

# Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction

Caterina Maffei<sup>1,2</sup>, Daniel Armando Morris<sup>2</sup>, Evgeny Belyavskiy<sup>2</sup>, Martin Kropf<sup>2</sup>, Aravind Kumar Radhakrishnan<sup>2</sup>, Veronika Zach<sup>2,3</sup>, Cristina Rozados da Conceicao<sup>2,3</sup>, Tobias Daniel Trippel<sup>2,3</sup>, Elisabeth Pieske-Kraigher<sup>2</sup>, Andrea Rossi<sup>1</sup>, Burkert Pieske<sup>2,3,4,5</sup> and Frank Edelmann<sup>2,3,5\*</sup>

<sup>1</sup>Department of Medicine, Section of Cardiology, University of Verona, Verona, Italy; <sup>2</sup>Department of Internal Medicine and Cardiology, Charité—Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, Berlin, 13353, Germany; <sup>3</sup>German Center for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; <sup>4</sup>Department of Internal Medicine and Cardiology, German Heart Institute, Berlin, Germany; <sup>5</sup>Berlin Institute of Health (BIH), Berlin, Germany

## Abstract

**Aims** Exercise intolerance is the leading manifestation of heart failure with preserved or mid-range ejection fraction (HFpEF or HFmrEF), and left atrial (LA) function might contribute to modulating left ventricular filling and pulmonary venous pressures. We aim to assess the association between LA function and maximal exercise capacity in patients with HFpEF or HFmrEF.

**Methods and results** Sixty-five patients, prospectively enrolled in the German HFpEF Registry, were analysed. Inclusion criteria were New York Heart Association functional class  $\geq$  II, left ventricular ejection fraction  $>$  40%, structural heart disease or diastolic dysfunction, and elevated levels of N terminal pro brain natriuretic peptide (NT-proBNP). LA function was evaluated through speckle-tracking echocardiography by central reading in the Charité Academic Echocardiography core lab. All patients underwent maximal cardiopulmonary exercise test and were classified according to a peak  $\text{VO}_2$  cut-off of prognostic value (14 mL/kg/min). NT-pro-BNP was measured. Twenty-nine patients (45%) reached a peak  $\text{VO}_2 <$  14 mL/kg/min (mean value  $12.4 \pm 1.5$ ) and 36 patients (55%) peak  $\text{VO}_2 \geq$  14 mL/kg/min (mean value  $19.4 \pm 3.9$ ). There was no significant difference in left ventricular ejection fraction ( $60 \pm 9$  vs.  $59 \pm 8\%$ ), left ventricular mass ( $109 \pm 23$  vs.  $112 \pm 32$  g/m<sup>2</sup>), LA volume index ( $45 \pm 17$  vs.  $47 \pm 22$  mL/m<sup>2</sup>), or  $E/e'$  ( $13.1 \pm 4.7$  vs.  $13.0 \pm 6.0$ ) between these groups. In contrast, all LA strain measures were impaired in patients with lower peak  $\text{VO}_2$  (reservoir strain  $14 \pm 5$  vs.  $21 \pm 9\%$ ,  $P = 0.002$ ; conduit strain  $9 \pm 2$  vs.  $13 \pm 4\%$ ,  $P = 0.001$ ; contractile strain  $7 \pm 4$  vs.  $11 \pm 6\%$ ,  $P = 0.02$ ; reported lower limits of normality for LA reservoir, conduit and contractile strains: 26.1%, 12.0%, and 7.7%). In linear regression analysis, lower values of LA reservoir strain were associated with impaired peak  $\text{VO}_2$  after adjustment for age, sex, body mass index, heart rhythm (sinus/AFib), and log-NTproBNP [ $\beta$  0.29, 95% confidence interval (CI) 0.02–0.30,  $P = 0.02$ ], with an odds ratio 1.22 (95% CI 1.05–1.42,  $P = 0.01$ ) for peak  $\text{VO}_2 <$  14 mL/kg/min for LA reservoir strain decrease after adjustment for these five covariates. Adding left ventricular ejection fraction, it did not influence the results. On the other hand, the addition of LA strain to the adjustment parameters alone described above provided a significant increase of the predictive value for lower peak  $\text{VO}_2$  values ( $R^2$  0.50 vs. 0.45,  $P = 0.02$ ). With receiver operating characteristic curve analysis, we identified LA reservoir strain  $<$  22% to have 93% sensitivity and 49% specificity in predicting peak  $\text{VO}_2 <$  14 mL/kg/min. Using this cut-off, LA reservoir strain  $<$  22% was associated with peak  $\text{VO}_2 <$  14 mL/kg/min in logistic regression analysis after comprehensive adjustment for age, sex, body mass index, heart rhythm, and log-NTproBNP [odds ratio 95% CI 10.4 (1.4–74),  $P = 0.02$ ].

**Conclusions** In this HFpEF and HFmrEF cohort, a reduction in LA reservoir strain was a sensible marker of decreased peak exercise capacity. Therefore, LA reservoir strain might be of clinical value in predicting exercise capacity in patients with HFpEF or HFmrEF.

**Keywords** Left atrial strain; Cardiopulmonary exercise test; Heart failure; Preserved ejection fraction; Mid-range ejection fraction

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\*Correspondence to: Frank Edelmann, Department of Internal Medicine and Cardiology, Charité University Medicine, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 (0)30 450 653731; Fax: +49 (0)30 450 7553731. Email: frank.edelmann@charite.de

## Introduction

Heart failure (HF) with preserved and mid-range ejection fraction (HFpEF, HFmrEF) accounted for more than half of patients with HF syndrome and are associated with high morbidity and mortality.<sup>1,2</sup> Exercise intolerance, objectivized by means of peak oxygen consumption, is the leading manifestation, but the underlying pathophysiology is still uncertain.

Several cardiac and peripheral mechanisms are involved in determining a reduced exercise capacity, and an exaggerated increase in pulmonary capillary wedge pressure (PCWP) with exercise is one of the most consistent.<sup>3</sup> However, neither echocardiographic parameters of diastolic function nor neuro-humoral activation were independently associated with exercise capacity in clinically stable HFpEF patients.<sup>4</sup> Also, single echocardiographic variables at rest cannot reliably estimate cardiac pressure when left ventricular ejection fraction (LVEF) is >40%, so an integrated approach evidencing structural or functional alterations is suggested in the effort to diagnose HFpEF and HFmrEF.<sup>5</sup> Interestingly, the left atrium (LA) contributes to modulate left ventricular (LV) filling pressure through its reservoir, conduit, and booster functions both at rest and with exercise. In particular, LA compliance allows LA volume to increase during the reservoir phase without an increase in filling pressure and at the same time providing an adequate LV filling during diastole through a preload mechanism.

