ischaemic heart disease (defined by a positive coronary angiogram or inducible ischaemia during exercise testing), moderate and severe valvular heart disease, established or suspected pulmonary diseases (vital capacity <80% or forced expiratory volume in 1 s <80% of age- and gender-specific reference values), haemoglobin ≤11 g/dL, and other significant comorbidities including malignancy, infections, autoimmune, skeletal, thyroid, and renal diseases [including renal insufficiency with serum creatinine >1.5 mg/dL (132 µmol/L)], hyperkalaemia >5.0 mmol/L, known intolerance or treatment with mineralocorticoid receptor antagonists within the last 3 months, concomitant therapy with a potassium-sparing agent, current lithium use, and pregnancy. The rationale for the exclusion of significant coronary artery disease was the elimination of myocardial ischaemia as a potential determinant of exercise limitation.

All participants were informed of the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the institutional ethics committee.

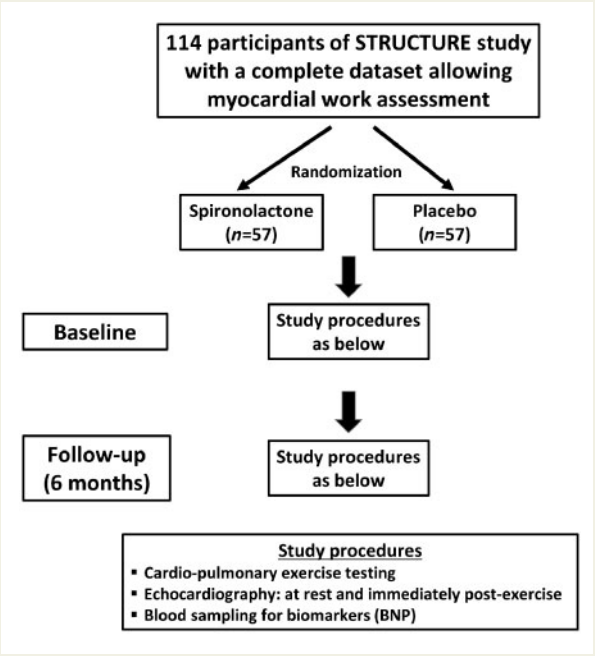

Figure 1 A flowchart illustrating the study protocol.

Eligible patients were randomly allocated to either spironolactone 25 mg/day or matching placebo. At baseline and 6-month follow-up, patients underwent cardiopulmonary exercise testing, resting and immediate post-exercise echocardiogram, and blood sampling for laboratory assessments. Other prescribed therapies remained unchanged throughout the study period.

In this subanalysis, we included 114 patients (57 randomized to spironolactone and 57 to placebo) with a complete cardiopulmonary exercise testing and imaging dataset allowing MW assessment. A flowchart illustrating the study protocol is shown in *Figure 1*.

Echocardiography

Echocardiography was performed using standard equipment (Vivid e9, General Electric Medical Systems, Milwaukee, WI, USA). The same imaging protocol was used at baseline and follow-up visits and performed by the same sonographer. Multiple consecutive cardiac cycles of standard echocardiographic views were acquired and stored digitally for subsequent analysis. Cardiac dimensions and wall thicknesses were measured according to standard recommendations.[14] LV volumes and left atrial volume were evaluated by the biplane Simpson and area-length methods. All cardiac volumes were indexed to body surface area. Cardiac output was computed as the product of heart-rate and stroke volume.

Peak early (E) and late diastolic flow velocity (A), and deceleration time of early diastolic flow wave were measured from the apical four-chamber view by pulsed-wave Doppler with the sample volume placed between the tips of the mitral leaflets. Pulsed-wave tissue Doppler was used to assess peak early diastolic tissue velocity (e'). The ratio of mitral inflow early diastolic velocity to the average e' velocity obtained from the septal and lateral portions of the mitral annulus (*E*/e') was calculated to estimate LV filling pressure. According to previous validation, exertional *E*/e' >13 was considered as a marker of exercise-induced elevation of LV filling pressure.[15]

