ORIGINAL ARTICLE

Training-induced change of diastolic function in heart failure with preserved ejection fraction

Andreas B. Gevaert[1,2]* [ID], Ephraim B. Winzer[3], Stephan Mueller[4,5], Stephanie De Schutter[1], Paul J. Beckers[6], Jennifer Hommel[3], Axel Linke[3], Ulrik Wisløff[7], Volker Adams[3], Burkert Pieske[8], Martin Halle[4,5], Emeline M. Van Craenenbroeck[1,2] and Caroline M. Van De Heyning[1,2]

[1]*Research Group Cardiovascular Diseases, GENCOR Department, University of Antwerp, Antwerp, Belgium;* [2]*Department of Cardiology, Antwerp University Hospital (UZA), Edegem, Belgium;* [3]*Department of Internal Medicine and Cardiology, Technische Universität Dresden, Heart Centre Dresden, University Hospital, Dresden, Germany;* [4]*Department of Preventive Sports Medicine and Sports Cardiology, University Hospital Klinikum rechts der Isar, Technical University of Munich, Munich, Germany;* [5]*DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany;* [6]*Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp, Antwerp, Belgium;* [7]*Cardiac Exercise Research Group, Norwegian University of Science and Technology (NTNU), Trondheim, Norway;* and [8]*Division of Cardiology, Department of Internal Medicine, University Medicine Rostock, Rostock, Germany*

Abstract

Aims   Exercise training improves aerobic capacity ($\dot{V}O_2$peak) in patients with heart failure and preserved ejection fraction (HFpEF), but underlying mechanisms remain unclear. We aimed to evaluate whether exercise training could improve systolic and diastolic function during exercise.

Methods   This was a substudy of the multicentre Optimizing Exercise Training in HFpEF (OptimEx-Clin) trial, in which 180 patients with HFpEF were randomized 1:1:1 to guideline control, moderate continuous training or high-intensity interval training. All patients included at two out of five participating sites underwent exercise echocardiography at baseline and 3 months. Patients of both training groups were pooled and compared with guideline control.

Results   A total of 61 patients (mean age 73 ± 7 years, 72% female) were included. At baseline, E/e′ increased from 17.0 ± 5.7 to 19.5 ± 6.1 and systolic pulmonary artery pressure from 31 ± 8 to 51 ± 11 mmHg (both $P < 0.001$). Right ventricular function did not change significantly (maximal tricuspid annular plane systolic excursion 24.7 ± 4.0 mm, $P = 0.051$ vs. baseline).
At 3 months, patients randomized to exercise training improved $\dot{V}O_2$peak (control +0.2, training +2.7 mL/kg/min, $P = 0.006$) and demonstrated small but significant improvements in exercise E/e′ (control 21.7 ± 7.5 to 22.8 ± 9.2, training 18.3 ± 5.0 to 17.2 ± 4.1, $P = 0.044$). No significant changes were observed in ejection fraction, mitral or tricuspid annular plane systolic excursion, S′, A′ or systolic pulmonary artery pressure ($P > 0.05$). Changes in E/e′ were not associated with the change in $\dot{V}O_2$peak.

Conclusions   In patients with HFpEF, exercise echocardiography revealed increases in filling pressures as well as a failure to augment right ventricular function during exercise. After 3 months of exercise training, HFpEF patients demonstrated a small improvement in diastolic function (exercise E/e′), but this did not explain the improved aerobic capacity.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is one of few cardiovascular diseases with increasing prevalence.[1] Despite recent advances in drug management,

HFpEF treatment remains challenging.[2] Exercise capacity and quality of life remain poor even after treatment with sodium-glucose transporter 2 inhibitors.[3]

In HFpEF patients, supervised exercise training (ET) is able to improve quality of life as well as aerobic capacity,

measured objectively as peak oxygen uptake ($\dot{V}O_2$peak).[4] The mechanisms responsible for this improvement in $\dot{V}O_2$peak are however still controversial. Small studies have suggested that ET improves resting systolic function by increasing left ventricular ejection fraction (LVEF) or diastolic function by reducing the E/e' ratio and altering deceleration time at rest.[5,6] However, other studies indicated that the change in $\dot{V}O_2$peak is primarily associated with changes in peripheral oxygen extraction with a higher peak arterial–venous oxygen difference.[7,8]

Improvements in cardiac function may be more evident during exercise testing, as systolic and diastolic function may be within normal ranges at rest.[2] Exercise right heart catheterization is considered the gold standard in this setting, but is not in general use due to its invasive nature and limited availability. Exercise echocardiography serves as a more widely available and clinically applicable non-invasive examination, demonstrating technical feasibility and acceptable correlation with invasive measurements of LV filling pressure.[9,10] Only one study assessed the effects of ET on exercise echo parameters in HFpEF, and this did not include diastolic function parameters.[7]

Optimizing Exercise Training in HFpEF (OptimEx-Clin) was a randomized multicentre trial assessing the effect of different training modalities on $\dot{V}O_2$peak in patients with HFpEF. The primary endpoint of the main trial was a change in $\dot{V}O_2$peak at 3 months; while $\dot{V}O_2$peak improvement was significantly higher in moderate continuous training (MCT) and high-intensity interval training (HIIT) groups as compared with guideline control, the predefined margin of clinical relevance (2.5 mL/kg/min) was not met.[11]

In this prespecified subanalysis of OptimEx-Clin, we assessed whether ET could improve parameters of systolic and diastolic function assessed during exercise echocardiography.

Methods

Main trial design

The OptimEx-Clin trial was conducted between September 2014 and July 2018 at the University Hospital 'Klinikum rechts der Isar' (Technical University of Munich), Heart Centre Leipzig, Charité Universitätsmedizin Berlin in Germany and Antwerp University Hospital in Belgium.[11,12] A total of 180 HFpEF patients were enrolled. HFpEF was defined as LVEF $\geq$ 50%, with signs and symptoms of HF and elevated LV filling pressure (E/e' septal $\geq$ 15 or E/e' septal $\geq$ 8 with concurrent elevated natriuretic peptides).[11] Inclusion criteria are listed in Table S1.

Patients were randomized 1:1:1 to MCT (5 times per week, 40 min exercise at 35%–50% of heart rate reserve), HIIT (3

times per week, 38 min exercise: 4 × 4 min intervals at 80%–90% heart rate reserve preceded by 10 min warm up and interspaced by 3 min exercise, both at 35%–50% heart rate reserve) or guideline control (physician recommendation to perform regular exercise). For MCT and HIIT, exercise sessions were supervised in cardiac rehabilitation centres three times per week for 3 months. The remaining exercise sessions were performed at home using telemonitoring supervision: patients were asked to wear a heart rate monitor (Polar, Finland), and heart rate data were transferred digitally via a smartphone application (Polar, Finland) at the end of the session. Adherence was reviewed weekly by the study team and telephonic motivational feedback was provided in case of non-adherence to protocol.

