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Impaired myocardial work efficiency in heart failure with preserved ejection fraction

Antonello D'Andrea [1,2]*, Federica Ilardi[3], Flavio D'Ascenzi[4], Francesco Bandera[5], Giovanni Benfari[6], Roberta Esposito[3], Alessandro Malagoli[7], Giulia Elena Mandoli[4], Ciro Santoro[3], Vincenzo Russo[1], Michele D'Alto[1], and Matteo Cameli[4]; On Behalf of Working Group of Echocardiography of the Italian Society of Cardiology (SIC)

[1]Department of Traslational Medical Sciences, Unit of Cardiology, University of Campania "Luigi Vanvitelli", Monaldi Hospital, Naples, Italy; [2]Unit of Cardiology and Intensive Coronary Care, "Umberto I" Hospital, Nocera Inferiore, Italy; [3]Department of Advanced Biomedical Sciences, Federico II University Hospital, Naples, Italy; [4]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy; [5]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; [6]Department of Medicine, Section of Cardiology, University of Verona, Verona, Italy; and [7]Department of Cardiology, Guglielmo da Saliceto Hospital, Piacenza, Italy

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Aims Heart failure with preserved ejection fraction (HFpEF) is a growing public health problem. Impairment in left ventricular (LV) diastolic function has been proposed as a key pathophysiologic determinant. However, the role of concomitant systolic dysfunction despite preserved LV ejection fraction (LVEF) has not been well characterized. To analyse LV myocardial deformation, diastolic function, and contractile reserve (CR) in patients with HFpEF at rest and while during exercise, as well as their correlation with functional capacity.

Methods and results Standard echo, lung ultrasound, LV 2D speckle-tracking strain, and myocardial work efficiency (MWE) were performed at rest and during exercise in 230 patients with HFpEF (female sex 61.2%; 71.3 ± 5.3 years) in 150 age- and sex-comparable healthy controls. LV mass index and LAVI were significantly increased in HFpEF. Conversely, global longitudinal strain (GLS) and MWE were consequently reduced in HFpEF patients. During effort, HFpEF showed reduced exercise time, capacity, and VO_2 peak. Increase in LVEF and LV GLS was significantly lower in HFpEF patients, while LV *E*/*e*′ ratio, pulmonary pressures, and B-lines by lung ultrasound rose. A multivariable analysis outlined that LV MWE at rest was closely related to maximal Watts reached (beta coefficient: 0.43; $P < 0.001$), peak VO_2 (beta: 0.50; $P < 0.001$), LV *E*/*e*′ (beta: 0.52, $P < 0.001$), and number of B-lines during effort (beta: -0.36; $P < 0.01$).

Conclusions The lower resting values of LV GLS and MWE in HFpEF patients suggest an early subclinical myocardial damage, which seems to be closely associated with lower exercise capacity, greater pulmonary congestion, and blunted LV contractile reserve during effort.

Keywords heart failure with preserved ejection fraction • contractile reserve • two-dimensional strain • myocardial work • stress echocardiography

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and developing public health problem, which is associated with significant morbidity and an increased risk of in-hospital, short-term, and long-term mortality.[1,2] Impairment in left ventricular (LV) diastolic function has been proposed as a key pathophysiologic determinant.[3–5] Although the role of concomitant systolic dysfunction despite preserved LV ejection fraction (LVEF) has not been well characterized, even if it may help to inform future treatment strategies by defining subphenotypes in this heterogeneous population.[6,7]

According to EAVCI/ASE stress echo recommendations,[8] exercise stress echocardiography (ESE) can be used in unexplained exertional

* Corresponding author. Tel: +39 081 9213111, +39 081 9213377, +39 081 9213382; Fax: +39 081 9213361. E-mail: antonellodandrea@libero.it

dyspnoea in order to reveal symptoms. Additionally, it can concomitantly reveal exercise-induced LV dynamic diastolic dysfunction and lack of contractile reserve (CR). On the other hand, there is insufficient evidence to support these indications.

Systolic function decline does seem to start before the reduction of LVEF. Prior studies suggested that LV longitudinal function assessed by tissue Doppler imaging and strain imaging, two load-dependent techniques, may be impaired in HFpEF.[9–12] Recently, myocardial work (MW) was introduced as a new non-invasive index for the evaluation of LV systolic function. This takes afterload into account through analysis of strain in relation to non-invasive LV pressure.[13–17]

We hypothesized that in symptomatic patients with HFpEF, speckle tracking and MW indices could provide a more objective and loading-independent evaluation of LV systolic function, and could be able to predict functional capacity during ESE.

On this grounds, the aim of this study is to analyse LV systolic function using speckle tracking, MW, and ESE in symptomatic patients with HFpEF, while looking for a possible correlation between baseline and stress echocardiographic parameters, and functional capacity during physical effort.