Table 1 Demographic and clinical characteristics of the study population

	Spironolactone ($n = 57$)	Placebo ($n = 57$)	*P*-value
Age (years)	66.1 ± 7.9	67.5 ± 8.2	0.35
Sex (female), *n* (%)	50 (88)	46 (81)	0.30
Body mass index (kg/m^2)	30.8 ± 4.5	30 ± 4.4	0.34
Hypertension, *n* (%)	53 (93)	51 (89)	0.51
Diabetes, *n* (%)	23 (40)	19 (33)	0.44
NYHA functional Class II, *n* (%)	45 (79)	44 (77)	0.83
NYHA functional Class III, *n* (%)	12 (21)	13 (23)	
Pre-exercise SBP (mmHg)	130.8 ± 14.8	130.0 ± 19.1	0.81
Pre-exercise DBP (mmHg)	76.1 ± 9.2	75.1 ± 10.8	0.61
Peak SBP (mmHg)	163.4 ± 18.4	165.7 ± 23.4	0.56
Peak DBP (mmHg)	64.0 ± 10.9	65.5 ± 13.3	0.51
Pre-exercise HR (1/min)	71.4 ± 9.3	72.8 ± 10.3	0.44
Peak HR (1/min)	120.1 ± 16.6	120.2 ± 17.5	0.99
Peak VO_2 (mL/min/kg)	14.4 ± 3.8	15.3 ± 4	0.23
BNP (pg/mL)	41 (27–63)	54 (29–87)	0.73
Haemoglobin (g/dL)	13.6 ± 1.0	13.6 ± 1.1	0.65
Creatinine (mg/dL)	0.99 ± 0.21	1.03 ± 0.21	0.40
eGFR (mL/min/1.73 m^2)	64.3 ± 12.5	63 ± 12.9	0.59
LV mass index (g/m$^{2.7}$)	55.3 ± 12.4	55.9 ± 12.8	0.86
LA volume index (mL/m^2)	37.3 ± 7.7	35.7 ± 9.6	0.31
E/*A*	0.95 ± 0.45	0.91 ± 0.46	0.64
E/e'	12.0 ± 4.2	11.5 ± 2.5	0.43
Global longitudinal strain (%)	18.3 ± 3.3	18.5 ± 2.9	0.69
LV ejection fraction (%)	72.5 ± 7.7	71.7 ± 8.5	0.60
VA coupling	0.40 ± 0.19	0.42 ± 0.17	0.68
ACE/ARB, *n* (%)	55 (96)	54 (95)	0.65
Beta-blockers, *n* (%)	45 (79)	39 (68)	0.20
Calcium-blockers, *n* (%)	20 (35)	27 (47)	0.18
Thiazides, *n* (%)	31 (54)	29 (51)	0.71
Loop diuretics, *n* (%)	8 (14)	11 (19)	0.45

A, late diastolic mitral flow velocity; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; *E*, peak early diastolic mitral flow velocity; e', peak early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; HR, heart rate; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; SBP, systolic blood pressure; VA, ventricular-arterial.

Table 2 Changes in exercise characteristics at follow-up in the study population

	Spironolactone ($n = 57$)	Placebo ($n = 57$)	*P*-value
Delta pre-exercise SBP (mmHg)	-5.9 ± 21.4	-2.5 ± 21.7	0.41
Delta pre-exercise DBP (mmHg)	-3.1 ± 13.4	-1.6 ± 11.3	0.52
Delta peak SBP (mmHg)	-1.7 ± 20.3	-3.1 ± 20.5	0.71
Delta peak DBP (mmHg)	-1.5 ± 10.3	-1.1 ± 12.3	0.87
Delta pre-exercise HR (1/min)	-0.7 ± 4	-0.9 ± 5.2	0.81
Delta peak HR (1/min)	7.1 ± 16.4	-1.6 ± 17	0.01
Delta peak VO_2 (mL/kg/min)	2.7 ± 3.8	0.2 ± 3.1	<0.001

Delta indicates change at follow-up.
DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Speckle tracking imaging

Longitudinal myocardial deformation was assessed using a semi-automated 2D speckle tracking technique (Echopac PC, General Electric Medical Systems) in the three apical views with typical temporal resolution of 60–90 frames/s. After manual tracing of the endocardial border and selecting the appropriate wall thickness, the software automatically identified six segments in each view and tracked the motion of acoustic markers. Segments that failed to track satisfactorily were readjusted manually and, if this was ineffective, they were excluded from further analysis. The measurements comprised the greatest negative value on the strain curve. Timing of the aortic and mitral valve opening and closure was obtained using single-gated pulsed-wave Doppler traces. GLS was computed as the average value from all LV segments subjected to analysis. All echocardiographic parameters were averaged over three consecutive cardiac cycles.