The study complied with the Declaration of Helsinki and was approved by the local ethics committees at the participating centres. We obtained written informed consent from each participant.

Exercise echocardiography substudy design

All patients recruited at Heart Centre Leipzig and Antwerp University Hospital were invited to undergo symptom-limited exercise echocardiography at baseline and 3 months, and included in the current substudy (Figure 1). As the main analysis of change in $\dot{V}O_2$peak did not demonstrate meaningful differences between MCT and HIIT groups, we pooled both ET groups for this substudy, to increase statistical power.

A protocol of 20 W with 10 W increments per minute was used for exercise testing on a semi-supine bicycle until exhaustion (peak exercise). At each increment, patients indicated dyspnoea level on a 15-step Borg scale (6–20), and blood pressure was measured. Heart rate and electrocardiogram were recorded continuously. Echocardiographic images (Vivid E9, GE Healthcare, Norway) were acquired at each increment, including parameters of systolic and diastolic function, left atrial size and right ventricular (RV) function. Reported values of diastolic function include both resting measurements, the value recorded at 50% of peak workload ('submaximal') and the highest value obtained during exercise ('maximal'). As for the remaining echocardiographic parameters, we reported values at both rest and peak exercise ('peak').

Echocardiographic data were analysed offline (EchoPAC, GE Medical Systems, Norway). All measurements were averaged over three cardiac cycles for patients in sinus rhythm and five cycles for patients with atrial fibrillation. LV ejection fraction was quantified by the modified Simpson's method in the apical four- and two-chamber view. Left atrial volume was measured using the area–length method in the apical four- and two-chamber view and indexed to body surface area. Mitral E and A wave velocities were measured with pulsed wave Doppler at the tips of the mitral leaflets in the apical

Figure 1 Study flowchart. Patients were assessed at baseline and 3 months. Of 180 patients randomized, 61 were included in this substudy, after excluding patients who were ineligible after core lab review of inclusion criteria, patients included at centres without exercise echo facilities and patients who did not perform exercise echo for other reasons. A total of 51 patients underwent exercise echocardiography at 3 months follow-up. All patients who had exercise echocardiography at baseline were included for statistical analysis.
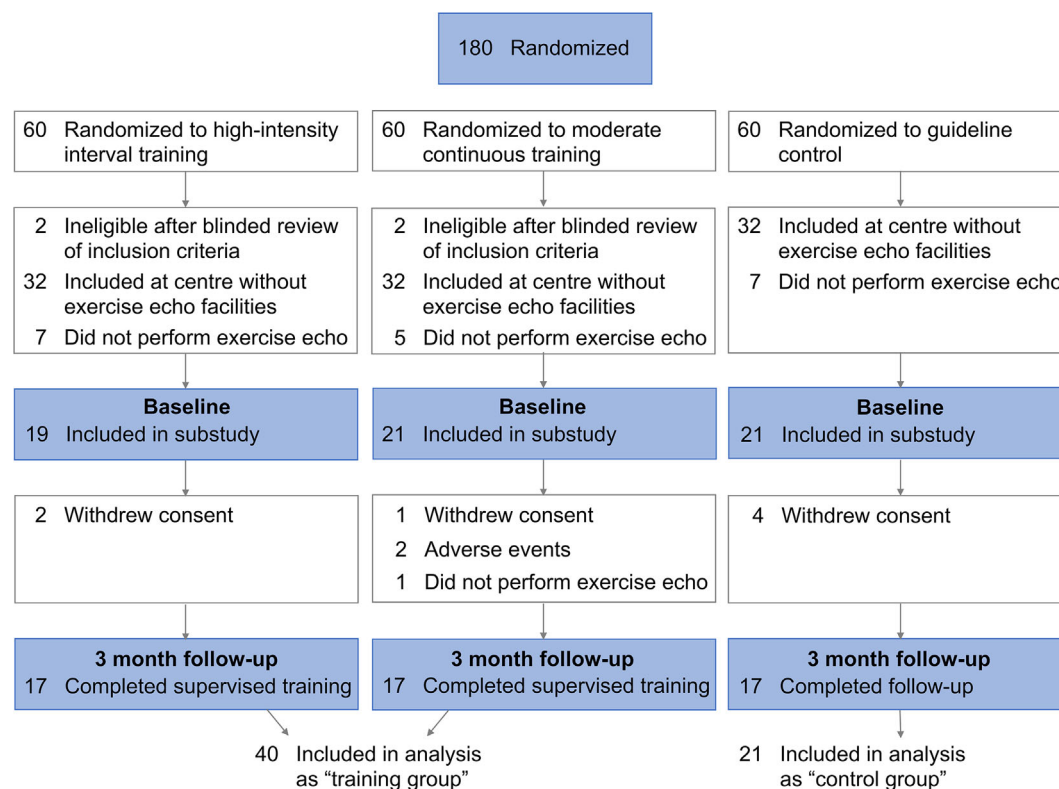
four-chamber view. Early relaxation (e') and systolic (S') velocities were obtained by tissue Doppler imaging at the septal and lateral mitral annulus at rest. During exercise, only septal e' and S' were recorded due to time constraints.[13] Systolic pulmonary artery pressure (PAP) was calculated as the sum of the maximal trans-tricuspid pressure gradient and an estimate of the resting right atrial pressure based on the inferior caval vein dimension and collapsibility. Mitral and tricuspid annular plane systolic excursion (TAPSE) was measured at the septal and lateral annulus, respectively. RV–vascular coupling was measured by TAPSE/PAPs ratio.[14] The procedure and analysis were performed by cardiologists with extensive experience in exercise echocardiography (E. B. W, C. M. V. D. H. and A. B. G.).

Other measurements

Cardiopulmonary exercise testing was performed on a separate day (within 7 days of exercise echocardiography) and analysed in a blinded manner at the study core laboratory (Munich), as described previously.[15] Briefly, patients exercised until exhaustion on a bicycle ergometer while gas

exchange (ventilation, oxygen uptake and carbon dioxide production) was measured continuously. $\dot{V}O_2$peak was defined as the highest 30 s average oxygen uptake within the last minute of exercise. Predicted $\dot{V}O_2$peak was calculated by the Jones formulas.[16] Ventilatory efficiency was calculated using the entire exercise data. Patients with a relative increase of 6% in $\dot{V}O_2$peak were considered 'responders', based on a recent consensus statement as well as the mortality benefit associated with this threshold in patients with HFrEF.[17,18]

HFpEF clinical scores (H2FPEF, HFA–PEFF) were calculated based on clinical and echocardiographic variables at rest, as published.[19,20] N-terminal pro B-type natriuretic peptide (NT-proBNP) values were analysed by a central core laboratory (Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria).