Methods

Study population

HFpEF group

In accordance with ESC guidelines, in our prospective study we enrolled 270 consecutive patients with signs and symptoms of heart failure (HF), New York Heart Association class II to IV symptoms, LVEF ≥50%, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level >125 pg/mL, in two cardiologic divisions: Monaldi Hospital (Naples) and Umberto I° Hospital (Nocera Inferiore—Salerno). The recruitment period lasted from May 2019 to February 2020.

Exclusion criteria were the following: unstable angina or acute myocardial infarction; more than mild aortic valve disease; prosthetic heart valve or prosthetic ring; severe mitral annular calcification; severe (>3+) mitral regurgitation; significant (>50% of stenosis) coronary artery disease by coronary angiography; uncontrolled hypertension; severe chronic obstructive pulmonary disease; any contraindication to physical activity (e.g. gonarthrosis, symptomatic peripheral artery disease); inability to exercise; poor acoustic window.

According to these criteria, 40 patients were excluded for: significant valvular heart disease (13 patients); severe chronic obstructive pulmonary disease (10 patients); contraindication to physical activity (7 patients); unstable angina (5 patients); and poor acoustic window (5 patients).

Control group

A group of 150 age- and sex-comparable asymptomatic subjects referred to our echo lab for screening were also included as controls. Control individuals were consecutively identified and recorded if they were normotensive, had a normal 12-lead electrocardiogram (ECG), regular LVEF (>55%) and wall motion score index. Subjects were removed if they had: (i) arterial systemic hypertension (BP ≥135/85 mmHg as average of three different visits) and/or were on active anti-hypertensive treatment; (ii) overt coronary artery disease; (iii) primary cardiomyopathy and/or genetic cardiovascular disease; (iv) congenital heart disease; (v) mitral or aortic valvular insufficiency of higher degree than trivial, valvular stenosis of any degree; (vi) any previous cardiac or vascular surgery or interventional procedure (including ablation of accessory pathways); (vii) any kind of cardiac therapy; and (viii) previous cardioembolic stroke, including transient ischaemic attacks.

The study was approved by the institution's ethics board and each participant provided informed consent.

Study protocol

All the patients enrolled underwent a complete clinical and laboratory evaluation. ECG, standard echocardiography, and LV 2D speckle-tracking strain analysis were also performed at rest and during ESE.

Standard Doppler echocardiography

A standard transthoracic echocardiography was performed using the commercially available ultrasound machine Vivid E9 (GE Ultrasound, Milwaukee, WI, USA).

The following LV systolic function measures were collected: LVEF, using the biplane Simpson method, the stroke volume, obtained from the LV outflow tract (LVOT) diameter, and LVOT time–velocity integral. LV mass was calculated using the Devereux formula and LV mass index (LVMI) was obtained by dividing the LV mass for the patients' body surface area. A LVMI >115 g/m^2 for men and >95 g/m^2 for women defined the LV hypertrophy.[18] Relative wall thickness (RWT) was calculated as a ratio between 2 LV posterior wall thickness and LV end-diastolic diameter with a value >0.42 being considered as abnormal. The area–length technique was used to assess the left atrial volume index (LAVI). The following diastolic measurements for the LV were gathered: *E* and *A* peak velocities (m/s), *E*/*A* ratio, the early diastolic septal and lateral velocities e′, the mean between them (average e′), and the average *E*/e′ ratio, as expression of LV filling pressures.[3,19] Peak tricuspid regurgitant velocity (TRV) and the systolic trans-tricuspid gradient were assessed through the continuous wave Doppler on the tricuspid regurgitation jet. Pulmonary artery systolic pressure (PASP) was calculated by adding to the systolic trans-tricuspid gradient the value of right atrial pressure (RAP). The latter was estimated by the inferior vena cava (IVC) dimension and inspiratory collapsibility, while the lung ultrasound was also performed to assess pulmonary B-lines.[20]

Two-dimensional speckle tracking echocardiography

LV global longitudinal strain (GLS) was obtained by utilizing the 2D speckle tracking echocardiography (STE) technique. Loops of three successive cardiac cycles from the apical four-chamber, two-chamber, and three-chamber views were acquired, with a frame rate between 30 and 70 frames/s (mean 58.4 ± 7.3 frames/s). These images were transferred to the workstation and analysed through the software EchoPAC Version 202 (GE Vingmed Ultrasound, Norway). Endocardial borders were manually traced in the end-systolic frame of the cardiac cycle, starting from the apical long-axis view where it is simpler to identify the timing of the aortic valve closure. The software generated a region of interest (ROI) of the entire myocardial thickness, which could be manually adjusted in width if deemed necessary, and a moving image displaying the tracking. If the tracking was considered inaccurate, the operator could repeat the process, readjusting the ROI or selecting a new ROI. The software then divided the LV myocardium in six segments, calculating segmental and GLS. The same process was repeated for the apical four- and two-chamber images, and the GLS was determined by averaging local strains of all myocardial segments.[16,18]