The ideal method to evaluate LA function is by invasively determined LA pressure–volume curves. Speckle-tracking echocardiography (STE) is a promising non-invasive semi-automated less load-dependent method to measure LA function and indirectly estimate LV filling pressure. In fact, a negative correlation was found between impaired LA strain and invasively measured LV end-diastolic pressure and PCWP.<sup>6,7,8</sup>

In patients with preserved LVEF, first evidences showed that LA strain was associated with exercise capacity expressed as estimated metabolic equivalent among patients with clinical indication to perform an exercise test<sup>9</sup> and haemodynamic and cardiopulmonary exercise test (CPET) variables, especially in younger patients with less comorbidities, in an HFpEF population.<sup>10</sup> In line with these findings, we aimed to assess the value of LA functional remodelling in predicting exercise intolerance in a cohort of HFpEF or HFmrEF patients above traditional echocardiographic parameters.

## Methods

### Study population

Between August 2016 and December 2019, consecutive patients with a diagnosis of HFpEF or HFmrEF evaluated in an outpatients setting or during hospitalization for HF at the Charité University Hospital were prospectively enrolled in the German HFpEF Registry. Inclusion criteria of the German HFpEF Registry were (1) LVEF > 40% (for patients with LVEF

40–50%, irrespective of a previous history of HFpEF with subsequent LVEF impairment < 50%); (2) age ≥ 18 years; (3) New York Heart Association (NYHA) functional class ≥ II; (4) elevated levels of natriuretic peptides [N terminal pro brain natriuretic peptide (NT-proBNP) > 125 pg/mL]; and (5) at least one additional criterion for structural heart disease or diastolic dysfunction (LV mass index ≥ 115 g/m<sup>2</sup> for men and ≥95 g/m<sup>2</sup> for women; LA volume index > 34 mL/m<sup>2</sup>; mean E/e' ≥ 13 and mean E' < 9 cm/s).<sup>11</sup> Registry exclusion criteria were acute coronary syndrome or cardiac surgery/percutaneous intervention during the past 3 months, haemodynamic relevant pericardial disease, and severe kidney disease. For the present study, we applied more restrictive exclusion criteria. Patients enrolled in the registry were excluded from the final study population in presence of further conditions, which could affect the cardiopulmonary haemodynamic or bias the evaluation of atrial and/or ventricular function, that is if they had more than moderate valve disease, significant mitral annular calcification, congenital heart disease, previous cardiac transplantation, restrictive cardiomyopathy, severe chronic obstructive pulmonary disease, severe kidney disease (estimated GFR<sub>MDRD</sub> ≤ 30 mL/min/1.73 m<sup>2</sup> or requiring dialysis), or severe liver disease (Child–Pugh class B and C or with indication for liver transplantation). Moreover, patients were excluded if they could not perform echocardiography in stable condition or could not perform a maximal exercise testing. The study complies with the Declaration of Helsinki. The Ethics Committee of Charité University Hospital approved the research project and written informed consent was obtained from all subjects.

### Clinical characteristics

The following data were collected in all study participants: demographics, body mass index (BMI), cardiovascular risk factors, comorbidities, clinical history, NYHA functional class, and medications. An electrocardiogram was performed at the time of the first clinical evaluation after enrolment. Blood samples were collected for laboratory testing, including haemoglobin, creatinine, HbA1c, hs-RP, and NT-proBNP.

### Echocardiography

All study participants underwent comprehensive 2D echocardiography at rest using commercially available ultrasound systems (Philips EPIQ 7, Philips Medical Systems, Andover, MA). Echocardiography was performed in conditions of respiratory (<20 breaths/min), haemodynamic (systolic blood pressure 90–140 mmHg), and electrical (51–99 beats/min) stability. All images acquired for STE analysis were obtained at a frame rate of 50 to 80 frame/s, and a minimum of three cardiac cycles (for patients in sinus rhythm) or five cardiac cycles (for patients in atrial fibrillation) were acquired. All sonographers

were trained in accordance with a pre-specified standard operation procedure. All 2D, Doppler, and strain measurements were performed offline, at the echocardiographic core laboratory, using a customized software package (TomTec Image Arena, Unterschleissheim, Germany). All analyses were performed according to ASE/EACVI recommendations<sup>12,13,14</sup> by a single investigator, with over-reading by a second investigator. Both researchers were blinded to the clinical characteristics of the patients. The presence of sinus rhythm or atrial fibrillation during echocardiography was recorded.

Left ventricular endocardial longitudinal strain was measured with an algorithm designed for the LV in apical four-chamber and two-chamber view and averaged; the biplane longitudinal strain was considered for the analyses as global longitudinal strain. LV endocardial border was contoured at LV end-diastole and end-systole and manually adjusted when required. When in two or more segments out of six there were dropout or poor tracking, LV strain was not measured.

LA maximal and minimal volumes were measured in apical four-chamber and two-chamber view and LA ejection fraction (EF) was calculated. LA strain was measured in an LA-focused apical four-chamber and two-chamber views, with an algorithm designed for the LA (Figure 1). The onset of QRS was used as the referent point, and the average of three consecutive measurements was made. LA endocardial border was manually contoured at LV end-diastole and end-systole, with visual tracking quality and manual adjustment when required. When in one out of three segments there were dropout or poor tracking due to inadequate image quality, LA strain and strain rate were not measured and patients without measurable LA strain in four-chamber view were excluded. Overall, a total of 122/131 (93%) LA apical four-chamber and 90/131 (69%) LA apical two-chamber tracings were suitable for

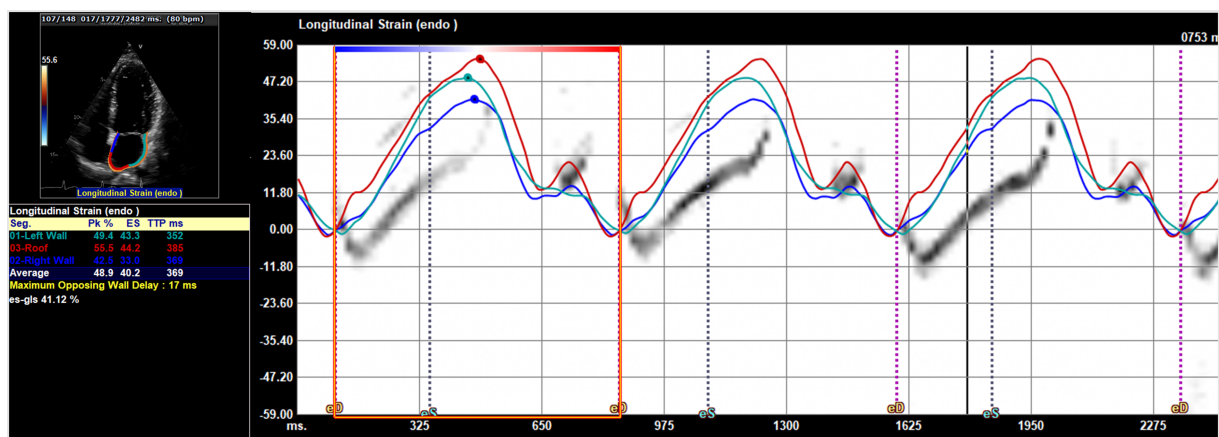
analysis. In 41 patients (31%), the image quality in apical two-chamber view was inadequate for the analysis due to poor tracking, especially in the anterior LA segment. Therefore, only four-chamber volumes and strain parameters were used for further LA analyses. Three components of LA function were evaluated: reservoir (the LA filling phase, corresponding to LV systole), conduit (the passive LA emptying phase, from mitral valve opening to P-wave), and contractile (the active LA emptying phase, from the onset of P-wave to mitral valve closure). For each phase, strain and strain rate were measured.