Sex was defined as 'sex assigned at birth' for all analyses.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median (25th–75th percentile) when distribution was skewed. Group comparisons (Table S2) were per-

formed using one-way analysis of variance (continuous variables), Kruskal–Wallis test (skewed continuous variables) or Pearson's χ^2 test (categorical variables). Correlations were analysed using Spearman's correlation coefficient.

Linear mixed models were used to analyse repeated measures data. An uncorrected model was constructed using randomization number as random factor and time, training group and their interaction as fixed factors. Logistic regression models were used to assess independent determinants of training response (change in $\dot{V}O_2$peak $\geq$ 6% or <6%).[17] If anomalies were noted on quantile–quantile plots, residual histograms or standardized residuals versus fitted values plots, the analysis was repeated after log-transformation of the outcome variable.

Inter-observer reproducibility was assessed by the intraclass correlation coefficient on data measured independently by two experienced observers (A. B. G. and C. M. V. D. H.).

A two-sided P value < 0.05 was considered significant. All data were analysed using R v4.4.0 (R Foundation for Statistical Computing) with packages *irr*, *multcomp*, *nlme* and *tidyverse*.

Results

Patient characteristics

A total of 61 patients were included in this substudy: 21 randomized to guideline control and 40 randomized to ET, of which 19 were allocated to HIIT and 21 to MCT (*Figure* 1). Follow-up exercise echocardiography was performed in 34 patients (85%) allocated to training and 17 patients (81%) allocated to guideline control (*Figure* 1).

Patient characteristics are summarized in *Table* 1. Patients were older adults (mean age 73 ± 7 years), predominantly female (72% women) and overweight (mean body mass index 30.7 ± 5.9 kg/m^2). Typical comorbidities included hypertension (93%), hyperlipidaemia (77%), chronic kidney disease (67%) and atrial fibrillation (38%). Natriuretic peptide levels and HFpEF clinical scores were elevated [median NT-proBNP 363 (243–820) pg/mL, median H2FPEF score 5 (4–6), median HFA–PEFF score 5 (4–6)].

Of note, patients included in this substudy had a more severe HFpEF phenotype compared to the other patients in OptimEx-Clin. They were older, more symptomatic, had more comorbidities and higher NT-proBNP (Table S2).

Baseline exercise echocardiography

Exercise echocardiography was performed until exhaustion in all patients (mean Borg score $\geq$ 16). Most patients had echocardiographic signs of elevated filling pressures already at

Table 1 Patient characteristics.

	Control (*n* = 21)	Training (*n* = 40)
Clinical examination		
Age (years)	73 ± 8	73 ± 6
Sex (*n*, % female)	15 (71)	29 (73)
Body mass index (kg/m^2)	30.6 ± 3.7	30.7 ± 6.9
New York Heart Association class		
II (*n*, %)	11 (52)	22 (55)
III (*n*, %)	10 (48)	18 (45)
Systolic blood pressure (mmHg)	129 ± 16	128 ± 15
Diastolic blood pressure (mmHg)	71 ± 12	69 ± 10
Rest heart rate (min^{-1})	62 ± 8	65 ± 10
Past medical history		
Atrial fibrillation (*n*, %)	6 (29)	17 (43)
Chronic kidney disease (*n*, %)	12 (57)	29 (73)
Coronary heart disease (*n*, %)	5 (26)	5 (13)
Diabetes (*n*, %)	5 (24)	11 (28)
Hypertension (*n*, %)	20 (95)	37 (93)
Hyperlipidaemia (*n*, %)	17 (81)	29 (74)
Sleep apnoea (*n*, %)	5 (24)	9 (23)
Medication use		
ACE inhibitor or ARB (*n*, %)	16 (76)	31 (78)
Anti-coagulant (*n*, %)	6 (28)	20 (50)
Anti-platelet (*n*, %)	2 (10)	2 (5)
Beta-blocker (*n*, %)	19 (91)	29 (73)
Calcium antagonist (*n*, %)	13 (62)	18 (45)
Diuretic (*n*, %)	17 (81)	28 (70)
Glucose lowering (*n*, %)	3 (14)	4 (10)
Statin (*n*, %)	12 (57)	22 (55)
Laboratory analysis		
eGFR (mL/min/1.73 m^2)	62 ± 19	59 ± 21
Haemoglobin (g/L)	128 ± 12	131 ± 16
Leukocytes (×10^6/L)	6.8 ± 2.1	6.4 ± 1.6
NT-proBNP (pg/mL)	354 (294–1,038)	392 (230–755)
H2FPEF logistic (%)	90 (67–97)	94 (70–97)
H2FPEF score	5 (3–6)	5 (4–6)
HFA–PEFF score	5 (4–6)	5 (4–6)

Note: Continuous variables are represented as mean ± standard deviation and were compared using one-way analysis of variance. Skewed continuous variables are represented as median (25th–75th percentile) and were compared with Kruskal–Wallis test. Categorical variables are represented as *n* (%) and were compared with Pearson's χ^2 test.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker, EGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

rest, including low e' (mean 5.8 ± 1.6 cm/s), high E/e' ratio (mean 17.0 ± 5.7), high left atrial volume index (mean 40 ± 14 mL/m^2) and high PAPs (mean 31 ± 8 mmHg). In total, 34 patients (60%) had E/e' $\geq$ 15 at rest, and 23 patients (51%) had PAPs $\geq$ 30 mmHg at rest. In contrast, parameters of LV and RV systolic function were within normal ranges at rest (mean LV ejection fraction 61 ± 8%, mean TAPSE 22.6 ± 3.8 mm).

At peak exercise, significant increases were seen in all parameters, except TAPSE (nonsignificant increase, $P = 0.051$) and RV–vascular coupling (significant decrease, $P < 0.001$, *Table* 2). Changes were similar in control and ET group at baseline, although LVEF and MAPSE increase did not reach statistical significance in controls (*Table* 2).

Table 2 Exercise echocardiography at baseline and 3 months.