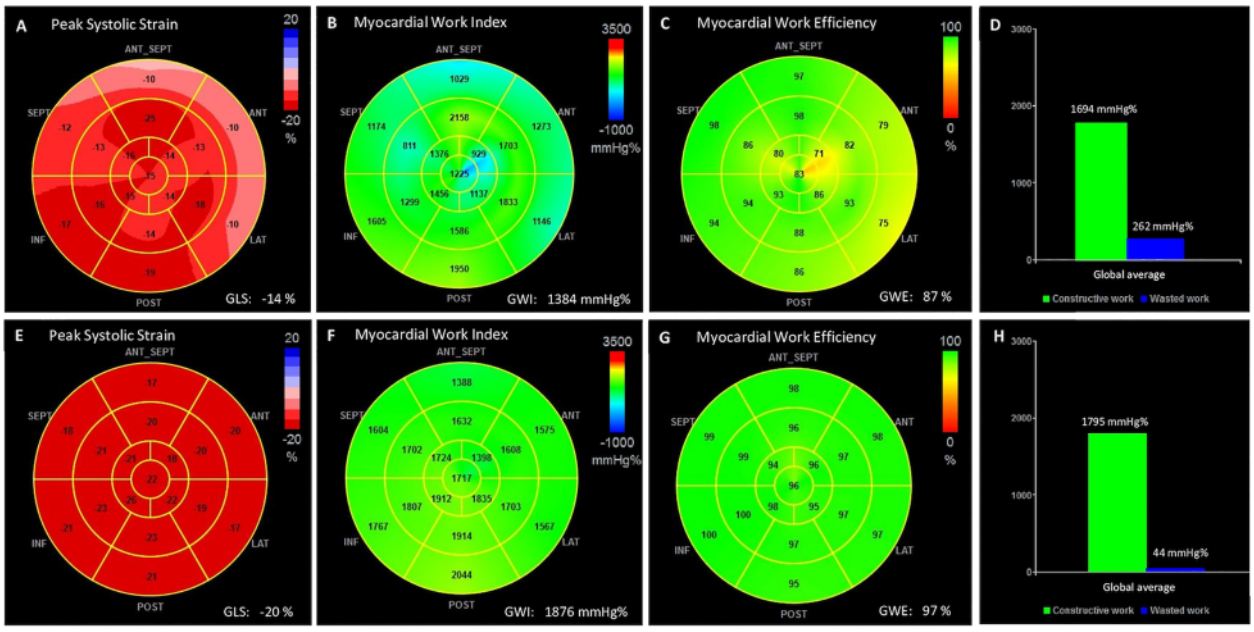

Figure 1 Seventeen-segment bull's-eye representation of Global Longitudinal strain (*A–E*), Myocardial Work Index (*B–F*), MWE (*C–G*) in a patient with HFpEF (upper) and in healthy subject (lower). Bar graphs showing the amount of Myocardial Constructive Work (green) and Global Wasted Work (blue, *D–H*).

Myocardial work

MW was calculated using a specific software (EchoPAC Version 202 - GE Vingmed Ultrasound, Norway), which incorporates the LV pressure non-invasively estimated through a cuff to the LV strain. Arterial pressure was measured three times at rest immediately before the echocardiographic study. The average of the three values of systolic blood pressure, assumed to be equal to the peak systolic LV pressure, was introduced in the software, which constructed an LV pressure–strain loop and the area within the loop was used as index of MW.[13–17] Along with segmental and global values for MW, additional indices were also provided:

- Constructive work (CW): work performed by myocardial segments during the systolic shortening which contributes to the LV ejection;
- Wasted work (WW): work generated by some myocardial segments needed to cause the systolic lengthening of other dyssynchronous segments, which does not contribute to LV ejection. The post-systolic shortening also contributes to the WW.
- Myocardial work efficiency (MWE): is the ratio CW/(CW + WW) reported in percentage (0–100%)

A Bull's eye with the segmental and global Time to peak, MW, CW, WW, and MWE values were provided. The global amounts were calculated as the average of all segmental values (*Figures 1 and 2*).

Standardized submaximal exercise stress echocardiography

After the resting echocardiography, all of the enrolled patients underwent a semi-supine bicycle ESE using a standard protocol of incremental 25 W steps lasting 2 min, with the pedaling rate at 55 rpm.

