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Optimizing Exercise Training in Patients with Heart Failure with Preserved Ejection Fraction:

The Effects of Different Exercise Training Modes and Predictors of Change in Peak Oxygen Consumption

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Vollständiger Abdruck der von der
Fakultät für Sport- und Gesundheitswissenschaften
der Technischen Universität München zur Erlangung des akademischen Grades
eines Doktors der Naturwissenschaften (Dr. rer. nat.)
genehmigten Dissertation.

Vorsitz: Prof. Dr. Henning Wackerhage

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Die Dissertation wurde am 01.02.2023 bei der Technischen Universität München eingereicht und durch die Fakultät für Sport- und Gesundheitswissenschaften am 07.06.2023 angenommen.

Acknowledgment

I would like to express my sincere gratitude to my supervisor Prof. Martin Halle (MD) for his continuous support and the possibility and trust to take a major responsibility in the conduct and evaluation of the OptimEx-Clin trial, as well as his critical and valuable feedback, which helped me a lot. Moreover, I would like to greatly thank the whole OptimEx consortium (from principle investigators, physicians, exercise physiologists, medical assistants, study nurses, administrative staff and research assistants) for their hard work and support during the conduct of the study – it was my pleasure to get to know you, learn so much and be a part of such a great international research consortium. Special thanks go to PD Bernhard Haller (Dr. rer. nat.) who always supported me with excellent statistical advice and help, and André Duvinage (MD) who has been a great mentor and supporter in any matters. I am also very grateful for the fantastic (financial) support of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) through the TUM International Graduate School of Science and Engineering (IGSSE), which enabled me to attend great congresses and trainings and to finance my stay abroad. In this sense, I would also like to express my gratitude to Jeff Christle (PhD) and Profs. Francois Haddad (MD) and Jonathan Myers (PhD) for having me at Stanford University and the Veterans Affairs Palo Alto Health Care System. This was a terrific experience that I will never forget. Moreover, I am very thankful to Prof. Mark Haykowsky (PhD) for inviting me to visit his former institute in Dallas, Texas, and for all the great discussions and fabulous support over the past few years. I am happy to have met you and look forward to our future collaboration. Many thanks should also go to PD Monika Siegrist (Dr. phil.) for her critical review and feedback on this dissertation.

Lastly, I would like to express my deepest gratitude to my parents, my grandmother and my parents in law for their continuous support, and especially to my wife Melanie for her endless love and support that makes my life happier, for being my balance and for putting up with all my overtime. I love you so much and look forward to our wonderful future with our lovely daughter Luise. Thank you so much!

Abstract

Background: More than 2% of the world's adult population has been diagnosed with heart failure, and approximately 50% of these patients have heart failure with preserved ejection fraction (HFpEF). Moreover, both the overall prevalence of heart failure and the proportion of patients with HFpEF are expected to further increase. To reduce exercise intolerance, the hallmark symptom in patients with HFpEF, exercise training (ET) has been shown to be one of, if not the, most effective treatment in HFpEF. However, it is not well investigated whether high-intensity interval training (HIIT) and moderate continuous training (MCT) have different effects, and predictors of change in peak oxygen consumption ($\dot{V}O_2$) with ET, a prerequisite for effective personalized medicine to improve exercise tolerance, are not yet known.

Objectives: The objectives of the two investigations presented in this dissertation were 1) to investigate whether HIIT, MCT and guideline-based physical activity recommendations (CON) have different effects on exercise tolerance, diastolic function and quality of life after 3 and 12 months, and 2) to investigate whether baseline peak O_2-pulse (reflecting peak stroke volume × arteriovenous oxygen content difference) is a predictor of the ET-induced change in peak $\dot{V}O_2$ after 3 months.

Methods: The OptimEx-Clin trial – a prospective, randomized, controlled, multicenter trial – was conducted at 5 European sites from July 2014 to September 2018. A total of 180 patients with stable HFpEF were randomly allocated (1:1:1, n = 60 patients per group) to HIIT (3 × 38 min/week, including 4 × 4 min at 80-90% of heart rate reserve), MCT (5 × 40 min/week at 35-50% heart rate reserve) or CON. For the first 3 months, ET was performed 3 times a week under supervision in the clinic (plus 2 additional home-based sessions in MCT), followed by 9 months of telemedically supervised ET at home. The primary endpoint of the study was the change in peak $\dot{V}O_2$ after 3 months, assessed by analysis of covariance and pairwise t-tests for independent samples. In a secondary analysis to assess potential baseline predictors, change in peak $\dot{V}O_2$ after 3 months was analyzed as a function of study group (combination of HIIT and MCT vs. CON) and baseline peak $\dot{V}O_2$ and its determinants (peak O_2-pulse, peak heart rate, weight, hemoglobin) using robust linear regression analyses. In addition, the extent to which changes in peak O_2-pulse, peak heart rate and weight explained the change in peak $\dot{V}O_2$ was analyzed using mediation analyses.

Results: Among the 180 randomized patients (mean age, 70 years; 120 women), 166 (92%) and 154 patients (86%) completed the supervised phase at 3 months and the unsupervised phase at 12 months, respectively. After 3 months, mean change in peak $\dot{V}O_2$ was significantly different between groups (HIIT: +1.1 ± 3.0 mL/kg/min, MCT: 1.6 ± 2.5 mL/kg/min; CON: -0.6 ± 3.3 mL/kg/min, P = 0.002), with pairwise comparisons (including imputed data) showing significant differences between HIIT vs. CON (1.5 mL/kg/min [95% CI, 0.4 to 2.7]) and MCT vs. CON (2.0 mL/kg/min [95% CI, 0.9 to 3.1]), whereas changes were not significantly different between HIIT and MCT (-0.4 mL/kg/min [95% CI, -1.4 to 0.6]). After 12 months, change in peak $\dot{V}O_2$ was not significantly different between groups (P = 0.11). Furthermore, changes in diastolic function were not significantly different at either 3 or 12 months (P > 0.05). At 3 months, approximately 72% of the difference in relative change in peak $\dot{V}O_2$ between the combined ET group and CON (mean difference, 10.0% [95% CI, 4.1 to 15.9]) was explained by changes in peak O_2-pulse. In addition, baseline peak O_2-pulse was negatively associated with the change in peak $\dot{V}O_2$ in the ET group (-1.45% [95% CI, -2.30 to 0.60] for every 1 mL/beat higher baseline peak O_2-pulse), whereas no significant association was found in CON (-0.08% [95% CI, -1.11 to 0.96]; interaction P = 0.04). None of the other parameters (including baseline peak $\dot{V}O_2$) were significant predictors of the difference in change in peak $\dot{V}O_2$ between groups. Moreover, neither baseline peak O_2-pulse nor any of the other parameters were significantly associated with the change in $\dot{V}O_2$ at the first ventilatory threshold (VT1), a marker of submaximal exercise tolerance.

Conclusions: In patients with HFpEF, HIIT and MCT yielded similar effects on change in peak $\dot{V}O_2$ after 3 months, indicating that the optimization of ET likely needs to be performed on an individual basis. Independent of ET mode, baseline peak O_2-pulse was identified as a predictor of the ET-induced change in peak $\dot{V}O_2$ after 3 months. While change in $\dot{V}O_2$ at VT1 was not dependent on baseline peak O_2-pulse, patients with a higher baseline peak O_2-pulse likely require additional therapies that improve peak heart rate (e.g., reduction of negative chronotropic agents, rate-adaptive pacing) to significantly increase peak $\dot{V}O_2$. Future ET studies should aim at improving long-term effects (≥ 12 months), identifying further covariate-treatment interactions and mediators of treatment-effects to improve personalized medicine, and combining treatments that target different mechanisms of exercise tolerance.

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List of Abbreviations

6-MWT ..... 6-minute walking test

ACE-I ..... angiotensin-converting enzyme inhibitors

AE ..... adverse event

ARB ..... angiotensin II receptor blockers

ARNI ..... angiotensin receptor-neprilysin inhibitor

ATP ..... adenosine triphosphate

BMI ..... body mass index

BP ..... blood pressure

CAD ..... coronary artery disease

C[a-v]O_2 ..... arteriovenous oxygen content difference

CaO_2 ..... arterial oxygen content

CI ..... confidence interval

CO ..... cardiac output

CO_2 ..... carbon dioxide

CON ..... control

CPET ..... cardiopulmonary exercise testing

CvO_2 ..... venous oxygen content

DT ..... deceleration time

e' ..... early diastolic mitral annular tissue velocity

E/A ratio ..... ratio of early to late atrial diastolic transmitral flow velocity

E/e' ..... estimated left ventricular filling pressure

EDV ..... end-diastolic volume

ECG ..... electrocardiogram

EF ..... ejection fraction

ESC ..... European Society of Cardiology

ESV ..... end-systolic volume

ET ..... exercise training

FES ..... functional electrical stimulation

FiO_2 ..... fraction of inspired oxygen

$FiCO_2$ ..... fraction of inspired carbon dioxide

FeO_2 ..... fraction of expired oxygen

$FeCO_2$ ..... fraction of expired carbon dioxide

H^+ ..... proton

H_2O ..... water

$HCO\overline{3}$ ..... bicarbonate

HF ..... heart failure

HFimpEF ..... heart failure with improved ejection fraction

HFmrEF ..... heart failure with mildly reduced ejection fraction

HFpEF ..... heart failure with preserved ejection fraction

HFrEF ..... heart failure with reduced ejection fraction

HIIT ..... high-intensity interval training

HR ..... heart rate

HRR ..... heart rate reserve

IKE ..... isolated knee extensor

IMT ..... inspiratory muscle training

IQR ..... interquartile range

KCCQ ..... Kansas City Cardiomyopathy Questionnaire

LAVI ..... left atrial volume index

LV ..... left ventricular

LVEF ..... left ventricular ejection fraction

MCID ..... minimal clinically important difference

MCT ..... moderate continuous training

MET ..... metabolic equivalent of task

MLHFQ ..... Minnesota Living with Heart Failure Questionnaire

MRA ..... mineralocorticoid receptor antagonist

NO ..... nitric oxide

NT proBNP ..... N-terminal pro brain natriuretic peptide

NYHA ..... New York Heart Association

O_2 ..... oxygen

$PaCO_2$ ..... partial pressure of arterial CO_2

PCWP ..... pulmonary capillary wedge pressure

$\dot{Q}CO_2$ ..... carbon dioxide production inside the muscles

$\dot{Q}O_2$ ..... oxygen consumption inside the muscles

QoL ..... quality of life

RCT ..... randomized controlled trial

RER ..... respiratory exchange ratio

RPE ..... rating of perceived exertion

RQ ..... respiratory quotient

RV ..... right ventricular

SAE ..... serious adverse event

SD ..... standard deviation

SF-36 ..... Short Form Health Questionnaire 36

SGLT2 ..... sodium-glucose co-transporter 2

SV ..... stroke volume

VBA ..... Visual Basic for Application

$\dot{V}E$ ..... ventilation

V_D ..... physiological dead space ventilation

$\dot{V}O_2$ ..... oxygen consumption

V_T ..... tidal volume

VT1 ..... first ventilatory threshold

VT2 ..... second ventilatory threshold

1. Introduction

Since the 1990's, heart failure (HF) has been described as an emerging epidemic.[1-3] According to the Global Burden of Disease Study,[4] approximately 64.3 million people [95% confidence interval (CI), 57.2 to 71.6 million] worldwide were living with HF in 2017. Based on self-reported data between 2015 and 2018, the prevalence of known HF in Americans aged 20 years and older was higher than 2%.[5] Even though the incidence of new onset HF has been declining within the last 30 years,[6-8] due to the global population growth, the ageing of the population and improved survival after diagnosis, the prevalence has been increasing over time and is projected to further increase to about 3.0% by 2030.[9-11] However, according to a 2016 meta-analysis applying objective echocardiographic criteria, the prevalence of HF in the adult population of developed countries may be already substantially higher.[12] Based on 9 articles (data collection between 1995 and 2010; N = 12,894), a median of 11.8% of individuals aged 60 years and older had HF, which led to a calculated prevalence as high as 4.2% in the overall adult population.[12] Risk factors for HF include, amongst others, coronary heart disease, hypertension, diabetes mellitus, obesity, smoking, physical inactivity, and alcohol consumption.[5,13-16]

Incident HF (adjusted for age and other risk factors) is associated with a more than 5-fold increased risk of death,[17] and despite improvements in prognosis over time, according to a meta-analysis of studies involving more than 1.5 million patients, the estimated 5-year mortality rate is 43.3% (95% CI, 40.6% to 46.0%).[18] Furthermore, HF is associated with a huge economic burden.[19] It was the main diagnosis in 809,000 hospital admissions in the United States in 2016[5] and represents one of the most common causes for hospitalizations, especially in the elderly.[20,21] Once hospitalized, readmission rates for all-cause hospitalization are high (~20-27% within 30 days,[22-25] ~80% within 5 years[26]), and the 5-year mortality rises to approximately 75%.[26,27] Due to accompanying symptoms, quality of life (QoL) is also severely reduced in patients with HF.[28,29] Symptoms include exertional dyspnea / breathlessness, swelling, and fatigue and its cardinal symptom is generally described as exercise intolerance.[30,31] In general, symptoms are graded according to the New York Heart Association (NYHA) functional classification *(Table 1)*.

Table 1: New York Heart Association (NYHA) functional classification based on the symptoms of patients with heart failure[30]

NYHA class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in undue breathlessness, fatigue, or palpitations.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

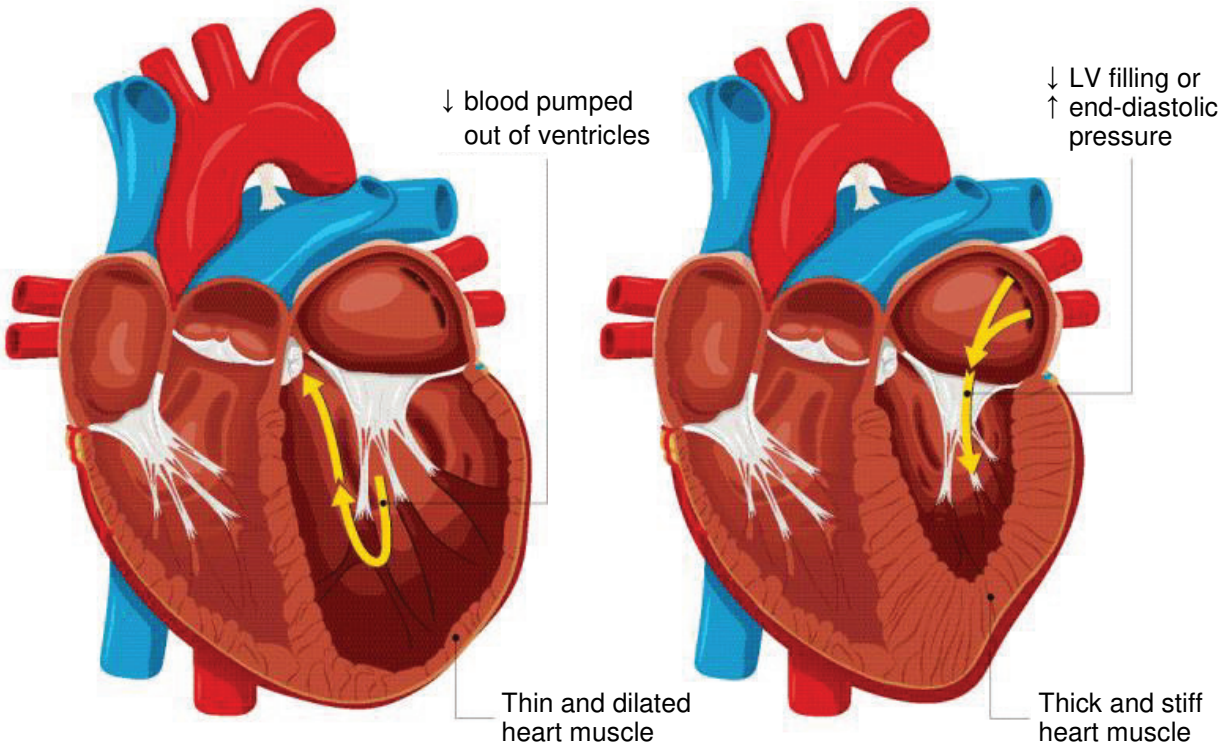
With the exception of early stage or optimally treated patients, those symptoms are usually accompanied by HF-related signs including, amongst others, elevated jugular venous pressure, pulmonary crackles, and peripheral edema.[30] The presence of signs and symptoms build the basis for the diagnosis of HF. They can be due to structural and / or functional abnormalities of the heart that result in a reduced cardiac output (CO) and / or elevated intracardiac pressures.[30] According to the European Society of Cardiology (ESC),[30] HF can be divided into 3 types based on the patient's left ventricular (LV) ejection fraction (EF; LVEF) *(Table 1)*, which is the ratio of the blood ejected from the ventricle (stroke volume, SV) to its end-diastolic volume (EDV) *(1)*, where SV is the difference between EDV and end-systolic volume (ESV) *(2)*.

$$EF = (SV \div EDV) \times 100 \quad (1)$$

$$SV = EDV - ESV \quad (2)$$

HF with reduced ejection fraction (HFrEF) (LVEF < 40%) is generally characterized by a thin and weakened heart muscle resulting in a reduced blood outflow from the ventricles (higher ESV) (Figure 1). HFrEF is the predominant type of HF in men and younger patients[32,33] and can be broadly categorized into an ischemic (about 50% of patients in developed countries) and non-ischemic etiology (e.g., due to idiopathic dilated cardiomyopathy, hypertension, diabetes mellitus or valvular heart disease).[8,30,34]
HF with preserved ejection fraction (HFpEF) (LVEF ≥ 50%) is generally characterized by a thickened heart muscle with increased passive stiffness and impaired active relaxation resulting in higher end-diastolic filling pressures to adequately fill the left ventricle and / or reduced blood inflow into the ventricles (lower EDV) *(Figure 1)*.[35] HFpEF is defined by a (normal) LVEF and the evidence of impaired LV

diastolic function or elevated LV filling pressures (structural and / or functional abnormalities). In the elderly and in females, HFpEF is the most common type of HF.[32,36] ***HF with mildly reduced ejection fraction (HFmrEF) (LVEF 41-49%)*** was introduced in the 2016 ESC guidelines to fill the gap between HFrEF and HFpEF.[37] Due to its short existence, evidence for this type of HF is scarce and mainly results from sub-analyses of studies including a broader LVEF range. While HFmrEF shares some of the pathophysiological mechanism of HFpEF, clinical characteristics seem to be more similar to those seen in patients with HFrEF.[30,38,39]



HFrEF	HFmrEF	HFpEF
LVEF ≤ 40%	LVEF 41-49%	LVEF ≥ 50%
Signs + Symptoms of Heart Failure [a]		
-	-	Structural and / or functional abnormalities related to • ↓ LV diastolic dysfunction or • ↑ LV filling pressures (including natriuretic peptides)

Figure 1: Typical characteristics of heart failure (HF) with reduced ejection fraction (HFrEF, left) and HF with preserved ejection fraction (HFpEF, right), and diagnostic criteria of HFrEF, HF with mildly reduced ejection fraction (HFmrEF) and HFpEF (Table adapted from McDonagh et al.,[30] graphs modified from iStock.com/go-un lee; with permission).

***Abbreviations*: *LVEF** = Left ventricular ejection fraction; **LV** = Left ventricular*

[a] signs and symptoms may not be present in early-stage HF

Several studies have shown that approximately 50% of all patients with HF have a normal LVEF[6,10,40-42] and because the incidence of new-onset HFpEF is declining less rapidly than that of HFrEF,[6] the proportion of patients with HFpEF is expected to further increase. Furthermore, most studies have shown similar hospitalization, readmission and mortality rates between the different types of HF.[23,26,43] While patients with HFpEF have a lower risk for HF and cardiovascular readmissions, the all-cause readmission rate is higher than in patients with HFrEF.[23,26] This may be largely explained by the higher age and the higher burden of (non-cardiovascular) comorbidities in HFpEF.[44,45] Consequently, when adjusted for age, gender and several comorbidities, the results of an individual patient data meta-analysis of 41,972 patients with HF has shown a significantly reduced mortality risk in HFpEF compared to HFrEF (hazard ratio: 0.68 [95% CI, 0.64 to 0.71]).[46] Nevertheless, the increasing proportion of patients with HFpEF is alarming. Regardless of its etiology, HFrEF has been extensively studied for decades and several effective therapies exist. On the other side, even though HFpEF has been first described in 1982,[47] the disease is still insufficiently understood. Within the last 20 years, the understanding of the pathophysiology of HFpEF has evolved from purely cardiac cause to a systemic multi-organ disease involving abnormalities of the vasculature, heart, lung, skeletal muscles and kidneys.[35,48-51] While it was once assumed that HFpEF is an intermediate state in the development from hypertension to HFrEF, it is now recognized as an independent disease. The currently prevailing concept assumes a complex interaction between cardiac as well as non-cardiac mechanisms and comorbidities leading to a chronic systemic inflammation and coronary microvascular endothelial dysfunction, which subsequently results in LV hypertrophy with impaired relaxation and a decreased compliance of the left ventricle.[48,51]

1.1. Guideline Recommendations for the Treatment of Heart Failure

Drug therapy forms the cornerstone in the treatment of HFrEF.[30] Angiotensin-converting enzyme inhibitors (ACE-I),[52-55] beta-blockers,[56-62] mineralocorticoid receptor antagonists (MRA),[63,64] sodium-glucose co-transporter 2 (SGLT2) inhibitors[65-67] and the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan[68] have been shown to reduce symptoms and the risk of HF hospitalization and death. Therefore, a combination of ACE-I / ARNI plus beta-blocker plus MRA plus SGLT2 inhibitor is recommended in all patients with HFrEF (class I, level A / B).[30] Furthermore, other drugs

(loop diuretics, angiotensin II receptor blockers (ARB), I_f-channel inhibitors, soluble guanylate cyclase stimulators, hydralazine and isosorbide dinitrate, digoxin) have been shown to be effective and are recommended (class I) or should / may be considered (Class IIa / IIb) in selected patients with HFrEF (evidence level B / C).[30] On top of an optimal pharmacotherapy, a multi-professional disease management and exercise rehabilitation are recommended (class I, level A) in all, and the use of implantable cardioverter-defibrillators and cardiac resynchronization therapy in selected patients (class I, level A) with HFrEF to reduce signs and symptoms, HF hospitalization and mortality, and improve QoL.[30]

In contrast to HFrEF, effective therapies of HFpEF are still scarce. Even though some subgroup analyses have shown favorable effects of spironolactone (MRA)[69] and sacubitril/valsartan (ARNI),[70] all randomized controlled trials (RCTs) evaluating the effects of ACE-I,[71] ARBs,[72,73] MRA,[74] ARNI,[75] digitalis[76] and beta-blocker[77] have missed their primary endpoints of all-cause mortality, cardiovascular mortality or HF hospitalization. Furthermore, only few pharmacological trials have revealed significant improvements in QoL or exercise tolerance.[78,79] Therefore, current guideline recommendations for the treatment of HFpEF[30] are limited to the use of diuretics to reduce signs and symptoms in congested patients (class I, level C) and the identification and treatment of cardiovascular and non-cardiovascular comorbidities (class I, level C). Furthermore, regular exercise training (ET) and the reduction of body weight in patients with obesity should be considered to reduce signs and symptoms.[30] In addition to the current guideline recommendations, recent evidence points to a possible breakthrough in the pharmacological treatment of HFpEF as the use of SGLT2 inhibitors, originally prescribed for the treatment of diabetes mellitus, have shown very promising results. In the Emperor-Preserved trial (N = 4,005 patients with HFpEF; N = 1,983 patients with HFmrEF),[80] empagliflozin significantly reduced the risk of cardiovascular death or hospitalization for HF over a median follow-up of 26 months, an effect that was consistent across LVEF subgroups and patients with / without diabetes mellitus. Moreover, in the most recently published DELIVER trial (N = 6,263 patients with LVEF > 40%), dapagliflozin has significantly reduced the primary endpoint of worsening HF and cardiovascular mortality over a median follow-up of 2.3 years, also independent of LVEF and diabetes mellitus.[81] Dapagliflozin has also been shown to significantly reduce patient-reported symptoms and physical limitations and increase 6-minute

walking test (6-MWT) distance over 12 weeks in 324 patients with heart failure and an LVEF of at least 45%.[82]

1.2. Measuring Exercise Tolerance

Reduced exercise tolerance is not only the hallmark symptom of HF and associated with reduced QoL,[83-85] but also significantly associated with an increased risk of mortality and hospitalization, both in the general population[86,87] and patients with HF.[88-90] It can be defined as "the reduced ability to perform activities that involve dynamic movement of large skeletal muscles because of symptoms of dyspnea or fatigue".[91 (p. 1210)] Exercise tolerance can be further differentiated into exercise capacity and functional capacity. Even though exercise capacity and functional capacity are often considered synonymous,[92] differentiated definitions are important for the selection of measuring methods and therapies. While exercise capacity is "the maximum amount of physical exertion that a subject can sustain",[31 (p. 2211)] functional capacity has been described as "the ability to perform activities of daily living that require sustained, submaximal aerobic metabolism".[31 (p. 2211)]

1.2.1. Simple Tests for the Assessment of Exercise Tolerance

The most commonly used subjective parameter of exercise intolerance is the NYHA functional classification *(Table 1)*. It is a simple and quick to use free measurement tool that is part of every medical history interview in patients with HF. However, important limitations are a low accuracy and inconsistencies in the methods for assessing NYHA functional classification, which results in a poor inter-operator variability as well as a low sensitivity to changes over time.[31,93,94] Standardized simple methods for quantifying exercise tolerance include the 6-MWT or graded exercise tests with an electrocardiogram (ECG) on a treadmill or bicycle ergometer.

The 6-MWT is a simple, cost-effective test for quantifying functional capacity. In a flat, straight corridor at least 30 meters long, patients are asked to walk back and forth as fast as possible for 6 min. If necessary, they can take a break in between. Total distance and change over time have been shown to predict mortality and hospitalizations in HF,[95-97] however, the test has several shortcomings. Although the test can provide important information about the ability to perform activities of daily living, it is highly dependent on patient motivation (which cannot be quantified) and

correct self-assessment. Therefore, the test is associated with a learning effect that must be taken into account when interpreting changes.[98] Furthermore, it does not provide any information on the underlying mechanisms of exercise intolerance and gives no information on maximum exercise capacity.[31,95]

Symptom-limited graded exercise stress testing with ECG is a simple and cost-effective method to evaluate parameters of maximum exercise capacity. It allows the determination of maximum power output, time to exhaustion, the heart rate (HR) and blood pressure (BP) response to exercise, and the detection of ECG abnormalities. Maximum watts (absolute or relative to body weight) and time to exhaustion can be compared to normative values or used to predict oxygen consumption ($\dot{V}O_2$), usually expressed as metabolic equivalents of task (MET; 1 MET ≈ 3.5 mL/kg/min of $\dot{V}O_2$).[99,100] Metrics derived from an exercise ECG have been shown to predict outcomes in HF.[101,102] However, the test does not provide information about functional capacity, provides only incomplete information about the mechanisms of exercise intolerance, and maximum exhaustion may not be quantifiable.[31]

1.2.2. Cardiopulmonary Exercise Testing

The gold standard for measuring exercise tolerance, both functional capacity and maximum exercise capacity, is cardiopulmonary exercise testing (CPET).[103] CPET is a strong tool that displays the physiology of the whole body during exercise and has versatile areas of application such as performance testing in athletes, ET prescription in health and disease, evaluation of unexplained dyspnea, perioperative risk assessment for non-cardiac surgeries, evaluation of disease severity and prognosis, monitoring of interventions or selection of patients for heart transplantation.[103-108] Methodologically, the so-called breath-by-breath CPET systems measure the ventilatory flow, which allows to calculate minute ventilation ($\dot{V}E$), and the fractions of expired O_2 (FeO_2) and carbon dioxide ($FeCO_2$) approximately 50 times per breath, taking into account the ambient temperature, humidity and air pressure.[104] The fractions of inspired O_2 and CO_2 (FiO_2, $FiCO_2$) are either measured continuously (same as for FeO_2 and $FeCO_2$), once before every test or assumed according to standard environmental conditions (20.93% for FiO_2; 0.03 - 0.04% for $FiCO_2$). All other metrics are calculated based on these and other values that are measured by additional devices (e.g., power output, HR, BP).[104] For example, the most relevant parameters $\dot{V}O_2$ *(3)* and

$\dot{V}CO_2$ *(4)*, which mirror the O_2 consumption ($\dot{Q}O_2$) and CO_2 production ($\dot{Q}CO_2$) inside the muscles, are calculated by the following formulas:

$$\dot{V}O_2 = \dot{V}E \times (FiO_2 - FeO_2) \quad (3)$$

$$\dot{V}CO_2 = \dot{V}E \times (FeCO_2 - FiCO_2) \quad (4)$$

In any exercise lasting longer than 2 minutes, the energy required is provided mainly by aerobic metabolism.[109] Consequently, the evaluation of CPET results usually starts with the interpretation of the $\dot{V}O_2$ trajectory and the highest $\dot{V}O_2$ that is achieved at the end of a graded exercise test (peak $\dot{V}O_2$), which is the gold standard parameter for maximum exercise capacity. Peak $\dot{V}O_2$ can basically be described as the most powerful and widely applied CPET metric and while it can be lower than 10 ml/kg/min in severely impaired patients with HF, highly endurance trained athletes can reach $\dot{V}O_2$ values of up to 85 mL/kg/min.[110] In HF, peak $\dot{V}O_2$ is used to quantify exercise intolerance, the hallmark symptom of HF, and is considered as a strong surrogate marker for adverse events (AEs) and mortality.[88-90,107,111,112] Therefore, it is often applied as a prognostic marker in clinical routine or an endpoint in clinical trials, to monitor the effects of an intervention or to select patients for heart transplantation or ventricular assist device implantation.[106,113-115]

CPET is also a valuable tool to measure functional capacity. The anaerobic threshold, also called first ventilatory threshold (VT1), depicts the point during exercise at which the anaerobic glycolysis increasingly contributes to energy production. In brief, during low-to-moderate intense exercise, the oxidation of fatty acids *(5)* and glucose *(6)* is sufficient to cover the energy requirement and results in the production of CO_2 and water (H_2O). The CO_2 then diffuses into the blood and is exhaled through the lungs.[104]

$$C_{15}H_{31}\mathrm{COOH} + 23\,O_2 \longrightarrow 16\,CO_2 + 16\,H_2\mathrm{O} \quad (5)$$

$$C_6H_{12}O_6 + 6\,O_2 \longrightarrow 6\,CO_2 + 6\,H_2O \quad (6)$$

The oxidation of lipids requires a relatively high amount of O_2, but results in the highest energy per mmol substrate [130 adenosine triphosphates (ATP)].[104,116] The ratio of produced $\dot{Q}CO_2$ to consumed $\dot{Q}O_2$ in the cells (metabolic respiratory quotient, RQ) is approximately 0.7.[104,116] The oxidation of carbohydrates requires less O_2 and results in 36 / 37 ATP per unit (glucose / glycogen) with an RQ of 1.0.[104,116] During aerobic metabolism and the absence of hyper- or hypoventilation, the RQ is reflected by the

ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ (respiratory exchange ratio, RER) as measured at the airway by CPET. Thus, exercising below VT1 is generally associated with a slope of $\dot{V}CO_2$ vs. $\dot{V}O_2$ ≤ 1.0 and an RER ≤ 1.0. During higher intensities, when mitochondrial oxidation of carbohydrates and fatty acids can no longer cover the energy demand, the aerobic metabolism is complemented by anaerobic energy production. Without the use of O_2, glucose can also be broken down to 2 lactate anions with 2 associated protons (H^+) *(7)*, resulting in a net gain of 2 ATP per glucose molecule (3 ATP per glycosyl unit).[104,116] To prevent acidosis, the H^+ is buffered by bicarbonate (HCO_3^-), resulting in H_2O and additional CO_2 *(8)*, which leads to a disproportionate increase in $\dot{V}CO_2$ that can be measured by CPET.[104,116,117]

$$C_6H_{12}O_6 \longrightarrow 2\,C_3H_5O_3^- + 2\,H^+ \tag{7}$$

$$HCO_3^- + H^+ \longrightarrow CO_2 + H_2O \tag{8}$$

In the absence of nonspecific hyperventilation, which can be ruled out by inspection of other CPET metrics,[116] VT1 is defined as the breakpoint at which the slope of $\dot{V}CO_2$ vs. $\dot{V}O_2$ becomes > 1.0 (V-slope method) *(Figure 2)*,[117] as this increase reflects

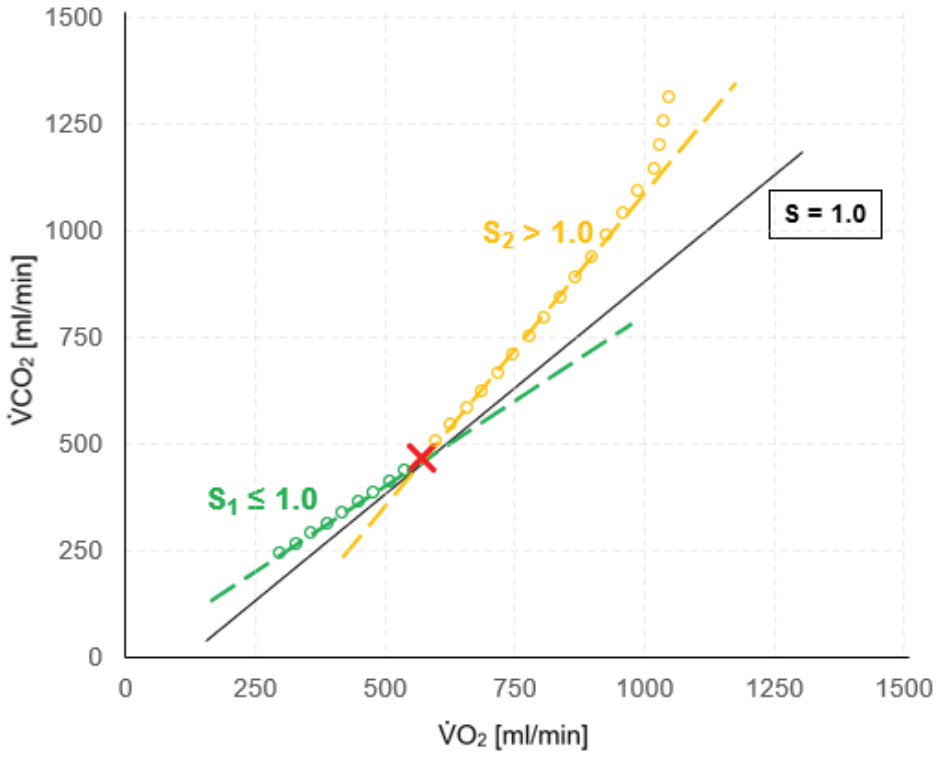


*Figure 2: Determination of the first ventilatory threshold (VT1) by the V-slope method. VT1 (**X**) is set at the breakpoint at which the slope of carbon dioxide production ($\dot{V}CO_2$) vs. oxygen consumption ($\dot{V}O_2$) changes from ≤ 1.0 (**S_1** — ⊖ —) to > 1.0 (**S_2** — ⊖ —).[117] It is helpful to use a line with slope S = 1.0 (——) that is moved to the data points to identify the breakpoint.*

the excess CO_2 from HCO_3^- buffering of H^+ during anaerobic glycolysis. As the efficiency of ATP provision is significantly less for anaerobic compared to aerobic glycolysis (2 vs. 36 ATP for glucose, 3 vs. 37 ATP per glycosyl unit), exercising above VT1 results in premature exercise termination due to earlier depletion of carbohydrate stores or acidosis.[116] Therefore, VT1 has a very strong correlation with prolonged exercise performance and has important implications in the individualized exercise prescription.[104,118-123] Similar to peak $\dot{V}O_2$, VT1 is a powerful prognostic marker in patients with HF and is also used to select patients for heart transplantation or ventricular assist device implantation, with the great advantage of being independent of volitional effort.[124-127]

Another important CPET metric is the $\dot{V}E/\dot{V}CO_2$ slope, which has been shown to be an independent factor of disease severity and prognosis in HF.[88,106,115,127-132] In addition to factors directly related to the delivery and utilization of O_2 for energy production, failure to adequately exhale the accumulating CO_2 can also lead to reduced exercise capacity. This may occur when a significant increase in LV filling pressures during exercise leads to lung congestion and subsequent alterations in pulmonary mechanics, gas diffusion and / or ventilation-perfusion mismatch *(see chapter 1.3)*.[133,134] During exercise, $\dot{V}E$ increases to regulate the arterial pH level, which is determined by the arterial H^+ concentration and the production of CO_2 from aerobic metabolism as well as the excess CO_2 from HCO_3^- buffering.[104,116] Moreover, the adequate exhalation is dependent on the partial pressure of arterial CO_2 ($PaCO_2$) and the physiological dead space ventilation (V_D) to tidal volume ratio (V_T) *(9)*.[104,116,132]

$$\dot{V}E = 863 \times \dot{V}CO_2 \div (PaCO_2 \times [1 - VD \div VT]) \quad (9)$$

Thus, below VT1 and as long as H^+ can be adequately buffered by HCO_3^-, $\dot{V}E$ closely tracks the increase in $\dot{V}CO_2$, leading to a linear increase in $\dot{V}E$ over $\dot{V}CO_2$ over the major part of an incremental exercise test.[104,116,132] Therefore, $\dot{V}E$ during exercise can also be described by the following formula, where the slope (m) and the y-intercept (c) are associated with (changes in) $PaCO_2$ and V_D/V_T *(10)*.[104,116,132]

$$\dot{V}E = m \times \dot{V}CO_2 + c \quad (10)$$

At the time when HCO_3^- is no longer able to adequately buffer the accumulating H^+ from anaerobic glycolysis, the increasing acidosis leads to an additional stimulation

of peripheral chemoreceptors and a disproportionate increase in $\dot{V}E$ over $\dot{V}CO_2$, which is termed respiratory compensation point or second ventilatory threshold (VT2).[104,116,132] While the 'physiological' $\dot{V}E/\dot{V}CO_2$ slope is calculated over the linear increase until VT2, some trials have shown superior prognostic value in patients with HF if the slope is calculated over the entire exercise duration (including the respiratory compensation between VT2 and peak exercise) *(Appendix A)*.[135,136] In normal individuals, the $\dot{V}E/\dot{V}CO_2$ slope is approximately 25, whereas in patients with HF, slope values > 35 are generally associated with a significantly worse prognosis and values > 45 are indicative of severe HF or pulmonary hypertension.[106,137]

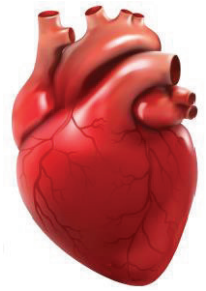
1.3. Components of Exercise Intolerance in Patients with Heart Failure

According to the Fick principle, $\dot{V}O_2$ is the product of CO and arteriovenous O_2 content difference ($C[a\text{-}v]O_2$) *(11)*, where CO can be further divided into the product of HR and SV, whereas $C[a\text{-}v]O_2$ is the difference between the arterial O_2 content (CaO_2), i.e., the O_2 carried from the lungs and left heart to the periphery, and the mixed venous O_2 content (CvO_2), which is the amount of O_2 returning from the periphery to the right heart and lungs *(12)*.[31]

$$\dot{V}O_2 = \quad CO \quad \times \quad C[a\text{–}v]O_2 \tag{11}$$

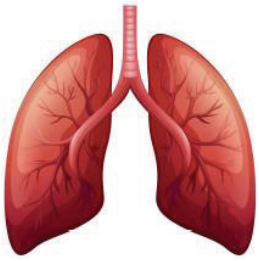
$$\dot{V}O_2 = HR \times SV \times (CaO_2 - CvO_2) \tag{12}$$

During exercise, healthy individuals can increase HR and $C[a\text{-}v]O_2$ to approximately 250%, whereas SV increases to approximately 130% of resting values.[91,138,139] The increase in SV is accomplished by a higher filling volume to increase EDV and a more complete emptying of the left ventricle to decrease ESV, whereas HR is increased by reduced parasympathetic and higher sympathetic activity.[31,91] The increase in $C[a\text{-}v]O_2$ is accomplished by blood flow redistribution from non-exercising tissues to exercising muscles and higher O_2 extraction in the exercising muscles.[31,91,116,140,141] Therefore, besides the O_2 and CO_2 content in the ambient air, the increase in $\dot{V}O_2$ with exercise depends on the proper increases in these determinants and impairments in any components included in the O_2 transport and utilization (i.e., pulmonary function, cardiac function, peripheral vascular function, O_2 carrying capacity and skeletal muscle function) can contribute to exercise intolerance *(Figure 3)*.[31,106]



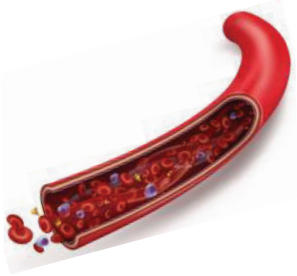
Impaired Cardiac Function:

- Systolic dysfunction
- Diastolic dysfunction / ↑ Filling pressures
- Chronotropic incompetence
- Atrial remodeling
- Mitral regurgitation
- Ventricular dyssynchrony
- Ventricular-arterial uncoupling



Impaired Pulmonary function:

- ↓ Pulmonary vasodilation & vascular recruitment
- ↓ Lung compliance
- ↓ O_2 lung diffusion
- Ventilation-perfusion mismatching
- Respiratory muscle weakness
- Abnormal ventilatory regulation

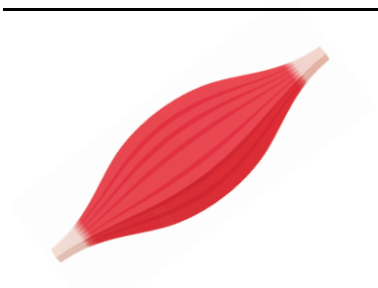


Impaired Peripheral Vascular Function:

- ↑ Arterial vasoconstriction
- ↓ Arterial vasodilation
- ↓ Capillary red cell flux

Impaired Oxygen Carrying Capacity:

- ↓ Hemoglobin concentration
- ↓ Iron content



Impaired Skeletal Muscle Function:

- ↓ Muscle mass
- ↑ intermuscular adipose tissue
- Shift from type I → type II muscle fibers
- ↓ Capillary density
- ↓ Reduced mitochondrial density, size & function
- ↓ Oxidative enzymes

Figure 3: Impairments in cardiac and extracardiac factors (pulmonary function, vascular function, oxygen carrying capacity, and skeletal muscle function) associated with reduced exercise tolerance in patients with heart failure (Table adapted from Del Buono et al.,[31] graphs modified from BlueRingMedia/Shutterstock.com, studiovin/Shutterstock.com, Good Job/Shutterstock.com and Barks/Shutterstock.com; with permission)

Traditionally, exercise intolerance in HF has been attributed primarily to central limitations, i.e., reduced CO.[35,142,143] This may still be true for the average patient with HFrEF.[115,138,144] However, particularly in HFpEF, emerging 'paradigm shifting' evidence has shown that peripheral abnormalities leading to a reduced C[a-v]O_2 are important and may even be the most relevant contributors to reduced exercise capacity.[138,145,146] In HFrEF, SV response is primarily limited due to LV systolic dysfunction (LVEF < 40%) at rest and the inability to adequately augment LVEF during exercise that result from

reduced myocardial contractility, replacement fibrosis, reduced beta-receptor activity, and a high afterload through increased systemic vascular resistance, i.e., reduced vasodilation and increased vasoconstriction.[31,91]

Diastolic dysfunction is essential for the diagnosis of HFpEF and can be defined as “the inability to fill the [left] ventricle to an adequate preload (EDV) at acceptably low pressures”,[147 (p. 2)] which is due to both impaired active relaxation and passive stiffness,[35] and increases with ageing.[148,149] While diastolic function may be normal at rest, some patients with HFpEF show significant impairments only with increasing physical exertion.[150-152] Due to the increased stiffness of the LV, even small changes in volume can be associated with large changes in diastolic pressures.[35,153] Furthermore, the prolonged relaxation time leads to an inadequate LV pressure decay during diastole, which becomes increasingly important as the HR rises, i.e., when the duration of the diastole decreases.[35,154-156] Whereas in healthy individuals, the left ventricle is primarily filled by early diastolic suction through intraventricular pressure gradients,[157-159] the pathological changes in HFpEF require these patients to rely on an increased left atrial pressure to ‘push’ blood into the ventricle.[147,150,155,160] These high filling pressures lead to a decreased compliance of the lungs, thereby increasing the work of breathing and causing exercise intolerance by premature exercise termination due to dyspnea.[35,147,161-163] Furthermore, high filling pressures increase the risk of developing pulmonary edema,[35] and can lead to pulmonary hypertension and atrial remodeling, which are precursors for right ventricular (RV) dysfunction and atrial fibrillation.[147,164] In HFpEF, it has long been assumed that reduced ventricular filling is the major limitation in increasing SV and the primary reason for exercise intolerance.[35,153] However, even though the absolute EDV may be reduced at rest and during exercise,[35,145] the EDV reserve (difference or ratio between resting and peak EDV) seems to be similar as compared to healthy controls.[145,161] This implies that despite the reliance on higher filling pressures associated with exercise intolerance, reduced diastolic filling is unlikely to be the major determinant of reduced SV response during exercise.[147,161,164] In contrast to normal LVEF at rest, patients with HFpEF also have a significantly lower systolic reserve (increase in LVEF with exercise) and a smaller decline in systemic vascular reserve due to a reduced vasodilator reserve during exercise.[161,165-167] Importantly, diastolic dysfunction is not exclusive to HFpEF, but is also frequently observed and associated with reduced survival in patients with HFrEF.[168,169] Other mechanisms that can reduce

the SV response in HF include ventricular dyssynchrony, abnormal RV-pulmonary artery coupling, left atrial dysfunction, atrial fibrillation, mitral regurgitation, or myocyte injury in absence of ischemic coronary disease.[31,147,170-173]

Furthermore, chronotropic incompetence, defined as "the inability of the heart to increase its rate commensurate with increased activity or demand",[174 (p. 1010)] is frequently observed in HF.[174,175] In addition to reduced peak HR, chronotropic incompetence may also be defined by a reduced heart rate reserve (HRR), a delayed HR response, HR instability, or inadequate HR recovery after exercise.[174,175] Although the exact mechanisms of chronotropic incompetence are not yet clear, autonomic dysfunction with decreased density and sensitivity of beta-adrenergic receptors due to chronic sympathetic overstimulation is considered the main mechanism.[174-178] Chronotropic incompetence significantly contributes to the blunted CO response and exercise intolerance, and is associated with increased mortality in HF.[161,165,174,175,179-182] In a recent meta-analysis in patients with HFpEF, a reduced HRR has even been shown to be the most pronounced reserve abnormality that is associated with exercise intolerance.[161] In addition to chronotropic incompetence, peak HR may be further reduced by cardiovascular medication (e.g., beta-blockers),[174,175] however, these drugs generally have a lesser effect on HRR because the reduction in sympathetic activity affects both resting and peak HR.[175]

Extracardiac factors that limit exercise tolerance in HF include pulmonary, vascular and skeletal muscle abnormalities as well as an impaired O_2 carrying capacity (anemia). Pulmonary abnormalities may include reduced pulmonary reserve with impaired pulmonary vasodilation and vascular recruitment, a reduced lung compliance leading to a lower V_T and greater V_D, ventilation-perfusion mismatching, impaired lung diffusion, respiratory muscle weakness and an abnormal ventilatory regulation with impaired metaboreflex and exercise oscillatory ventilation.[31,183-188] As described above, impaired peripheral vascular function caused by increased sympathetic nervous system activity, systemic inflammation, or oxidative stress significantly reduces skeletal muscle O_2 supply through its effects on CO.[31,144,189-191] However, it does also lead to a blunted endothelium-dependent arteriolar and skeletal muscle vasodilation and affects the muscle O_2 diffusion capacity by lower bioavailability of vasodilator nitric oxide (NO), increased vasoconstrictor endothelin-1 and angiotensin-II, and the overactivation of metabolic receptors, which worsens with increasing exercise intensities.[31,190-194] Arterial

stiffening and abnormal vasorelaxation are also directly related to increased filling pressures,[195] supporting the occurrence of dyspnea. Additionally, it has been shown in an animal model that the capillary red cell flux is significantly reduced and slowed down, which increases the O_2 deficit at exercise onset, further contributing to exercise intolerance.[31,196-199] Anatomical muscle abnormalities include muscle atrophy as well as increased intermuscular adipose tissue and an increased intermuscular adipose to skeletal muscle mass ratio.[200-206] Patients with HF may also experience a shift from oxidative type I towards glycolytic type II muscle fibers, reduced capillary-to-fiber ratio, reduced oxidative enzymes and reduced mitochondria density, size and function,[205-210] which significantly impair oxidative metabolism and limit functional capacity and exercise tolerance.[31,205] Furthermore, reduced hemoglobin concentration (anemia) and iron deficiency are common in patients with HF and significantly limit the O_2 carrying capacity of the blood. Due to the reduced CaO_2, anemia is significantly associated with an impaired $C[a\text{-}v]O_2$ and peak $\dot{V}O_2$.[31,211,212]

In summary, patients with HFpEF and HFrEF have a similarly depressed chronotropic response to exercise, whereas the ability to increase SV seems to play a larger role in patients with HFrEF compared to HFpEF, who are more likely limited by extracardiac factors.[138,144,199,213,214] However, it is important to emphasize that the abnormalities responsible for exercise intolerance are highly heterogeneous across the spectrum of patients with HF and should not be considered in isolation as they may interact with each other.[146,199] In addition to factors directly related to the pathophysiology of HF, many patients, particularly those with HFpEF, have multiple comorbidities (e.g., obesity, hypertension, diabetes mellitus, chronic obstructive lung disease, psychiatric disorders) that may further exacerbate exercise intolerance.[31,45,48,215] Accordingly, patients with HFpEF are generally suffering from multiple defects affecting both O_2 delivery and utilization.[146]

1.4. Effects of Exercise Training in Heart Failure

Even though some pharmacological trials have revealed positive outcomes, the overall effects of pharmacological agents on exercise tolerance and QoL are not convincing, particularly in HFpEF.[78] Instead, these parameters are generally considered to be most effectively increased by regular ET.[78] According to a recent meta-analysis including 131 ET studies in HF with a mean duration of 18 weeks (69 endurance training only,

6 resistance training only, 56 combination of both), 84 ET studies evaluated the effects on peak $\dot{V}O_2$.[216] Of those, 78 (93%) reported a significantly higher change in peak $\dot{V}O_2$ following ET compared to non-exercising control groups (mean difference: 3.0 [95% CI, 2.5 to 3.4]).[216] Most of these studies were conducted in HFrEF, and besides a large variety of different ET regimens (e.g., cycling, walking, resistance training, dancing, step aerobics, Tai Chi), many studies have been conducted with a relatively long follow-up. For instance, the most recent Cochrane review included 44 ET studies in HFrEF lasting ≥ 6 months.[217] Based on these trials, ET is associated with improved QoL (standardized mean difference: -0.60 [95% CI, -0.82 to -0.39]), a reduced risk for all-cause hospitalizations (relative risk: 0.70 [95% CI, 0.60 to 0.83]) and HF-specific hospitalization (relative risk: 0.59 [95% CI, 0.42 to 0.84]), and may reduce long-term (> 12 months) all-cause mortality (relative risk: 0.88 [95% CI, 0.75 to 1.02]).[217] Whereas most studies were performed with a duration ≤ 1 year, it was also shown that regular ET can produce sustainable improvements in exercise tolerance and QoL, as well as a lower rate of hospital admissions and mortality during a 10-year follow-up.[218]

In HFpEF, evidence for the effects of regular ET mainly results from small short-term intervention trials. So far, only 7 RCTs with a total (mean) patient number of N = 376 (N = 54) and a maximum (mean) duration of 24 weeks (16.6 weeks) evaluated the effects of 'conventional' ET vs. control (CON) *(Table 2)*.[220-226] Compared to CON, ET significantly improved parameters of exercise tolerance in 6 studies,[220-222,224-226] QoL in 3 studies,[220,222,225] and metrics of diastolic or systolic function in 2 studies *(Table 2)*.[222,224] All of these studies evaluated the effects of endurance ET. However, in the SECRET trial, patients were randomly allocated to 4 groups (ET, diet, ET plus diet or CON) and analyzed in a 2 × 2 factorial design (ET vs. no ET; diet vs. no diet),[226] and in the Ex-DHF pilot trial, endurance ET was supplemented by resistance training, which produced the so far highest difference in change in peak $\dot{V}O_2$ between groups (mean difference 3.3 ml/kg/min [95% CI, 1.8 to 4.8]).[222] According to a recent meta-analysis[229] including all of the these RCTs and one non-randomized ET trial in HFpEF,[213,220-226] the ET groups had a significantly higher change in peak $\dot{V}O_2$ (mean difference 1.7 mL/kg/min [95% CI, 1.0 to 2.3]), 6-MWT (mean difference 33.9 m [95% CI, 12.4 to 55.4]) and QoL (Minnesota Living with Heart Failure Questionnaire [MLHFQ]; Short Form Health Questionnaire 36 [SF-36] Physical Component Score; both $P < 0.05$)

Table 2: Overview of randomized clinical trials evaluating the effects between exercise training (ET) and non-exercising controls (CON) or between high intensity interval training (HIIT) and moderate continuous exercise training (MCT) in patients with heart failure with preserved ejection fraction (adapted from Mueller & Halle[219])

Study [Trial Duration]	No. of Patients	Exercise Training Characteristics (Frequency×Duration per Week, Intensity, Mode)	Differences between groups for change in … Exercise Tolerance	Echo Measures	Quality of Life
Exercise Training (ET) vs. Control (CON)					
Gary 2004 [220] [12 weeks]	**ET:** n=16 **CON:** n=16	Increase from 3× individual duration/week at 40% HRR to 3×30 min/week at 60% HRR (Walking)	**6-MWT:** favors ET	- - -	**MLHFQ, GDS:** favors ET
Kitzman 2010 [221] [16 weeks]	**ET:** n=26 **CON:** n=27	Increase from 3× individual duration/week at 40-50% HRR to 3×60 min/week at 60-70% HRR (Walking + Cycling)	**Peak $\dot{V}O_2$, VT1, 6-MWT:** favors ET	no sign. diff.	**MHLFQ, SF-36, CES-D:** no sign. diff.
Edelmann 2011 [222] [12 weeks]	**ET:** n=46 **CON:** n=21	**Endurance:** Increase from 2×20 min/week at 40-50% peak $\dot{V}O_2$ to 3×40 min/week at 70%-peak-$\dot{V}O_2$ (Cycling) **plus Strength (from week 5):** 2×6 exercises/week with 1×15 repetitions/exercise at 60-65% 1-RM)	**Peak $\dot{V}O_2$, VT1, NYHA class:** favors ET **6-MWT:** no sign. diff.	**E/e', e', LAVI:** favors ET	**SF-36 PCS:** favors ET **MLHFQ:** no sign. diff.
Smart 2012 [223] [16 weeks]	**ET:** n=16 **CON:** n=14	3x30 min/week at 60-70% peak $\dot{V}O_2$, increase of intensity by 2-5 watts/week (Cycling)	**Peak $\dot{V}O_2$, VT1:** no sign. diff.	no sign. diff.	**MLHFQ, CDS:** no sign. diff.
Alves 2012 [224] [24 weeks]	**ET:** n=20 **CON:** n=11	Increase from 3×40 min/week to 3×62 min/week, 10 min Warm-Up, 5×3 min to 7×5 min at 70-75% peak HR, interspersed by 1min active recovery at 45-55% peak HR, 10 min Cool-Down with stretching (Walking or Cycling)	**Calculated MET [a]:** favors ET	**LVEF, E/A, DT:** favors ET	- - -
Kitzman 2013 [225] [16 weeks]	**ET:** n=32 **CON:** n=31	Increase from 3×40 min/week at 40-50% HRR to 3×60 min/week at 70% HRR (Walking + Cycling + Arm Ergometer)	**Peak $\dot{V}O_2$, VT1, 6-MWT:** favors ET	no sign. diff.	**SF-36 PCS / MCS:** favors ET **MLHFQ:** no sign. diff.
Kitzman 2016 [226] [20 weeks]	**ET:** n=26 **Diet:** n=24 **ET+Diet:** n=25 **CON:** n=25	3×60 min/week, individual increase of intensity, as tolerated (Walking)	**Peak $\dot{V}O_2$, 6-MWT, NYHA class:** favors ET **VT1:** no sign. diff.	no sign. diff.	**KCCQ, SF-36 PCS:** no sign. diff.

continued on next page…

Table 2 (continued)

Study [Trial Duration]	No. of Patients	Exercise Training Characteristics (Frequency×Duration per Week, Intensity, Mode)	Differences between groups for change in … Exercise Tolerance	Echo Measures	Quality of Life
High-Intensity Interval Training (HIIT) vs. Moderate Continuous Training (MCT)					
Angadi 2015 [227] [4 weeks]	**MCT:** n=6 **HIIT:** n=9	**MCT:** Increase from 3×30 min/week to 3×45 min/week, 10 min Warm-Up at 50% peak HR, 15 min at 60% peak HR to 30 min at 70% peak HR, 5 min Cool-Down at 50% peak HR (Walking) **HIIT:** Change from 3×45 min/week to 3×38 min/week, 10 min Warm-Up at 50% peak HR, 8×2 min at 80-85% peak HR to 4×4 min at 85-90% peak HR, interspersed by 2 min to 3 min active recovery, 5 min Cool-Down at 50% peak HR (Walking)	**Peak $\dot{V}O_2$:** sign. improvement in HIIT [b] **VT1:** no sign. changes [b]	**DD grade, E, DT:** sign. improvement in HIIT [b]	- - -
Donelli da Silveira 2020 [228] [12 weeks]	**MCT:** n=12 **HIIT:** n=12	**MCT:** 3×47 min/week at 50-60% peak $\dot{V}O_2$ / 60-70% peak HR / Borg RPE scale 11-13 (Walking) **HIIT:** 3×38 min/week, 10 min Warm-up, 4×4 min at 80-90% peak $\dot{V}O_2$ / 85-95% peak HR / Borg RPE scale 15-17, interspersed by 3 min active recovery (Walking)	**Peak $\dot{V}O_2$:** favors HIIT **VT1:** no sign. diff.	no sign. diff.	**MLHFQ:** no sign. diff.