MW evaluation

MW was assessed by the combination of LV strain data and a non-invasively estimated LV pressure curve, as previously described.[16] Based on the assumption that peak LV systolic pressure was equal to systolic blood pressure (SBP) measured with a cuff manometer during the echocardiographic study, the patient-specific LV pressure curve was constructed by adjusting the standard LV pressure curve to the duration of isovolumic and ejection phases defined by the timing of valvular events. Strain and pressure data were synchronized using the onset of R-wave in ECG, and the area of the pressure strain loop served as an index of MW (WI). Constructive work (CW) was defined as work during segmental shortening in systole and during lengthening in isovolumic relaxation. Conversely, MW performed during lengthening in systole and shortening in isovolumic relaxation, associated with energy loss, was termed as wasted work (WW). CW divided by the sum of CW and WW represented MW efficiency. All MW parameters are presented as global values, calculated as the averages from all segmental values [i.e. global work index (GWI), global constructive work (GCW), global wasted work (GWW), and global work efficiency (GWE)].

Ventricular-arterial (VA) coupling was computed as the quotient of effective arterial elastance index (ratio of end-systolic pressure to stroke volume index) and LV end-systolic elastance index (ratio of end-systolic pressure to end-systolic volume index). End-systolic pressure was obtained from the equation 0.9 × brachial SBP.[17]

Cuff blood pressure was measured immediately before resting echocardiogram and during post-exercise echocardiographic acquisitions with the patient in the recumbent position. The average of two sequential readings was used for MW and VA coupling calculations.

Cardiopulmonary exercise testing

Symptom-limited treadmill exercise testing was performed on a treadmill using a modified Bruce protocol and with standard cardiopulmonary stress equipment. Ventilation, oxygen uptake, and carbon dioxide production were monitored continuously and peak oxygen uptake (peak VO_2) was calculated as the average oxygen consumption during the last 30 s of exercise. Echocardiographic assessment of wall motion,

Table 3 Baseline and follow-up myocardial work parameters in the spironolactone and placebo groups

	Spironolactone ($n = 57$)		Placebo ($n = 57$)		*P*-value treatment effect
	Baseline	Follow-up	Baseline	Follow-up	
Rest					
GWI (mmHg%)	1869.1 ± 415.9	1780.6 ± 359.4	1903.3 ± 393.2	1887.6 ± 411.7	0.36
GCW (mmHg%)	2173.5 ± 461.7	2012.9 ± 415.6	2162.6 ± 448.2	2132.7 ± 460.8	0.14
GWW (mmHg%)	135.8 ± 107.3	117.3 ± 72.2	124.4 ± 88.0	113.8 ± 76.9	0.61
GWE (%)	92.5 ± 5.7	92.8 ± 5.0	93.2 ± 3.9	93.6 ± 3.6	0.87
Exercise					
GWI (mmHg%)	2298.9 ± 595.1	2242.5 ± 665.3	2341.9 ± 476.5	2304.7 ± 559.3	0.87
GCW (mmHg%)	2967.5 ± 636.4	3115.2 ± 664.1	2967.2 ± 649.0	2943.6 ± 633.2	0.15
GWW (mmHg%)	278.1 ± 173.9	358.2 ± 227.2	253.5 ± 203.2	270.7 ± 234.1	0.18
GWE (%)	90.5 ± 6.0	88.9 ± 6.3	91.2 ± 4.3	91 ± 4.9	0.21

GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work.

Table 4 Myocardial deformation, myocardial work, diastolic (*E*/e'), and ventricular-arterial coupling exercise reserve in the spironolactone and placebo groups

Change from BL to FU in exertional increase	Spironolactone ($n = 57$)	Placebo ($n = 57$)	*P*-value
GLS (%)	0.7 ± 3.3	0.1 ± 3.2	0.30
GWI (mmHg%)	32.1 ± 484.0	-21.4 ± 563.1	0.59
GCW (mmHg%)	308.2 ± 491.2	6.3 ± 530.9	0.002
GWW (mmHg%)	98.5 ± 251.4	27.8 ± 244.7	0.13
GWE (%)	-1.9 ± 7.5	-0.6 ± 6.2	0.32
E/e'	-2.4 ± 2.7	-0.3 ± 3.2	<0.001
VA coupling	-0.04 ± 0.14	-0.03 ± 0.17	0.65

BL, baseline; *E*, peak early diastolic mitral flow velocity; e', peak early diastolic mitral annular velocity; FU, follow-up; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; VA, ventricular-arterial.

myocardial deformation, and diastolic function was carried out before and immediately after termination of the test. LV inflow and myocardial velocities were evaluated after the acquisition of 2D imaging loops. In case of fusion of early and late diastolic Doppler signals (*E* and *A* or/and e' and *a*') at high heart-rates, imaging was postponed until separation of respective waves.

