

# Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction

Nina E. Hasselberg<sup>1,2,3,4</sup>, Kristina H. Haugaa<sup>1,2,3,4</sup>, Sebastian I. Sarvari<sup>1,2,3,4</sup>, Lars Gullestad<sup>1,3,5</sup>, Arne K. Andreassen<sup>1</sup>, Otto A. Smiseth<sup>1,2,3,4</sup>, and Thor Edvardsen<sup>1,2,3,4\*</sup>

<sup>1</sup>Department of Cardiology, Rikshospitalet, Oslo University Hospital, Sognsvannsveien 20, Oslo, Norway; <sup>2</sup>Center for Cardiological Innovation, Oslo, Norway; <sup>3</sup>Faculty of Medicine, University of Oslo, Oslo, Norway; <sup>4</sup>Institute for Surgical Research, Rikshospitalet, Oslo University Hospital, Oslo, Norway; and <sup>5</sup>K.G. Jebsen Cardiac Research Centre and Center for Heart Failure Research, Oslo, Norway

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## Aims

Heart failure patients with reduced and preserved left ventricular (LV) ejection fraction (EF) show reduced exercise capacity. We explored the relationship between exercise capacity and systolic and diastolic myocardial function in heart failure patients.

## Methods and results

Exercise capacity, by peak oxygen uptake ( $\text{VO}_2$ ), was assessed in 100 patients ( $56 \pm 12$  years, NYHA functional class:  $2.5 \pm 0.9$ , EF:  $42 \pm 19\%$ ). LV systolic function, as EF and global longitudinal strain (GLS), and right ventricular function were assessed by echocardiography. Left atrial volume index and the ratio of peak early diastolic filling velocity ( $E$ ) to early diastolic mitral annular velocity ( $e'$ ) were measures of diastolic function. Thirty-seven patients had heart failure with preserved EF (HFpEF), defined as EF  $\geq 50\%$  and echocardiographic diastolic dysfunction. LV GLS and peak pulmonary arterial systolic pressure were independently correlated to peak  $\text{VO}_2$  in the total study population and in HFpEF separately. LV GLS was superior to EF in identifying patients with impaired peak  $\text{VO}_2 < 20$  mL/kg/min as shown by receiver operating characteristic analyses [areas under curves 0.93 (0.89–0.98) vs. 0.85 (0.77–0.93),  $P < 0.05$ ]. In patients with HFpEF, GLS was reduced below normal ( $-17.5 \pm 3.2\%$ ) and correlated to  $E/e'$  ( $R = 0.45$ ,  $P = 0.005$ ) and left atrial volume index ( $R = 0.48$ ,  $P = 0.003$ ), while EF did not.

## Conclusion

GLS correlated independently to peak  $\text{VO}_2$  in patients with reduced and preserved EF and was superior in identifying patients with reduced exercise capacity. In HFpEF, systolic function by GLS was impaired. There was a significant relationship between diastolic function and GLS, confirming a coupling between diastolic and longitudinal systolic function in HFpEF.

## Keywords

speckle tracking echocardiography • diastolic function • heart failure • myocardial mechanics • exercise testing

## Introduction

At least half of patients with heart failure have reduced left ventricular (LV) ejection fraction (EF). The remaining are defined as having heart failure with preserved EF (HFpEF)<sup>1</sup> with as poor prognosis as those with reduced EF.<sup>2</sup> Cardiopulmonary exercise testing (CPX) with

peak oxygen uptake ( $\text{VO}_2$ ) is a strong predictor of mortality, in the healthy population and in heart failure patients including HFpEF.<sup>3–7</sup> Despite vast and consistent data on CPX's prognostic value, it remains underutilized.<sup>7</sup> Previous studies have failed to find a relationship between LV systolic function by EF and exercise capacity<sup>8–10</sup> while diastolic function<sup>11–13</sup> and right ventricular (RV) function<sup>14–16</sup> have

\* Corresponding author. Tel: +47 23 07 00 00; Fax: +47 23 07 13 97, E-mail: thor.edvardsen@medisin.uio.no

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been shown to correlate well. LV systolic function is an established prognostic marker, and it is unclear why CPX apparently is not correlated to EF. Echocardiographic strain is an accurate method for quantifying systolic function,<sup>17</sup> is shown superior to EF in detecting early reduction in myocardial systolic function,<sup>18</sup> and has prognostic impact.<sup>19,20</sup> We explored the relationship between exercise capacity and myocardial mechanics in heart failure patients with preserved and reduced EF. We hypothesized that exercise capacity is more closely related to LV strain than to EF. In HFpEF, diastolic dysfunction is considered to be the underlying abnormality<sup>1</sup> and has been shown to predict mortality.<sup>21</sup> We hypothesized that patients with HFpEF also show mild systolic dysfunction detectable by echocardiographic strain.