The same ultrasound system of the standard rest echocardiography was used. Images from parasternal long-axis and short-axis, from apical four-, two-, and three-chamber views were continuously recorded during the different steps of the exam. Causes of interruption of the study included new wall motion abnormalities, significant ST-segment changes (i.e. ST-segment depression or elevation ≥1 mm or more in two contiguous leads), and the onset of symptoms or arrhythmias. Functional parameters collected at rest and at peak effort included: heart rate, systolic blood pressure, workload achieved in Watts, and rate–pressure product. Peak oxygen consumption ($VO_{2\ peak}$) was also assessed by cardiopulmonary test performed during the ESE study. The following echocardiographic parameters were measured at baseline and at pinnacle effort: LVEF, LV GLS, LV average *E*/*e*′, tricuspid annular plane systolic excursion (TAPSE), and PASP. Increase in EF >5% defined a serious CR, according to the European guidelines.[8] An impaired LV diastolic reserve was defined as a post-exercise *E*/*e*′ ≥15 indicating elevated LV filling pressures. LV GLS at peak effort was calculated through the same procedure as described above for the rest analysis, taken from the apical four-chamber, two-chamber, and three-chamber views acquired during exercise.[17] B-lines were evaluated with the four-site simplified scan, from mid-axillary to midclavicular lines on the third intercostal space. Each site scored from 0 = A-lines to 10 = white lung. The positivity criterion for B-lines was a stress score higher than rest for ≥2points.[20]

Statistical analysis

All of the statistical analyses were performed by SPSS for Windows release 21.0 (Chicago, IL, USA). Continuous variables were expressed as median (I, III quartile) or means ± standard deviation (SD). Unpaired *t*-tests were carried out to, respectively, estimate differences intra-groups and between groups. Linear regression analyses and partial correlation tests by Pearson's method were done to assess univariable relations. To identify significant independent determinants of functional capacity, their individual association with clinically relevant and echocardiographic variables was assessed by multivariable linear regression analysis. The

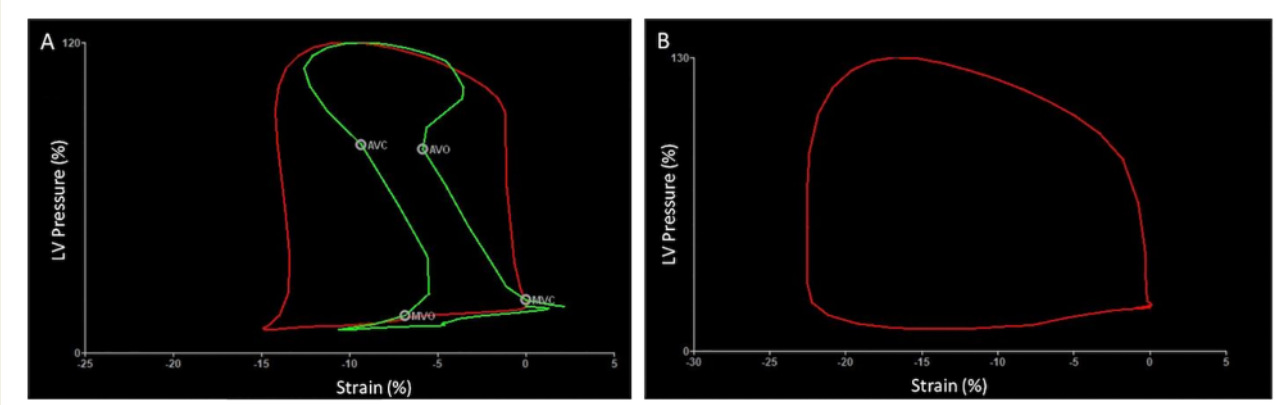

Figure 2 Representative traces of global left ventricular (LV) pressure–strain loop (red) and segmental pressure–strain loop measured at the mid infero-septal LV segment (green) in a patient with HFpEF (*A*). Global LV pressure–strain loop in a healthy subject (*B*).

Table 1 Demographics and clinical features of HFpEF patients and healthy controls

