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**ORIGINAL PAPER**

# Impaired biventricular contractile reserve in patients with diastolic dysfunction: insights from exercise stress echocardiography

**Mathias Claeys [1,2]*, Thibault Petit [1,3], Andre La Gerche [1,4], Lieven Herbots [1,5], Piet Claus [1], Ruben De Bosscher [1,2], Walter Droogne [1,2], Johan Van Cleemput [1,2], Jens-Uwe Voigt [1,2], Marion Delcroix [6,7], Stefan Janssens [1,2], Rik Willems [1,2], Jan Verwerft [5†], and Guido Claessen [1,2†]**

[1]Department of Cardiovascular Sciences, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium; [2]Division of Cardiology, University Hospitals Leuven, Leuven, Belgium; [3]Adult Congenital and Pediatric Heart Unit, Freeman Hospital, Newcastle Upon Tyne, UK; [4]Baker Heart and Diabetes Institute, Melbourne, Australia; [5]Division of Cardiology, Jessa Hospital, Hasselt, Belgium; [6]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium; and [7]Respiratory Division, Department CHROMETA, KU Leuven, Leuven, Belgium

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**Aims** Cardiac output limitation is a fundamental feature of heart failure with preserved ejection fraction (HFpEF) but the relative contribution of its determinants in symptomatic vs. asymptomatic stages are not well characterized. We aimed to gain insight into disease mechanisms by performing comprehensive comparative non-invasive exercise imaging in patients across the disease spectrum.

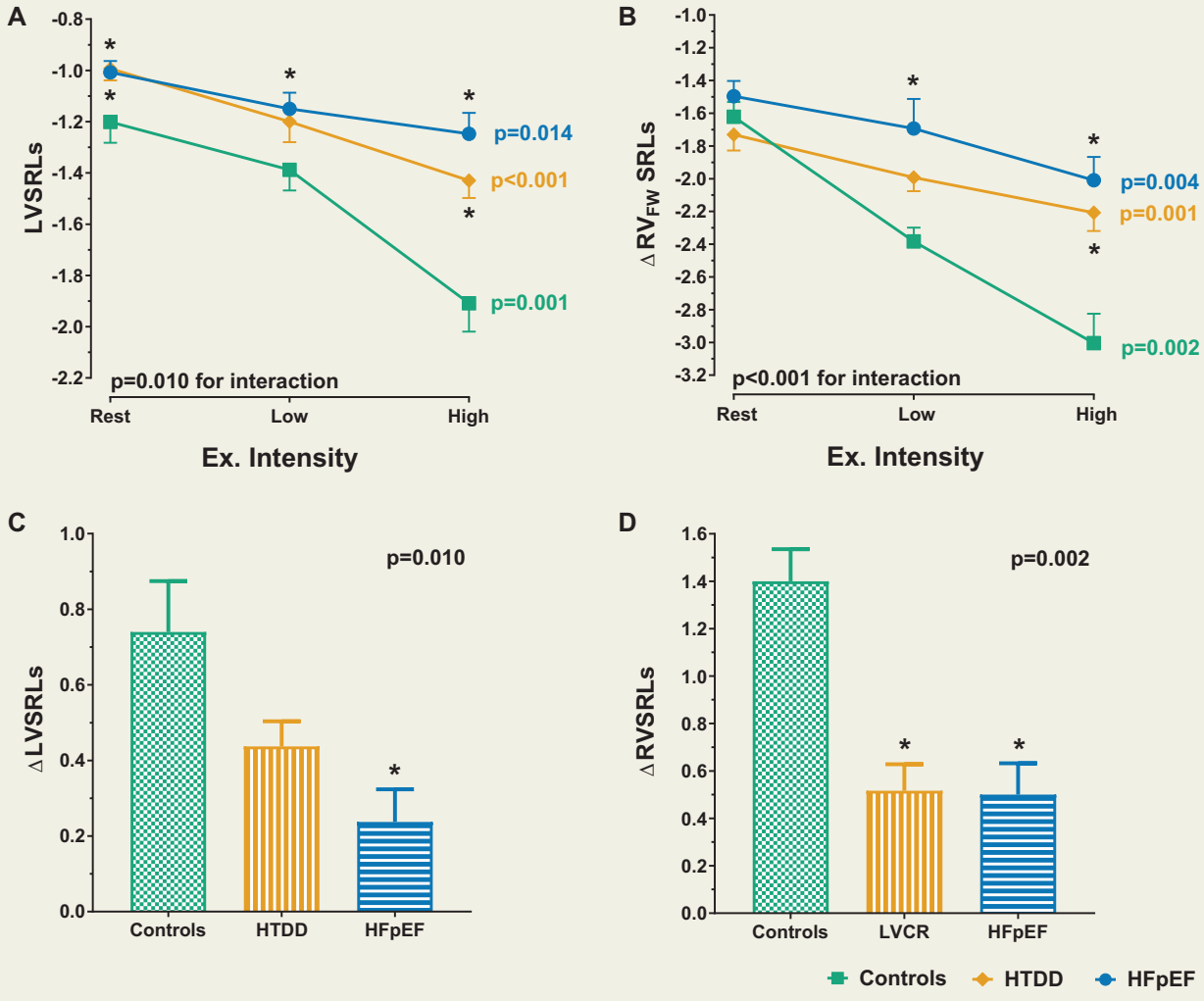
**Methods and results** We performed bicycle stress echocardiography in 10 healthy controls, 13 patients with hypertensive left ventricular (LV) concentric remodelling and asymptomatic diastolic dysfunction (HTDD), 15 HFpEF patients, and 15 subjects with isolated right ventricular (RV) dysfunction secondary to chronic thromboembolic pulmonary hypertension (CTEPH). During exercise, ventricular performance differed across the groups (all $P \leq 0.01$ for interaction). Notably in controls, LV and RV function significantly increased (all $P < 0.05$) while both LV systolic and diastolic reserve were significantly reduced in HFpEF patients. Likewise, RV systolic reserve was also impaired in HFpEF but not to the extent of CTEPH patients ($P < 0.001$ between groups). HTDD patients behaved as an intermediary group with borderline LV systolic and diastolic reserve and reduced RV systolic reserve. The increased pulmonary vascular (PV) load in HFpEF and CTEPH patients in combination with impaired RV reserve resulted in RV–pulmonary artery uncoupling during exercise.