The intraobserver variability for key measures was estimated by means of intraclass correlation coefficients (ICCs). Reproducibility was excellent for strain parameters (ICC 91–92) and good for strain rate (ICC 78–85).

### Cardiopulmonary exercise test

All patients performed a symptom-limited CPET using a cycle ergometer protocol, cycling with a pedal speed of 60 rpm, starting at a workload of 20 W, followed by a stepwise 20 W increment every 2 min until exhaustion. Heart rate was continuously monitored by electrocardiography at rest and during exercise; blood pressure was measured at rest and every 2 min. Breath-by-breath oxygen consumption (VO<sub>2</sub>), carbon dioxide production (VCO<sub>2</sub>), and minute ventilation (VE) were acquired and averaged over 30 s intervals using a ventilator expired gas analysis system. Test termination criteria considered were patients' request due to symptoms, ventricular arrhythmia, ST segment depression  $\geq 2.0$  mm, and drop in systolic blood pressure  $\geq 20$  mmHg. All oral medications were continued before and through CPET.

**Figure 1** Left atrial function assessed by the speckle tracking echocardiography. Example of three-beat strain curves in the three atrial segments in apical four-chamber view. The mean value of the first positive peak of the three curves represent the reservoir strain, and that of the second lower positive peak represents the contractile strain.



Peak  $\text{VO}_2$  ( $\text{pVO}_2$ ) was defined as the highest averaged  $\text{VO}_2$  during the last stage of exercise. Percentage values of predicted  $\text{pVO}_2$  were calculated using the Wasserman formula.<sup>15</sup>  $\text{VE}/\text{VCO}_2$  slope was calculated to estimate the ventilator response to exercise. The maximal respiratory exchange ratio (RER) was calculated as the  $\text{VCO}_2/\text{VO}_2$  ratio during the last stage of exercise before recovery and was considered as index of maximal exercise. The ability to perform maximal exercise testing was considered a mandatory inclusion criterion. Therefore, patients with maximal RER < 1.0 were excluded from the study analyses.<sup>16</sup>

## Statistical analysis

Data are presented as mean  $\pm$  standard deviation or absolute values and percentages, as appropriate. Patients were categorized in two groups based on a validated  $\text{pVO}_2$  cut-off considered of prognostic value in HF patients' populations ( $\text{pVO}_2$  14 mL/kg/min).<sup>17,18,19,20</sup> Student's *t*-test and  $\chi^2$  test were used to compare continuous and categorical variables between groups, respectively. Pearson's correlation coefficient was used to evaluate the relationship between echocardiographic parameters as continuous variables. The independent association of LA strain with  $\text{pVO}_2$  was studied with regression analysis. As independent variables, we considered age, gender, and BMI, which are non-cardiac factors known to have an influence on  $\text{pVO}_2$  values<sup>20</sup>; heart rhythm [sinus or atrial fibrillation (AFib)], because lower values of LA strain are expected in patients with AFib<sup>21</sup>; and NT-proBNP as validated marker associated with HF symptoms. Because NT-proBNP distribution was skewed, it was log-transformed for analysis. Logistic regression analysis was performed to assess the predictability of  $\text{pVO}_2$  < 14 mL/kg/min for LA strain and key echocardiographic variables [LVEF, LV mass, left atrial volume (LAV) index, and  $E/e'$ ]. Continuous values of the described covariates were used. Moreover, receiver operating characteristic curve and Youden test were performed to identify LA strain cut-off value to be used in subsequent logistic regression analysis to assess the predictability of  $\text{pVO}_2$  < 14 mL/kg/min. All tests were two-tailed. A *P* value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL).

## Results

### Population characteristics

Of the 131 patients enrolled in the German HFpEF Registry, 44 patients were excluded due to submaximal exercise testing (premature stop of testing with peak RER < 1.0), 10 due to not performing CPET, 3 due to resting heart rate < 45 bpm or >100 bpm, 1 due to severe valve disease,

and 8 due to unsuitable LA strain analysis. Sixty-five patients formed the final study population. Average age was  $72 \pm 8$  years; 37 (57%) were men, and 17 (26%) were obese (BMI  $\geq 30$  kg/m<sup>2</sup>). Median NT-proBNP was 510 pg/mL (interquartile range 308–906). Comorbidities were common, especially hypertension, dyslipidaemia, diabetes, ischaemic heart disease, and chronic kidney injury. Fifteen patients (23%) presented AFib during echocardiography, and among these, pacemaker rhythm was present in five patients.

Overall, average  $\text{pVO}_2$  was  $16.3 \pm 4.7$  mL/kg/min, with median (interquartile range) 15.3 (13.0–19.1) mL/kg/min. Twenty-nine patients (45%) had a  $\text{pVO}_2$  < 14 mL/kg/min (mean value  $12.4 \pm 1.5$ ), and 36 patients (55%) reached a  $\text{pVO}_2 \geq 14$  mL/kg/min (mean value  $19.4 \pm 4.0$ ). Echocardiography and cardiopulmonary exercise test were performed in the same day or with 1 day time interval in all patients. Fifty-two patients assumed beta-blockers regularly (81%), but any effect of the medication was noted on exercise tolerance. Compared with patients who didn't assume beta-blockers, there was no significant difference in terms of maximal workload, rest heart rate, maximal exercise heart rate, differential heart rate, Borg score, RER,  $\text{pVO}_2$ , and  $\text{VE}/\text{VCO}_2$  (*P* > 0.05 for all). Clinical and echocardiographic characteristics of patients divided according to  $\text{pVO}_2$  are shown in *Tables 1* and *2*. Patients with severely reduced functional capacity were older, with greater BMI, more symptomatic (NYHA class III vs. II; no one was classified as NYHA IV in either groups), and with higher values of NT-proBNP but did not present significant differences in terms of comorbidities, medical therapy, and other laboratory tests. Overall, patients had LV of normal dimensions with concentric remodelling in 20 (29%), concentric hypertrophy in 21 (32%), eccentric hypertrophy in 6 (9%), preserved or mildly reduced EF (55 and 10 patients with EF > 50% and 40–50%, respectively), decreased mean tissue Doppler-derived *S'* ( $5.9 \pm 0.9$  and  $6.6 \pm 1.6$  cm/s in patients with EF > 50% and  $\leq 50\%$ , respectively, *P* = 0.1). Among patients with LVEF > 50%, 24 (44%) reached a  $\text{pVO}_2$  < 14 and 31 (56%) a  $\text{pVO}_2 \geq 14$  mL/kg/min; among patients with LVEF 40–50%, five (50%) reached a  $\text{pVO}_2$  < 14 and five (50%) a  $\text{pVO}_2 \geq 14$  mL/kg/min. Patients with  $\text{pVO}_2$  < 14 mL/kg/min had lower stroke volume and LV *S'* and slightly higher peak tricuspid regurgitation velocity, but there was no difference in terms of LVEF, LV remodelling pattern, mitral inflow parameters, or  $E/e'$ . Mild mitral regurgitation was slightly more prevalent in patients with severely reduced  $\text{pVO}_2$  and only one patient presented moderate mitral regurgitation (*Table 2*).

