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ORIGINAL ARTICLE

Peak O_2-pulse predicts exercise training-induced changes in peak $\dot{V}O_2$ in heart failure with preserved ejection fraction

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Abstract **Aims** Exercise training (ET) has been consistently shown to increase peak oxygen consumption ($\dot{V}O_2$) in patients with heart failure with preserved ejection fraction (HFpEF); however, inter-individual responses vary significantly. Because it is unlikely that ET-induced improvements in peak $\dot{V}O_2$ are significantly mediated by an increase in peak heart rate (HR), we aimed to investigate whether baseline peak O_2-pulse ($\dot{V}O_2 \times HR^{-1}$, reflecting the product of stroke volume and arteriovenous oxygen difference), not baseline peak $\dot{V}O_2$, is inversely associated with the change in peak $\dot{V}O_2$ (adjusted by body weight) following ET versus guideline control (CON) in patients with HFpEF.

Methods and results This was a secondary analysis of the OptimEx-Clin (Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure, NCT02078947) trial, including all 158 patients with complete baseline and 3 month cardiopulmonary exercise testing measurements (106 ET, 52 CON). Change in peak $\dot{V}O_2$ (%) was analysed as a function of baseline peak $\dot{V}O_2$ and its determinants (absolute peak $\dot{V}O_2$, peak O_2-pulse, peak HR, weight, haemoglobin) using robust linear regression analyses. Mediating effects on change in peak $\dot{V}O_2$ through changes in peak O_2-pulse, peak HR and weight were analysed by a causal mediation analysis with multiple correlated mediators. Change in submaximal exercise tolerance ($\dot{V}O_2$ at the ventilatory threshold, VT1) was analysed as a secondary endpoint. Among 158 patients with HFpEF (66% female; mean age, 70 ± 8 years), changes in peak O_2-pulse explained approximately 72% of the difference in changes in peak $\dot{V}O_2$ between ET and CON [10.0% (95% CI, 4.1 to 15.9), $P = 0.001$]. There was a significant interaction between the groups for the influence of baseline peak O_2-pulse on change in peak $\dot{V}O_2$ (interaction $P = 0.04$). In the ET group, every 1 mL/beat higher baseline peak O_2-pulse was associated with a decreased mean change in peak $\dot{V}O_2$ of −1.45% (95% CI, −2.30 to −0.60, $P = 0.001$) compared with a mean change of −0.08% (95% CI, −1.11 to 0.96, $P = 0.88$) following CON. None of the other factors showed significant interactions with study groups for the change in peak $\dot{V}O_2$ ($P > 0.05$). Change in $\dot{V}O_2$ at VT1 was not associated with any of the investigated factors ($P > 0.05$).

Conclusions In patients with HFpEF, the easily measurable peak O_2-pulse seems to be a good indicator of the potential for improving peak $\dot{V}O_2$ through exercise training. While changes in submaximal exercise tolerance were independent of baseline peak O_2-pulse, patients with high O_2-pulse may need to use additional therapies to significantly increase peak $\dot{V}O_2$.

Keywords Endurance training; Exercise test; Precision medicine; Regression analysis; Oxygen pulse; Responder

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Introduction

Exercise training (ET) has a Class I recommendation for patients with heart failure with preserved ejection fraction (HFpEF).[1] While pharmacological trials, except for the recently published EMPEROR-HF trial,[2] have been overall unsuccessful,[3] ET has been shown to reduce exercise intolerance—the hallmark symptom in HFpEF—as measured by increased peak oxygen consumption ($\dot{V}O_2$).[4,5] However, as for any given treatment, ET is associated with a certain response heterogeneity with some patients showing better responses than others despite exercising to a similar extent. Heterogeneous responses to therapies led to the concept of personalized medicine which requires the identification of factors associated with treatment effects. This is especially important in HFpEF, as it is known to be a multifactorial and highly heterogeneous disease with several co-existing co-morbidities[6,7] and patients are almost exclusively suffering from multiple defects affecting the convective and diffusive oxygen delivery and utilization.[8] In addition to abnormal active relaxation and increased passive stiffness (i.e. diastolic dysfunction) resulting in a blunted stroke volume (SV) response during exercise,[9] a high prevalence of chronotropic incompetence, which is considered as the most relevant haemodynamic limitation in HFpEF,[10] further limits the cardiac output response to incremental exercise. On the other hand, emerging data suggest that abnormalities in extracardiac factors such as haemoglobin concentration, alveolar ventilation, lung or muscle diffusion capacity, or mitochondrial respiration, which lead to a reduced arteriovenous oxygen content difference [$C(a\text{-}v)O_2$], play a significantly greater role in HFpEF compared with heart failure with reduced ejection fraction (HFrEF).[8,11,12]

It is generally assumed that individuals with a lower baseline peak $\dot{V}O_2$ have a higher potential to benefit from ET; however, this could not be confirmed in a recent meta-analysis in patients with heart failure.[13] According to the Fick Principle, $\dot{V}O_2$ is the product of heart rate (HR), SV, and $C(a\text{-}v)O_2$, and therefore, the increase in peak $\dot{V}O_2$ following ET is mediated through an increase in any or a combination of these variables. Peak HR is known to be highly dependent upon age but not significantly different between trained and sedentary individuals.[14] Accordingly, a meta-analysis from trials in healthy middle aged and older adults[15] revealed that endurance ET did not significantly improve peak HR and that the improved peak $\dot{V}O_2$ was related to significant changes in both peak SV and peak $C(a\text{-}v)O_2$. During cardiopulmonary exercise testing (CPET), the product of SV and $C(a\text{-}v)O_2$ can be indirectly obtained as O_2-pulse [$\dot{V}O_2 \times HR^{-1} = SV \times C(a\text{-}v)O_2$].

Even though peak HR, SV and $C(a\text{-}v)O_2$ can all be significantly reduced in patients with HFpEF, limited evidence suggests that the ET-induced improvements in peak $\dot{V}O_2$ are mainly due to increases in $C(a\text{-}v)O_2$,[16,17] whereas most studies did not show increases in either peak HR (7/9 studies)[5,16,18–24] or peak SV (2/2 studies).[16,17] Based on these findings and the concept of a higher potential for improvement when starting with a lower baseline, the hypothesis of this study was that baseline peak O_2-pulse—not baseline peak $\dot{V}O_2$—is inversely associated with the ET-induced change in peak $\dot{V}O_2$ following 3 months of supervised ET compared with guideline control (CON).