**Conclusion** The multifaceted decline of cardiac and PV function accompanying disease progression in HFpEF is unmasked by exercise and already emerges in preclinical disease. The revelation of these subtle abnormalities during exercise illustrates the benefit of exercise imaging and creates new prospects for early diagnosis and management.



*Corresponding author. Tel: +32 16 344 235; Fax: +32 16 344 240. E-mail: mathias.claeys@uzleuven.be
†These authors are joint senior author.

**Graphical Abstract**




**Keywords** HfpEF • heart failure • deformation imaging • right ventricle • exercise

# Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for roughly half of heart failure cases. Evolving evidence suggests HFpEF is a heterogeneous disease entailing a complex interplay of maleficent systemic processes.[1] Clinically, HFpEF is characterized by progressive exercise intolerance related to a steady decline of cardiovascular and peripheral function.[2–4] Unfortunately, therapeutic advances have been curtailed by significant disease heterogeneity and the distinct molecular signalling profile of HFpEF compared with heart failure with reduced ejection fraction. In response, the focus of HFpEF management has shifted towards early diagnosis and tailored treatment according to the particular phenotype.[5] This approach, however, requires potent diagnostic tools that allow accurate discrimination of the pathophysiological abnormalities underpinning clinical symptoms.

Both exercise and more advanced echocardiographic techniques like deformation imaging have advanced the diagnosis and grant additional insight into disease mechanisms.[6–8] Accordingly, a combination of both would likely have incremental benefit. Kosmala *et al.*[9,10] pioneered this strategy in asymptomatic (stage B) heart failure patients and demonstrated that an interplay of progressive cardiovascular derangements underlies the transition to symptomatic heart failure (stage C). However, they evaluated cardiac function post-exercise which might have limited their ability to detect subtle changes as haemodynamics rapidly return to baseline post-exertion. Furthermore, major contributors to disease severity such as right ventricular (RV) function and pulmonary vascular (PV) function, which are often only appreciable during exercise, were not assessed.[11,12] More recently, Pugliese *et al.*[13] linked the reduced exercise capacity in hypertensive patients with and without HFpEF to

peripheral dysfunction and impaired left ventricular (LV) systolic and diastolic reserve. While RV reserve appeared to be preserved, their protocol did not include RV deformation imaging which potentially limited their ability to unmask subtle RV dysfunction.

This study aimed to demonstrate the value of comprehensive imaging during exercise in the non-invasive evaluation of patients across the heart failure spectrum. Therefore, we evaluated both symptomatic HFpEF patients (i.e. stage C heart failure) and hypertensive patients with asymptomatic diastolic dysfunction (HTDD) (i.e. stage B heart failure) and compared these with a group of healthy controls. In addition, we also included patients with known RV dysfunction caused by chronic thromboembolic pulmonary hypertension (CTEPH) to compare impaired RV performance during exercise from post-capillary (or mixed) pulmonary hypertension with a pre-capillary phenotype. We hypothesized that deformation imaging might be more sensitive to identify dysfunction and provide more insight into the pathophysiology underlying exercise intolerance and impaired cardiac output generation. Finally, we hypothesized that even in stage B heart failure subtle RV and PV function abnormalities are present.

# Methods

## Subjects

This study was conducted at two centres: the University Hospitals Leuven and Jessa Hospital Hasselt. HFpEF patients were recruited from the heart failure clinic. HFpEF was defined by symptoms and/or signs of heart failure, normal LV ejection fraction (LVEF ≥50%), and elevated left heart filling pressures (pulmonary artery occlusion pressure ≥ 15 mmHg at rest and/or ≥ 25 mmHg with exercise) on right heart catheterization ($n = 10$) or presence of structural or functional alterations consistent with HFpEF on echocardiography ($n = 5$).[14] HTDD patients had long-standing arterial hypertension, LV concentric remodelling with a relative wall thickness >0.42 and an impaired LV relaxation pattern ($E/A < 0.8$). They were without signs or symptoms of heart failure. Thirdly, CTEPH patients, diagnosed according to current guidelines, were recruited from the University Hospitals Leuven centre for PV diseases.[15] Finally, control subjects volunteered to participate or were recruited after referral for evaluation of exercise capacity when no evidence of cardiopulmonary disease was found. All control subjects had a normal electrocardiogram, transthoracic echocardiogram and a normal (ergo)spirometry. Patients with significant valvular heart disease (>mild stenosis, >moderate regurgitation), unstable coronary artery disease, cardiomyopathy, renal or hepatic disease, and significant ventilatory disease were excluded. All participants had to be able to perform at least 50 W on a bicycle stress test. The study protocol conformed to the Declaration of Helsinki and was approved by the local Ethics Committees. All participants provided written informed consent prior to inclusion.

## Study design

Stepwise cardiopulmonary exercise testing (ER900 and Oxycon Alpha, Jaeger, Germany) and bicycle exercise echocardiography were performed by experienced operators (T.P., G.C., and J.V.) on a programmable, electronically-braked semi-supine ergometer (Easystress, Ecogito Medical sprl, Liege, Belgium). Exercise load was gradually increased (in steps of 5, 10, and 20 W based on predicted exercise capacity) until exhaustion. Through breath-by-breath analysis, minute ventilation (VE), oxygen consumption ($VO_2$), and carbon dioxide production ($VCO_2$) were assessed. Additional measures included peak heart rate (HR), peak power and the ventilatory equivalent for carbon dioxide ($VE/VCO_2$) slope, calculated using a linear regression function from baseline to peak exercise. Predicted peak $VO_2$ was determined using the Wasserman equation. Images were acquired at rest and during exercise at moderate (±70% of peak HR) and high exercise intensity (±90% of peak HR). Each acquisition stage lasted approximately 5 minutes depending, on image quality and respiratory interference. Rate lowering medications were withheld for at least 24 h prior to the study protocol. Age-predicted maximal HR, HR reserve (HRR), and adjusted HRR were defined according to the literature.[16]