Variable	HFpEF patients ($n = 230$)	Controls ($n = 150$)	*P*-value
Female sex (%)	61.2	60.3	NS
Age (years)	71.3 ± 5.3	70.3 ± 5.4	NS
BSA (m^2)	1.85 ± 0.17	1.81 ± 0.15	<0.05
BMI (kg/m^2)	29.9 ± 3.6	25.7 ± 3.4	<0.01
Systolic blood pressure (mmHg)	136.5 ± 8.4	124.4 ± 5.8	<0.01
Diastolic blood pressure (mmHg)	87.4 ± 6.2	78.3 ± 9.2	<0.01
Heart rate (bpm)	73.4 ± 10.3	76.4 ± 11.4	NS
Arterial hypertension (%)	81.9		
Diabetes mellitus (%)	33.2		
Renal disease (eGFR < 60 mL/kg/1.73 m^2, %)	38.4		
Smoking or history of smoking (%)	19.4		
Obesity (%)	31.8		
Hyperlipidaemia (%)	24.6		
Coronary heart disease (%)	22.7		
Permanent atrial fibrillation (%)	32.3		
NT-proBNP (pg/mL)	771 ± 303.6		
Beta-blockers (%)	88.4		
ACE inhibitors or ARB blockers (%)	89.5		
Aldosterone receptor antagonists (%)	22.5		
Antiplatelet agents/oral anticoagulants (%)	35.5		
Diuretics (%)	85.8		

Data are expressed as absolute number (%) or mean ± SD.
BMI, body mass index; BSA, body surface area; NS, non significant.

following variables were included into the analysis: clinical data (age, sex, BMI, mean blood pressure, NT-proBNP), standard echocardiographic indices (LV volumes, LV mass index, resting and stress LV *E*/*e*′, LAVI), B-lines and strain measurements (resting and stress LV GLS and MWE). These variables were selected according to their clinical relevance and potential impact on LV cardiac purpose and on functional capacity.[1–5] Variable selection was performed in the multivariable linear regression as an interactive stepwise backward elimination method, with each time excluding the one variable with the highest *P*-value, according to Wald statistics. To decrease the inflation of the Type 1 error rate due to multiple testing, the statistical significance was defined as two-sided *P*-value <0.01. Receiver operating characteristic (ROC) curve analysis was performed to select optimal cut-off values of strain measurements. Reproducibility of GLS measurements was determined in all of the subjects. Intra/inter-observer variability were examined using the coefficient of variation (COV), defined as the ratio of the standard deviation (σ) to the mean (μ, %), by Bland–Altman analysis. CV, 95% confidence intervals (CIs), and percent errors were reported.

Table 2 Baseline standard Doppler echo and strain measurements in HFpEF patients compared with controls

Variable	HfpEF ($n = 230$)	Controls ($n = 150$)	*P*-value
IVSd (mm)	12.3 ± 2.1	9.1 ± 2.3	<0.001
PWd (mm)	12.1 ± 2.2	8.9 ± 2.6	<0.01
LVEDV (mL)	126.4 ± 22.3	118.4 ± 12.6	NS
LVESV (mL)	55.2 ± 11.1	48.8 ± 8.2	NS
LV mass index (g/m^2)	140.3 ± 25.4	80.4 ± 16.8	<0.001
RWT	0.48 ± 0.05	0.39 ± 0.03	<0.01
Biplane LVEF (%)	56.3 ± 3.5	58.4 ± 4.6	NS
LV GLS (%)	-15.2 ± 2.8	-20.4 ± 3.3	<0.01
Myocardial work efficiency (%)	86.4 ± 3.2	93.2 ± 3.3	<0.0001
Myocardial constructive work (mmHg%)	2155.3 ± 423.2	2532 ± 305.4	<0.01
Myocardial wasted work (mmHg%)	257.6 ± 105.3	96.6 ± 44.1	<0.001
LV stroke volume (mL)	72.3 ± 17.8	71.4 ± 16.8	NS
Mitral *E* velocity (cm/s)	0.93 ± 0.7	0.80 ± 0.4	<0.01
Mitral *A* velocity (cm/s)	0.75 ± 0.6	0.83 ± 0.1	<0.01
E/*A* ratio	1.23 ± 0.3	0.95 ± 0.6	<0.01
Mitral septal *E*′ velocity (cm/s)	0.06 ± 0.3	0.11 ± 0.4	<0.001
Mitral lateral *E*′ velocity (cm/s)	0.07 ± 0.3	0.13 ± 0.5	<0.001
E/*e*′ ratio	14.5 ± 3.1	5.7 ± 2.8	<0.0001
Aortic root diameter (mm)	33.3 ± 3.2	30.2 ± 3.4	<0.05
LAVI (mL/m^2)	33.4 ± 4.1	25.3 ± 3.6	<0.001
PASP (mmHg)	35.5 ± 3.8	23.6 ± 3.1	<0.001
TAPSE (mm)	21.4 ± 3.4	23.6 ± 3.4	NS
Tricuspid *S*′ velocity (cm/s)	13.8 ± 3.3	14.6 ± 4.2	NS
B-lines (median and IQR)	1.5 (0–35)	0.70 (0–24)	<0.001

AV, aortic valve; IVSd, inter-ventricular septum thickness at end-diastole; LAVI, left atrial volume index; LV GLS, left ventricular global longitudinal strain; LV, left ventricle; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NS, non significant; PASP, systolic pulmonary artery pressure; PWd, posterior wall thickness at end diastole; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.