## Methods

### Patient characteristics and clinical data

This single-centre, cross-sectional study included clinically stable patients referred to the Department of Cardiology, Oslo University Hospital, Norway for symptoms and signs of heart failure. Exclusion criteria were chronic lung disease, severe valvular disease, or anaemia.<sup>1</sup>

All patients were clinically examined and assessed by New York Heart Association (NYHA) functional classification. Blood samples were collected for analysis of N-terminal pro-B-type natriuretic peptide (NT-proBNP) ( $n = 81$ ). All patients gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics.

### Cardiopulmonary exercise testing

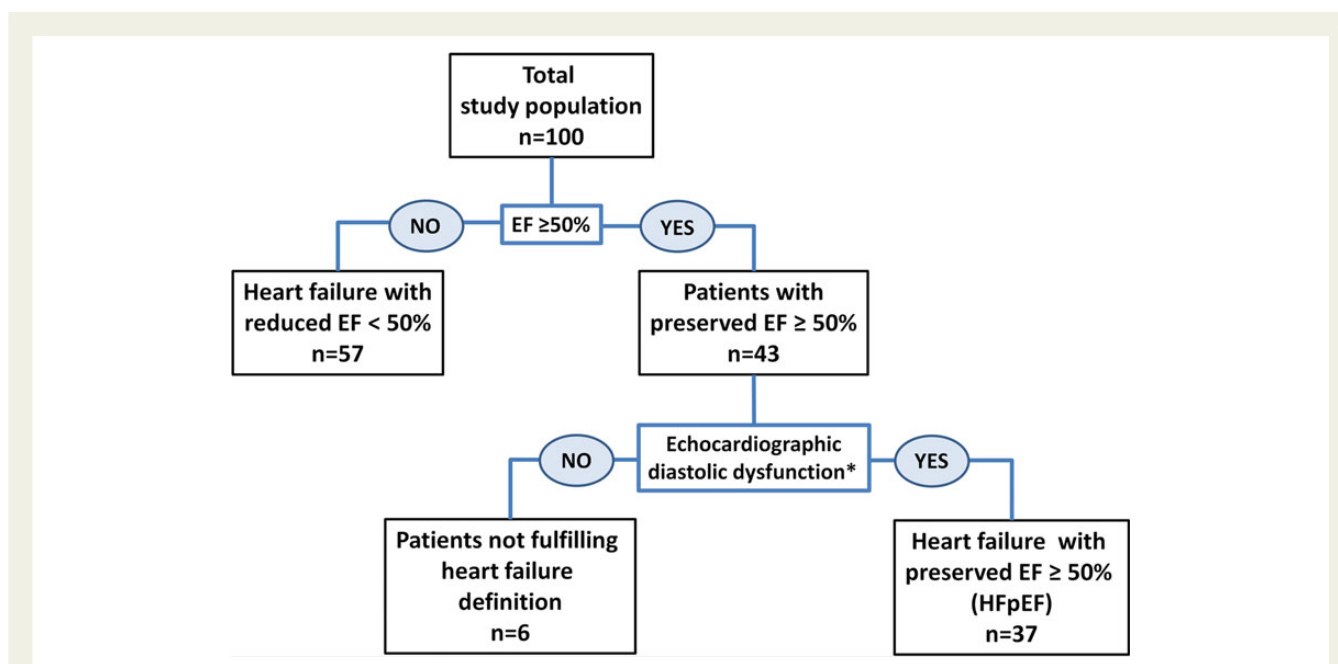
All patients performed exercise testing with ventilatory expired gas analysis. Maximal, graded, exercise testing was performed on an upright electrical braked bicycle ergometer (Jäger ER900; Viasys Healthcare GmbH,

Hochberg, Germany) starting at 20 W, with the pedal rate kept at 60 rotations/min and stepwise increments of 10–20 W/min. The test ended by patients' symptoms of exhaustion, if obtaining maximal physical level or by signs of severe pathology.  $\text{VO}_2$ ,  $\text{CO}_2$  production, and ventilation were measured on a breath-to-breath basis and calculated by the software MVmax 229 (Viasys Healthcare GmbH). Gas exchange values were obtained throughout the baseline rest, exercise, and early recovery period and were averaged from 20 s intervals. Peak  $\text{VO}_2$  and respiratory exchange ratio (RER) were measured in the last 20 s at maximal exercise. Patients with peak RER  $\leq 1.1$  were not included in the study. Heart rate and 12-lead electrocardiogram were continuously recorded, and cuff blood pressure was measured every minute. We defined peak  $\text{VO}_2$  as the highest  $\text{VO}_2$  obtained during an adequately performed test.<sup>3</sup> At peak exercise, we recorded Watts, metabolic equivalents, heart rate, and blood pressure.