## Exercise echocardiography

Images were acquired using a Vivid E9 ultrasound system, digitally stored and analysed offline using EchoPAC version 113 (both GE Vingmed Ultrasound AS, Horten, Norway) at UZ Leuven. During the stress protocol, seven sets of images (LV four-chamber, PW Doppler of mitral inflow, PW Doppler of LV outflow tract, PW Tissue Doppler of the septal LV annulus, RV focused four-chamber and Tricuspid Continuous Wave Doppler ×2) were acquired at each stage (rest, low, peak). At least 10 cardiac cycles were stored for each set during exercise. In CTEPH patients PW (TDI) images of mitral inflow and annulus were only acquired at rest. Cardiac output was calculated as heart rate multiplied with stroke volume (Doppler velocity-time integral method). Systolic pulmonary artery pressure (PASP) was estimated from the maximal transtricuspid regurgitant velocity on CW Doppler without adding the right atrial pressure.[17] Mean pulmonary artery pressure was calculated using the Chemla formula.[18] Two-dimensional (2D) speckle tracking LV and RV free-wall ($_{FW}$) longitudinal strain (SL) and strain rate (SRL) were acquired and analysed from single-plane (RV focused) apical four-chamber grey-scale images (60–90 frames.s$^{-}$1) according to contemporary consensus documents.[19,20]

## Statistics

Data were analysed using SPSS Statistics version 24 (IBM Corporation, Armonk, USA). Normality was ensured (Kolmogorov–Smirnov) and variables are presented as means (±standard deviation) or as medians (with 25% and 75% percentiles) accordingly. Baseline data were compared using a $\chi 2$ (or Fischer exact) test for categorical data and a Kruskal–Wallis *H* test or a one-way analysis of variance for continuous data. The exercise response was assessed using a mixed linear model with group, exercise stage and their interaction as fixed effects. An unstructured variance-covariance matrix was included in the model to account for the repeated nature of the data. Bonferroni *post hoc* correction was applied for multiple comparisons. Pressure-flow relationships (i.e. *P/Q* slopes) were calculated through linear regression of the individual mean pulmonary artery pressure-cardiac output points obtained during exercise. RV contractile reserve was determined using the peak-exercise-to-resting RV end-systolic pressure area ratio (RVESPAR).[17] A *P/Q* slope >3 mmHg.L$^{-1}$.min and a RVESPAR <1.6 were considered abnormal. Intra- and interobserver reproducibility (reported in Supplementary data online) was assessed at rest and during exercise in a sample of 16 subjects (4 out of each group) using the coefficient of variation and the intra-class correlation coefficient (two-way mixed and absolute agreement quoted),

analysed on different cardiac cycles within the image set. A *P*-value of <0.05 was considered statistically significant.

# Results

## Baseline characteristics, cardiopulmonary exercise test, and baseline echocardiography

Fifty-three subjects (10 controls, 13 HTDD patients, 15 HFpEF patients, and 15 CTEPH patients) were included in the study. The baseline characteristics and examinations are summarized in *Table 1*. There were no significant differences in age or sex between groups. All controls subjects were in NYHA class I whereas all HFpEF and CTEPH patients were in NYHA class II or III. Two HTDD patients had minimal exercise intolerance attributed to non-cardiac causes: morbid obesity (BMI 35 $kg.m^{-2}$) in one patient and deconditioning in another. Exercise capacity was reduced in HFpEF and CTEPH patients and borderline in HTDD. As expected, HTDD and HFpEF patients had smaller LV volumes and greater wall thickness than controls. Consequently, RWT was significantly higher in HTDD and HFpEF patients. Seven HTDD (53%), five HFpEF patients (33%), and three CTEPH patients (20%) met echocardiographic criteria for LV hypertrophy.

## RV function during exercise in HFpEF vs. CTEPH

The results of the exercise protocol are summarized in *Table 2*. During exercise, major differences were noted in RV function

**Table 1 Baseline characteristics**

| | Controls (*n* = 10) | HTDD (*n* = 13) | HFpEF (*n* = 15) | CTEPH (*n* = 15) | *P*-value |
|---|---|---|---|---|---|
| Age (years) | 61 ± 6 | 67 ± 7 | 68 ± 8 | 62 ± 12 | 0.100 |
| Gender (m) | 7 | 4 | 3 | 8 | 0.060 |
| BMI ($kg.m^{-2}$) | 23.8 ± 3.2 | 28.7 ± 3.6 | 28.5 ± 3.6 | 28.4 ± 4.9 | 0.029 |
| BSA ($m^2$) | 1.85 ± 0.19 | 1.84 ± 0.19 | 1.86 ± 0.17 | 1.94 ± 0.26 | 0.579 |
| NYHA | | | | | 0.001 |
| I | 10 (100%) | 13 (100%) | | | |
| II | | | 13 (87%) | 8 (53%) | |
| III | | | 2 (13%) | 7 (47%°) | |
| Paroxysmal AF (*n*) | 0 | 2 (15%) | 7 (47%) | 1 (7%) | 0.111 |
| Diabetes (*n*) | 0 | 2 (15%) | 3 (20%) | 2 (13%) | 0.290 |
| Dyslipidaemia | 1 (10%) | 12 (92%)* | 8 (53%) | 5 (33%)‡ | <0.001 |
| AHT (*n*) | 1 (10%) | 13 (100%)* | 15 (100%)* | 7 (47%)†,‡ | <0.001 |
| AHT drugs (*n*) | 0 (0–1) | 2 (2–5)* | 3 (2–3)* | 0 (0–2)‡ | <0.001 |
| Cardiopulmonary exercise test | | | | | |
| Peak HR (bpm) | 152 ± 22 | 125 ± 19* | 121 ± 24* | 128 ± 17* | 0.010 |
| Peak power (W) | 200 ± 69 | 104 ± 33* | 82 ± 24* | 78 ± 28* | <0.001 |
| Peak $VO_2$ ($mL.min^{-1}.kg^{-1}$) | 32.8 (26.5–39.2) | 17.7 (15.4–20.3)* | 14.1 (13.0–19.0)* | 13.2 (11.1–16.0)* | <0.001 |
| Peak $VO_2$ (%) | 119 ± 13 | 87 ± 21* | 76 ± 23* | 59 ± 16*‡ | <0.001 |
| Peak RER | 1.15 ± 0.07 | 1.16 ± 0.07 | 1.07 ± 0.06‡ | 1.06 ± 0.11*‡ | 0.001 |
| $VE/VCO_2$ slope | 24.5 ± 0.2 | 28.4 ± 0.6 | 34.3 ± 0.9* | 43.7 ± 0.9*,†,‡ | <0.001 |
| Baseline echocardiography | | | | | |
| IVS (mm) | 9.1 ± 0.9 | 12.1 ± 1.8* | 11.5 ± 1.8* | 9.5 ± 1.1†,‡ | <0.001 |
| LVDD (mm) | 49.0 ± 5.9 | 41.6 ± 5.5* | 44.5 ± 3.2 | 44.2 ± 4.8 | 0.008 |
| PWT (mm) | 9.2 ± 1.5 | 12.0 ± 1.7* | 12.0 ± 1.7* | 10.1 ± 0.9†,‡ | <0.001 |
| RWT | 0.36 ± 0.05 | 0.58 ± 0.08* | 0.54 ± 0.07* | 0.46 ± 0.06*,†,‡ | <0.001 |
| $LVmass_i$ ($g.m^{-2}$) | 83 (68–91) | 94 (73–117) | 89 (86–119) | 80 (59–91)†,‡ | 0.033 |
| $LAvol_i$ ($mL.m^{-2}$) | 21 ± 6 | 28 ± 10 | 38 ± 12* | 19 ± 9† | <0.001 |
| $LVEDV_{bip}$ (mL) | 121 ± 27 | 90 ± 26* | 91 ± 25* | 81 ± 17* | 0.001 |
| $LVESV_{bip}$ (mL) | 52 ± 14 | 37 ± 10* | 39 ± 13* | 34 ± 8* | 0.002 |
| $LVEF_{bip}$ (%) | 58 ± 3 | 59 ± 4 | 58 ± 4 | 58 ± 4 | 0.893 |