Statistical analysis

Data are presented as mean ± standard deviation for normally distributed variables, as median (interquartile range) for skewed variables [brain natriuretic peptide (BNP)], and as counts and percentages for categorical variables. Between-group comparisons were carried out with an unpaired two-sided Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Homogeneity of variance was evaluated by the Levene test. Longitudinal analyses were carried out using a mixed-design analysis of variance for repeated measures, with the test of interest being an interaction of treatment and time (baseline to 6 months) on the dependent variable. Associations between variables were evaluated by univariable and stepwise multiple regression analysis. Interaction between treatment and change in MW at follow-up was tested using a general linear model. Skewed variables (BNP) were log-transformed before being analysed. Changes in particular parameters with intervention were computed by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. The reproducibility of echocardiographic measurements (GLS and *E*/e') was assessed by the Bland–Altman method (mean difference and 95% confidence interval), intraclass correlation coefficient and coefficient of variation, and presented previously.[11] All analyses were performed with standard statistical software (Statistica for Windows 12, StatSoft Inc., Tulsa, OK, USA). A *P*-value of 0.05 was deemed to be statistically significant.

Results

Patient characteristics

Baseline demographic, clinical, and echocardiographic characteristics of the cohort included in this analysis were similar between the spironolactone and placebo groups (*Table 1*). In comparison with placebo, treatment with spironolactone significantly increased peak VO_2 and peak exercise heart rate. No between-group differences were found for blood pressure (*Table 2*). Despite clinical improvement, no significant post-treatment changes in BNP were shown (delta BNP -18 ± 77 vs. 5 ± 53 pg/