### Echocardiography

Echocardiography was performed the same day as CPX using Vivid 7 and Vivid E9 system (GE Healthcare, Horten, Norway) and analysed offline (EchoPAC<sup>®</sup>). We calculated LV diameters by M-mode and LV EF by Simpson's biplane method. RV function was assessed by tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity ( $S'$ ) by pulsed tissue Doppler, and fractional area change (FAC).<sup>22</sup> Peak pulmonary arterial systolic pressure (PASP) was estimated as the sum of peak RV-right atrial gradient from the tricuspid valve regurgitant jet and right atrial pressure on the basis of size and collapse of inferior vena cava.<sup>22</sup>

LV and RV longitudinal strains were analysed by speckle tracking echocardiography, with frame rate  $\geq 50 \text{ s}^{-1}$ . From apical four-chamber, two-chamber, and long-axis view, peak longitudinal strains from each of the 16 LV segments, either negative or positive, were averaged to LV global longitudinal strain (GLS).<sup>18,19</sup> The RV strain was averaged from the three RV free wall segments from apical four-chamber view.<sup>23</sup>



**Figure 1** The total study population (top) and the separated HFpEF group (lower right) were studied. Six patients with preserved EF (lower left) did not fulfil echocardiographic diastolic dysfunction and were not included for analysis in the HFpEF group (the asterick refers to McMurray et al.<sup>1</sup> and Nagueh et al.<sup>24</sup>).

Diastolic function parameters were peak early diastolic filling ( $E$ ) and late diastolic filling ( $A$ ) velocities,  $E/A$  ratio,  $E$  deceleration time, early diastolic septal mitral annular velocity ( $e'$ ) (averaged from three cardiac cycles), and  $E/e'$  as an index of LV filling pressure.<sup>24</sup> Left atrial area and volume index were calculated from apical four- and two-chamber views, using area-length formula.  $E/A$  ratio,  $E$  deceleration time,

$e'$ ,  $E/e'$ , and left atrial volume index were classified as normal or abnormal adjusted for age.<sup>24</sup> Diastolic dysfunction was fulfilled if at least two of these indices were abnormal.<sup>1,24</sup>

Patients with heart failure symptoms,  $EF \geq 50\%$ , and fulfilling echocardiographic criteria for diastolic dysfunction were defined as having HFpEF (Figure 1).

**Table 1 Patient characteristics**

	Total study population (n = 100)	Patients with HFpEF (n = 37)
Age (years)	56 ± 12	58 ± 11
Gender (male/female) (n)	73/27	25/12
HR (bpm)	74 ± 15	77 ± 16
Systolic BP (mmHg)	116 ± 26	135 ± 21
Diastolic BP (mmHg)	71 ± 14	79 ± 11
BMI (kg/m <sup>2</sup> )	26 ± 4	26 ± 4
NYHA class	2.5 ± 0.9	2.0 ± 0.5
Diabetes (n)	13 (13%)	5 (14%)
Hypertension (n)	25 (25%)	15 (41%)
NT-proBNP (pmol/L) (n = 81) (n = 24)	464 ± 612	115 ± 164
Aetiology of heart failure		
Ischaemic heart disease (n)	47 (47%)	22 (60%)
Dilated CM (n)	34 (34%)	0
Hypertrophic CM (n)	3 (3%)	2 (5%)
CM from hypertension, diabetes, and other (n)	16 (16%)	13 (35%)
CPX parameters		
Peak exercise (Watt)	102 ± 62	136 ± 59
Peak exercise (METs)	4.4 ± 1.8	5.7 ± 2.0
HR at peak exercise (bpm)	125 ± 25	133 ± 20
Systolic BP at peak exercise (mmHg)	154 ± 49	187 ± 34
Diastolic BP at peak exercise (mmHg)	84 ± 30	92 ± 21
Peak $\dot{V}O_2$ (mL/kg/min)	15.4 ± 6.3	20.1 ± 6.9
$VE/\dot{V}CO_2$ (n = 76)	30.7 ± 7.8	26.1 ± 4.0
Echocardiographic parameters		
LV ESV index (mL/m <sup>2</sup> )	49 ± 44	14 ± 5
LV EDD index (mm/m <sup>2</sup> )	32 ± 7	26 ± 2
LV EF (%)	42 ± 19	62 ± 7
LV GLS (%)	-11.9 ± 6.6	-17.5 ± 3.2
TAPSE (cm)	1.6 ± 0.9	1.8 ± 0.6
RV S' (cm/s)	8.6 ± 3.3	9.4 ± 3.1
Peak PASP (mmHg)	38 ± 13	31 ± 10
RV FAC (%)	37 ± 14	48 ± 11
RV strain (%)	-14.9 ± 6.5	-22.8 ± 5.7
$E$ (cm/s)	78 ± 28	72 ± 23
$E$ deceleration time (ms)	206 ± 76	245 ± 75
$E/A$ ratio	1.97 ± 1.30	1.53 ± 1.08
$e'$ (cm/s) (n = 92)	5.8 ± 2.5	7.1 ± 2.0
$E/e'$ (n = 92)	17 ± 12	11 ± 5
Left atrial area (cm <sup>2</sup> )	28.1 ± 9.0	24.4 ± 7.4
Left atrial volume index (mL/m <sup>2</sup> )	56 ± 26	45 ± 22