*P*-values for group comparison.
*$P < 0.05$ Bonferroni *post hoc* compared with controls/HFpEF/HTDD, respectively.
†$P < 0.05$ Bonferroni *post hoc* compared with controls/HFpEF/HTDD, respectively.
‡$P < 0.05$ Bonferroni *post hoc* compared with controls/HFpEF/HTDD, respectively.
AHT, arterial hypertension; bip, biplane; BMI, body mass index; BSA, body surface area, IVS, interventricular septum; $LAvol_i$, indexed left atrial volume; NYHA, New York Heart Association; PWT, posterior wall thickness; RER, respiratory exchange ratio; RWT, relative wall thickness; VE/VCO2, ventilatory equivalent for carbon dioxide; $VO_2$, oxygen consumption.

**Table 2 Biventricular systolic function at rest and during peak exercise**

| | Controls ($n = 10$) | HTDD ($n = 13$) | HFpEF ($n = 15$) | CTEPH ($n = 15$) | *P*-value |
|---|---|---|---|---|---|
| Rest | | | | | |
| HR (bpm) | 64 ± 8 | 68 ± 11 | 65 ± 9 | 74 ± 14 | 0.070 |
| LVSV (mL) | 66 ± 14 | 55 ± 16 | 56 ± 12 | 47 ± 12* | 0.012 |
| EF (%) | 57 ± 2 | 60 ± 4 | 57 ± 6 | 63 ± 5*,‡ | 0.003 |
| LVSL | -18.9 ± 2.4 | -18 ± 2.4 | -17.4 ± 2.7 | -17.7 ± 2.4 | 0.539 |
| LVSRLs | -1.2 ± 0.3 | -1.0 ± 0.2 | -1.0 ± 0.2 | -1.2 ± 0.2 | 0.011 |
| CO (L.min$^{-1}$) | 5.1 ± 0.7 | 5.8 ± 1.5 | 4.9 ± 1.4 | 4.7 ± 1.0 | 0.137 |
| RVFAC (%) | 47 ± 6 | 49 ± 6 | 44 ± 7 | 32 ± 12*,†,‡ | <0.001 |
| TAPSE (mm) | 25 ± 3 | 23 ± 3 | 20 ± 3* | 17 ± 2*,†,‡ | <0.001 |
| $RV_{FW}SL$ | -27.2 ± 3.2 | -27.4 ± 4.4 | -24.3 ± 4.8 | -19.4 ± 7.9*,‡ | 0.002 |
| $RV_{FW}SRLs$ | -1.6 ± 0.3 | -1.7 ± 0.3 | -1.5 ± 0.3 | -1.2 ± 0.4*,‡ | 0.003 |
| PASP (mmHg) | 20 ± 2 | 26 ± 6 | 31 ± 12* | 68 ± 13*,†,‡ | <0.001 |
| Peak Exercise | | | | | |
| HR (bpm) | 131 ± 17 | 114 ± 15 | 105 ± 17* | 106 ± 14* | 0.001 |
| LVSV (mL) | 84 ± 18 | 61 ± 15* | 61 ± 16* | 42 ± 13*,†,‡ | <0.001 |
| EF (%) | 69 ± 2 | 68 ± 4 | 62 ± 7 | 66 ± 9 | 0.025 |
| LVSL | -23.2 ± 2.5 | -21.4 ± 2.6 | -17.9 ± 3.3* | -19.2 ± 3.1* | 0.001 |
| LVSRLs | -1.9 ± 0.3 | -1.4 ± 0.2* | -1.2 ± 0.3* | -1.6 ± 0.4 | <0.001 |
| CO (L.min$^{-1}$) | 12.9 ± 2.1 | 11.5 ± 2.2 | 8.5 ± 1.5*,‡ | 8.1 ± 2.2*,‡ | <0.001 |
| RVFAC (%) | 57 ± 5 | 53 ± 4 | 45 ± 11* | 29 ± 10*,†,‡ | <0.001 |
| TAPSE (mm) | 34 ± 2 | 29 ± 4 | 25 ± 6* | 21 ± 4*,†,‡ | <0.001 |
| $RV_{FW}SL$ | -32.7 ± 2.2 | -28.9 ± 4.5 | -26.1 ± 5.5* | -18.8 ± 8.4*,†,‡ | <0.001 |
| $RV_{FW}SRLs$ | -3.0 ± 0.5 | -2.2 ± 0.4* | -2.0 ± 0.4* | -1.4 ± 0.4*,†,‡ | <0.001 |
| PASP (mmHg) | 49 ± 3 | 51 ± 8.9 | 59 ± 12 | 102 ± 20*,†,‡ | <0.001 |

*P*-values for group comparison.
*,†,‡$P < 0.05$ Bonferroni *post hoc* compared with controls/HFpEF/HTDD, respectively.
CO, cardiac output, HR, heart rate; PASP, systolic pulmonary artery pressure; SV, stroke volume.