Methods

Study setting

This study is a secondary analysis of the initial 3 month supervised period of the OptimEx-Clin (Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure) trial—a prospective, randomized, controlled, multicentre-trial investigating the effects of high-intensity interval training (HIIT), moderate continuous training (MCT) and CON in 180 sedentary patients with stable HFpEF (New York Heart Association Class II-III; left ventricular ejection fraction ≥50%; elevated estimated LV filling pressure [E/e' medial ≥15] or E/e' medial ≥8 with elevated natriuretic peptides [NT-proBNP ≥ 220 pg/mL or BNP ≥ 80 pg/mL]).[25] The study design[26] and the main results of the trial[5] have been published before.

In brief, participants were randomly assigned to HIIT (3 × 38 min/week with 4 × 4-min intervals at 80–90% of heart rate reserve), MCT (5 × 40 min/week at 35–50% heart rate reserve) and CON (one-time advice on physical activity). All patients were assessed at baseline and 3 months after randomization. CPET was performed on bicycle ergometers (starting at 20 watts, increasing by 10 watts per minute) and analysed at the study core lab in Munich, blinded to treatment arm assignment. Peak $\dot{V}O_2$ was defined as the highest 30 s average within the last minute of exercise.[27] Peak HR and peak O_2-pulse were defined as the 30 s average derived from the

same time span as peak $\dot{V}O_2$. $\dot{V}O_2$ at the first ventilatory threshold (VT1), a measure of submaximal exercise tolerance, was determined by the V-slope method.[28] The study was approved by the local ethic committees at all participating sites and conforms with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

As the current research question did not aim at differences between HIIT and MCT, the results of the main analysis were not significantly different between both modes,[5] and the required sample size to identify covariate–treatment interactions is substantially higher than for comparing group means,[29] the main analyses were performed with one ET group (combination of HIIT and MCT) versus CON. Only patients with complete paired baseline and 3 month follow-up CPET measurements were included.

Statistical analyses

The primary endpoint in the present analysis was the change in relative peak $\dot{V}O_2$ (mL/kg/min). The change in relative $\dot{V}O_2$ at VT1 (mL/kg/min) was analysed as a secondary endpoint. To ensure comparability in the evaluation of individual responses between single subjects with varying baseline values, all changes are expressed as %-change from baseline to 3 month follow-up. Next to baseline peak O_2-pulse, relative peak $\dot{V}O_2$ and its other determinants (absolute peak $\dot{V}O_2$, peak HR, weight, and haemoglobin as one of the determinants of C(a-v)O_2) were examined. Group means were compared with *t*-tests for independent means. For comparisons of ordinal data, the Mann–Whitney *U*-test was used. To determine the proportions of change in relative peak $\dot{V}O_2$ that can be explained by the changes in peak O_2-pulse, peak HR and weight, a causal mediation analysis with multiple correlated mediators[30] was performed (R library 'multimediate'[31]). Furthermore, the relationships between changes in relative peak $\dot{V}O_2$, changes in peak HR, changes in peak O_2-pulse and changes in weight were analysed. The impact of baseline peak $\dot{V}O_2$ and its determinants on the change in relative peak $\dot{V}O_2$ was assessed using linear regression models with main effects of the independent variable and group as well as their interaction term (group × independent variable). These analyses were performed using robust linear regressions with MM-type estimators (function 'rlm' in R library 'MASS'[32] and function 'f.robftest' in R library 'sfsmisc'[33]). This method uses an iteratively reweighted least-squares procedure fitting bisquare estimators that is insensitive to influential data points and remains highly efficient (in comparison to ordinary least square estimates) in case of no outliers.[34] Analyses of the primary endpoint were performed in a complete data set (including all patients with valid assessments of the variables of interest) and a per-protocol set (excluding patients randomized to ET with adherence of <70% to the scheduled exercise sessions). Furthermore, we performed a sensitivity analysis within the original groups (HIIT vs. MCT vs. CON). Global interaction *p*-values were calculated using the function 'lmrob' with the recommended setting 'KS2014' in R library 'robustbase'.[35] All statistical analyses were performed using R Statistical Software (Version 3.6.1, Foundation for Statistical Computing, Vienna, Austria)[36] with local significant levels of $\alpha = 0.05$. As a secondary analysis, the results presented in this manuscript should be interpreted as exploratory.

Results

All 158 patients [106 (ET) vs. 52 (CON); 66% women; mean age of 70 ± 8 years; *Table 1*] with complete CPET data at follow-up were included in this sub-study (*Figure 1*). Due to indeterminable VT1, analyses including this endpoint were performed on all 154 patients with determinable VT1 at baseline and follow-up [104 (ET) vs. 50 (CON)]. The per-protocol set of ET patients included 87 individuals who performed at least 70% of the prescribed exercise sessions.

Comparison of mean changes

Relative peak $\dot{V}O_2$ increased by 8.0 ± 15.7% in the ET group compared with a reduction of −2.0 ± 18.3% in the CON group. Mean changes were significantly different between ET and CON for relative peak $\dot{V}O_2$, absolute peak $\dot{V}O_2$, peak O_2-pulse and weight ($P < 0.05$), while no significant differences have been observed for the change in peak HR, haemoglobin (*Figure 2*, *Table 2*) or the levels of exhaustion as measured by peak respiratory exchange ratio (RER) (*Table 2*). Mean change in relative $\dot{V}O_2$ at VT1 was significantly different between groups ($P = 0.03$; *Table 2*). The difference in change in relative peak $\dot{V}O_2$ between groups was primary mediated by changes in peak O_2-pulse (~72%), while changes in peak HR and weight accounted for approximately 18% and 10%, respectively. From baseline to follow-up, the beta-blocker dosage was changed in 14 patients with an increase in two patients randomized to ET (none in CON) and a decrease in 10 ET and 2 CON patients ($P = 0.13$). When these patients were excluded, the difference in mean change in peak HR between groups diminished to 0.3% (95% CI, −3.5 to 4.1, $P = 0.89$), whereas the mean changes in peak $\dot{V}O_2$, peak O_2-pulse, and weight remained significantly different between the groups (data not shown). In this subset, change in peak O_2-pulse accounted for approximately 88% of the difference in change in relative peak $\dot{V}O_2$ between groups.