A, late diastolic filling velocity; BMI, body mass index; BP, arterial blood pressure; bpm, beats per minute; CM, cardiomyopathy; CPX, cardiopulmonary exercise testing;  $E$ , peak early diastolic filling velocity;  $e'$ , early diastolic mitral annular velocity (septal); EDD, end diastolic diameter; EF, ejection fraction; ESV, end systolic volume; FAC, fractional area change; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LV, left ventricular; METs, metabolic equivalents; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; RV, right ventricular; S', tricuspid lateral annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion;  $VE/\dot{V}CO_2$ , minute ventilation/carbon dioxide production;  $\dot{V}O_2$ , oxygen uptake.

Two independent investigators (N.E.H. and K.H.H.) analysed echocardiographic recordings blinded to clinical data.

## Statistical analysis

Continuous data were presented as mean  $\pm$  SD. Comparisons of means were analysed by Student's *t*-test (SPSS 18, SPSS Inc., Chicago, IL, USA). Bivariate correlations were assessed by Pearson coefficient for normally distributed continuous parameters.

The multivariate linear regression for assessing independent correlations to peak  $\text{VO}_2$  was performed by including clinically relevant, significant variables from the univariate model. Strong collinearity ( $R \geq 0.50$  or  $R \leq -0.50$ ) was found between parameters of LV function (GLS and EF) and RV function (FAC and RV strain) and LV function and NYHA classification in the total study population. In the HFpEF population, there were strong collinearities between GLS and NT-proBNP and GLS and TAPSE. These parameters were therefore not included in multivariate analyses together.

Receiver operating characteristic (ROC) curves were created and areas under curves were calculated for the ability of GLS, EF, RV strain, and  $E/e'$  to identify patients with peak  $\text{VO}_2 < 20$  mL/kg/min. The ROC curve value closest to the upper left corner was defined to provide optimal sensitivity and specificity for each parameter. Two-sided *P*-values  $< 0.05$  were considered significant for all analyses.

## Results

### Clinical characteristics

We included 100 patients (Table 1). Forty-seven patients had coronary artery disease, 34 dilated cardiomyopathy, and 3 had hypertrophic cardiomyopathy. The remaining 16 patients had heart failure symptoms and signs secondary to hypertension, diabetes, or other co-morbidities. Thirty-seven patients fulfilled the HFpEF definition.

### Cardiopulmonary exercise testing

Mean peak  $\text{VO}_2$  was  $15.4 \pm 6.3$  mL/kg/min in the total population and  $20.1 \pm 6.9$  mL/kg/min in HFpEF patients (Table 1).