(*Figure 1*, all $P < 0.005$ for interaction) between controls, HFpEF and CTEPH patients. As opposed to control subjects, measurements of RV function either did not increase ($RV_{FW}SL$ and $RV_{FW}SRL$, *Figure 1C and D*) or even tended to decline (RVFAC, *Figure 1B*) in CTEPH patients. Similarly, RV reserve was also impaired in HFpEF patients compared with controls but not to the same extent as in CTEPH patients. Consequently, RV systolic reserve (ΔRVSRLs) was significantly lower in both groups compared with healthy controls ($P < 0.001$ between groups, Supplementary data online, *Figure S1*). In the HTDD patients, RV systolic function during exercise was slightly lower compared with controls as only $RV_{FW}SRL$ was significantly reduced compared with controls (Supplementary data online, *Figures S1 and S2*).

## LV systolic function during exercise in HTDD vs. HFpEF

LV systolic function augmented steadily during exercise in control subjects. In contrast, LV systolic reserve was significantly impaired in HFpEF patients. Pulsed wave tissue Doppler yielded comparable results and revealed an attenuated exercise-induced increase of LVS′ ($P \leq 0.01$ for interaction group*exercise intensity for LVEF, LVS′, LVSL, and LVSRL, *Figure 2*). Patients with HTDD behaved as an intermediary group as only peak LVSRL was significantly lower than controls (*Figure 2C*). LV systolic reserve (ΔLVSRLs, the difference between rest and peak LVSRLs), differed across the groups ($P = 0.010$ for between-group difference, *Figure 2E*) and was significantly reduced in HFpEF patients compared with controls. Likewise, also the difference in systolic annular velocity (ΔLVS′) was lower in HFpEF patients ($P = 0.002$, *Figure 2F*).

## LV diastolic function during exercise in HTDD vs. HFpEF

Doppler indices of LV diastolic function are summarized in Supplementary data online, *Table S2*. Mitral Doppler indices were not obtained during exercise in CTEPH patients. In control subjects, mitral inflow velocities (E and A wave) and early diastolic annular motion velocity (e′) increased substantially with exercise and mitral e′ velocity at peak exercise was higher compared with HTDD patients and HFpEF patients ($P < 0.001$ for interaction, *Figure 3A*). In HTDD patients, mitral E velocity increased more than e′ velocity, whilst only small proportional increases were noted in HFpEF patients. Consequently, *E*/e′ ratio at low exercise intensity (before fusion of E and A waves) remained unchanged in control subjects and increased in HTDD patients. In HFpEF patients, resting values were already

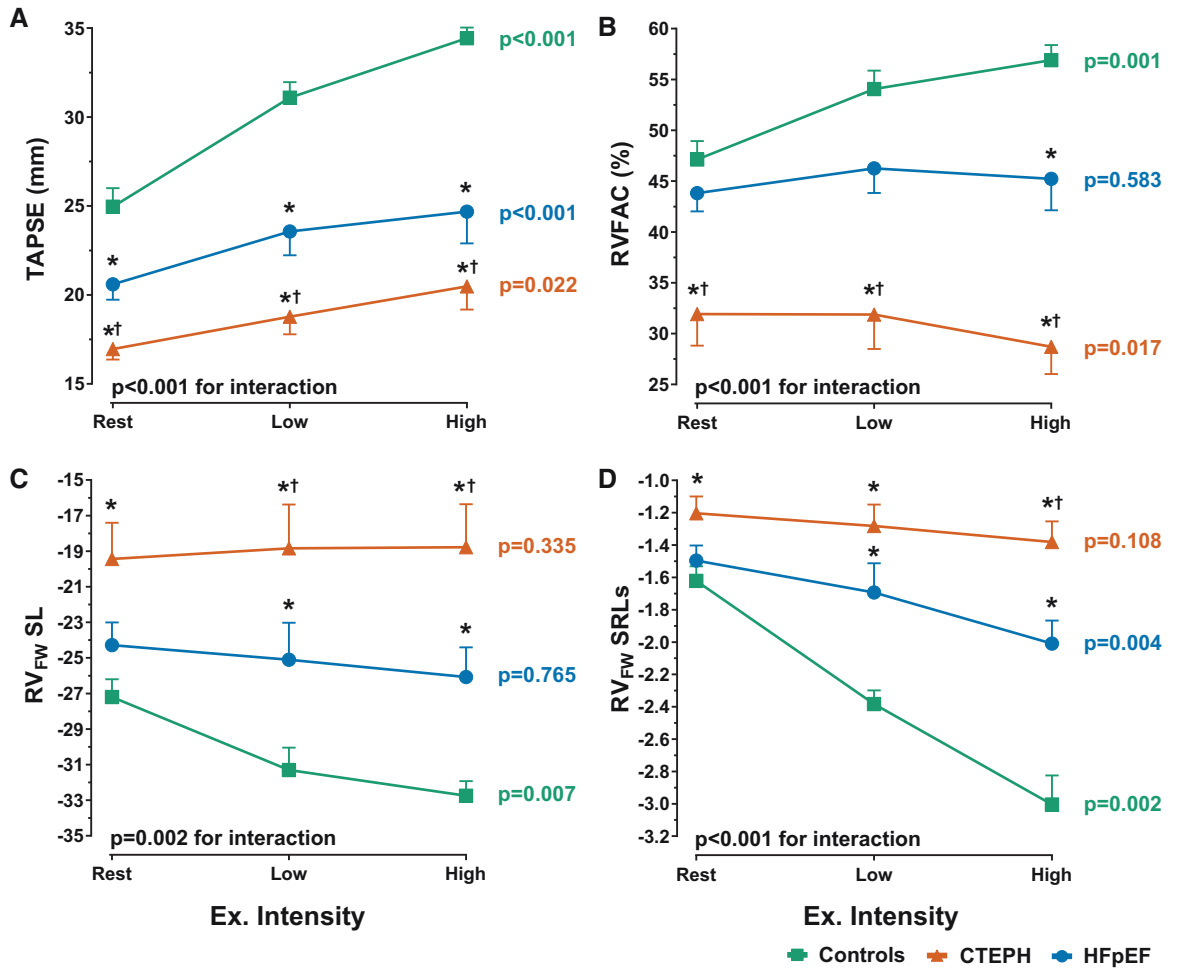



**Figure 1** Comparison of RV systolic function during exercise in HFpEF vs. CTEPH. Evolution of (*A*) TAPSE, (*B*) RVFAC, (*C*) $RV_{FW}SL$, and (*D*) $RV_{FW}SRLs$ during exercise in controls, HFpEF and CTEPH patients. Data are presented as means and standard error of the mean at each workload. Coloured *P*-values indicate main effect of exercise. *,† *P*<0.05 Bonferroni *post hoc* compared with controls and HFpEF, respectively.

high and only a minor increase was noted during exercise. LV early diastolic strain rate (LVSRLe) was similar at rest, but substantially increased during exercise in control subjects and HTDD patients while only modest increases were observed in HFpEF patients ($P = 0.001$, *Figure 3B*). LV diastolic reserve, defined as ΔLVSRLe, was lower in HFpEF patients compared with control subjects ($P < 0.001$ between groups, *Figure 3D*), whereas ΔLVe′ was reduced in both HTDD and HFpEF patients ($P = 0.001$ between groups, *Figure 3C*).