Table 1 Demographic and clinical characteristics at baseline

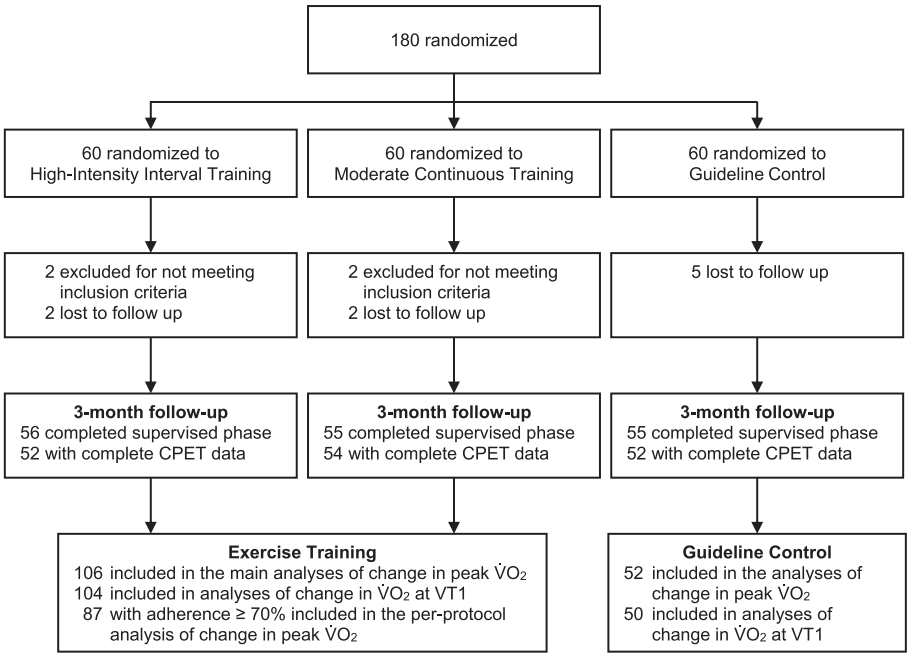
	Exercise (N = 106)	Guideline control (N = 52)
Sex		
Female	70 (66%)	34 (65%)
Male	36 (34%)	18 (35%)
Age, years	70 (7)	69 (10)
Weight, kg	84.6 ± 18.0	78.7 ± 15.2
Body mass index, kg/m^2	30.6 ± 6.1	29.0 ± 4.9
Resting heart rate, min	65 ± 11	65 ± 11
Blood pressure, mmHg		
Systolic	128 ± 13	127 ± 15
Diastolic	74 ± 10	74 ± 10
Cardiovascular risk factors		
Hypertension	90 (85%)	46 (88%)
Diabetes	30 (28%)	12 (23%)
Dyslipidaemia	74 (70%)	40 (77%)
Smoking		
Never smoked	55 (52%)	30 (58%)
Ex-smoker	45 (42%)	21 (40%)
Current Smoker	6 (6%)	1 (2%)
Sleep apnoea	19 (18%)	9 (17%)
Severity of HFpEF		
New York Heart Association class		
II	80 (75%)	35 (67%)
III	26 (25%)	17 (33%)
E/e' average, [no.]	13.4 ± 3.4 [103]	13.3 ± 4.7 [49]
E/A, [no.]	1.23 ± 0.65 [88]	1.20 ± 0.62 [46]
NT-proBNP, pg/mL, [no.]	321 (161–689) [102]	341 (175–622) [52]
Haemoglobin, mg/dL, [no.]	13.6 ± 1.6 [103]	13.2 ± 1.4 [52]
Other cardiac diagnoses		
Coronary artery disease	29 (27%)	16 (31%)
Atrial fibrillation		
Paroxysmal	13 (12%)	7 (13%)
Persistent	8 (8%)	3 (6%)
Permanent	10 (9%)	2 (4%)
Heart failure medication		
Beta-blocker	68 (64%)	37 (71%)
Thiazide/loop diuretics	60 (57%)	31 (60%)
Angiotensin receptor blocker	44 (42%)	21 (40%)
Angiotensin-converting enzyme inhibitor	36 (34%)	16 (31%)
Aldosterone antagonists	12 (11%)	5 (10%)
Cardiopulmonary exercise testing parameters		
Peak oxygen consumption, mL/kg/min	18.5 ± 5.1	19.5 ± 5.8
Peak oxygen pulse, mL/beat	12.7 ± 3.5	12.9 ± 4.0
Peak heart rate, b.p.m.	123 ± 26	121 ± 28
Peak respiratory exchange ratio	1.11 ± 0.09	1.10 ± 0.13

Values are expressed as mean ± SD, median (inter-quartile range) or absolute values (percentage). E, peak velocity blood flow from ventricular relaxation in early diastole; e', mitral annular early diastolic velocity; A, peak velocity flow in late diastole caused by atrial contraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; pg = picogram.

Covariate-treatment interactions

The influence of baseline peak O_2-pulse (in mL/beat) on change in relative peak $\dot{V}O_2$ was significantly higher following ET compared with CON (interaction P = 0.04; *Figure 3A*). In the ET group, every 1 mL/beat higher baseline peak O_2-pulse was associated with a decreased mean change in relative peak $\dot{V}O_2$ of −1.45% (95% CI, −2.30 to −0.60, P = 0.001). In contrast, the change in relative peak $\dot{V}O_2$ following CON was not dependent on baseline peak O_2-pulse [β-coefficient: −0.08% (95% CI, −1.11 to 0.96), P = 0.88]. After adjustment for sex, age, and baseline weight, this difference remained significant [ET: −1.89% (95% CI, −2.84 to −0.94); CON: −0.42% (95% CI, −1.77 to 0.62); interaction P = 0.049]. The interaction between baseline peak O_2-pulse and group on change in peak $\dot{V}O_2$ may also depend on baseline peak RER with a higher difference between groups in patients with peak RER > 1.10 (Supporting Information, *Figure S1*). No significant interactions on change in relative peak $\dot{V}O_2$ were found between groups and relative peak $\dot{V}O_2$, absolute peak $\dot{V}O_2$, peak HR, weight, and haemoglobin (interaction $P > 0.05$; *Figure 3*, *Table 3*). None of these factors was significantly associated with the change in relative $\dot{V}O_2$ at VT1 in either group (Supporting Information, *Table S1*; *Figure S2*). The influence of baseline peak O_2-pulse on change in relative peak $\dot{V}O_2$ was similar in HIIT and MCT; however, neither peak O_2-pulse (interaction P = 0.15) nor any of the other factors showed a significant interaction with the original study

Figure 1 Study flow chart. Among 180 randomized patients, this study included all 158 patients with complete paired baseline and 3 month follow-up cardiopulmonary exercise testing measurements. For the main analyses, high-intensity interval training and moderate continuous training were combined to one exercise training group. A complete CONSORT flow chart of the study has been published previously.[5] CPET, cardiopulmonary exercise testing; $\dot{V}O_2$, oxygen consumption; VT1, ventilatory threshold.



groups (HIIT, MCT, and CON) on the change in relative peak $\dot{V}O_2$ (Supporting Information, *Table S2*; *Figure S3*). Results of the per-protocol analysis were similar to the main results (*Table 3*; Supporting Information, *Figure S4*). Following ET, every 1 mL/beat higher baseline peak O_2-pulse was associated with a decreased mean change in relative peak $\dot{V}O_2$ of −1.88% (95% CI, −2.79 to −0.97, $P < 0.001$; interaction $P = 0.01$). Accordingly, the mean difference in change in relative peak $\dot{V}O_2$ between a patient who attended at least 70% of ET sessions and a patient randomized to CON was 20.5% for a baseline peak O_2-pulse of 8.6 mL/beat (10th percentile), and 3.7% for a baseline peak O_2-pulse of 17.9 mL/beat (90th percentile).