		Control		Training		P value		
		Baseline	3 months	Baseline	3 months	Time	Group	Interaction
Exercise								
Workload (W)	Peak	70 (50–80)	70 (50–80)	60 (50–80)	70 (60–70)	0.663	0.251	0.629
Borg dyspnoea scale	Rest	8 ± 2	8 ± 2	9 ± 2	9 ± 3	0.682	0.346	0.814
	Peak	17 ± 1*	17 ± 1*	17 ± 1*	17 ± 1*	0.222	0.334	0.210
Heart rate (min^{-1})	Rest	62 ± 10	65 ± 13	67 ± 11	66 ± 10*	0.287	0.145	0.337
	Peak	98 ± 19*	101 ± 17*	99 ± 22*	100 ± 16*	0.348	0.791	0.572
	Change rest-peak	36 ± 16	36 ± 16	33 ± 19	33 ± 13	0.807	0.572	0.954
Left ventricular systolic								
Left ventricular ejection fraction (%)	Rest	61 ± 10	62 ± 8	61 ± 7	62 ± 7	0.802	0.806	0.930
	Peak	65 ± 8	63 ± 10	67 ± 7*	67 ± 7*	0.232	0.391	0.280
	Change rest-peak	5 ± 9	1 ± 5	6 ± 10	5 ± 7	0.170	0.599	0.375
Mitral annular plane systolic excursion (cm)	Rest	1.29 ± 0.15	1.26 ± 0.24	1.22 ± 0.18	1.30 ± 0.19	0.569	0.316	0.177
	Peak	1.45 ± 0.33	1.34 ± 0.35	1.44 ± 0.32*	1.48 ± 0.22*	0.254	0.974	0.219
	Change rest-peak	0.16 ± 0.29	0.09 ± 0.21	0.22 ± 0.25	0.17 ± 0.18	0.517	0.458	0.895
S' septal (cm/s)	Rest	5.18 ± 1.20	5.28 ± 1.24	5.53 ± 1.15	5.42 ± 1.21	0.852	0.278	0.521
	Peak	7.11 ± 1.78*	6.72 ± 2.08*	7.00 ± 1.65*	7.25 ± 2.04*	0.180	0.831	0.130
	Change rest-peak	1.93 ± 1.03	1.44 ± 1.25	1.54 ± 1.42	1.81 ± 1.84	0.131	0.300	0.072
Left ventricular diastolic								
E wave (cm/s)	Rest	106 ± 25	110 ± 45	101 ± 26	94 ± 43	0.762	0.700	0.535
	Maximal	167 ± 62	189 ± 43	150 ± 41	137 ± 34	0.289	0.312	0.148
	Change rest-maximal	62 ± 61	79 ± 43	47 ± 42	42 ± 53	0.843	***0.035***	0.247
e' septal (cm/s)	Rest	5.43 ± 1.39	5.72 ± 1.24	5.98 ± 1.65	5.89 ± 1.53	0.624	0.312	0.665
	Maximal	7.63 ± 3.13*	8.04 ± 2.30*	7.93 ± 1.93*	8.08 ± 2.49*	0.937	0.732	0.916
	Change rest-maximal	2.20 ± 2.98	2.32 ± 2.30	2.08 ± 1.75	2.03 ± 2.97	0.731	0.899	0.900
E/e' ratio septal	Rest	18.68 ± 5.89	17.24 ± 7.29	16.06 ± 5.52	14.99 ± 4.75	0.351	0.091	0.941
	Submaximal	20.30 ± 5.97	19.17 ± 9.13	17.16 ± 3.35	16.67 ± 3.81	0.524	***0.010***	0.776
	Maximal	21.70 ± 7.47*	22.88 ± 9.23*	18.26 ± 5.01*	17.23 ± 4.14*	0.080	***0.041***	***0.044***
	Change rest-maximal	3.11 ± 4.4	5.43 ± 3.7	1.75 ± 4.68	2.74 ± 3.36	0.050	0.261	0.379
Left atrial								
A' septal (cm/s)	Rest	6.30 ± 1.52	6.59 ± 1.89	7.01 ± 2.13	7.22 ± 1.38	0.761	0.268	0.536
	Peak	8.67 ± 3.80*	10.92 ± 4.14*	8.37 ± 2.88*	10.03 ± 3.69*	0.603	0.814	0.577
	Change rest-peak	2.27 ± 2.97	4.39 ± 2.94	1.36 ± 2.07	2.65 ± 3.21	0.156	0.392	0.672
Right ventricular								
Systolic pulmonary artery pressure (mmHg)	Rest	31 ± 8	31 ± 12	32 ± 8	31 ± 11	0.705	0.671	0.517
	Peak	52 ± 13*	51 ± 10*	50 ± 10*	46 ± 11*	0.785	0.395	0.304
	Change rest-peak	21 ± 11	19 ± 10	18 ± 9	14 ± 10	0.617	0.168	0.574
Tricuspid annular plane systolic excursion (cm)	Rest	2.29 ± 0.46	2.43 ± 0.59	2.24 ± 0.33	2.34 ± 0.32	0.453	0.746	0.880
	Peak	2.35 ± 0.32	2.63 ± 0.61	2.43 ± 0.39	2.40 ± 0.48	0.129	0.767	0.186
	Change rest-peak	−0.03 ± 0.54	0.14 ± 0.76	0.18 ± 0.48	0.04 ± 0.36	0.729	0.553	0.429
Right ventricular–vascular coupling (mm/mmHg)	Rest	0.71 ± 0.18	0.69 ± 0.24	0.73 ± 0.21	0.78 ± 0.19	0.841	0.953	0.314
	Peak	0.45 ± 0.10*	0.52 ± 0.16*	0.47 ± 0.16*	0.55 ± 0.12*	0.439	0.225	0.702
	Change rest-peak	−0.28 ± 0.16	−0.33 ± 0.16	−0.20 ± 0.20	−0.22 ± 0.19	0.531	0.538	0.784

Note: All values displayed as mean ± standard deviation except workload as median (first quartile–third quartile) because of skewed distribution. P values from linear mixed models using patient ID as random effect and time, training group and their interaction as fixed effects. 'Peak' denotes the value obtained at peak exercise, 'maximal' denotes the highest value obtained during exercise and 'submaximal' denotes measurement taken at 50% of the peak load at baseline CPET. Bold and italic: P < 0.05.
*P < 0.05 when comparing peak/max with rest values (linear mixed models).

Inter-observer reproducibility was assessed for E/e' and TAPSE: for E/e' at rest, intraclass correlation was 0.95 (95% confidence interval 0.91–0.98), for maximal E/e' 0.92 (0.83–0.97), for TAPSE at rest 0.77 (0.53–0.89) and for TAPSE at peak 0.66 (0.42–0.82).

Effect of exercise training

Patients randomized to ET demonstrated excellent adherence: participation in exercise sessions was 88% (77%–95%). Aerobic capacity significantly increased in patients randomized to ET at 3 months compared with controls: $\dot{V}O_2$peak (+2.7 vs. +0.2 mL/kg/min, P-interaction = 0.006), percentage of predicted $\dot{V}O_2$peak (+7% vs. +1%, P-interaction = 0.021) and peak workload (+11 vs. −2 Watt, P-interaction < 0.001) (*Table* 3). NT-proBNP did not change significantly in patients randomized to control or training (P-interaction = 0.516). Several resting echo parameters (LV end-diastolic diameter, septum thickness and mass index) changed significantly in the control group at 3 months (Table S3).