### Relationship between left atrium and exercise capacity

In the study cohort, LA enlargement was present in 49 patients (75%), with mean LA maximal volume  $46 \pm 19$  mL/m<sup>2</sup>.

**Table 1** Demographic and clinical characteristics and cardiopulmonary exercise test variables

	Peak VO <sub>2</sub> < 14 mL/kg/min (n = 29)	Peak VO <sub>2</sub> ≥ 14 mL/kg/min (n = 36)	P value
Age, years	75 ± 6	70 ± 9	0.03
Male sex, n (%)	14 (48)	23 (64)	0.2
Body mass index, kg/m <sup>2</sup>	30 ± 5	26 ± 4	0.002
Systolic blood pressure, mmHg	132 ± 18	141 ± 22	0.09
Heart rate, bpm	68 ± 9	65 ± 10	0.3
Atrial fibrillation, n (%)	8 (28)	7 (19)	0.4
NYHA class III, n (%)	10 (34)	2 (5)	0.003
Medical history			
Hypertension, n (%)	27 (93)	31 (86)	0.3
Dyslipidaemia, n (%)	22 (76)	18 (50)	0.04
Diabetes mellitus, n (%)	10 (34)	12 (33)	0.9
Sleep apnoea syndrome, n (%)	1 (3)	9 (25)	0.02
Smoke, n (%)	13 (45)	20 (56)	0.5
Ischaemic heart disease, n (%)	15 (52)	18 (50)	0.9
Valve percutaneous intervention, n (%)	7 (24)	4 (11)	0.1
Peripheral artery disease, n (%)	3 (10)	3 (8)	0.8
Stroke/TIA, n (%)	4 (14)	6 (16)	0.7
Chronic obstructive pulmonary disease, n (%)	4 (14)	2 (5)	0.3
Chronic liver disease, n (%)	1 (3)	0 (0)	0.3
Chronic kidney injury, n (%)	9 (31)	7 (19)	0.3
Medications			
ACE inhibitors or ARBs, n (%)	22 (76)	31 (86)	0.3
Beta-blockers, n (%)	25 (86)	27 (75)	0.3
Anti-aldosterone, n (%)	5 (17)	9 (25)	0.4
Diuretics, n (%)	22 (76)	19 (52)	0.06
Laboratory			
Haemoglobin, g/dL	13.4 ± 1.2	13.5 ± 1.4	0.7
Total cholesterol, mg/dL	159 ± 41	180 ± 51	0.08
LDL cholesterol, mg/dL	95 ± 32	114 ± 49	0.08
HbA1c, %	5.5 ± 0.9	5.5 ± 0.9	0.9
Creatinine, mg/dL	1.1 ± 0.4	1.0 ± 0.4	0.4
Hs-C-reactive protein, mg/L	2.6 ± 3.0	4.2 ± 6.8	0.3
Ferritin, µg/L	113 ± 82	115 ± 100	0.9
NT-proBNP, pg/mL	640 (436–1022)	413 (249–786)	0.01
Cardiopulmonary exercise test			
Maximal work, Watt	75 ± 16	111 ± 27	<0.0001
Time of exercise, min	7 ± 1	11 ± 3	<0.0001
Peak VO <sub>2</sub> , mL/kg/min	12.4 ± 1.5	19.4 ± 4.0	<0.0001
Percent predicted peak VO <sub>2</sub> , %	74 ± 16	94 ± 18	<0.0001
Peak RER	1.05 ± 0.03	1.05 ± 0.05	0.5
VE/VCO <sub>2</sub> slope	39 ± 7	34 ± 6	0.001
Rest heart rate, bpm	73 ± 13	69 ± 10	0.1
Exercise maximal heart rate, bpm	102 ± 21	121 ± 25	0.002
Δheart rate, bpm	30 ± 18	52 ± 21	<0.0001
Borge score (6–20)	15.6 ± 2.2	15.9 ± 1.7	0.6

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; RER, respiratory exchange ratio; TIA, transient ischaemic attack.

All LA strain parameters (reservoir strain 18 ± 8%, conduit strain 11 ± 4%, and contractile strain 9 ± 5%) were impaired in comparison with described values in healthy populations.<sup>22,23</sup> Volume-derived morphological (maximal and minimal volumes) and functional (LA EF) LA indices were not significantly different according to pVO<sub>2</sub>, whereas a correlation was found between LA STE-derived functional parameters and pVO<sub>2</sub> in terms of reservoir, conduit, and contractile functions, with the stronger correlation between pVO<sub>2</sub> and LA reservoir function (Table 2 and Figure 2). Moreover, among all volume-derived and STE-derived LA parameters, only LA reservoir strain and LA systolic strain rate correlated with VE/VCO<sub>2</sub> slope (P = 0.02 and P = 0.004, respectively).

We further tested the correlation between LA strain and pVO<sub>2</sub> by means of linear regression analysis. Both LA reservoir strain and contractile strain were univariate associated with pVO<sub>2</sub> [β 0.36, P = 0.003, 95% confidence interval (CI) 0.07–0.34 and β 0.33, P = 0.02, 95% CI 0.05–0.53, respectively]. The association with LA reservoir strain persisted after a comprehensive adjustment for highly regarded determinants of exercise capacity (i.e. age, sex, and BMI), heart rhythm (sinus/AFib), and log-NT-proBNP (β 0.29, P = 0.02, 95% CI 0.02–0.30). The further addition of NYHA class as covariate didn't change the result (β 0.29, P = 0.02, 95% CI 0.03–0.31). On the other hand, of note, the addition of LA reservoir strain to the adjustment parameters alone