Associations between changes in peak $\dot{V}O_2$ and its determinants

In the overall sample, changes in relative peak $\dot{V}O_2$ were positively correlated with changes in peak O_2-pulse and peak HR and negatively correlated with weight ($P < 0.001$). Furthermore, the changes in peak O_2-pulse were negatively correlated with the changes in peak HR ($P < 0.001$). Changes in weight were not significantly correlated with either changes in peak HR nor changes in peak O_2-pulse ($P > 0.45$). A correlation matrix is shown in Supporting Information, *Figure S5*. None of these associations were significantly different between ET and CON (interaction $P > 0.05$; Supporting Information, *Table S3*).

Discussion

This is the first study to examine potential predictors of inter-individual response variability in relative peak $\dot{V}O_2$ following ET versus CON in HFpEF and, to the best of our knowledge, the first study to examine the effects of baseline peak O_2-pulse on the change in peak $\dot{V}O_2$ following ET in any population. The main finding of this study (confirming the primary hypothesis) is that in patients randomized to ET, lower baseline peak O_2-pulse was associated with a larger improvement in relative peak $\dot{V}O_2$, whereas no such association was found in CON patients. This difference between ET and CON remained significant after adjusting for sex, age and baseline weight, and increased after excluding ET-patients with an adherence lower than 70%. Furthermore, the predictive effect of baseline O_2-pulse seemed to be independent of the exercise mode (HIIT and MCT).

Figure 2 Change in relative peak $\dot{V}O_2$ and its determinants. Differences in individual changes (circles) plus mean and 95% confidence intervals (lines) of relative peak $\dot{V}O_2$ (A), absolute peak $\dot{V}O_2$ (B), O_2-pulse (C), peak heart rate (D), weight (E) and haemoglobin (F) between exercise training and guideline control.