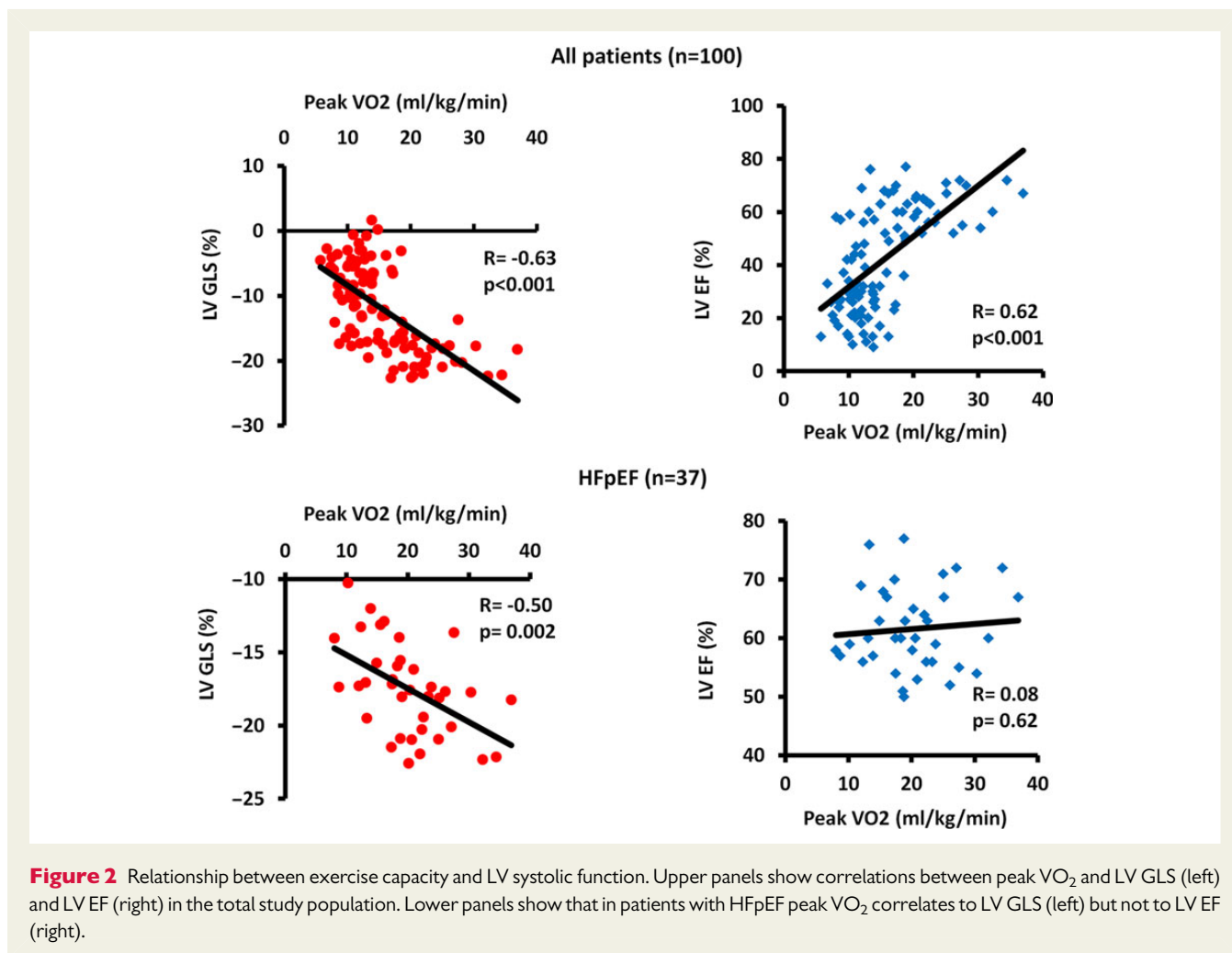
### Echocardiographic findings

Forty-three patients had preserved EF  $> 50\%$  (Table 1). Diastolic dysfunction was diagnosed in 37 of these, while 6 patients with preserved EF did not fulfil echocardiographic diastolic dysfunction and were not included in the HFpEF group (Figure 1). In the total study population, GLS was clearly reduced ( $-11.9 \pm 6.6\%$ ). In HFpEF, GLS was subnormal ( $-17.5 \pm 3.2\%$ ) indicating impaired systolic LV function.<sup>25–27</sup> Measures of RV function were normal or slightly below normal reference values<sup>22</sup> (Table 1). As expected, LV filling pressures

**Table 2** Univariate (*R*) and multivariate analyses ( $\beta$ ) of correlations between exercise capacity by peak  $\text{VO}_2$  and clinical and echocardiographic parameters in the total study population (left) and the HFpEF patients (right)

Relation to peak $\text{VO}_2$	Total study population (n = 100)				Patients with HFpEF (n = 37)			
	Univariate correlation		Multivariate regression		Univariate correlation		Multivariate regression	
	R	P-value	$\beta$ (95% CI)	P-value	R	P-value	$\beta$ (95% CI)	P-value
Age, per 5 years	0.13	0.20	-0.37 (-0.85 to 0.12)	0.13	-0.01	0.99	-1.07 (-2.07 to -0.07)	0.04
NYHA class	-0.77	<0.001			-0.65	<0.001		
NT-proBNP, per 10 pmol/L	-0.35	0.002	-0.02 (-0.04 to 0.01)	0.25	-0.47	0.02		
LV EDD index	-0.43	<0.001	0.08 (-0.16 to 0.33)	0.50	0.12	0.48		
LV EF	0.62	<0.001	-0.01 (-0.13 to 0.11)	0.87	0.08	0.62		
LV GLS	-0.63	<0.001	-0.42 (-0.79 to -0.04)	0.03	-0.50	0.002	-0.80 (-1.49 to -0.11)	0.02
TAPSE	0.27	0.008	0.39 (-1.18 to 1.96)	0.62	0.49	0.003		
RV S'	0.33	0.001	0.02 (-0.34 to 0.38)	0.92	0.35	0.04	0.54 (-0.10 to 1.19)	0.09
Peak PASP	-0.55	<0.001	-0.15 (-0.28 to -0.02)	0.02	-0.49	0.002	-0.35 (-0.68 to -0.02)	0.04
RV FAC	0.54	<0.001			0.35	0.03	0.08 (-0.11 to 0.28)	0.38
RV strain	-0.50	<0.001			-0.34	0.05		
E	-0.28	0.04			-0.39	0.02		
E deceleration time	0.48	<0.001			0.34	0.04		
E/A	-0.43	<0.001			-0.26	0.13		
e'	0.46	<0.001			0.20	0.24		
E/e'	-0.41	<0.001	0.06 (-0.05 to 0.18)	0.28	-0.43	0.008	0.12 (-0.44 to 0.69)	0.66
Left atrial area	-0.40	<0.001			-0.28	0.09		
Left atrial volume index	-0.41	<0.001	-0.03 (-0.08 to 0.02)	0.16	-0.28	0.09		