A significant difference in exercise E/e' ratio was seen between ET and control groups at 3 months (*Table* 2, *Figure* 2A). This was due to an exaggerated E/e' increase during exercise in controls. Also, E wave was significantly higher in controls overall (P-time = 0.035, P-interaction however did not reach statistical significance). No other between-group differences were found for resting or exercise echocardiography measurements (*Table* 2, *Figure* 2B–D).

Four patients had AF at baseline and follow-up. Additionally, two patients had sinus rhythm at baseline but AF at follow-up; sensitivity analysis excluding these two patients did not change our findings.

Associations with training response

In total, 60% of patients meaningfully increased $\dot{V}O_2$peak after training (>6% increase).[17] Compared with those with <6% increase, at baseline, these 'responders' had lower body mass index (28.8 ± 4.5 vs. 34.1 ± 9.0 kg/m2, P = 0.023), lower

TAPSE at rest (20.9 ± 2.9 vs. 24.6 ± 2.6 mm, P = 0.022) and lower TAPSE/PAPs ratio at rest (0.55 ± 0.15 vs. 0.87 ± 0.05 mm/mmHg, P = 0.010). Of note, 93% of non-responders were on a beta-blocker, compared with 59% of responders (P = 0.054). Other patient characteristics and echo parameters were similar.

In univariate logistic regression, only few parameters were associated with the training-induced $\dot{V}O_2$peak increase body mass index, beta blocker use and TAPSE (Table S4). None of these variables was significantly associated with the $\dot{V}O_2$peak increase in multivariate logistic regression analysis (Table S4). Changes in exercise echocardiographic parameters between baseline and 3 months did not correlate with the change in $\dot{V}O_2$peak (all P > 0.05, all rho < 0.5). More specifically, changes in E/e' did not relate to the $\dot{V}O_2$peak training response (*Figure* 3).

Discussion

This substudy of HFpEF patients included in the OptimEx-Clin trial is the largest to report on the effect of training on exercise echocardiography parameters in HFpEF and the first to include diastolic function parameters. We report the following main findings: (1) while parameters of LV and RV systolic function were both within normal ranges at rest, at peak exercise, LV systolic function increased whereas RV systolic function did not, leading to poor RV–vascular coupling. (2) Despite good adherence to training, patients randomized to ET had only a small difference in exercise E/e' compared with control at 3 months. (3) The $\dot{V}O_2$peak response to ET was not associated with exercise echocardiography parameters.

High filling pressures at rest

More than half of the patients included in this study already had evidence of elevated filling pressures at rest, including high E/e' ratio (60%) and high PAPs (51%), indicating a relatively 'advanced' stage of HFpEF in our population. This is certainly influenced by the inclusion criteria for OptimEx-Clin,

Table 3 Cardiopulmonary exercise test at baseline and 3 months.

| | Control | | Training | | P value | | |
	Baseline	3 months	Baseline	3 months	Time	Group	Interaction
$\dot{V}O_2$peak (mL/kg/min)	17.3 ± 4.7	17.5 ± 5.5	16.8 ± 5.7	19.5 ± 5.6	0.318	0.797	***0.006***
Percent predicted $\dot{V}O_2$peak (%)	87 ± 20	88 ± 25	85 ± 26	92 ± 22	0.354	0.976	***0.021***
Peak workload (W)	86 ± 26	84 ± 28	81 ± 29	92 ± 23	0.111	0.449	***<0.001***
Peak heart rate (bpm)	109 ± 21	110 ± 22	111 ± 22	118 ± 19	0.980	0.508	0.269
Peak systolic blood pressure (mmHg)	169 ±28	170 ±23	169 ±26	169 ±24	0.576	0.917	0.559
$\dot{V}E/\dot{V}CO_2$ slope	30.8 ± 5.7	30.3 ±3.5	30.6 ± 3.6	31.3 ±6.0	0.859	0.587	0.987

Note: P values from linear mixed models using patient ID as random effect and time, training group and their interaction as fixed effects. Bold and italic: P < 0.05.
Abbreviations: $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, ventilation; $\dot{V}O_2$, oxygen uptake.

Figure 2 Selected exercise echocardiography measurements at baseline and 3 months. Red circles represent patients in control group, blue triangles patients in training group. Left side of graph represent measurements at baseline, right side at 3 months. Percentage change from rest to peak is mentioned. (A) E/e' ratio, (B) LVEF, (C) PAPs and (D) TAPSE, *$P < 0.05$ for significant change from rest to max exercise at a given timepoint; †P-time < 0.05 indicating significant overall change from baseline to 3 months; $$P$-interaction < 0.05 indicating significantly different evolution over time between control and training group. LVEF, left ventricular ejection fraction; PAPs, pulmonary artery pressure systolic; TAPSE, tricuspid annular plane systolic excursion.
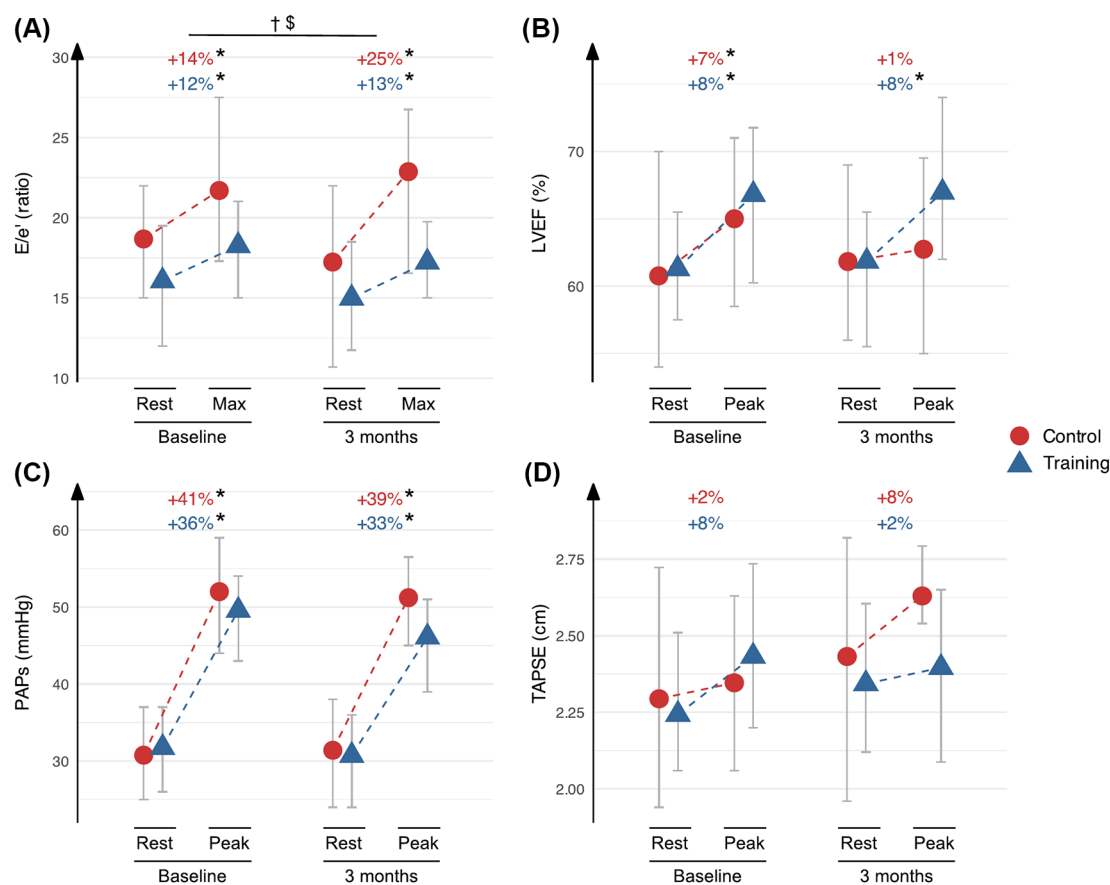
which mandated either resting E/e' $\geq$ 15 or E/e' 8–15 with elevated natriuretic peptides.[12] Additionally, the patients included in this substudy demonstrated more advanced disease than those not included in the substudy (Table S2) reflected by older age, higher prevalence of chronic kidney disease, higher NT-proBNP levels, more advanced NYHA class, lower $\dot{V}O_2$peak and higher HFA–PEFF scores. This could arise from differences in referral patterns or regional differences in healthcare practice (lack of NT-proBNP reimbursement in Belgium could favour inclusion by echo criteria and thus more advanced disease).