**Table 2** Echocardiographic parameters

	Peak VO <sub>2</sub> < 14 mL/kg/min (n = 29)	Peak VO <sub>2</sub> ≥ 14 mL/kg/min (n = 36)	P value	Coefficient for correlation with peak VO <sub>2</sub> , mL/kg/min	P value for correlation
<b>LV structure and function</b>					
LV EDV-i, mL/m <sup>2</sup>	51 ± 16	57 ± 14	0.2	0.10	0.5
LV-mass-i, g/m <sup>2</sup>	109 ± 23	112 ± 32	0.7	-0.07	0.6
RWT	0.45 ± 0.07	0.45 ± 0.09	0.8	-0.05	0.7
LVEF, %	60 ± 9	59 ± 8	0.9	0.13	0.3
LV GLS, %	-17.9 ± 3.6	-18.3 ± 2.9	0.7	-0.12	0.4
S', cm/s	6.1 ± 1.3	6.8 ± 1.6	0.09	0.27	0.03
SV-LVOT-i, mL/m <sup>2</sup>	27 ± 5	32 ± 7	0.008	0.21	0.1
<b>LA structure and function</b>					
LAV-max-i, mL/m <sup>2</sup>	45 ± 17	47 ± 22	0.6	-0.07	0.6
LAV-min-i, mL/m <sup>2</sup>	29 ± 14	30 ± 19	0.8	-0.08	0.5
LA EF, %	35 ± 10	39 ± 13	0.1	0.19	0.1
LA reservoir strain, %	14 ± 5	21 ± 9	0.002	0.36	0.003
LA conduit strain, %	9 ± 2	13 ± 4	0.001	0.29	0.04
LA contractile strain, %	7 ± 4	11 ± 6	0.02	0.33	0.02
LA systolic SR, %/s	0.6 ± 0.2	0.7 ± 0.3	0.01	0.32	0.01
LA early diastolic SR, %/s	-0.4 ± 0.1	-0.5 ± 0.2	0.03	-0.16	0.2
LA late diastolic SR, %/s	-0.5 ± 0.2	-0.6 ± 0.3	0.1	-0.29	0.04
<b>Doppler</b>					
E, cm/s	83 ± 32	76 ± 23	0.3	-0.21	0.1
A, cm/s	76 ± 26	70 ± 24	0.4	-0.09	0.5
DTE, ms	213 ± 73	213 ± 51	0.9	0.08	0.5
E/A	1.1 ± 0.6	1.1 ± 0.7	0.9	-0.13	0.4
E', cm/s	6.5 ± 1.8	6.3 ± 1.8	0.7	0.01	0.9
E/e'	13.1 ± 4.7	13.0 ± 6.0	0.9	-0.16	0.2
MR, n (%)	25 (86)	23 (64)	0.05	-0.21	0.04
TR, n (%)	23 (79)	23 (64)	0.1	-0.09	0.1
Peak TR velocity, m/s	2.7 ± 0.6	2.4 ± 0.4	0.08	-0.31	0.03
SPAP, mmHg	37 ± 19	29 ± 10	0.1	-0.30	0.06

DTE, E wave deceleration time; EDV-i, Simpson-biplane end-diastolic volume index; EF, Simpson-biplane ejection fraction; GLS, global endocardial longitudinal strain [GLS was measured in apical four-chamber and two-chamber view and averaged; biplane GLS was available in 54 (79%) patients]; LAV, left atrial volume; LV, left ventricular; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure [TR velocity and SPAP were measurable in 46 (68%) of total patients, 92% of patients with TR]; SR, strain rate; SV-LVOT, left ventricular outflow tract stroke volume; TR, tricuspid regurgitation [it was present in 50 (77%) patients].

described above provided a significant increase of the predictive value for lower pVO<sub>2</sub> values ( $R^2$  0.50 vs. 0.45,  $P = 0.02$ ).

At logistic regression analysis, lower LA reservoir strain values were associated with higher probability to reach pVO<sub>2</sub> < 14 mL/kg/min after adjustment for age, sex, BMI, heart rhythm (sinus/AFib), and log-NT-proBNP [for each 1 unit LA reservoir strain decrease odds ratio (OR) 95% CI 1.22 (1.05–1.42),  $P = 0.01$ ].

Adding LVEF to the covariates described above, the association between LA reservoir strain and pVO<sub>2</sub> was not affected ( $\beta$  0.27,  $P = 0.02$ , 95% CI 0.01–0.29), with an OR 95% CI 1.22 (1.04–1.44),  $P = 0.01$ , for each 1 unit LA reservoir strain decrease.

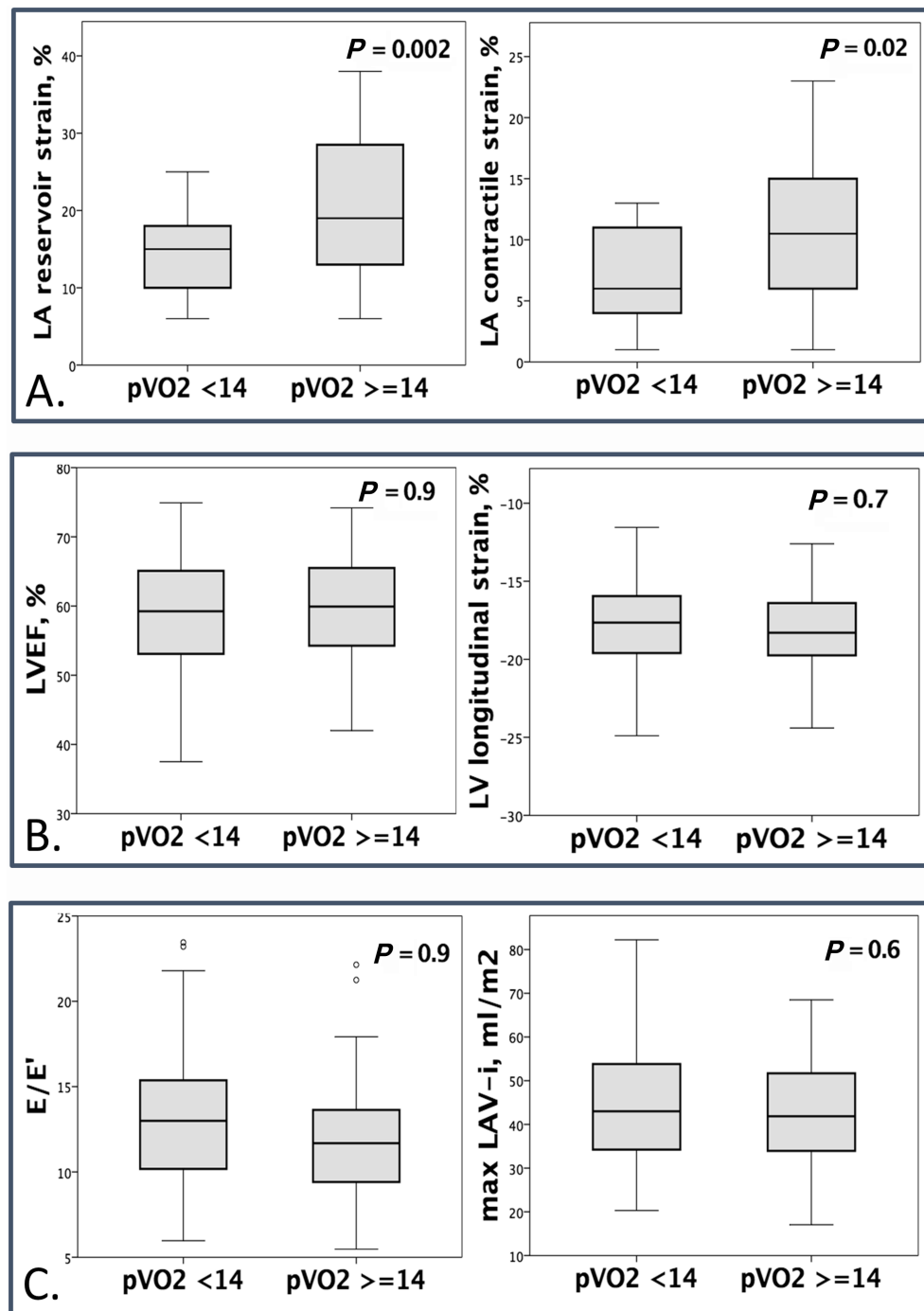
### Left atrial strain vs. traditional echocardiographic parameters and association with exercise capacity