Abbreviations: ***CDS*** *= Hare-Davis Cardiac Depression Scale;* ***CES-D*** *= Center for Epidemiological Studies Depression survey;* ***DD*** *= diastolic dysfunction;* ***DT*** *= deceleration time of the early diastolic transmitral flow velocity (a marker of left ventricular passive stiffness);* ***E*** *= early diastolic transmitral flow velocity;* ***e'*** *= early diastolic mitral annular tissue velocity (a marker of active relaxation);* ***E/A*** *= ratio of early (E) to late atrial (A) diastolic transmitral flow velocity (a marker of LV filling pressures);* ***E/e'*** *= ratio of early diastolic transmitral flow velocity (E) to early diastolic mitral annular tissue velocity (e') (a marker of left ventricular filling pressures);* ***GDS*** *= Geriatric Depression Score;* ***HRR*** *= heart rate reserve;* ***KCCQ*** *= Kansas City Cardiomyopathy Questionnaire;* ***LAVI*** *= left atrial volume indexed to body surface area (a marker of left atrial dilation / left ventricular filling pressures);* ***LVEF*** *= left ventricular ejection fraction;* ***MET*** *= metabolic equivalent of task;* ***MLHFQ*** *= Minnesota Living with Heart Failure Questionnaire;* ***NYHA*** *= New York Heart Association;* ***RPE*** *= Rating of Perceived Exertion;* ***SF-36 PCS*** *= Short Form Health Questionnaire 36 Mental Component Score;* ***SF-36 PCS*** *= Short Form Health Questionnaire 36 Physical Component Score;* ***$\dot{V}O_2$*** *= oxygen consumption;* ***VT1*** *= first ventilatory threshold;* ***1-RM*** *= 1-repetition maximum;* ***6-MWT*** *= Six-Minute Walking Test*

[a] *1 MET equals a $\dot{V}O_2$ of 3.5 mL/kg/min; MET were calculated from total exercise time during symptom-limited treadmill exercise testing via the following formula:* $MET = [(speed \times 0.1) + (grade \times speed \times 1.8) + 3.5] \div 3.5$*, where grade is expressed in decimal form and speed in meters per minute*

[b] *did not report between-group differences nor standard deviations for the within-group changes that would allow the calculation of between-group differences.*

compared to CON, whereas none of the echocardiographic measurements were significantly different between groups after 12 to 24 weeks (all P > 0.05).

1.4.1. High-Intensity Interval Training

In a landmark study published in 2007, Wisløff et al. evaluated the effects of high-intensity interval training (HIIT) vs. moderate continuous training (MCT) vs. CON in 27 patients with HFrEF.[230] According to the authors, the rationale for their HIIT program (10 min warm-up at 60-70% peak HR, 4 × 4 min high-intensity intervals at 90-95% peak HR, interspersed by 4 × 3 min active recovery at 50-70% peak HR) was that the intermittent low-intensity periods allow the patients to exercise at significantly higher intensities, which challenges the heart's pumping ability and may improve cardiac function and exercise tolerance to a greater degree compared to 'conventional' MCT.[230] Indeed, after 12 weeks of ET, peak $\dot{V}O_2$ improved by an average of 14% with MCT compared to 47% with HIIT (P < 0.001).[230] Despite the small number of participants (9 per group) and 74% males, this study created a lot of 'hype' about HIIT in patients with HF or other cardiac diseases. Although none of the follow-up studies in HFrEF have been able to replicate this (large) difference between HIIT and MCT,[231] including the SMART-EX trial with 261 patients and a mean difference between HIIT and MCT of -0.4 mL/kg/min [95% CI, -1.7 to 0.8],[232] HIIT has emerged as an alternative ET regimen that may be considered in stable, low-risk patients with HFrEF.[30,233]

In addition to one non-randomized controlled trial showing superiority of HIIT vs. CON,[213] only two small (N = 15 and N = 24) short-term (4 weeks and 12 weeks) RCTs have so far evaluated the effects of HIIT compared with MCT in patients with HFpEF *(Table 2)*.[227,228] These studies also indicated a potential benefit of HIIT in HFpEF, however, uncertainty remains regarding the effects of different exercise modes due to the low patient numbers and the lack of follow-up periods > 24 weeks. The primary aim of the study presented in this dissertation was to evaluate whether HIIT, MCT and CON have different effects on peak $\dot{V}O_2$ and other CPET parameters, indices of diastolic function and QoL after 3 and 12 months.[234]

1.4.2. Inter-individual Response Variability

Even though ET has a class I recommendation for patients with HFpEF[233] and might be the most effective treatment to increase exercise tolerance, it is associated with a

certain response heterogeneity. As for any given treatment, some patients show better responses than others despite a similar adherence rate. The so-called heterogeneity of treatment effects or inter-individual response variability can in part be explained by measuring errors or day-to-day variability, however, it is anticipated that certain baseline patient characteristics may be associated with the heterogeneous response to the same treatment.[235] To overcome the 'one-size-fits-all' approach that ignores these response heterogeneities, the concept of personalized medicine has led to an increasing interest in identifying these factors, which would enable physicians to select a treatment that has a high chance of being successful for every individual patient. This seems to be particularly important in HFpEF, as HFpEF is a multifactorial and highly heterogenous disease in which most patients suffer from several co-existing comorbidities and multiple O_2-pathway defects.[45,48,146]

It is generally assumed that patients with the highest deficits also have the highest potential to benefit from a treatment targeting these deficits. Accordingly, patients with a lower baseline peak $\dot{V}O_2$ should be able to more easily improve with ET. Interestingly, this has not been confirmed in a recent individual participant meta-analysis in 3,990 patients with HF (97% with HFrEF).[236] As previously described *(equation (11) and equation (12) in chapter 1.3)*, $\dot{V}O_2$ is the product of HR, SV and C[a-v]O_2. Accordingly, a change in peak $\dot{V}O_2$ (mL/min) must be mediated through a change in any or a combination of these components and / or a reduction in body weight, when expressed as mL/kg/min. Peak HR is highly dependent upon age and declines with approximately 6.4 beats/min per decade.[237] However, in contrast to peak SV and C[a-v]O_2, peak HR is generally not significantly different between trained and untrained individuals.[237-239] Consequently, a meta-analysis including ET trials in healthy middle aged and older adults showed that the improved peak $\dot{V}O_2$ following endurance ET was associated with an increase in SV and C[a-v]O_2, whereas peak HR did not significantly increase.[240] During CPET, the product of SV and C[a-v]O_2 can be indirectly obtained as O_2-pulse (ratio of $\dot{V}O_2$ and HR) *(13)*.

$$O_2\text{-}pulse = \dot{V}O_2 \div HR = SV \times C(a-v)O_2 \quad (13)$$

Even though all components of the Fick equation can be significantly reduced in HFpEF *(see chapter 1.3)*, most studies also did not show a significant improvement in peak HR despite a significant improvement in peak $\dot{V}O_2$ following ET in HFpEF (5 out

of 7 RCTs,[220,222-224,226] 1 out of 1 non-randomized trial[213]), indicating that – similar to healthy individuals – the primary mediators may be $C[a\text{-}v]O_2$ and / or SV. So far, only two controlled studies (1 substudy[241] of Kitzman et al. 2010[221], 1 non-randomized trial[213]) evaluated the effects of ET on SV and $C[a\text{-}v]O_2$. In both trials, ET significantly improved $C[a\text{-}v]O_2$, whereas change in peak SV was not significantly different between the groups. Based on these findings in both healthy subjects and patients with HFpEF, and the concept of a higher potential for improvement when baseline levels are more reduced, it was hypothesized that in patient with HFpEF, baseline peak O_2-pulse is inversely associated with the change in peak $\dot{V}O_2$ following 3 months of supervised ET (HIIT and MCT) compared with CON and may be a better predictor of the ET-induced change in peak $\dot{V}O_2$ than baseline peak $\dot{V}O_2$.[242]

2. Methods

This dissertation is based on the OptimEx-Clin trial (Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure) – a prospective, randomized, controlled multicenter trial that was conducted at five European sites (Munich, Germany; Leipzig, Germany; Antwerp; Belgium; Berlin, Germany; Trondheim, Norway) from 2014 to 2018. The primary aim of the study was to investigate the effects of HIIT, MCT and CON in patients with HFpEF over 12 months – divided into 3 months of supervised ET followed by 9 months of home-based ET. The study protocol conforms with the principles of the Declaration of Helsinki and was approved by the local ethic committees at all participating sites. All participants provided written informed consent. The study design and all results included in this dissertation have been previously published.[234,242,243] Moreover, a reply letter related to the main manuscript and 4 additional substudies of the OptimEx-Clin trial have been published to date.[244-248]

2.1. Participants and Intervention

Sedentary, stable patients with signs and symptoms of HFpEF[249] were eligible to participate in the trial. If all inclusion and none of the exclusion criteria were met *(Table* 3*)*, patients were randomly assigned (1:1:1) to HIIT, MCT and CON via block randomization (first block size of 12 followed by block sizes of 6) stratified by study site.

Table 3: Inclusion and exclusion criteria of the OptimEx-Clin trial (adapted from Suchy et al.[243])

Inclusion criteria	**Exclusion criteria**
• signs and symptoms of heart failure according to NYHA functional class II-III • LVEF ≥ 50% • E/e' medial > 15 **or** E/e' medial of 8-15 with increased NT-proBNP ≥ 220 pg/mL or BNP ≥ 80 pg/mL • Age ≥ 40 years • Clinically stable for ≥ 6 weeks • Optimal medical treatment ≥ 6 weeks • Structured exercise < 2×30 min/week • Written informed consent	• Non-HFpEF causes for heart failure symptoms (significant valvular or coronary disease, uncontrolled hypertension or arrhythmias, primary cardiomyopathies) • Significant pulmonary disease (FEV1 < 50% predicted; COPD GOLD III-IV) • Myocardial infarction in the last 3 months • Signs of ischemia during CPET • Comorbidity that may influence 1-year prognosis • Inability to exercise or other conditions that may interfere with exercise intervention • Participation in another clinical trial

Abbreviations*:** ***BNP *= brain natriuretic peptide;* ***COPD*** *= chronic obstructive pulmonary disease;* ***CPET*** *= cardiopulmonary exercise testing;* ***E/e'*** *= estimated left ventricular filling pressure;* ***FEV1*** *= forced expiratory volume within 1 second;* ***GOLD*** *= Global Initiative for Chronic Obstructive Lung Disease;* ***HFpEF*** *= heart failure with preserved ejection fraction;* ***LVEF*** *= left ventricular ejection fraction;* ***NT-proBNP*** *= N-terminal pro brain natriuretic peptide;* ***NYHA*** *= New York Heart Association*

Over the entire duration of the study, patients randomized to HIIT should have performed 3 ET sessions à 38 min/week, while patients randomized to MCT were scheduled to perform 5 sessions à 40 min/week. According to the initial study design,[243] exercise intensities were based on the percentage of peak HR. However, due to high prevalence of chronotropic incompetence in HFpEF, we applied percentage of HRR, which were individually calculated and adapted by each study site using the Karvonen formula at baseline, 6 weeks, 3 months and 6 months *(14)*.

$$Target\ HR = a\ \times (peak\ HR - resting\ HR) + resting\ HR \qquad (14)$$

where *a* is the prescribed percentage of HRR. Resting HR and peak HR were derived from resting ECG and the symptom-limited CPET at each visit. A HIIT session consisted of 10 min warm-up at 35-50% of HRR and was followed by 4 × 4 min intervals at 80-90% HRR, interspersed by 4 × 3 min of active recovery periods and exercise intensity during MCT sessions were prescribed at 35-50% HRR *(Figure 4)*. If % HRR was not applicable (e.g., patients with severe arrhythmia or a vibration-sensitive pacemaker), exercise intensities were prescribed using the Borg rating of perceived exertion (RPE) scale scores 15-17 for HIIT and 11-13 for MCT. The RPE scale ranges from 6 (no exertion at all) to 20 (maximal exertion) and is used to evaluate the subjective level of effort during exercise *(Appendix B)*. The basic idea of the scale was that it roughly corresponds to the HR during exercise when the value is multiplied by 10 (e.g., RPE 12 should be approximately 120 beats/min in 30-50 year old healthy individuals).[250]

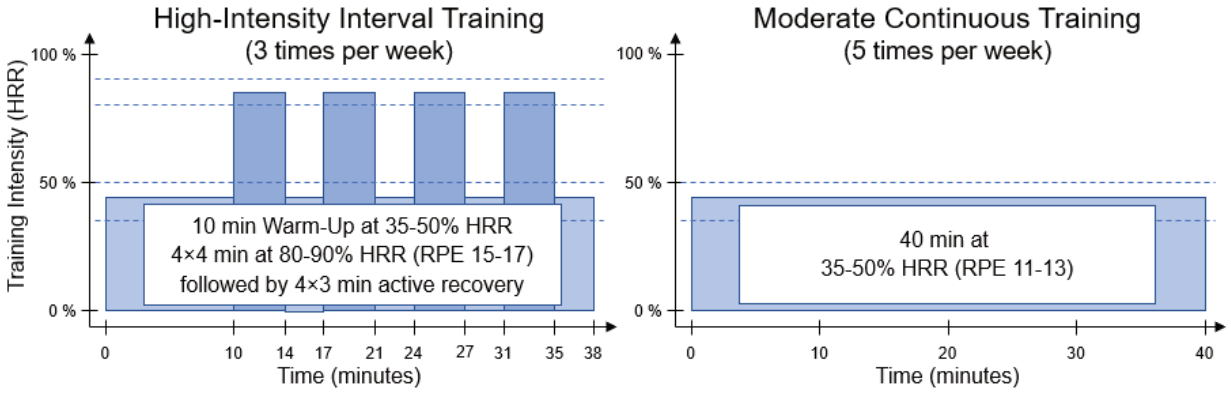


Figure 4: Exercise training prescriptions (frequency, duration and intensity) for patients allocated to 12 months of high-intensity interval training (left) and moderate continuous training (right). ***Abbreviations*****: HRR** *= heart rate reserve;* **RPE** *= rating of perceived exertion*

Until the 3-month follow-up visit, 3 ET sessions per week were performed under supervision, and patients in the MCT group performed 2 additional home-based sessions per week. From month 4, ET was continued at home. For the home-based training, all patients received a stationary cycle ergometer that was provided for free. Furthermore, all patients received a HR sensor (Polar H7, Polar Electro GmbH) and a smartphone (iPhone 4S, Apple Inc) to record the training sessions with an application created for the OptimEx-Clin trial (Vitaphone GmbH part of vitagroup AG). After each training session, patients received an immediate automatic feedback regarding their training intensity *(Figure 5)*. The records were also transferred to a telemedicine database (Vitaphone GmbH part of vitagroup AG) to allow a timely feedback by the study personnel, especially during home-based training. Records were checked at least every 2 weeks. If the attendance rate dropped below 70% of scheduled ET sessions, patients were contacted by phone and encouraged to increase adherence. In addition, trainers (for supervised training) and patients (for home-based training) filled out paper-based training diaries as a 'back-up' to the recorded data. All patients (ET and CON) were treated according to current guidelines including general recommendations for physical activity, i.e., regular physical activity of at least 150 min/week with moderate intensity or 75 min/week with severe intensity.[251]

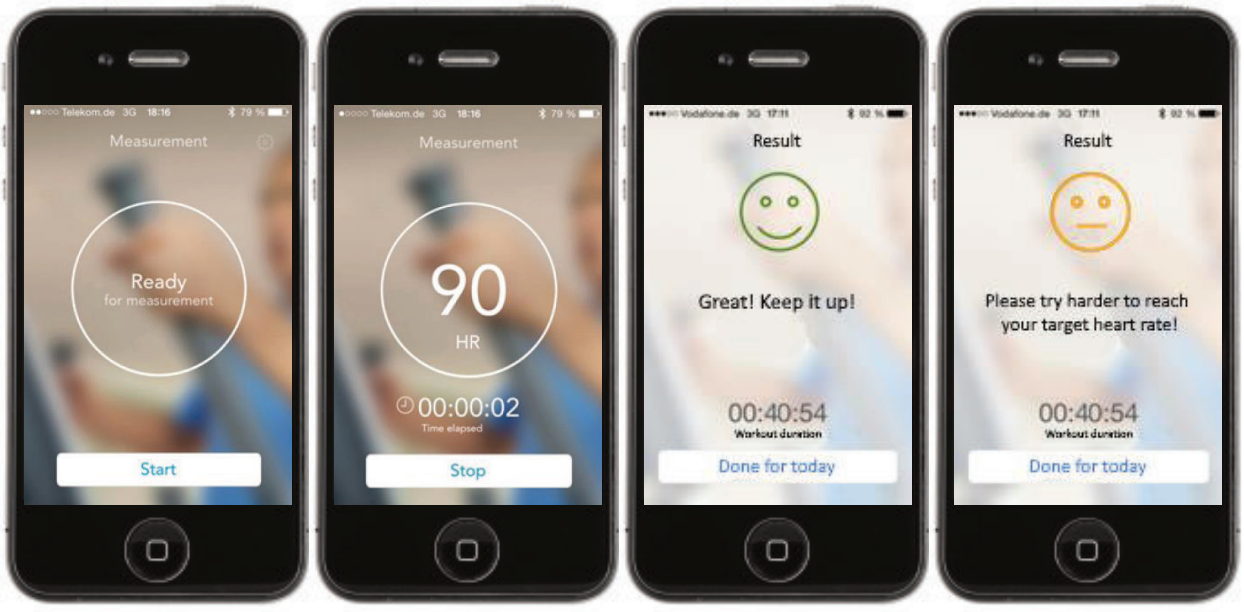


Figure 5: Smartphone application with (from left) starting screen, heart rate and duration monitor during the session, positive feedback (happy green smiley) if intensity targets were met, and neutral feedback (neutral orange smiley) if intensity targets were not met (modified from 19 Studio/Shutterstock.com; with permission)

2.2. Clinical Assessments

All examinations were performed by trained staff according to standard operating procedures at baseline and 3, 6 and 12 months after inclusion. These examinations comprised anamnesis, anthropometry, ECG, blood analysis, echocardiography, CPET and several questionnaires including the Kansas City Cardiomyopathy Questionnaire (KCCQ). Furthermore, body plethysmography was performed during screening to exclude significant pulmonary disease, and in ET groups, CPET was repeated after 6 weeks to adjust training intensity.

Blood samples were collected in a fasting state. Part of the blood samples were analyzed in local laboratories to ensure inclusion criteria (natriuretic peptides) and guideline recommended drug therapy, whereas the major part was stored in a biobanking system. Main analyses on N-terminal pro brain natriuretic peptide (NT-proBNP) *(see chapter 2.3)* were performed by a central core laboratory (Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria). ECG and echocardiography were performed in supine position. At screening, LVEF and estimated LV filling pressure (E/e' medial) were measured on-site to assess eligibility, however, all parameters used for statistical analyses were analyzed by the Academic Echocardiography Core Laboratory at Charité Berlin (Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany), blinded to treatment arm assignment.

CPET was performed on stationary cycle ergometers at the end of each visit. After 4 min under resting conditions, the active test phase started at 20 watts and was increased by 10 watts/min until symptom-limited exhaustion *(Figure 6)*. Raw data were exported (Microsoft Excel Export, 10-second averages) and transferred to the CPET Core Laboratory in Munich (Department of Prevention and Sports Medicine, University Hospital Klinikum rechts der Isar, Technical University of Munich, Munich, Germany) to perform blinded analyses using a customized evaluation software (Microsoft Excel) *(Appendix C)*. Peak $\dot{V}O_2$ was calculated as the highest 30-second average within the last minute of exercise.[252] VT1 was defined using the V-slope method[117] and $\dot{V}E/\dot{V}CO_2$ slope was calculated throughout the entire test,[135,136] excluding the first minute of exercise (onset of exercise). For the predictor analysis, peak HR and peak O_2-pulse were calculated as the 30-second-average from the same time span as peak $\dot{V}O_2$.[242]

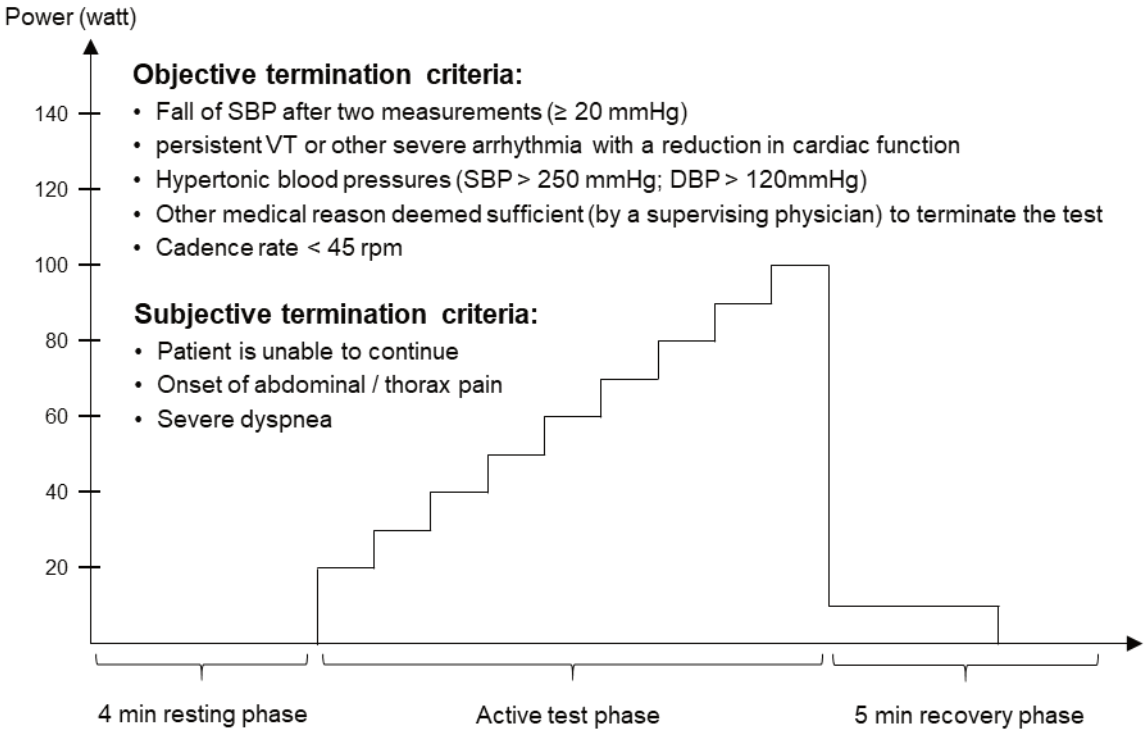


Figure 6: Protocol and termination criteria for the symptom-limited cardiopulmonary exercise tests. All tests started with a 4-min resting phase, before the initial load of 20 watts was increased by 10 watts/min until symptom-limited exhaustion (occurrence of objective or subjective termination criteria), followed by 3 min of active recovery at 10 watts and 2 min of passive recovery. ***Abbreviations:*** ***DBP*** *= diastolic blood pressure;* ***SBP*** *= systolic blood pressure;* ***rpm*** *= revolutions per minute;* ***VT*** *= ventricular tachycardia*

At each follow-up visit, any unfavorable or unintended medical events that occurred during the trial period were documented as an AE. If the event resulted in a life-threatening experience, inpatient hospitalization, prolongation of an existing hospitalization, persistent or significant disability, or death the event was categorized as a serious adverse event (SAE) by the local investigators. AEs and SAEs were finally evaluated by an independent safety committee, which was also blinded to treatment arm assignment. As previously described, adherence was closely monitored by the respective study site to allow timely feedback, however, final adherence data was assessed by the Exercise Training Core Laboratory in Munich (Department of Prevention and Sports Medicine, University Hospital Klinikum rechts der Isar, Technical University of Munich, Munich, Germany) based on the recorded data from the smartphone application and the individual paper-based training diaries *(Appendix D)*.

2.3. Outcomes

In the main analysis (evaluation whether HIIT, MCT and CON have different effects over 3 and 12 months), the primary endpoint was the change in relative peak $\dot{V}O_2$ (mL/kg/min) from baseline to 3 months.[234] Secondary endpoints included the change in relative peak $\dot{V}O_2$ from baseline to 12 months as well as changes in diastolic function [E/e' medial, early diastolic mitral annular tissue velocity (e' medial), left atrial volume index (LAVI)], workload at VT1, $\dot{V}E/\dot{V}CO_2$ slope, NT-proBNP and the health-related QoL domain of the KCCQ (score range: 0-100, higher scores reflect better QoL) from baseline to 3 and 12 months *(Table 4)*. Changes in flow-mediated dilation, a marker of endothelial (dys)function, were obtained only in a subgroup of patients and are therefore not reported in the present analysis. All endpoints were calculated as the difference between follow-up and baseline visit *(15)*.

$$Change = Follow\text{-}Up - Baseline \tag{15}$$

Table 4: A priori defined endpoints included in the main analysis of the OptimEx-Clin trial[234]

Endpoints	Rationale
Change in peak $\dot{V}O_2$ after 3 and 12 months	gold standard for the assessment of exercise capacity;[31] negatively associated with signs and symptoms of HF and risk of hospitalization and mortality[88,89,253]
Change in workload at VT1 after 3 and 12 months	gold standard for the assessment of functional capacity;[31] negatively associated with signs and symptoms of HF and risk of hospitalization and mortality[127,253]
Change in $\dot{V}E/\dot{V}CO_2$ slope after 3 and 12 months	most powerful parameter of ventilatory efficiency reflecting ventilation-perfusion mismatch;[106,115,254] positively associated with pulmonary and LV filling pressures and risk of hospitalization and mortality[88,130]
Change in the KCCQ-QoL after 3 and 12 months	highly relevant patient-oriented outcome; negatively associated with signs and symptoms of HF and risk of hospitalization and mortality[255]
Change in E/e' medial after 3 and 12 months	positively associated with LV filling pressures and the risk of major adverse cardiac events and mortality;[256-258] was used as the primary diagnostic criteria for HFpEF (according to Paulus et al.[249]) in the present study
Change e' medial after 3 and 12 months	reflects myocardial fiber lengthening; used as a marker of LV active relaxation (higher values are associated with better relaxation)[257,259]
Change in LAVI after 3 and 12 months	positively associated with left atrial dilation and pressure; reflects the cumulative effects of increased LV filling pressures over time[257]
Change in NT-proBNP after 3 and 12 months	synthesized and secreted in response to myocyte stretch trough LV pressure overload or volume expansion (high LV filling pressures);[260] positively associated with the risk of HF readmission and mortality[261,262]

***Abbreviations**: **E** = early diastolic transmitral flow velocity; **e'** = early diastolic mitral annular tissue velocity; **HF** = heart failure; **KCCQ** = Kansas City Cardiomyopathy Questionnaire; **LAVI** = left atrial volume indexed to body surface area; **LV** = left ventricular; **NT-proBNP** = N-terminal pro-brain natriuretic peptide; **QoL** = quality of life; **$\dot{V}E/\dot{V}CO_2$ slope** = ventilation to carbon dioxide production slope; **$\dot{V}O_2$** = oxygen consumption; **VT1** = first ventilatory threshold*

In the predictor analysis, the influence of baseline parameters on the change in relative peak VO_2 (mL/kg/min; primary endpoint) and the change in relative VO_2 at VT1 (mL/kg/min; secondary endpoint) were analyzed.[242] The analyses were limited to the supervised phase from baseline to 3 months. To ensure comparability between subjects with different baseline values, all changes were calculated as %-change from baseline *(16)*.[242]

$$\%\,Change = (Follow\text{-}Up \div Baseline - 1) \times 100 \quad (16)$$

Based on the aforementioned hypothesis of this secondary analysis, predictors were limited to the baseline values of relative peak $\dot{V}O_2$ and its determinants that were measured in the OptimEx-Clin trial, i.e., absolute peak $\dot{V}O_2$ (mL/min), peak HR, peak O_2-pulse, weight, and hemoglobin as one of the determinants of $C[a\text{-}v]O_2$.[242]

2.4. Sample Size Calculation

Based on the results of the Ex-DHF pilot trial,[222] a mean difference ± standard deviation (SD) in change in peak $\dot{V}O_2$ of 2.5 ± 3.5 mL/kg/min at 3 months was assumed between MCT and CON. This difference in peak $\dot{V}O_2$ of 2.5 ml/kg/min was also defined as the minimal clinically important difference (MCID) that would be relevant to detect. With an additional difference of 2.5 ± 3.5 mL/kg/min between HIIT and MCT and an α-level of 5%, a sample size of 45 patients per group enabled to obtain a power ≥ 90% for pairwise group comparisons. However, due to an expected moderate number of missing values and the multicenter design, the planned sample size was increased to 180 patients (60 per group).[234,243]

2.5. Statistical Analyses

All statistical analyses were performed using R Statistical Software Versions 3.6.0 to 4.1.1 (Foundation for Statistical Computing, Vienna, Austria)[263] with an α-level of 5%. In the main analysis, mean changes of all three groups were compared using analysis of variance considering all available data.[234] Additional pairwise comparisons were performed with t-tests for independent samples. To account for missing values in the primary endpoint (change in peak $\dot{V}O_2$ from baseline to 3 months), a prespecified multiple imputation was performed. Missing values at 3-month follow-up were imputed by predictive mean matching (R library MICE)[264] using a model including the baseline

variables age, sex, body mass index (BMI), NT-proBNP, E/e' medial, peak $\dot{V}O_2$ and HF-related medication (ACE inhibitors, ARNI, beta-blockers and diuretics). Ten datasets with imputed values were generated and pooled (function mi.anova provided in the R library miceadds).[265] If the global null hypothesis could be rejected (all group means being equal in the pooled data set), pairwise comparisons for each of the ten imputed datasets were performed and results were aggregated (pool function in R library mice).[264] Pooled estimates for the difference in change in peak $\dot{V}O_2$ between groups are presented as means and 95% CI. By not adding the randomization group as a variable for imputation, this approach produces rather conservative results.[234] Change in peak $\dot{V}O_2$ at 3 months was also analyzed within prespecified subgroups (study site, sex, BMI [split at 30 kg/m^2), age (median split), E/e′ medial (median split), and peak $\dot{V}O_2$ (median split)] considering complete cases only. In the subgroup analysis, tests for interaction between study group and each subgroup variable were performed by fitting linear regression models to the data.[234] Moreover, a per-protocol analysis excluding all patients that performed < 70% of the prespecified HIIT or MCT sessions at 3 and 12 months was conducted for all endpoints.[234]

For the primary analysis of individual responses, which requires a substantially larger sample size than group-based comparisons,[235] HIIT and MCT were combined to one ET group to increase power.[242] Analyses of group-based changes in relative peak $\dot{V}O_2$ and its determinants were performed using t-tests for independent means, whereas comparisons of ordinal data were performed with the Mann-Whitney-U test.[242] To determine the contribution of change in peak O_2-pulse, peak HR and weight for the change in relative peak $\dot{V}O_2$, a causal mediation analysis with multiple correlated mediators was performed (R library 'multimediate').[242,266,267] The influence of baseline peak $\dot{V}O_2$ (relative and absolute), peak HR, peak O_2-pulse, weight and hemoglobin on the change in relative peak $\dot{V}O_2$ was assessed by linear regression models with main effects of each predictor and group (independent variables) as well as their interaction term (predictor × group).[242] Because peak $\dot{V}O_2$, peak HR, peak O_2-pulse and body weight are partially related and accordingly influence each other, the relationships between the changes in these parameters were also analyzed. To account for influential data points (outliers or high leverage points), regression analyses were performed as robust linear regressions with MM-type estimators (function 'rlm' in R library 'MASS' and 'f.robftest' in R library 'sfsmisc').[268,269] By the use of an iteratively reweighted least

squares procedure fitting bisquare estimators, this method is less sensitive to single influential data points (which are still considered but receive a lower weight) and remains highly efficient as compared to ordinary least square estimates in the absence of influential data points.[242,270] The predictor analyses were also repeated in a per-protocol set excluding ET patients with adherence ≤ 70% and compared between patients with higher and lower peak RER at baseline (split at median peak RER). Moreover, we performed an additional sensitivity analysis within the original groups (HIIT vs. MCT vs. CON) using the function 'lmrob' with the recommended setting 'KS2014' in R library 'robustbase' to calculate the global P-values for the comparisons between all 3 groups.[242,271]

For all analyses, patients were analyzed according to the randomization (HIIT vs. MCT vs. CON or ET vs. CON) and CIs have not been adjusted for multiplicity. Therefore, the results of the secondary endpoints of the main analysis and the results of the predictor analysis should be interpreted as exploratory.[234,242]

3. Results

The results presented in this dissertation have been previously published.[234,242] The full manuscripts, supplemental materials[234,242] and copy right licenses can also be found in *Annex I (Publication I)* and *Annex II (Publication II)*.

3.1. Publication I – Main Analysis of the OptimEx-Clin Trial

All results presented in this section have been published in "***Mueller S**, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM, Esefeld K, von Korn P, Christle JW, Haykowsky MJ, Linke A, Wisløff U, Adams V, Pieske B, van Craenenbroeck EM, Halle M, for the OptimEx-Clin Study Group. 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(6):542-51*".[234]

3.1.1. Summary and Individual Contribution of the PhD Candidate (Publication I)

In this manuscript, we evaluated the effects of different forms of ET on changes in exercise tolerance, diastolic function and QoL in patients with HFpEF. A total of 180 patients with HFpEF were randomly assigned to receive 12 months of HIIT (3 × 38 min/week), MCT (5 × 40 min/week) or CON (1-time advice on physical activity according to current guidelines). During the first 3 months, 3 ET sessions/week were conducted on-site, followed by 9 months of telemedically supervised home-based ET. The primary endpoint was the change in peak $\dot{V}O_2$ after 3 months. Among the 180 randomized patients, 166 (92%) and 154 (86%) completed evaluation at 3 and 12 months, respectively. Change in peak $\dot{V}O_2$ over 3 months was significantly higher for HIIT vs. CON (1.1 vs. -0.6 mL/kg/min; mean difference (including imputed data), 1.5 mL/kg/min [95% CI, 0.4 to 2.7]) and MCT vs. CON (1.6 vs. -0.6 mL/kg/min; mean difference (including imputed data), 2.0 mL/kg/min [95% CI, 0.9 to 3.1]), whereas changes between HIIT and MCT were not significantly different (1.1 vs. 1.6 mL/kg/min; mean difference (including imputed data), -0.4 mL/kg/min [95% CI, -1.4 to 0.6]). Changes in workload at VT1 were significantly higher for MCT vs. CON (8 vs. 1 watts; mean difference, 6 watts [95% CI, 2 to 11]) only. After 12 months, neither changes in peak $\dot{V}O_2$ nor workload at VT1 were significantly different between the groups

(P > 0.05). Changes in indices of diastolic function were not significantly different between groups at 3 and 12 months (all P > 0.05). After 12 months, patients in MCT had a significantly higher change in QoL compared to CON (17 vs. 6 points; mean difference, 11 points [95% CI, 2 to 19]) and significantly reduced $\dot{V}E/\dot{V}CO_2$ slope compared to HIIT (-0.7 vs. 2.0; mean difference, -2.8 [95% CI, -4.8 to -0.7]).

The doctoral candidate was not involved in the development of the study concept, design or application process. After joining the team in May 2015, he was primarily responsible for patient care at the study site in Munich, including involvement in the recruitment process, coordination of study appointments, preparation, supervision and follow-up of the study visits (e.g., performing CPETs, processing of blood samples, data entry into the database), and supervision of the ET intervention. Since Munich was the leading study site, he served as contact person and coordinator for study-related correspondence and questions within the trial consortium including the study sites, statistician, and the provider of the telemedical application and database. Furthermore, he conducted regular monitoring visits within the different study sites and was involved in preparing and conducting the regular meetings of the study group. As part of the core laboratories for CPET and ET, he was also primarily responsible for the evaluation of all CPETs and ET data of all study participants including the development of customized semi-automatic evaluation tools using Microsoft Excel and the programming language Visual Basic for Application (VBA) *(see Appendix C and Appendix D)*. After closing the database, the doctoral candidate was the primary contact person for correspondence with the statistician, was involved in the interpretation of the data and drafting of the manuscript. He prepared the figures of the manuscript and was primarily responsible for the submission process and the adaptations and responses to the reviewer and editor comments during the peer-review process. The doctoral candidate and the statistician had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

3.1.2. Results of the Main Analysis (Publication I)

Inclusion of patients lasted from July 2014 to May 2017 and the last follow-up was completed in September 2018. Among 532 patients screened for eligibility, 180 were enrolled in the trial. After blinded review of eligibility criteria for all participants based on their status before randomization,[272] 4 patients not meeting the inclusion criteria for

HFpEF were excluded from all analyses *(Appendix E)*. Ten patients were lost to follow-up within the first 3 months, and an additional 12 patients were lost until 12-month follow-up *(Figure 7)*. Baseline demographic and clinical characteristics of the included patients are shown in *Table 5*.

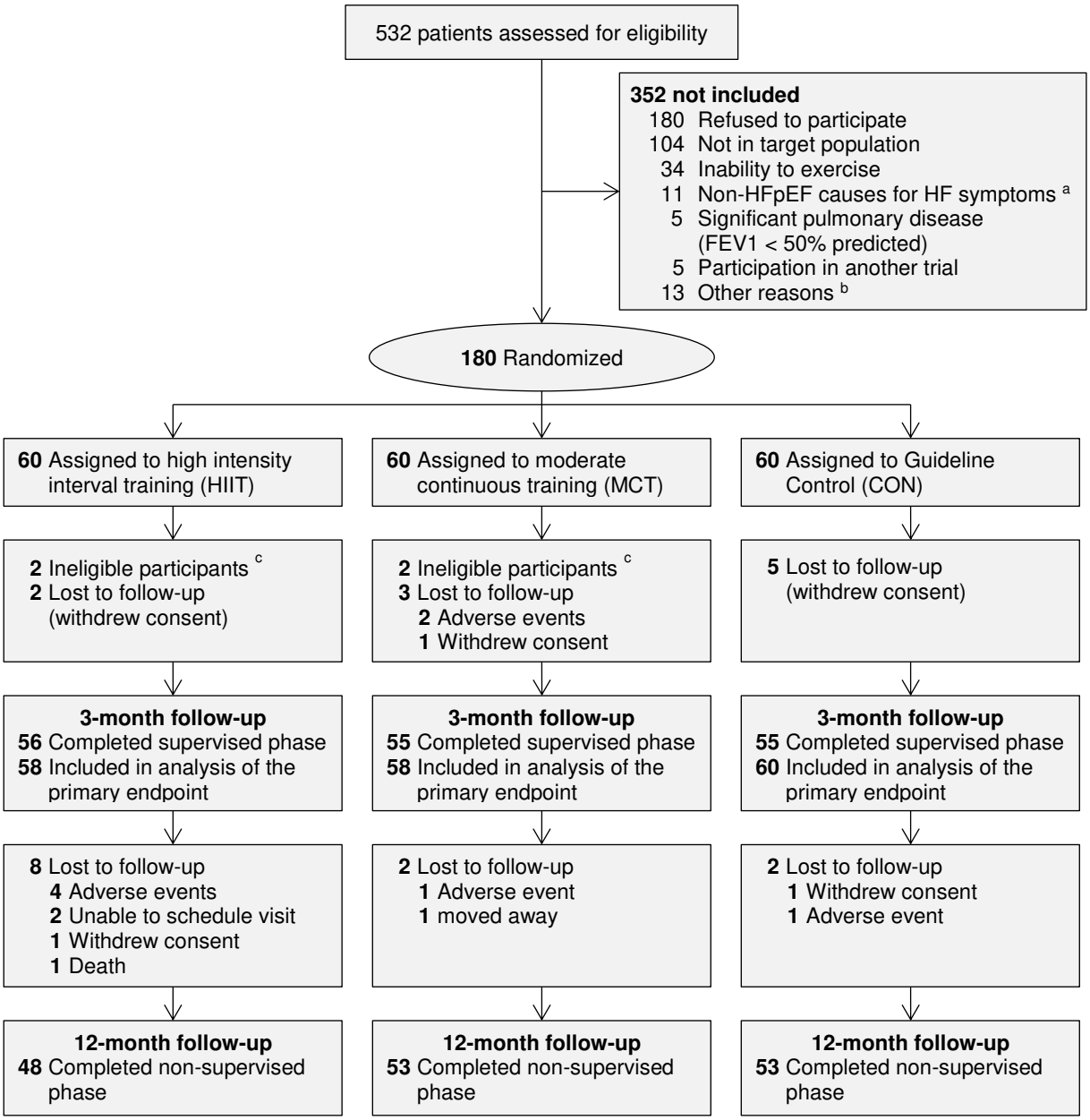


Figure 7: Patient recruitment, randomization and follow-up (adapted from Mueller et al.[234]). ***Abbreviations:*** ***FEV1*** *= forced expiratory volume within 1 second;* ***HF*** *= heart failure;* ***HFpEF*** *= heart failure with preserved ejection fraction*

[a] *including significant valvular disease, coronary disease, uncontrolled hypertension or arrhythmia, or primary cardiomyopathies*

[b] *including signs of ischemia during cardiopulmonary exercise testing (n = 3), comorbidities that may influence 1-year prognosis (n = 3), upcoming planned surgery (n = 2), social reasons (n = 2), concerns about patient's adherence (n = 1), recurrent syncopes (n = 1), planned travel (n = 1)*

[c] *did not meet inclusion criteria and were removed from analysis after blinded review of eligibility*

Table 5: Baseline characteristics from patients randomized to high-intensity interval training (HIIT), moderate continuous training (MCT) or guideline control (CON) (adapted from Mueller et al.[234])

	HIIT (n = 58)	MCT (n = 58)	CON (n = 60)
Sex			
Female, no. (%)	41 (71)	35 (60)	41 (68)
Male, no. (%)	17 (29)	23 (40)	19 (32)
Age at inclusion, mean ± SD, y	70 ± 7	70 ± 8	69 ± 10
Body Mass Index, mean ± SD, kg/m^2	30.0 ± 5.7	31.1 ± 6.2	29.0 ± 4.7
Resting heart rate, mean ± SD, min^{-1}	65 ± 12	65 ± 10	65 ± 11
Systolic blood pressure, mean ± SD, mmHg	127 ± 14	131 ± 13	127 ± 14
Diastolic blood pressure, mean ± SD, mmHg	74 ± 11	75 ± 10	74 ± 10
New York Heart Association class, no. (%)			
II: mild symptoms	44 (76)	44 (76)	42 (70)
III: marked symptoms	14 (24)	14 (24)	18 (30)
Cardiovascular risk factors			
Hypertension, no. (%)	50 (86)	49 (84)	51 (85)
Hyperlipidemia, no. (%)	38 (66)	40 (69)	45 (75)
Diabetes mellitus, no. (%)	16 (28)	16 (28)	14 (23)
Smoking, no. (%)			
No (never smoked)	30 (52)	32 (55)	35 (58)
Ex-Smoker	25 (43)	23 (40)	23 (38)
Current	3 (5)	3 (5)	2 (3)
Cardiovascular disease			
Coronary artery disease, no. (%)	15 (26)	18 (31)	17 (28)
Atrial Fibrillation, no. (%)			
No	38 (66)	42 (72)	47 (78)
Paroxysmal	10 (17)	5 (9)	8 (14)
Persistent	4 (7)	6 (10)	3 (5)
Permanent	6 (10)	5 (8)	2 (3)
Sleep apnea syndrome, no. (%)	11 (19)	11 (19)	11 (18)
Peripheral artery disease, no. (%)	3 (5)	4 (7)	2 (3)
Heart failure medication			
Beta-blockers, no. (%)	40 (69)	34 (59)	40 (67)
Thiazide / Loop Diuretics, no. (%)	36 (62)	30 (52)	34 (57)
Angiotensin receptor blocker, no. (%)	25 (43)	26 (45)	24 (40)
Angiotensin-converting enzyme inhibitor, no. (%)	19 (33)	18 (31)	17 (28)
Aldosterone antagonists, no. (%)	8 (14)	6 (10)	5 (8)

Data are presented as absolute (relative) frequency or mean ± standard deviation (SD).

Primary and Secondary Outcomes

Table 6 shows an overview of the baseline, 3-month and 12-month data as well as the within-group changes of all prespecified endpoints, whereas the between-group differences are shown in *Table 7*. Within the first 3 months, peak $\dot{V}O_2$ increased by

1.1 ± 3.0 mL/kg/min following HIIT and 1.6 ± 3.1 mL/kg/min following MCT, and decreased by -0.6 ± 3.4 mL/kg/min following CON (P = 0.002) *(Figure 8A)*. Pairwise comparisons (including imputed data) showed significant differences between HIIT vs. CON (mean difference, 1.5 mL/kg/min [95% CI, 0.4 to 2.7]) and MCT vs. CON (mean difference, 2.0 mL/kg/min [95% CI, 0.9 to 3.1]) with no significant differences between HIIT and MCT (mean difference, -0.4 mL/kg/min [95% CI, -1.4 to 0.6]). Changes in peak $\dot{V}O_2$ after 3 months were not significantly different between any of the investigated

Table 6: Baseline, 3-month and 12-month data including within-group changes for the primary endpoint (change in peak $\dot{V}O_2$ after 3 months) and all secondary endpoints following high-intensity interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) (adapted from Mueller et al.[234])

		Mean ± SD [n]					
		HIIT		**MCT**		**CON**	
	Month	**Visit Data**	**Delta**	**Visit Data**	**Delta**	**Visit Data**	**Delta**
Peak $\dot{V}O_2$ mL/min/kg	0	18.9 ± 5.4 [58]	- - -	18.2 ± 5.1 [58]	- - -	19.4 ± 5.6 [60]	- - -
	3	20.2 ± 6.0 [53]	1.1 ± 3.0 [53]	19.8 ± 5.8 [54]	1.6 ± 2.5 [54]	18.9 ± 5.7 [52]	-0.6 ± 3.3 [52]
	12	19.9 ± 6.1 [42]	0.9 ± 3.0 [42]	18.1 ± 5.9 [48]	0.0 ± 3.1 [48]	19.5 ± 5.1 [49]	-0.6 ± 3.4 [49]
Workload at VT1 watts	0	45 ± 17 [58]	- - -	46 ± 21 [57]	- - -	45 ± 15 [58]	- - -
	3	49 ± 18 [53]	4 ± 12 [53]	53 ± 25 [53]	8 ± 13 [52]	47 ± 16 [50]	1 ± 10 [50]
	12	46 ± 17 [41]	1 ± 12 [41]	45 ± 21 [47]	-1 ± 12 [46]	43 ± 14 [49]	-3 ± 11 [49]
$\dot{V}E/\dot{V}CO_2$ slope	0	34.5 ± 7.9 [58]	- - -	34.2 ± 7.2 [58]	- - -	33.2 ± 5.9 [59]	- - -
	3	35.0 ± 9.8 [53]	0.7 ± 4.4 [53]	33.7 ± 6.8 [54]	-0.7 ± 4.4 [54]	32.6 ± 5.3 [51]	-1.0 ± 5.4 [51]
	12	36.6 ± 8.4 [42]	2.0 ± 5.1 [42]	33.9 ± 7.1 [48]	-0.7 ± 4.6 [48]	34.3 ± 7.4 [49]	1.1 ± 4.9 [49]
KCCQ QoL domain [a]	0	68 ± 24 [58]	- - -	62 ± 26 [56]	- - -	66 ± 20 [58]	- - -
	3	73 ± 26 [54]	7 ± 21 [54]	72 ± 21 [55]	10 ± 17 [54]	72 ± 23 [55]	6 ± 21 [54]
	12	80 ± 21 [47]	11 ± 20 [47]	77 ± 19 [45]	17 ± 21 [44	72 ± 24 [51]	6 ± 18 [50]
E/e' medial	0	15.8 ± 3.7 [57]	- - -	15.9 ± 4.1 [58]	- - -	15.7 ± 5.6 [57]	- - -
	3	15.2 ± 4.8 [54]	-0.9 ± 4.5 [53]	15.6 ± 5.0 [54]	-0.5 ± 3.7 [54]	16.5 ± 7.2 [53]	0.6 ± 4.6 [50]
	12	14.2 ± 3.9 [47]	-1.8 ± 3.3 [46]	15.6 ± 4.4 [52]	-0.3 ± 4.2 [52]	15.7 ± 5.5 [52]	-0.4 ± 4.0 [50]
e' medial cm/s	0	6.2 ± 1.8 [57]	- - -	6.1 ± 1.6 [58]	- - -	6.3 ± 1.8 [57]	- - -
	3	6.2 ± 1.7 [54]	0.0 ± 1.7 [53]	6.0 ± 1.6 [54]	-0.1 ± 1.3 [54]	6.0 ± 1.8 [53]	-0.3 ± 1.5 [50]
	12	6.2 ± 1.7 [47]	0.1 ± 1.5 [46]	5.9 ± 1.5 [52]	-0.2 ± 1.1 [52]	6.1 ± 1.7 [52]	-0.2 ± 1.5 [50]
LAVI, mL/m^2	0	35.4 ± 9.0 [39]	- - -	37.9 ± 13.0 [42]	- - -	39.8 ± 13.5 [48]	- - -
	3	35.2 ± 10.2 [34]	-0.4 ± 4.0 [26]	36.8 ± 10.5 [28]	0.5 ± 4.1 [25]	38.4 ± 14.7 [40]	-0.7 ± 4.0 [35]
	12	37.4 ± 10.9 [26]	0.7 ± 5.8 [21]	36.6 ± 9.2 [23]	1.2 ± 3.8 [20]	39.2 ± 1.8 [38]	0.3 ± 5.2 [33]
NT-proBNP pg/mL	0	475 ± 522 [57]	- - -	656 ± 806 [55]	- - -	875 ± 1950 [59]	- - -
	3	520 ± 646 [53]	25 ± 469 [53]	695 ± 1212 [53]	43 ± 598 [53]	1164 ± 2871 [53]	226 ± 1010 [53]
	12	471 ± 468 [47]	-24 ± 539 [47]	698 ± 1026 [52]	42 ± 422 [49]	1037 ± 1026 [52]	237 ± 1177 [52]

***Abbreviations*: *E/e'* = estimated left ventricular filling pressure; *e'* = early diastolic mitral annular tissue velocity; *KCCQ* = Kansas City Cardiomyopathy Questionnaire; *LAVI* = left atrial volume indexed to body surface area; *LV* = left ventricular; *n* = number of patients; *NT-proBNP* = N-terminal pro-brain natriuretic peptide; *QoL* = quality of life; *SD* = standard deviation; *$\dot{V}E/\dot{V}CO_2$ slope* = ventilation to carbon dioxide production slope; *$\dot{V}O_2$* = oxygen consumption; *VT1* = first ventilatory threshold**

[a] *KCCQ score range: 0-100, higher scores reflect better QoL, minimal clinically important difference: 5 points[273]*

Table 7: Between-group comparisons for the changes from baseline to 3 and 12 months following high-intensity interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) (adapted from Mueller et al.[234])

	Change after Month	Difference (95% CI) [n_{Group1} / n_{Group2}]			Global P-value [a]
		HIIT vs. CON	MCT vs. CON	HIIT vs. MCT	
Peak $\dot{V}O_2$ mL/min/kg	3	1.5 (0.4 to 2.7) [58/60] [b]	2.0 (0.9 to 3.1) [58/60] [b]	-0.4 (-1.4 to 0.6) [58/58] [b]	0.002 [b]
		1.8 (0.5 to 3.0) [53/52] [c]	2.3 (1.1 to 3.4) [54/52] [c]	-0.5 (-1.5 to 0.6) [53/54] [c]	< 0.001 [c]
	12	1.4 (0.1 to 2.8) [42/49]	0.6 (-0.7 to 1.9) [48/49]	0.8 (-0.5 to 2.1) [42/48]	0.11
Workload at VT1 watts	3	3 (-2 to 7) [53/50]	6 (2 to 11) [52/50]	-4 (-9 to 1) [53/52]	0.02
	12	4 (-1 to 9) [41/49]	3 (-2 to 7) [46/49]	2 (-4 to 7) [41/46]	0.20
$\dot{V}E/\dot{V}CO_2$ slope	3	1.7 (-0.2 to 3.6) [53/51]	0.2 (-1.7 to 2.2) [54/51]	1.5 (-0.3 to 3.2) [53/54]	0.15
	12	0.9 (-1.2 to 3.0) [42/49]	-1.9 (-3.8 to 0.0) [48/49]	2.8 (0.7 to 4.8) [42/48]	0.02
KCCQ QoL domain [d]	3	1 (-7 to 9) [54/54]	5 (-3 to 12) [54/54]	-4 (-11 to 4) [54/54]	0.43
	12	4 (-3 to 12) [47/50]	11 (2 to 19) [44/50]	-6 (-15 to 2) [47/44]	0.03
E/e' medial	3	-1.5 (-3.2 to 0.3) [53/50]	-1.1 (-2.7 to 0.5) [54/50]	-0.4 (-1.9 to 1.2) [53/54]	0.20
	12	-1.4 (-2.9 to 0.1) [46/50]	0.1 (-1.5 to 1.7) [52/50]	-1.5 (-3.0 to 0.0) [46/52]	0.11
e' medial cm/s	3	0.3 (-0.3 to 1.0) [53/50]	0.2 (-0.3 to 0.8) [54/50]	0.1 (-0.5 to 0.7) [53/54]	0.53
	12	0.3 (-0.3 to 0.9) [46/50]	0.0 (-0.5 to 0.5) [52/50]	0.3 (-0.2 to 0.9) [46/52]	0.38
LAVI mL/m^2	3	0.3 (-1.7 to 2.4) [26/35]	1.2 (-0.9 to 3.4) [25/35]	-0.9 (-3.2 to 1.4) [26/25]	0.50
	12	0.4 (-2.7 to 3.5) [21/33]	0.9 (-1.6 to 3.3) [20/33]	-0.5 (-3.5 to 2.6) [21/20]	0.83
NT-proBNP pg/mL	3	-201 (-505 to 104) [53/53]	-183 (-505 to 139) [53/53]	-18 (-228 to 192) [53/53]	0.30
	12	-261 (-622 to 100) [47/52]	-195 (-543 to 152) [49/52]	-66 (-263 to 131) [47/49]	0.24

***Abbreviations*: *CI** = confidence interval; **E/e'** = estimated left ventricular filling pressure; **e'** = early diastolic mitral annular tissue velocity; **KCCQ** = Kansas City Cardiomyopathy Questionnaire; **LAVI** = left atrial volume indexed to body surface area; **LV** = left ventricular; **n** = number of patients; **NT-proBNP** = N-terminal pro-brain natriuretic peptide; **QoL** = quality of life; **$\dot{V}E/\dot{V}CO_2$ slope** = ventilation to carbon dioxide production slope; **$\dot{V}O_2$** = oxygen consumption; **VT1** = first ventilatory threshold*

[a] The global P-value is related to the analysis of variance that compares the means of all 3 groups

[b] Results of the primary analysis using a prespecified multiple imputation approach for missing values (only for primary endpoint)

[c] Results of the complete case analysis for the primary end point considering all available data (without imputation)

[d] KCCQ score range: 0-100, higher scores reflect better QoL, minimal clinically important difference: 5 points[273]

subgroups (interaction P >0.05) *(Appendix F)*. After 12 months, within-group changes from baseline were 0.9 ± 3.0 mL/kg/min in HIIT, 0.0 ± 3.1 mL/kg/min in MCT and -0.6 ± 3.4 mL/kg/min in CON (P = 0.11) *(Figure 8A)*. Changes in workload at VT1 were significantly different between MCT and CON (mean difference, 6 watts [95% CI, 2 to 11], global P = 0.02) only. After 12 months change in workload at VT1 was not significantly different between groups (P = 0.20) *(Figure 8B)*. At both 3 and 12 months, QoL improved by > 5 points in all groups, however, the only significant difference in pairwise comparisons was observed for MCT vs. CON after 12 months (mean difference, 11 points [95% CI, 2 to 19]; global P = 0.03) *(Figure 8C)*. Moreover, change in $\dot{V}E/\dot{V}CO_2$ slope was not significantly different between groups after 3 months, but was significantly improved in MCT vs. HIIT after 12 months (mean difference,

-2.8 [95% CI, -4.8 to -0.7], global P = 0.02) *(Figure 8D)*. Neither changes in indices of diastolic function (E/e' medial, e' medial, LAVI) nor changes in NT-proBNP were significantly different between groups at 3 or 12 months (P > 0.05) (*Figure 9*).