However, other HFpEF randomized clinical trials found a similar number of patients with elevated LV filling pressures. For example in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure II (REDUCE-LAP-HF-II) trial, 71% of patients had elevated LV filling pressures at rest.[21] Patients with 'early' HFpEF may present with normal LV filling pressures at rest, as such our findings cannot be extrapolated to

this subset of patients. Indeed exercise echocardiography has been mostly advocated as a means to enhance diagnosis of HFpEF at an early stage, as it is known that exercise may unmask discrepant elevation of filling pressures during exercise non-invasively.[22–24]

Importance of RV reserve during exercise in HFpEF

While LV and RV systolic function parameters were within normal ranges in most patients at rest, during exercise, HFpEF patients demonstrated impaired RV reserve (failure to increase TAPSE) despite increasing PAPs. Thus, RV–vascular coupling measured by TAPSE/PAPs was severely impaired in this population. Borlaug et al. previously demonstrated impaired RV–vascular coupling in HFpEF patients despite preserved RV function at rest using exercise right heart catheterization.[25]

Figure 3 Correlation between changes in aerobic capacity and diastolic function. Changes in E/e' were correlated to changes in V̇O₂peak in patients randomized to training, to assess the contribution of improved diastolic function to training response. (A) Change in maximal E/e' between baseline and 3 months, relative to change in V̇O₂peak between baseline and 3 months. (B) Change in ΔE/e' (i.e., E/e' max − E/e' rest) between baseline and 3 months, relative to change in V̇O₂peak between baseline and 3 months. Rho values indicate Spearman's correlation coefficient, with values <0.5 indicating poor correlation. Max E/e', highest E/e' recorded during stress echocardiography; ΔE/e', increase in E/e' from rest to exercise; V̇O₂peak, peak aerobic capacity.
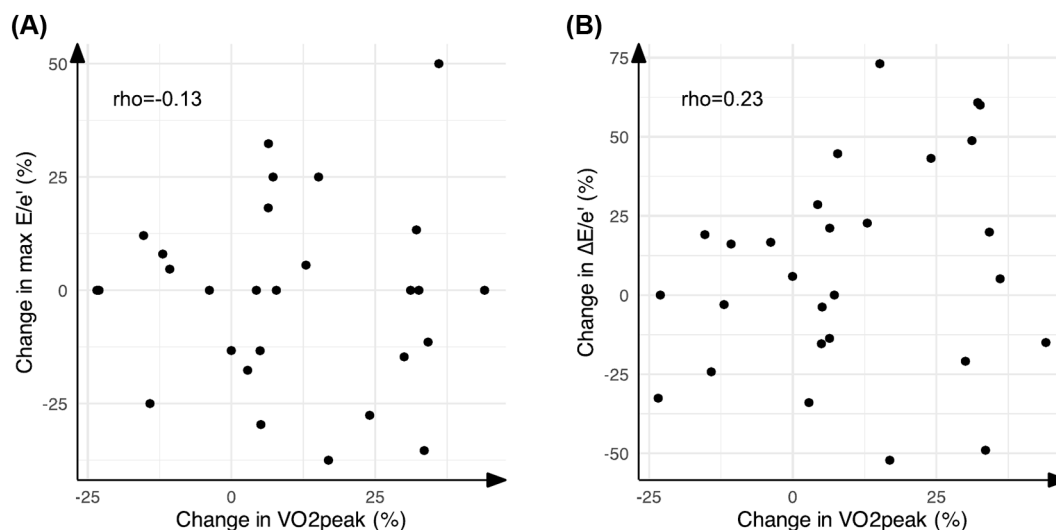
Of note, the authors found that abnormal RV–vascular coupling was strongly correlated with biventricular filling pressures. The TAPSE/PAPs ratio, while being a broad indicator of RV–vascular coupling, is of prognostic value in HF and may discern different HFpEF phenotypes.[26]

It is known that RV structure and function deteriorates over time after a diagnosis of HFpEF.[27] Unfortunately, ET did not improve RV resting or exercise parameters in our 'advanced' HFpEF population. However, it cannot be excluded that at earlier stages of HFpEF, modulation of RV function and RV–vascular coupling is still possible.

Improvements by training in HFpEF

Despite the relatively 'advanced' HFpEF population included in the present substudy, patients had good adherence to the ET protocol and significantly increased V̇O₂peak (+2.7 mL/kg/min). Nevertheless, only small changes in exercise echocardiography parameters were seen after 3 months in patients randomized to ET, and the changes in E/e' ratio did not correlate to V̇O₂peak increase. Thus, it is unlikely that these are responsible for the increase in aerobic capacity. Haykowsky et al. previously performed exercise echocardiography in HFpEF patients before and after training and found that increases in arteriovenous oxygen difference could explain most of the changes induced by training.[7] The current study adds to the knowledge that changes in LV diastolic function are likely not responsible for the increase in exercise capacity after training.