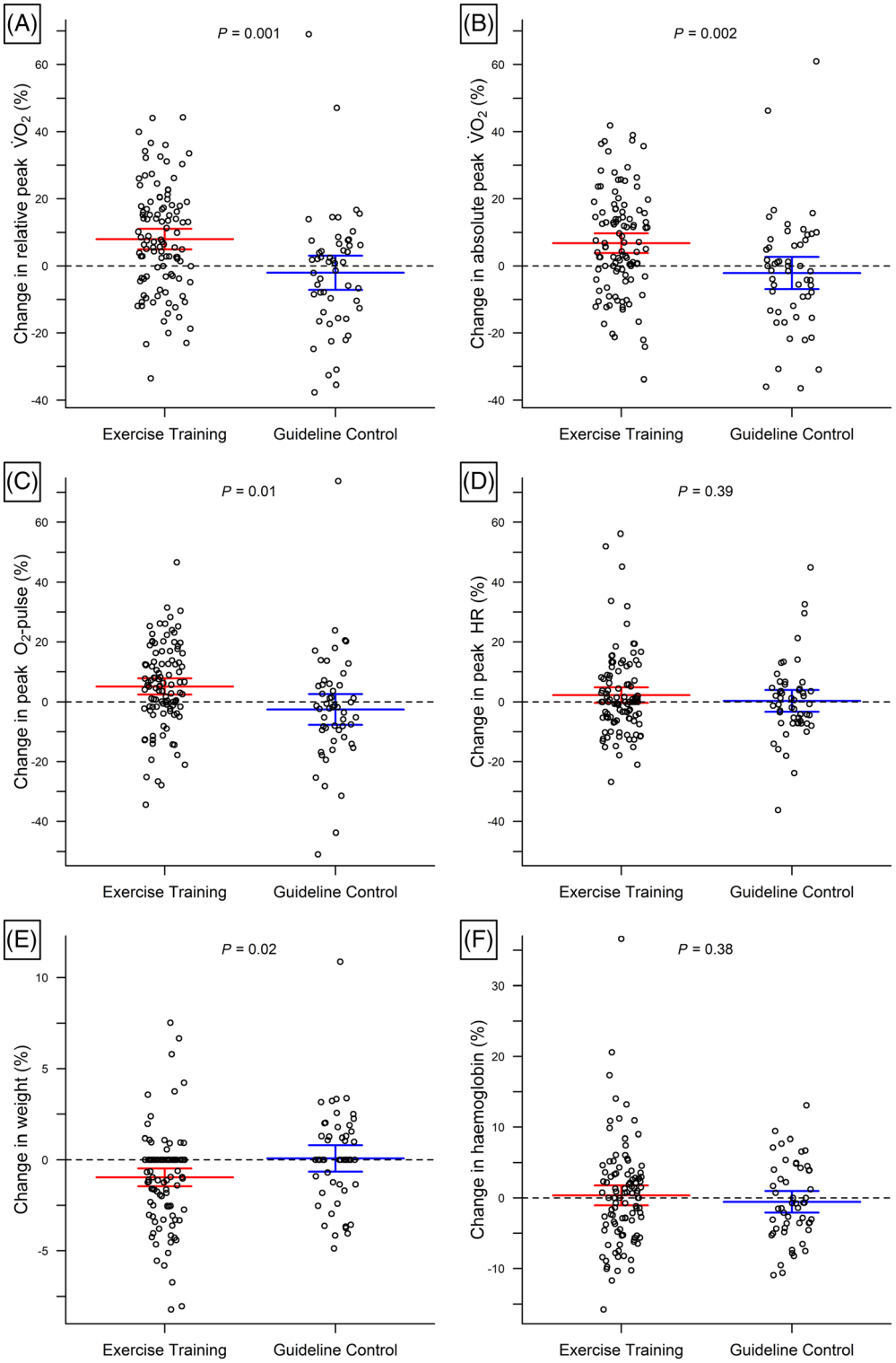


Table 2 Mean changes following exercise training and guideline control

	Mean ± SD						
	Exercise training [*N* = 106]*			Guideline control [*N* = 52]*			
	Baseline	3 months	Change	Baseline	3 months	Change	Difference (95% CI), *P*-value
Relative peak $\dot{V}O_2$, mL/kg/min	18.5 ± 5.1	19.8 ± 5.7	8.0 ± 15.7%	19.5 ± 5.8	18.9 ± 5.7	−2.0 ± 18.3%	10.0% (4.1 to 15.9), *P* = 0.001
Absolute peak $\dot{V}O_2$, mL/min	1,528 ± 447	1,617 ± 465	6.8 ± 15.2%	1,519 ± 488	1,475 ± 485	−2.1 ± 17.3%	8.9% (3.3 to 14.5), *P* = 0.002
Peak O_2-pulse, mL/beat	12.7 ± 3.5	13.2 ± 3.1	5.1 ± 13.9%	12.9 ± 4.0	12.5 ± 4.3	−2.5 ± 18.5%	7.7% (1.9 to 13.4), *P* = 0.01
Peak heart rate, b.p.m.	123 ± 26	124 ± 25	2.3 ± 13.5%	121 ± 28	121 ± 30	0.3 ± 13.1%	2.6% (−2.5 to 6.4), *P* = 0.39
Weight, kg	84.6 ± 18.0	83.8 ± 18.1	−1.0 ± 2.6%	78.7 ± 15.2	78.8 ± 15.6	0.1 ± 2.6%	−1.0% (−1.9 to −0.2), *P* = 0.02
Haemoglobin, g/dL*	13.6 ± 1.6	13.6 ± 1.4	0.4 ± 7.2%	13.2 ± 1.4	13.1 ± 1.4	−0.6 ± 5.5%	0.9% (−1.1 to 3.0), *P* = 0.38
Relative $\dot{V}O_2$ at VT1, mL/kg/min*	11.1 ± 3.1	11.9 ± 3.1	9.4 ± 16.5%	11.5 ± 2.9	11.4 ± 2.6	2.0 ± 21.3%	7.4% (2.0 to 14.2), *P* = 0.03
Peak Respiratory Exchange Ratio	1.11 ± 0.09	1.10 ± 0.13	−1.0 ± 5.9%	1.10 ± 0.09	1.11 ± 0.12	0.9 ± 11.0%	−0.1% (−5.2 to 1.3), *P* = 0.24

*Different *N* (due to missing values) for the analyses including haemoglobin (exercise training: 103; guideline control: 52) and VT1 (exercise training: 104; guideline control: 50). $\dot{V}O_2O_2$, oxygen consumption; VT1, ventilatory threshold.

O_2-pulse is the fraction of $\dot{V}O_2$ and HR; therefore, low peak O_2-pulse can be caused by either low peak $\dot{V}O_2$, high peak HR or a combination of both. Nevertheless, the association of baseline peak $\dot{V}O_2$ (absolute or adjusted to body weight) with the change in relative peak $\dot{V}O_2$ was not significantly different between groups, confirming the results of a recent meta-analysis in heart failure.[13] When adjusted to body weight, we observed an almost parallel decline in change in peak $\dot{V}O_2$ with increasing baseline peak $\dot{V}O_2$ in both groups. Accordingly, the baseline level of relative peak $\dot{V}O_2$ may only be a prognostic marker for its change in patients with HFpEF, with differences between ET and CON being similar for different base levels. In a cohort study including 120 patients with heart failure with reduced ejection fraction,[37] it has already been shown that the severity of chronotropic incompetence may be associated with an impaired response to ET. However, in the present trial, peak HR alone was not a significant predictor of the ET-induced changes in relative peak $\dot{V}O_2$. Alternatively, a high O_2-pulse can also be defined as a high SV and/or C(a-v)O_2. Accordingly, a higher peak O_2-pulse at baseline is accompanied with a lower reserve to increase peak SV and/or C(a-v)O_2—the components of peak $\dot{V}O_2$ that are most likely to improve following ET.[15] This interpretation is supported by the results after splitting the sample based on baseline peak RER. While a peak RER ≥1.10 is considered excellent effort and maximal exhaustion,[38] patients with a lower peak RER could have stopped for other reasons (e.g. low motivation or musculoskeletal complaints), which seems to reduce the predictive power of baseline peak O_2-pulse for ET-induced changes in peak $\dot{V}O_2$ in this subgroup. On the other hand, patients with a low peak O_2-pulse despite high volitional effort are very likely to be truly limited by their ability to increase SV and/or C(a-v)O_2. Therefore, in addition to the results of the per-protocol analysis, the higher difference between groups in patients with peak RER ≥ 1.10 strengthens the assumption of a true association between baseline peak O_2-pulse and change in peak $\dot{V}O_2$ through ET. Consequently, the change in peak O_2-pulse was also the primary mediator for the change in relative peak $\dot{V}O_2$ following ET in this study. Importantly, the predictive power of baseline peak O_2-pulse did not apply to the change of $\dot{V}O_2$ at VT1. Instead, patients were able to equally improve their functional capacity through exercise training irrespective of baseline peak O_2-pulse. This may be explained by the fact that peak O_2-pulse is not a determinant of $\dot{V}O_2$ at VT1. Furthermore, the extent to which ET-induced changes in $\dot{V}O_2$ at VT1 are mediated by changes in HR, SV and C(a-v)O_2 is less well investigated.

To date, only two studies have examined the effects of ET versus CON on SV and C(a-v)O_2 in HFpEF.[16,17] In a non-randomized study, Fu *et al.*[16] found a significant improvement in peak $\dot{V}O_2$ after 12 weeks of HIIT compared with CON (*n* = 60) along with significant improvements in peak C(a-v)O_2 and without significant changes in either peak SV or

Figure 3 Predictors of change in relative $\dot{V}O_2$. Relationships between changes in relative peak $\dot{V}O_2$ and baseline peak O_2-pulse (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak $\dot{V}O_2$ at baseline (C), baseline peak heart rate (D), baseline weight (E), and baseline haemoglobin (F). Individual relationships and robust linear regression lines and 95% confidence bands are shown separately for exercise training (– △ –) and guideline control (—○—). Black dashed lines (– – –) represent null lines.