## RV contractile reserve, pulmonary vascular load, and RV–PV coupling during exercise

RV contractile reserve (RVESPAR) was normal in controls and HTDD patients but abnormally low (i.e. <1.6) in CTEPH patients and borderline in HFpEF patients (*Figure 4A*, $P < 0.001$ for interaction). Both CTEPH (7.2 ± 3.6) and HFpEF (4.2 ± 1.4) patients had an increased PV load (*Figure 4B*) which was considerably elevated compared with control subjects (2.2 ± 0.5). HTDD patients (2.6 ± 0.9), on the other hand, had a borderline *P/Q* slope. Consequently, ventricular-arterial coupling at peak exercise was preserved in controls whereas RV–PV uncoupling occurred in HFpEF and CTEPH patients (*Figure 4C*).

## Chronotropic reserve

Compared with control subjects, HTDD and HFpEF patients had a lower peak HR (both $P < 0.05$) and HRR (50 ± 26 and 59 ± 21 vs. 91 ± 26 bpm; both $P < 0.05$). Adjusted HRR, however, was only reduced in HFpEF patients (61 ± 34 vs. 91 ± 21; $P < 0.05$). During exercise, HR was higher in the three patient groups for any value of exercise load or $VO_2$ but the slopes of the relationship did not significantly differ between groups (Supplementary data online, *Figure S3A and B*). However, when HR was expressed vs. relative workload, control subjects had a significantly higher slope than the other three groups (Supplementary data online, *Figure S3C*).

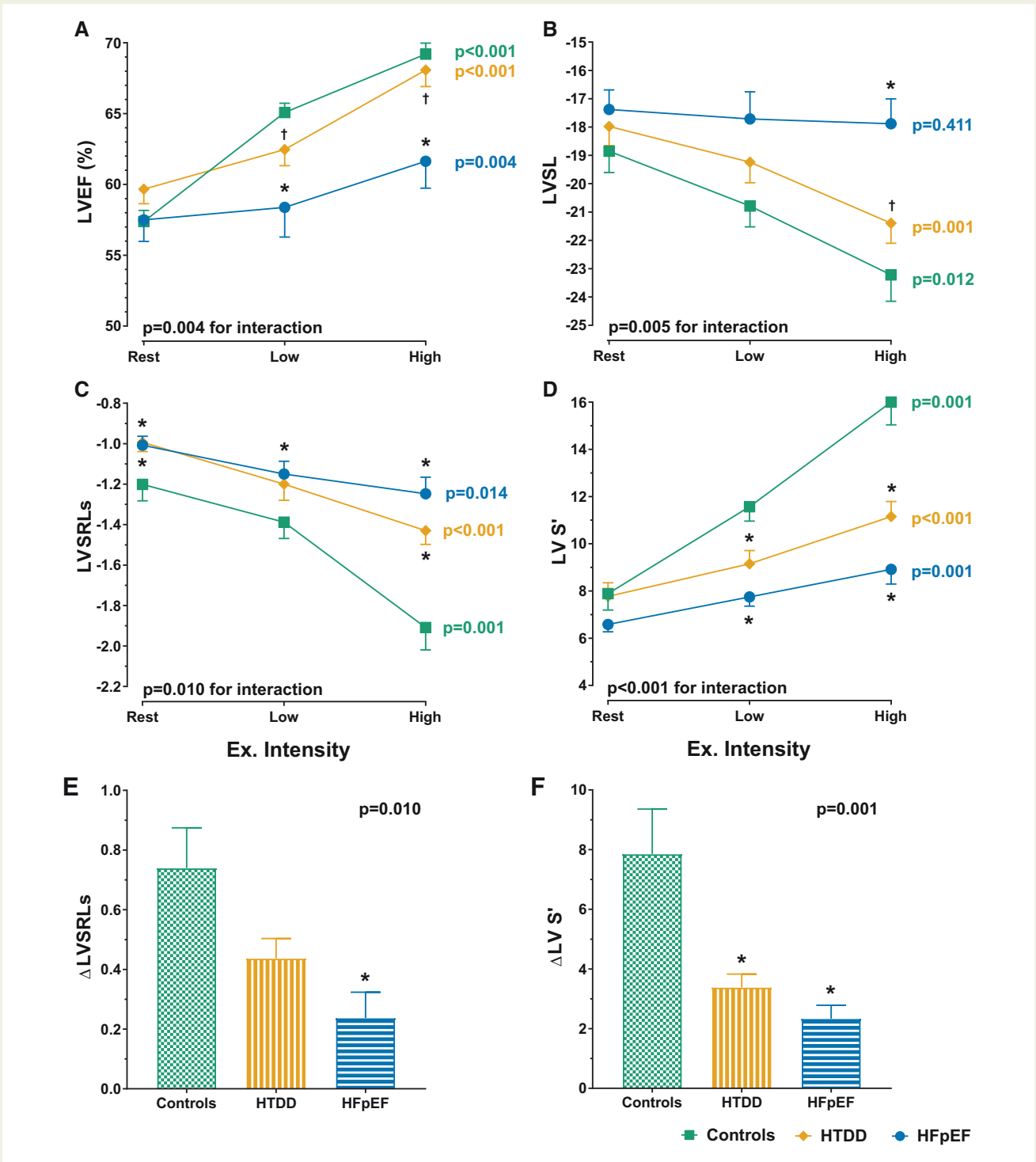



**Figure 2** Comparison of LV systolic function during exercise in HTDD vs. HFpEF. Evolution of (*A*) LVEF, (*B*) LVSL, (*C*) LVSRLs, and (*D*) LVS′ during exercise and rest-to-peak exercise difference of (*E*) ΔLVSRLs and (*F*) ΔLVS′ in controls, HTDD and HFpEF patients. Data are presented as means and standard error of the mean at each workload (A–D) or group (E and F). Coloured *P*-values indicate main effect of exercise. *,† *P*<0.05 Bonferroni *post hoc* compared with controls and HFpEF, respectively.