Left atrium reservoir strain was correlated to all other LA morphological and functional parameters, mitral inflow variables (E wave, A wave, E/A), LV tissue Doppler S', and SV-i (Table 3) but not to peak tricuspidal regurgitation (TR)

velocity. However, among all echocardiographic parameters, only S', LA reservoir strain, and peak TR velocity were associated with pVO<sub>2</sub> (Table 2 and Figure 3). Moreover, LA reservoir strain was associated with pVO<sub>2</sub> independently from S' and peak TR velocity (Supporting Information, Table S1), and of note, the addition of LA reservoir strain to peak TR velocity alone provided a significant increase of the predictive value for lower pVO<sub>2</sub> values ( $R^2 = 0.27$  vs.  $R^2 = 0.1$ ;  $P = 0.002$ ).

A receiver operating characteristic curve analysis was performed to identify the cut-off of LA reservoir strain that could predict pVO<sub>2</sub> < 14 mL/kg/min. LA reservoir strain < 22% showed 93% sensitivity and 49% specificity to predict pVO<sub>2</sub> (area under the receiver operating characteristic curve 0.69,  $P = 0.008$ , 95% CI 0.56–0.82). On the contrary, any predictive capacity was not found by receiver operating characteristic curve analyses for LAV index and E/e' regarding pVO<sub>2</sub> < 14 mL/kg/min (area under the receiver operating characteristic curve 0.49 and 0.54, respectively). A logistic regression analysis was performed to ascertain the additive effect of LA reservoir strain < 22% on pVO<sub>2</sub> < 14 mL/kg/min prediction on top of age, sex, BMI, heart rhythm (sinus/AFib), and log-NT-proBNP. LA reservoir strain added a significant contribution to the predictability of the model ( $\chi^2$  30.704 vs.

**Figure 2** Association of left atrial reservoir strain and contractile strain (A), left ventricular ejection fraction and left ventricular global longitudinal strain (B), and E/e' and left atrial volume index (C) with peak VO<sub>2</sub> (mL/kg/min).



23.831,  $P = 0.009$ ), which correctly classified 75% of cases. In particular, patients showing LA reservoir strain < 22% and higher BMI were more likely to exhibit pVO<sub>2</sub> < 14 mL/kg/min [OR 95% CI 10.4 (1.4–74),  $P = 0.02$ , OR 95% CI 1.4 (1.1–1.7),  $P = 0.004$ , respectively].

### Left atrial strain and exercise capacity in heart failure with preserved ejection fraction

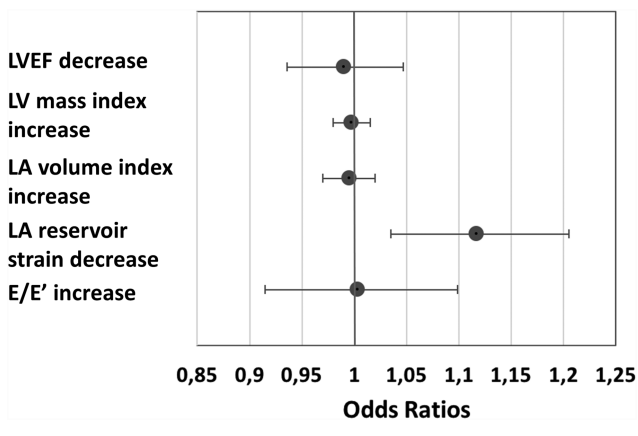
With the intention to validate the study results in the HFpEF population, we tested the association between LA

**Table 3** Pearson correlation of left atrial reservoir strain with echocardiographic variables

	Correlation coefficient	P value
LA structure and function		
LAV-max-i, mL/m <sup>2</sup>	-0.49	<0.0001
LAV-min-i, mL/m <sup>2</sup>	-0.59	<0.0001
LA EF, %	0.77	<0.0001
LA conduit strain, %	0.78	<0.0001
LA contractile strain, %	0.88	<0.0001
LA systolic SR, %/s	0.89	<0.0001
LA early diastolic SR, %/s	-0.46	<0.0001
LA late diastolic SR, %/s	-0.75	<0.0001
LV structure and function		
LV EDV-i, mL/m <sup>2</sup>	0.21	0.08
LV-mass-i, g/m <sup>2</sup>	-0.15	0.2
LVEF, %	-0.01	0.9
LV GLS, %	-0.13	0.3
LV S', cm/s	0.39	0.001
SV-LVOT-i, mL/m <sup>2</sup>	0.30	0.03
E, cm/s	-0.30	0.02
A, cm/s	0.32	0.02
DTE, ms	0.09	0.5
E/A	-0.39	0.005
E', cm/s	-0.25	0.05
E/e'	-0.03	0.8

DTE, E wave deceleration time; EDV-i, Simpson-biplane end-diastolic volume index; EF, ejection fraction; GLS, global endocardial longitudinal strain; LAV, left atrial volume; LV, left ventricular; SR, strain rate; SV-LVOT, left ventricular outflow tract stroke volume; TR, tricuspid regurgitation.