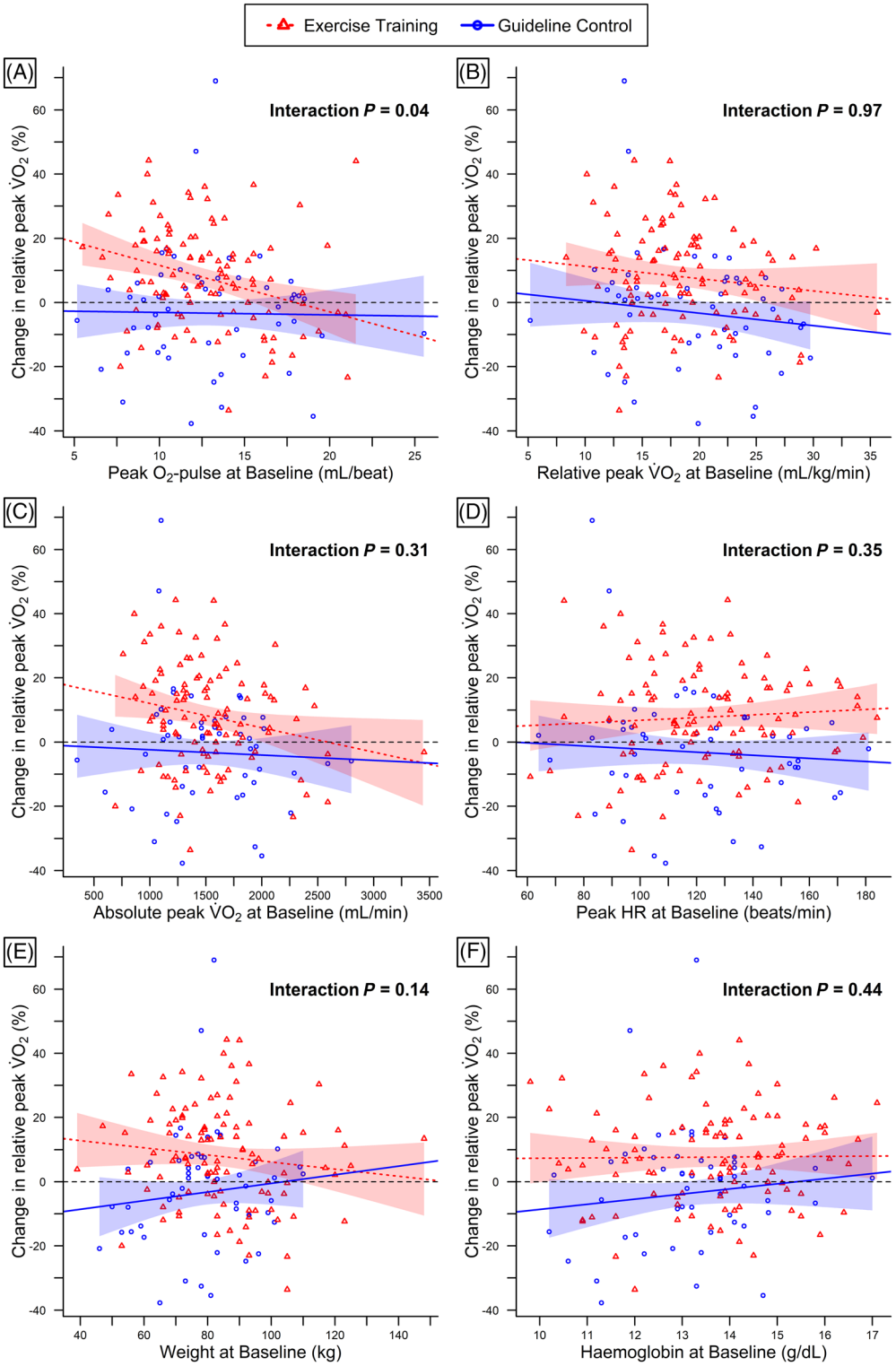


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Table 3 Results of the predictor analyses for the inter-individual response variability in peak $\dot{V}O_2$ for the main and per protocol analysis

	Mean change in relative peak $\dot{V}O_2$ [β-coefficient (95% CI), *P*-value]			Interaction *P* for exercise training vs. guideline control	
	Exercise training				
	Complete set [*N* = 106]*	Per protocol set [*N* = 87]*	Guideline control [*N* = 52]*	Main analysis	Per protocol analysis
Peak O_2-pulse (per 1 mL/beat)	−1.45% (−2.30 to −0.60), *P* = 0.001	−1.88% (−2.79 to −0.97), *P* < 0.001	−0.08% (−1.11 to 0.96), *P* = 0.88	0.04	0.01
Peak $\dot{V}O_2$ (per 1 mL/kg/min)	−0.38% (−0.99 to 0.22), *P* = 0.17	−0.26% (−0.98 to 0.45), *P* = 0.47	−0.39% (−1.10 to 0.32), *P* = 0.28	0.97	0.78
Peak $\dot{V}O_2$ (per 100 mL/min)	−0.76% (−1.45 to 0.07), *P* = 0.03	−0.74% (−1.51 to 0.02), *P* = 0.06	−0.17% (−1.03 to 0.69), *P* = 0.70	0.31	0.34
Peak heart rate (per 10 b.p.m.)	0.42% (−0.79 to 1.63), *P* = 0.50	0.74% (−0.57 to 2.06), *P* = 0.27	−0.48% (−1.96 to 0.99), *P* = 0.52	0.35	0.22
Weight (per 10 kg)	−1.11% (−2.84 to 0.63), *P* = 0.21	−2.04% (−4.15 to 0.08), *P* = 0.06	1.35% (−1.35 to 4.05), *P* = 0.32	0.14	0.054
Haemoglobin (per 1 mg/dL)*	0.10% (−1.81 to 2.00), *P* = 0.92	0.21% (−1.91 to 2.33), *P* = 0.85	1.60% (−1.46 to 4.65), *P* = 0.30	0.44	0.49

*Different *N* for the analyses including haemoglobin (exercise training complete set: 103; exercise training per-protocol set: 84; guideline control: 52). $\dot{V}O_2$, oxygen consumption.

peak HR. In a secondary analysis of the randomized controlled PARIS study (*n* = 40), Haykowsky *et al*.[17] showed that the improvement in peak $\dot{V}O_2$ following ET was due to significant increases in peak HR and peak C(a-v)O_2. However, despite the significant increase in peak HR, only 16% of the training related improvement in peak $\dot{V}O_2$ was attributed to an improved cardiac output. While changes in peak HR were not significantly different between the groups in most ET trials in HFpEF,[5,16,19–22] significant improvements as observed in two trials[23,24] could also be influenced by factors not directly related to ET, that is, changes in levels of exhaustion or changes in HR-affecting medications (e.g. beta-blockers). For instance, patients randomized to the ET group of the PARIS study[23] had a significantly higher change in peak HR compared with CON (+4 vs. −7 b.p.m.); however, the results for peak systolic blood pressure (+1 mmHg vs. −10 mmHg, *P* = 0.04), and peak RER (+0.03 vs. −0.02, *P* = 0.07) indicate that different levels of exhaustion between groups may have contributed to the significant difference in peak HR. In the present trial, changes in beta-blocker dosage were more common in the ET group (11.3%) compared with CON (3.8%) and when these patients were excluded, the difference in change in peak HR between groups diminished from 1.9% to 0.3% (both $P > 0.05$).