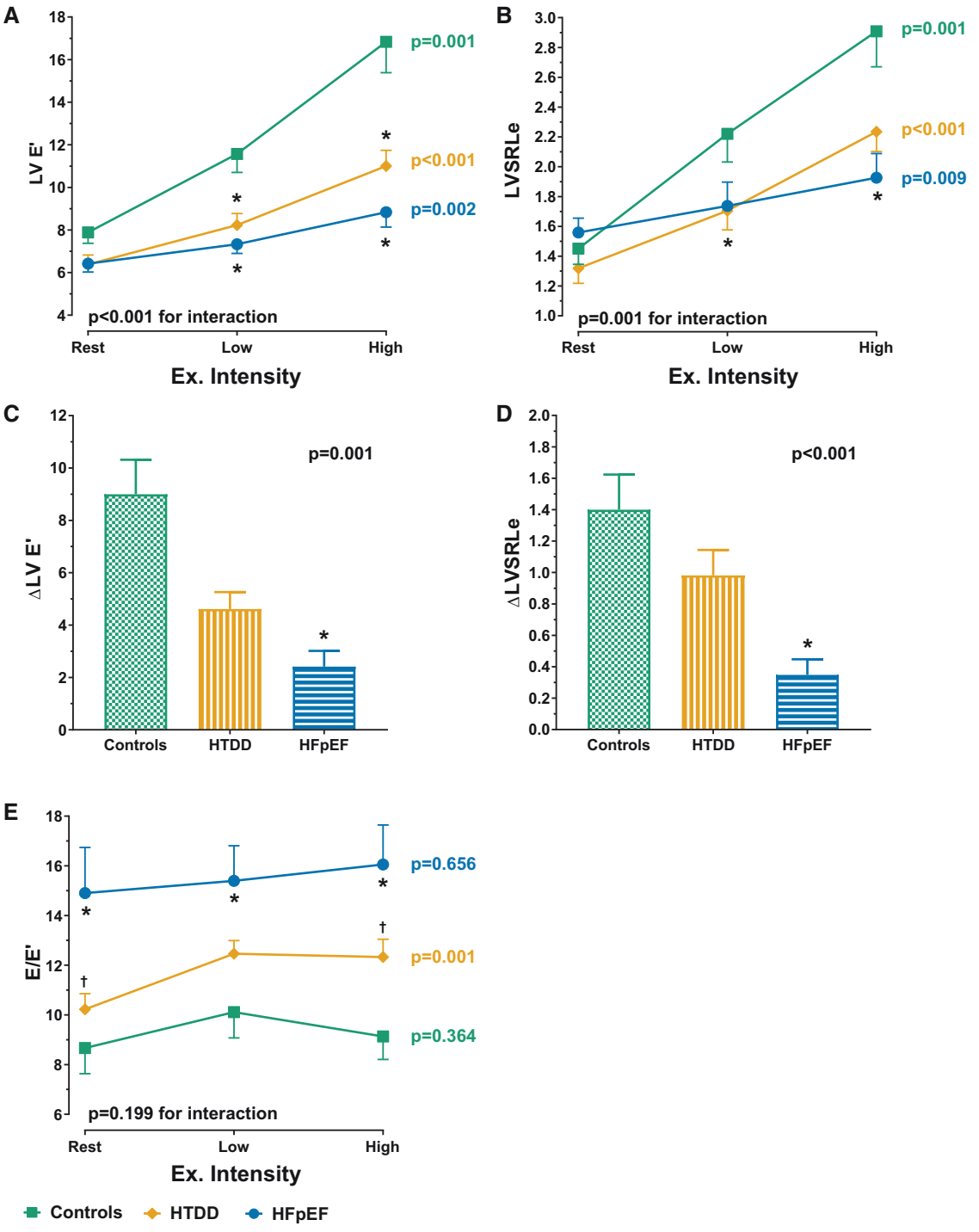



**Figure 3** Comparison of LV diastolic function during exercise in HTDD vs. HFpEF. Evolution of (*A*) LVe′ and (*B*) LVSRLe during exercise and rest-to-peak exercise difference of (*C*) ΔLVe′ and (*D*) ΔLVSRLe in controls, HTDD and HFpEF patients. Data are presented as means and standard error of the mean at each workload (A and B) or group (C and D). *,†$P<0.05$ Bonferroni *post hoc* compared with controls and HFpEF, respectively.

# Discussion

In this study, we performed a comprehensive, non-invasive evaluation of cardiac function during exercise in subjects across the HFpEF spectrum. Our results indicate that disease progression entails a multifaceted decline of cardiac function, not fully appreciable at rest. In HFpEF, the picture is governed by RV–PV uncoupling and limitations in cardiac, PV, and chronotropic reserve. Interestingly, these abnormalities already emerge early on in the disease. Notably,

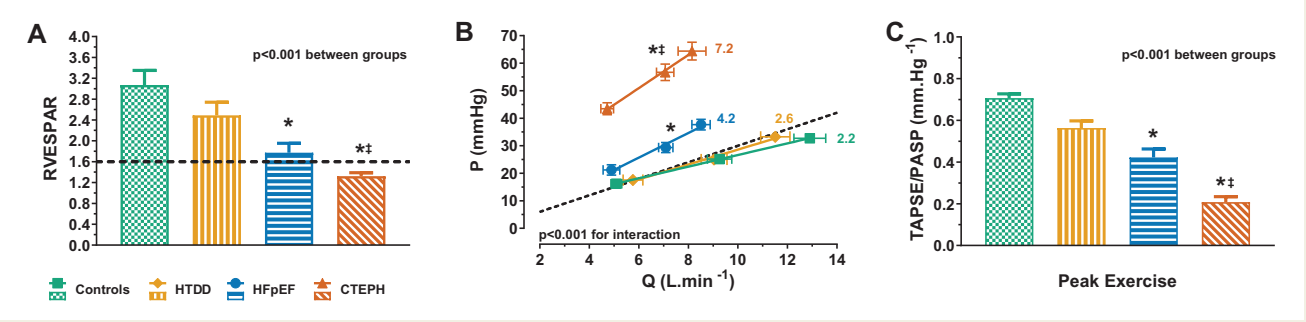



**Figure 4** RV contractile reserve, pulmonary vascular load, and RV–PV coupling during exercise. RV contractile reserve (*A*), pulmonary vascular load (*B*), and RV–PV coupling defined as TAPSE/PASP at peak exercise (*C*). Coloured number indicate mean *P*/*Q* slope for group. *,†,‡*P*<0.05 Bonferroni *post hoc* compared with controls, HFpEF and HTDD, respectively.