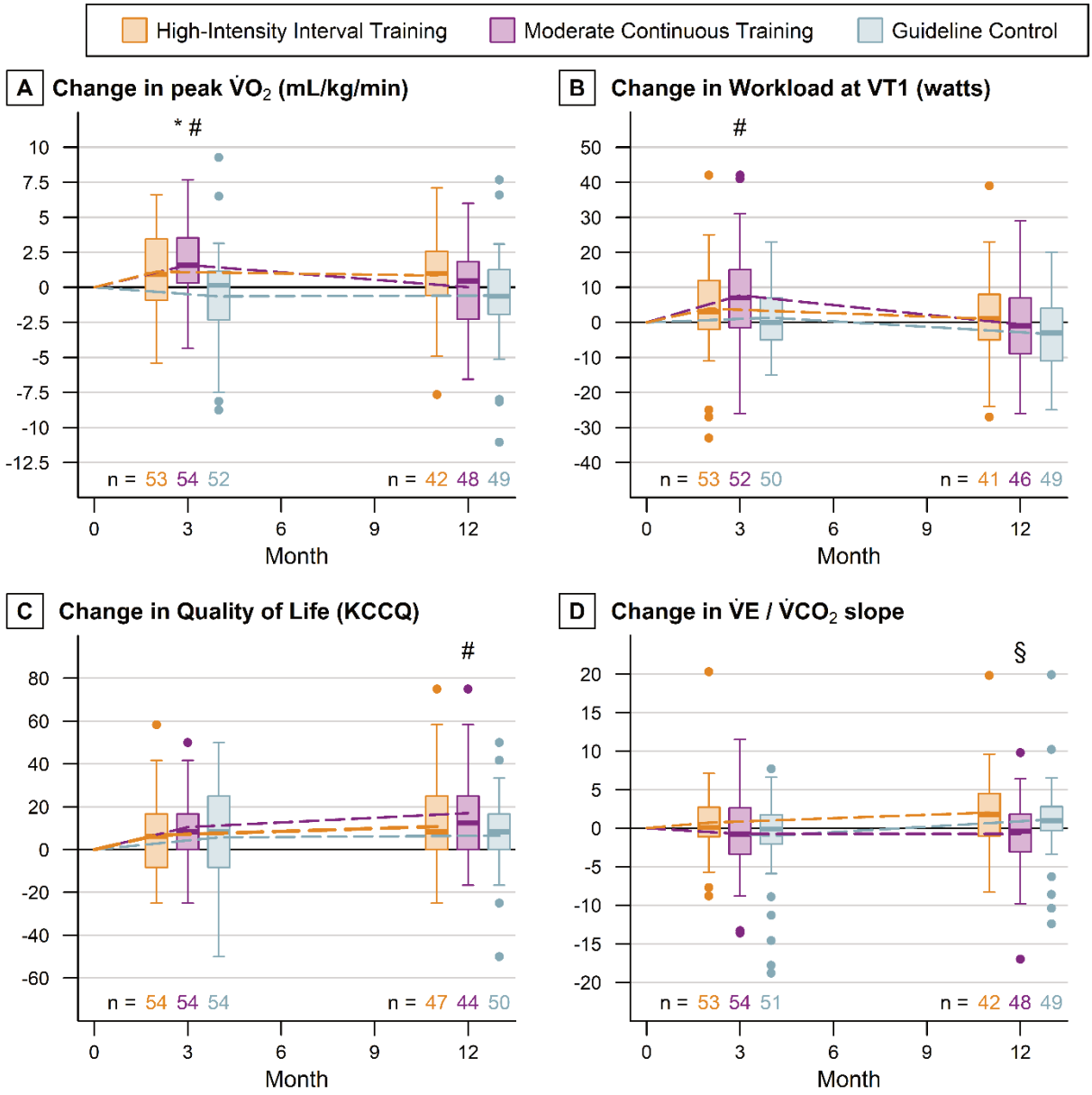


Figure 8 *Changes in peak oxygen consumption ($\dot{V}O_2$), workload at first ventilatory threshold (VT1), quality of life (QoL) and ventilation-to-carbon-dioxide-production ($\dot{V}E/\dot{V}CO_2$) slope for high-intensity-interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) from baseline to 3 and 12 months (adapted from Mueller et al.[234]). Dotted lines connect mean changes from baseline to 3 and 12 months. In the Kansas City Cardiomyopathy Questionnaire (KCCQ), higher scores indicate better QoL (score range, 0-100).*

** significant difference (P < 0.05) in change between HIIT and CON*

 # significant difference (P < 0.05) in change between MCT and CON

§ significant difference (P < 0.05) in change between HIIT and MCT

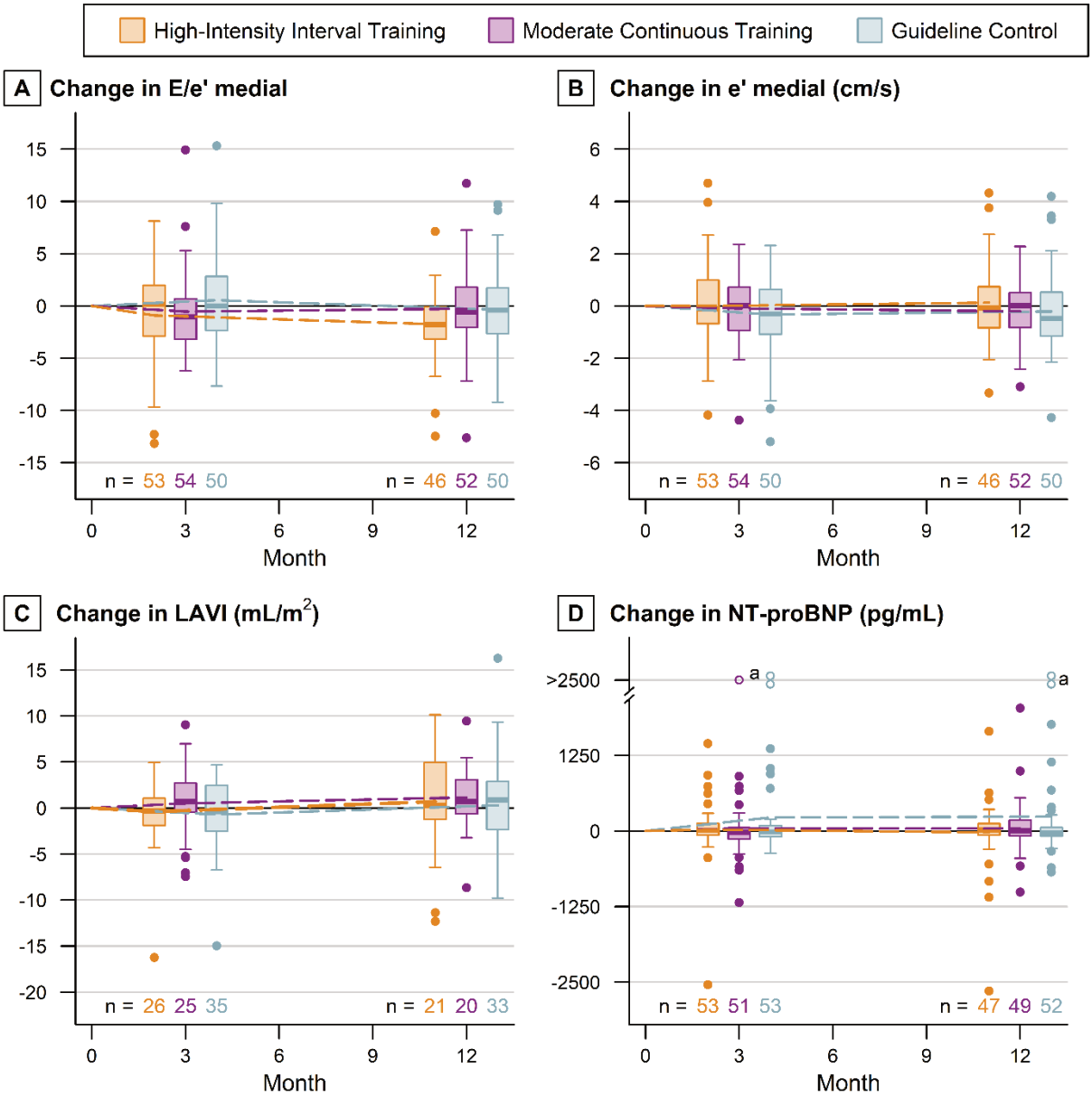


Figure 9 *Changes in estimated left ventricular filling pressure (E/e'), early diastolic mitral annular tissue velocity (e'), left atrial volume index (LAVI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) for high-intensity-interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) from baseline to 3 and 12 months (adapted from Mueller et al.[234]). Dotted lines connect mean changes from baseline to 3 and 12 months.*

[a] open points are at 3586 pg/mL (MCT at 3 months), 4133 and 5783 pg/mL (CON at 3 months), 4134 and 7063 pg/mL (CON at 12 months)

Adherence and Per-Protocol Analysis

During the supervised phase, HIIT patients performed a median of 2.5 sessions per week (interquartile range [IQR], 2.1-2.8), while MCT patients performed a median of 4.4 sessions per week (IQR, 3.4-4.7). This equals a median adherence rate of 84% (IQR, 73-94) for HIIT and 85% (70-97) for MCT *(Figure 10)*. During the home-based

phase, median adherence dropped in both HIIT [2.0 sessions per week (IQR, 1.2-2.4); 69% (IQR, 41-82)]; and MCT [3.6 sessions per week (IQR, 2.7-4.3); 72% (IQR, 54-86)]. For the complete intervention, HIIT patients performed a median of 2.1 sessions per week (IQR, 1.6-2.4) or 73% of scheduled sessions (IQR, 53-82), while MCT patients performed a median of 3.8 sessions per week (IQR, 2.9-4.4) or 76% of scheduled sessions (IQR, 58-89) *(Figure 10)*. Of those patients completing the 3-month follow-up, 45 of 56 HIIT patients (80.4%) and 42 of 55 MCT patients (76.4%) performed ≥ 70% of scheduled exercise sessions and were included in the per-protocol analysis. After 12 months, the per-protocol analysis included 23 of 48 patients doing HIIT (47.9%) and 31 of 53 patients doing MCT (58.5%). Drop offs in adherence < 70% were mainly due to clinical reasons (n = 60 [n = 11 cardiological, n = 17 musculoskeletal,

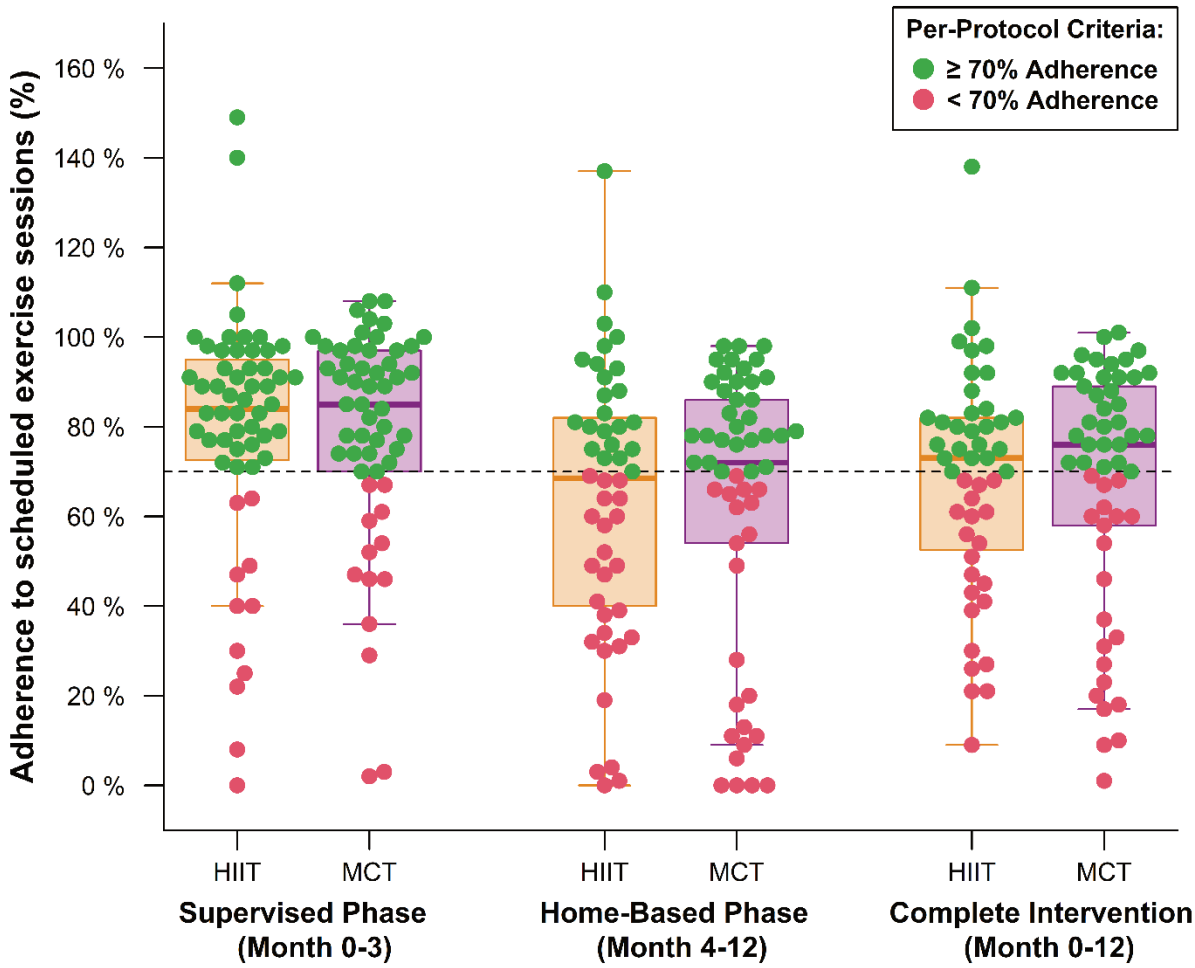


Figure 10: Relative frequency of performed high-intensity interval training (HIIT) and moderate continuous training (MCT) sessions within the supervised phase (Month 0-3), home-based phase (Month 4-12) and the complete intervention (Month 0-12) (adapted from Mueller et al.[234]). The dotted line represents the 70%-cutoff that was defined as the lower limit of adequate adherence. Green points (●) represent all individuals with an adherence ≥ 70%, red points (●) represent all individuals with adherence < 70% within the respective time period.

n = 14 pulmological, n = 18 other]), personal reasons such as vacation (n = 20), motivational reasons (n = 12), and trouble with the ergometer or telemedical device (n = 2) (multiple responses possible). Results of the per-protocol analysis were comparable to the results of the complete case analysis with significant between-group differences (HIIT vs. MCT vs. CON) for the change in peak $\dot{V}O_2$ after 3 months (1.4 vs. 1.9 vs. -0.6 mL/kg/min, P < 0.001), change in workload at VT1 after 3 and 12 months (4 vs. 9 vs. 1 watts, P = 0.008 at 3 months; 5 vs. 1 vs. -3 watts, P = 0.01 at 12 months) and change in QoL at 12 months (10 vs. 20 vs. 6, P =0.01), whereas the between-group differences for all other endpoints remained non-significant *(Table 8)*.

Table 8 Between-group comparisons for the changes from baseline to 3 and 12 months in the per-protocol population (excluding patients with adherence < 70%) following high-intensity interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) (adapted from Mueller et al.[234]).

	Change after Month	Difference (95% CI) [n_{Group1} / n_{Group2}]			Global P-value [a]
		HIIT vs. CON	MCT vs. CON	HIIT vs. MCT	
Peak $\dot{V}O_2$ mL/min/kg	3	2.1 (0.9 to 3.3) [45/52]	2.6 (1.4 to 3.8) [42/52]	-0.5 (-1.6 to 0.7) [45/42]	< 0.001
	12	1.7 (0.3 to 3.0) [25/49]	1.1 (-0.4 to 2.6) [32/49]	0.6 (-0.9 to 2.1) [25/32]	0.07
Workload at VT1 watts	3	3 (-1 to 7) [45/50]	8 (3 to 13) [41/50]	-5 (-10 to 1) [45/41]	0.008
	12	8 (3 to 14) [25/49]	4 (-1 to 10) [31/49]	4 (-2 to 10) [25/31]	0.01
$\dot{V}E/\dot{V}CO_2$ slope	3	1.6 (-0.4 to 3.7) [45/51]	0.3 (-1.8 to 2.3) [42/51]	1.4 (-0.6 to 3.3) [45/42]	0.22
	12	0.6 (-1.6 to 2.8) [25/49]	-2.1 (-4.2 to -0.1) [32/49]	2.7 (0.4 to 5.0) [25/32]	0.05
KCCQ QoL domain [b]	3	0 (-8 to 9) [45/54]	6 (-2 to 13) [42/54]	-6 (-14 to 3) [45/42]	0.34
	12	4 (-5 to 13) [27/50]	14 (4 to 24) [30/50]	-10 (-21 to 1) [27/30]	0.01
E/e' medial	3	-1.6 (-3.5 to 0.3) [44/50]	-1.3 (-3.1 to 0.5) [41/50]	-0.3 (-2.2 to 1.6) [44/41]	0.18
	12	-1.8 (-3.5 to -0.2) [25/50]	-0.4 (-2.2 to 1.5) [32/50]	-1.5 (-3.4 to 0.5) [25/32]	0.15
e' medial cm/s	3	0.4 (-0.3 to 1.1) [44/50]	0.3 (-0.2 to 0.7) [41/50]	0.1 (-0.6 to 0.7) [44/41]	0.43
	12	0.6 (0.0 to 1.2) [25/50]	0.2 (-0.4 to 0.7) [32/50]	0.4 (-0.2 to 1.1) [25/32]	0.16
LAVI mL/m²	3	0.2 (-2.1 to 2.5) [21/35]	1.2 (-1.2 to 3.6) [21/35]	-1.0 (-3.7 to 1.7) [21/21]	0.56
	12	0.9 (-3.2 to 5.1) [11/33]	1.1 (-1.7 to 3.9) [16/33]	-0.2 (-4.4 to 4.1) [11/16]	0.73
NT-proBNP pg/mL	3	-193 (-510 to 124) [43/53]	-182 (-535 to 171) [38/53]	-11 (-282 to 261) [43/38]	0.41
	12	-256 (-611 to 99) [26/52]	-197 (-567 to 173) [30/52]	-59 (-286 to 168) [26/30]	0.40

***Abbreviations*: *CI* = confidence interval; *E/e'* = estimated left ventricular filling pressure; *e'* = early diastolic mitral annular tissue velocity; *KCCQ* = Kansas City Cardiomyopathy Questionnaire; *LAVI* = left atrial volume indexed to body surface area; *LV* = left ventricular; *n* = number of patients; *NT-proBNP* = N-terminal pro-brain natriuretic peptide; *QoL* = quality of life; *$\dot{V}E/\dot{V}CO_2$ slope* = ventilation to carbon dioxide production slope; *$\dot{V}O_2$* = oxygen consumption; *VT1* = first ventilatory threshold**

[a] *The global P-value is related to the analysis of variance that compares the means of all 3 groups*

[b] *KCCQ score range: 0-100, higher scores reflect better QoL, minimal clinically important difference: 5 points[273]*

Adverse Events

There were a total of 209 documented AEs in 102 patients (HIIT: 80 AEs in 36 patients [62%], MCT: 79 AEs in 39 patients [67%], CON: 50 AEs in 27 patients [45%]) *(Table 9)*.

Of those, 88 events in 52 patients (30%) were classified as SAEs (HIIT: 33 SAEs in 18 patients [31%], MCT: 28 SAEs in 18 patients [31%], CON: 27 SAEs in 16 patients [27%]) *(Table 9)*. The most common cardiovascular AEs were atrial fibrillation (19 events in 9 patients [5%]), worsening HF (15 events in 9 patients [5%]) and acute coronary syndrome (13 events in 12 patients [7%]). There was 1 cardiac death in the HIIT group that was deemed unrelated to exercise; and 6 events that occurred during (HIIT: compression of the coccyx due to a fall from the bicycle ergometer, muscle weakness; MCT: atrial fibrillation, syncope, back pain) or within 2 hours after ET (HIIT: occlusion of peripheral bypass). An overview of all AEs and SAEs can be found in *Appendix G* (for AEs) and *Appendix H* (for SAEs).

Table 9: Descriptive overview of adverse events (AEs) and serious adverse events (SAEs) following 12 months of high-intensity interval training (HIIT), moderate continuous training (MCT) or guideline control (CON)

	No. of events (no. of participants [%])		
	HIIT	**MCT**	**CON**
Adverse Events (AEs)			
All AEs	80 events (36 patients [62%])	79 events (39 patients [67%])	50 events (27 patients [45%])
All cardiovascular AEs	32 events (14 patients [24%])	29 events (17 patients [29%])	19 events (12 patients [20%])
Heart failure related AEs	15 events (7 patients [12%])	13 events (6 patients [10%])	10 events (6 patients [10%])
Non-cardiovascular AEs	48 events (29 patients [50%])	50 events (31 patients [53%])	31 events (19 patients [32%])
Serious Adverse Events (SAEs)			
All SAEs	33 events (18 patients [31%])	28 events (18 patients [31%])	27 events (16 patients [27%])
All cardiovascular SAEs	21 events (10 patients [17%])	18 events (12 patients [21%])	14 events (10 patients [17%])
Heart failure related SAEs	7 events (5 patients [9%])	8 events (4 patients [7%])	5 events (3 patients [5%])
Non-cardiovascular SAEs	12 events (10 patients [17%])	10 events (9 patients [16%])	13 events (9 patients [15%])

The number of SAEs is also included in the number of AEs. Heart failure related AEs and SAEs included worsening HF, atrial fibrillation, pleural effusion, ventricular arrhythmias and cardiac arrest.

3.2. Publication II – Predictor Analysis of the OptimEx-Clin Trial

All results presented in this section have been published in "***Mueller S**, Haller B, Feuerstein A, Winzer EB, Beckers P, Haykowsky MJ, Gevaert, A. B., Hommel, J., Azevedo, L. F., Duvinage, A., Esefeld, K., Fegers-Wustrow, I., Christle, J. W., Pieske-Kraigher, E., Belyavskiy, E., Morris, D. A., Kropf, M., Aravind-Kumar, R., Edelmann, F., Linke, A., Adams, V., Van Craenenbroeck, E. M., Pieske, B., Halle, M., and the OptimEx-Clin Study Group. 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(5):3393-406.*[242]

3.2.1. Summary and Individual Contribution of the PhD Candidate (Publication II)

In this manuscript, we evaluated the influence of baseline relative peak $\dot{V}O_2$ and its determinants (absolute peak $\dot{V}O_2$, peak O_2-pulse, peak HR, weight, hemoglobin) on the change in peak $\dot{V}O_2$ within the supervised 3-month period of the OptimEx-Clin trial. To achieve a higher power and reduce the impact of influential data points, HIIT and MCT were combined to one ET group and the predictor analyses were performed using robust linear regression analyses. Moreover, mediating effects on change in peak $\dot{V}O_2$ through changes in peak O_2-pulse, peak HR and weight were analyzed. Among the 158 patients with complete CPET measurements at baseline and 3 months, changes in peak O_2-pulse (mean difference, 7.7% [95% CI, 1.9 to 13.4]; P = 0.01) explained approximately 72% of the difference in changes in peak $\dot{V}O_2$ between ET and CON (mean difference, 10.0% [95% CI, 4.1 to 15.9], P = 0.001). Furthermore, baseline peak O_2-pulse was found to be a significant predictor of the ET-induced change in peak $\dot{V}O_2$ (interaction P = 0.04). Each 1 mL/beat higher peak O_2-pulse at baseline was associated with a reduced mean change in peak $\dot{V}O_2$ of -1.45% ([95% CI, -2.30 to 0.60], P = 0.001) following ET, whereas no significant association was found in CON (-0.08% for every 1 mL/beat higher peak O_2-pulse [95% CI, -1.11 to 0.96], P = 0.88). None of the other parameters (including baseline peak $\dot{V}O_2$) were shown to be significant predictors of the difference in change in peak $\dot{V}O_2$ between groups.

The idea for this pre-defined theory-driven substudy of the OptimEx-Clin trial was developed and formulated by the doctoral candidate. He also selected the statistical methods for this manuscript, which were additionally discussed with a statistician. The statistical analyses were then performed exclusively by the doctoral candidate, who also

created all the figures and drafted the complete manuscript before receiving critical review by the co-authors. Moreover, the doctoral candidate was responsible for the entire submission process, and the necessary changes and responses based on the reviewers' comments.

3.2.2. Results of the Predictor Analysis (Publication II)

Among the 159 patients performing CPET at 3-month follow-up, 1 patient was excluded due to a technical error in the exercise ECG. Therefore, all 158 patients with complete CPET data at baseline and 3-month follow-up (106 ET patients vs. 52 CON patients; 66% women; mean age, 70 years) were included in this substudy. Due to missing values, analyses on change in VT1 were conducted on all 154 patients with determinable VT1 at baseline and follow-up (104 ET patients vs. 50 CON patients). Moreover, the per-protocol analysis of change in peak $\dot{V}O_2$ was conducted in 139 patients (87 ET patients with adherence ≥ 70% vs. 52 CON patients) *(Figure 11)*. Baseline demographic and clinical characteristics of the patients included in this substudy are shown in *Table 10*.

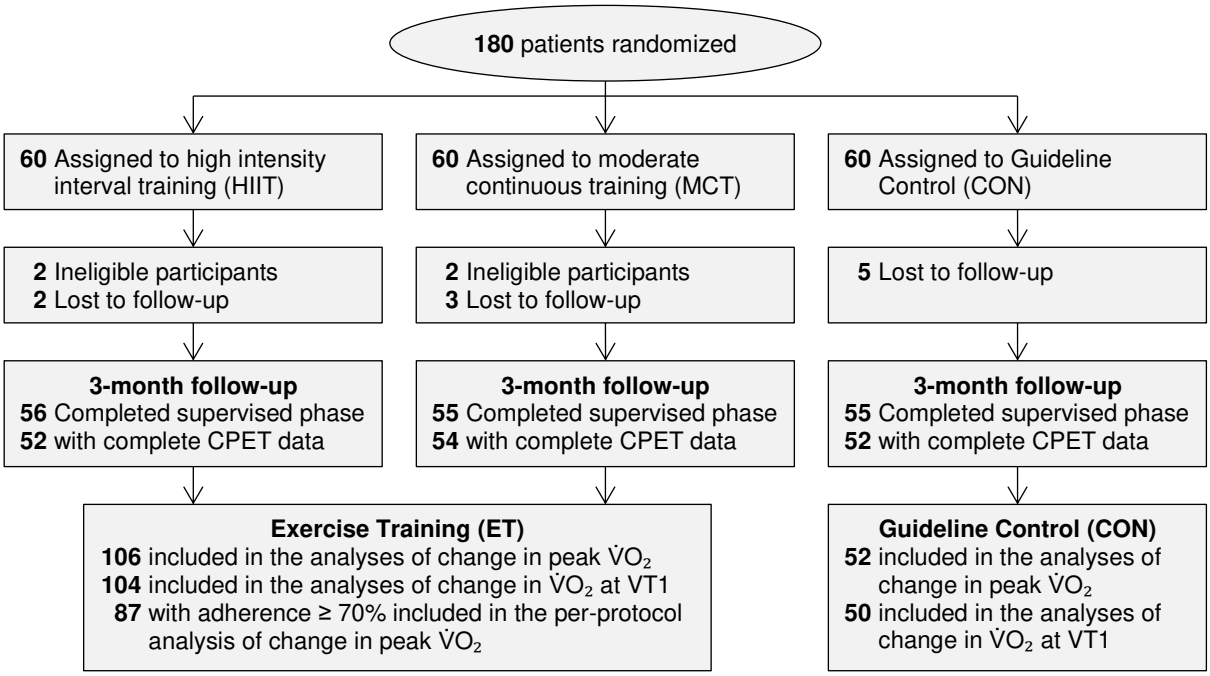


Figure 11: Substudy flow chart (adapted from Mueller et al.[242]). For the primary analyses, high-intensity interval training (HIIT) and moderate continuous training (MCT) were combined to one exercise training (ET) group. A complete CONSORT flow chart of the entire OptimEx-Clin trial is shown in Figure 7.
Abbreviations: ***CPET*** *= cardiopulmonary exercise testing;* ***$\dot{V}O_2$*** *= oxygen consumption;* ***VT1*** *= first ventilatory threshold*

Table 10: Baseline demographic and clinical characteristics of the patients included in the predictor analysis of the OptimEx-Clin trial (adapted from Mueller et al.[242])

	Exercise Training [n = 106]	Guideline Control [n = 52]
Sex		
Female, no. (%)	70 (66)	34 (65)
Male, no. (%)	36 (34)	18 (35)
Age, mean ± SD, years	70 ± 7	69 ± 10
Body Mass Index, mean ± SD, kg / m^2	30.6 ± 6.1	29.0 ± 4.9
Resting heart rate, mean ± SD, min^{-1}	65 ± 11	65 ± 11
Blood Pressure, mean ± SD, mmHg		
Systolic	128 ± 13	127 ± 15
Diastolic	74 ± 10	74 ± 10
Cardiovascular Risk Factors		
Hypertension, no. (%)	90 (85)	46 (88)
Diabetes mellitus, no. (%)	30 (28)	12 (23)
Dyslipidemia, no. (%)	74 (70)	40 (77)
Smoking, no. (%)		
Never smoked	55 (52)	30 (58)
Ex-smoker	45 (42)	21 (40)
Current Smoker	6 (6)	1 (2)
Sleep apnea, no. (%)	19 (18)	9 (17)
Severity of HFpEF		
New York Heart Association class, no. (%)		
II: mild symptoms	80 (75)	35 (67)
III: marked symptoms	26 (25)	17 (33)
E/e' average, mean ± SD [no.]	13.4 ± 3.4 [103]	13.3 ± 4.7 [49]
NT-proBNP, mean (1^{st} - 3^{rd} quartile) [no.], pg/mL	321 (161 - 689) [102]	341 (175 - 622) [52]
Other cardiac diagnoses		
Coronary artery disease, no. (%)	29 (27)	16 (31)
Atrial Fibrillation, no. (%)		
Paroxysmal / Persistent	21 (20)	10 (19)
Permanent	10 (9)	2 (4)
Heart Failure Medication		
Beta-blocker, no. (%)	68 (64)	37 (71)
Thiazide / loop diuretics, no. (%)	60 (57)	31 (60)
Angiotensin receptor blocker, no. (%)	44 (42)	21 (40)
Angiotensin-converting enzyme inhibitor, no. (%)	36 (34)	16 (31)
Aldosterone antagonists, no. (%)	12 (11)	5 (10)

Data are presented as absolute (relative) frequency; mean ± standard deviation (SD) or median (1^{st} - 3^{rd} quartile).
Abbreviations: E/e' = estimated left ventricular filling pressure; **n** = number of patients; **NT-proBNP** = N-terminal pro-brain natriuretic peptide

Relative Mean Changes of Peak Oxygen Consumption and its Determinants

After 3 months, relative peak $\dot{V}O_2$ (mL/kg/min) increased by 8.0 ± 15.7% following ET compared with -2.0 ± 18.3% following CON with a broad variability ranging from -33.6 to 44.3% in the ET group and -37.7 to 69.0% in the CON group. Mean changes in relative peak $\dot{V}O_2$, absolute peak $\dot{V}O_2$, peak O_2-pulse and weight were significantly different between ET and CON (all $P < 0.05$), while no significant differences have been found for the change in peak HR and hemoglobin ($P > 0.05$) *(Table 11; Figure 12)*. Furthermore, the mean change in relative $\dot{V}O_2$ at VT1 was significantly different between ET and CON ($P = 0.03$) *(Table 11)*. Mean peak RER was ≥ 1.10 in both groups and visits and not significantly different between groups ($P = 0.24$) *(Table 11)*. According to the mediation analysis, individual changes in peak O_2-pulse accounted for approximately 72% of the difference in change in relative peak $\dot{V}O_2$ between groups, while changes in peak HR and weight explained approximately 18% and 10%, respectively.

Table 11: Baseline and 3-month data including relative within- and between-group changes (%) following exercise training (ET) and guideline control (CON) (adapted from Mueller et al.[242])

		Mean ± SD				
		ET (n = 106) [a,b]		CON (n = 52) [a,b]		
	Month	Visit Data	Delta	Visit Data	Delta	Difference (95% CI), P-value
Relative peak $\dot{V}O_2$, mL/kg/min	0	18.5 ± 5.1	- - -	19.5 ± 5.8	- - -	- - -
	3	19.8 ± 5.7	8.0 ± 15.7%	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	0	1528 ± 447	- - -	1519 ± 488	- - -	- - -
	3	1617 ± 465	6.8 ± 15.2%	1475 ± 485	-2.1 ± 17.3%	8.9% (3.3 to 14.5), P = 0.002
Peak O_2-pulse, mL/beat	0	12.7 ± 3.5	- - -	12.9 ± 4.0	- - -	- - -
	3	13.2 ± 3.1	5.1 ± 13.9%	12.5 ± 4.3	-2.5 ± 18.5%	7.7% (1.9 to 13.4), P = 0.01
Peak heart rate, beats/min	0	123 ± 26	- - -	121 ± 28	- - -	- - -
	3	124 ± 25	2.3 ± 13.5%	121 ± 30	0.3 ± 13.1%	1.9% (-2.5 to 6.4), P = 0.39
Body weight, kg	0	84.6 ± 18.0	- - -	78.7 ± 15.2	- - -	- - -
	3	83.8 ± 18.1	-1.0 ± 2.6%	78.8 ± 15.6	0.1 ± 2.6%	-1.0% (-1.9 to -0.2), P = 0.02
Hemoglobin, g/dL [a]	0	13.6 ± 1.6	- - -	13.2 ± 1.4	- - -	- - -
	3	13.6 ± 1.4	0.4 ± 7.2%	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 [b]	0	11.1 ± 3.1	- - -	11.5 ± 2.9	- - -	- - -
	3	11.9 ± 3.1	9.4 ± 16.5%	11.4 ± 2.6	2.0 ± 21.3%	7.4% (2.0 to 14.2), P = 0.03
Peak RER	0	1.11 ± 0.09	- - -	1.10 ± 0.09	- - -	- - -
	3	1.10 ± 0.13	-1.0 ± 5.9%	1.11 ± 0.12	0.9 ± 11.0%	-0.1% (-5.2 to 1.3), P = 0.24

***Abbreviations*: *CI* = confidence interval; *n* = number of patients; *RER* = respiratory exchange ratio; *SD* = standard deviation; *$\dot{V}O_2$* = oxygen consumption; *VT1* = first ventilatory threshold**

[a] *different n (due to missing values) for the analysis of hemoglobin (ET: 103 patients, CON: 52 patients)*

[b] *different n (due to indeterminable VT1) for the analysis of relative $\dot{V}O_2$ at VT1 (ET: 104 patients, CON: 50 patients)*

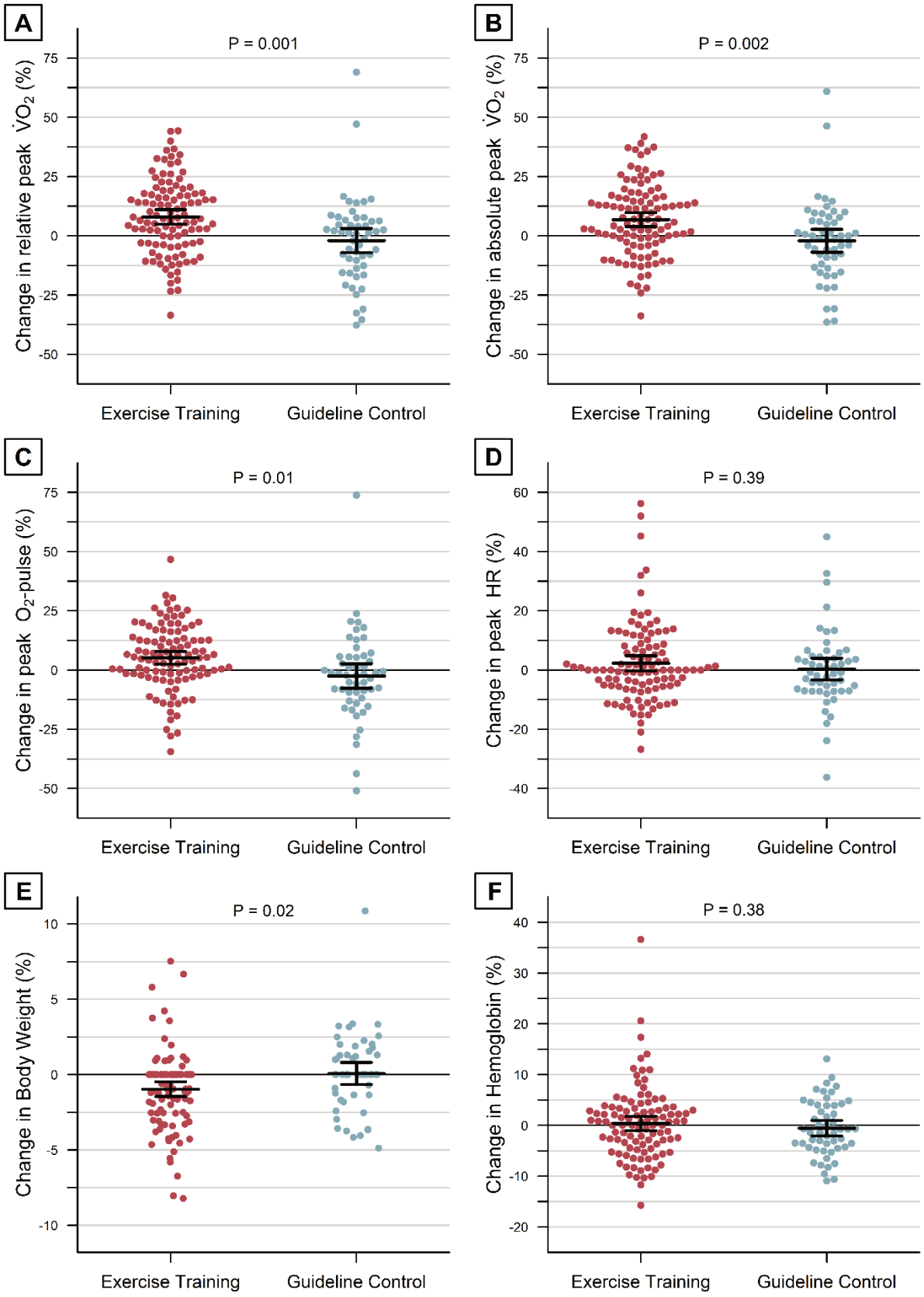


Figure 12: Changes in relative peak oxygen consumption ($\dot{V}O_2$) [A], absolute peak $\dot{V}O_2$ [B], O_2-pulse [C], peak heart rate (HR) [D], body weight [E] and hemoglobin [F] (adapted from Mueller et al.[242]). Mean and 95% confidence intervals (⊣⊢) plus individual changes are shown separately for exercise training (●) and guideline control (●).

Within the first 3 months of the OptimEx-Clin trial, a change in beta-blocker dosage was documented in 14 patients with an increase in 2 ET patients and a decrease in 10 ET and 2 CON patients (P = 0.13). When excluding these patients, the mean difference in change in peak HR between groups diminished to 0.3% (95% CI, -3.5 to 4.1, P = 0.89), whereas mean changes remained significantly different between the groups for peak $\dot{V}O_2$ (10.8% [95% CI, 4.8 to 16.9], P < 0.001), peak O_2-pulse (9.9% [95% CI, 4.2 to 15.7], P < 0.001) and weight (-1.2% [95% CI, -2.1 to -0.3], P = 0.009]. In this subset, the difference in changes in peak $\dot{V}O_2$ between groups that was explained by changes in peak O_2-pulse increased to approximately 88%, while changes in peak HR and weight accounted for approximately 2% and 10%, respectively.

Covariate-Treatment Interactions – Complete Case Analysis

Baseline peak O_2-pulse was found to be a significant predictor of the ET-induced change in relative peak $\dot{V}O_2$ (interaction P = 0.04) *(Figure* 13*A)*. Each 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) following ET compared with -0.08% ([95% CI, -1.11 to 0.96], P = 0.88) following CON. In contrast, no significant interactions on change in relative peak $\dot{V}O_2$ were found between groups and baseline relative peak $\dot{V}O_2$ (interaction P = 0.97), baseline absolute peak $\dot{V}O_2$ (interaction P = 0.31), baseline peak HR (interaction P = 0.35), baseline weight (interaction P = 0.14) and baseline hemoglobin (interaction P = 0.44) *(Figure 13)*. None of the investigated factors was significantly associated with the change in relative $\dot{V}O_2$ at VT1 *(Figure 14; Appendix I)*. The significant interaction for baseline peak O_2-pulse and study group on change in relative peak $\dot{V}O_2$ remained after adjustment for sex, age and baseline weight (ET: -1.89% [95% CI, -2.84 to -0.94); CON: -0.42% [95% CI, -1.77 to 0.62]; interaction P = 0.049). Moreover, a sensitivity analysis within the original study groups (HIIT, MCT, CON) revealed that the influence of baseline peak O_2-pulse on change in relative peak $\dot{V}O_2$ was similar between HIIT (-1.44% for every 1 mL/beat higher peak O_2-pulse [95% CI, -2.80 to -0.08], P = 0.04) and MCT (-1.50% for every 1 mL/beat higher peak O_2-pulse [95% CI, -2.52 to -0.48], P = 0.007). However, no significant interaction with the original study groups on the change in relative peak $\dot{V}O_2$ was observed for peak O_2-pulse (interaction P = 0.15) or for any of the other investigated factors *(Appendix J and* Appendix K*)*.

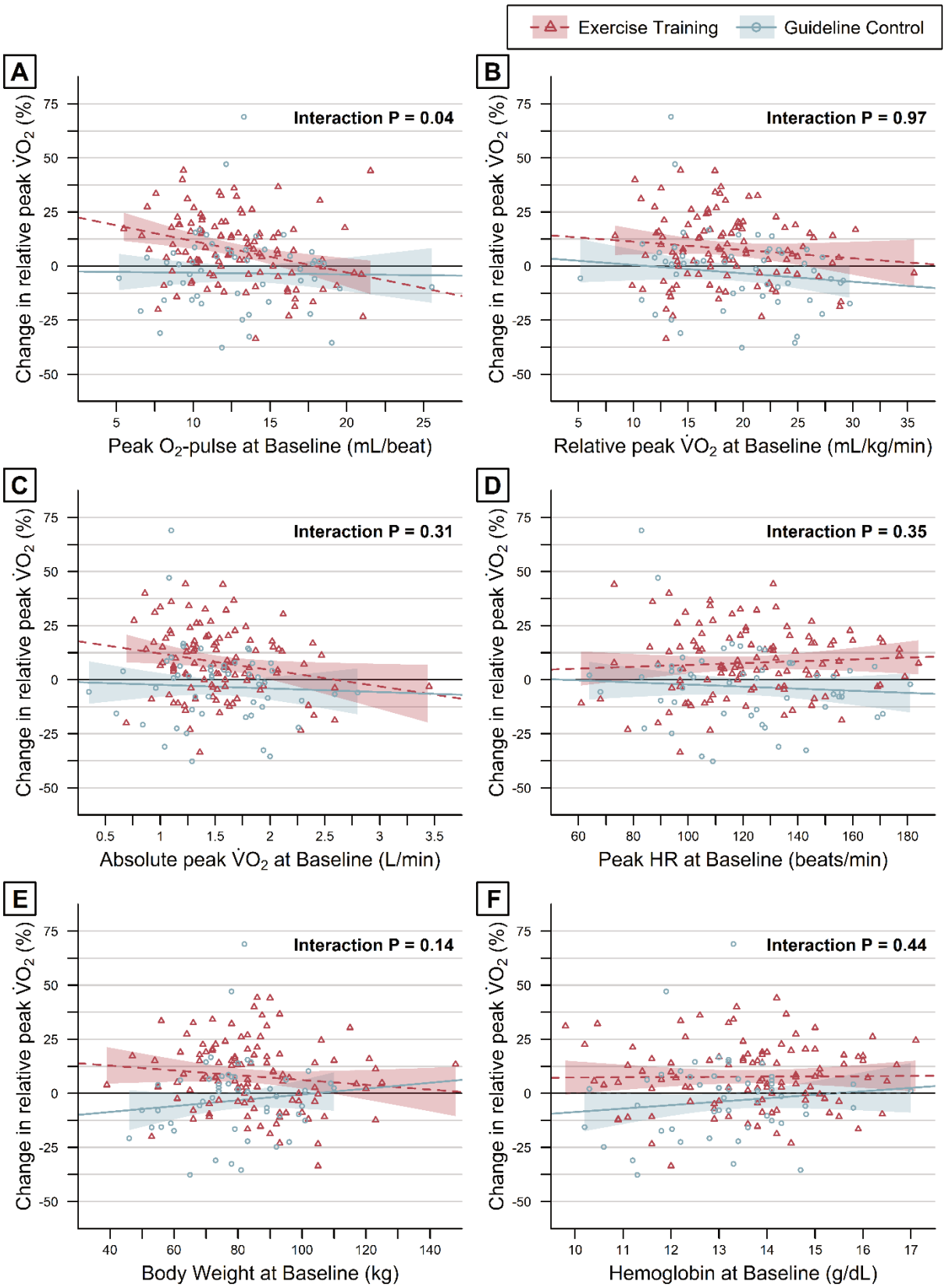


Figure 13: Relationships between changes in relative peak oxygen consumption ($\dot{V}O_2$) and baseline values of peak O_2-pulse [A], relative peak $\dot{V}O_2$ [B], absolute peak $\dot{V}O_2$ [C], peak heart rate (HR) [D], body weight [E], and hemoglobin [F] (adapted from Mueller et al.[242]). Individual relationships, robust linear regression lines and 95% confidence bands are shown separately for exercise training (– Δ –) and guideline control (–○–).

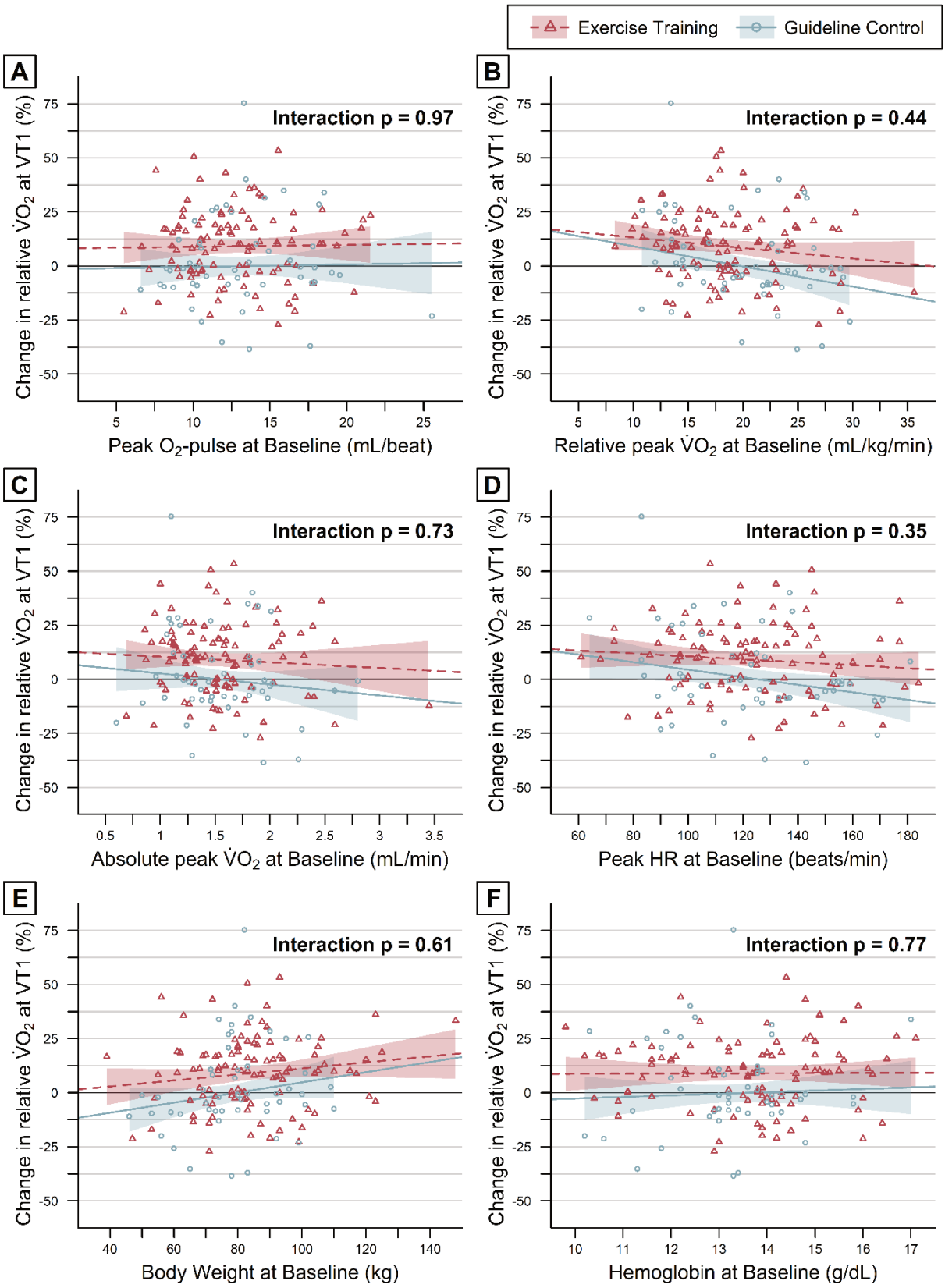


Figure 14: Relationships between changes in relative oxygen consumption ($\dot{V}O_2$) at the first ventilatory threshold (VT1) and baseline values of peak O_2-pulse [A], relative peak $\dot{V}O_2$ [B], absolute peak $\dot{V}O_2$ [C], peak heart rate (HR) [D], body weight [E], and hemoglobin [F] (adapted from Mueller et al.[242]). Individual relationships, robust linear regression lines and 95% confidence bands are shown separately for exercise training (– Δ –) and guideline control (–○–).