A, late diastolic filling velocity;  $\beta$ , beta regression coefficient; CI, confidence interval; E, peak early diastolic filling velocity; e', early diastolic mitral annular velocity (septal); EDD, end diastolic diameter; EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; R, Pearson coefficient; RV, right ventricular; S', tricuspid lateral annular systolic velocity; TAPSE, tricuspid annular plane systolic excursion;  $\text{VO}_2$ , oxygen uptake.



as indexed by  $E/e'$  were elevated in both the total study population and HFpEF patients. Mean frame rate was  $58 \pm 19 \text{ s}^{-1}$ . Intra- and inter-observer, intra-class correlation coefficients for strain analyses were 0.94 and 0.90, respectively.

## Myocardial function and exercise capacity

### Total study population

Parameters of myocardial systolic and diastolic function correlated to peak VO<sub>2</sub> (Table 2 and Figure 2, upper panel). GLS and peak PASP were independently correlated to exercise capacity by multivariate analysis (Table 2). In separate multivariate analysis including RV function, RV strain showed an independent correlation to exercise capacity (Supplementary data online, Table S1).

ROC analyses showed that GLS had significantly better ability to detect reduced peak VO<sub>2</sub> of <20 mL/kg/min compared with EF, RV strain, and  $E/e'$  (Figure 3). A GLS value of -17.3% had excellent sensitivity of 0.89 (95% CI 0.79–0.95) and specificity of 0.91 (95% CI 0.71–0.99) to identify patients with a peak VO<sub>2</sub> of <20 mL/kg/min.

$E/e'$  and left atrial volume index correlated to GLS ( $R = 0.63$ ,  $P < 0.001$  and  $R = 0.44$ ,  $P < 0.001$ ) and to EF ( $R = -0.56$ ,  $P < 0.001$  and  $R = -0.46$ ,  $P < 0.001$ ).

In patients with reduced EF <50%, peak VO<sub>2</sub> did neither correlate to EF nor GLS nor RV function.

### Patients with HFpEF

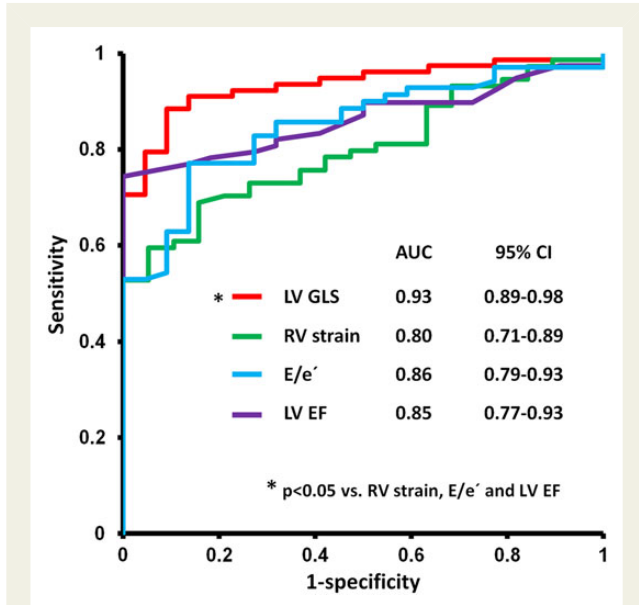
GLS and  $E/e'$  correlated to peak VO<sub>2</sub>, while EF did not (Table 2 and Figure 2, lower panel). Furthermore, GLS was an independent predictor of peak VO<sub>2</sub> (Table 2). GLS correlated moderately to  $E/e'$  ( $R = 0.45$ ,  $P = 0.005$ ) (Figure 4) and to left atrial volume index ( $R = 0.48$ ,  $P = 0.003$ ). In contrast, EF correlated neither to  $E/e'$  ( $R = 0.10$ ,  $P = 0.57$ ) (Figure 4) nor to left atrial volume index ( $R = -0.04$ ,  $P = 0.80$ ). This may indicate a relation between diastolic function and systolic longitudinal LV function detectable by strain only.

## N-terminal pro-B-type natriuretic peptide

NT-proBNP was increased above normal values (Table 1) and correlated to peak VO<sub>2</sub> (Table 2). In the total population, NT-proBNP had a moderate correlation to both GLS and EF ( $R = 0.36$ ,  $P = 0.001$  and  $R = -0.40$ ,  $P < 0.001$ ). Interestingly in HFpEF patients, NT-proBNP correlated strongly to GLS ( $R = 0.60$ ,  $P = 0.002$ ) but not to EF ( $R = 0.03$ ,  $P = 0.88$ ).