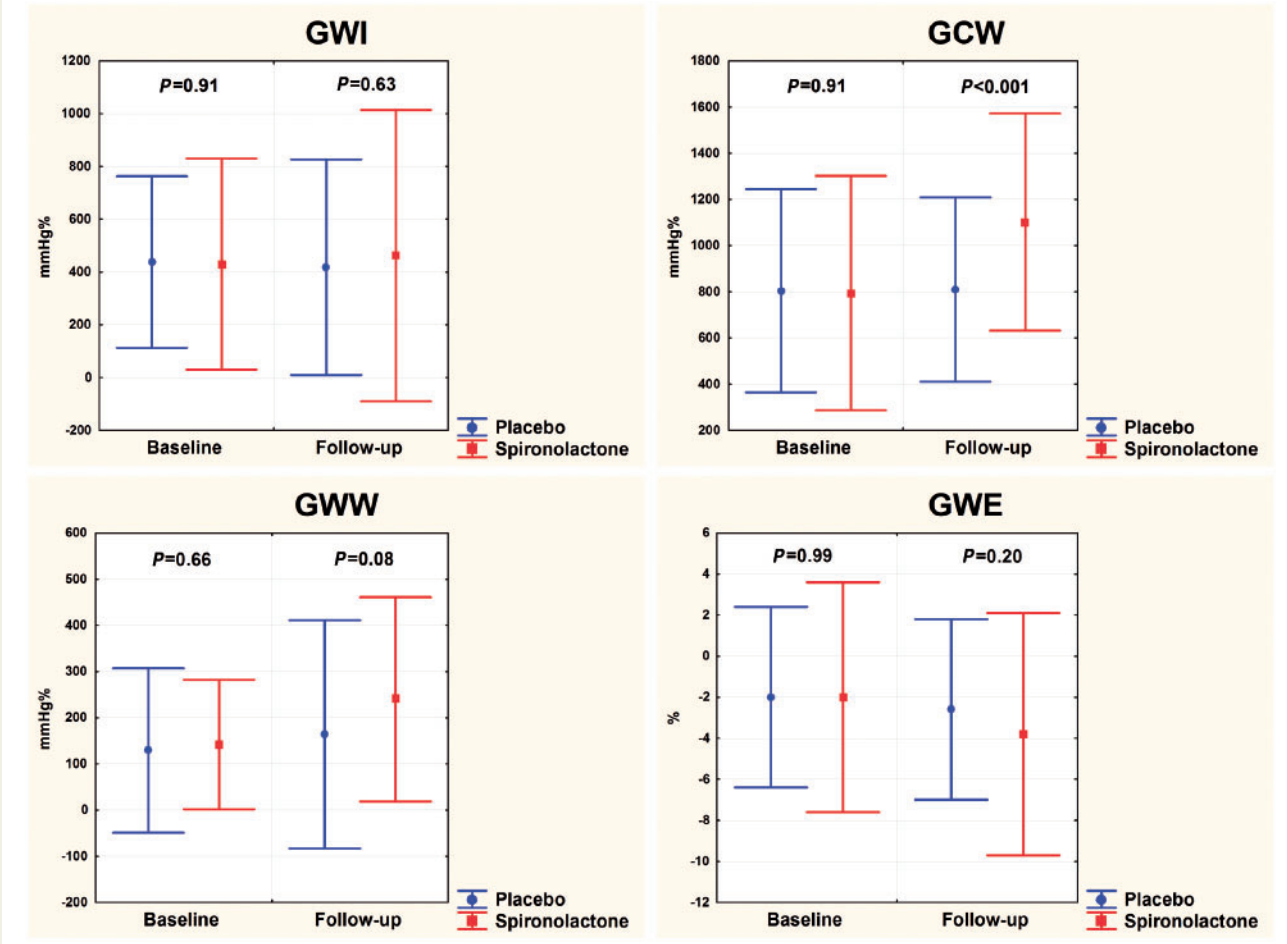

Figure 2 Changes from rest to exercise in myocardial work parameters in the spironolactone and placebo groups. GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global wasted work.

mL, $P = 0.24$ in the spironolactone and placebo groups, respectively).

MW assessment

No differences in baseline and follow-up values of MW parameters were revealed (*Table 3*); however, a significant increase in exertional increment in GCW at follow-up was noted in the spironolactone arm (*Table 4*, *Figure 2*). An example of the assessment of LV systolic response to treatment using MW and deformation indices is presented in *Figure 3*.

Patients assigned to spironolactone demonstrated significantly larger reduction in exertional increase in *E*/e', but no between-group differences were found for analogous changes in GLS and VA coupling (*Table 4*).

Associations of MW with LV filling

Modest but significant correlations were shown between MW indices: GCW and GWI, and *E*/e' ratio at exercise (both $r = -0.25$; $P = 0.007$), and between changes in exertional increments from baseline to follow-up in GCW and *E*/e' ($r = -0.18$; $P < 0.05$). No significant associations were found between MW parameters and *E*/e' at rest.

Associations of improvement in exercise capacity

Multivariable linear regression models testing the predictive utility of myocardial deformation and work parameters, adjusted for age, presence of hypertension and diabetes, body mass index, BNP level, and left atrial size, showed that increase in exercise capacity at 6 months was independently correlated with change in exertional increase in GCW from baseline to follow-up ($P = 0.009$) but not with an analogous change in GLS ($P = 0.14$) (*Table 5*). Consistent with our previous analysis, among the independent determinants of functional improvement were also exertional increase in *E*/e' and VA coupling from baseline to follow-up. No significant interaction between improvement in exertional increase in GCW and treatment with spironolactone on peak VO_2 was demonstrated ($P = 0.97$). An analogous interaction was significant for *E*/e' ($P = 0.04$) but insignificant for VA coupling ($P = 0.88$).