Covariate-Treatment Interactions – Per-Protocol and Subgroup-Analysis

In the per-protocol analysis, baseline peak O_2-pulse was confirmed as a significant predictor of the ET-induced change in relative peak $\dot{V}O_2$ (interaction P = 0.01) with -1.88% for each 1 mL/beat higher baseline peak O_2-pulse ([95% CI, -2.79 to -0.97], P < 0.001) in ET patients who performed at least 70% of the prescribed ET sessions. Accordingly, for a baseline peak O_2-pulse of 8.6 mL/beat (10th percentile of the study sample), the mean difference between an ET patient who performed at least 70% of the prescribed ET training sessions and a CON patient was 20.5% (ET: 17.5%, CON: -3.0%), and 3.7% (ET: 0.0%; CON: -3.7%) for a baseline peak O_2-pulse of 17.9 mL/beat (90th percentile of the study sample). Moreover, we observed a trend for a reduced ET-induced change in relative peak $\dot{V}O_2$ for increasing body weight at baseline (interaction P = 0.054) with -2.04% for every 10 kg higher baseline body weight ([95% CI, -4.15 to 0.08], P = 0.08) following ET compared to -1.11% ([95% CI, -2.84 to 0.83], P = 0.32) following CON. None of the other factors had a significant interaction with study group on change in relative peak $\dot{V}O_2$ (interaction P > 0.05). A comparison between the complete case and the per-protocol analysis can be found in *Table 12*.

Table 12: Comparison of the associations between the investigated baseline factors and the change in relative peak oxygen consumption ($\dot{V}O_2$) following exercise training (ET) vs. guideline control (CON) for the complete case analysis (CCA) and the per-protocol analysis (PPA) (adapted from Mueller et al.[242])

		ß-coefficient (95% CI), P-value for mean change in relative peak $\dot{V}O_2$		
	Analysis Set	**Exercise Training (ET) [CCA: n = 106 | PPA: n = 87] [a]**	**Guideline Control (CON) [n = 52] [a]**	**Interaction P for ET vs. CON**
Peak O_2-pulse (per 1 mL/beat)	CCA	-1.45% (-2.30 to -0.60), P = 0.001	-0.08% (-1.11 to 0.96), P = 0.88	0.04
	PPA	-1.88% (-2.79 to -0.97), P < 0.001		0.01
Relative peak $\dot{V}O_2$ (per 1 mL/kg/min)	CCA	-0.38% (-0.99 to 0.22), P = 0.17	-0.39% (-1.10 to 0.32), P = 0.28	0.97
	PPA	-0.26% (-0.98 to 0.45), P = 0.47		0.78
Absolute peak $\dot{V}O_2$ (per 100 mL/min)	CCA	-0.76% (-1.45 to 0.07), P = 0.03	-0.17% (-1.03 to 0.69), P = 0.70	0.31
	PPA	-0.74% (-1.51 to 0.02), P = 0.06		0.34
Peak heart rate (per 10 beats/min)	CCA	0.42% (-0.79 to 1.63), P = 0.50	-0.48% (-1.96 to 0.99), P = 0.52	0.35
	PPA	0.74% (-0.57 to 2.06), P = 0.27		0.22
Body Weight (per 10 kg)	CCA	-1.11% (-2.84 to 0.63), P = 0.21	1.35% (-1.35 to 4.05), P = 0.32	0.14
	PPA	-2.04% (-4.15 to 0.08), P = 0.06		0.054
Hemoglobin (per 1 mg/dL) [a]	CCA	0.10% (-1.81 to 2.00), P = 0.92	1.60% (-1.46 to 4.65), P = 0.30	0.44
	PPA	0.21% (-1.91 to 2.33), P = 0.85		0.49

The CCA comprised all patients with complete baseline and 3-month follow-up data, whereas in the PPA, patients who were randomized to ET and complete less than 70% of the prescribed ET sessions were excluded from the analysis.

[a] different number of patients (n) (due to missing values) for the analyses of hemoglobin (ET - CCA: 103 patients; ET - PPA: 84 patients; CON: 52 patients)

Besides adherence, the predictive power of baseline peak O_2-pulse on the ET-induced change in relative peak $\dot{V}O_2$ may also be dependent on baseline peak RER. Compared to patients with a baseline peak RER ≥ 1.10 (ET: -1.89% [95% CI, -3.07 to -0.70], P = 0.003; CON: 0.58% [95% CI, -1.07 to 2.23], P = 0.49; interaction P = 0.02), the association between baseline peak O_2-pulse (mL/beat) and change in relative peak $\dot{V}O_2$ was not significantly different between groups in patients with peak RER < 1.10 (ET: -0.87% [95% CI, -2.16 to 0.41], P = 0.20; CON: -0.44% [95% CI, -1.83 to 0.94], P = 0.53; interaction P = 0.66) *(Figure 15)*.

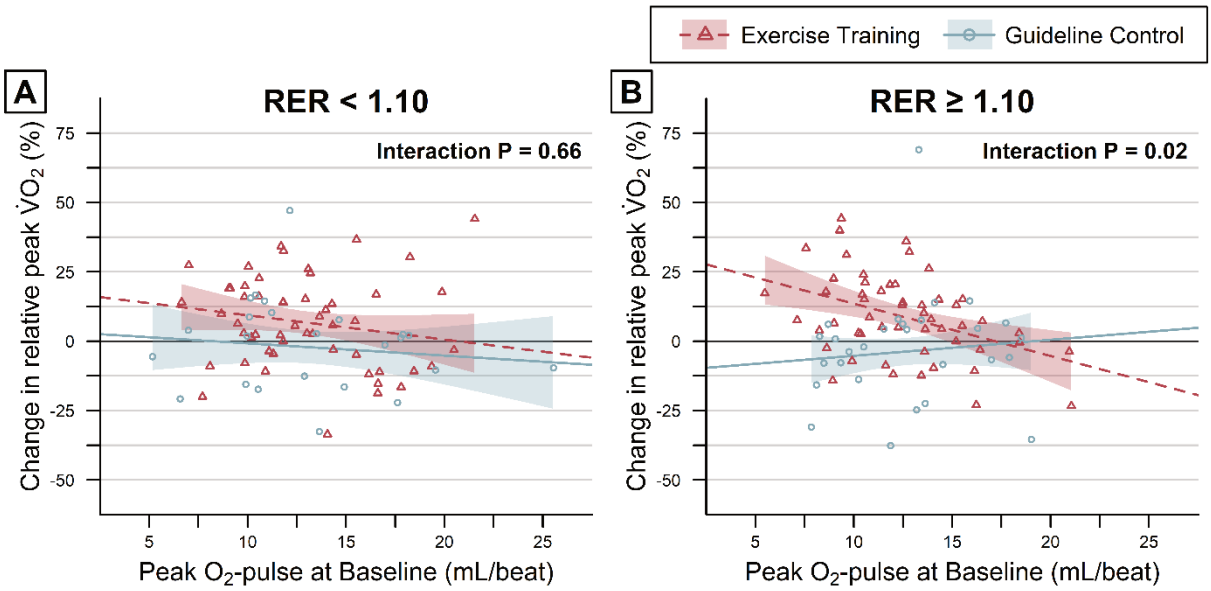


Figure 15: Relationships between changes in relative peak oxygen consumption ($\dot{V}O_2$) and baseline peak O_2-pulse in patients with baseline peak respiratory exchange ratio (RER) < 1.10 [A] and peak RER ≥ 1.10 [B] (adapted from Mueller et al.[242]). Individual relationships, robust linear regression lines and 95% confidence bands are shown separately for exercise training (–Δ–) and guideline control (–○–).

Associations between Changes in Peak $\dot{V}O_2$ and its Determinants

In the complete study sample (all 3 groups combined), changes in relative peak VO_2 (%) were positively correlated with changes in peak HR (%) (P < 0.001) and changes in peak O_2-pulse (%) (P < 0.001), and negatively correlated with changes in body weight (%) (P < 0.001). Moreover, changes in peak O_2-pulse (%) were negatively correlated with the changes in peak HR (%) (P < 0.001). There were no significant associations between changes in body weight (%) and change in peak HR (%) (P = 0.08) or peak O_2-pulse (%) (P = 0.45) *(Figure 16)*. None of these associations were significantly different between ET and CON (interaction P > 0.05) *(Appendix M)*.

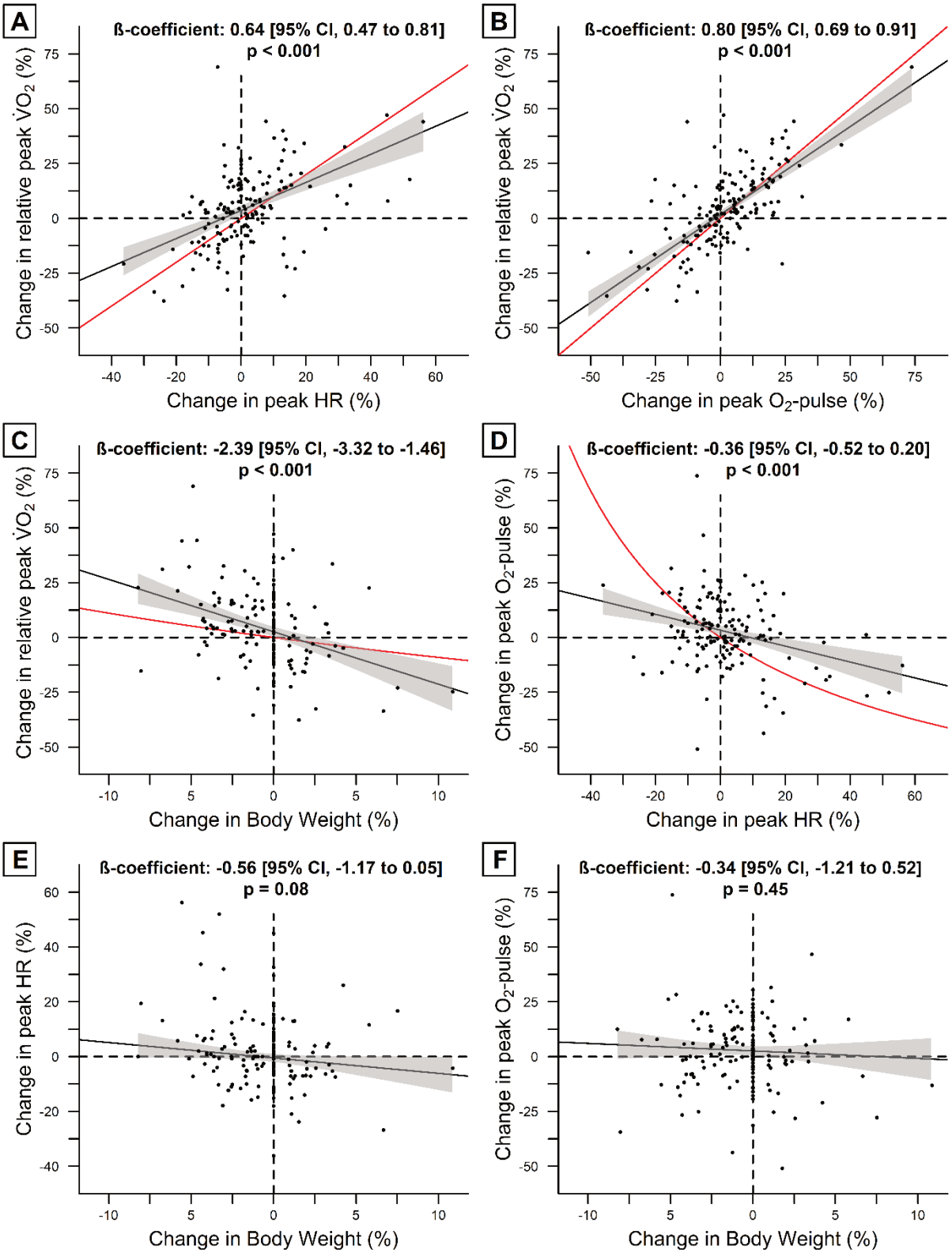


Figure 16: Associations between changes in peak oxygen consumption ($\dot{V}O_2$) and peak heart rate (HR) [A], changes in peak $\dot{V}O_2$ and peak O_2-pulse [B], changes in peak $\dot{V}O_2$ and body weight [C], changes in peak O_2-pulse and peak HR [D], changes in peak HR and body weight [E] and between changes in peak O_2-pulse and body weight [F] in the complete study population (adapted from Mueller et al.[242]). Associations are shown with regression lines and 95% confidence bands (——). Red lines (——) in panels A-D represent the predicted associations if the other determinant(s) remain constant.

4. Discussion

The OptimEx-Clin trial is the largest RCT evaluating the effects of ET in HFpEF to date and the only one in which ET was conducted over a duration of 12 months.[234] Moreover, it is the first study in HFpEF in which potential a priori defined predictors of inter-individual response variability in relative peak $\dot{V}O_2$ were examined between ET and CON and, to the best of our knowledge, the first study to evaluate the influence of baseline peak O_2-pulse on the ET-induced change in peak $\dot{V}O_2$ in any population.[242] In contrast to our main hypothesis, we did not find substantial evidence for the superiority of HIIT over MCT, indicating that both ET modes may be appropriate components of the therapeutic regimen for patients with HFpEF.[234] The key finding of our predictor analysis was that a lower baseline peak O_2-pulse, reflecting the product of peak SV and peak C[a-v]O_2, was significantly associated with larger improvements in relative peak $\dot{V}O_2$, providing a useful easily measurable parameter towards a more personalized deficit-oriented treatment in HFpEF.[242]

4.1. Changes in Exercise Capacity after 3 (Primary Endpoint) and 12 Months

After 3 months, peak $\dot{V}O_2$ was significantly improved in both ET groups compared to CON. The observed differences in change in peak $\dot{V}O_2$ (1.5 mL/kg/min for HIIT vs. CON; 2.0 mL/kg/min for MCT vs. CON [including imputation of missing values]; ~10% for the combined ET group vs. CON) were similar to the results of a recent meta-analysis of 436 patients with HFpEF from 8 smaller trials (1.7 mL/kg/min for ET vs. CON over a duration of 12-24 weeks),[229] but were lower than the a priori defined MCID of 2.5 mL/kg/min compared to CON. In response to the publication of the OptimEx-Clin article,[234] the selected threshold of 2.5 mL/kg/min has been criticized as too ambitious and exaggerated by several authors.[274-276] Indeed, increases in peak $\dot{V}O_2$ of 1.0 mL/kg/min or up to 10% have been described as 'traditionally' accepted MCIDs in previous manuscripts about ET in HFpEF,[221,226,277] however, it is unclear on what basis these thresholds were set. Nevertheless, within the last decade, 2 studies in cardiac patients undergoing an ET program have shown significant reductions in hospital admissions and mortality with considerably lower changes in peak $\dot{V}O_2$ than our a priori defined MCID of 2.5 mL/kg/min. In a sub-analysis of the largest ET trial in HFrEF (HF-ACTION, N = 2,331)[278] including 1,620 patients with CPET data at baseline and after 3 months (72 % male; median age, 59.4 years), the authors evaluated the

associations between change in peak $\dot{V}O_2$ and clinical outcomes.[279] After adjusting for other significant predictors, every 6% increase in peak $\dot{V}O_2$ over 3 months was associated with a lower risk for the combined primary end point of all-cause mortality and all-cause hospitalization (-5%), cardiovascular mortality and cardiovascular hospitalization (-4%), cardiovascular mortality and HF hospitalization (-8%), and all cause-mortality (-7%) during a median follow-up of approximately 2.3 years.[279] Moreover, in a retrospective analysis of 1,561 cardiac patients participating in an outpatient cardiac rehabilitation program over 8 weeks (84% with coronary artery disease [CAD], 74% male; mean age, 63.6), an increase in peak $\dot{V}O_2$ of 1 mL/kg/min was associated with a 25% lower risk of hospital readmission and a 20% lower risk of all-cause mortality without prior hospital admission over a median follow-up of 2.3 years.[280] If these associations between change in peak $\dot{V}O_2$ and clinical outcomes in predominantly younger male patients with HFrEF and CAD can also be applied for the predominantly older female patients with HFpEF[32,36] needs to be investigated, since evidence for HFpEF is so far limited to cross-sectional data.[88,281] Of note, even though MCIDs are often related to clinical outcomes like hospitalization or mortality, the concept of the MCID was initially defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management”[282 (p. 408)] or succinctly summarized as “the smallest difference a patient, or the patient’s clinician, would be willing to accept to use a new intervention”.[283 (p. 3)] Given these definitions and the high symptom burden in patients with HF, it may be more appropriate to also consider symptomatology, quality of life, or the ability to more easily perform activities of daily living for the determination of an MCID. In summary, it is indeed very likely that a change in peak $\dot{V}O_2$ lower than our a priori defined 2.5 mL/kg/min can be interpreted as a clinically relevant change in patients with HFpEF.

Besides the discussion about what might be of clinical relevance, a major result of the OptimEx-Clin trial[234] was that we did not confirm the results of 2 small single-center trials suggesting superiority of HIIT over MCT in HFpEF.[227,228] Importantly, in addition to low patient numbers, these studies have several limitations that may affect the generalizability of their findings. In the study by Angadi et al.[227] (HIIT: N = 9; MCT: N = 6), 4 weeks of HIIT significantly improved peak $\dot{V}O_2$ from 19.2 ± 5.2 to 21.0 ± 5.2 mL/kg/min (P = 0.04), whereas no significant changes were

observed following MCT (from 16.9 ± 3.0 to 16.8 ± 4.0; P = 0.93). However, the authors did not report between-group differences (nor SDs for the within-group changes that would allow the calculation of between-group differences) and the exercise volume for MCT (3 × 30 min/week) could have been too low to induce changes in peak $\dot{V}O_2$ over 4 weeks. Furthermore, 12 out of 15 patients were male (80%), which is in stark contrast to the generally predominantly female HFpEF population.[32,36] In the study by Donelli da Silveira et al.[228] (HIIT: N = 10, MCT: N = 9), changes in peak $\dot{V}O_2$ were almost twice as high following HIIT compared to MCT (mean change of 3.5 vs. 1.9 mL/kg/min; P < 0.001), however the patients in this study were considerably younger (mean age, 60 years) and had fewer comorbidities. Also considering the very high adherence rate of approximately 96% of prescribed ET sessions, there must have been very few, if any, adverse events during the trial, which indicates that the patients might have been less sick then the general patient with HFpEF, who typically has multiple comorbidities and a high risk of adverse events.[45,48,284] In contrast, patients included in the OptimEx-Clin trial had baseline characteristics that were similar (mean age, 70 years; mean BMI, 30 kg/m^2; multiple comorbidities) or even more severe (mean E/e', 15.8) as compared to other clinical trials in HFpEF (e.g., ALDO-DHF[285]: mean age, 67 years; mean E/e', 12.8; PARAGON[75]: mean age, 73 years; mean BMI, 30.3 kg/m^2).

Interestingly, the OptimEx-Clin trial is in line with other large multicenter RCTs failing to reproduce the superiority of HIIT vs. MCT seen in small-sized single-center RCTs or meta-analyses of small single-center trials in HFrEF[230,286] or CAD.[287,288] Neither the SMARTEX trial (N = 261 patients with HFrEF)[232] nor the SAINTEX-CAD trial (N = 200 patients with CAD)[289] found significant differences for the change in peak $\dot{V}O_2$ between HIIT and MCT. Significantly larger treatment effects in small vs. large and single- vs. multicenter trials are a known problem in clinical research.[290-292] In general, single-center and small-size clinical trials are more likely conducted and analyzed with lower methodological quality (e.g., in terms of allocation concealment, blinding, inadequate analysis, selective analysis reporting, fraud),[290,293-295] which is associated with higher treatment effects.[296,297] Single-center and / or small studies are also more prone to selective reporting of outcomes or publication bias (e.g., smaller trials with negative results are less likely published than larger trials with negative results).[290,292,295,298] Moreover, smaller and / or single-center trials often include more homogeneous and highly selected (e.g., very motivated) patients,[290,295] whereas larger

trials need to use less selective inclusion procedures to meet recruitment rates resulting in a sample closer to the real / entire population. In addition, due to generally lower caregiver-to-patient ratios, larger trials often need to implement less intensive interventions (e.g., less time spent with each patient), which can be associated with lower treatment effects,[295] but is also more closely to a 'real-life scenario' in which ET is prescribed to an outpatient. In contrast to most of the smaller ET trials in HFpEF, the OptimEx-Clin trial was conducted according to a rigorous multicenter design with standardized operating procedures and the use of blinded core laboratories to assess study outcomes, which also significantly reduces the risk of bias as compared to trials not using this feature.

Surprisingly, changes in peak $\dot{V}O_2$ were no longer significantly different between groups after 12 months ($P = 0.11$),[234] which is in accordance with a previously conducted individual patient data meta-analysis in patients with HFrEF (mean difference, 0.69 mL/kg/min [95% CI, -0.24 to 1.62]).[236] In the OptimEx-Clin trial, the mean difference in peak $\dot{V}O_2$ in the complete case analysis between HIIT and CON decreased only slightly (1.8 mL/kg/min after 3 months vs. 1.4 mL/kg/min after 12 months), whereas the mean difference between MCT and CON strongly decreased from 2.3 mL/kg/min after 3 months to 0.6 mL/kg/min after 12 months.[234] This drop may in part be explained by the reduced adherence during the home-based ET phase, however, even in those who performed at least 70% of prescribed ET sessions, the mean group differences in change in peak $\dot{V}O_2$ after 3 and 12 months (HIIT vs. CON: 2.1 mL/kg/min at 3 months and 1.7 mL/kg/min at 12 months; MCT vs. CON: 2.6 mL/kg/min at 3 months and 1.1 mL/kg/min at 12 months) were similarly decreased as compared to the complete case analysis. Therefore, other, so far unknown reasons, seem to play a significant role for this finding. From an exercise physiology point of view, one might expect stagnation over time when performing a monotonous ET regimen over 1 year, however, especially the strongly diminishing effects seen in MCT merit further investigation. A potential reason for this finding could be that the design of the OptimEx-Clin trial did not follow the general training principles of individualization and overload (including the secondary principles of variation and progression).[99,109] Based on the principle of individualization, ET prescriptions should be tailored to each individual' baseline condition and regularly adjusted based on the individual responses during follow-up.[99,109] According to the overload principle, a training stimuli must be above an individual threshold to be

effective, and especially in the long term, such overload may only be achieved by regular progression and / or variation of ET modes, frequency, duration or intensities.[99,109] In the OptimEx-Clin trial, ET prescriptions were not varied, progressively designed or individualized in either mode. While HIIT may have provided an effective training stimulus throughout the duration of the study (because of the high intensity) that resulted in maintaining the improvement in peak $\dot{V}O_2$ between 3 and 12 months, it is possible, that the decline in MCT was also due to the constant ET stimulus, which may have been too low to be effective after the initial improvement in peak $\dot{V}O_2$ over the first 3 months (ET principle of reversibility after discontinuation of [effective] ET).[99,109] Therefore, future trials should examine the effects of varying ET modes and intensities to provide different stimuli in the same patient and apply more personalized ET prescription based on the individual patient's physiological state (e.g., ET prescriptions that account for baseline values, are based on ventilatory thresholds rather than % HRR, and are regularly adjusted for patient's responses) *(see also chapter 4.8.2)*. Moreover, the results of other ET trials such as the Ex-DHF trial (N = 320 patients; 12 months of MCT plus resistance training vs. CON)[299] are eagerly awaited and may help to better understand the long-term effects of ET in HFpEF.

4.2. Changes in Secondary Endpoints after 3 and 12 Months

Even though the secondary endpoints of the OptimEx-Clin trial[234] should be interpreted as exploratory, they can illuminate and point out important aspects related to the ET-induced changes in HFpEF.

4.2.1. Changes in Functional Capacity

Changes at VT1 were similar to the results observed for peak $\dot{V}O_2$, however, in the complete-case analysis, only MCT resulted in a statistically significant difference compared to CON after 3 months (mean difference, 6 watts [95% CI, 2 to 11]).[234] In contrast, only adherent HIIT patients showed a significant difference compared to CON at 12 months (mean difference, 8 watts [95% CI, 3 to 14]),[234] which supports the previous interpretation that patients randomized to HIIT were more likely to maintain the improved exercise tolerance over 12 months. The results are also consistent with previous ET trials in HFpEF, most of which have shown an improvement in VT1[221,222,225] or 6-MWT,[220,221,225,226] another marker of functional capacity, following ET compared to

CON.[221,222,225] Next to maximal exercise capacity (i.e., peak $\dot{V}O_2$), change in functional capacity is an at least equally relevant effect of ET interventions, because functional capacity is more closely related to (light) activities of daily living. Therefore, an improvement in functional capacity (not only peak $\dot{V}O_2$) enables patients to more easily manage everyday activities such as getting dressed, making the bed, sweeping or vacuuming, walking to the bakery, etc., without experiencing dyspnea and possibly being forced to take a break.[300] Compared to peak $\dot{V}O_2$, VT1 has the advantage of being independent of the subject's effort or motivation. On the other side, correct determination of VT1 requires a certain experience and skill level, has a non-negligible inter- and intra-observer variability, even among experienced evaluators,[301] and may not be determinable in all patients with HF (due to very early onset of anaerobic metabolism or severe exercise oscillatory ventilation).[125]

4.2.2. Changes in Indices of Diastolic Function

In the OptimEx-Clin trial,[234] we did not find any significant differences in E/e', e', LAVI or NT-proBNP between groups, even though there was a trend over time towards a reduced E/e' after HIIT. In some of the previous ET trials in HFpEF, significant differences between groups were found for E/e', e' and LAVI[222] or the ratio of early to late atrial diastolic transmitral flow velocity (E/A ratio) and deceleration time (DT),[224] whereas other studies found significant within-group changes for E/e'[213,228] or diastolic dysfunction grade, E and DT.[227] Moreover, Edelmann et al.[222] and Donelli da Silveira et al.[228] demonstrated significant correlations between changes in E/e' and changes in peak $\dot{V}O_2$ for their entire study cohorts (r = -0.37 [P = 0.002] and r = -0.475 [P = 0.04], respectively). In contrast, in a meta-analysis that included all 'smaller' published HFpEF trials comparing ET vs. CON,[229] no significant differences in changes in echocardiographic indices of diastolic function (E/A, DT, E/e', e') between groups were found. In another study that invasively investigated the pressure-volume curves in 7 patients with HFpEF (without a control group), no significant within-group changes following 12 months of ET were observed.[302]

Interestingly, invasively measured pressure-volume curves have been shown to be improved after ET in healthy middle-aged,[303] but not older individuals,[304] whereas significant within- and / or between-group changes in indices of diastolic function measured by echocardiography following ET have been reported for patients with

diabetes mellitus and diastolic dysfunction,[305] atrial fibrillation,[306] hypertension[307,308] or HFrEF.[309,310] These results have led to the conclusion that ET is able to improve diastolic function when initiated early enough, whereas improvements are at least much harder to obtain after pathophysiological changes have manifested.[311] To investigate whether patients at high risk for developing HFpEF can improve LV compliance, Hieda et al. most recently evaluated the effects of a 12-month ET program (combination of MCT, HIIT and resistance training) vs. CON using invasive pressure-volume curves in 45- to 64-year-old patients with LV hypertrophy and elevated biomarkers associated with subclinical myocardial injury or hemodynamic stress (cardiac troponin T > 0.6 pg/mL or NT-proBNP > 40 pg/mL).[311] In line with the previously reported results and besides a significantly improved peak $\dot{V}O_2$ of 5.8 mL/kg/min compared to CON, they found a significantly ET-induced increase in EDV, significantly reduced LV chamber stiffness (lower increase in pulmonary capillary wedge pressure [PCWP] in relation to end-diastolic volume) and myocardial stiffness (lower increase in transmural pressure [difference between PCWP and right atrial pressure] in relation to end-diastolic volume), and a slightly increased SV index for any given PCWP.[311]

Whether longer, more intensive (e.g., HIIT) or combined ET programs (similar to the one applied by Hieda et al.)[311] can reverse diastolic dysfunction in patients with manifest HFpEF needs to be further investigated in future studies. Importantly, these studies should potentially pay attention to a very important aspect that has been largely ignored so far. Previous ET trials in HFpEF have mainly focused on evaluating diastolic function at rest, however, the cardinal symptom of HFpEF (i.e., premature dyspnea due to exercise intolerance) occurs on exertion, and while some patients may have (pseudo-)normal diastolic function at rest, they show exaggerated increases in filling pressures during exercise.[150-152] Therefore, it is probably much more important to evaluate how ET alters diastolic function and, in particular, filling pressures at submaximal or maximal exercise, which should be a major focus of future ET trials in HFpEF.

4.2.3. Changes in Ventilation to Carbon Dioxide Production Slope

Although ventilatory efficiency during CPET can be evaluated by several additional parameters (e.g., partial pressure of end-tidal CO_2, the ventilatory equivalent of $\dot{V}E$ vs. $\dot{V}CO_2$ over time, y-intercept of the $\dot{V}E/\dot{V}CO_2$ slope),[132] an increased slope of the

$\dot{V}E/\dot{V}CO_2$ relationship is a major characteristic of patients with HF and has emerged as the most relevant and well-studied ventilatory efficiency parameter with an additive and similar to superior prognostic power compared with peak $\dot{V}O_2$, especially in patients with insufficient exertion during CPET.[88,127-131] As described above *(see equation (9) in chapter 1.2.2)* an overly increase in $\dot{V}E$ responsible for the increased $\dot{V}E/\dot{V}CO_2$ slope can be caused by a significantly decreasing $PaCO_2$ or a progressive increase of V_D/V_T during exercise. This can be due to several reasons including high LV filling pressures, pulmonary congestion or fibrosis, increased pulmonary vascular resistance and secondary pulmonary hypertension, RV dysfunction, increased chemo- and metaboreflex sensitivity, or early anaerobic metabolism.[106,115,130,132,254,312-316] Increased reflex sensitivity leading to reduced $PaCO_2$ at peak exercise appears to be the main cause of the increased $\dot{V}E/\dot{V}CO_2$ slope in patients with HFrEF, whereas in HFpEF, peak V_D/V_T was identified as the main cause of the increased $\dot{V}E/\dot{V}CO_2$ slope.[132,313,317]

In patients with HFrEF, ET has been associated with significant improvements in $\dot{V}E/\dot{V}CO_2$ slope[318] without significant differences between HIIT and MCT.[231] In HFpEF, the effects of ET on $\dot{V}E/\dot{V}CO_2$ slope are less well investigated. Only 1 study to date has shown a significant ET-induced decrease in $\dot{V}E/\dot{V}CO_2$ slope compared to CON,[223] whereas 3 other studies showed no significant differences in change in $\dot{V}E/\dot{V}CO_2$ slope between groups.[221,225,226] Moreover, two studies showed significant within-group improvements of $\dot{V}E/\dot{V}CO_2$ slope after 12 weeks of HIIT[213,228] with no significant differences between HIIT and MCT,[228] whereas in the study by Angadi et al., neither 4 weeks of HIIT nor MCT significantly changed the $\dot{V}E/\dot{V}CO_2$ slope.[227] Therefore, the OptimEx-Clin trial provides important data on whether the $\dot{V}E/\dot{V}CO_2$ slope is modifiable by (different modes of) ET in HFpEF. Patients randomized to MCT showed a stable mean improvement in $\dot{V}E/\dot{V}CO_2$ slope at 3 and 12 months (mean within-group change at both time points, -0.7), which was significantly different from both HIIT (mean difference of MCT vs. HIIT, -2.8) and CON (mean difference of MCT vs. CON, -1.9) at 12 months.[234] While these results highlight the ability of MCT to alter this important pathophysiological and prognostic factor in patients with HFpEF, the continuous increase in $\dot{V}E/\dot{V}CO_2$ slope following HIIT (mean within-group changes of 0.7 and 2.0 at 3 and 12 months, respectively) is a disconcerting finding that may indicate disease progression and should be investigated further. For example, a high $\dot{V}E/\dot{V}CO_2$ slope is associated with pulmonary hypertension,[106,132] a common comorbidity and / or sequela

in patients with HFpEF,[147,164,319] and because of the risk of increasing pulmonary artery pressure, which can lead to circulatory collapse and right heart failure, ET recommendations in patients with pulmonary hypertension are limited to low- and moderate-intensity exercise.[320]

On the other side, these findings could also be due to chance, an unphysiologically altered breathing pattern as a result of HIIT (higher breathing frequency compared with lower V_T, which would increase V_D), or the methodology used to assess $\dot{V}E/\dot{V}CO_2$ slope. As previously described *(chapter 1.2.2)*, the 'physiological' $\dot{V}E/\dot{V}CO_2$ slope is determined by the linear increase of $\dot{V}E$ over $\dot{V}CO_2$ until VT2. In contrast, the $\dot{V}E/\dot{V}CO_2$ slope in the OptimEx-Clin trial was evaluated using the entire exercise data, as this method has previously been shown to be prognostically superior in patients with HF.[135,136] However, if patients can better tolerate metabolic acidosis (after VT2) following HIIT, this could lead to a prolonged steep part of the $\dot{V}E/\dot{V}CO_2$ relationship that increases the entire slope but not the 'physiological' slope until VT2. Therefore, a future sub-analysis of the OptimEx-Clin trial evaluating the linear increase of the $\dot{V}E/\dot{V}CO_2$ slope until VT2, as well as other parameters of ventilatory efficiency or potential predictors of the increase in $\dot{V}E/\dot{V}CO_2$ slope following HIIT, may already shed additional light on this exploratory, potentially worrisome finding.

4.2.4. Changes in Quality of Life

After 3 months, mean QoL, assessed by the KCCQ-QoL domain, had improved by more than 5 points in all groups (HIIT: + 7 points, MCT: + 10 points, CON: + 6 points), which is usually interpreted as a clinically relevant improvement.[273] This treatment-independent improvement in QoL is a phenomenon that has also been observed in previous ET trials in HFpEF and HFrEF[226,232] and may be related to the so-called 'Hawthorne effect' or other reactivity effects that may account for improvements in both experimental and control groups.[321] According to the 'Hawthorne effect', participants may consciously or unconsciously change their behaviors simply because they are being studied, and even in the absence of behavioral change, participation in a clinical trial that involves a broader range of examinations, more intensive interaction with caregivers and more frequent clinical visits compared with clinical routine may also lead to improvements in QoL that are independent of group assignment.[321] However, in contrast to the CON group, whose mean QoL did not further

improve after the 3-month visit (± 0 points until month 12), mean QoL continued to increase between month 4 and 12 in patients receiving HIIT (+ 4 points) and MCT (+ 7 points), with a significant difference in change in QoL between MCT and CON at 12 months (mean difference, 11 points), which indicates that these further improvements are truly associated with ET. While effects on QoL were inconsistent across ET trials in HFpEF *(Table 2)*, our findings are in accordance with a recent meta-analysis that pooled these studies and found significant differences in favor of ET,[229] which has also been shown for patients with HFrEF.[322]

Based on the mean within-group change in peak $\dot{V}O_2$ after 12 months of MCT (± 0.0 mL/kg/min), it is unlikely that the improvement in QoL can be explained by changes in peak $\dot{V}O_2$. This may initially seem surprising, given that previous evidence indicates significant associations between peak $\dot{V}O_2$ and various QoL measures in patients with HF (HFrEF and HFpEF)[253,323,324] or cardiac patients participating in exercise-based cardiac rehabilitation (CAD, HF and heart valve disease).[325] However, most ET studies evaluating the associations between changes in peak $\dot{V}O_2$ and changes in QoL found only very weak, if any, significant correlations between these two variables,[323,325-328] indicating that correlations from cross-sectional analyses have limited applicability to longitudinal research designs. Another potential mediator for changes in QoL could be the change in $\dot{V}E/\dot{V}CO_2$ slope, as the $\dot{V}E/\dot{V}CO_2$ slope has also been found to be significantly correlated with the KCCQ summary score,[329] MLHFQ[330] and SF-36[324] in cross-sectional studies including patients with HFrEF. Moreover, in a study evaluating the effects of sildenafil in patients with HFrEF, changes in $\dot{V}E/\dot{V}CO_2$ slope were strongly correlated ($r = 0.69$, $P < 0.001$) with changes in exercise pulmonary vascular resistance,[316] which is closely related to dyspnea. Overall, the evidence for a potential association between changes in QoL and $\dot{V}E/\dot{V}CO_2$ slope is scarce, especially in HFpEF, but given the close relationship between changes in ventilatory inefficiency and pulmonary vascular resistance, it is reasonable to assume that changes in $\dot{V}E/\dot{V}CO_2$ slope may have relevant effects on changes in QoL, which should be investigated in further studies.

4.3. Safety Aspects and Effects of Exercise Training on Adverse Events

In general, it has long been recognized that both exercise testing and ET can be safely performed without significantly increasing the risk of acute events in patients with

cardiac disease.[331] For example, in a study of 65 French cardiac rehabilitation centers with 25,420 patients who performed 42,419 exercise tests and completed 743,471 hours of ET, only 5 and 15 events occurred during or within 1 hour after exercise testing (5 AEs per 8,484 tests) or training (1 AE per 49,565 training hours), respectively.[332] However, compared to exercise testing or moderate-intensity training, vigorous physical activity (including HIIT) has been traditionally associated with an increased risk of sudden cardiac death and acute myocardial infarction.[331] In 2012, Rognmo et al. evaluated the risk of cardiac arrest or acute myocardial infarction during or within 1 hour after a HIIT or MCT session among 4,846 patients with CAD participating in an exercise-based cardiac rehabilitation program (combination of MCT and HIIT in all patients) in Norway between 2004 and 2011.[333] Within 129,456 hours of MCT and 46,364 hours of HIIT, there was only 1 fatal cardiac arrest during MCT (1 AE per 129,456 training hours) and 2 non-fatal cardiac arrests during HIIT (1 AE per 23,182 training hours).[333] Similar results were also reported in a meta-analysis of HFrEF and CAD trials, which included 23 trials with 547 HIIT patients exercising for 11,333 hours and 570 MCT patients exercising for 11,213 hours.[334] Overall, there were 5 AEs during or shortly after HIIT (ventricular arrhythmia leading to cardiac arrest, syncope, knee pain, inappropriate implantable cardioverter-defibrillator discharge, dizziness; 1 AE per 2.267 training hours) and 2 AEs during or shortly after MCT (anxiety / panic attack, leg pain; 1 AE per 5.607 training hours).[334] These results highlight that the risk for an acute AE during exercise is very low, however, even though the results were not significantly different between groups, the event rate might be higher during HIIT compared to MCT. Importantly, both studies included data from supervised ET only and were limited to a relatively short time after patients were evaluated for their eligibility to safely perform ET (mean [maximum] duration of 11.8 [26] weeks[334] or average of 36.3 sessions[333]). Therefore, the risk for acute events during home-based ET or longer periods without a comprehensive cardiac examination remains unclear. In the OptimEx-Clin trial, 6 events occurred during or within 2 hours after ET (3 × HIIT, 3 × MCT),[234] which corresponds to approximately 1 event per 2,100 and 1,150 hours of MCT and HIIT, respectively. Therefore, this result is in line with the slightly (but not significantly) higher relative acute event rates of HIIT compared with MCT reported in the aforementioned trials.

Importantly, the safety of ET or a particular exercise mode should not be evaluated based on acute effects alone, as AEs that do not occur during or shortly after an exercise session may also be caused by the chronic effects of ET. Because of the small number, size and duration of RCTs evaluating ET in HFpEF, the chronic effects of ET on AEs are largely unknown. In the OptimEx-Clin trial, we observed a considerably higher number of AEs (209 events in 102 patients) and SAEs (88 events in 52 patients) compared to what has been reported in previous ET trials in HFpEF.[220-222,224-226] This reflects the multimorbidity of the included patients with HFpEF, which may have also contributed to the increased number of AEs observed in the ET groups (both MCT and HIIT) compared to CON. However, the higher number of non-serious and non-cardiovascular AEs in the ET groups (e.g., respiratory tract infections and knee/hip pain) may be explained by a higher reporting rate due to more frequent contacts in these groups,[234] as, for example, patients randomized to HIIT or MCT were regularly called when they did not record exercise sessions, whereas patients randomized to CON may not have remembered some of their 'minor' illnesses after being asked about AEs at the next study visit. This is also supported by the fact that with regard to SAEs, there were no significant differences in the number of events or the number of affected patients between groups, although it is important to emphasize that the study was not sufficiently powered for this comparison. The overall higher number of AEs and SAEs compared with previous trials may be explained by shorter trial duration or more selective recruitment in the previously conducted smaller trials. Of note, all patients enrolled in the OptimEx-Clin trial were carefully screened for conditions that might interfere with an ET intervention (e.g., signs of ischemia during CPET; concomitant diseases that might affect 1-year prognosis). Based on a retrospective analysis of 18,485 patients with HFpEF from the USA, patients who participated in an exercise-based cardiac rehabilitation program had 35% lower odds of all-cause mortality within the next 2 years compared with propensity score-matched patients who did not participate in such a program.[335]

In contrast to HFpEF, there is much more data on the chronic effects of ET on AEs and mortality in HFrEF or other cardiac diseases such as CAD. As described above *(chapter 1.4)*, based on the most recent Cochrane review, which included 44 ET studies in HFrEF lasting at least 6 months, ET was associated with a 30% lower risk for all-cause hospitalizations, a 41% lower risk for HF-specific hospitalization and a

tendency towards a lower medium-term (> 12 months) all-cause mortality (relative risk, 0.88, P = 0.09).[217] Moreover, regular long-term ET has been shown to be associated with a lower rate of hospital admissions and mortality during a 10-year follow-up in patients with HFrEF.[218] Regarding the chronic effects of HIIT on SAEs in HF, data is very limited, and no study had a follow-up of more than 12 months. After 12 months, neither in the OptimEx-Clin trial (HFpEF)[234] nor in the SmartEx trial (HFrEF),[232] the number of patients with SAEs differed significantly between groups. However, the SmartEx trial was also not sufficiently powered for this endpoint, and there was a trend toward a higher number of patients with SAEs after HIIT compared with MCT, particularly during the follow-up between month 4-12 (n = 22 vs. n = 10 patients with total SAEs, P = 0.10; n = 19 vs. n = 8 patients with cardiovascular SAEs, P = 0.06).[232]

In summary, there is no clear evidence on whether HIIT is associated with a relevantly higher acute or long-term risk for AEs, disease progression or mortality in patients with HF or other cardiac diseases. However, especially due to the lack of data regarding long-term effects and outcomes after acute HIIT bouts that were performed more than 3 months after the last cardiac examination, the current evidence does not allow to draw a reliable conclusion on the overall safety of HIIT in cardiac patients. To minimize the risk of HIIT or ET in general, it is of utmost importance to conduct pre-participation screenings to identify unstable and high-risk patients, perform regular follow-ups every 3 to 6 months and, if possible, start in a supervised setting before gradually shifting to home-based ET.[233,331] Moreover, subject to further investigation of the exploratory finding on change in $\dot{V}E/\dot{V}CO_2$ slope in the Optimex-Clin trial *(see chapter 4.2.3)*, HIIT should perhaps be limited to stable, low-risk patients with lower $\dot{V}E/\dot{V}CO_2$ slopes who should be regularly reassessed.

4.4. Adherence to Exercise Training

Adherence to prescribed treatment is probably the most relevant factor in the success of any therapy. Therefore, if a treatment is effective, the effects should always be higher in patients with high adherence than in patients with low adherence (or the complete sample of adherent and nonadherent patients). Nevertheless, the effectiveness of a therapy should always be primarily judged on the basis of an analysis that also includes patients who did not adhere to the therapy, because the best therapy is not beneficial when patients, for whatever reason, do not use it. In addition, the use of a ‘per-protocol

criterion' that cannot be applied to patients in the CON group in the same way as to patients in the intervention groups can introduce a substantial bias for the estimation of treatment effects. While this is only possible in placebo-controlled studies with adequate blinding of the participants (e.g., taking more than 90% of the prescribed medication / placebo independent of group assignment), it is a particular problem in lifestyle intervention trials or other trials without adequate blinding and placebo control. For example, if a patient in a lifestyle intervention group is hospitalized for a heart attack, it is likely that his or her exercise tolerance is worse at the next examination. However, because the cardiac event also affects adherence to ET, this patient is likely excluded from the per-protocol analysis. In contrast, if the patient had been randomized to CON, he or she would not have been excluded from the per-protocol analysis despite the same effect on exercise tolerance.

In the OptimEx-Clin trial, adherence was good within the first 3 months, but markedly declined during home-based ET in month 4-12, with only about half of patients meeting the target cutoff of at least 70% of prescribed ET sessions,[234] which is similar to what has been previously reported in patients with HFrEF.[278,336] The lower adherence over the entire 12 months may in part be explained by the relatively high number of AEs that patients reported as the main reason for reduced adherence.[234] However, reasons for nonadherence are multifactorial and not exclusive to lifestyle intervention trials. For example, common reasons for medication nonadherence comprise intentional and unintentional reasons such as forgetfulness or overload due to taking multiple medications and complex dosing schemes, lack of understanding or trust in the purpose of the treatment, belief that the treatment is not necessary, psychiatric problems, or (fear of potential) side effects.[337] While most of these factors are probably also applicable to ET trials, adherence to ET interventions (or, more broadly, lifestyle-related interventions) is more likely to be influenced by AEs, as the performance of ET requires patients to be in a stable condition and free of any acute diseases, which is generally not the case for taking medication. Moreover, ET interventions also face more complex motivational and volitional obstacles to initiating and maintaining behavior change. The motivation-volition process model introduced by Fuchs et al.[338] incorporates several elements from research on social cognition, primarily focusing on motivational aspects, as well as self-regulatory volitional aspects of behavioral control.[339-344] According to this

model, the likelihood of successfully initiating and maintaining a lifestyle-related behavior change is based on:

A) the strength of the goal intention after weighing costs and benefits, as well as one's own ability to carry out the behavior change (self-efficacy),
B) the self-concordance of the goal intention (e.g., how well the goal fits the patient's interests and values),
C) the implementation intentions (e.g., when, where and how the behavior change should be implemented),
D) the volitional strategies to protect the behavior change against external (e.g., overtime at work; being invited for dinner by friends) or internal barriers (e.g., being tired or listless), and
E) the outcome experiences (e.g., feelings associated with the implementation of the behavior change).[345]

Therefore, despite being motivated (e.g., believing in the effectiveness and necessity of the treatment) and not having negative outcome experiences (e.g., side effects), which may be sufficient for medication adherence, many individuals are unable to maintain ET in the long term. In a meta-analysis of ET studies in older people (mean age > 65 years), several person-level factors such as higher socioeconomic status, better education, living alone, better self-rated health, fewer health conditions and medications, lower BMI, better physical function, higher cognitive ability and fewer other psychological factors (fear of falling, depressive symptoms, psychoactive medications, feeling of loneliness) were associated with higher participation in ET programs.[346] Similarly, in another recent meta-analysis of studies in older patients (mean age > 65 years) referred to ET programs for medical reasons (cardiac, pulmonary, neurological, surgical or other non-musculoskeletal conditions), high self-efficiency, good self-rated mental health, less depression and living closer to the exercise facility were identified as predictors of adherence, whereas risk factors such as higher BMI, smoking, hypertension, hypercholesterolemia or a comorbidity index were not predictive of adherence.[347] Moreover, several studies in patients with HF have identified factors such as higher comorbidity, longer HF duration, lower BMI and lower hostility,[348] lower social support and the presence of more exercise-related barriers,[349] or medical reasons (AEs), lower physical function, smoking and a history of myocardial infarction or depression,[350] as significant predictors of nonadherence to ET programs. For a

comprehensive overview of factors associated with nonadherence to ET in cardiac patients, see Conraads et al.[351]

Besides the person-level factors, adherence is also related to program characteristics with higher adherence in supervised vs. home-based and short-term vs. long-term interventions.[346,352] These associations are problematic because to achieve sustainable effects, ET should be implemented in the long term, but long-term supervised interventions are neither time- nor cost-efficient enough to be implemented on a large scale. This also includes patient barriers such as cost and travel time to the training facility, which may be accepted in the short term but can become burdensome as the program progresses. The design of the OptimEx-Clin trial with a supervised start that transitioned into a telemedically assisted home-based ET, which was well accepted even in the group of elderly patients with a mean age of 70 years (many of whom did not own a smartphone), represents a first step toward a future-oriented ET design. This could also be a reason why, despite the decrease in adherence, the median amount of home-based exercise per week (MCT: ~ 144 min/week, HIIT: ~ 77 min/week) was still comparable with the current minimum guideline recommendations (150 min of moderate intensity or 75 min of higher intensity per week)[251,353] and in the MCT group almost twice as high compared to the HF-ACTION trial, which did not apply telemedicine.[278] Importantly, when applying a telemedical approach, several design features should be considered. In a recent review, we evaluated the associations between various design features with adherence and outcomes in lifestyle intervention trials in preventive cardiology. Even though the low number of available studies did not allow a clear conclusion, recurring personal contact was suggested as a potentially important factor for high adherence in telemedical studies.[352] As cardiac rehabilitation programs are significantly underused and often not adequately reimbursed,[354-357] telemedically assisted home-based ET including comprehensive monitoring and regular feedback could also contribute to broader application of ET programs. Such programs are highly recommended by American and European cardiac associations as an alternative to center-based cardiac rehabilitation and are already in use in several countries such as Australia, Canada or the United Kingdom.[251,354] Another way to increase adherence to regular ET could be an earlier resumption after an acute event. In a recently published ET trial in 349 elderly patients who were admitted to the hospital for acute decompensated HF (53% of patients had HFpEF), Kitzman et al. evaluated

the effects of an individualized ET program that was already initiated during or early after hospitalization and continued for 36 outpatient sessions within 12 weeks after discharge.[358] After 3 months, patients randomized to the intervention group had a significantly higher score on the Short Physical Performance Battery (a measure of physical function) compared to patients randomized to usual care, of whom 43% also took part in routine physical or occupational therapy or cardiac / pulmonary rehabilitation.[358] Importantly, an early resumption may not 'only' increase adherence to an ongoing ET intervention, but also reduce the deconditioning effects that are generally associated with the reduced mobility during and after AEs and hospitalizations, which will also likely translate to higher long-term effects.

In summary, potential ways to increase adherence to ET programs could be the integration of cognitive-behavioral strategies that target all of the aforementioned steps as outlined in the motivation-volition process model,[345] e.g., by incorporating the patient's perspectives and preferences regarding the type and mode of ET ('shared decision-making'), supporting the patient in setting realistic, self-concordant goals, implementing them into daily life and identifying potential barriers and subsequent coping strategies, improving ET-related education and / or providing regular feedback and positive reinforcement.[345,351,357,359] Moreover, widespread education of primary care physicians about the physiological benefits of and resources related to ET (to improve patient participation in ET programs), better financial coverage or reimbursement, earlier application or resumption of ET after an acute event, use of telemedicine (especially for home-based ET), more gradual shift from supervised to home-based ET, maintenance of regular supervised sessions during home-based ET (e.g., once per month), as well as more comprehensive monitoring and faster feedback of telemedically assisted home-based ET to simulate a situation that is closer to supervised ET could help to further increase adherence and long-term participation in ET programs.[274,351,357,360]

4.5. Mediation of the Change in Peak Oxygen Consumption and Interaction between the Different Mechanisms of Exercise Intolerance

There is clear evidence that ET has a positive impact on exercise tolerance in patients with HF. However, to improve the development of therapies and, in particular, the personalization of medicine, it is important to understand both the mechanisms of

exercise intolerance *(see chapter 1.3)* and the mechanisms responsible for the improvements observed with different therapies. As described above *(chapter 1.4.2)*, changes in peak $\dot{V}O_2$ must be caused by changes in SV, HR, $C[a\text{-}v]O_2$ and / or body weight (when peak $\dot{V}O_2$ is expressed in mL/kg/min), and ET trials in patients with HF have shown significant improvements in several mechanisms that may be responsible for improvements in one or more of these determinants.[357,361] These include, amongst others, adaptations of:

A) skeletal muscle structure and function (e.g., shift in fiber composition from type II to type I fibers; higher capillary density; improved mitochondrial density and function; increase in muscle strength, mass and function; improved O_2 extraction),
B) autonomic balance and cardiac function (e.g., reduced sympathetic tone; increased vagal tone; reduced ESV and EDV; increased LVEF; improved LV diastolic function and reduced LV filling pressures),
C) vascular function (e.g., reduced systemic vascular reserve at rest and peak exercise; increased endothelial-dependent and endothelial-independent function; increased arterial compliance; reduced hypertension; increased leg blood flow and O_2 delivery),
D) lung function (e.g., higher respiratory muscle strength; lower dyspnea),
E) kidney function (e.g., reduced plasma renin, angiotensin and aldosterone),
F) metabolism (e.g., reduced adiposity; reduced hyperlipidemia; reduced insulin resistance), and
G) inflammatory cytokines.[357,361,362]

Importantly, most of these findings were obtained in patients with HFrEF, and because most clinical trials mainly evaluated the causal group-based effects of an independent variable X (in general randomization groups, e.g., ET vs. CON) on several dependent variables Y_1, Y_2, …, Y_n ($X \longrightarrow Y_1$, $X \longrightarrow Y_2$), it is generally unclear whether (and to what extent) improvements in Y_1 (e.g., exercise tolerance) are directly related to, or even caused by, improvements in Y_2 (e.g., lung function). To evaluate the mechanisms responsible for a causal $X \longrightarrow Y$ effect, it is necessary to perform mediation analyses, a method that is widely applied in psychology[363] and is also becoming increasingly popular in medical research, as it is a prerequisite for improving personalized medicine.[364,365] Although there are various methods of mediation analysis, the basic idea is to test whether and how much of the $X \longrightarrow Y$ relationship can be

explained by a third variable – the mediator M – where X causes M, and M causes Y ($X \longrightarrow M \longrightarrow Y$).[363,365]

In the OptimEx-Clin trial, we were not able to directly measure all of the aforementioned mechanisms for the improvements in peak $\dot{V}O_2$. However, using CPET, we were able to evaluate the extent to which the difference in change in peak $\dot{V}O_2$ between groups was related to changes in peak HR, peak O_2-pulse (reflecting peak SV × peak C[a-v]O_2) and body weight. On group level, the difference in change in peak HR between groups was not significant,[234,242] whereas peak O_2-pulse significantly increased and body weight significantly decreased following ET (combination of HIIT and MCT) compared to CON.[242] Importantly, 'simple' mediator analyses assess the mediating effects of one factor at a time, and combining the results of multiple simple mediator analyses is critical, especially when evaluating different potential mediators that are correlated with each other (e.g., peak HR and peak O_2-pulse), because these mediators then partially explain the same variance (comparable to multicollinearity in multiple regression analyses). However, using a recently developed method that allows to include multiple uncausally related mediators,[266] we demonstrated that changes in peak O_2-pulse (i.e., peak SV and / or peak C[a-v]O_2) accounted for approximately 72% of the difference in change in peak $\dot{V}O_2$ between ET and CON, whereas changes in peak HR and body weight explained the additional 18% and 10%, respectively.[242]

In HFpEF, only 4 trials (1 RCT, 1 non-randomized controlled trial, 2 non-controlled trials) have so far evaluated the effects of ET on SV and C[a-v]O_2, indicating that if peak $\dot{V}O_2$ is increased by ET, peak C[a-v]O_2 is likely the primary mediator. In the first of these studies, a sub-analysis of the PARIS trial[221] trial involving 40 patients with HFpEF, Haykowsky et al. showed that the difference in peak $\dot{V}O_2$ between groups was accompanied by a significant difference in peak C[a-v]O_2 and peak HR.[241] However, even though there was a significant increase in peak HR following ET, only 16% of the change in peak $\dot{V}O_2$ was explained by the improved peak CO (i.e., peak HR × peak SV).[241] Similarly, in a study examining the effects of HIIT vs. CON over 12 weeks in 60 patients with HFpEF, the ET-induced improvement in peak $\dot{V}O_2$ was accompanied by a significant improvement in peak C[a-v]O_2, whereas neither peak HR nor peak SV were significantly increased. Moreover, in a recently published non-controlled study, 8 weeks of isolated knee extensor (IKE) exercise significantly improved peak C[a-v]O_2 and peak $\dot{V}O_2$ without significantly altering peak HR or SV in

9 patients with HFpEF.[366] In contrast, another non-controlled study of 7 patients with HFpEF showed no significant improvements in either peak $\dot{V}O_2$, peak C[a-v]O_2, peak HR or peak SV after 1 year of progressive endurance ET.[302]

Although some ET trials have shown a significant increase in peak HR in HFrEF[213,367-369] or HFpEF,[221,225] most studies did not find significant differences between groups,[234,242,361] and the general consensus is that ET-induced changes in peak $\dot{V}O_2$ in both healthy individuals and patients with HF are primarily induced by improvements in either SV or C[a-v]O_2.[91,239,240] While small ET-induced changes in autonomic function leading to an increase in peak HR cannot be completely excluded,[357,367] the improvements in peak HR observed in some ET trials may also be due to other reasons. For example, in the PARIS trial, change in peak HR was significantly different between ET and CON (+4 vs. -7 beats/min),[221,241] but the changes in peak systolic BP (+1 vs. -10 mmHg, P = 0.04) and peak RER (+0.03 vs. -0.02, P = 0.07) indicate that different changes in levels of exhaustion between baseline and follow-up may have contributed to that finding.[242] In addition, changes in peak HR may also be explained by changes in HR-affecting medication. In the OptimEx-Clin trial, changes in beta-blocker dosage were more frequent in the ET groups compared to CON (11.3 vs. 3.8% of patients), and when these patients were excluded, the mean group difference in change in peak HR decreased from 1.9% (P = 0.39) to 0.3% (P = 0.89).[242] This also led to the result that without this subset of patients, the mediating effects of changes in peak HR were reduced to only 2%, whereas the changes in peak O_2-pulse now accounted for up to 88% of the difference in change in peak $\dot{V}O_2$. In addition to these factors not directly related to ET, one of the studies that showed significant improvement in peak HR in patients with HFrEF also evaluated the change of the HRR to norepinephrine reserve ratio, which is an indirect index of the sympathetic responsiveness of the sinoatrial node.[368] As this parameter did not significantly change despite a significant improvement in peak HR, the authors concluded that the increase in peak HR may simply be due to improved leg muscle strength that enables longer exercise duration,[368] which would imply that despite having a low peak HR at baseline, chronotropic incompetence was not a relevant limitation in these patients.