We have previously demonstrated that training had no effect on vascular function and HIIT induced important changes in skeletal muscle: reduced markers of muscle atrophy, increased mitochondrial enzyme activity and expression and increased amount of satellite cells.[28,29] Of note, the patients included in the skeletal muscle study and the exercise echocardiography study overlap. These changes occurred despite a focus on aerobic ET in OptimEx-Clin while resistance training or combined training may provide incremental benefit in patients with cardiovascular disease.[30] The Personalized Remotely Guided Preventive Exercise Therapy in HFpEF (PRIORITY) study will further explore the effects of combined aerobic and resistance training in HFpEF patients.[31] In the current study, we demonstrate that cardiac parameters remained mostly unchanged; thus, it is most likely that the V̇O₂peak increase is mediated by changes in peripheral oxygen extraction at the level of the skeletal muscle.[32]

As not all HFpEF patients increase V̇O₂peak meaningfully by training, we explored whether we could predict which patients would respond favourably using baseline parameters. None of the baseline clinical, resting echocardiography or exercise echocardiography parameters could predict the V̇O₂peak response to training. Previously, we demonstrated that peak O₂ pulse (by CPET) and microRNA-181c (by polymerase chain reaction) could predict the V̇O₂peak response in the same population.[15,33]

The overall high prevalence of comorbidities underlines the multifactorial nature of HFpEF. Even subtle impact of ET on these comorbidities might contribute to improved exer-

cise tolerance. We have previously demonstrated that the OptimEx-CLIN population is phenotypically heterogeneous, reflecting a general variation in HFpEF patient characteristics which is seen in all HFpEF studies.[34,35] Training response could certainly vary according to patient phenotype; however, the sample size of the current substudy precludes further subdivision for such an analysis.

Limitations

Our findings need to be interpreted in the light of the following limitations. Sample size calculation for OptimEx-Clin was based on the primary endpoint (change in $\dot{V}O_2$peak at 3 months). Given the sample size and the precision of the measured variables, it is not possible to completely rule out a minor effect of ET on cardiac function, particularly within specific patient subgroups. However, to the best of our knowledge, this study represents the largest investigation to date comparing exercise echocardiography before and after ET in patients with HFpEF. Even in populations with HFrEF or coronary artery disease, available datasets on exercise echocardiography pre- and post-training interventions are notably smaller. We cannot rule out that a longer ET intervention could lead to more favourable effects on cardiac function.

We have pooled the MCT and HIIT training groups to increase statistical power. While neither the main study nor most substudies have demonstrated relevant differences between MCT and HIIT groups,[11,15,29,33,34] in theory, a significant effect in either training modality could be influenced by a neutral effect in the other training modality.

Body habitus of the HFpEF population precluded accurate measurement of PAPs in a subset of patients. RV fractional area change was not measured: image acquisition during exercise was constrained in HFpEF patients with limited exercise tolerance. Anticipating poor RV-focused views in elderly and overweight patients, we prioritized to obtain high-quality TAPSE measurements during the exercise echocardiography assessment. Also, image quality was insufficient for measuring speckle-tracking strain in the majority of patients. We did report the more easily obtained MAPSE and septal S'. These measurements are not as dependent on image quality as the speckle-tracking strain, and they equally reflect longitudinal LV function.[36]

Diagnosis of HFpEF has evolved significantly since the start of the OptimEx-CLIN study in 2014. Diagnostic HFpEF scores did not exist yet, and thus, our inclusion criteria were based on the European Society of Cardiology 2012 guidelines.[37] Nevertheless, we demonstrate in *Table* 1 that the study population has a diagnosis of HFpEF also according to more recent diagnostic scores.

Finally, our study protocol did neither include the measurement of stroke volume, which would have allowed the calcu-

lation of cardiac output, nor simultaneous measurement of $\dot{V}O_2$ and echocardiographic parameters during exercise, which could provide further insight in the discrimination of cardiac versus peripheral limitations of patients with HFpEF, but was not the focus of the current study.[22]

Conclusions

We performed exercise echocardiography in HFpEF patients who were recruited for the OptimEx-Clin study and randomized to ET or guideline control. While LVEF and RV parameters were within normal range at rest, patients were unable to increase RV systolic function during exercise, resulting in impaired RV–vascular coupling. ET increased $\dot{V}O_2$peak after 3 months, whereas only minor changes in diastolic reserve were observed (smaller increase in E/e' during exercise). Furthermore, the E/e' change was not related to the $\dot{V}O_2$peak response. These minor cardiac changes contrast with the important molecular and structural effects of ET in skeletal muscle, which we have previously demonstrated in the same population. As such, the $\dot{V}O_2$peak response to training in HFpEF patients cannot be explained by improved diastolic function or other cardiac changes determined by exercise echocardiography.

Acknowledgements

Conflict of interest statement

Novartis (steering committee, lectures) and Servier outside the submitted work. M. H. reported receiving grants from Novartis and personal fees from Abbott (advisory board), AstraZeneca, Bayer, Berlin Chemie-Menarini, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Novartis, Roche, Sanofi and Pfizer and serves as an advisor for Medical Park SE, Germany, outside the submitted work. E. M. V. C. reported receiving grants from Vifor Pharma outside the submitted work. No other disclosures were reported. C. M. V. D. H. reported receiving personal fees from Abbott, Daiichi-Sankyo, Bayer and Edwards Lifesciences (lectures) outside the submitted work.

Data availability statement

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

Supporting information

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

Table S1: Detailed inclusion and exclusion criteria.
Table S2: Patient characteristics compared to main study population.
Table S3: Resting echocardiography parameters.
Table S4: Regression analysis for variables associated with training response.

References

1. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2023;**81**: 1810-1834.
2. Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, et al. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. *Heart* 2022; **108**:1342-1350. doi:10.1136/heartjnl-2021-319605
3. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur Heart J* 2021;**42**:700-710. doi:10.1093/eurheartj/ehaa943
4. Edwards JJ, O'Driscoll JM. Exercise training in heart failure with preserved and reduced ejection fraction: a systematic review and meta-analysis. *Sports Med-Open* 2022;**8**:76. doi:10.1186/s40798-022-00464-5
5. Edelmann F, Gelbrich G, Düngen H-D, Fröhling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction (Ex-DHF). *J Am Coll Cardiol* 2011;**58**:1780-1791. doi:10.1016/j.jacc.2011.06.054
6. Alves A, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana J, et al. Exercise training improves diastolic function in heart failure patients. *Med Sci Sports Exerc* 2012;**44**:776-785. doi:10.1249/MSS.0b013e31823cd16a
7. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2012;**60**:120-128.
8. Fu T-C, Yang N-I, Wang C-H, Cherng WJ, Chou SL, Pan TL, et al. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. *Am J Phys Med Rehabil* 2016;**95**:15-27. doi:10.1097/PHM.0000000000000312
9. Ha J-W, Andersen OS, Smiseth OA. Diastolic stress test: invasive and noninvasive testing. *JACC Cardiovasc Imaging* 2020;**13**:272-282. doi:10.1016/j.jcmg.2019.01.037
10. Verwerft J, Verbrugge FH, Claessen G, Herbots L, Dendale P, Gevaert AB. Exercise systolic reserve and exercise pulmonary hypertension improve diagnosis of heart failure with preserved ejection fraction. *Front Cardiovasc Med* 2022;**9**:814601. doi:10.3389/fcvm.2022.814601
11. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2021;**325**:542-551. doi:10.1001/jama.2020.26812
12. Suchy C, Massen L, Rognmo O, van Craenenbroeck EM, Beckers P, Kraigher-Krainer E, et al. Optimising exercise training in prevention and treatment of diastolic heart failure (OptimEx-CLIN): rationale and design of a prospective, randomised, controlled trial. *Eur J Prev Cardiol* 2014;**21**:18-25. doi:10.1177/2047487314552764
13. Lancellotti P, Pellikka PA, Budts W, Chaudhry F, Donal E, Dulgheru R, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1191-1229. doi:10.1093/ehjci/jew190
14. Guazzi M, Naeije R, Arena R, Corrà U, Ghio S, Forfia P, et al. Echocardiography