**Figure 3** Association of LV and LA parameters with severely reduced exercise capacity (peak VO<sub>2</sub> < 14 mL/kg/min). Logistic regression analysis for predictability of peak VO<sub>2</sub> < 14 mL/kg/min: LVEF 1 unit (%) decrease odds ratio (OR) 95% confidence interval (CI) 0.99 (0.93–1.05), LV mass index 1 unit (g/m<sup>2</sup>) increase OR 95% CI 0.99 (0.98–1.01), LA volume index 1 unit (mL/m<sup>2</sup>) increase OR 95% CI 0.99 (0.97–1.02), LA reservoir strain 1 unit (%) decrease OR 95% CI 1.12 (1.03–1.20), E/e' 1 unit increase OR 95% CI 1.01 (0.91–1.10). LA, left atrium; LVEF, left ventricular ejection fraction.



reservoir strain and pVO<sub>2</sub> in patients who met the most recent HFpEF diagnostic criteria. Within the entire cohort, 55 (85%) and 47 (72%) patients had 2016 European Society of Cardiology (ESC) HF guideline<sup>11</sup> and 2020 Heart Failure

Association of the ESC consensus recommendation<sup>24</sup> criteria for HFpEF, respectively. Moreover, as further confirmation, among the cohort of 55 patients with HFpEF (according to 2016 ESC criteria), we decided to exclude from the analysis patients presenting characteristics that could interfere in the evaluation of LA function, that is, atrial fibrillation, previous pacemaker implantation, and previous severe valve disease requiring interventional procedure (e.g. transcatheter aortic valve implantation). With such approach, 40 patients were identified. In these three patient subgroups, LA reservoir, conduit, and contractile strains were impaired in patients with pVO<sub>2</sub> < 14 mL/kg/min. On the contrary, LAV index and E/e' did not differentiate between patients with lower and higher functional capacity (Supporting Information, Table S2). In linear regression analysis, lower LA reservoir strain and lower pVO<sub>2</sub> values were positively associated at univariate analysis and after adjustment for age, sex, and BMI (Table 4).

## Discussion

In a cohort of patients enrolled in the German HFpEF Registry, we found that (1) all STE-derived measures of LA function were associated with exercise intolerance in terms of pVO<sub>2</sub>, whereas traditional indices of LV diastolic dysfunction and filling pressure (LAV, mitral inflow Doppler parameters, E/e', and LV structure and function) didn't discriminate patients according to pVO<sub>2</sub> and (2) the assessment of LA reservoir strain added value to predict lower pVO<sub>2</sub> independently from age, sex, BMI, rhythm of presentation, and NT-proBNP levels. Moreover, LA reservoir strain < 22% predict pVO<sub>2</sub> < 14 mL/kg/min with high sensitivity. Results suggest that STE-derived LA function parameters portend clinical utility in clinical judgement as well as risk stratification and prognostic assessment of patients with clinically diagnosed HFpEF and HFmrEF.

### Left atrial function in heart failure with preserved and mid-range ejection fraction haemodynamic

Several mechanisms are implicated in exercise intolerance and reduced oxygen consumption. In a pooled analysis of 910 HFpEF patients from 17 cohorts, the most consistent haemodynamic reserve alteration was an exaggerated increase in filling pressure, together with reduced chronotropic reserve.<sup>3</sup> Patients with HFmrEF seem to exhibit a haemodynamic performance more similar to HFpEF than HFrEF.<sup>25</sup> In HFmrEF, chronotropic incompetence, peripheral factors, limited stroke volume reserve, right ventricle dysfunction, and mitral regurgitation have been called into question,<sup>26</sup> but



**Table 4** Linear regression analysis for association between left atrial reservoir strain and peak VO<sub>2</sub> according to different patient selection criteria

LA reservoir strain, %	2016 ESC HF guideline (n = 55)	2020 HFA of the ESC consensus recommendation (n = 47)	LVEF ≥ 50%, sinus rhythm, without valve procedure (n = 40)
Unadjusted	$\beta$ 0.36, $P = 0.006$ , 95% CI 0.06–0.33	$\beta$ 0.32, $P = 0.03$ , 95% CI 0.01–0.29	$\beta$ 0.37, $P = 0.01$ , 95% CI 0.04–0.38
Adjusted for age, sex, BMI	$\beta$ 0.36, $P = 0.005$ , 95% CI 0.06–0.32	$\beta$ 0.31, $P = 0.03$ , 95% CI 0.01–0.29	$\beta$ 0.36, $P = 0.009$ , 95% CI 0.05–0.35

BMI, body mass index; CI, confidence interval; ESC, European Society of Cardiology; HFA, Heart Failure Association; LA, left atrium; LVEF, left ventricular ejection fraction.

there is a paucity of studies addressing mechanism of exercise intolerance in HFmrEF.

Left ventricular diastolic dysfunction has long been considered mainly responsible for the development of overt HFpEF, with elevation in LV, LA, and pulmonary pressure. Diastolic dysfunction could be of relevance also in haemodynamic of HFmrEF, as far as the current HFmrEF diagnostic criteria are parallel to those for HFpEF, requiring elevated natriuretic peptides and structural heart disease or diastolic dysfunction. Also, LV systolic functional impairment characterize both HFpEF (in terms of longitudinal systolic function)<sup>27</sup> and HFmrEF. However, the relative contribution of systolic and diastolic impairment is not completely understood. LV and LA function are linked to each other and a relevant role in modulating the relationship between LV and pulmonary circle haemodynamic has been increasingly recognized to the LA.<sup>28</sup> Under physiological conditions, a preserved LA reservoir and contractile function allow an adequate LV filling during exercise, so this impairment due to chronic pressure overload and progressive reduced LA compliance in HFpEF patients contributes to poor augmentation in stroke volume and increase in filling pressure during exercise.<sup>29</sup>

The impairment in LA function reflects the close interplay between LA and LV. In fact, LA reservoir function is affected by LA relaxation and compliance and modulated by LV longitudinal systolic contraction through the downward motion of the mitral annular plane in systole; LA conduit function is influenced by LV stiffness and early diastolic relaxation; and LA booster function reflects intrinsic LA contractility and LV end-diastolic compliance and pressure.

Therefore, as LV systolic and diastolic function worsens, the increase in pressure overload leads the LA to remodel and two phases have been described: in the early stages, LA reservoir and contractile function slightly increase to augment LV filling and preserve cardiac output; chronically elevated LV afterload determines progressive LA compliance impairment with decrease in LA reservoir and contractile function due to work mismatch. Such failing LA leads to high LA pressure and pulmonary congestion.<sup>30</sup> At this stage, LA dilation occurs primarily as consequence of long-standing elevated LA pressure, at rest or at least during exercise.

Consistent with previous HFpEF and HFmrEF studies,<sup>21,31</sup> we found an impaired LA haemodynamic with decline in all

phases of LA function. Interestingly, LA strain was associated with  $S'$ , indices of basal LV systolic function, but not with LVEF or global longitudinal strain. Moreover, LA strain didn't correlate with  $E/e'$  or peak TR velocity, two major components for LA pressure estimation.<sup>12</sup> However, a relevant proportion of HFpEF patients is known to develop high filling pressure only during exercise<sup>32</sup> and  $E/e'$  and peak TR velocity could both significantly rise during exercise induced loading conditions.

### Left atrium and prognosis in heart failure with preserved and mid-range ejection fraction

In the spectrum of HF, HFpEF pathophysiology is characterized by great heterogeneity in cardiac and extra-cardiac underlying mechanisms, which hamper diagnosis, risk stratification, and treating options development. In fact, hospitalization and mortality rates of HFpEF patients are similar to HFrEF, but evidences of disease-modifying therapies in HFpEF are lacking.<sup>33,34,35</sup> Pathophysiology of HFmrEF is further unclear, and it has been hypothesized that it represents a transition category from or to lower LVEF and not a distinct pathophysiological entity, with long-term prognosis similar to that of HFpEF.<sup>36</sup> The identification of key parameters that help in risk and prognosis assessment is of paramount importance, because patients' stratification represents a first step for orientation in the conundrum of HFpEF syndrome and definition of therapeutic targets.