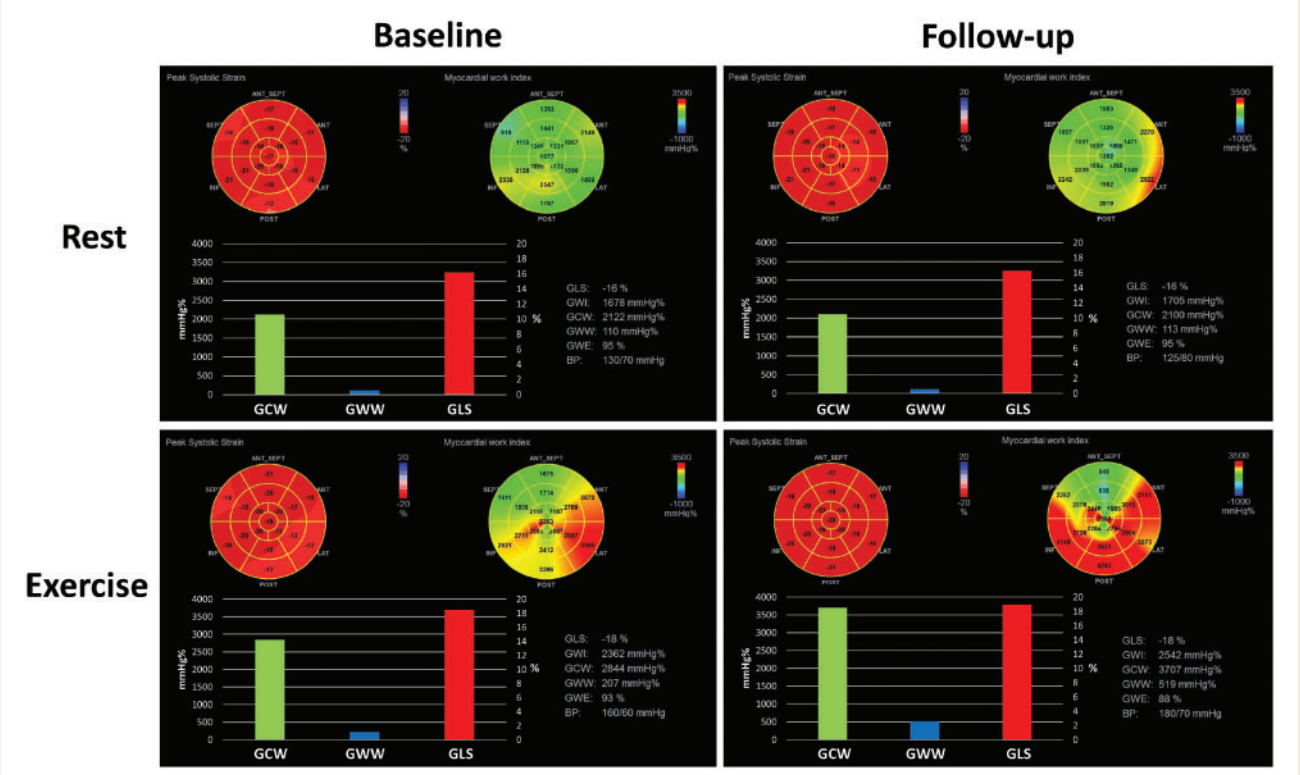

Figure 3 An example of the assessment of LV contractile response to treatment. In view of the higher systolic blood pressure at peak exercise (160 mmHg at baseline vs. 180 mmHg at follow-up), improvement in LV contractility at follow-up is better reflected by GCW (increase in exertional reserve at 6 months 885 mmHg%) than by GLS (increase in exertional reserve at 6 months only 0.3%). BP, blood pressure; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work.

Table 5 Univariable and multivariable associations of improvement in exercise capacity (peak VO_2) at follow-up

Change from BL to FU in exertional increase	Univariable			Model with GLS (R^2 = 0.11)			Model with GCW (R^2 = 0.15)		
	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value
GWI	0.14	0.09	0.14						
GCW	0.26	0.09	0.005				0.24	0.09	0.009
GWW	0.15	0.09	0.11						
GWE	-0.05	0.09	0.60						
GLS	0.14	0.09	0.12	0.13	0.09	0.14			
E/e'	-0.21	0.09	0.02	-0.20	0.09	0.02	-0.18	0.09	0.05
VA coupling	-0.20	0.09	0.03	-0.22	0.09	0.02	-0.22	0.09	0.02

E, peak early diastolic mitral flow velocity; e', peak early diastolic mitral annular velocity; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; VA, ventricular-arterial.

To further investigate the association of MW indices and GLS with exercise capacity, the studied population was divided into two groups: with and without improvement in peak oxygen consumption at follow-up. The former subset consisted of 76 patients (43 receiving spironolactone and 33 placebo) and the latter comprised 38 patients (14 and 24 assigned to spironolactone and placebo, respectively). This analysis demonstrated that change in GCW at follow-up was the only LV functional parameter showing significant between-group differences, and larger increase in GCW in the subset with improvement in peak VO_2 was accompanied by a relatively greater increase in SBP at exercise (*Table 6*).

Table 6 Changes from baseline to follow-up in myocardial work and longitudinal deformation reserve, and exercise blood pressure according to exercise capacity improvement

Change from BL to FU	↑Peak VO_2 ($n = 76$)	↓Peak VO_2 ($n = 38$)	*P*-value
Exercise SBP (mmHg)	0.5 ± 19.1	-8.0 ± 21.6	0.03
Exercise DBP (mmHg)	-1.3 ± 10.9	-1.3 ± 12.0	0.98
Ex increment in GLS (%)	0.6 ± 3.3	0.2 ± 3.1	0.53
Ex increment in GWI (mmHg%)	27.8 ± 507.5	-39.6 ± 558.1	0.51
Ex increment in GCW (mmHg%)	233.2 ± 512.4	5.5 ± 542.4	0.03
Ex increment in GWW (mmHg%)	84.8 ± 248.8	19.8 ± 248.2	0.19
Ex increment in GWE (%)	-1.2 ± 7.1	-1.4 ± 6.3	0.88

↑ Peak VO_2, increase in peak VO_2 at follow-up; ↓ Peak VO_2, decrease in peak VO_2 at follow-up; BL, baseline; DBP, diastolic blood pressure; Ex, exercise; FU, follow-up; GCW, global constructive work; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GWW, global wasted work; SBP, systolic blood pressure.