This underscores that a strict separation into central and peripheral adaptations (or the different components of the Fick equation) might be counterproductive or even misleading, as it largely ignores the relationships and interactions between these

mechanisms of exercise intolerance. While some relationships or interactions, such as the relationship between impaired peripheral vascular function and SV, are obvious *(see chapter 1.3)*, others may easily be overlooked. For example, improvement in diastolic function may often be associated with a higher SV response to exercise. However, while HR increases until peak exercise, which is generally also assumed for $C[a\text{-}v]O_2$,[104,141,370,371] SV may already reach its highest value at approximately 40-50% of peak exercise.[104,238,371,372] Therefore, by the time when the exaggerated increase in filling pressures leads to the premature exercise termination due to dyspnea, SV may have already risen near its peak value while HR and $C[a\text{-}v]O_2$ are still submaximal. Accordingly, an apparent peripheral limitation (reduced peak $C[a\text{-}v]O_2$) may also be caused by an obvious central impairment (high filling pressures), and similarly, an apparent chronotropic incompetence may also be caused by high filling pressures or impaired peripheral mechanisms as described above. This is also supported by the findings of Sarma et al.,[373] who hypothesized that the reduced HR response observed in HFpEF may not be a cause but a consequence of exercise intolerance and evaluated the intrinsic HR and beta-adrenergic receptor sensitivity to graded isoproterenol infusion in patients with HFpEF and healthy controls. Indeed, 7 of the 13 patients had normal beta-receptor responsiveness and intrinsic HR despite significantly reduced peak HR, underscoring that other mechanisms leading to premature exercise cessation were likely responsible for the reduced peak HR in approximately half of these patients with HFpEF.[373]

On the other hand, there are also non-negligible opposing interactions that should be considered when interpreting both the mechanisms of exercise intolerance and the changes observed during therapies. Two studies have demonstrated that in patients with HFpEF, normalization of impaired convective O_2 delivery results in a smaller increase in peak $\dot{V}O_2$ than normalization of O_2 diffusion.[138,146] Interestingly, this was not primarily related to the extent of the impairments. Especially in the study by Houstis et al., the impairment in CO (-27% compared to healthy controls) was approximately 3.5 times higher compared to the impairment in $C[a\text{-}v]O_2$ (-8% compared to healthy controls), which could be misinterpreted as an indication that peripheral limitations are less important in HFpEF.[146,374] However, Houstis et al. pointed out that CO and $C[a\text{-}v]O_2$ are not independent, as higher CO results in faster blood flow, which in turn results in a lower muscle transit time for each red blood cell and less time for O_2

to diffuse into mitochondria.[146,375,376] Conversely, when CO is reduced, there is more time for O_2 diffusion in the capillaries, which would increase $C[a\text{-}v]O_2$.[146,374,377] Moreover, higher CO has also been associated with altered blood flow distribution, resulting in lower total $C[a\text{-}v]O_2$ because blood not returning from exercising muscles is less depleted of O_2.[375,378] To account for these interactions, Houstis et al. relativized the peak $C[a\text{-}v]O_2$ in patients with HFpEF to the peak CO / $C[a\text{-}v]O_2$ relationship of the healthy control group, which resulted in a mean peak $C[a\text{-}v]O_2$ (in HFpEF) that was 26% lower than predicted (compared to -8% without this relativization).[146] Moreover, they demonstrated that also previous HFpEF trials, in which peak $C[a\text{-}v]O_2$ was found to be normal,[377,379] showed a reduced $C[a\text{-}v]O_2$ response when the results are relativized to the impaired CO response to exercise.[146] By applying a theoretical simulation analysis in a representative patient with HFpEF, they further demonstrated that doubling the CO in this patient would have resulted in only a 10% increase in peak $\dot{V}O_2$, as $C[a\text{-}v]O_2$ would have dropped by 45%, whereas correcting the mean CO deficit (-27%) was predicted to improve peak $\dot{V}O_2$ by only 7%.[146] In contrast, correction of the mean deficit in muscle O_2 diffusion capacity (-36%) was predicted to increase peak $\dot{V}O_2$ by 27%.[146] Similarly, the results of the OptimEx-Clin trial showed that a change in peak HR (independent of treatment arm assignment) resulted in a lower than expected increase in peak $\dot{V}O_2$ (if body weight and peak O_2-pulse would have remained unchanged). In fact, a 10% increase in peak HR was associated with a mean change in peak $\dot{V}O_2$ of approximately 6.4%, which may be explained by the aforementioned interaction between CO and O_2 diffusion capacity but also by the interaction between HR and SV, as a higher HR also leads to a shorter diastolic duration, which shortens the time for ventricular filling and may hinders the increase in EDV and SV during exercise.[139,154,238,372,380,381]

Given these interactions between HR, SV and $C[a\text{-}v]O_2$, caution is also warranted when interpreting impairments expressed as absolute peak values compared with reserve parameters. In a pooled analysis of 910 patients with HFpEF and 476 control subjects, Pandey et al. identified the HRR as the most relevant reserve abnormality in HFpEF.[161] However, in addition to the previously described findings that a reduced peak HR may not always be a cause but also a consequence of premature exercise cessation and that peak $C[a\text{-}v]O_2$ should rather be interpreted in relation to CO, the opposing interactions between resting values are also important and often not considered.

Resting HR, SV and C[a-v]O_2 are interrelated to match the resting metabolic demand of 1 MET (~ 3.5 mL/kg/min of $\dot{V}O_2$),[99,100] which means that a reduction in one of these parameters must be compensated by the other two parameters to meet the energy requirement at rest. For example, a higher resting HR may simply be caused by a pathophysiologically low resting SV or low C[a-v]O_2 due to deconditioning, whereas a higher resting C[a-v]O_2 may also be a consequence of a low resting SV or a low resting HR due to medications such as beta-blockers. Accordingly, reserve abnormalities can be caused by both high resting values and low peak values, but the interpretation regarding the exercise limitation should be different depending on whether the resting or peak value is the driving force for the lower reserve. Therefore, without knowing and considering the causal relationships between resting HR, SV and C[a-v]O_2 in each individual, reliance on these reserve abnormalities by adding 'potentially biased' resting values to the equation may even exacerbate the misinterpretation of what may be the most prominent cause of exercise intolerance. As ET is capable of improving several mechanisms responsible for exercise intolerance and, especially, for reducing peak C[a-v]O_2 in patients with HFpEF, the above findings of a uniformly reduced peak C[a-v]O_2 (at least when relativized to CO) and the suspected higher improvements in peak $\dot{V}O_2$ when correcting the diffusive vs. convective defects may be the main reason why ET is one of the most effective therapies in HFpEF to date.[146,242]

4.6. Analysis of Inter-Individual Response Variability

Although several patients receive the same treatment and have similar adherence rates, there is always some inter-individual heterogeneity, with some patients responding better than others. While some variance can be explained by measuring errors or day-to-day variability, the rationale behind personalized medicine (compared to a 'one-size-fits-all' approach) is that some patient characteristics may be associated with the success of a particular treatment.[235] Therefore, based on the previously discussed findings that peak C[a-v]O_2 is significantly reduced in most patients with HFpEF, that the ET-induced changes in peak $\dot{V}O_2$ are most likely mediated through improvements in C[a-v]O_2 and SV in both patients with HF and healthy individuals, and the concept of a higher potential for improvement with lower baseline levels, the hypothesis of the predictor analysis of the OptimEx-Clin trial was that a lower baseline peak O_2-pulse (reflecting peak SV × peak C[a-v]O_2) is associated with a higher difference in change in

peak $\dot{V}O_2$ between ET and CON.[242] Moreover, we investigated whether this may also be true for the change in functional capacity ($\dot{V}O_2$ at VT1). Unlike many previously conducted studies that claimed to assess predictors of inter-individual response to ET, we applied a rigorous methodological approach that included a control group, limited analyses to a theory-driven, a priori defined set of independent variables, and did not (arbitrarily) categorize predictors or response variables *(see chapter 4.6.3)*.[242]

4.6.1. Predictors of Exercise Training-Induced Change in Peak Oxygen Consumption

As hypothesized, we found a significant inverse relationship between baseline peak O_2-pulse and change in relative peak $\dot{V}O_2$ in the combined ET group (HIIT and MCT), whereas no such association existed in the CON group. Each 1 mL/beat higher peak O_2-pulse at baseline was associated with a reduced mean change in relative peak $\dot{V}O_2$ of -1.45% following ET in the complete case analysis and -1.88% in the per-protocol analysis,[242] indicating that this was not random finding *(see chapter 4.4)*. Moreover, the associations remained significantly different after adjusting for sex, age and weight at baseline.[242] Given the evidence that in patients with HFrEF and CAD, even modest increases in peak $\dot{V}O_2$ are associated with significant reductions in AEs and mortality *(see chapter 4.1)*,[279,280] baseline peak O_2-pulse appears to be a powerful marker to identify those patients most likely to have relevant improvements in peak $\dot{V}O_2$ with ET.

Because peak O_2-pulse is the ratio of peak $\dot{V}O_2$ to peak HR, a low peak O_2-pulse may be caused by a low peak $\dot{V}O_2$, a high peak HR, or a combination of both. Although higher baseline peak $\dot{V}O_2$ was weakly associated with smaller changes in peak $\dot{V}O_2$ in the OptimEx-Clin trial, these associations were very similar following ET and CON *(see Figure 13B)*.[242] This highlights the importance of including a control group, as baseline peak $\dot{V}O_2$ may only be a prognostic factor for the change in peak $\dot{V}O_2$ that is unaffected by the intervention, or the weak association was simply caused by regression to the mean *(see chapter 4.6.3)*.[242] Even in an individual patient data meta-analysis that included 3,332 patients with HF (ET: N = 1,662; CON: N = 1,670 patients; ~ 97% HFrEF, ~73 % men, median follow-up: 26 weeks), which has a significantly higher power compared with individual trials, no significant interaction was found between baseline peak $\dot{V}O_2$ and changes in peak $\dot{V}O_2$.[236] In contrast, a meta-regression analysis evaluating mean baseline and intervention characteristics at study level as

potential predictors of the change in peak $\dot{V}O_2$ in patients with HF and CAD (34 ET vs. CON comparisons from 31 studies) found that studies with higher mean baseline peak $\dot{V}O_2$ had slightly but significantly higher ET-induced improvements in peak $\dot{V}O_2$.[382] However, the changes in peak $\dot{V}O_2$ were expressed in mL/kg/min and not as %-change, and an equal %-change in peak $\dot{V}O_2$ refers to a higher absolute change in patients with higher compared to lower baseline peak $\dot{V}O_2$. Furthermore, lower age and higher proportion of male participants, both associated with higher baseline peak $\dot{V}O_2$, were also significantly associated with higher changes in peak $\dot{V}O_2$.[382] Consequently, none of these parameters remained a significant predictor of the change in peak $\dot{V}O_2$ in the multivariate analysis.[382]

Similarly, peak HR alone was not a significant predictor of the ET-induced change in peak $\dot{V}O_2$ in the OptimEx-Clin trial.[242] In contrast, lower peak HR or other parameters of chronotropic incompetence (HRR < 30 beats/min; HR recovery within 1 min < 6 beats/min) have been associated with an impaired response to ET in 2 studies that investigated the effects of cardiac rehabilitation over 8 and 12 weeks in patients with HFrEF (N = 70 and 120, respectively).[378,383] However, these results should be interpreted with caution because, as with many other studies aiming to identify predictors of ET response, these studies had several methodological limitations (no comparator arms,[378,383] categorization of independent variables based on cutoffs from the same dataset,[383] categorization of outcome variables[383]) that may significantly affect the validity of the results, as discussed in *chapter 4.6.3*.

Therefore, the identification of baseline peak O_2-pulse as a significant predictor of change in peak $\dot{V}O_2$ following ET can likely be interpreted as indicating that patients with lower peak $C[a\text{-}v]O_2$ and / or peak SV have a higher potential to improve these parameters, which are the most likely mediators of improved peak $\dot{V}O_2$ by regular ET.[213,240,241] This interpretation is also supported by the comparison of patients with a baseline peak RER ≥ 1.10 (interaction P = 0.02) vs. baseline peak RER < 1.10 (interaction P = 0.66), which further strengthens the assumption of a true association between maximal SV and / or $C[a\text{-}v]O_2$ and the change in ET-induced peak $\dot{V}O_2$. In patients with a peak RER ≥ 1.10, which can be interpreted as excellent effort and maximal exhaustion,[107] it is likely that peak O_2-pulse really reflects the product of the maximally achievable SV and $C[a\text{-}v]O_2$, whereas in patients with peak RER < 1.10, there is a higher probability that the test was prematurely terminated for other reasons

(e.g., low motivation or musculoskeletal problems) that cause the low peak O_2-pulse. As expected, the sensitivity analysis in the original 3-group-design (HIIT vs. MCT vs. CON) of the OptimEx-Clin trial showed that the predictive effect of baseline peak O_2-pulse on change in peak $\dot{V}O_2$ seems to be independent of the ET mode, with comparable associations between baseline peak O_2-pulse and change in peak $\dot{V}O_2$ in HIIT and MCT *(see Appendix J and Appendix K)*.[242] Based on the strong theoretical rationale that led to the hypothesis of this predictor analysis *(see chapter 1.4.2 or chapter 4.6)*, it may not be surprising that a lower baseline peak O_2-pulse is predictive of higher ET-induced changes in peak $\dot{V}O_2$ in HFpEF (and likely also in most other populations). However, we are not aware of any other studies that investigated the predictive power of baseline peak O_2-pulse on change in peak $\dot{V}O_2$ in any population. Moreover, as previously discussed, it is also generally assumed that patients with lower baseline peak $\dot{V}O_2$ have a higher potential to improve peak $\dot{V}O_2$ with ET, which has not been confirmed in previous studies in HFrEF and CAD nor in the OptimEx-Clin trial.[236,242,382]

Baseline body weight and hemoglobin level had no significant interaction with study group on change in relative peak $\dot{V}O_2$, but we found a trend toward lower ET-induced changes with higher baseline body weight (interaction P = 0.14 and 0.054 in the complete case analysis and per-protocol analysis, respectively).[242] Moreover, the analysis in the original 3-group-design indicated that this association may be more prevalent with HIIT than with MCT, although the differences were not significant (interaction P = 0.15). Nonetheless, this is an interesting hypothesis-generating finding suggesting that patients with HFpEF and a higher body weight should potentially be advised to do MCT rather than HIIT. Given that more than 80% of patients with HFpEF are overweight or obese[45,48,242] and that a change in body weight has a disproportionate effect on change in relative peak $\dot{V}O_2$ (if, for example, all other components are kept constant, a 20% weight loss results in a 25% increase in relative peak $\dot{V}O_2$),[242] it is probably useful to advise an additional weight loss intervention, which has also been shown to improve relative peak $\dot{V}O_2$ in HFpEF *(see chapter 4.7.2)*.[226]

As it is very likely that other factors are also associated with the ET-induced changes in peak $\dot{V}O_2$, further studies are needed to evaluate the predictive power of additional parameters, including the investigation of differences between various modes (e.g., MCT vs. HIIT) or forms of ET (e.g., endurance vs. strength). For example, in the

multivariate analysis of the aforementioned meta-regression analysis from Uddin et al., only higher exercise intensity (expressed as % peak $\dot{V}O_2$ or % peak HR) remained significantly associated with higher changes in peak $\dot{V}O_2$.[382] However, this does not seem to be confirmed in the OptimEx-Clin trial when comparing the effects of HIIT vs. MCT,[234] or the preliminary results on the associations between exercise intensity and change in peak $\dot{V}O_2$ following MCT.[384] In the individual patient data meta-analysis by Taylor et al., the only significant predictor of the ET-induced change in peak $\dot{V}O_2$ was being a woman.[236] A similar trend was also observed in the subgroup analysis of the OptimEx-Clin trial *(Appendix F)*.[234] This is very interesting, because the change in peak $\dot{V}O_2$ was expressed in mL/kg/min in both investigations, suggesting even greater differences when expressed as %-changes. In contrast, a recent meta-analysis in healthy young to middle-aged adults found higher ET-induced changes in peak $\dot{V}O_2$ in men compared with women,[385] whereas in ET studies in healthy older subjects, mean changes in peak $\dot{V}O_2$ were similar between women and men but mediated by different mechanisms.[386] While changes in men seemed to be primarily mediated by increases in SV,[386] limited evidence suggests that in healthy older women, ET-induced changes in peak $\dot{V}O_2$ result almost exclusively from changes in C[a-v]O_2.[386-388] Combining these findings with those of patients with HF (in particular, the predominantly female patients with HFpEF, in whom peripheral adaptations are likely to be more important than central adaptations in improving peak $\dot{V}O_2$),[241,361] this may explain why women with HF tend to benefit more from ET – a finding that should be further investigated in other studies.

4.6.2. Predictors of the Exercise Training-Induced Change in Oxygen Consumption at the First Ventilatory Threshold

Neither baseline peak O_2-pulse nor any of the other investigated parameters proved to be a significant predictor of the ET-induced change in $\dot{V}O_2$ at VT1. Instead, patients randomized to ET were able to equally improve their functional capacity irrespective of baseline peak O_2-pulse (mean change in peak $\dot{V}O_2$ of 0.09% for every ever 1 mL/beat higher peak O_2-pulse). However, we also did not expect an inverse relationship between baseline peak O_2-pulse and changes in $\dot{V}O_2$ at VT1 because the assumptions that led to the primary hypothesis of the predictor analysis do not apply for this secondary endpoint. First, peak O_2-pulse is not a determinant of $\dot{V}O_2$ at VT1, and second, the extent to which changes in HR, SV and C[a-v]O_2 mediate ET-induced changes in $\dot{V}O_2$

at VT1 is less well investigated and likely more complex than for peak $\dot{V}O_2$.[242] As previously discussed *(chapter 4.5)*, HR and C[a-v]O_2 are generally assumed to increase until peak exercise,[104,141,370] whereas various SV responses (progressive increase until peak exercise, early plateau at ~ 40% of peak $\dot{V}O_2$, early plateau with a secondary increase until peak exercise, early plateau with a subsequent decrease)[238] have been described in the literature,[104,238,372] and it is not well investigated if and how these patterns can be altered by ET, especially in patients with HFpEF. While a typical ET effect is associated with a lower HR at the same submaximal $\dot{V}O_2$ or workload,[389-392] which would imply a higher SV and / or C[a-v]O_2,[390-392] an improvement in $\dot{V}O_2$ and workload at VT1 would likely be associated with an opposite effect on HR, such that the two mechanisms may offset each other. This is supported by the results of the OptimEx-Clin trial, in which changes in HR at VT1 were not significantly different between groups, despite significant differences in $\dot{V}O_2$ and workload at VT1,[234] however, individual differences are largely unknown. The reason for including the change in $\dot{V}O_2$ at VT1 as a secondary endpoint in the predictor analysis was to investigate whether patients with a higher baseline peak O_2-pulse are able to improve their functional capacity despite a lower potential to improve maximal exercise capacity. Accordingly, the results of the predictor analysis indicate that although patients with a higher baseline peak O_2-pulse may be less able to improve their peak $\dot{V}O_2$ by ET alone, they may equally improve functional capacity and probably also other parameters such as QoL compared to patients with a lower peak O_2-pulse at baseline.[242] Moreover, ET in these patients may still reduce the decline in peak $\dot{V}O_2$ with ageing and disease progression compared to patients with the same baseline characteristics who do not exercise. Therefore, it should still be highly recommended to perform regular ET in all stable patients with HFpEF. However, if the primary goal is to improve peak $\dot{V}O_2$, additional therapies may need to be supplemented in patients with higher baseline peak O_2-pulse *(see chapter 4.7 and chapter 4.8)*.[242]

4.6.3. Methodical Aspects for the Evaluation of Inter-Individual Response Variability

When analyzing clinical trial data, it is important to consider several factors that may influence the changes between baseline and follow-up, as not every observed pre-post change is caused by the intervention. Instead, change between baseline and follow-up can be divided into 3 categories:

A) a ‘true change’ that is caused by the intervention
B) a ‘true change’ over time that is independent of the intervention (e.g., ageing, difference between summer and winter)
C) a ‘random error’ that is independent of the intervention (e.g., measurement errors, regression to the mean, biological day-to-day variability, motivational differences between the two tests).[235]

The awareness that there are factors that influence outcomes despite being independent of treatment has led to the inclusion of a comparator arm in clinical trials and the fact that RCTs have become the widely used and accepted gold standard in clinical research. Although these components are likely to be even more important in assessing individual differences because random errors are generally averaged out in sufficiently large group-based analyses, most studies that claim to evaluate potential predictors of inter-individual response variability to ET did not include a comparator arm in their analysis.[245,378,383,393-396] Therefore, these studies did not examine predictive factors for change after training, but rather prognostic factors for change over time, for which it is unclear whether they are actually related to the intervention or primarily influenced by treatment-independent factors or statistical phenomena such as regression to the mean. In the predictor analysis of the OptimEx-Clin trial,[242] neither dependent nor independent variables were categorized, which is also in contrast to many previously performed ‘predictor’ analyses. Aggregation of continuous variables into categories allows the comparison of different groups (e.g., the lowest vs. highest tertiles) by using familiar group-based statistical tests,[394,397] but has several shortcomings:

A) Cutoffs are often arbitrarily chosen.
B) It leads to a loss of information and reduced statistical power.
C) It treats individuals with small differences (slightly below vs. slightly above the cutoff) in different categories and individuals with large differences (e.g., slightly and extremely above the cutoff) in the same category.
D) It usually ignores random errors (e.g., measurement errors, day-to-day variability), resulting in ‘misclassifications’ of several individuals (e.g., patients with a ‘true’ value that is above the cutoff may be included in the group below the cutoff and vice versa).

Therefore, analyses should generally be performed using the highest possible scale level (interval > ordinal). However, if for whatever reason a continuous parameter is categorized, it is important to use cutoffs that were not created in the same dataset (e.g., median or tertiles; cutoffs from the literature such as peak $\dot{V}O_2$ < 14 mL/kg/min; applying cross-validation). This is due to the fact that using 'optimal' cutoffs from the same dataset (e.g., based on receiver operating characteristic curves as in the previously mentioned analysis that showed lower ET-induced changes in peak $\dot{V}O_2$ in patients with HFrEF and chronotropic incompetence)[383] leads to a dramatically increased false-positive rate with significant results ($P < 0.05$) in approximately 40% when the factor is not prognostically relevant at all.[398] The classification of outcome variables into responders and non-responders also has similar shortcomings:

A) An often arbitrarily chosen cutoff for who is a responder or non-responder has to be defined.
B) Even when cutoffs are based on a previously published MCID or coefficient of variation, this also leads to relevant misclassification of individuals and likely shows that even some patients randomized to CON are classified as responders to no treatment.
C) It also leads to the previously discussed loss of information and reduced statistical power.

Therefore, it is generally advisable to also use the outcome variable as a continuous variable rather than classifying individuals into responders or non-responders. However, when categorization of response variables is necessary or desired, alternative methods compared with binary classification into 'definitive' responders and non-responders have been described.[235,393] For example, taking into account the response variation of a control group and a previously defined MCID, individuals can be classified based on their probability of having a 'true' clinically meaningful response into unlikely, possibly, likely or very likely being a responder.[235,393]

Some authors have argued that true inter-individual differences in response to treatment can only exist if the change score in the intervention group has a clinically relevant higher SD than the change score of the control group, and if this is not the case, further investigation of inter-individual response variability is superfluous.[393,399,400] Along these lines, a lower SD in the intervention group can be described as a homogenizing treatment effect and the opposite of individual variability.[393,400,401] This sounds logical at

first glance, but some important things may have been overlooked. Indeed, several ET trials, including the OptimEx-Clin trial,[234,242] have shown a lower SD in the change in peak $\dot{V}O_2$ after ET vs. CON, which, based on the above interpretation, obviates the need to perform analyses to detect covariate-treatment interactions. However, the lower SD in the ET groups may primarily be explained by the fact that the comparator groups are generally neither 'forced' nor closely monitored to not change their pre-randomization activity levels. Instead, patients randomized to CON groups often receive guideline-based physical activity recommendations. Thus, while physical activity in the ET groups is steered in one direction (i.e., increased physical activity), which reduces the SD of the change, it is likely that several patients in the CON groups either reduce or increase their previous physical activity level, resulting in a higher SD than if all patients would maintain their physical activity level. Moreover, even if there is no significant difference in variability between groups, it is difficult to imagine why a relevant covariate-treatment interaction, such as that observed in the present predictor analysis of the OptimEx-Clin trial,[242] should not be possible. This is also supported by a synthesis review and a recent consensus statement on precision exercise medicine, which pointed out that a difference in the SD of change between groups is neither required nor sufficient to detect significant covariate-treatment interactions.[235,402]

Finally, the inclusion of parameters collected after the baseline visit, either as predictor variables (e.g., change in workload during ET or change in peak HR)[394] or to define the population to be studied (e.g., only adherent patients),[245] has several disadvantages. While the latter would also reduce sample size (and power) and the generalizability of the results because the randomization process is manipulated, the inclusion of post-treatment variables interferes with the general principle of predictor analyses, which is to allow the pre-identification of individuals who have a high or low probability for improvement following an upcoming intervention compared with usual care. Moreover, the use of a non-baseline variable, especially if it may also be influenced by the intervention (e.g., change in workload during ET, change in medication), may lead to a substantial so-called 'post-treatment bias' that would further limit the validity and clinical applicability of the results.[403-405] Therefore, only variables available before treatment should be used for the main analysis, whereas analyses that include post-treatment information, such as a per-protocol analysis, should only be used as sensitivity analyses.

In summary, the predictor analysis of the OptimEx-Clin trial was one of the very few analyses in which a priori defined predictors (limited to baseline parameters) of change after ET were compared with a comparator arm (which is of utmost importance to control for treatment-independent associations) and in which no (arbitrary) categorization of either the dependent or independent variables was performed. This shows that the results, although they should be interpreted as exploratory due to their post-hoc nature, are based on a rigorous methodological approach that supports their validity.

4.7. Alternative Treatments to Improve Exercise Tolerance in Patients with Heart Failure with Preserved Ejection Fraction

The results of the predictor analysis of the OptimEx-Clin trial indicate that not all patients with HFpEF can equally improve peak $\dot{V}O_2$ by traditional MCT or HIIT. Therefore, it is important to be aware of alternative treatment options to increase exercise capacity in HFpEF and to understand the mechanisms by which these treatments can either directly increase peak $\dot{V}O_2$ and / or have the potential to indirectly increase peak $\dot{V}O_2$ when followed by or combined with regular endurance ET. The examination of how these different treatments work and how they may interact with ET, and the subsequent investigation of baseline predictors of individual responses to each of these therapies, may significantly facilitate the research and application of personalized medicine, which is likely the most effective and efficient treatment strategy in a disease as heterogenous as HFpEF. Moreover, knowledge of alternative treatment options also allows patients to be offered a broader range of therapies, which can promote (long-term) adherence and improvement, as patients are able to choose their preferred treatment modality among several effective therapies.

4.7.1. Alternative Exercise Training Modalities

In addition to regular endurance ET, several small single-center RCTs have shown significant improvements in exercise tolerance, ventilatory efficiency and / or QoL following inspiratory muscle training (IMT) (3 studies, total N = 107 patients, follow-up of 12 and 24 weeks),[406-408] functional electrical stimulation (FES) (2 studies, total N = 91 patients, follow-up of 6 to 24 weeks)[408,409] or Tai chi (1 study, N = 16 patients, follow-up of 12 weeks).[410] IMT has been shown to significantly increase maximal

inspiratory pressure and improve ventilatory efficiency, which may reduce the perceived dyspnea leading to improved exercise tolerance and QoL.[406-408] The proposed underlying mechanisms for these improvements are an increase of respiratory muscle strength and endurance, leading to a decrease in the inspiratory muscle metaboreflex that is responsible for sympathetic activation, peripheral vasoconstriction, and premature peripheral muscle exhaustion.[406-408] Although these mechanisms have yet to be proven in patients with HFpEF, IMT may be useful in patients with respiratory muscle weakness and / or impaired ventilatory efficiency. FES may help to increase exercise tolerance and QoL by improving muscle mass and strength or to prevent muscle wasting,[408,409,411,412] which is a relevant comorbidity associated with reduced exercise capacity as well as increased morbidity and mortality in patients with HF *(see chapter 1.3)*.[200-206] In addition, FES has been shown to improve endothelial function in patients with both HFpEF or HFrEF.[409,413] Therefore, FES has been primarily proposed as a bridge to conventional ET in highly deconditioned patients or in those who are unable or unwilling to perform traditional ET.[408,411,412] Whether resistance training alone or in combination with endurance training can significantly increase muscle mass or further improve exercise tolerance compared with endurance training only has not yet been investigated in patients with HFpEF. However, the only trial that evaluated a combination of endurance training plus resistance training to date has shown the most pronounced changes in peak $\dot{V}O_2$ compared with usual care (Ex-DHF Pilot trial, N = 64 patients, follow-up of 3 months, mean difference in change in peak $\dot{V}O_2$ of 3.3 ml/kg/min between ET vs. CON), and the results of the Ex-DHF main study (N = 320 patients, follow-up of 12 months)[299] are expected soon.

Traditional endurance ET (walking or cycling) that involves large muscle mass results in a significant increase in CO during exercise, which may lead to exaggerated increases in cardiac filling pressures in patients with HF and may result in premature exercise termination.[199,366] Therefore, single-leg isolated knee extensor (IKE) training has been proposed as an alternative small muscle mass training method to effectively target peripheral limitations without stressing the central circulation.[199,366,414] In a recently published single-arm study, patients with HFpEF (N = 9) had a significantly lower blood flow response during IKE exercise compared with healthy age-matched controls (N = 9), which was related to a significantly blunted leg vascular conductance, an index of vasodilation.[366] Moreover, patients with HFpEF had a significantly lower

relative peak $\dot{V}O_2$, peak C[a-v]O_2 and CO/$\dot{V}O_2$ slope during CPET, whereas peak CO was not significantly lower than in healthy controls. After 8 weeks of IKE training (3 × 30 min/week), patients with HFpEF significantly improved leg vascular conductance with slight but non-significant improvements in leg blood flow and mean arterial BP during IKE. Furthermore, IKE significantly improved peak $\dot{V}O_2$, peak C[a-v]O_2 and the CO/$\dot{V}O_2$ slope without significant changes in peak CO during CPET,[366] which is in agreement with previous results obtained in patients with HFrEF.[414,415] The authors concluded that IKE training may be of particular benefit for patients with primary peripheral limitations or severe dyspnea during traditional ET, and that the improved blood delivery and utilization following IKE training may also result in improved HR and BP control and lower venous return, which ultimately reduces cardiac filling pressures.[366] Nevertheless, further investigations, preferably larger RCTs, are needed to confirm and extend the results found with this interesting ET approach.

4.7.2. Caloric Restriction and Supplementation of Inorganic Nitrates / Nitrites

Obesity is one of the major risk factors for the development of HFpEF, and most patients with HFpEF are either overweight or obese (e.g., ~85% in the OptimEx-Clin trial).[5,15,16,45,48,234,242] Despite the fact that peak $\dot{V}O_2$ is normalized to body weight in most trials and that weight loss has a disproportionate impact on changes in relative peak $\dot{V}O_2$ *(see chapter 4.6.1)*, weight loss interventions through caloric restriction have been largely neglected in HFpEF research. To date, only one lifestyle intervention RCT (100 patients randomized to 4 months of ET, diet, ET plus diet or CON) has investigated the effects of intentional weight loss in patients with HFpEF.[226] Using a 2 × 2 factorial design (ET vs. no ET; diet vs. no diet), ET and caloric restriction induced similar changes in relative peak $\dot{V}O_2$ (1.2 mL/kg/min following ET and 1.3 mL/min/kg following diet) by significantly increasing absolute peak $\dot{V}O_2$ (ET) and reducing body weight / fat (ET and diet). Furthermore, these effects were found to be additive, resulting in a joint effect of 2.5 mL/kg/min.[226] The weight loss during caloric restriction was primarily due to a reduction in fat mass (- 5 kg), but also a small reduction in lean body mass (- 2 kg). In addition to the effects on body composition and peak $\dot{V}O_2$, caloric restriction also resulted in improvements in QoL (KCCQ and SF-36), 6-MWT distance, NYHA classification, and cardiac function (significant reductions in LV mass, LV relative wall thickness and mitral E/A velocity ratio).[226] Together with the results of the predictor

analysis of the OptimEx-Clin study,[242] in which higher baseline weight was found to be potentially associated with a lower ET-induced improvement in peak $\dot{V}O_2$ (especially with HIIT), and 3 months of ET resulted in only a small, though significant weight reduction (- 1% compared with CON), these findings highlight that specific weight loss programs may be useful to further improve exercise tolerance in patients with HFpEF, particularly in those who are obese.

Besides caloric restriction, 1 week of daily dosing (70 mL) of beetroot juice significantly improved submaximal exercise tolerance (time to exhaustion at ~ 75% of peak $\dot{V}O_2$), significantly lowered systolic BP at rest and during unloaded cycling, and showed a trend toward lowering systolic BP at 2 minutes, 4 minutes and maximal exhaustion during exercise compared with placebo (N = 20 patients with HFpEF).[416] Similarly, a single dose of beetroot juice (140 mL) significantly increased peak $\dot{V}O_2$ (mean difference, 1.0 mL/kg/min) and $\dot{V}O_2$ at VT1 (mean difference, 0.5 mL/kg/min) by significantly reducing systemic vascular reserve and increasing peak CO in a placebo-controlled double-blind study in 17 patients with HFpEF.[417] Furthermore, the aortic augmentation index, a marker of aortic stiffness, improved significantly.[417] Beetroot juice contains a high concentration of inorganic nitrate (~ 9 mmoL / 100 mL)[416,417] that is reduced to inorganic nitrite in the oral cavity, transferred from the digestive system into the blood and converted to NO, which has a vasodilatory effect.[416,418] Conversion to NO primarily occurs under hypoxia or acidosis, for example, during exercise, and has a vasodilatory effect on the hypoxic tissues, which may explain the previously described findings.[416,418] In contrast, a small pilot trial (N = 20 patients with HFpEF) that began immediately after the follow-up visit of one of the previously described beetroot juice supplementation studies,[416] ET (3 × 40 min/week) plus beet root juice (~ 45 min before each session) did not significantly improve exercise tolerance compared with ET plus placebo, however, this may be explained by the low sample size, a lower dosage of beet root juice or a relatively short time between beet root juice supplementation and ET or testing.[419] In addition to beet root juice, single doses of sodium nitrite by infusion or inhalation have been shown to significantly lower PCWP, right atrial pressure, and pulmonary artery pressure at rest and particularly during exercise (> 2-fold reduction in PCWP during exercise compared with rest),[420,421] and confirmed the effects on aortic augmentation index observed with beet root juice.[195] Infusion of sodium nitrite also significantly reduced systemic vascular

reserve at rest,[420] whereas inhalation also significantly reduced pulmonary artery compliance at rest.[421] In contrast, inhalation of inorganic nitrites thrice a day for 4 weeks did not significantly improve peak $\dot{V}O_2$ or echocardiographically measured cardiac filling pressure (E/e').[422] A possible reason for the discrepancy with the previous studies, in addition to the reasons mentioned by the authors (short half-life of inhaled nitrite, relatively brief trial duration, difficulties with proper use of the nebulizer)[422], could be that the majority of patients were probably not limited by an exaggerated increase in filling pressures leading to premature exercise termination, as indicated by the mean peak RER of 1.10 and the inclusion criterion of peak RER > 1.0, as this may have excluded those patients who might benefit most from this treatment. Other pharmacological agents that contain organic nitrate (isosorbide mononitrate)[423] or increase the efficacy of NO (phosphodiesterase-5 inhibitor sildenafil[424] or the soluble guanylate cyclase stimulators praliciguat[425] and vericiguat[426]) did not significantly improve 6-MWT distance, peak $\dot{V}O_2$ or QoL compared with placebo[423-426] and even reduced average daily physical activity in one trial.[423] Compared with inorganic nitrate (beet root juice) or inorganic nitrite (infusion or inhalation), these pharmacological agents are not able to target NO to hypoxic tissues, which could be the main reason for the lack of efficacy observed in these trials.[416] In summary, inorganic nitrate / nitrite could be an effective option to lower the exercise-induced increases in cardiac filling pressures, with the potential to improve exercise tolerance in patients primarily limited by such increases. However, larger and longer studies are needed to confirm the promising results observed in the small, short-term, single-center trials and to test whether a combination with ET (in larger RCTs) may be of additional benefit for these patients.

4.7.3. Medication

As described above *(chapter 1.1)*, until the recent breakthrough with SGLT2 inhibitors,[80,81] pharmacological agents have been overall unsuccessful in reducing morbidity and mortality in patients with HFpEF. Furthermore, the pharmacological effects on parameters of exercise tolerance are not convincing.[78,79] Compared with placebo, small but significant improvements in 6-MWT distance (mean differences of 14 and 20 meters)[71,82] or treadmill exercise time (mean difference of 43 seconds)[427] have been found with the selective endothelin-A receptor antagonist sitaxsentan[427], the SGLT2 inhibitor dapagliflozin,[82] or the ACE-I perindopril.[71] In contrast, several other

agents (the ACE-I / ARBs ramipril, irbesartan[428] and valsartan;[429] subcutaneous injections with the interleukin-1 blocker anakinra[430] and the antianginal agent ranolazine[431]) did not significantly increase 6-MWT distance[428,429] or peak $\dot{V}O_2$[429-431]. Some promising results have been observed for the MRA spironolactone. In 422 patients with HFpEF, spironolactone induced a small but significant reduction in 6-MWT distance (mean difference of 15 meters compared with placebo) and a significant reduction in E/e' (mean difference of -1.5), but the change in peak $\dot{V}O_2$ was not significantly different between groups. In contrast, Kosmala et al., who evaluated the effects of spironolactone in 150 selected patients with HFpEF and an exercise-induced increase in E/e', found relatively large and significant improvements in peak $\dot{V}O_2$ (mean difference, 2.6 mL/kg/min, $P < 0.001$) and $\dot{V}O_2$ at VT1 (mean difference, 2.9 mL/kg/min, $P = 0.03$), along with a significant reduction in exercise-induced increase in E/e' (mean difference, -2.5, $P < 0.001$).[432] Because there was also a significant interaction of spironolactone and change in E/e' on change in peak $\dot{V}O_2$,[432] this study indicates that spironolactone, similar to inorganic nitrate (via beetroot juice) or inorganic nitirite (via infusion or inhalation), may be a potential agent to improve exercise tolerance in this HFpEF-subgroup of patients with exaggerated increases in filling pressures during exercise.

Lower resting HR and higher beta-blocker dosage are significantly associated with reduced morbidity and mortality in patients with HFrEF.[56-62,433-436] Consequently, beta-blockers are recommended in all patients with HFrEF (recommendation class I, evidence level A), and the use of the I_f-channel inhibitor ivabradine should also be considered in patients with a remaining high resting HR (> 70 beats/min) despite maximum (tolerated) treatment with beta-blockers (recommendation class II, evidence level B).[30] Because HR slowing drugs decrease not only resting HR but also peak HR, and peak HR is one of the determinants of peak $\dot{V}O_2$, one might conclude that the use of these drugs could have negative effects on exercise tolerance. In HFrEF, HR lowering drugs are not associated with reduced exercise tolerance, and some studies have even shown positive effects of beta-blockers or ivabradine on 6-MWT distance, peak $\dot{V}O_2$, $\dot{V}O_2$ at VT1 and exercise time.[78,437-439] This can be explained by the fact that a lower HR likely leads to a compensatory increase in SV and $C[a\text{-}v]O_2$ due to a higher diastolic duration, blood flow redistribution and / or a longer transit time of red blood cells in the muscle *(see chapter 4.5)*. In HFpEF, higher resting HR (> 70 beats/min) has also been

shown to be associated with a higher risk of mortality.[440] However, the use of HR-lowering drugs such as beta-blockers or ivabradine is controversial and increasingly questioned or even considered potentially harmful in patients with HFpEF.[441,442] While taking 5 mg ivabradine twice daily for 7 days resulted in a significant increase in peak $\dot{V}O_2$ (mean difference of 2.6 mL/kg/min),[443] further studies did not reveal significant differences between ivabradine (up to 7.5 mg twice daily) and placebo on 6-MWT distance over 8 months[444] or even showed significant deteriorations in peak $\dot{V}O_2$ (mean difference of -3.0 mL/kg/min) with 2 doses of 7.5 mg/day vs. placebo over 2 weeks.[445] Possible reasons for these discrepancies could be different study durations, drug dosages, or study designs (crossover vs. parallel arms),[445] but most likely the striking differences in changes in peak HR. Whereas the positive effects were accompanied by minor, non-significant effects on peak HR (-4 beats/min) and a significant improvement in peak O_2-pulse (i.e., peak SV and / or $C[a\text{-}v]O_2$),[443] the negative findings were associated with an enormous reduction in peak HR from an average of 129 to 107 beats/min.[445] This indicates that the effects of ivabradine on peak $\dot{V}O_2$ may be negatively related to the drug-induced changes in peak HR, as higher reductions in peak HR may not be compensated by increases in SV and / or $C[a\text{-}v]O_2$. Similarly, the beta-blocker nebivolol was found to significantly reduce 6-MWT distance compared with placebo (mean difference, 33.5 meters, $P < 0.001$).[446] While changes in peak $\dot{V}O_2$ and peak HR did not significantly differ between groups (both $P > 0.05$), there was a significant correlation between change in peak HR and change in peak $\dot{V}O_2$ ($r = 0.391$; $P = 0.003$),[446] supporting the above interpretation of an unfavorable association between HR slowing and exercise tolerance in HFpEF. Moreover, subgroup analyses of the TOPCAT trial that investigated the effects of spironolactone[74] showed unfavorable associations between beta-blocker use and outcomes.[447,448] Specifically, beta-blocker use was associated with a significantly higher risk of the composite endpoint of cardiovascular death, cardiac arrest, HF hospitalization and nonfatal stroke or myocardial infarction, particularly in patients without prior myocardial infarction (adjusted mean hazard ratio of 1.39 [95% CI, 1.11 to 1.75]).[447] In addition, beta-blocker use was associated with a significantly increased risk of HF hospitalizations in patients with an LVEF > 50% (adjusted mean hazard ratio of 1.74 [95% CI, 1.28 to 2.37]), which further increased with higher LVEF cutoffs, whereas no such association was found in patients with an LVEF of 45-49%.[448] Although there is neither an indication nor guideline recommendation for beta-blockers in HFpEF, most patients with HFpEF are treated with

beta-blockers (e.g., 66% in the OptimEx-Clin trial,[234,242] 72% in ALDO-DHF,[285] 78-79% in the TOPCAT trial[74,447,448], 80% in PARAGON-HF[75]), primarily because of comorbidities or maybe also because of the misconception that they are similarly beneficial in HFpEF compared with HFrEF. Based on the above evidence, and because the efficacy of long-term beta-blocker use has also been questioned or even downgraded from a preferred long-term treatment in patients with hypertension, stable coronary artery disease, or atrial fibrillation (which are frequent comorbidities in HFpEF),[436,441,449-455] it is likely that the proportion of patients with HFpEF taking beta-blockers will decrease. Thus, the effects of beta-blocker withdrawal in patients with HFpEF have recently been investigated.[456] In a small, multicenter, crossover RCT of 26 patients with HFpEF, peak $\dot{V}O_2$ significantly improved by approximately 17% after 2 weeks of beta-blocker withdrawal, whereas peak HR increased by approximately 31%,[456] indicating a concomitant decrease in peak SV and / or peak C[a-v]O_2 (i.e., O_2-pulse). Clearly, these findings need to be replicated and followed up in larger and longer studies. However, the present evidence indicates that HR-slowing drugs such as beta-blockers are not only associated with direct negative effects on exercise tolerance and perhaps also prognosis in HFpEF but, based on the results of the predictor analysis of the OptimEx-Clin trial,[242] may also contribute to a blunted ET-induced improvement in peak $\dot{V}O_2$ through their indirect effects on peak O_2-pulse. Therefore, reducing the administration of HR-lowering drugs or applying other interventions to increase peak HR, also in combination with subsequent prescriptions of ET, should be (further) investigated in patients with HFpEF.

4.7.4. Invasive Treatments

Invasive treatments are a relatively new field in the therapy of patients with HFpEF, and none of the potentially useful methods has yet received regulatory approval for the routine treatment of HFpEF.[457] A comprehensive overview of potential device-based solutions for patients with HFpEF can be found in the recently published state-of-the-art review by Rosalia et al.[457] These include various devices that can be broadly categorized as atrial shunt devices, LV expanders, mechanical circulatory support devices and electrical stimulators.[457] Although most studies, especially those beyond feasibility studies, have not yet been completed, some small trials have shown promising effects of interatrial shunt devices and cardiac resynchronization therapy on

exercise tolerance. Interatrial shunt devices are used to create an opening between the left and right atria, allowing a reduction in left atrial pressure based on the interatrial pressure gradient.[457] Using a simulation study based on resting and exercise hemodynamic data from two independent studies of patients with HFpEF, a shunt diameter of 8 mm was deemed sufficient to significantly reduce left atrial pressure at rest (simulated reduction in PCWP from 10 mmHG to 7 mmHG) and during exercise (simulated reduction in PCWP from 28 mmHG to 17 mmHG) without overly compromising SV.[458] Although a left to right atrial shunt must necessarily reduce SV, it is hypothesized that the reduction in filling pressures will allow patients to exercise longer and that the accompanying higher peak HR will result in an overall higher CO.[458] Indeed, the results of a single-arm trial in 68 patients with HF and LVEF > 40% showed a significant reduction in mean exercise PCWP at 20 watts and peak exercise despite a significantly increased mean exercise duration 6 months after shunt device implantation.[459] At 1-year, patients still had lower workload-corrected exercise PCWP and a significant improvement in NYHA class, QoL and 6-MWT distance compared to baseline (all $P < 0.01$), with no device-related complications and a survival rate of 95%.[460] Moreover, a first double-blind RCT in 44 patients with HF and LVEF > 40% confirmed that implantation of an interatrial shunt device significantly reduced exercise PCWP compared with a sham procedure.[461] In contrast, a recently published large double-blind RCT in 626 patients with HF and LVEF > 40% found no significant differences in the rate of HF events or health status (KCCQ overall summary score) in the overall study population.[462] However, in a secondary analysis of this trial, the authors found a significant interaction between treatment and the presence of pulmonary vascular disease (defined by pulmonary vascular resistance ≥ 1.74 Wood units).[463] While patients with pulmonary vascular disease had a significantly worse outcome (composite endpoint of cardiovascular death, nonfatal ischemic stroke, recurrent HF events and change in health status) compared with the sham group (win ratio, 0.60 [95% CI, 0.42 to 0.86]), those without pulmonary vascular disease significantly benefited from the treatment (win ratio, 1.31 [95% CI, 1.02 to 1.68]).[463] While this finding has already led to the conceptualization of another prospective confirmation study in patients with pulmonary vascular resistance < 1.75 Wood units, it indicates that interatrial shunt devices might be another (future) treatment option to reduce the excessive increase in cardiac filling pressures that can cause premature exercise

termination and potentially improve exercise capacity in those patients who are less likely to improve peak $\dot{V}O_2$ with traditional ET alone.

Cardiac resynchronization therapy has an evidence level A, class I recommendation in selected patients with HFrEF,[30] but to date, only one small RCT has investigated its effect in patients with HFpEF (N = 6).[464] Three months after implantation and active pacing, active left atrial pacing was compared with inactive pacing in a 2-week double-blind cross-over phase.[464] The 6-MWT distance was significantly higher with atrial pacing (mean 6-MWT distance of 237 m) than before implantation (mean of 190 m) and with inactive atrial pacing (mean of 187 m).[464] Unfortunately, another study designed to investigate the effects of HR augmentation by rate-adaptive pacing in patients with HFpEF was prematurely terminated due to lack of enrollment.[175,465] Although further research is needed, given the rationale and the previously discussed positive associations with increasing peak HR in patients with HFpEF, it is very likely that pacemaker implantation will at some time be recommended in selected patients with HFpEF.

In addition to device-based therapies, bariatric surgery could be an effective treatment option to significantly reduce body weight in patients with HFpEF and severe obesity.[466] Given the close relationship between body weight and exercise tolerance, and in particular the disproportionate increase in $\dot{V}O_2$ with a reduction in body weight (when $\dot{V}O_2$ is expressed relative to body weight, as is usually the case) *(see chapter 4.6.1)*, it is likely that bariatric surgery will not 'merely' reduce body weight but will significantly increase exercise tolerance during weight-bearing activities. In patients with HF, bariatric surgery is associated with fewer emergency department visits and hospitalizations for worsening HF,[467] as well as shorter length of stay and lower in-hospital mortality on hospital readmissions.[468,469] Furthermore, two studies found a significant reduction in all-cause mortality and hospitalizations for HF and atrial fibrillation,[470] and a significant reduction in major cardiovascular AEs (all cause-mortality, myocardial infarction, coronary revascularization, cerebrovascular events or HF hospitalization)[471] during a median follow-up of 4.0 to 4.5 years.[470,471] However, there are no RCTs that have evaluated the effects of bariatric surgery and, to date, evidence for longitudinal changes in patients with HF (especially HFpEF) is scarce.[466] In the only study that exclusively examined patients with HFpEF (N = 12), the surgery-induced weight loss (average of -37 kg from pre-surgery to 6 months

post-surgery) was associated with a significant increase in QoL and high-density lipoprotein as well as a significant reduction of resting HR, liver fat, cardiac mass (relative wall thickness) and e'.[472] Similarly, several studies in patients without known HF showed significant reductions in LV mass and wall thickness as well as improvements in diastolic function (including isovolumic relaxation, deceleration time, E, e', E/e', E/A, left atrial diameter, LAVI) after bariatric surgery,[473-475] which adds to the potential benefit of this treatment in patients with HFpEF and severe obesity. In terms of exercise tolerance, bariatric surgery has been shown to significantly improve relative peak $\dot{V}O_2$, whereas mean values of absolute peak $\dot{V}O_2$ up to 1 year after surgery were not significantly improved or even decreased,[476-478] especially in individuals with a greater loss of body weight.[479] Moreover, some studies also found a reduction in absolute $\dot{V}O_2$ at VT1 following bariatric surgery.[478,480,481] The reduction in absolute $\dot{V}O_2$ at either VT1 or peak exercise within the first year after surgery can be explained by the fact that massive weight loss is also accompanied by a reduction in lean body mass / muscle mass.[478] Therefore, bariatric surgery should be supplemented with increased levels of physical activity or even structured ET to compensate for the loss of muscle mass and the concomitant reduction in absolute $\dot{V}O_2$ at VT1 and peak exercise. Along these lines, one large study investigated the effects of bariatric surgery supplemented by a pre-surgery educational program with weekly visits over a 7-week period and a 15-month post-surgery lifestyle modification program consisting of 1-hour group sessions with psychologists, dieticians and physiotherapists every 3 weeks.[482] In 4,785 individuals with a mean BMI of 44.9 kg/m^2, this comprehensive approach resulted in a significant improvement in absolute peak $\dot{V}O_2$ 24 months after surgery.[482] Compared to baseline, individuals reported significantly increased leisure time and sport activity at 9, 15 and 24 months after surgery, and while changes in leisure time activity were significantly associated with weight loss, the individual improvements in peak $\dot{V}O_2$ were significantly related to changes in sports activity.[482] Importantly, the diagnosis of HF is associated with a higher risk of post-operative complications and in-hospital mortality following bariatric surgery compared with individuals without HF, which should be taken into account when considering this treatment option in HFpEF.[483]

4.8. Implications for Future Research

Based on the results of the OptimEx-Clin trial and the overall evidence regarding ET and alternative treatments to improve exercise tolerance in patients with HFpEF *(see chapter 4.7)*, there are several implications for future research in this field. Although the efficacy of ET to reduce exercise intolerance, the hallmark symptom in patients with HFpEF, can hardly be denied, not all patients equally benefit from the same ET stimuli, and several research questions regarding the optimal ET approach, long-term effects, combined interventions, covariate-treatment interactions, effects on morbidity and mortality, and strategies to improve adherence and access to cardiac rehabilitation programs remain to be investigated in upcoming trials.