## Discussion

Our study provide novel data showing that LV longitudinal function by GLS was independently correlated to exercise capacity. GLS was better than LV EF to identify patients with impaired exercise



**Figure 3** Receiver operating characteristic curve analyses showing that GLS is superior to other myocardial function parameters to identify patients with a peak  $\text{VO}_2$  of  $<20$  mL/kg/min ( $n = 100$ ). AUC, area under curve; CI, confidence interval; E, peak early diastolic filling velocity; e', early diastolic mitral annular velocity (septal).

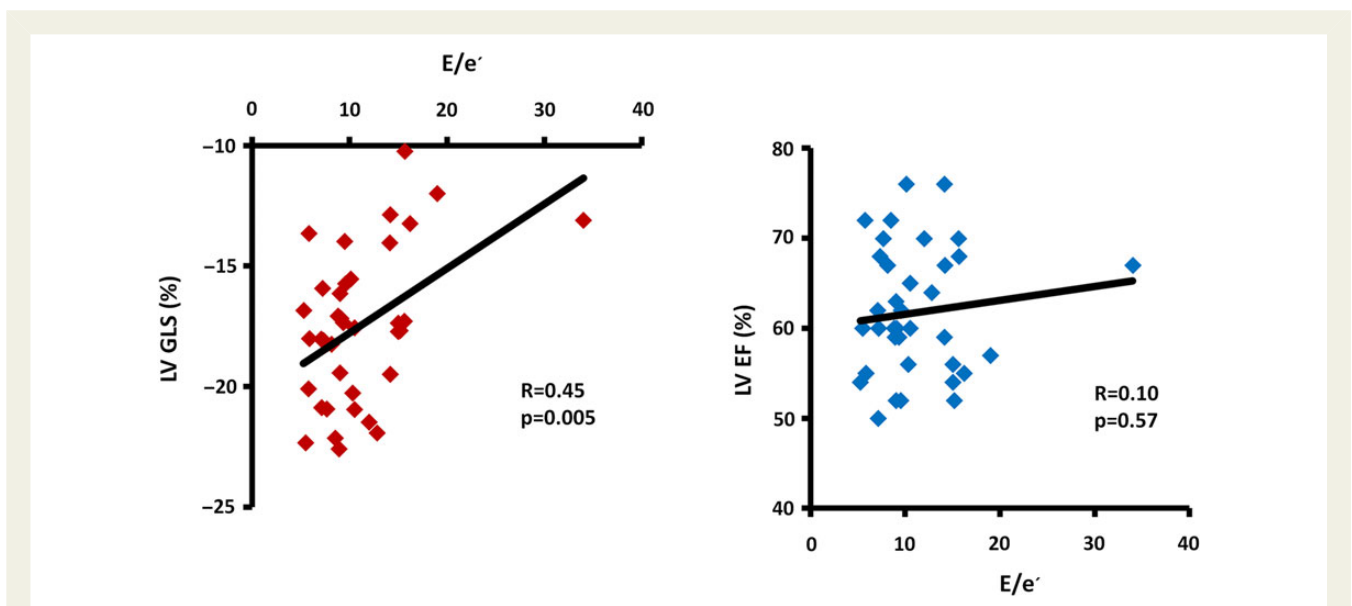
capacity. Considering the strong relationship between exercise capacity and cardiac prognosis, these results are in line with recent reports showing the strong prognostic power of GLS.<sup>19,20</sup> Myocardial strain may have the potential to identify reduced exercise capacity and poor prognosis at an early disease stage when traditional parameters fail. In HFpEF patients, GLS demonstrated reduced systolic function, emphasizing that the term 'heart failure with preserved EF' should not be equalled to heart failure with preserved systolic function. Furthermore, GLS related to diastolic function, indicating a coupling of systolic and diastolic function in HFpEF.

## Myocardial function and exercise capacity

Previous studies have failed to find a relationship between peak  $\text{VO}_2$  and systolic LV function by EF,<sup>8-10</sup> and rather found a correlation to RV function.<sup>14-16</sup> In line with previous observations, we found strong correlations between exercise capacity and both RV function and diastolic function (Table 2 and Supplementary data online, Table S1). Our novel finding was that LV function by strain also related strongly to exercise capacity. LV GLS was independently correlated to exercise capacity both in the total population and in HFpEF patients (Table 2).