The evidence that ET-related improvements in peak $\dot{V}O_2$ are most likely mediated through increases in peak C(a-v)O_2 may also explain the overall positive effects of ET in patients with HFpEF as C(a-v)O_2 has been shown to be reduced in 75% and being the leading cause of exercise intolerance in 40% of patients with HFpEF.[12] Furthermore, it has been shown that a normalization of impaired muscle oxygen diffusion would result in a significantly larger improvement in peak $\dot{V}O_2$ than a normalization of convective oxygen delivery.[8,12] Due to interactions between the components of the Fick equation, Houstis *et al*.[8] demonstrated that doubling a patient's cardiac output would lead to a decrease in C(a-v)O_2 of 45%, and thus, peak $\dot{V}O_2$ would increase by only 10%. On the other hand, normalization of the 36% deficit in skeletal muscle oxygen diffusion that was observed in their study led to a predicted improvement in peak $\dot{V}O_2$ of 27%. Similarly, the results of the present trial show that a change in peak HR (independent of groups assignment) was not associated with an equivalent change in relative peak $\dot{V}O_2$ (a 10% increase in peak HR was associated with ~6.4% increase in peak $\dot{V}O_2$), which is likely to be explained by a reduced SV (shortening the time of the diastole) and a reduced C(a-v)O_2 (reducing the contact time in the muscle).

Future implications

The results of this exploratory analysis implicate that patients with HFpEF and high O_2-pulse may not be able to significantly improve their peak $\dot{V}O_2$ by performing regular ET. Although

we still highly recommend regular ET for patients with HFpEF and high O_2-pulse to reduce the decline in peak $\dot{V}O_2$ with ageing and disease progression and to improve parameters beyond peak $\dot{V}O_2$ (e.g. $\dot{V}O_2$ at VT1), it should probably be supplemented by additional therapies if the intention is to increase maximal exercise tolerance.

Despite lacking evidence for its benefits in HFpEF, most patients were treated with beta-blockers (66% in the present trial). This proportion is likely to be decreasing, as the effects of a long-term administration of beta-blockers in hypertension, stable coronary artery disease or atrial fibrillation (common co-morbidities in HFpEF) are questioned and some studies led to the concern that beta-blockers may be even deleterious in HFpEF.[39] By increasing the duration of diastole, a reduced HR may allow a better left ventricular filling; however, it may also impair the cardiac output response to exercise[40] and according to the results of the present analysis may contribute to a blunted ET response by its effect on peak O_2-pulse. Indeed, a recently published trial investigating the effects of beta-blocker withdrawal in HFpEF[41] has shown a significant short-term increase in peak HR (~31%) and peak $\dot{V}O_2$ (~17%). However, further research is necessary to show whether interventions to increase peak HR in patients with HFpEF (e.g. by reducing beta-blockers or rate-adaptive pacing[42]) have a positive long-term effect on clinical outcomes and exercise capacity.

Interestingly, we also found a trend towards lower ET-induced changes in relative peak $\dot{V}O_2$ for patients with higher body weight at baseline (P = 0.14 in the full analysis, P = 0.054 in the per-protocol analysis). Whether patients with HFpEF and higher baseline weight benefit less from exercise training or especially HIIT (see Supporting Information, *Figure S3E*) should be investigated in future studies. Nevertheless, the results of the present study underscore the need for additional trials that specifically target weight loss in HFpEF. As most patients with HFpEF are overweight or obese (85% in the present trial), losing weight, which has a disproportionate impact on relative peak $\dot{V}O_2$ (a weight loss of 20% leads to an increase in relative peak $\dot{V}O_2$ of 25%), is another important option to increase exercise tolerance in HFpEF that has been largely ignored so far. To date, in the only lifestyle intervention trial targeting weight loss in patients with HFpEF (N = 100; mean BMI, 39.3 kg/m^2),[21] ET and caloric restriction resulted in similar and additive changes in relative peak $\dot{V}O_2$ (main effect of ET: 1.2 mL/kg/min vs. diet: 1.3 mL/kg/min; joint effect: 2.5 mL/kg/min) by significantly improving absolute peak $\dot{V}O_2$ (ET) and reducing weight (ET and caloric restriction).

A combination of treatments targeting several deficits may overcome the interaction effects between the determinants of peak $\dot{V}O_2$ and will likely have a disproportionate impact compared with the correction of a single deficit.[8] For example, based on the interaction with SV and C(a-v)O_2, that is, O_2-pulse, increasing peak HR will possibly not only have a direct effect on peak $\dot{V}O_2$,[41] but also enhance the potential for improving peak $\dot{V}O_2$ following ET in patients with high O_2-pulse.

Methodological aspects, strengths, and limitations

This study has several strengths and limitations. The individual pre-post change in peak $\dot{V}O_2$ can be divided into a 'true' change depending on the intervention, a 'true' change which is independent of the intervention (e.g. ageing), and a change due to random errors which is also independent of group assignment (e.g. measurement errors, day-to-day variability, different levels of exhaustion during the CPETs at baseline and follow-up).[29] Therefore, to examine predictors of the ET-induced response variability (instead of prognostic factors that are independent of the intervention and possibly influenced by regression to the mean) it is mandatory to include a comparator arm, which, however, has not been performed in many previous studies. Furthermore, the dependent and all independent parameters were analysed as continuous variables, which has several advantages over arbitrary categorization (e.g. retaining higher power and avoiding misclassification due to random errors).

Despite these strengths, the original trial was designed to detect differences between group means and therefore, methods to further reduce the bias of random errors (e.g. repeated pre-measurements and post-measurements)[29] have not been applied. The wide scatter of individual changes underlines the importance of conducting predictor analyses; however, this heterogeneity might have been amplified by the multimorbid condition of the patients with a high number of adverse events in both groups[5] and the fact that, strictly speaking, this study was not a predictor analysis for 'ET versus control' as it compared the offer for supervised ET (HIIT and MCT) with a recommendation to perform regular physical activity (CON). To account for different levels in adherence, we performed a per-protocol analysis excluding ET patients with an adherence of $<$70%; however, it is unclear if and how many patients assigned to CON started exercising between baseline and follow-up. Nevertheless, as mean peak $\dot{V}O_2$ slightly decreased following CON, it is unlikely that many patients performed regular exercise training in this group. On average, patients included in the present trial had a relatively preserved exercise capacity at baseline. However, the wide range of baseline values and their linear relationships with the change in peak $\dot{V}O_2$ suggest that the results of the regression analyses are likely to be generalizable. Lastly, the measurement of O_2-pulse does not allow to distinguish between SV and C(a-v)O_2; however, it can be more easily obtained in routine care. While both peak SV and peak C(a-v)O_2 are significantly reduced in HFpEF,[10] further research is necessary to show whether both factors play a relevant role for the improvements in peak $\dot{V}O_2$ following ET.