4.8.1. Paving the Way for Personalized Medicine

The identification of baseline peak O_2-pulse as a predictor of the ET-induced change in peak $\dot{V}O_2$ was not a random finding, because the a priori hypothesis was based on the strong theoretical assumption that patients who are primarily limited by the factors that are also the primary mediators of improvement in peak $\dot{V}O_2$ with ET would benefit most. Therefore, it is likely that this approach can also be applied to other treatments that have the potential to improve exercise tolerance in patients with HFpEF (and other diseases), resulting in several implications for further research.

First, it is important to explore methods to more easily determine the primary mechanisms responsible for exercise intolerance in individual patients. Houstis et al. presented an elegantly conducted study in patients with HFpEF that allowed to diagnose and rank the causes of exercise intolerance using their so-called 'personalized O_2 pathway analysis'.[146] However, although invasive hemodynamic exercise testing may be recommended in some patients with HFpEF, the complexity, costs and associated risks of such methods do not permit the use in all patients, especially not on a regular basis.[30,133,484] Therefore, less complex, ideally non-invasive and less expensive methods to better identify the causes of exercise intolerance and to enable broader application of such analyses need to be developed.[146] CPET is a useful tool for identifying exercise limitations (e.g., cardiovascular, pulmonary or gas exchange limitations), but generally does not allow determination of a specific cause for these limitations without further examinations. For example, the identification of peak O_2-pulse as the primary mediator and significant baseline predictor of the ET-induced change in

peak $\dot{V}O_2$ is very important, but because low peak O_2-pulse can be caused by low peak SV and / or C[a-v]O_2 and both SV and C[a-v]O_2 can also be caused by several more specific limitations *(see chapter 1.3)* that cannot be identified by CPET alone, it is also likely that not all patients with a low peak O_2-pulse will largely improve peak $\dot{V}O_2$ by ET.

Second, future studies should also attempt to assess the mediating factors that are associated with improvements in exercise tolerance. Only when these mediating effects are known, patients can be offered the most effective treatments for their individually identified deficits. When interpreting the mediating effects, it should also be considered that if one determinant improves, another determinant could worsen due to interactions between these variables *(see chapter 4.5)*.

Third, besides improving the identification of exercise limitations and mediating effects associated with improvements in peak $\dot{V}O_2$ or other parameters of exercise tolerance, the identification of, if possible easily measurable, covariate-treatment interactions is of utmost importance on the way to a more personalized medicine. These parameters could emerge from the identification of limiting factors and mediating effects that form the hypothesis for analysis of covariate-treatment interactions, as in the predictor analysis of the OptimEx-Clin trial, but untargeted approaches such as blood analyses to determine micro ribonucleic acids, metabolomics, or proteomics are also promising.[485,486] If covariate-treatment interactions (based on a study design including a comparator arm) can be detected and validated in an external dataset, these parameters can be used to calculate a pre-treatment probability for a positive treatment-related outcome for each individual patient and form the basis for personalized medicine. Because identifying covariate-treatment interactions requires a substantially larger sample size compared with group-based analyses,[235] an appropriate method may also be to conduct individual patient data meta-analyses.[487]

Forth, as shown in the simulation study by Houstis et al., a simultaneous therapy of multiple O_2 pathway defects likely has the greatest potential for sustained improvements in exercise tolerance.[146] Importantly, combining interventions that target different limitations may not only produce additive effects (e.g., caloric restriction plus ET)[226], but may also buffer the interactions between the determinants of peak $\dot{V}O_2$ or even induce catalytic effects between therapies. For example, reducing beta-blocker dosage to increase peak HR has been shown to directly increase peak $\dot{V}O_2$,[456] but the

simultaneous reduction in peak SV and / or C[a-v]O_2 (i.e., O_2-pulse) *(see chapter 4.5 and chapter 4.7.3)* may additionally increase the potential to further improve peak $\dot{V}O_2$ by additional ET. Similarly, inorganic nitrates / nitrites, spironolactone or interatrial shunts to reduce the excessive rise in cardiac filling pressures during exercise may not only have direct effects on peak $\dot{V}O_2$ in patients prematurely limited by the increase in filling pressures, but may also increase their potential for ET-induced improvements by allowing peak SV and / or C[a-v]O_2 to become the limiting factors of exercise tolerance. Therefore, identifying appropriate combinations of different therapies to increase their efficacy should be a major research objective in future HFpEF trials.

Lastly, interventions applying personalized therapies based on the individually identified exercise-limiting factors should be evaluated in comparison with a traditional 'one-size-fits-all' intervention that includes one or more treatments that have been found to be most effective on a group-based level (e.g., recommendation class I, evidence level A). This allows to determine whether the increased effort for personalized medicine is justified by substantially greater treatment effects compared to standard medical care. Given the highly heterogenous treatment responses to almost all therapies, it is very likely that this will be the case for patients with HFpEF.[48]

4.8.2. Individualized Exercise Training Prescriptions

Combined and personalized interventions are not only subject to the broad superordinate treatment scheme, but also specific to ET. The results of the OptimEx-Clin trial indicate there is probably no single 'optimal' training mode or intensity that is superior to another in patients with HFpEF (and probably in several other conditions as well), and as previously discussed *(chapter 4.1)*, failure to adhere to the general ET principles of individualization and overload may also be a reason for the reduced effects at 12 compared to 3 months. In addition to regular variations and progression of frequency, duration and intensity (within the same or different modes such as MCT and HIIT) based on the patient's individual conditions and responses, another way to improve individualization of ET prescriptions is to apply recommendations based on ventilatory thresholds rather than the 'semi-individual' standardized recommendations based on peak values or the reserve of HR and $\dot{V}O_2$. In general, recommendations based on HR or $\dot{V}O_2$ reserve should be preferred over % peak HR or % peak $\dot{V}O_2$ because, especially in patients with low peak HR or severe

exercise intolerance, general recommendations based on peak values may be unrealistically low (even below resting values for % peak HR). However, the use of reserve values may also lead to significant inter-individual differences in terms of underlying energy metabolism, especially in cardiac patients.[119,488,489] In contrast, the ventilatory thresholds (especially VT1) are based on the individual energy metabolism *(see chapter 1.2.2)*, which allows a much more detailed and individualized ET prescription compared with peak or reserve values and is therefore recommended as the gold standard for prescribing ET in patients with cardiovascular disease.[120,123,490] Moreover, prescribing ET based on ventilatory thresholds (especially when prescribing MCT) will not only improve the individualization and probably the effects of ET, but will also lead to a better comparability of ET prescriptions between different individuals.[119,490] Importantly, recommendations based on ventilatory thresholds also need to be regularly re-evaluated and revised based on repeated CPETs, individual ET responses, and patient feedback during ET sessions (e.g., based on the Borg RPE scale) to account for individual differences between subjects and adaptations to the training process.[120,490] Furthermore, the patient preferences and possible time constraints should be considered, because the best ET prescription is useless if the patient, for whatever reason, is unable or unwilling to adhere to the program. These principles and methods are being increasingly applied in clinical ET trials,[302,311,491] and although correct determination of ventilatory thresholds is dependent on the evaluator and requires a certain skill level, this should not prevent further promotion and implementation of this method as the preferred approach for prescribing ET in clinical research and routine care of patients with HFpEF and other cardiovascular diseases.

4.8.3. Long-term Application of Exercise Training

Even though there are still relatively few randomized controlled ET trials performed in patients with HFpEF, the ‘overall’ short-term efficacy of ET is well investigated. On the other hand, the long-term effects remain largely unknown because, to date, the OptimEx-Clin trial is the only published RCT in patients with HFpEF that investigated the effects of ET over 12 months.[234] This is problematic because in ‘real life’, ET has to be performed on a long term basis, as the effects are highly reversible if regular ET is discontinued (general ET principle of reversibility).[99,109] Therefore, future studies (both in patients with HFpEF and with other cardiovascular diseases) should focus on the

long-term effects of ET (> 1 year), including evaluation of strategies to improve adherence as outlined in *chapter 4.4*, as well as the chronic effects on morbidity and mortality, especially following long-term application of HIIT. Because assessing the impact on hospitalizations and mortality requires large samples sizes and long follow-ups, the latter should also include standardized collection of AEs and mortality beyond the last study visit to assess these risks over multiple years. Moreover, data-sharing to allow the conduct of individual patient data meta-analyses that combine databases from several individual trials could be a valuable method to better identify the long-term effects of ET in HFpEF and other diseases (in total or respective to different ET modes).

4.9. Limitations

The OptimEx-Clin trial and the analyses presented in the present dissertation have several limitations. While blinding of patients was not feasible and is a general limitation in lifestyle intervention trials, the staff conducting the on-site evaluations was also not blinded to the treatment arm assignment, which may have had an influence on the maximal exhaustion during CPET.[234] However, as peak RER was not significantly different between groups and time points, and the analyses of the echocardiography and CPET data were performed by blinded central core laboratories, it is unlikely that this had a relevant effect on the results.[234] The lack of exercise echocardiography or other imaging techniques during exercise to assess changes in diastolic function and filling pressures during exercise, which are more closely related to exercise limitations than resting parameters, precluded a differentiated identification of exercise limitations and limited the interpretation of the effects of HIIT and MCT on cardiac function.[234] Since peak O_2-pulse also does not allow to differentiate between SV and $C[a\text{-}v]O_2$, further research is needed to show whether both parameters are baseline predictors and mediators for the change in peak $\dot{V}O_2$ with ET in HFpEF.[242]

Because the OptimEx-Clin trial was designed to evaluate differences between group means, design features to reduce random errors, which are more relevant in analyses of covariate-treatment interactions than in group-based analyses (e.g., repeated measurements before and after treatment, cross-over design)[235] have not been applied.[242] The large scatter in changes in peak $\dot{V}O_2$ values underscores the importance of conducting predictor analyses, however, the observed heterogeneity may

have been amplified by the relatively high number of AEs in all groups, which is characteristic for an older multimorbid HFpEF population.[234,242] Moreover, due to the fact that this study compared the offer of a structured ET program (HIIT and MCT) with the recommendation to perform regular physical activity (CON), adherence in the ET groups and individual implementation of the guideline recommendations in patients randomized to CON may have also led to a larger scatter in individual changes.[242] To account for differences in adherence across ET groups, we also performed a per-protocol analysis in which patients who completed less than 70% of prescribed ET sessions were excluded from both the group-based and the predictor analyses.[234,242] However, it is unclear if (and how many) patients randomized to CON started regular ET after inclusion into the trial.[242] The drop in adherence during the home-based phase limits the interpretation of the long-term effects of ET. While this is also partly explained by the number of AEs that are likely to occur in every HFpEF population, it also undermines the urgent need for more effective strategies to improve long-term adherence to ET.[234]

Patients included in the OptimEx-Clin trial had a relatively preserved mean peak $\dot{V}O_2$ at baseline, which could be considered a limitation in terms of generalizability. However, the wide range of peak $\dot{V}O_2$ values at baseline (from 5.2 to 35.6 mL/kg/min) and the non-significant relationship between baseline peak $\dot{V}O_2$ and change in peak $\dot{V}O_2$ suggest that the results of the OptimEx-Clin trial are likely generalizable.[234,242] On the other side, the changes in diagnostic criteria for HFpEF may limit the generalizability of the results to all HFpEF phenotypes. The OptimEx-Clin trial applied the diagnostic HFpEF criteria from the 2007 consensus statement of the Heart Failure and Echocardiography Associations of the ESC,[249] but since then, definitions, cutoffs and recommendations for the diagnosis of HFpEF have changed several times and even to date, the diagnosis remains challenging, and there is no universally accepted diagnostic approach for HFpEF.[30,37,133,152,484,492-494] Moreover, the 2022 American HF guidelines already included a fourth HF subtype, namely HF with improved EF (HFimpEF) with patients who recovered from LVEF < 40% to LVEF > 40%, and use different HF stages from stage A (‘at risk of HF’) to stage B (‘pre-HF’), stage C (‘confirmed diagnosis of HF with current or previous symptoms according to the NYHA classification’) and stage D (‘advanced HF with severe symptoms and / or disease progression despite maximum guideline-directed medical therapy’),[484] which are likely

to be included in other associations' guidelines, as suggested in a position paper from different societies.[495] As several works have shown that the application of different diagnostic criteria may result in significantly different patient populations with distinct clinical profiles, exercise responses and outcomes,[496-499] the transfer of results between HFpEF populations defined or diagnosed on the basis of different criteria may always be limited unless there is a commonly accepted definition and diagnostic approach or more comprehensive phenotyping that allows better subgrouping of patients with HFpEF.[496] Lastly, multiplicity of testing increased the likelihood of false-positive findings, which limits the validity and interpretability of the secondary outcomes and the results of the predictor analysis and requires the investigation of these parameters and associations in further prospective studies.[234,242]

5. Conclusions

Among patients with HFpEF, HIIT and MCT did not elicit statistically significant differences in change in peak $\dot{V}O_2$ at 3 months.[234] Although the changes were below the a priori defined MCID of 2.5 mL/kg/min, they are in accordance with the results of other ET trials in HFpEF. Moreover, among all currently available treatment options for HFpEF, ET is one of, if not, the best single treatment for improving exercise tolerance in this population.[244] Nevertheless, the results of the OptmEx-Clin trial indicate that there is no single best ET mode for patients with HFpEF and that optimizing ET effects likely requires individual ET prescriptions, possibly in combination with additional therapies. Higher baseline peak O_2-pulse, which is the product of peak SV and peak C[a-v]O_2, was found to be significantly associated with lower changes in peak $\dot{V}O_2$ following ET vs. CON.[242] Because the change in functional capacity ($\dot{V}O_2$ at VT1) was not dependent on baseline peak O_2-pulse, ET should still be recommended in all stable patients with HFpEF. However, patients with a higher baseline peak O_2-pulse (indicating that they are primarily limited by their increase in peak HR) may require additional therapies such as reduction of negative chronotropic agents, rate-adaptive pacing or weight loss to significantly increase maximal exercise tolerance.[242] As peak O_2-pulse can be easily obtained during CPET, this is an important finding on the way to a more deficit-oriented personalized medicine in HFpEF that can be broadly applied.[242] Changes in peak $\dot{V}O_2$ after 12 months were not significantly different between HIIT, MCT and CON. Therefore, further studies to assess long-term effects and improve long-term adherence are needed to better understand and define the clinical benefits associated with regular ET. Moreover, it is clearly indicated that instead of focusing on ‘one-size-fits-all’ solutions of single treatments in a disease as heterogeneous as HFpEF, future ET trials should primarily focus on identifying mechanisms related to the improvement of outcomes and the identification of covariate-treatment interactions to improve personalized medicine, as well as the combination of treatments that target different mechanisms of exercise intolerance.

6. References

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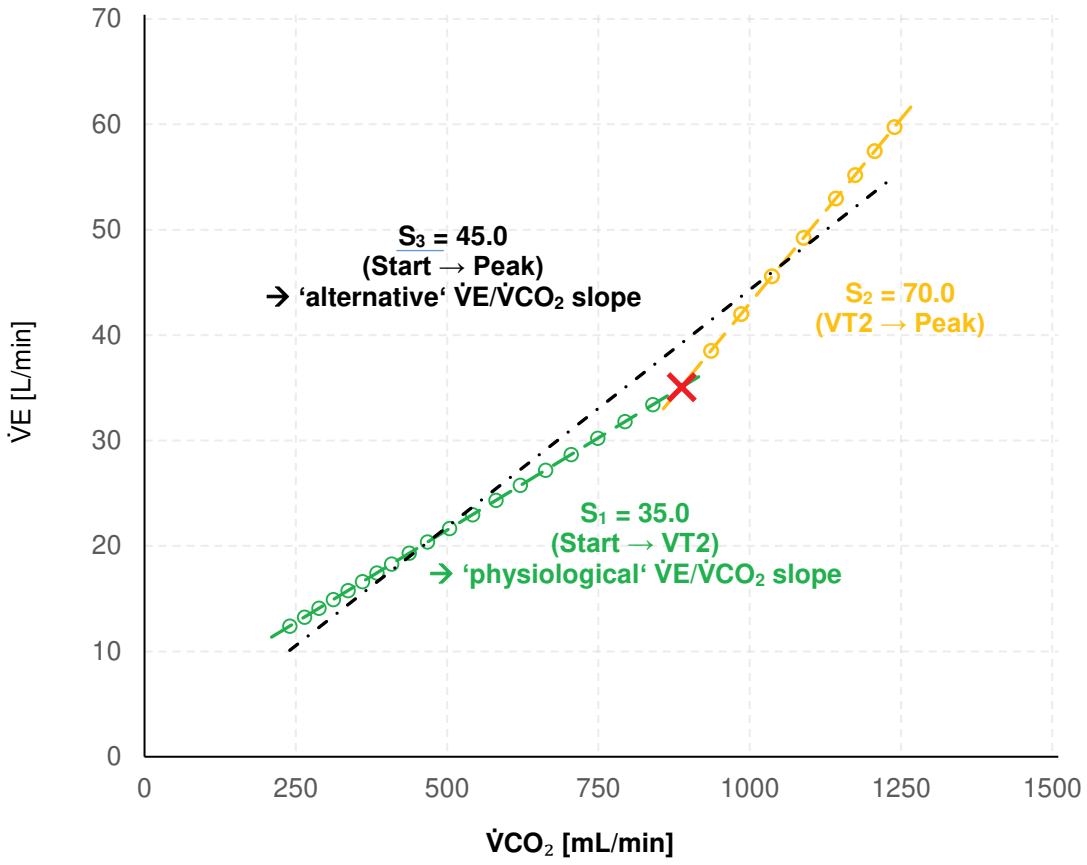
Disclosure of Potential Conflicts of Interest

The doctoral candidate received a speaker's fee from Novartis (2017; presentation regarding the conduction and interpretation of CPET in patients with HFrEF during an investigator meeting of another study) and served as a consultant for Bristol-Myers Squibb (2022-2023; consultation regarding the interpretation of CPET data in patients with hypertrophic cardiomyopathy).

Appendices

Appendix A: Relationship between ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$) during an incremental exercise test and the calculation of the $\dot{V}E/\dot{V}CO_2$ slope



$\dot{V}CO_2$ linearly increases in dependence on the increase in $\dot{V}E$ (S_1) during low to moderate intensity exercise, and disproportionally increases (S_2) during high intensities beyond the second ventilatory threshold (VT2). The 'physiological' $\dot{V}E/\dot{V}CO_2$ slope is calculated over the linear part until VT2 (S_1), whereas an alternative method considers the entire exercise data from start to peak exercise (S_3).

Appendix B: Borg rating of perceived exertion scale (adapted from Borg[250])

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	

Appendix C: Step-by-step description of the customized evaluation tool for the analysis of the cardiopulmonary exercise testing (CPET) data by the CPET Core Laboratory Munich

Step 1: Export of raw data with all relevant CPET metrics and time stamps (averaged over 10 seconds or breath-by-breath), as well as sex, age, body weight and height, randomization number, and study visit to an editable file (e.g., .xlsx, .xls, .csv, .txt). Transmission of these files to the CPET core laboratory in Munich.

Step 2: A Visual Basic for Application (VBA) macro in Microsoft Excel (one macro per study site, based on the format of the exports) automatically converts each export to a standardized format (one per study, independent of study sites). The macro continues until all available exports are processed.

Step 3: A second VBA macro replaces randomization number and study visit with a unique identifier (individual sequence of letters and numbers) to allow blinded evaluation. Each export file is saved using the unique identifier. The macro continues until all available files are processed.

Step 4: A third VBA macro automatically inserts all standardized export files into a customized spreadsheet, in which the data is averaged according to the standard operating procedure (SOP) of the study (e.g., 30 seconds rolling average or 5 out of 7 breaths), and presented in the 9-panel-plots. All objectively determinable CPET metrics (e.g., all resting and peak values, slopes, etc.…) are automatically calculated according to the study SOP. Each file is saved and closed using the unique identifier. The macro continues until all available files are processed.

Step 5: Each automatically evaluated file must be manually checked for plausibility and confirmed by the date of evaluation and an electronic signature. Moreover, the manual check allows to set the ventilatory thresholds VT1 and VT2 (which is not possible with an automated algorithm), to correct for obvious measuring errors, determine the overall quality of the CPET and heart rate data, determine the level of exhaustion (beyond peak respiratory exchange ratio) and make individual comments.

Step 6: After final evaluation, the original randomization number and study visit are reassigned to each file. The evaluation tool also allows to export (to .pdf) or print a customized report including the date of the evaluation and the signature of the evaluator (see ‘CPET CoreLab Evaluation Report’ below).

Step 7: A fourth VBA macro allows to automatically retrieve the evaluated data from all CPET files and insert them into the CPET database to avoid typing or transmission errors.

continued on next page…

Appendix C (continued)

CPET CoreLab Evaluation Report

OptimEx

Center	**Munich**
Randomization No.	[illegible]
Visit No.	**V1**
Visit Date	[illegible]**06.2016**

Plausibility Check:

CPET Data Plausible? yes [X] no [ ] doubtful [ ]

Comment:

Heart Rate Data Plausible? yes [X] no [ ] doubtful [ ]

Comment:

Other Data Plausible? yes [X] no [ ]

Comment:

General Information:

Maximal Exhaustion? yes [X] no [ ] doubtful [ ]

Additional Comment(s):

29.07.2016 [illegible]

Date Signature Stephan Müller

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University Hospital 'Klinikum rechts der Isar', Technical University of Munich
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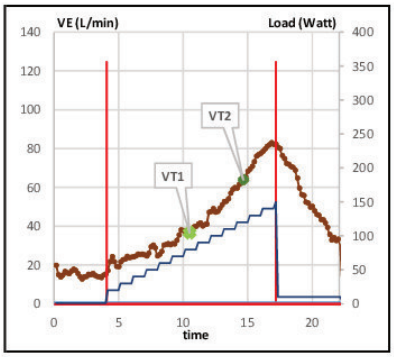
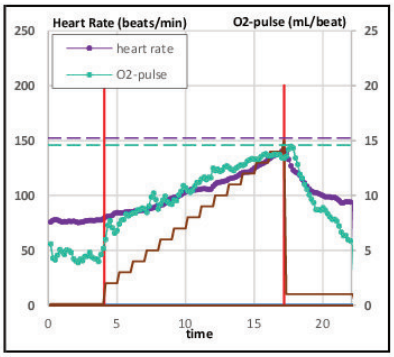
Appendix C (continued)

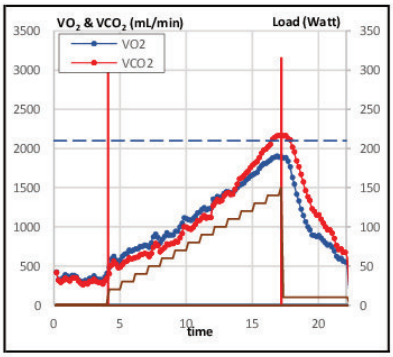
CPET CoreLab Evaluation Report

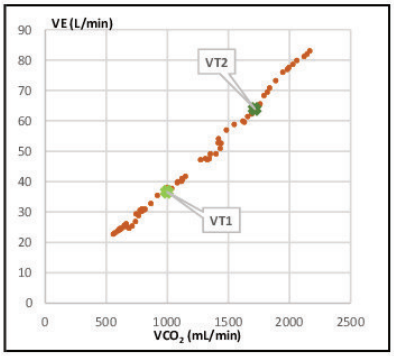
OptimEx

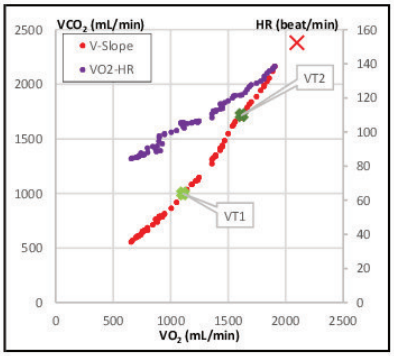
Patient ID:	[redacted]	**Test Date:**	[redacted].06.2016	**height (cm):**	165	**Bar. Press. (mmHg):**	946
Visit:	V1	**Gender:**	male	**weight (kg):**	92,0	**Amb.Temp. (°C):**	22,9
Center:	MUC	**Age:**	62	**BMI (kg/m²):**	33,8	**Amb. Rel. Hum. (%):**	51

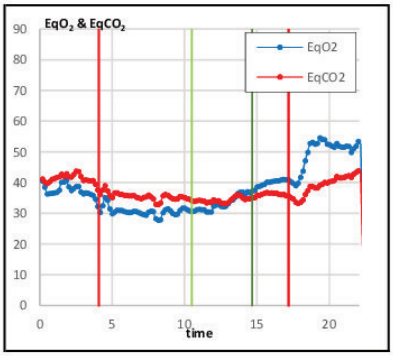


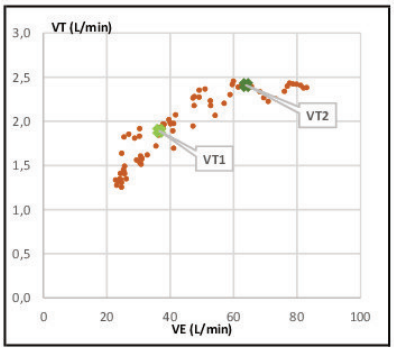


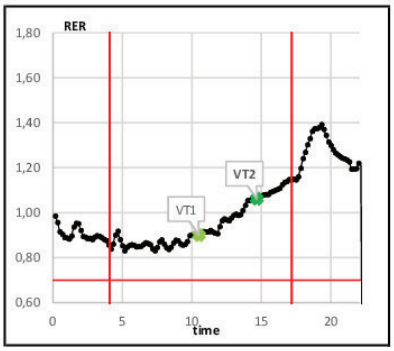


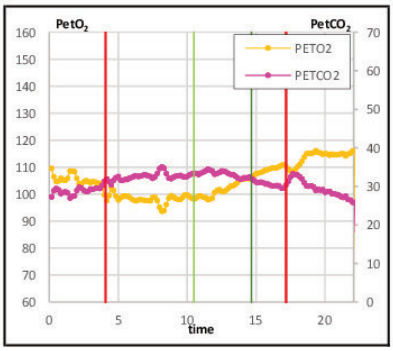










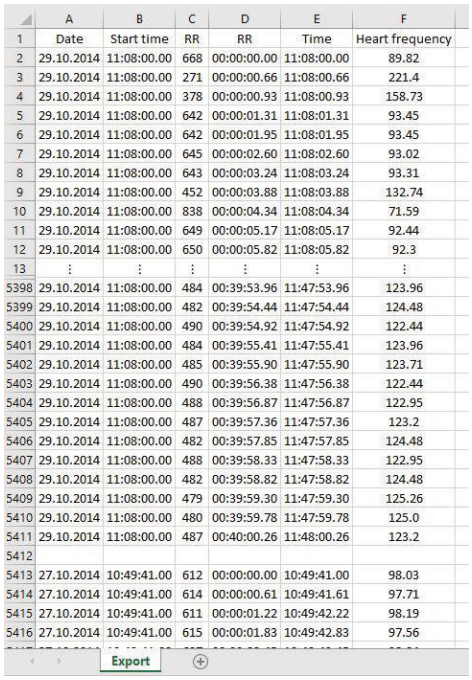


Test Protocol: 20/10/1		Rest	VT1			VT2			Peak Exercise		
			measured	% peak	% norm.	measured	% peak	% norm.	measured	norm	% norm.
VO_2 abs.	mL/min	309	1109	58%	53%	1618	85%	77%	1904	2099	91%
VO_2 rel.	mL/min/kg	3,4	12,0			17,6			20,7	22,8	
VCO_2	mL/min	279	997,80	46%	-	1717	79%	-	2166	-	-
RER		0,90	0,90	79%	-	1,06	93%	-	1,14	-	-
VE	L/min	14,0	36,6	44%	69%	63,9	77%	121%	83,0	53,0	157%
Power	Watt		80	52%	-	120	78%	-	153	-	-
HR	b/min	76	106	75%	69%	122	87%	80%	140	152	92%
O_2-Pulse	b/mL	4,1	10,5	76%	72%	13,3	97%	91%	13,7	14,6	94%
EqO_2		38,7	30,7	75%	-	37,3	91%	-	41,1	-	-
$EqCO_2$		42,9	34,1	94%	-	35,2	97%	-	36,2	-	-
$PetO_2$	mmHG	105,2	98,3	89%	-	106,4	96%	-	110,8	-	-
$PetCO_2$	mmHG	29,0	33,5	113%	-	32,0	108%	-	29,7	-	-

VE/VCO2 slope (-> peak): 37,78 | **VE/VCO2 slope (-> VT2): 35,1** | **OUES: 2,16** | **VO2/WR slope: 11,1**

Appendix D: Step-by-step description of the customized evaluation tool for the analysis of the training data by the Exercise Training Core Laboratory Munich

Step 1: Download of the recorded exercise training data as a .csv file containing beat-by-beat data with corresponding timestamps (1 row per recorded heartbeat; different sessions are separated by a blank row or by different sheets). Depending on the average heart rate, a 40-minute session has ~ 3.000 - 6.000 rows (see example to the right).



	A	B	C	D	E	F
1	Date	Start time	RR	RR	Time	Heart frequency
2	29.10.2014	11:08:00.00	668	00:00:00.00	11:08:00.00	89.82
3	29.10.2014	11:08:00.00	271	00:00:00.66	11:08:00.66	221.4
4	29.10.2014	11:08:00.00	378	00:00:00.93	11:08:00.93	158.73
5	29.10.2014	11:08:00.00	642	00:00:01.31	11:08:01.31	93.45
6	29.10.2014	11:08:00.00	642	00:00:01.95	11:08:01.95	93.45
7	29.10.2014	11:08:00.00	645	00:00:02.60	11:08:02.60	93.02
8	29.10.2014	11:08:00.00	643	00:00:03.24	11:08:03.24	93.31
9	29.10.2014	11:08:00.00	452	00:00:03.88	11:08:03.88	132.74
10	29.10.2014	11:08:00.00	838	00:00:04.34	11:08:04.34	71.59
11	29.10.2014	11:08:00.00	649	00:00:05.17	11:08:05.17	92.44
12	29.10.2014	11:08:00.00	650	00:00:05.82	11:08:05.82	92.3
13	⋮	⋮	⋮	⋮	⋮	⋮
5398	29.10.2014	11:08:00.00	484	00:39:53.96	11:47:53.96	123.96
5399	29.10.2014	11:08:00.00	482	00:39:54.44	11:47:54.44	124.48
5400	29.10.2014	11:08:00.00	490	00:39:54.92	11:47:54.92	122.44
5401	29.10.2014	11:08:00.00	484	00:39:55.41	11:47:55.41	123.96
5402	29.10.2014	11:08:00.00	485	00:39:55.90	11:47:55.90	123.71
5403	29.10.2014	11:08:00.00	490	00:39:56.38	11:47:56.38	122.44
5404	29.10.2014	11:08:00.00	488	00:39:56.87	11:47:56.87	122.95
5405	29.10.2014	11:08:00.00	487	00:39:57.36	11:47:57.36	123.2
5406	29.10.2014	11:08:00.00	482	00:39:57.85	11:47:57.85	124.48
5407	29.10.2014	11:08:00.00	488	00:39:58.33	11:47:58.33	122.95
5408	29.10.2014	11:08:00.00	482	00:39:58.82	11:47:58.82	124.48
5409	29.10.2014	11:08:00.00	479	00:39:59.30	11:47:59.30	125.26
5410	29.10.2014	11:08:00.00	480	00:39:59.78	11:47:59.78	125.0
5411	29.10.2014	11:08:00.00	487	00:40:00.26	11:48:00.26	123.2
5412						
5413	27.10.2014	10:49:41.00	612	00:00:00.00	10:49:41.00	98.03
5414	27.10.2014	10:49:41.00	614	00:00:00.61	10:49:41.61	97.71
5415	27.10.2014	10:49:41.00	611	00:00:01.22	10:49:42.22	98.19
5416	27.10.2014	10:49:41.00	615	00:00:01.83	10:49:42.83	97.56

Export

Step 2: A Visual Basic for Application (VBA) macro in Microsoft Excel converts the .csv files into .xlsx format and saves them with the respective randomization number and time period.

Step 3: If there is more than one file per patient to be evaluated together, they must be manually combined (copy and paste).

Step 4: A second VBA macro opens an export file and inserts the data into an empty customized 'master file' (based on the exercise training mode) consisting of an overview sheet and one additional sheet for each exercise training session (see examples below). The heart rate data is graphically displayed beat-by-beat and by using a rolling average based on the standard operating procedure of the study. The macro also retrieves relevant clinical data from a database that contains the exercise testing parameters (e.g., resting and peak heart rate), and transfers this data to the overview sheet. The overview sheet contains the relevant summarized metrics from each exercise training session (1 row per session) and additional summaries across all sessions. Each file is saved and closed, and the macro continues until all available files are processed.

Step 5: The heart rate measurements have to be checked, adjusted (e.g., in case of obvious measuring errors) and confirmed (by evaluation date and name of the evaluator) for each exercise training session.

Step 6: Review of the paper-based training diaries for additional sessions that have not been recorded. These additional sessions have to be manually entered into the overview sheet.

Step 7: A third VBA macro automatically retrieves the evaluated data from the overview sheets of all patient files and inserts them into the exercise training database to avoid typing or transmission errors.

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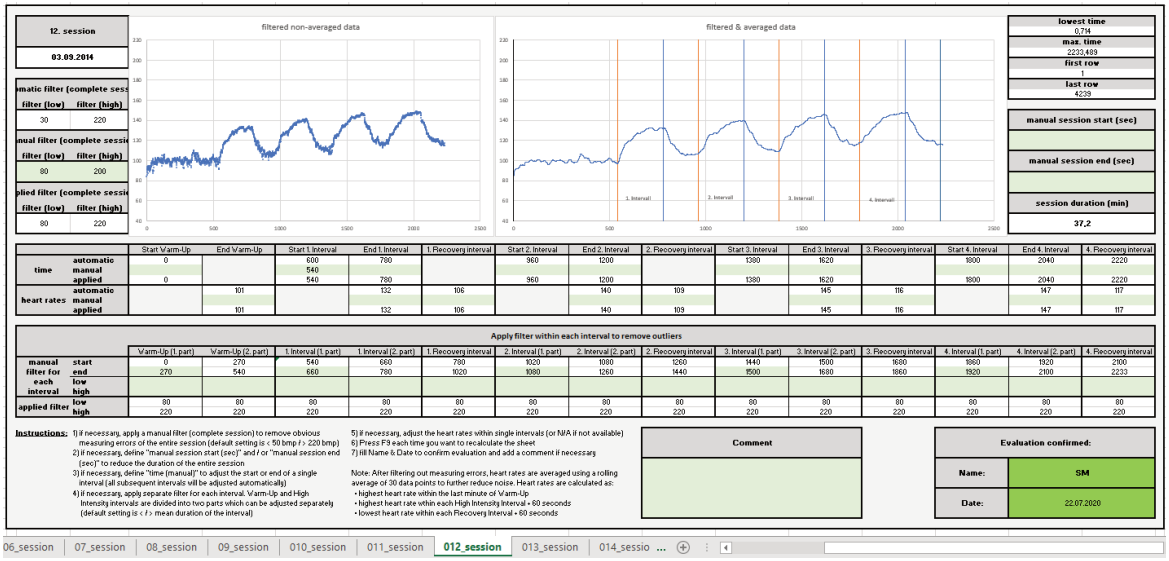
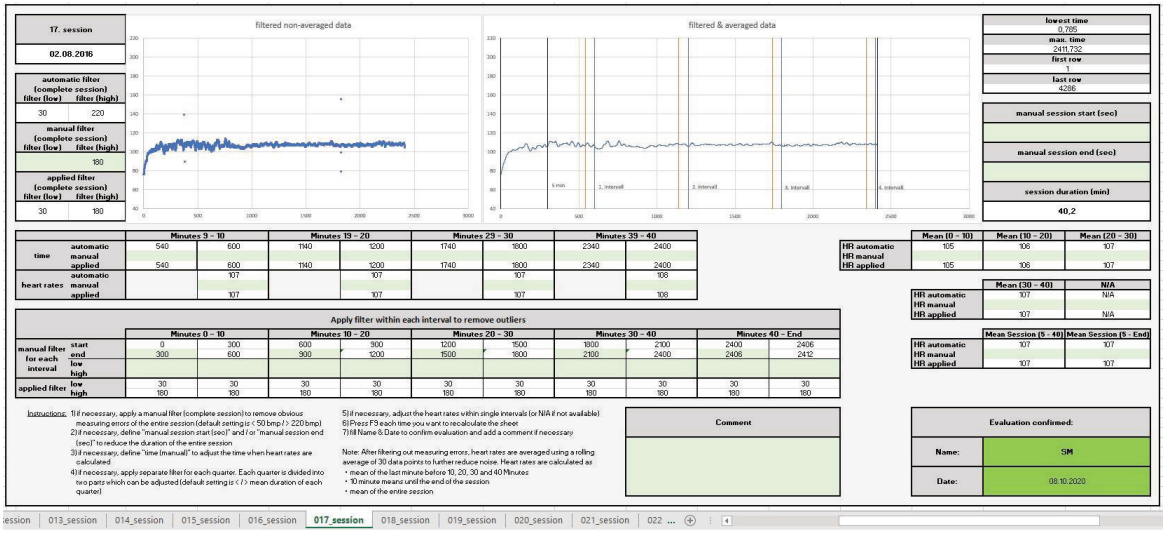
Appendix D (continued)

Example of the customized evaluation tool for High-Intensity Interval Training Sessions:



Example of the customized evaluation tool for Moderate Continuous Training Sessions:



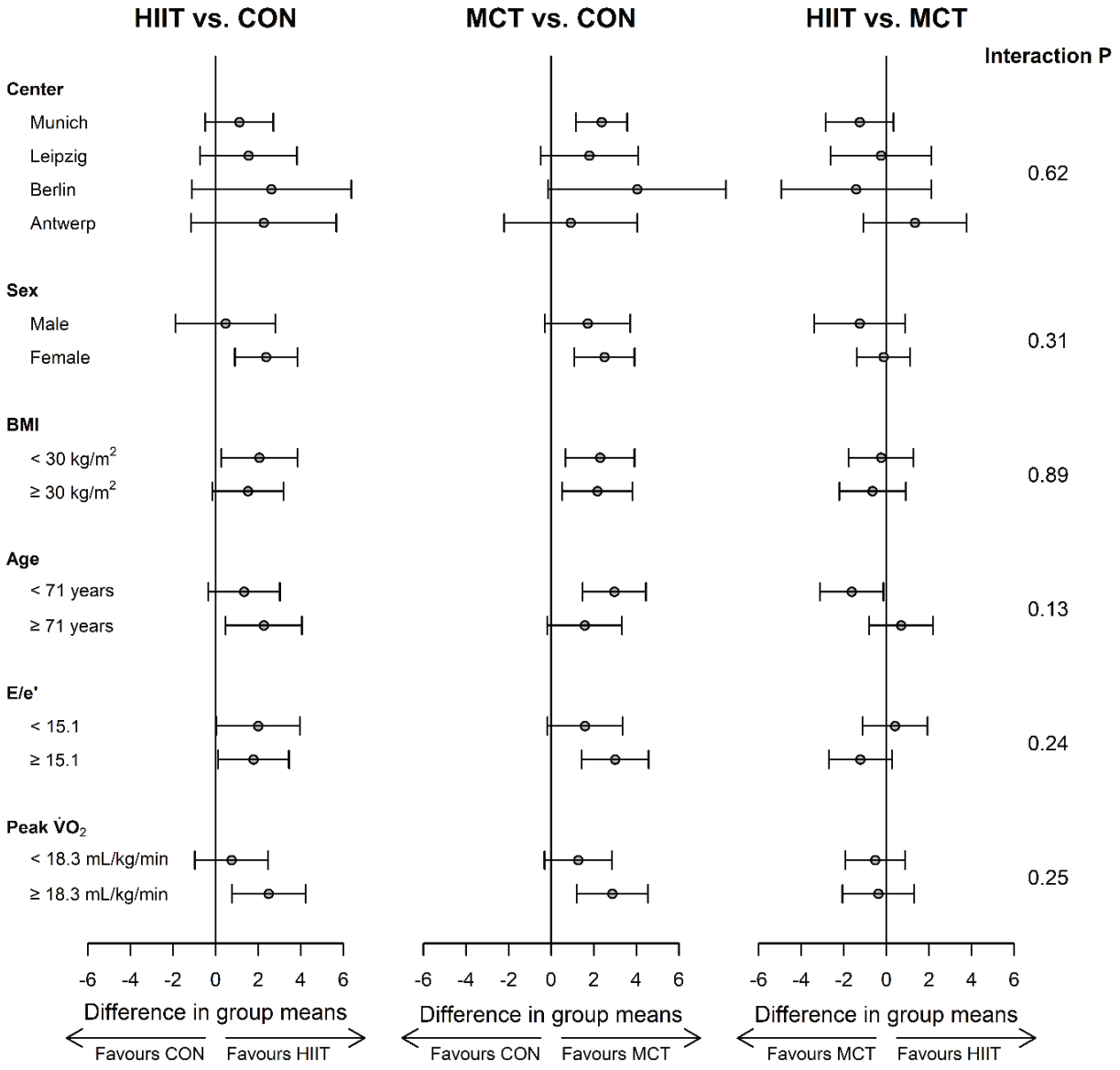
Appendix E: Ineligible participants not meeting the inclusion criteria for the diagnosis of heart failure with preserved ejection fraction who were inadvertently randomized and excluded from the analysis after blinded review of eligibility for all patients (adapted from Mueller et al.[234])

Group assignment	On-site measurements of		Core laboratory measurements of	
	E/e' medial	BNP (pg/mL)	E/e' medial	NT-proBNP (pg/mL)
MCT	10.8	33	9.6	102
MCT	10.9	30	9.9	92
HIIT	11.9	44	7.8	134
HIIT	9.8	8	9.4	55

The respective inclusion criteria were on-site measures of E/e' medial ≥ 15 or E/e' medial ≥ 8 with concomitant elevated natriuretic peptides (NT-proBNP ≥ 220 pg/mL or BNP ≥ 80 pg/mL)

***Abbreviations*: BNP** *= brain natriuretic peptide;* **E/e'** *= estimated left ventricular filling pressure;* **MCT** *= Moderate Continuous Training;* **HIIT** *= High-Intensity Interval Training;* **NT-proBNP** *= N-terminal prohormone of brain natriuretic peptide*

Appendix F: Subgroup analysis of the primary endpoint (change in peak oxygen consumption [$\dot{V}O_2$] after 3 months) between high-intensity interval training (HIIT), moderate continuous training (MCT) and guideline control (CON) (adapted from Mueller et al.[234])



Cutoff points were pre-specified as 30 kg/m² (BMI) and the median of age, E/e' medial and peak $\dot{V}O_2$.
Abbreviations*: BMI** *= body mass index;* ***E/e' *= estimated left ventricular filling pressure*

Appendix G: List of cardiovascular adverse events (AEs) for patients randomized to high-intensity interval training, moderate continuous training and guideline control (adapted from Mueller et al.[234])

	High Intensity Interval Training [n = 58]		Moderate Continuous Training [n = 58]		Guideline Control [n = 60]	
	No. of Events	**No. (%) of Participants**	**No. of Events**	**No. (%) of Participants**	**No. of Events**	**No. (%) of Participants**
All AEs	**80**	**36 (62)**	**79**	**39 (67)**	**50**	**27 (45)**
Cardiovascular AEs	**32**	**14 (24)**	**29**	**17 (29)**	**19**	**12 (20)**
Heart Failure related AEs	**15**	**7 (12)**	**13**	**6 (10)**	**10**	**6 (10)**
Worsening heart failure	4	3 (5)	5	3 (5)	6	3 (5)
Atrial fibrillation	9	4 (7)	7	3 (5)	3	2 (3)
Pleural effusion	1	1 (2)	-	-	1	1 (2)
Ventricular arrhythmias	-	-	1	1 (2)	-	-
Cardiac arrest / death	1	1 (2)	-	-	-	-
Other cardiovascular AEs	**17**	**10 (8)**	**16**	**12 (21)**	**9**	**9 (15)**
Acute coronary syndrome [a]	4	4 (7)	4	3 (5)	5	5 (8)
Supraventricular arrhythmias	2	1 (2)	1	1 (2)	1	1 (2)
Hypertension	-	-	6	4 (7)	-	-
Hypotension	2	1 (2)	2	2 (3)	-	-
Peripheral artery disease / Occlusion of peripheral bypass	2	1 (2)	-	-	-	-
Thromboembolic occlusion of a femoral artery	-	-	-	-	1	1 (2)
Sinus bradycardia	1	1 (2)	1	1 (2)	-	-
Cardiac syncope	1	1 (2)	1	1 (2)	-	-
Pulmonary embolism	1	1 (2)	-	-	-	-
Deep vein thrombosis	1	1 (2)	-	-	-	-
Ventilation-perfusion mismatch	1	1 (2)	-	-	-	-
Endocarditis	-	-	1	1 (2)	-	-
Dilated aorta with suspected dissection	1	1 (2)	-	-	-	-
Transient ischemic attack	1	1 (2)	-	-	-	-
3rd degree atrioventricular block	-	-	-	-	1	1 (2)
Pulmonary hypertension	-	-	-	-	1	1 (2)
Non-cardiovascular AEs	**48**	**29 (50)**	**50**	**31 (53)**	**31**	**19 (32)**
Respiratory tract infections	7	7 (12)	11	10 (17)	3	3 (5)
Knee / Hip pain (unrelated to falls)	8	7 (12)	2	2 (3)	1	1 (2)
Events related to falls	2	2 (3)	5	5 (9)	2	2 (3)
Back pain	3	3 (5)	2	2 (3)	2	2 (3)
Other non-cardiovascular AEs [b]	28	20 (34)	30	22 (38)	23	16 (27)

[a] *includes symptomatic aortic stenosis, progressive ischemic heart disease, symptomatic coronary stenosis, palpitations, progressive angina pectoris, atypical thoracic symptoms, symptomatic stenosis of A. carotis interna*

[b] *including events that occurred less than 5 times*

Appendix H: List of serious adverse events (SAEs) for patients randomized to high-intensity interval training, moderate continuous training and guideline control (adapted from Mueller et al.[234])

	High Intensity Interval Training [N = 58]		Moderate Continuous Training [N = 58]		Guideline Control [N = 60]	
	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants
All SAEs	**33**	**18 (31)**	**28**	**18 (31)**	**27**	**16 (27)**
Cardiovascular SAEs	**21**	**10 (17)**	**18**	**12 (21)**	**14**	**10 (17)**
Heart Failure related SAEs	**7**	**5 (9)**	**8**	**4 (7)**	**5**	**3 (5)**
Worsening heart failure	2	2 (3)	3	2 (3)	4	2 (3)
Atrial fibrillation	3	2 (3)	4	2 (3)	-	-
Pleural effusion	1	1 (2)	-	-	1	1 (2)
Ventricular arrhythmias	-	-	1	1 (2)	-	-
Cardiac arrest / death	1	1 (2)	-	-	-	-
Other cardiovascular SAEs	**14**	**8 (14)**	**10**	**8 (14)**	**9**	**9 (15)**
Acute coronary syndrome [a]	3	3 (5)	4	3 (5)	5	5 (8)
Supraventricular arrhythmias	2	1 (2)	1	1 (2)	1	1 (2)
Hypertension	-	-	2	2 (3)	-	-
Peripheral artery disease occlusion of peripheral bypass	2	1 (2)	-	-	-	-
Thromboembolic occlusion of a femoral artery	-	-	-	-	1	1 (2)
Sinus bradycardia	1	1 (2)	1	1 (2)	-	-
Cardiac syncope	1	1 (2)	1	1 (2)	-	-
Pulmonary embolism	1	1 (2)	-	-	-	-
Deep vein thrombosis	1	1 (2)	-	-	-	-
Ventilation-perfusion mismatch	1	1 (2)	-	-	-	-
Endocarditis	-	-	1	1 (2)	-	-
Dilated aorta	1	1 (2)	-	-	-	-
Transient ischemic attack	1	1 (2)	-	-	-	-
3rd degree atrioventricular block	-	-	-	-	1	1 (2)
Pulmonary hypertension	-	-	-	-	1	1 (2)
Non-cardiovascular SAEs	**12**	**10 (17)**	**10**	**9 (16)**	**13**	**9 (15)**
Gastroenterological	3	3 (5)	3	3 (5)	4	4 (7)
Viral gastro-enteritis	2	2 (3)	1	1 (2)	-	-
Gastritis	-	-	1	1 (2)	1	1 (2)
Gastric ulcer	-	-	1	1 (2)	-	-
Symptomatic choledocholithiasis	1	1 (2)	-	-	-	-
Diabetic gastroparesis	-	-	-	-	1	1 (2)
Diverticulitis	-	-	-	-	1	1 (2)
Abdominal wall hernia	-	-	-	-	1	1 (2)

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Appendix E (continued)

	High Intensity Interval Training [n = 58]		Moderate Continuous Training [n = 58]		Guideline Control [n = 60]	
	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants
Orthopedic	**1**	**1 (2)**	**4**	**4 (7)**	**1**	**1 (2)**
Femur fracture	-	-	1	1 (2)	-	-
Biceps tendon rupture	-	-	1	1 (2)	-	-
Subacromial syndrome	-	-	1	1 (2)	-	-
Inflammatory arthritis	-	-	1	1 (2)	-	-
Gonarthrosis	1	1 (2)	-	-	-	-
Bacterial osteomyelitis	-	-	-	-	1	1 (2)
Endocrinological/ Metabolic	2	2 (3)	-	-	3	3 (5)
Conn´s syndrome	1	1 (2)	-	-	-	-
Hypokalemia	-	-	-	-	1	1 (2)
Hypothyroidism	1	1 (2)	-	-	-	-
Metabolic disturbance in diabetes	-	-	-	-	1	1 (2)
Hypoglycemia	-	-	-	-	1	1 (2)
Pulmonological	3	2 (3)	1	1 (2)	1	1(2)
COPD exacerbation	2	1 (2)	-	-	-	-
Pleural effusion	-	-	1	1 (2)	-	-
Pneumonia	-	-	-	-	1	1 (2)
Mantel cell lymphoma	1	1 (2)	-	-	-	-
Neurological	1	1 (2)	2	2 (3)	1	1 (2)
Concussion	1	1 (2)	1	1 (2)	-	-
Subdural hematoma	-	-	-	-	1	1 (2)
Epileptical attack	-	-	1	1 (2)	-	-
Urological/ Nephrological	2	1 (2)	-	-	2	2 (3)
Stricture of the urethra	2	1 (2)	-	-	-	-
Acute renal failure	-	-	-	-	1	1 (2)
Nephrolithiasis	-	-	-	-	1	1 (2)
Gynecological	-	-	-	-	1	1 (2)
Ovary cysts	-	-	-	-	1	1 (2)

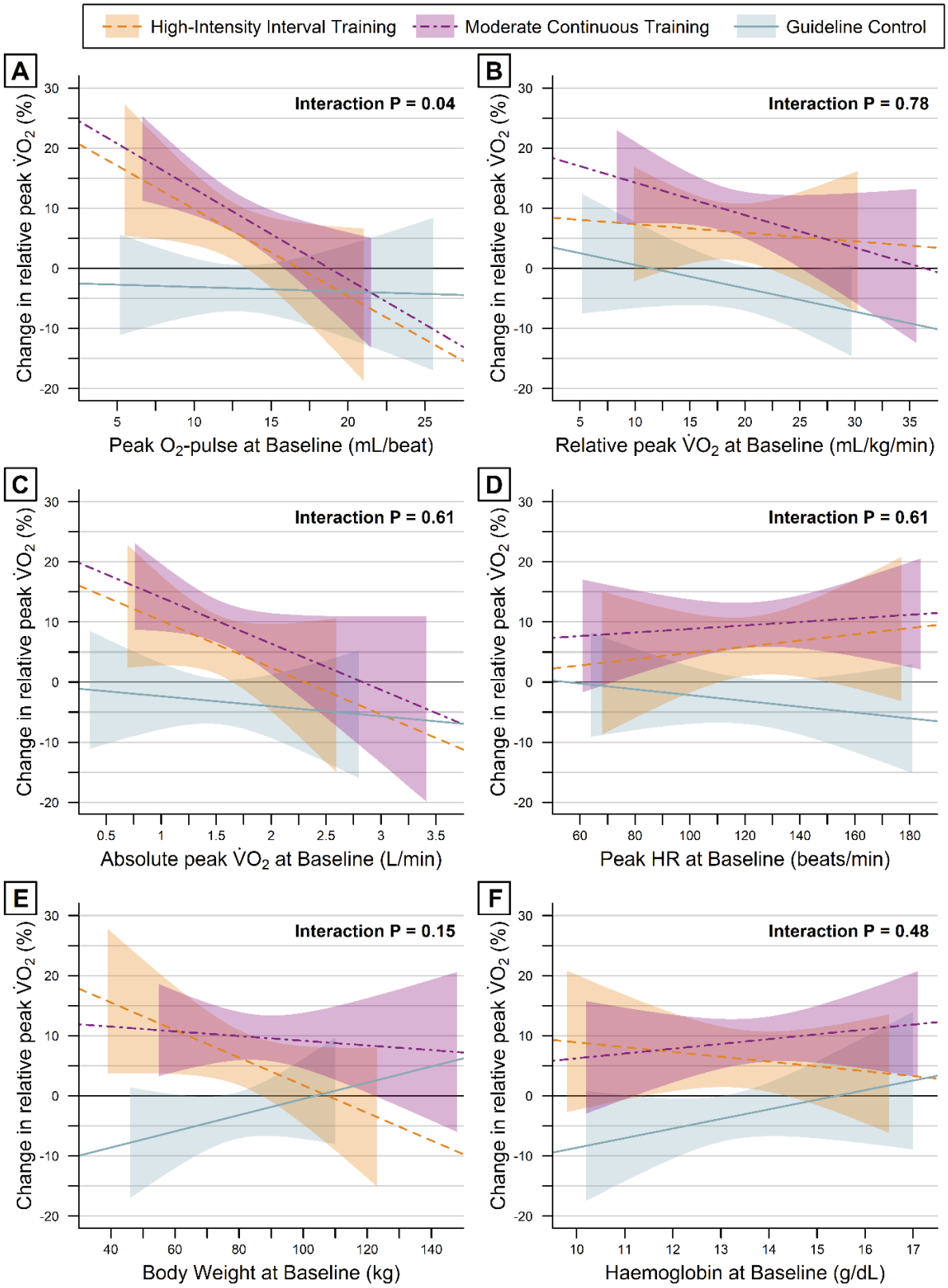
[a] includes symptomatic aortic stenosis, progressive ischemic heart disease, symptomatic coronary stenosis, palpitations, progressive angina pectoris, atypical thoracic symptoms, symptomatic stenosis of A. carotis interna