In the present study, we indirectly investigated the prognostic role of LA function through its association with CPET variables, which demonstrated high prognostic value in HFpEF, even if with contrasting results regarding the best parameter to predict hospitalization for HF and death ( $pVO_2$ ,  $VE/VCO_2$  slope).<sup>37,38,39</sup> Interestingly, Nadruz *et al.* observed a relevant association between  $pVO_2$  and  $VE/VCO_2$  slope and adverse outcome in HFpEF, even stronger compared with HFrEF, demonstrating a great ability of CPET in discriminating HFpEF patients' risk profile.<sup>18</sup> Evidence from CPET studies showed  $pVO_2$  predictive ability also in HFmrEF, with a rate of adverse events similar between HFmrEF and HFpEF.<sup>39</sup>

The association between LA mechanics and prognosis finds its rationale in the development of elevated LA pressure and PCWP, especially during exercise, which are mainly

responsible for HF symptoms. The prognostic role of LA in HFpEF has been extensively demonstrated for LA size,<sup>40,41,42</sup> being LA dilation expression of chronically elevated LV filling pressure and disease progression. However, LA size was not prognostic in 1,097 patients enrolled in the PARAGON-HF, probably due to the high prevalence of LA structural remodelling in the substudy population.<sup>43</sup> Similarly, in our study, the majority of patients had a moderately dilated LA, suggesting a more advanced syndrome stage, in which LA size capability in patients' stratification could be reduced.

It has been extensively demonstrated that all LA strain parameters are significantly reduced in HFpEF patients,<sup>21,44</sup> so that LA function evaluation has been proposed to discriminate asymptomatic diastolic dysfunction from HFpEF.<sup>45</sup> An association exists between LA functional and structural remodelling,<sup>21</sup> but recent evidences demonstrated the strong independent prognostic value of LA dysfunction in HFpEF, more powerful than LV longitudinal function, whereas LAV was actually not associated with adverse outcomes in some studies.<sup>10</sup> Also, in patients enrolled in the TOPCAT trial, a worse LA function was associated with HF hospitalization; however, these are not independent from LV systolic deformation and filling pressure.<sup>46</sup>

In our study, LA reservoir strain was a powerful predictor of CPET  $pVO_2$ , whereas no association was found for LAV and  $E/e'$ . In the study cohort, all LA strain parameters were well below the reported reference ranges and were comparable with the lower LA strain value range in previous HFpEF study populations,<sup>21,46</sup> highlighting the relevant LA functional impairment in our population. Comparable enlarged LAV and impaired LA strain values were present in patients described by Hummel *et al.* Interestingly, they found that LA reservoir strain was a better predictor of invasively measured PCWP than LAV, irrespective of the underlying rhythm, whereas the correlation between  $E/e'$  and PCWP was only poor.<sup>47</sup>

$E/e'$  ratio has long been used as single parameter to estimate elevated LV filling pressure, because it was well validated against invasive measurements.<sup>48,49</sup> Moreover, it was the strongest haemodynamic predictor of outcome in an HFpEF study<sup>50</sup> and the most robust index of elevated filling pressure among parameters included in the 2016 ESC HF guidelines<sup>11</sup> and in the 2016 ASE/EACVI recommendations.<sup>12</sup> However, its value has been recently questioned, because its correlation with high LV filling pressure and sensitivity are actually both very poor. Also, the multiparametric approaches<sup>12,45</sup> were shown to be highly insufficient to reliably estimate PCWP.<sup>32</sup>

However, resting assessment of LV filling pressure in HFpEF is probably very insensitive per se, because a great proportion of patients develop elevated filling pressure only during exercise. Recently, Telles *et al.* demonstrated that LA reservoir and contractile strains were independently associated with exercise PCWP even after adjustment for diastolic dysfunction variables.<sup>8</sup> Moreover, they used an LA reservoir

strain value  $\leq 33\%$  as cut-off to demonstrate a greater diagnostic sensitivity and specificity in comparison with the 2016 ESC criteria.<sup>11</sup> In our study, we identified LA reservoir strain value  $< 22\%$  to predict  $pVO_2 < 14$  mL/kg/min with high sensitivity.

All together, these evidences suggest LA function as reliable marker of impaired haemodynamic in HFpEF and HFmrEF, particularly useful in evaluation at rest when other well-established echocardiographic parameters could be non-discriminative. Of note, the value of LA function showed to overcome that of LAV in advanced stages of disease, supporting its relevant role in prognostic stratification of patients with clinical HFpEF and HFmrEF diagnosis.

## Limitations

The major limitation of the study is the, to date, limited cohort size and single-centre setting. Therefore, results should be considered with caution. However, these preliminary results from the German HFpEF Registry are highly encouraging and highlight the powerful association between LA function and consolidated prognostic marker in HFpEF and HFmrEF patients. We used  $pVO_2 < 14$  mL/kg/min value as cut-off to divide our cohort, because it is of prognostic value in HF patients. However, as confirmatory analysis, we divided the study population according to  $pVO_2$  median value with comparable results.

Second, patients enrolled comprehend two types of HF (HFpEF and HFmrEF) according to the most recent guidelines.<sup>11</sup> In our cohort, the small proportion of patients with HFmrEF prevented us from analysing HFmrEF patients separately. However, LVEF  $> 40\%$  or  $\geq 45\%$  were the cut-offs used as inclusion criteria in most HFpEF clinical trials.<sup>43</sup> We performed the analyses also in cohort subgroups with preserved LVEF according to recently recommended inclusion criteria<sup>11,24</sup> and the association between LA functional parameters and  $pVO_2$  did not change.

Even though there is a plausible relationship between atrial dysfunction, AFib, and exercise capacity, we did not analyse separately patients with AFib due to the small sample size. However, we noted the aligned linear association between LA strain and  $pVO_2$  also after exclusion of patients with atrial fibrillation and/or pacemaker implantation, which are potential confounding factors.

## Conclusions

In a cohort of stable HFpEF and HFmrEF patients, the assessment of LA function in addition to LA structural remodelling and  $E/e'$  could help in further characterization of patients' haemodynamic. An impaired LA function, in particular LA

reservoir strain, emerged as sensitive and powerful marker of exercise intolerance, above echocardiographic parameters routinely used to estimate LV filling pressure and independently from known determinants of exercise capacity (age, sex, and BMI), heart rhythm, and NT-proBNP. Therefore, the evidence and degree of LA functional impairment could portend clinical utility in evaluation of HFpEF and HFmrEF patients.

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## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Association between echocardiographic variables and peakVO2 (ml/kg/min).

**Table S2.** Volumetric and speckle-tracking-echocardiography derived left atrial parameters and E/e' in patients with peakVO2 < or ≥14 mL/kg/min according to different patients' selection criteria.

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