Conclusions

In patients with HFpEF, lower baseline peak O_2-pulse is associated with higher ET-induced changes in relative peak $\dot{V}O_2$. This is an important finding towards a deficit-oriented personalized medicine in HFpEF, provides an easily measurable indicator of the potential for improving maximal exercise tolerance through exercise training and underlines the value of CPET to guide therapy. While changes in submaximal exercise tolerance were independent of baseline peak O_2-pulse, patients with HFpEF and high O_2-pulse may need to use additional therapies (e.g. reduction of negative chronotropic drugs, rate-adaptive pacing, and/or weight loss) to significantly increase maximal exercise tolerance.

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Conflict of interest

Stephan Mueller reported receiving grants from Deutsche Forschungsgemeinschaft (DFG) through the TUM International Graduate School of Science and Engineering and the German Centre for Cardiovascular Research (DZHK) during the conduct of the study. Ephraim B. Winzer reported receiving personal fees from Novartis (honoraria for lectures and advisory board activities), Boehringer Ingelheim (honoraria for advisory board activities), and CVRX (honoraria for lectures) outside the submitted work. Luciene F. Azevedo reported receiving grants from Brazilian National Council for Scientific and Technological Development and Technical University of Munich—Laura Bassi Award. André Duvinage reported receiving grants from Novartis outside the submitted work. Frank Edelmann reported receiving grants from DFG, BMBF, Servier, and personal fees from Bayer Healthcare, Merck, Novartis, Servier, Berlin Chemie, Boehringer Ingelheim, Vifor Pharma, AstraZeneca, PharmaCosmos outside the submitted work. Axel Linke reported receiving speaker fees from Abbott, Medtronic, Edwards Lifesciences, AstraZeneca, Boston Scientific, and Novartis; grants from Edwards Lifesciences and Novartis; advisory board fees from Transverse Medical, Picardia, Edwards Lifesciences, and Heart Leaflet Technology; and stock options from Claret Medical and Transverse Medical, and being a co-owner of Dresden Cardiovascular Research Institute and Core Laboratories outside the submitted work. Emeline M. Van Craenenbroeck reported receiving grants from the Flemish Research Funds (FWO) as a senior clinical investigator during the conduct of the study. Burkert Pieske reported receiving personal fees from Bayer Healthcare (steering committee, lectures), Merck (steering committee, lectures), Novartis (steering committee, lectures), Servier, AstraZeneca (lectures), Bristol-Myers Squibb (lectures), and Medscape (lectures) outside the submitted work. Martin Halle reported receiving grants from the TUM International Graduate School of Science and Engineering and the German Centre for Cardiovascular Research (DZHK) during the conduct of the study and grants from Novartis (principal investigator of the Activity Study in HFrEF) and personal fees from Bristol-Myers Squibb, Berlin Chemie-Menarini, Novartis, Daiichi-Sankyo, AstraZeneca, Roche, Abbott (advisory board on exercise and diabetes), Sanofi, Pfizer, Boehringer Ingelheim, and Bayer, and serves as an advisor for Medical Park SE, Germany outside the submitted work. No other disclosures were reported. Bernhard Haller, Anna Feuerstein, Paul Beckers, Mark J. Haykowsky, Andreas B. Gevaert, Jennifer Hommel, Katrin Esefeld, Isabel Fegers-Wustrow, Jeffrey W. Christle, Elisabeth Pieske-Kraigher, Evgeny Belyavskiy, Daniel A. Morris, Martin Kropf, and Radhakrishnan Aravind-Kumar declared that they have no conflict of interest.

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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: Results of the predictor analyses for the inter-individual response variability in $\dot{V}O_2$ at VT1.
*Different N for the analyses including haemoglobin (Exercise Training: 101, Guideline Control: 50); $\dot{V}O_2$ = oxygen consumption, VT1 = ventilatory threshold.
Table S2: Results of the predictor analyses for the

inter-individual response variability in peak $\dot{V}O_2$ in the three-group design.

*Different N for the analyses including haemoglobin (High-Intensity Interval Training: 50, Moderate Continuous Training: 53; Guideline Control: 52); $\dot{V}O_2$ = oxygen consumption.

Table S3: Correlations between changes in peak $\dot{V}O_2$, peak heart rate, peak O_2-pulse, and weight $\dot{V}O_2$ = oxygen consumption.

Figure S1: Relationships between baseline peak O_2-pulse and change in peak $\dot{V}O_2$, separated by median baseline peak respiratory exchange ratio (RER). In patients with baseline peak RER $<$ 1.10 (A), there was no significant interaction between baseline peak O_2-pulse × group on change in peak $\dot{V}O_2$ (Exercise Training: −0.87% [95% CI, −2.16 to 0.41], P = 0.20; Guideline Control: −0.44% [95% CI, −1.83 to 0.94), P = 0.53]). In patients with RER $\geq$ 1.10 (B), the association between baseline peak O2-pulse and change in peak VO2 was significantly different between groups (Exercise Training: −1.89% [95% CI, −3.07 to −0.70), P = 0.003]; Guideline Control: 0.58% [95% CI, −1.07 to 2.23], P = 0.49). Individual relationships and robust linear regression lines and 95% confidence bands are shown separately for Exercise Training (Δ) and Guideline Control (⊖). Black dashed lines (− − −) represent null lines.

Figure S2: **Predictors of change in $\dot{V}O_2$ at VT1.** Relationships between changes in relative $\dot{V}O_2$ at VT1 and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak $\dot{V}O_2$ at baseline (C), peak heart rate at baseline (D), baseline weight (E), and baseline haemoglobin (F). Individual relationships and robust linear regression lines and 95% confidence bands are shown separately for Exercise Training (Δ) and Guideline Control (⊖). Black dashed lines (− − −) represent null lines.

Figure S3: **Predictors of change in peak $\dot{V}O_2$ following High-Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control (Con).** Relationships between changes in relative peak $\dot{V}O_2$ and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak $\dot{V}O_2$ at baseline (C), peak heart rate at baseline (D), baseline weight (E), and baseline haemoglobin (F). Individual relationships and robust linear regression lines and 95% confidence bands are shown separately for HIIT (Δ), MCT (· ⊟ ·) and Con (⊖). Black dashed lines (− − −) represent null lines.

Figure S4: **Predictors of change in peak $\dot{V}O_2$ (excluding patients with adherence $<$ 70%).** Relationships between changes in peak $\dot{V}O_2$ and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak VO2 at baseline (C), peak heart rate at baseline (D), baseline weight (E) and baseline haemoglobin (F). Individual relationships and linear regression lines and 95% confidence bands are shown separately for the Exercise Training Per-Protocol Set (Δ) and Usual Care (⊖). Black dashed lines (− − −) represent null lines.

Figure S5: Associations between the changes in peak $\dot{V}O_2$ and its determinants including regression lines and 95% confidence bands. Red lines (—) in A-C represent the predicted associations if all other determinants remain constant. Black dashed lines (− − −) represent null lines.

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