Appendix I: Results of the predictor analyses for the inter-individual response variability in oxygen consumption ($\dot{V}O_2$) at the first ventilatory threshold (VT1) (adapted from Mueller et al.[242])

	ß-coefficient (95% CI), P-value for mean change in relative $\dot{V}O_2$ at VT1		
	Exercise Training (ET) [n = 104] [a]	**Guideline Control (CON) [n = 50] [a]**	**Interaction P for ET vs. CON**
Peak O_2-pulse (per 1 mL/beat)	0.09% (-0.87 to -1.04), P = 0.86	0.11% (-1.34 to 1.57), P = 0.88	0.97
Peak $\dot{V}O_2$ (per 1 mL/kg/min)	-0.49% (-1.13 to 0.15), P = 0.13	-0.93% (-1.91 to 0.05), P = 0.07	0.44
Peak $\dot{V}O_2$ (per 100 mL/min)	-0.26% (-1.00 to 0.48), P = 0.49	-0.51% (-1.76 to 0.74), P = 0.42	0.73
Peak heart rate (per 10 beats/min)	-0.68% (-1.94 to 0.57), P = 0.29	-1.74% (-3.73 to 0.25), P = 0.09	0.35
Body Weight (per 10 kg)	1.39% (-0.42 to 3.20), P = 0.13	2.35% (-1.29 to 5.99), P = 0.19	0.61
Hemoglobin (per 1 g/dL) [a]	0.07% (-1.92 to 2.06), P = 0.95	0.77% (-3.41 to 4.95), P = 0.73	0.77

[a] different n (due to missing values) for the analyses of hemoglobin (ET: 101 patients; CON: 50 patients)

Appendix J: Relationships between changes in relative peak oxygen consumption ($\dot{V}O_2$) and baseline values of peak O_2-pulse [A], relative peak $\dot{V}O_2$ [B], absolute peak $\dot{V}O_2$ [C], peak heart rate (HR) [D], body weight [E], and hemoglobin [F] (adapted from Mueller et al.[242])



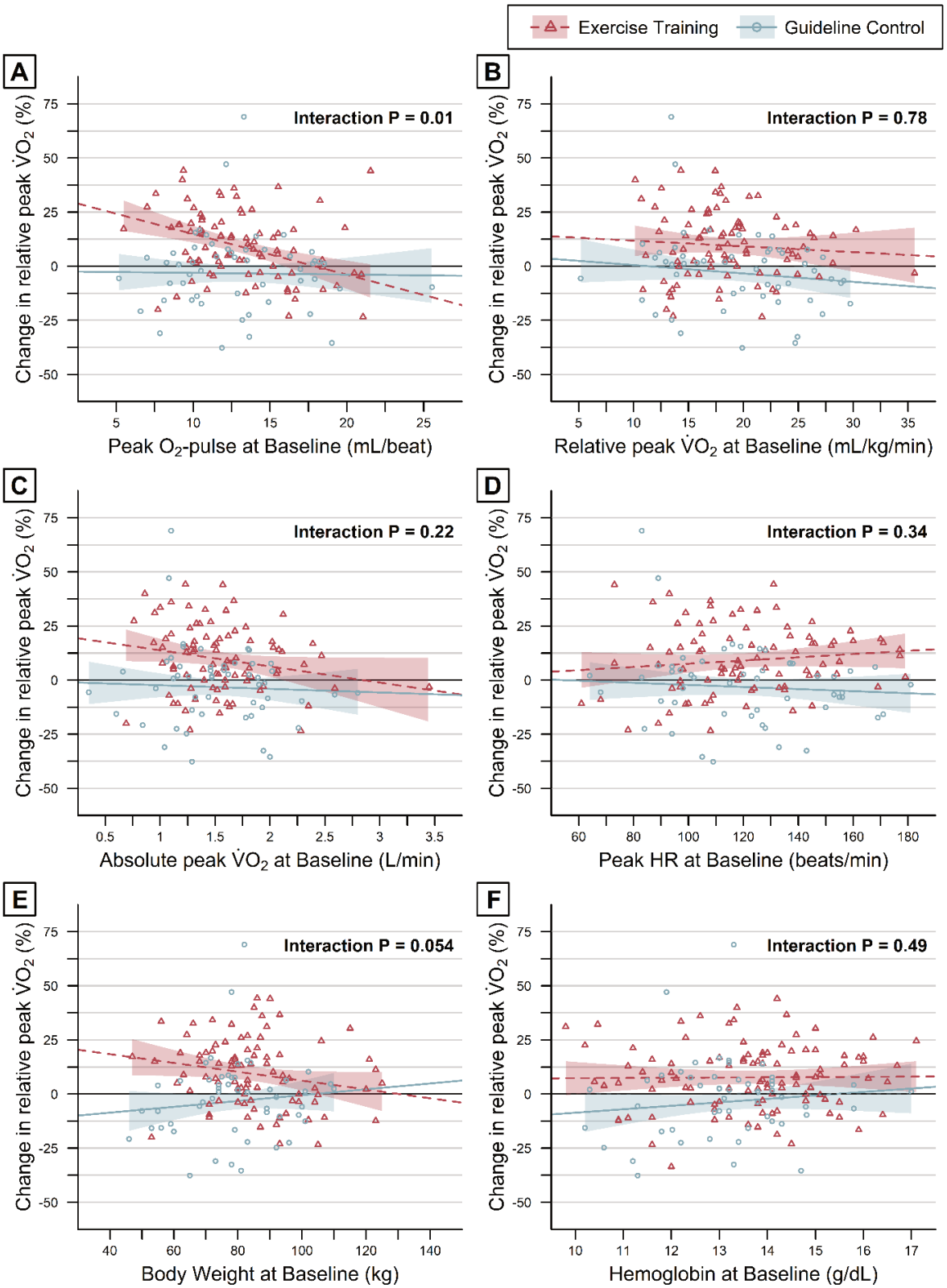
Robust linear regression lines and 95% confidence bands are shown separately for high-intensity interval training (– – –), moderate continuous training (– • –) and guideline control (———)

Appendix K: Results of the predictor analyses for the inter-individual response variability in peak oxygen consumption ($\dot{V}O_2$) between high-intensity interval training, moderate continuous training and guideline control (adapted from Mueller et al.[242])

	ß-coefficient (95% CI), P-value for mean change in relative peak $\dot{V}O_2$			
	High-Intensity Interval Training [n = 52] [a]	**Moderate Continuous Training [n = 54] [a]**	**Guideline Control [n = 52] [a]**	**Global Interaction P**
Peak O_2-pulse (per 1 mL/beat)	-1.44% (-2.80 to -0.08), P = 0.04	-1.50% (-2.52 to -0.48) P = 0.007	-0.08% (-1.11 to 0.96) P = 0.88	0.15
Peak $\dot{V}O_2$ (per 1 mL/kg/min)	-0.14% (-1.13 to 0.85) P = 0.78	-0.54% (-1.28 to 0.19) P = 0.15	-0.39% (-1.10 to 0.32) P = 0.28	0.78
Peak $\dot{V}O_2$ (per 100 mL/min)	-0.78% (-1.85 to 0.29) P = 0.16	-0.77% (-1.63 to 0.09) P = 0.08	-0.17% (-1.03 to 0.69) P = 0.70	0.61
Peak heart rate (per 10 beats/min)	0.52% (-1.49 to 2.53) P = 0.61	0.30% (-1.15 to 1.75) P = 0.69	-0.48% (-1.96 to 0.99) P = 0.52	0.61
Body Weight (per 10 kg)	-2.30% (-4.99 to 0.40) P = 0.10	-0.39% (-2.59 to 1.81) P = 0.72	1.35% (-1.35 to 4.05) P = 0.32	0.15
Hemoglobin (per 1 g/dL) [a]	-0.80% (-3.63 to 2.03) P = 0.58	0.80% (-1.76 to 3.36) P = 0.54	1.60% (-1.46 to 4.65) P = 0.30	0.48

[a] different n (due to missing values) for the analyses including hemoglobin (high-intensity interval training: 50 patients, moderate continuous training: 53 patients; guideline control: 52 patients)

Appendix L: Relationships between changes in relative peak oxygen consumption ($\dot{V}O_2$) and baseline values of peak O_2-pulse [A], relative peak $\dot{V}O_2$ [B], absolute peak $\dot{V}O_2$ [C], peak heart rate (HR) [D], body weight [E], and hemoglobin [F] in the per-protocol analysis (adapted from Mueller et al.[242])



Individual relationships, robust linear regression lines and 95% confidence bands are shown separately for exercise training (– Δ –) and guideline control (–○–)

Appendix M: Associations between changes in peak oxygen consumption ($\dot{V}O_2$), changes in peak heart rate (HR), changes in peak O_2-pulse, and changes in body weight among all patients and within patients randomized to exercise training and guideline control (adapted from Mueller et al.[242])

	ß-coefficient (95 % CI), P-value			
	All Patients [N = 158]	**Exercise Training (ET) [N = 106]**	**Guideline Control (CON) [N = 52]**	**Interaction P for ET vs. CON**
Mean change in peak $\dot{V}O_2$ for every 1% change in peak HR	0.64% (0.47 to 0.81) P < 0.001	0.61% (0.40 to 0.81) P < 0.001	0.67% (0.40 to 0.95) P < 0.001	0.77
Mean change in peak $\dot{V}O_2$ for every 1% change in peak O_2-pulse	0.80% (0.69 to 0.91) P < 0.001	0.78% (0.61 to 0.94) P < 0.001	0.77% (0.61 to 0.93) P < 0.001	0.80
Mean change in peak $\dot{V}O_2$ for every 1% change in Body Weight	-2.39% (1.46 to 3.32) P < 0.001	-2.14% (-3.31 to -0.97) P < 0.001	-1.77% (-3.24 to -0.30) P = 0.02	0.70
Mean change in peak O_2-pulse for every 1% change in peak HR	-0.36% (-0.52 to -0.20) P < 0.001	-0.38% (-0.57 to -0.19) P < 0.001	-0.36% (-0.65 to -0.08) P = 0.02	0.95
Mean change in peak HR for every 1% change in weight	-0.56% (-1.17 to 0.05) P = 0.08	-0.38% (-1.18 to 0.43) P = 0.39	-0.71% (-1.68 to 0.26) P = 0.14	0.59
Mean change in peak O_2-pulse for every 1% change in weight	-0.34% (-1.21 to 0.52) P = 0.45	-0.02% (-1.06 to 1.02) P = 0.97	-0.06% (-1.59 to 1.46) P = 0.94	0.96

Annex I – Main Publication of the OptimEx-Clin trial

of

"***Mueller S***, *Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM, Esefeld K, von Korn P, Christle JW, Haykowsky MJ, Linke A, Wisløff U, Adams V, Pieske B, van Craenenbroeck EM, Halle M; OptimEx-Clin Study Group. 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(6):542-51*"[234].

Original Publication

Research

JAMA | Original Investigation

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

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IMPORTANCE Endurance exercise is effective in improving peak oxygen consumption (peak $\dot{V}O_2$) in patients with heart failure with preserved ejection fraction (HFpEF). However, it remains unknown whether differing modes of exercise have different effects.

OBJECTIVE To determine whether high-intensity interval training, moderate continuous training, and guideline-based advice on physical activity have different effects on change in peak $\dot{V}O_2$ in patients with HFpEF.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at 5 sites (Berlin, Leipzig, and Munich, Germany; Antwerp, Belgium; and Trondheim, Norway) from July 2014 to September 2018. From 532 screened patients, 180 sedentary patients with chronic, stable HFpEF were enrolled. Outcomes were analyzed by core laboratories blinded to treatment groups; however, the patients and staff conducting the evaluations were not blinded.

INTERVENTIONS Patients were randomly assigned (1:1:1; n = 60 per group) to high-intensity interval training (3 × 38 minutes/week), moderate continuous training (5 × 40 minutes/week), or guideline control (1-time advice on physical activity according to guidelines) for 12 months (3 months in clinic followed by 9 months telemedically supervised home-based exercise).

MAIN OUTCOMES AND MEASURES Primary end point was change in peak $\dot{V}O_2$ after 3 months, with the minimal clinically important difference set at 2.5 mL/kg/min. Secondary end points included changes in metrics of cardiorespiratory fitness, diastolic function, and natriuretic peptides after 3 and 12 months.

RESULTS Among 180 patients who were randomized (mean age, 70 years; 120 women [67%]), 166 (92%) and 154 (86%) completed evaluation at 3 and 12 months, respectively. Change in peak $\dot{V}O_2$ over 3 months for high-intensity interval training vs guideline control was 1.1 vs −0.6 mL/kg/min (difference, 1.5 [95% CI, 0.4 to 2.7]); for moderate continuous training vs guideline control, 1.6 vs −0.6 mL/kg/min (difference, 2.0 [95% CI, 0.9 to 3.1]); and for high-intensity interval training vs moderate continuous training, 1.1 vs 1.6 mL/kg/min (difference, −0.4 [95% CI, −1.4 to 0.6]). No comparisons were statistically significant after 12 months. There were no significant changes in diastolic function or natriuretic peptides. Acute coronary syndrome was recorded in 4 high-intensity interval training patients (7%), 3 moderate continuous training patients (5%), and 5 guideline control patients (8%).

CONCLUSIONS AND RELEVANCE Among patients with HFpEF, there was no statistically significant difference in change in peak $\dot{V}O_2$ at 3 months between those assigned to high-intensity interval vs moderate continuous training, and neither group met the prespecified minimal clinically important difference compared with the guideline control. These findings do not support either high-intensity interval training or moderate continuous training compared with guideline-based physical activity for patients with HFpEF.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02078947

Visual Abstract

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Supplemental content

CME Quiz at jamacmelookup.com

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JAMA. 2021;325(6):542-551. doi:10.1001/jama.2020.26812

Heart failure (HF) affects more than 2% of the global adult population and resulted in 809 000 hospitalizations in the US in 2016.[1] An analysis of 28 820 patients from different cohort studies[2] (inclusion between 1979 and 2002; followed for up to 15 years) demonstrated that approximately 50% of patients with incident HF had a preserved ejection fraction (HFpEF) and based on data from community surveillance in 4 US communities (2005 to 2009), 47% of hospitalizations for incident HF events were due to HFpEF.[3] The prevalence of HFpEF is projected to further increase, primarily driven by an aging population.[1] Additional risk factors include hypertension, previous myocardial infarction, diabetes, obesity, and sedentary lifestyle.[2,4]

A cardinal feature of HFpEF is reduced exercise tolerance associated with reduced quality of life (QoL).[5] While pharmacological therapy for HFpEF has been unsuccessful,[6] exercise training has been shown to be effective in improving maximal exercise capacity assessed as peak oxygen consumption (peak $\dot{V}O_2$) in clinically stable patients with HFpEF. However, the few trials performed to date have only involved smaller sample sizes (≤100 patients) and limited exercise intervention periods (≤24 weeks).[7-10] To date, only 1 trial in 11 patients with HFpEF examined the effect of a 1-year exercise intervention.[11] Moreover, high-intensity interval training may be superior to traditionally prescribed moderate continuous training to improve peak $\dot{V}O_2$ and diastolic function in these patients.[9,10,12]

Given the uncertainty of the role of exercise intensity and duration of training in HFpEF, the aim of this trial was to test whether high-intensity interval training, moderate continuous training, and guideline-based advice on physical activity (guideline control) result in different changes in peak $\dot{V}O_2$ and other cardiopulmonary exercise test parameters, indices of left ventricular (LV) diastolic function, N-terminal pro-brain natriuretic peptide (NT-proBNP), and QoL after 3 and 12 months.

Key Points

Question Is there a difference in change in peak oxygen consumption ($\dot{V}O_2$) among patients with heart failure with preserved ejection fraction (HFpEF) treated with differing modes of exercise?

Findings This randomized clinical trial included 180 patients with HFpEF assigned to high-intensity interval training, moderate continuous training, or a control of guideline-based physical activity advice. At 3 months, the changes in peak $\dot{V}O_2$ were 1.1, 1.6, and −0.6 mL/kg/min, respectively. There was no statistically significant difference between high-intensity interval and moderate continuous training, and neither group met the a priori–defined minimal clinically important difference of 2.5 mL/kg/min compared with the guideline control.

Meaning These findings do not support either high-intensity interval training or moderate continuous training compared with guideline-based physical activity for patients with HFpEF.

Methods

Trial Oversight

OptimEx-Clin (Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure; European OptimEx Consortium; European Framework Program 7, grant No. EU 602405-2) was a randomized, multicenter trial with 3 groups conducted at 5 European sites (Berlin, Leipzig, and Munich, Germany; Antwerp, Belgium; and Trondheim, Norway) assessing different exercise intensities in patients with HFpEF over 3 months in clinic followed by 9 months of telemedically supervised home-based training. A detailed description of the study design has been previously published[13] and the study protocol can be found in Supplement 1. The study was approved by the local ethics committees for medical research at all participating sites. All participants provided written informed consent.

Patients

Sedentary patients with signs and symptoms of HFpEF (exertional dyspnea [New York Heart Association class II-III], LVEF of 50% or greater, and elevated estimated LV filling pressure [E/e′ medial ≥15] or E/e′ medial of 8 or greater with concurrent elevated natriuretic peptides [NT-proBNP ≥220 pg/mL or BNP ≥80 pg/mL])[14] were eligible to participate in the trial.

Randomization

A web-based system was used to assign patients in a 1:1:1 ratio to high-intensity interval training, moderate continuous training, or guideline control. Randomization was stratified by study site using block sizes of 12 (first block) and 6 (following blocks).

Intervention

High-intensity interval training was scheduled 3 times per week for 38 minutes per session (10-minute warm-up at 35%-50% of heart rate reserve, 4 × 4-minute intervals at 80%-90% of heart rate reserve, interspaced by 3 minutes of active recovery), while moderate continuous training was scheduled 5 times per week for 40 minutes per session (35%-50% of heart rate reserve). Patients assigned to guideline control received 1-time advice on physical activity according to guidelines.[15]

Individual exercise intensity was determined by a maximal cardiopulmonary exercise test at baseline and was adapted after 6 weeks, 3 months, and 6 months of exercise training based on repeated cardiopulmonary exercise tests. In contrast to the initial study design[13] (exercise intensity based on the percentage of maximum heart rate), we applied percentage of heart rate reserve because of known high prevalence of chronotropic incompetence in patients with HFpEF. In patients with atrial fibrillation, a constant workload was determined based on Borg Rating of Perceived Exertion Scale scores 15-17 (high-intensity intervals) or 11-13 (moderate continuous training).

From months 1 through 3, supervised training was offered thrice per week. Patients in the moderate continuous training group additionally performed 2 home-based sessions per week on stationary cycle ergometers. From months 4 through 12, training sessions were continued at home with the same exercise protocol as performed during the in-clinic phase. Training intensities were documented via telemonitoring with a heart rate sensor (Polar H7, Polar Electro GmbH) and connected to a mobile phone (iPhone 4S, Apple Inc) and a telemedicine database (vitaphone GmbH part of vitagroup AG) to enable immediate

feedback to patients. In case of a decline in attendance to less than 70% of scheduled exercise sessions or a decline in exercise intensity during sessions, patients were encouraged by telephone contact to increase adherence to meet study targets.

Clinical Assessments

All patients were assessed at baseline and 3, 6, and 12 months after randomization. Examinations were performed according to standard operating procedures and included medical history, physical examination, anthropometry, electrocardiogram, blood analysis, cardiopulmonary exercise testing, echocardiography, and the Kansas City Cardiomyopathy Questionnaire (KCCQ). The staff members conducting the evaluations were not blinded to treatment groups.

Cardiopulmonary exercise testing was performed according to current recommendations[16] and analyzed in a blinded manner at the study core laboratory in Munich. Peak $\dot{V}O_2$ was defined as the highest 30-second average within the last minute of exercise.[17] The first ventilatory threshold (VT_1) was set by the V-slope method[18] and the minute ventilation to carbon dioxide production slope ($\dot{V}E/\dot{V}CO_2$ slope) was calculated using the entire exercise data.

Echocardiography was performed by experienced and instructed sonographers. Study inclusion was based on on-site measures of LVEF and E/e' medial. All echocardiograhic analyses were performed centrally by the Academic Echocardiography Core Lab at Charité Berlin, blinded to treatment group assignment. Local NT-proBNP values were used for study inclusion; all NT-proBNP values reported were analyzed by a central core laboratory (Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria).

Outcomes

The primary end point was the change in peak $\dot{V}O_2$ after 3 months. Secondary end points included changes from baseline to 3 and 12 months for echocardiographic measures of diastolic function (E/e' medial, e' medial, left atrial volume index), NT-proBNP, cardiopulmonary exercise testing parameters (peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, submaximal workload at VT_1), and the health-related QoL domain of the KCCQ (score range: 0-100, higher scores reflect better QoL; minimal clinically important difference: 5 points[19]). The additional secondary end points of changes in flow-mediated dilatation from baseline to 3 and 12 months were obtained only in a subgroup of patients and are not reported here. Adverse events and serious adverse events were documented and categorized in each study site and then evaluated by an independent safety committee.

Statistics

The trial protocol defined 2.5 mL/kg/min as the smallest $\dot{V}O_2$ effect that would be important to detect, stating that any smaller effect would not be of clinical or substantive importance. Based on this and on the findings of a pilot study,[20] a mean (SD) difference in change of peak $\dot{V}O_2$ of 2.5 (3.5) mL/kg/min between moderate continuous training and guideline control was assumed. By assuming an additional mean (SD) difference of 2.5 (3.5) mL/kg/min between high-intensity interval training and moderate continuous training, a power of at least 90% for pairwise group comparisons was able to be obtained with a sample size of 45 patients per group (α = 5%). As a moderate number of missing values was expected and due to the multicenter design, a total number of 180 patients (60 per group) was intended to be included in the study.

For analysis of the primary end point, analysis of variance was prespecified in a first step to compare means of all groups using a significance level of α = 5%. Performance of pairwise mean comparisons with *t* tests for independent samples were planned, only if the global null hypothesis of all group means being equal could be rejected (α = 5%, 2-sided, closed testing principle). All patients were analyzed according to their randomization group. To account for missing values in the primary end point variable (peak $\dot{V}O_2$ at 3 months), a prespecified multiple imputation approach was performed (for details, see eMethods in Supplement 2). In a sensitivity analysis, only patients with complete paired baseline and 3-month follow-up peak $\dot{V}O_2$ measures were included.

For all secondary end points, analysis of variance was performed to compare mean changes between all 3 study groups considering all available data, and 95% CIs for differences in mean changes between groups are presented. CIs have not been adjusted for multiplicity; therefore, analyses of secondary end points should be interpreted as exploratory. The analysis of the primary end point was repeated within prespecified subgroups (center, sex, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared], age, baseline E/e', and baseline peak $\dot{V}O_2$) considering complete cases only, and tests for interaction between these variables and study group were performed by fitting corresponding linear regression models to the data. Furthermore, we performed a per-protocol analysis including only patients with adherence of 70% or greater to the scheduled exercise sessions. All statistical analyses were performed using R Statistical Software (Version 3.6.0; Foundation for Statistical Computing).

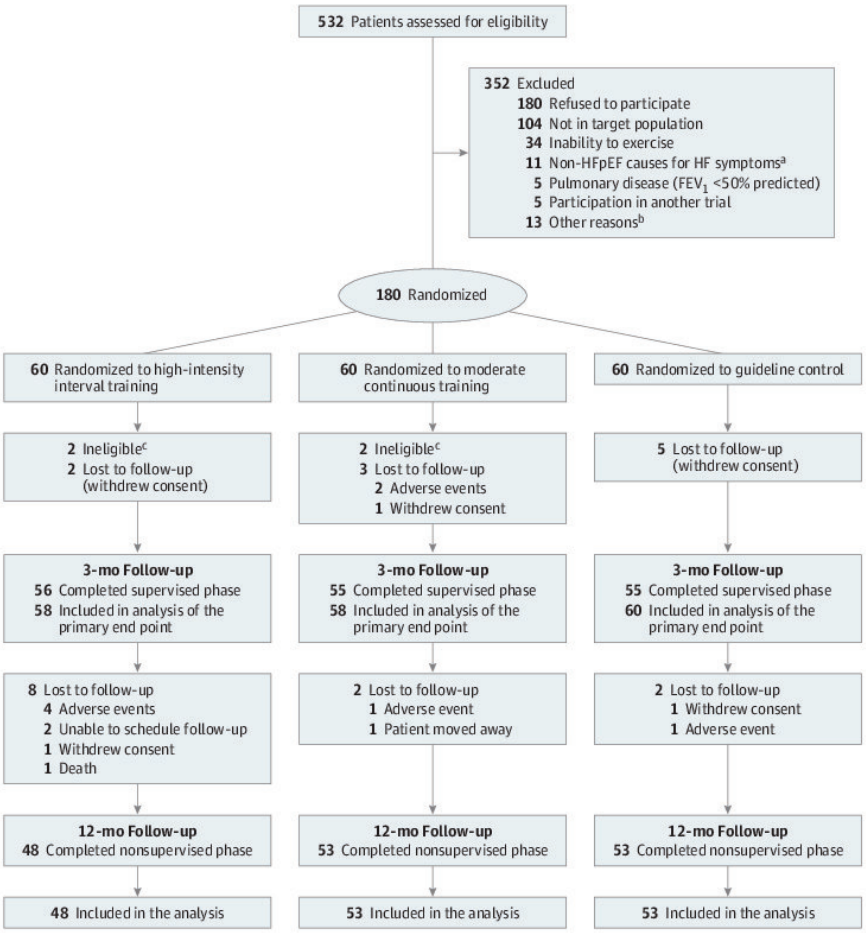
Results

Inclusion of patients started in July 2014 and the last patient completed the trial in September 2018. From 532 screenings, 180 patients were enrolled in the trial. Four participants not meeting HFpEF criteria[14] (eTable 1 in Supplement 2) were excluded from analysis after blinded review of eligibility for all participants based on their status before randomization.[21] Ten patients were lost to follow-up at 3 months, and an additional 12 lost to follow-up at 12 months (**Figure 1**). We recruited a typical HFpEF population of elderly, predominantly female patients with overweight/obesity with a typical risk and comorbidity background. Baseline patient demographic and clinical characteristics (mean age, 70 years; 120 women [67%]; mean BMI, 30.0; mean E/e' medial, 15.8; mean NT-proBNP, 671 pg/mL; mean peak $\dot{V}O_2$, 18.8 mL/kg/min) are shown in **Table 1**.

Primary Outcome

After 3 months of intervention, change in peak $\dot{V}O_2$ differed significantly between the groups (mean [SD] for high-intensity

Figure 1. Patient Recruitment, Randomization, and Follow-up in the OptimEx-Clin Study



FEV_1 indicates forced expiratory volume in first second of expiration; HF, heart failure; and HFpEF, heart failure with preserved ejection fraction.

[a] Non-HFpEF causes for HF symptoms included significant valvular disease, coronary disease, uncontrolled hypertension or arrhythmia, or primary cardiomyopathies.

[b] The other reasons were signs of ischemia during cardiopulmonary exercise testing (n = 3), comorbidities that may influence 1-year prognosis (n = 3), upcoming planned surgery (n = 2), social reasons (n = 2), concerns about patient's ability to adhere and compliance (n = 1), recurrent syncopes (n = 1), and planned travel (n = 1).

[c] Removed after blinded review of eligibility of all patients.

interval training: 1.1 [3.0] mL/kg/min; moderate continuous training: 1.6 [2.5] mL/kg/min; guideline control: −0.6 [3.3] mL/kg/min; $P = .002$). Pairwise comparisons showed significantly higher changes in high-intensity interval training vs guideline control (difference in mean changes: 1.5 mL/kg/min [95% CI, 0.4 to 2.7], $P = .01$) and moderate continuous training vs guideline control (2.0 mL/kg/min [95% CI, 0.9 to 3.1], $P = .001$) with no significant difference between high-intensity interval training and moderate continuous training (−0.4 mL/kg/min [95% CI, −1.4 to 0.6], $P = .41$) (**Figure 2**A, **Table 2**). Subgroup analysis for change in peak $\dot{V}O_2$ after 3 months did not show any significant interactions of relevant characteristics with study group (eFigure 1 and eTable 2 in Supplement 2).

Secondary Outcomes

After 12 months, the change in peak $\dot{V}O_2$ (Figure 2A, **Table 3**) was not significantly different between the groups (mean [SD] for high-intensity interval training: 0.9 [3.0] mL/kg/min, moderate continuous training: 0 [3.1] mL/kg/min, guideline control: −0.6 [3.4] mL/kg/min, $P = .11$). The change in workload at VT_1 after 3 months (Table 2) was significantly higher in the moderate continuous training group compared with the guideline control group (6 W [95% CI, 2 to 11]) without significant differences between high-intensity interval training and guideline control (3 W [95% CI, −2 to 7]) and between high-intensity interval training and moderate continuous training (−4 W [95% CI, −9 to 1]). No significant differences between groups were observed after 12 months (Table 3). Change in $\dot{V}E/\dot{V}CO_2$ slope after 3 months was not significantly different between groups (Table 2). There were no significant differences for changes in any echocardiographic parameters of diastolic function between the groups (Figure 2B, Tables 2 and 3). Moreover, the change in NT-proBNP did not significantly differ between the groups (Figure 2C, Tables 2 and 3). Changes in the QoL domain of the KCCQ did not significantly differ between groups after 3 months of exercise intervention (Figure 2D, Table 2). However, after 12 months, the change in the QoL domain was significantly higher in moderate continuous training compared with guideline control (11 [95% CI, 2 to 19]) without significant differences between high-intensity interval training and guideline control (4 [95% CI,

Table 1. Demographic and Clinical Characteristics at Baseline

Characteristic	No. (%)		
	High-intensity interval training (n = 58)[a]	Moderate continuous training (n = 58)[a]	Guideline control (n = 60)[a]
Sex			
Female	41 (71)	35 (60)	41 (68)
Male	17 (29)	23 (40)	19 (32)
Age at inclusion, mean (SD), y	70 (7)	70 (8)	69 (10)
Body mass index, mean (SD)[b]	30.0 (5.7)	31.1 (6.2)	29.0 (4.7)
Resting heart rate, mean (SD), beats/min	65 (12)	65 (10)	65 (11)
Blood pressure, mean (SD), mm Hg			
Systolic	127 (14)	131 (13)	127 (14)
Diastolic	74(11)	75 (10)	74 (10)
New York Heart Association class[c]			
II: mild symptoms	44 (76)	44 (76)	42 (70)
III: marked symptoms	14 (24)	14 (24)	18 (30)
Cardiovascular risk factors			
Hypertension	50 (86)	49 (84)	51 (85)
Hyperlipidemia	38 (66)	40 (69)	45 (75)
Diabetes	16 (28)	16 (28)	14 (23)
Smoking			
No (never smoked)	30 (52)	32 (55)	35 (58)
Ex-smoker	25 (43)	23 (40)	23 (38)
Current	3 (5)	3 (5)	2 (3)
Cardiovascular disease			
Coronary artery disease	15 (26)	18 (31)	17 (28)
Atrial fibrillation			
Paroxysmal	10 (17)	5 (9)	8 (14)
Persistent	4 (7)	6 (10)	3 (5)
Permanent	6 (10)	5 (8)	2 (3)
Sleep apnea syndrome	11 (19)	11 (19)	11 (18)
Peripheral artery disease	3 (5)	4 (7)	2 (3)
Heart failure medication			
β-Blockers	40 (69)	34 (59)	40 (67)
Thiazide/loop diuretics	36 (62)	30 (52)	34 (57)
Angiotensin receptor blocker	25 (43)	26 (45)	24 (40)
Angiotensin-converting enzyme inhibitor	19 (33)	18 (31)	17 (28)
Aldosterone antagonists	8 (14)	6 (10)	5 (8)
Echocardiography, mean (SD) [No.]			
E/e' medial	15.8 (3.7) [57]	15.9 (4.1) [58]	15.7 (5.6) [57]
e' medial, cm/s	6.2 (1.8) [57]	6.1 (1.6) [58]	6.3 (1.8) [57]
Left atrial volume index, mL/m^2	35.4 (9.0) [39]	37.9 (13.0) [42]	39.8 (13.5) [48]
E/A	1.3 (0.8) [47]	1.1 (0.4) [48]	1.1 (0.6) [54]
Others			
NT-proBNP			
Mean (SD), pg/mL [No.]	475 (522) [57]	656 (806) [55]	875 (1950) [59]
Median (IQR), pg/mL [No.]	281 (130-654) [57]	414 (199-751) [55]	321 (171-578) [59]
KCCQ QoL domain, mean (SD) [No.][d]	68.0 (24.2) [58]	62.2 (26.2) [56]	65.7 (20.4) [58]

Abbreviations: A, peak velocity flow in late diastole caused by atrial contraction; E, peak velocity blood flow from ventricular relaxation in early diastole; e', mitral annular early diastolic velocity; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; QoL, quality of life.

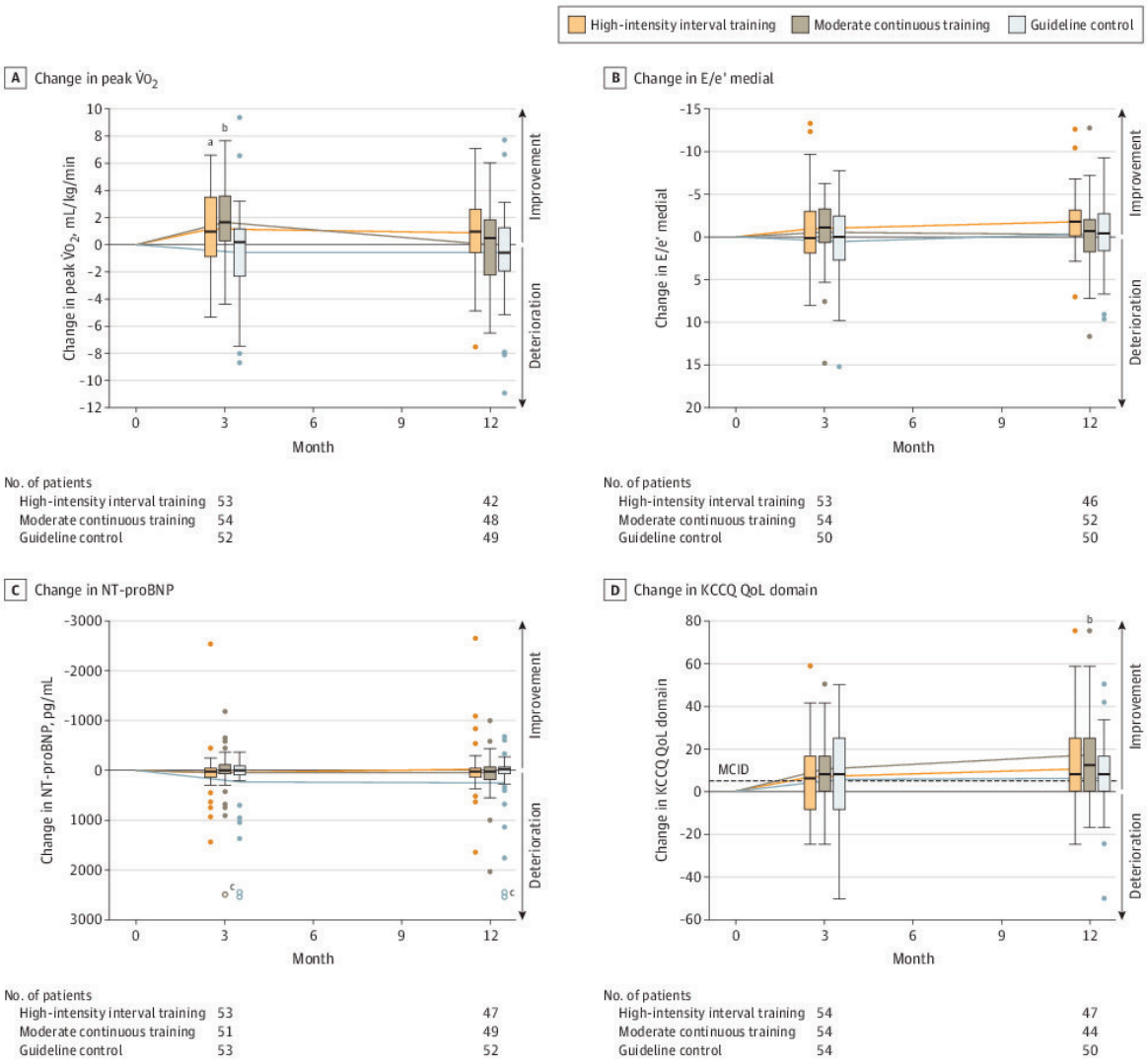
[a] Data are presented as absolute (relative) frequency, mean (SD) or median (IQR). Data for echocardiography, NT-proBNP and KCCQ have been analyzed at the corresponding core labs.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] New York Heart Association functional class quantifies the severity of functional limitation. Class I indicates no limiting symptoms with ordinary activity; class II, mild symptoms with ordinary activity; class III, marked symptoms with ordinary activity; and class IV, severe symptoms during ordinary activity with symptoms even at rest.

[d] Higher scores indicate better QoL (score range, 0-100, minimal clinically important difference, 5 points).

Figure 2. Changes in Peak Oxygen Consumption ($\dot{V}O_2$), Estimated Left Ventricular Filling Pressure (E/e' Medial), N-Terminal Pro–Brain Natriuretic Peptide (NT-proBNP), and Kansas City Cardiomyopathy Questionnaire (KCCQ) Quality of Life (QoL) at 3 and 12 Months



No. of patients

High-intensity interval training	53	42
Moderate continuous training	54	48
Guideline control	52	49

No. of patients

High-intensity interval training	53	46
Moderate continuous training	54	52
Guideline control	50	50

No. of patients

High-intensity interval training	53	47
Moderate continuous training	51	49
Guideline control	53	52

No. of patients

High-intensity interval training	54	47
Moderate continuous training	54	44
Guideline control	54	50

Changes are calculated from baseline to 3 and 12 months of intervention within each group (solid lines connect the mean changes from baseline to 3 months and baseline to 12 months). In the KCCQ, higher scores indicate better QoL (score range, 0-100; minimal clinically important difference [MCID, dashed line], 5 points).

[a] Significant difference ($P < .05$) in change between high-intensity interval training and guideline control.

[b] Significant difference ($P < .05$) in change between moderate continuous training and guideline control.

[c] Open points are at 3586 pg/mL (moderate continuous training, change to 3 months), 4133 and 5783 pg/mL (guideline control, change to 3 months), 4134 and 7063 pg/mL (guideline control, change to 12 months).

−3 to 12]) or high-intensity interval training and moderate continuous training (−6 [95% CI, −15 to 2]; Figure 2D, Table 3). Additional data for cardiopulmonary exercise testing, echocardiography, and KCCQ are provided in eTables 3, 4, and 5, respectively, in Supplement 2.

Adherence and Per-Protocol Analysis

Of those patients completing the 3-month follow-up (56 in the high-intensity interval training group, 55 in the moderate continuous training group; Figure 1), 45 (80.4%) doing high-intensity interval training and 42 (76.4%) doing moderate continuous training performed at least 70% of exercise sessions. Patients randomized to high-intensity interval training performed a median of 2.5 sessions (interquartile range [IQR], 2.1-2.8) or 96 minutes (IQR, 82-105) per week, while patients randomized to moderate continuous training performed 4.4 sessions (IQR, 3.4-4.7) or 176 minutes (IQR, 137-188) per week. During the home-based phase (months

Table 2. Primary and Secondary End Points After 3 Months

	Mean (SD) [sample size]									Difference (95% CI) [sample size]		
	HIIT			MCT			Guideline control					
	Baseline	3 mo	Difference	Baseline	3 mo	Difference	Baseline	3 mo	Difference	HIIT vs guideline control	MCT vs guideline control	HIIT vs MCT
Primary outcome												
Peak $\dot{V}o_2$, mL/kg/min	18.9 (5.4) [58]	20.2 (6.0) [53]	1.1 (3.0) [53]	18.2 (5.1) [58]	19.8 (5.8) [54]	1.6 (2.5) [54]	19.4 (5.6) [60]	18.9 (5.7) [52]	−0.6 (3.3) [52]	1.5 (0.4 to 2.7) [118][a]	2.0 (0.9 to 3.1) [118][a]	−0.4 (−1.4 to 0.6) [116][a]
										1.8 (0.5 to 3.0) [105][b]	2.3 (1.1 to 3.4) [106][b]	−0.5 (−1.5 to 0.6) [107][b]
Secondary outcomes												
$\dot{V}E/\dot{V}co_2$ slope	34.5 (7.9) [58]	35.0 (9.8) [53]	0.7 (4.4) [53]	34.2 (7.2) [58]	33.7 (6.8) [54]	−0.7 (4.4) [54]	33.2 (5.9) [59]	32.6 (5.3) [51]	−1.0 (5.4) [51]	1.7 (−0.2 to 3.6) [104]	0.2 (−1.7 to 2.2) [105]	1.5 (−0.3 to 3.2) [107]
Workload at VT_1, W	45 (17) [58]	49 (18) [53]	4 (12) [53]	46 (21) [57]	53 (25) [53]	8 (13) [52]	45 (15) [58]	47 (16) [50]	1 (10) [50]	3 (−2 to 7) [103]	6 (2 to 11) [102]	−4 (−9 to 1) [105]
E/e' medial	15.8 (3.7) [57]	15.2 (4.8) [54]	−0.9 (4.5) [53]	15.9 (4.1) [58]	15.6 (5.0) [54]	−0.5 (3.7) [54]	15.7 (5.6) [57]	16.5 (7.2) [53]	0.6 (4.6) [50]	−1.5 (−3.2 to 0.3) [103]	−1.1 (−2.7 to 0.5) [104]	−0.4 (−1.9 to 1.2) [107]
e' medial, cm/s	6.2 (1.8) [57]	6.23 (1.72) [54]	0.0 (1.7) [53]	6.1 (1.6) [58]	5.95 (1.65) [54]	−0.1 (1.3) [54]	6.3 (1.8) [57]	5.95 (1.84) [53]	−0.3 (1.5) [50]	0.3 (−0.3 to 1.0) [103]	0.2 (−0.3 to 0.8) [104]	0.1 (−0.5 to 0.7) [107]
LAVI, mL/m^2	35.4 (9.0) [39]	35.2 (10.2) [34]	−0.4 (4.0) [26]	37.9 (13.0) [42]	36.8 (10.5) [28]	0.5 (4.1) [25]	39.8 (13.5) [48]	38.4 (14.7) [40]	−0.7 (4.0) [35]	0.3 (−1.7 to 2.4) [61]	1.2 (−0.9 to 3.4) [60]	−0.9 (−3.2 to 1.4) [51]
NT-proBNP, pg/mL	475 (522) [57]	520 (646) [53]	25 (469) [53]	656 (806) [55]	695 (1212) [53]	43 (598) [53]	875 (1950) [59]	1164 (2871) [53]	226 (1010) [53]	−201 (−505 to 104) [106]	−183 (−505 to 139) [106]	−18 (−228 to 192) [106]
KCCQ QoL domain[c]	68 (24) [58]	73 (26) [54]	7 (21) [54]	62 (26) [56]	72 (21) [55]	10 (17) [54]	66 (20) [58]	72 (23) [55]	6 (21) [54]	1.0 (−7.2 to 9.2) [108]	4.8 (−2.6 to 12.2) [108]	−3.8 (−11.2 to 3.6) [108]

Abbreviations: E, peak velocity blood flow from ventricular relaxation in early diastole; e', mitral annular early diastolic velocity; HIIT, high-intensity interval training; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; MCT, moderate continuous training; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; QoL, quality of life; $\dot{V}E/\dot{V}co_2$ slope, minute ventilation to carbon dioxide output slope; $\dot{V}o2$, oxygen consumption; VT_1, ventilatory threshold.

[a] Results of the primary analysis using a prespecified multiple imputation approach for missing values.

[b] Results of the complete case analysis for the primary end point considering all available data (without imputation).

[c] Higher scores indicate better QoL (score range, 0-100; minimal clinically important difference, 5 points).

4-12), adherence dropped to 2.0 sessions (IQR, 1.2-2.4) or 77 minutes (IQR, 46 - 92) per week in the high-intensity interval training group and 3.6 sessions (IQR, 2.7-4.3) or 144 minutes (IQR, 108-171) per week in the moderate continuous training group. Of the 48 high-intensity interval training and 53 moderate continuous training patients who completed the full training program (12 months, see Figure 1), 27 (56.3%) and 32 (60.4%) patients performed at least 70% of exercise sessions, respectively (eFigure 2 and eTable 6 in Supplement 2). Drop offs in adherence to less than 70% of scheduled exercise sessions were mainly due to clinical reasons (n = 60) and personal reasons such as vacation (n = 20), motivational problems (n = 12), and trouble with the ergometer or telemedical device (n = 2) (multiple responses possible). Results of the per-protocol analysis were similar to the main results of the trial (eTable 7 in Supplement 2).

Adverse Events

There were adverse events in 102 patients (58%) (high-intensity interval training: 36 patients [62%], moderate continuous training: 39 patients [67%], guideline control: 27 patients [45%]). Moreover, 52 patients (30%) experienced events that were classified as serious adverse events (high-intensity interval training: 18 patients [31%], moderate continuous training: 18 patients [31%], guideline control: 16 patients [27%]). Acute coronary syndrome was the most common cardiovascular adverse event (high-intensity interval training: 4 patients [7%], moderate continuous training: 3 patients [5%], guideline control: 5 patients [8%]). Worsening heart failure occurred in 3 patients (5%) of each group. Atrial fibrillation was observed in 4 (7%), 3 (5%), and 2 (3%) patients randomized to high-intensity interval training, moderate continuous training, and guideline control, respectively (eTable 8 in Supplement 2). There was 1 cardiac death in the high-intensity interval training group (unrelated to exercise) and 6 events that occurred during (moderate continuous training: atrial fibrillation, syncope, back pain; high-intensity interval training: compression of the coccyx due to a fall while alighting the bicycle ergometer, muscle weakness) or within 2 hours after exercise training (high-intensity interval training: occlusion of peripheral bypass). An overview of adverse events and serious adverse events is provided in eTables 8 and 9 in Supplement 2.

Table 3. Group Differences in Exploratory End Points After 12 Months

Secondary outcome	Mean (SD) [sample size]									Difference (95% CI) [sample size]		
	HIIT			MCT			Guideline control			HIIT vs guideline control	MCT vs guideline control	HIIT vs MCT
	Baseline	12 mo	Difference	Baseline	12 mo	Difference	Baseline	12 mo	Difference			
Peak $\dot{V}O_2$, mL/kg/min	18.9 (5.4) [58]	19.9 (6.1) [42]	0.9 (3.0) [42]	18.2 (5.1) [58]	18.1 (5.9) [48]	0 (3.1) [48]	19.4 (5.6) [60]	19.5 (5.1) [49]	−0.6 (3.4) [49]	1.4 (0.1 to 2.8) [91]	0.6 (−0.7 to 1.9) [97]	0.8 (−0.5 to 2.1) [90]
$\dot{V}E/\dot{V}CO_2$ slope	34.5 (7.9) [58]	36.6 (8.4) [42]	2.0 (5.1) [42]	34.2 (7.2) [58]	33.9 (7.1) [48]	−0.7 (4.6) [48]	33.2 (5.9) [59]	34.3 (7.4) [49]	1.1 (4.9) [49]	0.9 (−1.2 to 3.0) [91]	−1.9 (−3.8 to 0.0) [97]	2.8 (0.7 to 4.8) [90]
Workload at VT_1, W	45 (17) [58]	46 (17) [41]	1 (12) [41]	46 (21) [57]	45 (21) [47]	−1 (12) [46]	45 (15) [58]	43 (14) [49]	−3 (11) [49]	4 (−1 to 9) [90]	3 (−2 to 7) [95]	2 (−4 to 7) [87]
E/e' medial	15.8 (3.7) [57]	14.2 (3.9) [47]	−1.8 (3.3) [46]	15.9 (4.1) [58]	15.6 (4.4) [52]	−0.3 (4.2) [52]	15.7 (5.6) [57]	15.7 (5.5) [52]	−0.4 (4.0) [50]	−1.4 (−2.9 to 0.1) [96]	0.1 (−1.5 to 1.7) [102]	−1.5 (−3.0 to 0.0) [98]
e' medial, cm/s	6.2 (1.8) [57]	6.2 (1.7) [47]	0.1 (1.5) [46]	6.1 (1.6) [58]	5.9 (1.5) [52]	−0.2 (1.1) [52]	6.3 (1.8) [57]	6.1 (1.7) [52]	−0.2 (1.5) [50]	0.3 (−0.3 to 0.9) [96]	0.0 (−0.5 to 0.5) [102]	0.3 (−0.2 to 0.9) [98]
LAVI, mL/m^2	35.4 (9.0) [39]	37.4 (10.9) [26]	0.7 (5.8) [21]	37.9 (13.0) [42]	36.6 (9.2) [23]	1.2 (3.8) [20]	39.8 (13.5) [48]	39.2 (1.8) [38]	0.3 (5.2) [33]	0.4 (−2.7 to 3.5) [54]	0.9 (−1.6 to 3.3) [53]	−0.5 (−3.5 to 2.6) [41]
NT-proBNP, pg/mL	475 (522) [57]	471 (468) [47]	−24 (539) [47]	656 (806) [55]	698 (1026) [52]	42 (422) [49]	875 (1950) [59]	1037 (1026) [52]	237 (1177) [52]	−261 (−622 to 100) [99]	−195 (−543 to 152) [101]	−66 (−263 to 131) [96]
KCCQ QoL domain[a]	68 (24) [58]	80 (21) [47]	11 (20) [47]	62 (26) [56]	77 (19) [45]	17 (21) [44]	66 (20) [58]	72 (24) [51]	6 (18) [50]	4 (−3 to 12) [97]	11 (2 to 19) [94]	−6 (−15 to 2) [91]

Abbreviations: E, peak velocity blood flow from ventricular relaxation in early diastole; e', mitral annular early diastolic velocity; HIIT, high-intensity interval training; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; MCT, moderate continuous training; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; QoL, quality of life; $\dot{V}O_2$, oxygen consumption; $\dot{V}E/\dot{V}CO_2$ slope, minute ventilation to carbon dioxide output slope; VT_1, ventilatory threshold.

[a] Higher scores indicate better QoL (score range, 0-100; minimal clinically important difference, 5 points).

Discussion

Among patients with HFpEF, changes in peak $\dot{V}O_2$ were not significantly different at 3 or 12 months between those assigned to high-intensity interval training vs moderate continuous training. Furthermore, neither group met the a priori–defined minimal clinically important difference of 2.5 mL/kg/min compared with the guideline control at any time point.

Changes in peak $\dot{V}O_2$ after 3 months were similar to those reported in a recent meta-analysis[7] of 8 smaller studies (n = 436 patients with HFpEF, 12-24 weeks, 1.7 mL/kg/min for exercise training vs control). However, the present trial could not confirm the findings of 2 smaller single-center studies in HFpEF showing superiority of high-intensity interval training over moderate continuous training.[9,10] While in the study by Angadi et al[9] (n = 15, 4 weeks' duration), the exercise volume for moderate continuous training (3 × 30 minutes/week) might have been too low, patients included in the trial by Donelli da Silveira et al[10] (n = 19, 12 weeks' duration) were relatively young (mean age, 60 years) with few comorbidities.

In accordance with most of the previous exercise trials in HFpEF,[7,11] the present study failed to demonstrate that the improvement in exercise capacity at 3 months was related to changes in diastolic function. These findings underscore that apart from diastolic dysfunction, other mechanisms likely contributed to the observed improvement in peak $\dot{V}O_2$.[22,23] In HFpEF, peripheral vascular function and skeletal muscle function are disturbed, and exercise training can partially reverse these changes.[24-26] QoL improved by more than 5 points in all groups including guideline control (from baseline to 3 and 12 months), which can be interpreted as clinically relevant[19] and is in line with previous exercise trials in HFpEF and HF with reduced EF.[27,28] At 12 months, the difference in change in QoL between moderate continuous training and guideline control was statistically significant; however, this has to be interpreted as an exploratory finding.

Adherence to exercise protocols is a major concern in long-term exercise intervention studies. In the present trial, despite telemedical support, which proved to have high acceptance even in the group of elderly individuals, only about one-half of the patients performed at least 70% of the prescribed training sessions during home-based exercise training (months 4-12). Even though the median amount of exercise per week was in line with current guideline recommendations[15,29] and for the moderate continuous training group almost twice as high as in the HF-ACTION study,[30] the adherence rate might have still been too low to induce significant long-term effects of exercise training.

The number of adverse and serious adverse events was considerably higher compared with previous exercise trials in HFpEF[20,27,31-34] and reflects the multimorbid condition of the patients included in the present trial. The higher number of nonserious, noncardiovascular adverse events in the training groups may be explained by the more frequent contacts and therefore higher reporting in these groups (eg, number of respiratory tract infections and knee/hip pain, eTable 8 in Supplement 2).

Comparing the current trial with the so far largest exercise trial in HFpEF assessing 100 patients,[27] patients in the present trial were slightly older (mean age, 70 vs 67 years), less obese (mean BMI, 30.0 vs 39.3), with more severe diastolic dysfunction (mean E/e', 15.8 vs 13.1), and comparable absolute values for peak $\dot{V}O_2$ (1530 vs 1515 mL/kg/min overall). In addition, patient characteristics are also comparable with pharmacological studies in HFpEF such as the ALDO-DHF trial (mean age, 67 years; peak $\dot{V}O_2$, 16.4 mL/kg/min; E/e', 12.8)[35] or the PARAGON trial (mean age, 73 years; BMI, 30.3).[36]

Limitations

This study has several limitations. First, the staff conducting the evaluations was not blinded to the treatment group assignment, which could have had an effect on the maximal exhaustion during cardiopulmonary exercise testing. However, the respiratory exchange ratio at peak exercise did not significantly differ between groups and time points (eTable 3 in Supplement 2). Second, the lack of exercise echocardiography, assessing changes of diastolic function during exercise, limits the interpretation of the effects of exercise training on cardiac function. Third, the attenuation in adherence limits the interpretation of long-term effects and underscores the need for more effective ways to improve long-term adherence.[37] Fourth, multiplicity of analyses limits the interpretability of the secondary outcomes.