Discussion

This study demonstrates that GCW used as a measure of LV contractile response to exertion is a better determinant of exercise capacity in HFpEF than GLS. Improvement in functional capacity in patients treated for 6 months with spironolactone is associated with improvement in exertional increment of GCW; however, the mediating effect of this medication seems to be unlikely. The use of MW may provide the incremental clinical value for decision making in comparison with the approach based on the strain imaging alone.

Role of systolic function abnormalities in HFpEF

LV longitudinal contractility, attributable mainly to the subendocardial layer of myofibers, plays a comprehensive role in overall myocardial performance throughout the cardiac cycle. This component of LV mechanics not merely contributes to the ejection phase but, by an impact on the twisting and untwisting physiology, is a relevant determinant of LV filling.[4,18,19] This is of paramount importance, especially during exercise, when in the setting of shortened diastole the maintenance of LV filling pressure at a normal level is largely dependent on the effectiveness of additional mechanisms facilitating mitral inflow. Accordingly, the disturbances of LV longitudinal deformation may compromise cardiac haemodynamics, thus contributing to pulmonary congestion and exercise intolerance. The pathophysiological framework for reduced LV contractile reserve in HFpEF is hypothesized to be flawed myocyte calcium handling, energy deficit due to mitochondrial dysfunction, neuroendocrine activation, and abnormal beta-adrenergic receptor density and signalling.[3,4,20,21]

Effect of spironolactone on longitudinal deformation

Previous studies on the impact of treatment with aldosterone antagonists on LV strain demonstrated improvements in resting values of this parameter in patients with hypertension, obesity, and metabolic syndrome, as well as a trend towards improvement in a subpopulation of HFpEF patients from the TOPCAT trial.[11,22–24] Among the mechanisms behind these benefits, antifibrotic, load-reducing, and arterial compliance-promoting effects were postulated.[23–26]

Incremental diagnostic value of MW

The primary analysis of data from the STRUCTURE study, including a specific HFpEF phenotype with an exercise-induced elevation of LV filling pressure, did not show statistical significance in spironolactone-associated increase in GLS.[11] However, our presumption was that given the load-dependence of GLS, the inability to demonstrate a positive impact of aldosterone antagonism on myocardial contractility reserve might have resulted from the concomitant increase in exercise blood pressure. This belief was underpinned by the fact that peak strain value is dependent on the combined effect of myocardial contractile properties and the opposing force exerted by afterload during systole.[7] Another important issue is that LV afterload is not constant throughout ventricular ejection, therefore, identical peak strain values occurring in different phases of systole do not reflect the same myocardial performance. To overcome this strain limitation, in the reanalysis of LV systolic response to exercise, we used MW parameters correcting LV deformation for afterload variations, and found that, in contrast to GLS, the increase in GCW was independently associated with improvement in exercise capacity at follow-up. Higher GCW reflects an increment in effective myocardial performance, which may translate into improved exercise tolerance. An augmentation of GCW was not accompanied by improvements in GWW and GWE, which indicates that the improvement in exercise capacity was not determined by a favourable alteration in the proportion between the CW and WW, but by an absolute increase in GCW.

Despite a significant inter-arm difference in the increase in GCW from baseline to follow-up, the beneficial effect cannot be directly linked with the action of spironolactone, as no interaction between the active treatment and GCW was found in relation to exercise capacity. This is in contrast to changes in *E*/e' ratio, for which, based on the presence of analogous interaction, such a scenario could be postulated. It is more likely that the increase in GCW is a part of the natural history of clinical improvement-associated alterations in LV function than a straightforward consequence of aldosterone receptor blockade (*Figure 4*). This notion is further supported by the analysis showing a larger increase in SBP at follow-up in the subset with improvement in exercise capacity, irrespective of treatment assignment (resulting from greater exercise load and duration) that paralleled improvement in GCW but not in GLS. In this study, we did not demonstrate a significant afterload-reducing effect of spironolactone in comparison with placebo. However, an apparent reduction of blood pressure occurring in some patients in response to this medication might modify the interaction with MW parameters.