exercise evaluation revealed borderline RV–PV coupling in HTDD patients, coinciding with both limited LV diastolic reserve and impaired biventricular systolic reserve. Strain rate was particularly sensitive to identify subtle dysfunction. This suggests that combining modern imaging techniques with exercise may accelerate the diagnosis and facilitate earlier therapeutic interventions.

## Contributors to reduced exercise capacity

Exercise intolerance is a cardinal manifestation of heart failure. Although diastolic dysfunction is a central feature of HFpEF, cardiac abnormalities extend beyond diastole and intricate mechanistic links have been uncovered between LV diastolic and systolic dysfunction.[7] The multifaceted decline of cardiac function in HFpEF was further illustrated in a recent study by Pugliese *et al.*[21] demonstrating that peak $VO_2$ in heart failure patients is best predicted by a combination of factors related to LV systolic function, chronotropic competence, RV–PV coupling and left atrial compliance. Moreover, measures of cardiopulmonary dysfunction and indices of exercise induced pulmonary congestion also identified HFpEF patients at risk for adverse events or disease progression.[22]

In the current study, we extend previous findings by Pugliese *et al.*[13] of reduced LV systolic reserve in stage B HFpEF to limitations in biventricular systolic reserve, despite the only mildly reduced peak $VO_2$ and apparently preserved systolic function at rest. This is particularly relevant as impaired systolic function is a powerful predictor of outcome in HFpEF and non-diastolic factors often predominate in milder disease stages.[9,23] Interestingly, strain rate, which has been asserted as a more representative measure of contractility, appeared most sensitive to uncover early systolic dysfunction and concurs with a previous observation that peak systolic velocity, another early systolic measure, has the highest accuracy in predicting peak exercise capacity.[21,24] In contrast, HTDD patients displayed only minor abnormalities in LV diastolic reserve which, opposed to HFpEF patients, did not yet result in an abnormal diastolic stress test (i.e. septal $E/e'>15$) during exercise. Hence, in preclinical stages, systolic factors may predominate while the transition to symptomatic stages involves the emergence of (exercise induced) pulmonary congestion, as also suggested in the weighted risk score by Pugliese *et al.*[22]

## Right ventricular dysfunction and ventricular-vascular uncoupling in early HFpEF

RV dysfunction is frequent in HFpEF and portends worse outcome.[25,26] Traditionally, RV dysfunction has been related to adverse ventricular interdependence (i.e. worse LV function) and increased RV afterload because of pulmonary venous congestion and adverse PV remodelling.[27,28] More recently, however, this concept was challenged when it became clear that RV reserve is already impaired in early HFpEF.[11] Borlaug *et al.*[2] thus suggested that HFpEF is rather characterized by global myocardial dysfunction.

In the current study, we substantiate this claim by showing that a lower RV systolic reserve, measured by RVSRLs, can even be appreciated at a preclinical stage. Our results closely correspond with recently published exercise MRI data from our group and confirm the premise that contractile dysfunction, which has been related to deficient myocardial energy management and disturbed calcium handling, emerges early on in the course of the disease and affects both ventricles alike.[29–31] The use of deformation imaging during exercise is particularly relevant in this regard as resting measures erroneously suggest preserved systolic function and traditional parameters of RV function may lack the sensitivity to identify subtle contractile dysfunction during exercise as implied by the normal RV reserve (determined by TAPSE) found by Pugliese *et al.*[13] in a similar cohort of stage B heart failure patients. Moreover, our results implicate that both borderline PV reserve (i.e. *P*/*Q* slope) and reduced RV systolic reserve contribute to reduced RV–PV coupling (i.e. TAPSE/PASP) during exercise in stage B heart failure, akin to observations in symptomatic HFpEF or CTEPH.[12,32]

## Clinical implications

Our results reinforce the growing body of literature that supports the dynamic evaluation of cardiac function (i.e. during exercise) in heart failure patients. Given its availability, cost-effectiveness and relation with outcome, stress echocardiography appears a particularly attractive modality.[10,13,21,33] Interestingly, Kosmala *et al.*[10] identified exertional $E/e'$ and strain rate (but not global longitudinal strain) as independent predictors of outcome in HFpEF beyond natriuretic peptides and the MAGGIC risk score. In contrast with previous findings,

but in concurrence with the report of Pugliese *et al.* our results indicate that exertional *E*/*e*′ might be of limited value in preclinical disease while systolic reserve (e.g. by peak strain rate or peak systolic velocity), instead, appears particularly promising.[9,13,21] Whether preclinical identification of abnormal systolic reserve and then subsequent therapeutic intervention alters patient outcome warrants further research.

## Limitations

The modest sample size may have increased the probability of type II statistical errors while multiple comparisons increase the likelihood of type I errors. Secondly, adequate image quality was not available in every subject during exercise. However high-quality images were still acquired in most subjects and similar patterns were observed by different echocardiographic measures, reinforcing the validity of our results. Finally, the limited temporal resolution of 2D strain may have led to under-sampling with an underestimation of actual peak values. However, this limitation pertains to all groups and even though heart rate was higher in control subjects, meaningful differences were still demonstrable. Tissue Doppler Imaging might be more suitable at higher heart rates, but is difficult to perform during exercise due to its angle-dependency and increased noise. In addition, we have previously demonstrated good agreement between both techniques at rest and during exercise.[34]

# Conclusion

Progression to symptomatic HFpEF, characterized by global cardiac and PV dysfunction, is unmasked by the haemodynamic load of exercise. The exposure of subtle systolic abnormalities in preclinical disease such as impaired augmentation of strain rate illustrates the benefit of combining exercise with deformation imaging and creates new prospects for timely diagnosis and management of HFpEF.

# Supplementary data

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

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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