Results

We selected a final population of 230 symptomatic patients with HFpEF, 150 age, and gender-comparable healthy controls. An overview of the baseline characteristics of the study population is provided in *Table 1*. The average age was 71.3 ± 5.3 years, and the majority of patients were female, who had increased BMI and a history of hypertension. Rates of therapy with diuretics, with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker and beta-blockers were high. The median NT-proBNP level was elevated (771 pg/mL, interquartile range: 426–1257 pg/mL).

Using standard echocardiography: LV wall thickness, LV mass index, and LAVI were dramatically increased in HFpEF. Both LVEF and right ventricular (RV) functional indexes (TAPSE and *S*' wave) at rest did not show compelling differences between the two groups. Conversely, baseline LV GLS and MWE were significantly reduced, and MWW was powerfully increased in HFpEF patients (*Table 2*).

As expected, LV filling pressures (average *E*/*e*′ ratio) were significantly increased in HFpEF group, and normal in the control group. B-lines (≥2) at rest were found in 21.3% of HFpEF patients and 5.1% of controls ($P < 0.001$).

During effort, HFpEF showed reduced exercise time, exercise capacity, and VO_2 peak, as reported in *Table 3*. A rise in RV systolic function indexes was similar between the two groups. Contrastingly, values of LVEF, LV GLS, and MWE were much lower in HFpEF patients when compared with healthy controls. Of note, the reduced MWE during effort was mainly determined by increased MWW during stress. Additionally, HFpEF patients showed at peak effort an increased LV *E*/*e*′ ratio, pulmonary pressures, and B-lines by lung ultrasound.

Univariable analysis detected independent associations of baseline GLS and MWE with maximal workload (Watts reached), peak VO_2, LV *E*/*e*′ ratio, and B-lines during effort, stronger than the association of LVEF with the same functional parameters (*Table 4*). What's more, both GLS (*r*: 0.55; $P < 0.001$) and MWE (*r*: -0.58; $P < 0.0001$) were significantly associated with NT-proBNP levels.

A multivariable analysis confirmed that LV MWE at rest was closely related to peak effort measurements expressed in maximal Watts reached (beta coefficient: 0.43; $P < 0.001$), peak VO_2 (beta: 0.50; $P < 0.001$), LV *E*/*e*′ (beta: 0.52, $P < 0.001$), and in the number of B-lines during effort (beta: -0.36; $P < 0.01$).

The independent association between resting LV MWE and peak VO_2 during ESE showed a powerful incremental value with respect to clinical and standard echocardiographic data (*Table 5*).

Intra-observer variability: COV: LV MWE: 5.37 (ICC 0.71); Bland–Altman analysis: LV MWE (95% CI ±1.7; percent error 3.2%).

Inter-observer variability: COV: LV MWE: 7.22 (ICC 0.77); Bland–Altman analysis: LV MWE (95% CI ±1.3; percent error 3.6%).

Table 3 Functional measurements and echocardiographic parameters at peak exertion in the overall study population

Variable	HfpEF	Controls	*P*-value
Functional measurements			
Exercise time (min)	6.8 ± 3.1	11.2 ± 4.3	<0.001
Exercise capacity (W)	63.6 ± 21.5	114.4 ± 25.6	<0.001
Peak heart rate (bpm)	130.7 ± 22.4	144.3 ± 18.4	<0.01
Peak systolic blood pressure (mmHg)	190.4 ± 15.6	170.4 ± 18.6	<0.01
Rate-pressure product (bpm × mmHg)	24.800 ± 6.500	24.400 ± 5.530	NS
Peak VO_2 (mL/kg/min)	16.4 ± 2.8	33.4 ± 3.4	<0.0001
Echocardiographic parameters			
Biplane LV EF (%)	59.4 ± 4.9	64.4 ± 3.9	<0.01
PAPs (mmHg)	48.4 ± 6.9	30.4 ± 5.6	<0.001
E/*e*′ ratio	19.5 ± 3.3	7.8 ± 3.3	<0.0001
LV GLS (%)	-16.6 ± 4.6	-22.8 ± 4.2	<0.001
MWE (%)	88.5 ± 2.2	97.8 ± 3.3	<0.0001
MCW (mmHg%)	2675.3 ± 353.45	3088 ± 404.6	<0.01
MWW (mmHg%)	347.3 ± 112.3	116.5 ± 34.3	<0.0001
TAPSE (mm)	25.4 ± 3.3	27.3 ± 3.1	NS
TDI RV peak systolic velocity Sm (cm/s)	15.6 ± 3.1	16.8 ± 3.3	NS
B-lines (median and IQR)	4.9 (0–43)	1.25 (0–27)	<0.001
Delta EF (%)	5.5 ± 2.8	10.1 ± 3.1	**<0.01**
Delta GLS (%)	5.2 ± 2.2	9.4 ± 2.8	**<0.01**
Delta MWE (%)	2.4 ± 1.2	5.4 ± 2.4	**<0.01**
Delta MCW (%)	24.1 ± 3.2	25.1 ± 3.1	**NS**
Delta MWW (%)	35.3 ± 3.1	19.2 ± 2.4	**<0.001**