of right wentriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. *Chest* 2015;**148**:226-234. doi:10.1378/chest.14-2065

15. Mueller S, Haller B, Feuerstein A, Winzer EB, Beckers P, Haykowsky MJ, *et al*. Peak O_2-pulse predicts exercise training-induced changes in peak $\dot{V}O_2$ in heart failure with preserved ejection fraction. *ESC Heart Fail* 2022;**9**: 3393-3406. doi:10.1002/ehf2.14070

16. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;**131**:700-708. doi:10.1164/arrd. 1985.131.5.700

17. Corrà U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, *et al*. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:3-15. doi:10.1002/ ejhf.979

18. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, *et al*. Modest increase in peak VO₂ is related to better clinical outcomes in chronic heart failure patients: results from Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training. *Circ Heart Fail* 2012;**5**:579-585. doi:10.1161/ CIRCHEARTFAILURE.111.965186

19. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**: 861-870. doi:10.1161/CIRCULATION AHA.118.034646

20. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, *et al*. How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**:3297-3317. doi:10.1093/eurheartj/ ehz641

21. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, *et al*. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *The Lancet* 2022; **399**:1130-1140. doi:10.1016/S0140-6736(22)00016-2

22. Verwerft J, Bertrand PB, Claessen G, Herbots L, Verbrugge FH. Cardiopulmonary exercise testing with simultaneous echocardiography. *JACC Heart Fail* 2023;**11**:243-249. doi:10.1016/j.jchf. 2022.11.004

23. Guazzi M, Wilhelm M, Halle M, van Craenenbroeck E, Kemps H, de Boer RA, *et al*. Exercise testing in HFpEF: an appraisal through diagnosis, pathophysiology and therapy a clinical consensus statement of the Heart Failure Association (HFA) and European Association of Preventive Cardiology (EAPC) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2022;**24**:1327-1345. doi:10.1002/ejhf.2601

24. Przewlocka-Kosmala M, Butler J, Donal E, Ponikowski P, Kosmala W. Prognostic value of the MAGGIC score, H2FPEF score, and HFA-PEFF algorithm in patients with exertional dyspnea and the incremental value of exercise echocardiography. *J Am Soc Echocardiogr* 2022; **35**:966-975.

25. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular–pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**:3293. doi:10.1093/eurheartj/ehw241

26. Guazzi M, Naeije R. Right heart phenotype in heart failure with preserved ejection fraction. *Circ Heart Fail* 2021;**14**:e007840. doi:10.1161/ CIRCHEARTFAILURE.120.007840

27. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J* 2019;**40**:689-697. doi:10.1093/ eurheartj/ehy809

28. Winzer EB, Augstein A, Schauer A, Mueller S, Fischer-Schaepmann T, Goto K, *et al*. Impact of different training modalities on molecular alterations in skeletal muscle of patients with heart failure with preserved ejection fraction: a substudy of the OptimEx trial. *Circ Heart Fail* 2022;**15**:e009124. doi:10.1161/ CIRCHEARTFAILURE.121.009124

29. Gevaert AB, Böhm B, Hartmann H, Goovaerts I, Stoop T, van de Heyning CM, *et al*. Effect of training on vascular function and repair in heart failure with preserved ejection fraction. *JACC Heart Fail* 2023;**11**:454-464. doi:10.1016/j. jchf.2022.12.011

30. Gevaert AB, Adams V, Bahls M, Bowen TS, Cornelissen V, Dörr M, *et al*. Towards a personalised approach in exercise-based cardiovascular rehabilitation:

how can translational research help? A 'call to action' from the section on secondary prevention and cardiac rehabilitation of the European Association of Preventive Cardiolo. *Eur J Prev Cardiol* 2020;**27**:1369-1385. doi:10.1177/ 2047487319877716

31. de Wilde C, Bekhuis Y, Kuznetsova T, Claes J, Claessen G, Coninx K, *et al*. Personalized remotely guided preventive exercise therapy for a healthy heart (PRIORITY): protocol for an assessor-blinded, multicenter randomized controlled trial. *Front Cardiovasc Med* 2023;**10**:1194693.

32. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. *Circ Heart Fail* 2017;**10**:e004281. doi:10.1161/ CIRCHEARTFAILURE.117.004281

33. Gevaert AB, Witvrouwen I, Van A, van Craenenbroeck EM, Boen J, Van C, *et al*. miR-181c level predicts response to exercise training in patients with heart failure and preserved ejection fraction: an analysis of the OptimEx-Clin trial. *Eur J Prev Cardiol* 2021;**28**:1722-1733. doi:10.1093/eurjpc/zwab151

34. Gevaert AB, Mueller S, Winzer EB, Duvinage A, van de Heyning CM, Pieske-Kraigher E, *et al*. Iron deficiency impacts diastolic function, aerobic exercise capacity, and patient phenotyping in heart failure with preserved ejection fraction: a subanalysis of the OptimEx-Clin study. *Front Physiol* 2022; **12**:757268. doi:10.3389/fphys.2021. 757268

35. Gevaert AB, Tibebu S, Mamas MA, Ravindra NG, Lee SF, Ahmad T, *et al*. Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail* 2021;**8**: 2741-2754. doi:10.1002/ehf2.13344

36. Støylen A, Mølmen HE, Dalen H. Relation between mitral annular plane systolic excursion and global longitudinal strain in normal subjects: the HUNT study. *Echocardiography* 2018;**35**: 603-610. doi:10.1111/echo.13825

37. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012; **33**:1787-1847. doi:10.1093/eurheartj/ ehs104