The association of MW with LV filling was demonstrated mainly during exercise. Change in exertional increment in GCW from baseline to follow-up was inversely correlated with an analogous change

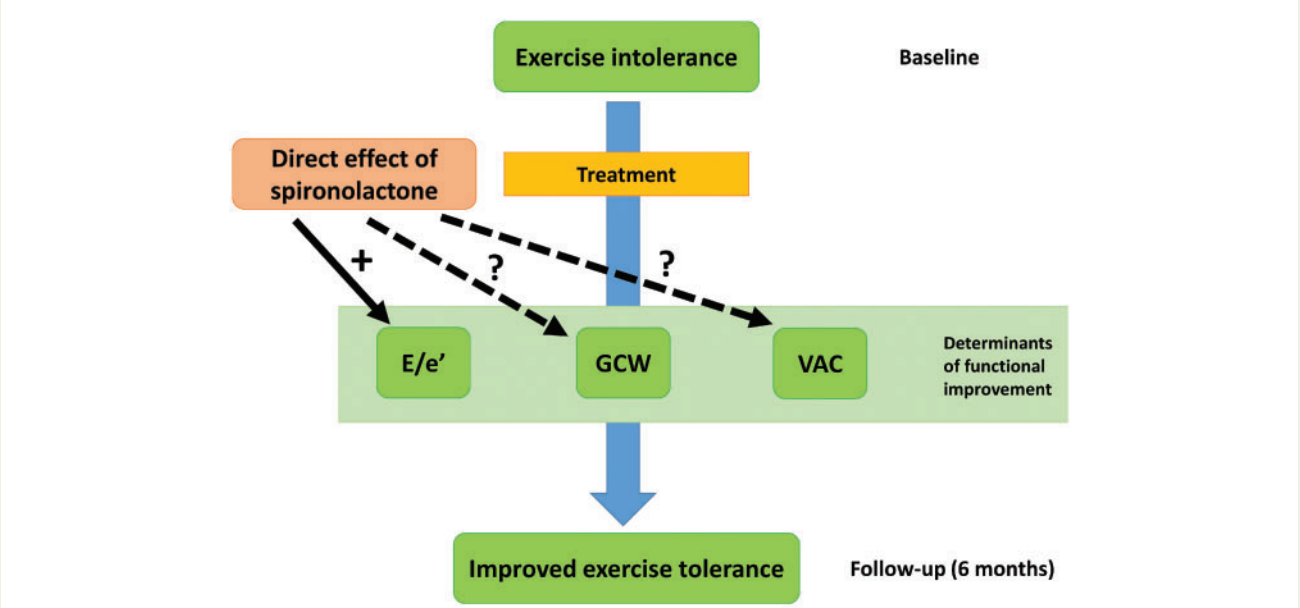

Figure 4 Putative mechanisms behind improvement in exercise tolerance at follow-up. Functional improvement at follow-up was independently associated with favourable changes in *E*/e', GCW, and VA coupling. However, a direct effect of spironolactone could be hypothesized only for *E*/e' (a significant interaction between treatment with spironolactone and improvement in *E*/e' on improvement in exercise capacity). GCW, global constructive work; VAC, ventricular-arterial coupling.

in *E*/e' ratio—an estimate of LV filling pressure. This is consistent with the aforementioned significance of LV longitudinal systolic function as a crucial determinant of mitral inflow during a shortened filling period at high heart rates.

Clinical implications

The use of MW, adjusting the information obtained from LV deformation for systolic pressure, may aid in the assessment of myocardial contractile function in relation to changing afterload. This issue is particularly important in case of measurements performed at exercise, in patients with inadequate blood pressure control, or repeated over time. The diagnostic strategy including MW might be considered in the evaluation of LV systolic reserve during exercise testing. However, the practical applicability of this new approach as a tool assisting in the decision-making process in HF patients' needs to be examined in further studies.

Limitations

Several study limitations should be considered. First, brachial cuff pressure was used as a non-invasive LV pressure derivative to calculate MW. This approach may not accurately replicate the haemodynamic profile during LV ejection. However, the validity of this method has been corroborated under a wide range of different haemodynamic conditions in previous studies.[16,27] Nonetheless, the lack of actual LV pressure values may pose a limitation for minor changes in MW. Second, the exclusion of patients with atrial fibrillation and myocardial ischaemia limit the external validity of our study. Third, a modest sample size and single-centre recruitment might diminish the generalizability of our findings. Fourth, the applicability of our results to HFpEF subsets with a more advanced pathology needs further validation.

Conclusions

In HFpEF patients with an exercise-induced increase in estimated LV filling pressure, GCW outperforms GLS in the assessment of LV systolic response to exercise, and is more closely associated with improvement in exercise capacity over time. The co-occurrence of clinical benefit from treatment with spironolactone and increase in GCW in this population appears to be unrelated to the introduction of aldosterone blockade to therapy. An afterload-independent evaluation of LV contractility provided by the MW-based approach may become an important component of diagnostic algorithms targeting improvement in myocardial function.

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