EF, ejection fraction; GLS, global longitudinal strain; MCW, myocardial constructive work; MWE, myocardial work efficiency; MWW, myocardial wasted work; NS, non significant; PAPs, systolic pulmonary artery pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.

Discussion

In a population of HFpEF patients undergoing stress echocardiography we found that: (i) compared with healthy controls, HF patients exhibit subclinical LV systolic dysfunction at baseline, despite a preserved LVEF, as outlined by impaired GLS, enhanced WW and reduced MWE; (ii) during exercise, an impaired LV systolic and diastolic reserve was observed in the HFpEF group, along with a reduced exercise tolerance; (iii) resting MWE is significantly correlated with functional measurements and pulmonary congestion during physical effort.

Previous reports about systolic function in HFpEF

Although LVEF is the most commonly used and accepted measure of systolic function, it is highly load-dependent and relatively insensitive to subtle abnormalities of LV function.[18,21] Previous studies involving HFpEF patients have failed to demonstrate abnormalities in systolic performance with traditional echocardiographic indexes.[5–7] Early data employing tissue Doppler Imaging suggested that longitudinal systolic function may be abnormal despite preserved LVEF in conditions predisposing to HF and in HFpEF.[9,10] Nevertheless, tissue Doppler imaging has technical limitations including preload/afterload dependence and is constrained in its ability to assess different planes of LV deformation other than longitudinal.[16,22] In the last decades, STE has shown a high sensitivity to detect subclinical cardiac dysfunction, even in presence of LVEF >55%. Thanks to its independence

Table 4 Univariable analysis: correlations between resting LV echo indexes and functional parameters during effort in HFpEF patients

Variable		*R*	*P*-value
LV EF	Watts (at peak effort)	0.28	NS
	VO_2 peak	0.25	NS
	LV *E*/*e*′ during ESE	-0.33	<0.05
	B lines during ESE	-0.24	NS
LV GLS	Watts (at peak effort)	-0.38	<0.05
	VO_2 peak	-0.42	<0.01
	LV *E*/*e*′ during ESE	0.36	<0.01
	B lines during ESE	0.27	NS
LV MWE	Watts (at peak effort)	0.43	<0.01
	VO_2 peak	0.50	<0.001
	LV *E*/*e*′ during ESE	-0.52	<0.001
	B lines during ESE	-0.36	<0.01

GLS, global longitudinal strain; LV EF, left ventricular ejection fraction; MWE, myocardial work efficiency; NS, non significant.

Table 5 Clinical and echocardiographic data associated with oxygen uptake (peak VO_2) during physical effort in HFpEF patients

Type of variables	Model R^2	*P*-value	Variables selected (beta coefficient; 95% CI; *P*-value)
Clinical	4.3	<0.01	NT-proBNP (-0.40; -0.22 to 0.55; <0.01)
Clinical + standard echo	13.8	<0.001	LV *E*/*e*′ during ESE (-0.41; -0.28 to 0.49; $P < 0.001$)
			B lines during ESE (-0.30; -0.22 to 0.40; <0.01)
Clinical + standard echo + strain and work	19.7	<0.0001	Resting MWE (0.46; -0.35 to 0.52; <0.001)

from angle of incidence, tethering, and cardiac translation, GLS has been considered a reliable predictor of HFpEF, inversely correlated to NT-proBNP levels even after adjusting for LVEF and diastolic measures.[11,12,23,24] Despite the superiority of GLS over LVEF and tissue Doppler in the deeper evaluation of LV systolic performance, this technique is still limited by loading dependence,[16,22] that could affect the correct measurement of myocardial contractile function in specific loading condition, such as hypertension or during effort.

In this context, MW analysis, incorporating LV pressure, is less load-dependent if compared with strain, and therefore could provide incremental information in the setting of HF patients.