Current recommendations for CPX in heart failure define a peak  $\text{VO}_2$  of  $\geq 20$  mL/kg/min as normal based on the Weber classification.<sup>7,28</sup> GLS was the best parameter to identify patients with a peak  $\text{VO}_2$  of  $<20$  mL/kg/min. Therefore, GLS might be useful to discriminate patients with normal from those with moderately and severely reduced exercise capacity. (Figure 3)

In patients with HFpEF, GLS was correlated to exercise capacity and to NT-proBNP, both of which have prognostic impact in HFpEF.<sup>3,29</sup> A few studies have shown correlations between myocardial strain and exercise capacity in patients with heart failure with reduced EF  $<40\%$ .<sup>16,30</sup> Our study is the first study showing a



**Figure 4** Relationship between LV systolic function and diastolic function by  $E/e'$  in patients with HFpEF ( $n = 37$ ). LV GLS correlates to diastolic function (left) while ejection fraction (EF) does not (right). If excluding the patient with  $E/e' = 34$  appearing as an outlier in the figure, the results remain unchanged; GLS correlates to  $E/e'$  ( $R = 0.42$ ,  $P = 0.01$ ) while EF does not ( $R = -0.03$ ,  $P = 0.88$ ). E, peak early diastolic filling velocity; e', early diastolic mitral annular velocity (septal).

strong correlation between systolic function and exercise capacity in patients with HFpEF. No relationship was observed between EF and exercise capacity nor between EF and NT-proBNP in HFpEF patients. This confirms EF's low sensitivity and limited quantitative value in patients with preserved EF.<sup>31</sup> Our findings suggest that LV longitudinal function by strain should be the preferred method to quantify LV systolic function in patients with HFpEF.

## Systolic–diastolic coupling in HFpEF

Others have reported that diastolic function correlates better to exercise capacity than systolic function.<sup>11–13</sup> In contrast to our study, these studies did not include patients with HFpEF. Systolic function by GLS was impaired in our HFpEF patients. Recent studies have indicated the presence of systolic dysfunction in HFpEF.<sup>32,33</sup> Our results underscore these findings and confirm that preserved EF is not equal to normal systolic function. Our correlations between GLS and diastolic parameters indicate a close coupling between systolic and diastolic function in HFpEF and are in accordance with an experimental study demonstrating that the diastolic parameter  $e'$  is dependent on and related to systolic function through restoring forces.<sup>34</sup>

## Clinical applications

EF is a strong predictor of outcome in patients with clearly reduced myocardial systolic function. Through its relation to exercise capacity, we suggest that GLS may have a similar prognostic function in HFpEF patients. Current recommendations for CPX define the assessment of peak  $VO_2$  as a primary prognostic marker.<sup>7</sup> However, despite the strong scientific evidence supporting CPX, CPX is underutilized in clinical practice due to costs and lack of equipment, time, and competence. Echocardiography is a routine examination in the evaluation of all patients with verified or suspected cardiac disease. In specific clinical settings, strain assessment could work as a first-line examination, avoiding unnecessary CPX in stable patients and repeated CPX in unstable patients.<sup>35</sup> Strain echocardiography might be a useful tool in the diagnostic workup of HFpEF.

## Limitations

Our study was a cross-sectional study, and we did not relate our findings to clinical outcome. Follow-up studies should be performed to directly compare echocardiographic measures to exercise capacity and outcome. Also, our HFpEF population was relatively small and our findings should be confirmed in larger populations.

The prognostic value of peak  $VO_2$  between 15 and 20 mL/kg/min is debated. Our proposal to use strain as a surrogate for peak  $VO_2$  to predict prognosis in early disease stages should therefore be confirmed in future studies.

The study population was heterogeneous in functional level, symptom score, and disease stage. Hence, the level of myocardial impairment assessed by echocardiography ranged from near normal till severely reduced.

In separate analyses of patients with reduced LV function (EF < 50%), EF, GLS, and RV function were not correlated to exercise capacity. We believe that the heterogeneous aetiologies and pathologies and the co-morbidities in patients with severe myocardial dysfunction interfere with the relations found at earlier stages of myocardial disease, as also shown by others.<sup>8–10</sup>

Due to strong correlations between LV and RV function parameters and the limited number of observations, we did not include these in multivariate regression analyses together. Therefore, we were not able to interpret whether LV function was correlated to exercise capacity independently of RV function.

We used the absolute peak  $VO_2$  values in our study as recommended to assess heart failure severity and prognosis.<sup>7</sup> The percentage of predicted peak  $VO_2$  has been used previously, but it has not shown superiority.<sup>3,36</sup>

We correlated echocardiographic parameters at rest to exercise parameters. Previous studies have shown better correlation between exercise parameters and stress echocardiographic LV filling pressures.<sup>37</sup> However, the fact that we demonstrated a relationship between exercise capacity and resting myocardial function may strengthen the clinical importance of our findings.

Lack of NT-proBNP analyses in some patients may have influenced our data.

## Conclusions

Longitudinal LV function by GLS was independently correlated to peak  $VO_2$ , and GLS was superior to identify patients with exercise capacity below normal values. Through its strong relation to the established prognostic marker exercise capacity, we propose that GLS may help with early identification of patients with poor prognosis.

In patients with HFpEF, GLS was impaired and was related to reduced diastolic function and reduced exercise capacity. These results emphasize that there is systolic dysfunction in patients with preserved EF and the presence of a tight coupling of systolic and diastolic function in HFpEF patients.

## Supplementary data

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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