Uniqueness of the present study

In the present study, a population of patients affected by HFpEF showed lower values of GLS at rest despite a preserved LVEF, and this is in line with previous reports[25] describing in this setting a homogeneous reduction of longitudinal and radial function. However, the study of MW adds further characterization of the present cohort, demonstrating that the subclinical impairment of LV systolic and diastolic function typical of this setting of patients translates into a significant MWW augmentation, with a related reduction of MWE. Actually, HFpEF is characterized by a prevalent diastolic dysfunction and, in hypertensive patients (largely represented in our study population), by a rise in arterial blood pressure, which led to an important elevation in LV wall stress (afterload).[26–30] Also the increase of LV mass, as observed in our study cohort, is a crucial determinant of wall stress and has been found to be an independent predictor of incident HF.[31] Since pressure overload and increased LV mass are associated with accelerated decline in GLS over time, this could be potentially responsible of LV contractility underestimation. Conversely, MW analysis, through the quantification of global LV function corrected by afterload, provides a more reliable information on myocardial performance in this population, permitting to individuate patients with incipient LV systolic decompensation.[13–17] Indeed, the homogeneous increase of MWW detected in our HFpEF compared with controls should be ascribable to the enhanced wall stress produced in an attempt to overcome the increased afterload. A similar finding was observed by Chan *et al.*,[32] who described progressively elevated values of MWW in hypertensive groups. Morbach *et al.*[33] provided further evidences, demonstrating that higher values of systolic and diastolic pressure, as well as higher LV mass are associated with both higher MCW and MWW, with subsequently reduced MWE.

In addition, it is known that HFpEF is characterized by an impairment of LV active relaxation and/or increased passive LV diastolic stiffness at rest,[4] which becomes even more prominent during exercise,[34] and might have contributed to MWW enhancement and MWE reduction.

In our study, both baseline GLS and MWE were also found to be correlated with functional capacity, LV filling pressures, and pulmonary congestion during effort. During stress, HFpEF population showed a lower increase in LVEF and GLS when compared with controls, as confirmed by previous reports that failed to demonstrate a systolic reserve response in HFpEF patients even when treated with spironolactone.[35] Recently, Przewlocka-Kosmala *et al.*[36] showed in 57 patients treated with spironolactone for 6 months that an improvement of functional capacity was detected by an MCW increase during effort. Thus, they demonstrated that MW is a better determinant than GLS of exercise capacity in HFpEF patients.

Our study provides further insight into the description of HFpEF population, showing, in a larger cohort of patients, that MW, and in particular MWW, is a sensible marker of systolic and diastolic dysfunction, that increases during effort. A greater augmentation of MWW in HFpEF compared with controls, not accompanied by a consistent improvement in MCW, is therefore associated with lower values of MWE, which becomes a prognostic index of exertional intolerance in HFpEF. The greater reliability of MW indices over GLS in the prediction of myocardial performance during exercise stands on the evidence that peak strain values are dependent on both LV contractile force during systole and the opposing force exerted by afterload; moreover, GLS does not take into account the variation of LV afterload throughout the ejection, which could be even more pronounced during effort. Conversely, non-invasive estimation of MW, integrating deformation with afterload variation, has demonstrated to overcome this strain limitation.

Our findings confirm that despite HFpEF is considered a chronic disease with a main impairment of the diastolic function, the preclinical subtle myocardial damage, that characterize the pathophysiologic mechanisms underlying LV stiffening in HFpEF and can be detected by cardiac magnetic resonance,[37,38] could show up with systolic impairment and haemodynamic maladaptation during exercise, detected by resting GLS and MWE.

Thus, a complete strain study at rest and during ESE could have an incremental role to support clinicians for the therapeutic management and decision making of patients with HFpEF.

Study limitations

One of the studies limitations is that the results can be applied only to the population of patients with HFpEF, who are capable of exercising in a semi-supine position. Moreover, it is a study conducted in two centres, with a sample size too small to drive definitive general

conclusions concerning the myocardial deformation and work in. Then, cardiac magnetic resonance evaluation would add further information about tissue characterization in HFpEF patients, however such data were not available in our study population. Finally, the possibility that reduction in strain could be influenced by an increased wall stress cannot be entirely excluded, since this changes in preload and afterload are important determinants of myocardial deformation. In order to overcome this constraint, we performed MW analysis which is less load-dependent if compared with strain.[13–16]

Conclusions

LV myocardial function in HFpEF patients is impaired and this suggests that the lower resting values of LV GLS and MW represent early subclinical myocardial damage,[37,38] closely associated with exercise capacity, pulmonary congestion, and LV contractile reserve.

Longitudinal strain predicts outcome in low LVEF patients independent of LVEF.[22,39] Whether impaired longitudinal deformation has prognostic significance in HFpEF remains to be determined. Additional prospective studies by strain and MW analyses are warranted to further understanding of the natural history of myocardial work in HFpEF, the extent of reversibility of LV dysfunction with medical therapy, and the possible long-term impact of such changes on outcomes in patients with HFpEF.

Conflict of interest: none declared.

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