Conclusions

Among patients with HFpEF, there was no statistically significant difference in change in peak $\dot{V}O_2$ at 3 months between those assigned to high-intensity interval vs moderate continuous training, and neither group met the prespecified minimal clinically important difference compared with the guideline control. These findings do not support either high-intensity interval training or moderate continuous training compared with guideline-based physical activity for patients with HFpEF.

ARTICLE INFORMATION

Accepted for Publication: December 28, 2020.

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Author Contributions: Mr Mueller and Dr Haller had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Mr Mueller and Drs Winzer, van Craenenbroeck, and Halle contributed equally.
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Obtained funding: Wisløff, Adams, Pieske, Halle.
Administrative, technical, or material support: Mueller, Gevaert, Edelmann, Beckers, Bobenko, Van de Heyning, von Korn, Christle, Linke, Wisløff, Adams, Halle.
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Conflict of Interest Disclosures: Dr Mueller reported receiving grants from Deutsche Forschungsgemeinschaft (DFG) through the TUM International Graduate School of Science and Engineering during the conduct of the study. Dr 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. Dr Duvinage reported receiving grants from Novartis outside the submitted work. Dr Van de Heyning reported receiving speaker fees from Abbott, Daiichi Sankyo, and Edwards Lifesciences outside the submitted work. Dr 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. Dr 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. Dr Van Craenenbroeck reported receiving grants from the Flemish Research Funds (FWO) during the conduct of the study. Dr Halle reported receiving grants from the TUM International Graduate School of Science and Engineering 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 outside the submitted work. No other disclosures were reported.

Funding/Support: This trial was funded by the European Commission, Framework Program 7, grant No. EU-602405-2; the Deutsche Forschungsgemeinschaft (DFG) through the TUM International Graduate School of Science and Engineering (IGSSE); and the Flemish Research Funds (FWO) through a Senior Clinical Investigator grant to Dr van Craenenbroeck.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The OptimEx-Clin Study Group members are listed in Supplement 2.

Data Sharing Statement: See Supplement 3.

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Supplemental Online Content

Mueller S, Winzer EB, Duvinage A, et al; OptimEx-Clin Study Group. 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. *JAMA*. Published February 9, 2021. doi:10.1001/jama.2020.26812

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Group Members

Lilian Massen, MSc, Axel Pressler, MD, and Christiane Suchy, MD (Munich, Germany), Øivind Rognmo, PhD, Natale Rolim, PhD, and Atefe R. Tari, MSc (Trondheim, Norway) contributed to the concept and design of the trial. Luciene Azevedo, PhD, Flavia Baldassarri, MSc, Birgit Böhm, PhD, Julia Elmenhorst, MD, Hannes Fricke, MD, Siri Goldschmidt, MSc, Sarah Lang, MSc, Lilian Massen, MSc, Renate Oberhoffer, MD, Kristina Schütt, MSc, Silja Schwarz, MD, Christiane Suchy, MD, Veronika Zeller and Sophia Wachner, MD (Munich, Germany), Justien Cornelis, PhD, Johan Denollet (†), PhD, Inge Goovaerts, Katrien Masset, MSc, Nadine Possemiers, Tibor Stoop, MSc, Christiaan Vrints, MD, PhD, and Kurt Wuyts, PhD (Antwerp, Belgium), Ines Frederix, PhD, and Paul Dendale, MD, PhD (Hasselt, Belgium), Evgeny Belyavskiy, MD, PhD, Martin Kropf, MSc, Daniel A. Morris, MD, and Aravind Kumar Radhakrishnan, MD (Berlin, Germany) contributed to acquisition, analysis, or interpretation of data. Doris Bach, MSc (Berlin, Germany), and Natale Rolim, PhD, (Trondheim, Norway) contributed to administrative, technical or material support. Daniel Kaiser, MA (vitagroup AG, Mannheim, Germany) was responsible for the development and technical support of the smartphone application and telemedical infrastructure. The salaries of Lilian Massen, Natale Rolim, Nadine Possemiers and Daniel Kaiser were (at least in part) funded by the grant of the European Commission. All the other contributors were paid staff members of their respective site but were not paid by the funds of the European Commission.

Viviane Conraads (MD, PhD, Antwerp, Belgium) was an integral part of developing the grant application and participating in the steering committee. Dr. Conraads died on December 12, 2013.

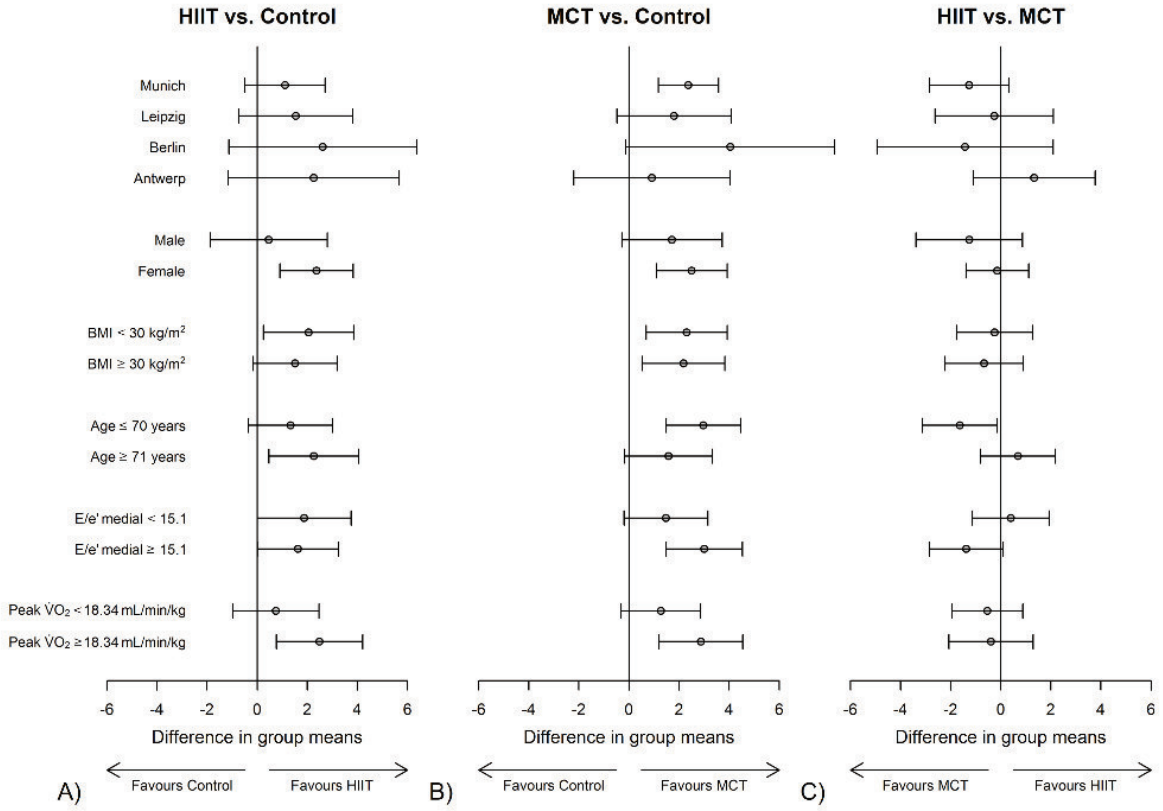
Steering Committee: Martin Halle, MD, Munich, Germany (Chair); Burkert Pieske, MD, Berlin, Germany; Emeline van Craenenbroeck, MD, PhD, Antwerp, Belgium; Volker Adams, PhD, Leipzig/Dresden, Germany; Ulrik Wisløff, PhD, Trondheim, Norway
Endpoint Committee: Marco Guazzi, MD, PhD, Milan, Italy (did not receive compensation)
Safety Committee: Ulf Landmesser, MD, Berlin, Germany; Lars Maier, MD, Regensburg, Germany (did not receive compensation)
Biometry: Bernhard Haller, Dr rer nat, Germany
Study Coordination and Monitoring: Stephan Mueller, MA, Munich, Germany
Responsible personnel in core laboratories:

- Cardiopulmonary Exercise Testing: Martin Halle, MD, Stephan Mueller, MA, Munich, Germany
- Echocardiography: Elisabeth Pieske-Kraigher, MD, Aravind Kumar Radhakrishnan, MD, Daniel Morris, MD, Berlin, Germany
- Clinical chemistry: Hubert Scharnagl, Dr rer nat, Graz, Austria (received compensation for measurements of NT-proBNP)
- Psychometric analysis: Emeline van Craenenbroeck, MD, PhD, Antwerp, Belgium
- Exercise Training: Martin Halle, MD, Stephan Mueller, MA, Munich, Germany

eMethods:

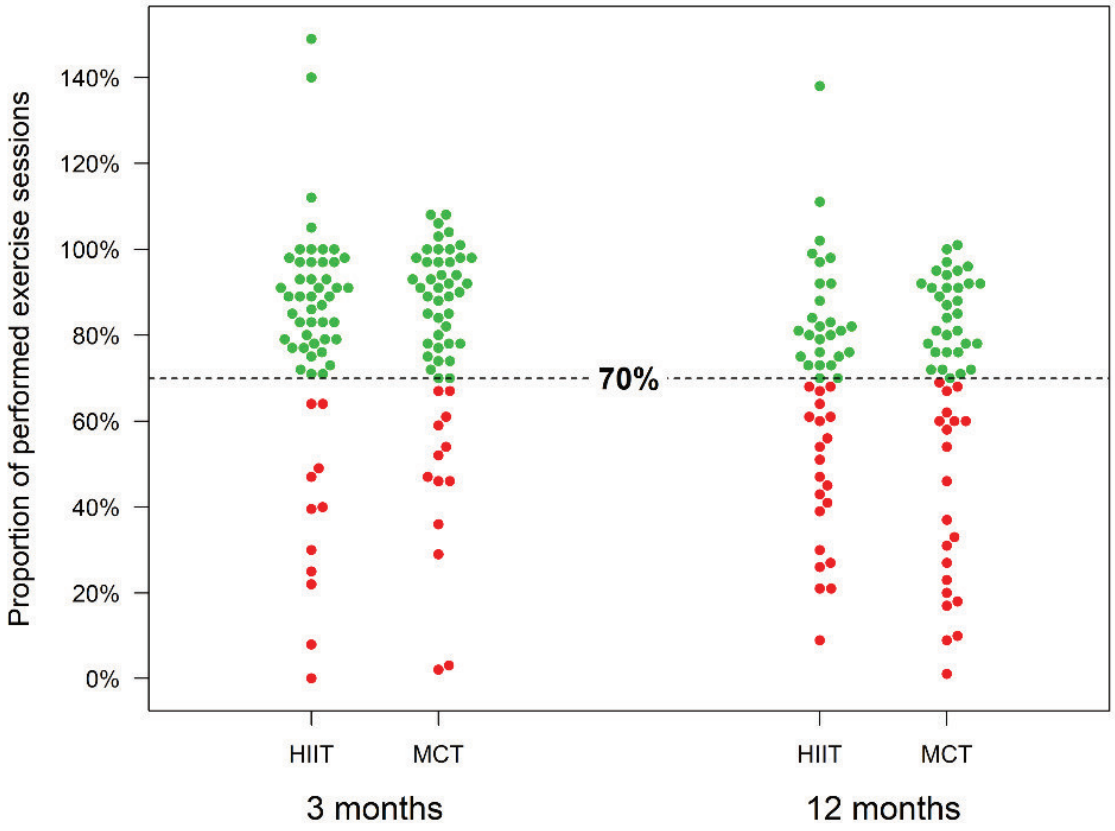
Description of multiple imputation approach:

To account for missing values in the primary efficacy endpoint [change of peak oxygen consumption (peak $\dot{V}O_2$) after three months] a multiple imputation approach was pre-specified in the statistical analysis plan.
Missing peak $\dot{V}O_2$ values were imputed using predictive mean matching implemented in the R[1] library *mice*[2]. Imputation was performed under consideration of the variables age, sex, body mass index, binary indicator for intake of heart failure related medication (angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blocker and/or diuretics), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), baseline peak $\dot{V}O_2$ and baseline left ventricular filling pressure (E/e' medial). By not adding the treatment group to the predictors of the imputation this approach should produce a rather conservative result, because similar values will be imputed for comparable patients from different groups.
Ten datasets with imputed values were generated and pooled using the function *mi.anova* provided in the R library *miceadds*[3] to test the global null hypothesis of equal group means for all three groups (ANOVA, significance level of $\alpha = 5\%$). All patients were analyzed in the group they were randomized to, irrespective of adherence to group allocation. As the global null hypothesis could be rejected based on the pooled data, pairwise comparisons were performed on a significance level of $\alpha = 5\%$ for each of the ten imputed datasets and results were aggregated using the *pool* function in R (library *mice*). Pooled estimates for the pairwise differences in group means for change of peak $\dot{V}O_2$ over three months are presented with corresponding 95% confidence intervals. Results are also presented considering patients with valid assessment of peak $\dot{V}O_2$ after three months only (complete case analysis).



eFigure 1: Subgroup analysis of the primary endpoint (change in peak $\dot{V}O_2$ after 3 months).

Cutoff points were pre-specified as 30 kg/m² (BMI) and the median of age, E/e' medial and peak $\dot{V}O_2$. HIIT: High Intensity Interval Training; MCT: Moderate Continuous Training; Control: Guideline Control; BMI: body mass index; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, peak $\dot{V}O_2$: peak oxygen consumption



eFigure 2: Relative frequency of performed exercise training sessions within 3-months and 12-months intervention period in High Intensity Interval Training (HIIT) and Moderate Continuous Training (MCT).

The dotted line represents the 70%-cutoff that was defined as the lower limit for an adequate adherence. Green points represent each individual exercising ≥ 70% of prescribed exercise sessions, red points represent individuals exercising < 70% of prescribed exercise sessions.

eTable 1: Ineligible participants not meeting HFpEF criteria who were inadvertently randomized and excluded from the analysis

Group assignment	On-site E/e' medial	On-site BNP (pg/mL)	CoreLab E/e' medial	CoreLab NT-proBNP (pg/mL)
MCT	10.8	33	9.6	102
MCT	10.9	30	9.9	92
HIIT	11.9	44	7.8	134
HIIT	9.8	8	9.4	55

Inclusion criteria: On-site measures of E/e' medial ≥ 15 or E/e' medial ≥ 8 and NT-proBNP ≥ 220 pg/mL or E/e' medial ≥ 8 and BNP ≥ 80 pg/mL MCT: Moderate Continuous Training; HIIT: High Intensity Interval Training; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, BNP: brain natriuretic peptide, NT-proBNP: N-terminal prohormone of brain natriuretic peptide

eTable 2: Subgroup analysis of the primary endpoint (change in peak $\dot{V}O_2$ after 3 months)

	Difference [95% CI]			Interaction p value
	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT	
Munich (n=72)	1.1 [-0.5 to 2.7]	2.4 [1.2 to 3.6]	-1.3 [-2.8 to 0.3]	.62
Leipzig (n=44)	1.5 [-0.7 to 3.8]	1.8 [-0.5 to 4.1]	-0.3 [-2.6 to 2.1]	
Berlin (n=24)	2.6 [-1.1 to 6.4]	4.0 [-0.1 to 8.2]	-1.4 [-4.9 to 2.1]	
Antwerp (n=36)	2.3 [-1.2 to 5.7]	0.9 [-2.2 to 4.0]	1.3 [-1.1 to 3.8]	
Male	0.5 [-1.9 to 2.8]	1.7 [-0.3 to 3.7]	-1.3 [-3.4 to 0.9]	.31
Female	2.4 [0.9 to 3.8]	2.5 [1.1 to 3.9]	-0.1 [-1.4 to 1.1]	
BMI < 30 kg/m^2	2.1 [0.3 to 3.9]	2.3 [0.7 to 3.9]	-0.2 [-1.8 to 1.3]	.89
BMI ≥30 kg/m^2	1.5 [-0.2 to 3.2]	2.2 [0.5 to 3.8]	-0.7 [-2.2 to 0.9]	
Age ≤ 70 years	1.3 [-0.3 to 3.0]	3.0 [1.5 to 4.5]	-1.6 [-3.1 to -0.1]	.13
Age ≥ 71 years	2.3 [0.5 to 4.1]	1.6 [-0.2 to 3.3]	0.7 [-0.8 to 2.2]	
E/e' medial < 15.1	1.9 [0.0 to 3.7]	1.5 [-0.2 to 3.1]	0.4 [-1.1 to 1.9]	.24
E/e' medial ≥ 15.1	1.6 [0.0 to 3.3]	3.0 [1.5 to 4.5]	-1.4 [-2.8 to 0.1]	
Peak $\dot{V}O_2$ < 18.34 mL/min/kg	0.7 [-1.0 to 2.5]	1.3 [-0.3 to 2.9]	-0.5 [-1.9 to 0.9]	.25
Peak $\dot{V}O_2$ ≥ 18.34 mL/min/kg	2.5 [0.8 to 4.2]	2.9 [1.2 to 4.5]	-0.4 [-2.1 to 1.3]	

Cutoff points were pre-specified as 30 kg/m^2 (BMI) and the median of age, E/e' medial and peak $\dot{V}O_2$. HIIT: High Intensity Interval Training; MCT: Moderate Continuous Training; Control: Guideline Control; BMI: body mass index; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, peak $\dot{V}O_2$: peak oxygen consumption

eTable 3: Results from cardiopulmonary exercise testing for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Values at rest							
$\dot{V}O_2$, mL/min/kg	Baseline	3.3 (0.9) [58]	3.3 (0.8) [58]	3.4 (0.7) [60]			
	3 mo	3.2 (0.8) [53]	3.2 (0.8) [54]	3.5 (0.9) [52]	-0.1 (-0.5 to 0.3) [105]	-0.2 (-0.5 to 0.1) [106]	0.1 (-0.2 to 0.5) [107]
	12 mo	3.3 (0.8) [42]	3.3 (0.7) [48]	3.7 (1.3) [49]	-0.3 (-0.8 to 0.3) [91]	-0.3 (-0.8 to 0.2) [97]	0.0 (-0.4 to 0.4) [90]
RER	Baseline	0.84 (0.07) [58]	0.85 (0.08) [58]	0.85 (0.08) [60]			
	3 mo	0.86 (0.06) [53]	0.85 (0.07) [54]	0.85 (0.08) [52]	0.01 (-0.03 to 0.04) [105]	-0.01 (-0.04 to 0.03) [106]	0.02 (-0.01 to 0.04) [107]
	12 mo	0.84 (0.10) [42]	0.85 (0.08) [48]	0.85 (0.06) [49]	-0.01 (-0.05 to 0.04) [91]	-0.01 (-0.05 to 0.03) [97]	0.00 (-0.05 to 0.04) [90]
systolic BP, mmHg	Baseline	127 (14) [58]	131 (13) [58]	127 (14) [60]			
	3 mo	127 (17) [53]	133 (18) [54]	131 (14) [52]	-2 (-8 to 5) [105]	0 (-7 to 6) [106]	-1 (-8 to 5) [107]
	12 mo	133 (20) [42]	134 (15) [48]	128 (15) [49]	6 (-1 to 14) [91]	2 (-4 to 8) [97]	4 (-3 to 12) [90]
Heart rate, bpm	Baseline	65 (12) [58]	65 (10) [58]	65 (11) [60]			
	3 mo	65 (10) [53]	65 (8) [54]	65 (12) [52]	0 (-4 to 4) [105]	-1 (-4 to 3) [106]	1 (-2 to 4) [107]
	12 mo	65 (11) [42]	68 (12) [48]	66 (11) [49]	-2 (-7 to 3) [91]	1 (-4 to 5) [97]	-3 (-7 to 2) [90]
Values at the first ventilatory threshold (VT1)							
$\dot{V}O_2$, mL/min/kg	Baseline	11.1 (2.8) [58]	11.2 (3.3) [57]	11.4 (2.8) [58]			
	3 mo	11.9 (2.7) [53]	12.1 (3.5) [53]	11.4 (2.6) [50]	0.8 (-0.1 to 1.7) [103]	1.0 (0.2 to 1.9) [102]	-0.3 (-1.0 to 0.5) [105]
	12 mo	11.3 (2.9) [41]	10.6 (3.1) [47]	10.9 (2.4) [49]	0.6 (-0.5 to 1.6) [90]	-0.1 (-1.0 to 0.9) [95]	0.6 (-0.4 to 1.7) [87]
Workload, watts	Baseline	45 (18) [58]	46 (21) [57]	45 (15) [58]			
	3 mo	49 (18) [53]	53 (25) [53]	47 (16) [50]	3 (-2 to 7) [103]	6 (2 to 11) [102]	-4 (-9 to 1) [105]
	12 mo	46 (17) [41]	45 (21) [47]	43 (14) [49]	4 (-1 to 9) [90]	3 (-2 to 7) [95]	2 (-4 to 7) [87]
Heart rate, bpm	Baseline	92 (16) [58]	94 (17) [57]	91 (18) [58]			
	3 mo	92 (14) [53]	96 (16) [53]	91 (17) [50]	-1 (-6 to 4) [103]	1 (-4 to 5) [102]	-2 (-6 to 2) [105]
	12 mo	93 (15) [41]	94 (17) [47]	93 (25) [49]	-4 (-13 to 5) [90]	-3 (-12 to 7) [95]	-1 (-7 to 5) [87]
RER	Baseline	0.86 (0.05) [58]	0.85 (0.06) [57]	0.84 (0.08) [58]			
	3 mo	0.86 (0.05) [53]	0.85 (0.06) [53]	0.87 (0.06) [50]	-0.04 (-0.07 to -0.01) [103]	-0.03 (-0.06 to 0.00) [102]	0.00 (-0.02 to 0.02) [105]
	12 mo	0.84 (0.06) [41]	0.83 (0.05) [47]	0.85 (0.06) [49]	-0.04 (-0.08 to -0.01) [90]	-0.02 (-0.06 to 0.01) [95]	-0.02 (-0.05 to 0.01) [87]

eTable 3 continued...

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Values at peak exercise							
$\dot{V}O_2$, mL/min/kg	Baseline	18.9 (5.4) [58]	18.2 (5.1) [58]	19.4 (5.6) [60]			
	3 mo	20.2 (6.0) [53]	19.8 (5.8) [54]	18.9 (5.7) [52]	1.8 (0.5 to 3.0) [105]	2.2 (1.1 to 3.4) [106]	-0.5 (-1.6 to 0.6) [107]
	12 mo	19.9 (6.1) [42]	18.1 (5.9) [48]	19.5 (5.1) [49]	1.4 (0.1 to 2.8) [91]	0.6 (-0.7 to 1.9) [97]	0.8 (-0.5 to 2.1) [90]
$\dot{V}O_2$, L/min	Baseline	1.54 (0.47) [58]	1.55 (0.43) [58]	1.50 (0.47) [60]			
	3 mo	1.59 (0.49) [53]	1.66 (0.46) [54]	1.48 (0.49) [52]	0.11 (0.01 to 0.20) [105]	0.16 (0.07 to 0.25) [106]	-0.05 (-0.14 to 0.03) [107]
	12 mo	1.55 (0.49) [42]	1.53 (0.46) [48]	1.54 (0.42) [49]	0.08 (-0.03 to 0.19) [91]	0.03 (-0.08 to 0.14) [97]	0.05 (-0.06 to 0.16) [90]
Workload, watts	Baseline	103 (38) [58]	103 (37) [58]	101 (36) [60]			
	3 mo	110 (38) [53]	112 (42) [54]	101 (39) [52]	9 (4 to 15) [105]	9 (4 to 14) [106]	0 (-6 to 6) [107]
	12 mo	109 (39) [42]	104 (42) [48]	104 (35) [49]	10 (4 to 16) [91]	4 (-1 to 10) [97]	5 (-1 to 12) [90]
RER	Baseline	1.12 (0.10) [58]	1.10 (0.09) [58]	1.10 (0.12) [60]			
	3 mo	1.11 (0.10) [53]	1.09 (0.08) [54]	1.11 (0.12) [52]	-0.01 (-0.05 to 0.03) [105]	-0.02 (-0.06 to 0.01) [106]	0.01 (-0.01 to 0.04) [107]
	12 mo	1.10 (0.11) [42]	1.08 (0.07) [48]	1.11 (0.10) [49]	-0.04 (-0.08 to 0.01) [91]	-0.02 (-0.05 to 0.02) [97]	-0.02 (-0.06 to 0.02) [90]
Systolic BP, mmHg	Baseline	178 (28) [58]	184 (30) [58]	175 (28) [59]			
	3 mo	180 (28) [53]	181 (30) [53]	177 (26) [52]	-2 (-12 to 7) [104]	-4 (-13 to 5) [104]	2 (-7 to 11) [106]
	12 mo	180 (30) [42]	176 (31) [45]	168 (27) [49]	10 (-2 to 21) [90]	4 (-6 to 14) [93]	6 (-6 to 18) [87]
Heart rate, BPM	Baseline	123 (24) [57]	123 (27) [58]	122 (28) [60]			
	3 mo	126 (25) [53]	127 (26) [54]	122 (29) [52]	2 (-4 to 7) [104]	2 (-3 to 8) [106]	-1 (-6 to 4) [106]
	12 mo	127 (27) [42]	127 (29) [48]	126 (26) [49]	-2 (-10 to 6) [90]	1 (-8 to 9) [97]	-3 (-12 to 7) [89]
Other values							
$\dot{V}E/\dot{V}CO_2$ slope	Baseline	34.5 (7.9) [58]	34.2 (7.2) [58]	33.2 (5.9) [59]			
	3 mo	35.0 (9.8) [53]	33.7 (6.8) [54]	32.6 (5.3) [51]	1.7 (-0.2 to 3.6) [104]	0.2 (-1.7 to 2.2) [105]	1.5 (-0.3 to 3.2) [107]
	12 mo	36.6 (8.4) [42]	33.9 (7.1) [48]	34.3 (7.4) [49]	0.9 (-1.2 to 3.0) [91]	-1.9 (-3.8 to 0.0) [97]	2.8 (0.7 to 4.8) [90]

$\dot{V}O_2$: oxygen uptake, RER: respiratory exchange ratio, BP: blood pressure, $\dot{V}E/\dot{V}CO_2$ slope: ventilation to carbon dioxide production slope

eTable 4: Results from echocardiography for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Diastolic Function							
E, cm/s	**Baseline**	94.3 (21.2) [58]	93.8 (21.2) [58]	93.4 (25.2) [59]			
	3 mo	91.1 (24.2) [54]	89.5 (26.9) [55]	91.3 (29.8) [53]	-1.2 (-8.0 to 5.5) [106]	-2.0 (-9.2 to 5.2) [107]	0.8 (-6.6 to 8.2) [109]
	12 mo	86.3 (23.7) [48]	89.5 (23.8) [52]	91.3 (26.7) [52]	-4.6 (-11.6 to 2.4) [99]	-0.8 (-8.6 to 7.0) [103]	-3.8 (-11.8 to 4.3) [100]
A, cm/s	**Baseline**	82.1 (26.9) [47]	88.5 (27.2) [48]	89.1 (23.2) [54]			
	3 mo	82.7 (24.9) [46]	85.1 (27.3) [47]	81.2 (27.9) [49]	4.1 (-1.6 to 9.7) [89]	-1.8 (-7.3 to 3.6) [90]	5.9 (0.4 to 11.4) [89]
	12 mo	78.7 (26.1) [39]	89.3 (27.4) [45]	87.6 (26.9) [44]	-0.8 (-7.3 to 5.7) [82]	2.4 (-5.1 to 10.0) [86]	-3.2 (-10.6 to 4.2) [80]
E/A	**Baseline**	1.30 (0.79) [47]	1.13 (0.45) [48]	1.15 (0.59) [54]			
	3 mo	1.21 (0.64) [46]	1.11 (0.61) [47]	1.35 (0.97) [49]	-0.14 (-0.32 to 0.04) [89]	-0.04 (-0.23 to 0.15) [90]	-0.10 (-0.27 to 0.07) [89]
	12 mo	1.25 (0.83) [39]	1.07 (0.57) [45]	1.18 (0.73) [44]	-0.09 (-0.27 to 0.09) [82]	-0.07 (-0.25 to 0.11) [86]	-0.02 (-0.2 to 0.15) [80]
e' medial, cm/s	**Baseline**	6.16 (1.79) [57]	6.11 (1.57) [58]	6.25 (1.76) [57]			
	3 mo	6.23 (1.72) [54]	5.95 (1.65) [54]	5.95 (1.84) [53]	0.33 (-0.30 to 0.95) [103]	0.23 (-0.32 to 0.78) [104]	0.09 (-0.48 to 0.66) [107]
	12 mo	6.23 (1.73) [47]	5.93 (1.51) [52]	6.10 (1.66) [52]	0.34 (-0.26 to 0.94) [96]	0.01 (-0.51 to 0.52) [102]	0.33 (-0.20 to 0.86) [98]
e' lateral, cm/s	**Baseline**	8.11 (2.02) [58]	8.78 (2.68) [56]	8.34 (1.98) [58]			
	3 mo	8.18 (2.27) [54]	8.67 (2.48) [55]	8.01 (2.10) [52]	0.13 (-0.53 to 0.79) [104]	-0.03 (-0.76 to 0.70) [103]	0.16 (-0.63 to 0.95) [107]
	12 mo	8.33 (2.23) [47]	8.55 (2.34) [52]	8.36 (2.26) [51]	0.14 (-0.68 to 0.96) [96]	-0.26 (-1.03 to 0.51) [100]	0.40 (-0.40 to 1.20) [98]
e' average, cm/s	**Baseline**	7.15 (1.72) [57]	7.45 (1.92) [56]	7.31 (1.61) [57]			
	3 mo	7.20 (1.71) [54]	7.28 (1.86) [54]	6.96 (1.73) [52]	0.23 (-0.32 to 0.79) [102]	0.11 (-0.43 to 0.65) [101]	0.12 (-0.46 to 0.71) [105]
	12 mo	7.29 (1.82) [46]	7.24 (1.68) [52]	7.25 (1.77) [51]	0.22 (-0.40 to 0.84) [94]	-0.12 (-0.65 to 0.42) [100]	0.33 (-0.25 to 0.91) [96]
E/e' medial	**Baseline**	15.8 (3.7) [57]	15.9 (4.1) [58]	15.7 (5.6) [57]			
	3 mo	15.2 (4.8) [54]	15.6 (5.0) [54]	16.5 (7.2) [53]	-1.5 (-3.2 to 0.3) [103]	-1.1 (-2.7 to 0.5) [104]	-0.4 (-1.9 to 1.2) [107]
	12 mo	14.2 (3.9) [47]	15.6 (4.4) [52]	15.7 (5.5) [52]	-1.4 (-2.9 to 0.1) [96]	0.1 (-1.5 to 1.7) [102]	-1.5 (-3.0 to 0.0) [98]
E/e' lateral	**Baseline**	12.1 (3.3) [58]	11.4 (4.0) [56]	11.7 (4.1) [58]			
	3 mo	11.9 (4.4) [54]	10.9 (3.8) [55]	11.8 (4.2) [52]	0.1 (-1.0 to 1.1) [104]	-0.2 (-1.3 to 0.8) [103]	0.3 (-0.9 to 1.4) [107]
	12 mo	10.9 (3.4) [47]	11.0 (3.6) [52]	11.9 (5.9) [51]	-1.1 (-2.6 to 0.4) [96]	-0.4 (-2.1 to 1.2) [100]	-0.6 (-1.8 to 0.5) [98]
E/e' average	**Baseline**	13.5 (3.2) [57]	13.1 (3.5) [56]	13.2 (4.4) [57]			
	3 mo	13.1 (4.3) [54]	12.7 (3.8) [54]	13.5 (4.9) [52]	-0.6 (-1.7 to 0.6) [102]	-0.4 (-1.5 to 0.7) [101]	-0.2 (-1.3 to 1.0) [105]
	12 mo	12.2 (3.3) [46]	12.7 (3.6) [52]	13.2 (5.1) [51]	-1.0 (-2.3 to 0.3) [94]	-0.1 (-1.5 to 1.3) [100]	-0.9 (-2.0 to 0.2) [96]

eTable 4 continued...

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Dimensions							
LVEDD, mm	**Baseline**	46.9 (5.5) [27]	48.3 (5.2) [26]	45.7 (5.0) [34]			
	3 mo	45.8 (5.6) [24]	47.3 (3.7) [24]	44.6 (3.8) [23]	0.4 (-1.0 to 1.8) [35]	-0.6 (-2.5 to 1.3) [36]	1.0 (-0.5 to 2.6) [33]
	12 mo	46.4 (6.1) [23]	46.5 (3.6) [25]	44.9 (4.1) [23]	-0.6 (-2.9 to 1.6) [33]	0.3 (-1.7 to 2.3) [35]	-0.9 (-3.3 to 1.5) [36]
IVSD, mm	**Baseline**	11.0 (1.9) [27]	10.9 (1.6) [27]	11.1 (2.4) [34]			
	3 mo	10.8 (1.5) [24]	10.7 (1.8) [24]	11.2 (2.8) [23]	0.5 (-0.1 to 1.0) [35]	0.5 (0.0 to 1.1) [36]	-0.1 (-0.7 to 0.5) [33]
	12 mo	10.8 (1.5) [23]	10.9 (1.6) [25]	11.4 (2.8) [23]	0.2 (-0.4 to 0.7) [33]	0.2 (-0.2 to 0.6) [35]	0.0 (-0.6 to 0.5) [36]
LVPWD, mm	**Baseline**	10.1 (1.0) [27]	10.2 (1.6) [26]	10.1 (1.5) [34]			
	3 mo	10.3 (0.8) [24]	10.3 (1.5) [24]	10.4 (1.5) [23]	0.2 (-0.4 to 0.7) [35]	0.1 (-0.7 to 0.8) [35]	0.1 (-0.6 to 0.8) [32]
	12 mo	10.0 (0.9) [23]	10.0 (1.5) [25]	10.4 (1.6) [22]	0.0 (-0.8 to 0.7) [33]	0.4 (-0.4 to 1.1) [34]	-0.4 (-1.2 to 0.4) [35]
Other values							
LVEF - BP, %	**Baseline**	62.1 (6.4) [37]	61.6 (5.7) [38]	62.1 (4.7) [48]			
	3 mo	64.9 (7.3) [35]	61.8 (6.2) [29]	61.6 (4.9) [37]	1.6 (-1.1 to 4.3) [63]	0.4 (-2.2 to 3.0) [60]	1.2 (-1.9 to 4.3) [53]
	12 mo	63.9 (6.4) [33]	63.8 (5.9) [36]	63.2 (5.6) [40]	0.4 (-2.0 to 2.9) [65]	2.0 (-0.4 to 4.4) [68]	-1.6 (-4.3 to 1.1) [57]
TR Vmax, m/s	**Baseline**	2.54 (0.37) [44]	2.51 (0.39) [44]	2.47 (0.41) [48]			
	3 mo	2.52 (0.39) [42]	2.59 (0.33) [39]	2.63 (0.63) [40]	-0.16 (-0.34 to 0.03) [69]	-0.12 (-0.30 to 0.05) [70]	-0.03 (-0.19 to 0.13) [69]
	12 mo	2.55 (0.41) [36]	2.55 (0.36) [34]	2.53 (0.44) [41]	-0.08 (-0.25 to 0.09) [63]	-0.10 (-0.26 to 0.07) [63]	0.02 (-0.15 to 0.18) [58]
TAPSE, mm	**Baseline**	21.8 (3.6) [50]	21.0 (3.8) [53]	21.6 (3.6) [53]			
	3 mo	22.0 (4.1) [47]	20.8 (3.6) [45]	21.8 (4.5) [49]	0.0 (-1.5 to 1.6) [87]	0.0 (-1.4 to 1.3) [88]	0.0 (-1.5 to 1.6) [85]
	12 mo	21.0 (4.1) [41]	20.9 (3.3) [46]	21.8 (3.7) [49]	-1.1 (-2.9 to 0.7) [80]	0.1 (-1.5 to 1.8) [89]	-1.2 (-3.2 to 0.8) [79]
FAC, %	**Baseline**	43.1 (6.1) [21]	50.7 (10.5) [16]	46.0 (6.8) [20]			
	3 mo	45.4 (9.7) [14]	48.4 (8.3) [13]	40.0 (10.8) [13]	7.0 (0.2 to 13.8) [13]	-0.3 (-9.5 to 8.9) [13]	7.3 (-0.9 to 15.5) [14]
	12 mo	50.4 (8.5) [7]	43.2 (11.5) [5]	47.8 (9.8) [9]	- - -	- - -	- - -
LAVI, mL/m^2	**Baseline**	35.4 (9.0) [39]	37.9 (13.0) [42]	39.8 (13.5) [48]			
	3 mo	35.2 (10.2) [34]	36.8 (10.5) [28]	38.4 (14.7) [40]	0.3 (-1.7 to 2.4) [61]	1.2 (-0.9 to 3.4) [60]	-0.9 (-3.2 to 1.4) [51]
	12 mo	37.4 (10.9) [26]	36.6 (9.2) [23]	39.2 (13.8) [38]	0.4 (-2.7 to 3.5) [54]	0.9 (-1.6 to 3.3) [53]	-0.5 (-3.5 to 2.6) [41]
LV mass, g	**Baseline**	178 (45) [27]	189 (52) [26]	174 (51) [34]			
	3 mo	165 (44) [24]	180 (44) [24]	172 (55) [23]	10 (-3 to 23) [35]	3 (-15 to 20) [35]	7 (-8 to 23) [32]
	12 mo	172 (41) [23]	175 (48) [25]	177 (59) [22]	-2 (-21 to 17) [33]	9 (-5 to 23) [34]	-11 (-30 to 8) [35]

E: peak velocity blood flow from ventricular relaxation in early diastole, A: peak velocity flow in late diastole caused by atrial contraction, e': mitral annular early diastolic velocity, LVEDD: left ventricular end diastolic diameter, IVSD: interventricular septum thickness in diastole, LVPWD: left ventricular posterior wall in diastole, LVEF: left ventricular ejection fraction, BP: biplane, TR Vmax: maximum tricuspid regurgitation velocity, TAPSE: tricuspid annular plan systolic excursion, FAC: fractional area change, LAVI: left atrial volume index, LV mass: left ventricular mass

eTable 5: Results from Kansas City Cardiomyopathy Questionnaire for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Physical limitation	Baseline	68 (24) [57]	62 (25) [55]	64 (26) [57]			
	3 mo	70 (23) [52]	67 (24) [54]	69 (23) [55]	-6 (-12 to 0) [105]	-4 (-11 to 2) [105]	-2 (-8 to 4) [104]
	12 mo	75 (25) [47]	71 (23) [46]	71 (27) [51]	-2 (-9 to 5) [96]	2 (-5 to 9) [93]	-4 (-12 to 4) [91]
Symptom stability	Baseline	50 (13) [58]	49 (17) [56]	52 (16) [58]			
	3 mo	59 (19) [54]	60 (22) [55]	51 (18) [55]	9 (2 to 17) [106]	12 (3 to 20) [106]	-2 (-8 to 4) [108]
	12 mo	55 (14) [47]	55 (20) [46]	48 (16) [51]	10 (2 to 18) [96]	10 (0 to 20) [94]	0 (-9 to 10) [92]
Symptom frequency	Baseline	76 (24) [58]	69 (22) [56]	67 (23) [58]			
	3 mo	77 (21) [54]	75 (22) [54]	74 (21) [55]	-4 (-11 to 2) [108]	-3 (-9 to 4) [107]	-2 (-7 to 4) [107]
	12 mo	80 (19) [47]	75 (22) [46]	73 (23) [51]	0 (-7 to 7) [97]	1 (-6 to 9) [95]	-1 (-9 to 6) [92]
Symptom burden	Baseline	75 (24) [58]	68 (22) [56]	67 (22) [58]			
	3 mo	74 (21) [54]	75 (20) [55]	70 (20) [55]	-3 (-10 to 4) [108]	3 (-3 to 10) [108]	-7 (-12 to -1) [108]
	12 mo	79 (19) [47]	77 (19) [46]	71 (25) [51]	1 (-7 to 8) [97]	7 (0 to 14) [95]	-6 (-13 to 1) [92]
Total symptoms	Baseline	75 (23) [58]	68 (21) [56]	67 (22) [58]			
	3 mo	75 (20) [54]	74 (20) [55]	72 (20) [55]	-4 (-10 to 3) [108]	0 (-6 to 6) [108]	-4 (-9 to 1) [108]
	12 mo	80 (19) [47]	76 (20) [46]	72 (23) [51]	0 (-6 to 7) [97]	4 (-2 to 11) [95]	-4 (-10 to 3) [92]
Self-efficacy	Baseline	67 (27) [57]	63 (23) [56]	66 (29) [58]			
	3 mo	71 (25) [54]	70 (22) [55]	70 (23) [55]	-2 (-12 to 7) [107]	0 (-8 to 9) [108]	-2 (-10 to 6) [107]
	12 mo	82 (19) [47]	76 (20) [46]	68 (23) [51]	8 (-2 to 19) [96]	8 (-2 to 17) [95]	1 (-8 to 9) [91]
Quality of life	Baseline	68 (24) [58]	62 (26) [56]	66 (20) [58]			
	3 mo	73 (26) [54]	74 (20) [55]	72 (21) [55]	1 (-7 to 9) [108]	5 (-3 to 12) [108]	-4 (-11 to 4) [108]
	12 mo	80 (21) [47]	77 (19) [45]	72 (24) [51]	4 (-3 to 12) [97]	11 (2 to 19) [94]	-6 (-15 to 2) [91]
Social limitation	Baseline	72 (25) [56]	66 (29) [53]	67 (25) [57]			
	3 mo	76 (26) [51]	75 (28) [54]	73 (23) [54]	-2 (-10 to 6) [101]	0 (-8 to 7) [102]	-2 (-9 to 6) [99]
	12 mo	85 (22) [47]	80 (25) [45]	78 (27) [51]	0 (-9 to 9) [94]	2 (-8 to 11) [92]	-2 (-11 to 8) [88]
Overall summary	Baseline	70 (22) [55]	64 (23) [53]	66 (20) [56]			
	3 mo	74 (21) [50]	72 (20) [53]	72 (18) [54]	-3 (-9 to 3) [99]	0 (-6 to 5) [100]	-3 (-8 to 2) [97]
	12 mo	80 (19) [47]	76 (19) [45]	73 (21) [51]	0 (-5 to 6) [93]	4 (-2 to 11) [91]	-4 (-10 to 3) [88]
Clinical summary	Baseline	72 (22) [57]	65 (22) [55]	66 (22) [57]			
	3 mo	73 (20) [52]	70 (20) [54]	71 (19) [55]	-5 (-11 to 0) [105]	-2 (-7 to 3) [105]	-3 (-8 to 2) [104]
	12 mo	77 (21) [47]	74 (20) [46]	71 (23) [51]	-1 (-7 to 5) [96]	3 (-3 to 9) [93]	-4 (-10 to 2) [91]

Higher scores indicate better health (score range 1-100, minimal clinically important differences: 5 points).

eTable 6: Exercise training data and adherence to the prescribed exercise intervention for High Intensity Interval Training (HIIT) and Moderate Continuous Training (MCT)

Study phase	group	No. (%)		Median [1st – 3rd quartile]		
		Patients completing each phase	Patients performing ≥ 70% of scheduled exercise sessions	Adherence (%) to scheduled exercise sessions	Performed exercise sessions (no.) per week	Amount (min) of exercise per week
Supervised (month 0-3)	HIIT	56 (96.6)	45 (80.4)	84 [73-94]	2.5 [2.1-2.8]	96 [82-105]
	MCT	55 (94.8)	42 (76.4)	85 [70-97]	4.4 [3.4-4.7]	176 [137-188]
Home-based (month 4-12)	HIIT	48 (82.8)	23 (47.9)	69 [41-82]	2.0 [1.2-2.4]	77 [46-92]
	MCT	53 (91.4)	31 (58.5)	72 [54-86]	3.6 [2.7-4.3]	144 [108-171]
entire phase (month 0-12)	HIIT	48 (82.8)	27 (56.3)	73 [53-82]	2.1 [1.6-2.4]	82 [59-92]
	MCT	53 (91.4)	32 (60.4)	76 [58-89]	3.8 [2.9-4.4]	150 [115-176]

eTable 7: Group differences in primary and secondary endpoints after 3 and 12 months including only the per-protocol population of patients who performed at least 70% of the scheduled training sessions

	Difference [95% CI]			p-value
	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT	
Change baseline to 3 months				
Peak $\dot{V}O_2$, mL/min/kg	2.1 [0.9 to 3.3]	2.6 [1.4 to 3.8]	-0.5 [-1.6 to 0.7]	<.001
$\dot{V}E/\dot{V}CO_2$ slope	1.6 [-0.4 to 3.7]	0.3 [-1.8 to 2.3]	1.4 [-0.6 to 3.3]	.22
Workload at VT1, watts	3 [-1 to 7]	8 [3 to 13]	-5 [-10 to 1]	.008
E/e' medial	-1.6 [-3.5 to 0.3]	-1.3 [-3.1 to 0.5]	-0.3 [-2.2 to 1.6]	.18
e' medial, cm/s	0.4 [-0.3 to 1.1]	0.3 [-0.2 to 0.7]	0.1 [-0.6 to 0.7]	.43
LAVI, mL/m^2	0.2 [-2.1 to 2.5]	1.2 [-1.2 to 3.6]	-1.0 [-3.7 to 1.7]	.56
NT-proBNP, pg/mL	-193 [-510 to 124]	-182 [-535 to 171]	-11 [-282 to 261]	.41
KCCQ QoL domain	0.1 [-8.5 to 8.8]	5.6 [-2.2 to 13.4]	-5.5 [-13.8 to 2.8]	.34
Change baseline to 12 months				
Peak $\dot{V}O_2$, mL/min/kg	1.7 [0.3 to 3.0]	1.1 [-0.4 to 2.6]	0.6 [-0.9 to 2.1]	.07
$\dot{V}E/\dot{V}CO_2$ slope	0.6 [-1.6 to 2.8]	-2.1 [-4.2 to -0.1]	2.7 [0.4 to 5.0]	.05
Workload at VT1, watts	8 [3 to 14]	4 [-1 to 10]	4 [-2 to 10]	.01
E/e' medial	-1.8 [-3.5 to -0.2]	-0.4 [-2.2 to 1.5]	-1.5 [-3.4 to 0.5]	.15
e' medial, cm/s	0.6 [0.0 to 1.2]	0.2 [-0.4 to 0.7]	0.4 [-0.2 to 1.1]	.16
LAVI, mL/m^2	0.9 [-3.2 to 5.1]	1.1 [-1.7 to 3.9]	-0.2 [-4.4 to 4.1]	.73
NT-proBNP, pg/mL	-256 [-611 to 99]	-197 [-567 to 173]	-59 [-286 to 168]	.40
KCCQ – QoL [a]	3.8 [-5.2 to 12.9]	13.8 [3.7 to 23.8]	-9.9 [-21.3 to 1.4]	.01

[a] higher scores indicate better quality of life (score range 1-100, minimial clinically important differences: 5 points); HIIT: High Intensity Interval Training, MCT: Moderate Continuous Training, Control: Guideline Control, CI: Confidence Interval, $\dot{V}O_2$: oxygen consumption, $\dot{V}E/\dot{V}CO_2$ slope: minute ventilation to carbon dioxide output slope, VT1: ventilatory threshold, E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, LAVI: Left atrial volume index, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, KCCQ: Kansas City Cardiomyopathy Questionnaire, QoL: Quality of life

eTable 9: List of Serious Adverse Events (SAEs) for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

	HIIT		MCT		Guideline Control	
	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants
Serious Adverse Events (SAEs)	**33**	**18 (31%)**	**28**	**18 (31%)**	**27**	**16 (27%)**
Cardiovascular SAEs	**21**	**10 (17%)**	**18**	**12 (21%)**	**14**	**10 (17%)**
Heart Failure related	**7**	**5 (9%)**	**8**	**4 (7%)**	**5**	**3 (5%)**
Worsening heart failure	2	2 (3%)	3	2 (3%)	4	2 (3%)
Atrial fibrillation	3	2 (3%)	4	2 (3%)	-	-
Pleural effusion	1	1 (2%)	-	-	1	1 (2%)
Ventricular arrhythmias	-	-	1	1 (2%)	-	-
Cardiac arrest / death	1	1 (2%)	-	-	-	-
Other cardiovascular	**14**	**8 (14%)**	**10**	**8 (14%)**	**9**	**9 (15%)**
Acute coronary syndrome	3	3 (5%)	4	3 (5%)	5	5 (8%)
Supraventricular arrhythmias	2	1 (2%)	1	1 (2%)	1	1 (2%)
Hypertension	-	-	2	2 (3%)	-	-
Peripheral artery disease occlusion of peripheral bypass	2	1 (2%)	-	-	-	-
Thromboembolic occlusion of a femoral artery	-	-	-	-	1	1 (2%)
Sinus bradycardia	1	1 (2%)	1	1 (2%)	-	-
Cardiac Syncope	1	1 (2%)	1	1 (2%)	-	-
Pulmonary embolism	1	1 (2%)	-	-	-	-
Deep vein thrombosis	1	1 (2%)	-	-	-	-
Ventilation-perfusion mismatch	1	1 (2%)	-	-	-	-
Endocarditis	-	-	1	1 (2%)	-	-
Dilated aorta	1	1 (2%)	-	-	-	-
Transient ischemic attack	1	1 (2%)	-	-	-	-
3rd degree AV block	-	-	-	-	1	1 (2%)
Pulmonary hypertension	-	-	-	-	1	1 (2%)
Non-cardiovascular SAEs	**12**	**10 (17%)**	**10**	**9 (16%)**	**13**	**9 (15%)**
Orthopedic	**1**	**1 (2%)**	**4**	**4 (7%)**	**1**	**1 (2%)**
Femur fracture	-	-	1	1 (2%)	-	-
Biceps tendon rupture	-	-	1	1 (2%)	-	-
Subacromial syndrome	-	-	1	1 (2%)	-	-
Inflammatory arthritis	-	-	1	1 (2%)	-	-
Gonarthrosis	1	1 (2%)	-	-	-	-
Bacterial osteomyelitis	-	-	-	-	1	1 (2%)

eTable 9 continued...

	HIIT		MCT		Guideline Control	
	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants
Pulmonological	3	2 (3%)	1	1 (2%)	1	1(2%)
COPD exacerbation	2	1 (2%)	-	-	-	-
Pleural effusion	-	-	1	1 (2%)	-	-
Pneumonia	-	-	-	-	1	1 (2%)
Mantel cell lymphoma	1	1 (2%)	-	-	-	-
Gastroenterological	3	3 (5%)	3	3 (5%)	4	4 (7%)
Viral gastro-enteritis	2	2 (3%)	1	1 (2%)	-	-
Gastritis	-	-	1	1 (2%)	1	1 (2%)
Gastric ulcer	-	-	1	1 (2%)	-	-
Symptomatic Choledocholithiasis	1	1 (2%)	-	-	-	-
Diabetic gastroparesis	-	-	-	-	1	1 (2%)
Diverticulitis	-	-	-	-	1	1 (2%)
Abdominal wall hernia	-	-	-	-	1	1 (2%)
Gynecological	-	-	-	-	1	1 (2%)
Ovary cysts	-	-	-	-	1	1 (2%)
Urological/ Nephrological	2	1 (2%)	-	-	2	2 (3%)
Stricture of the urethra	2	1 (2%)	-	-	-	-
Acute renal failure	-	-	-	-	1	1 (2%)
Nephrolithiasis	-	-	-	-	1	1 (2%)
Endocrinological/ Metabolic	2	2 (3%)	-	-	3	3 (5%)
Conn´s syndrome	1	1 (2%)	-	-	-	-
Hypokalemia	-	-	-	-	1	1 (2%)
Hypothyroidism	1	1 (2%)	-	-	-	-
Metabolic disturbance in diabetes	-	-	-	-	1	1 (2%)
Hypoglycemia	-	-	-	-	1	1 (2%)
Neurological	1	1 (2%)	2	2 (3%)	1	1 (2%)
Concussion	1	1 (2%)	1	1 (2%)	-	-
Subdural hematoma	-	-	-	-	1	1 (2%)
Epileptical attack	-	-	1	1 (2%)	-	-

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of

"***Mueller S****, Haller B, Feuerstein A, Winzer EB, Beckers P, Haykowsky MJ, Gevaert, A. B., Hommel, J., Azevedo, L. F., Duvinage, A., Esefeld, K., Fegers-Wustrow, I., Christle, J. W., Pieske-Kraigher, E., Belyavskiy, E., Morris, D. A., Kropf, M., Aravind-Kumar, R., Edelmann, F., Linke, A., Adams, V., Van Craenenbroeck, E. M., Pieske, B., Halle, M. and the OptimEx-Clin Study Group. 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(5):3393-406.*"[242]

Original Publication

ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 3393–3406
Published online 15 July 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14070

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

Received: 17 March 2022; Revised: 28 May 2022; Accepted: 27 June 2022
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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

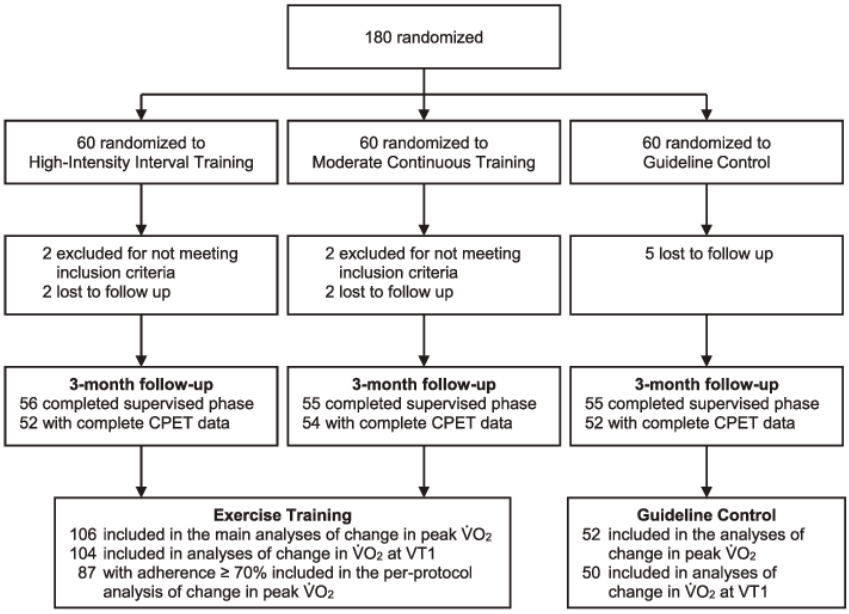
	Exercise (N = 106)	Guideline control (N = 52)
Sex		
Female	70 (66%)	34 (65%)
Male	36 (34%)	18 (35%)
Age, years	70 (7)	69 (10)
Weight, kg	84.6 ± 18.0	78.7 ± 15.2
Body mass index, kg/m^2	30.6 ± 6.1	29.0 ± 4.9
Resting heart rate, min	65 ± 11	65 ± 11
Blood pressure, mmHg		
Systolic	128 ± 13	127 ± 15
Diastolic	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).

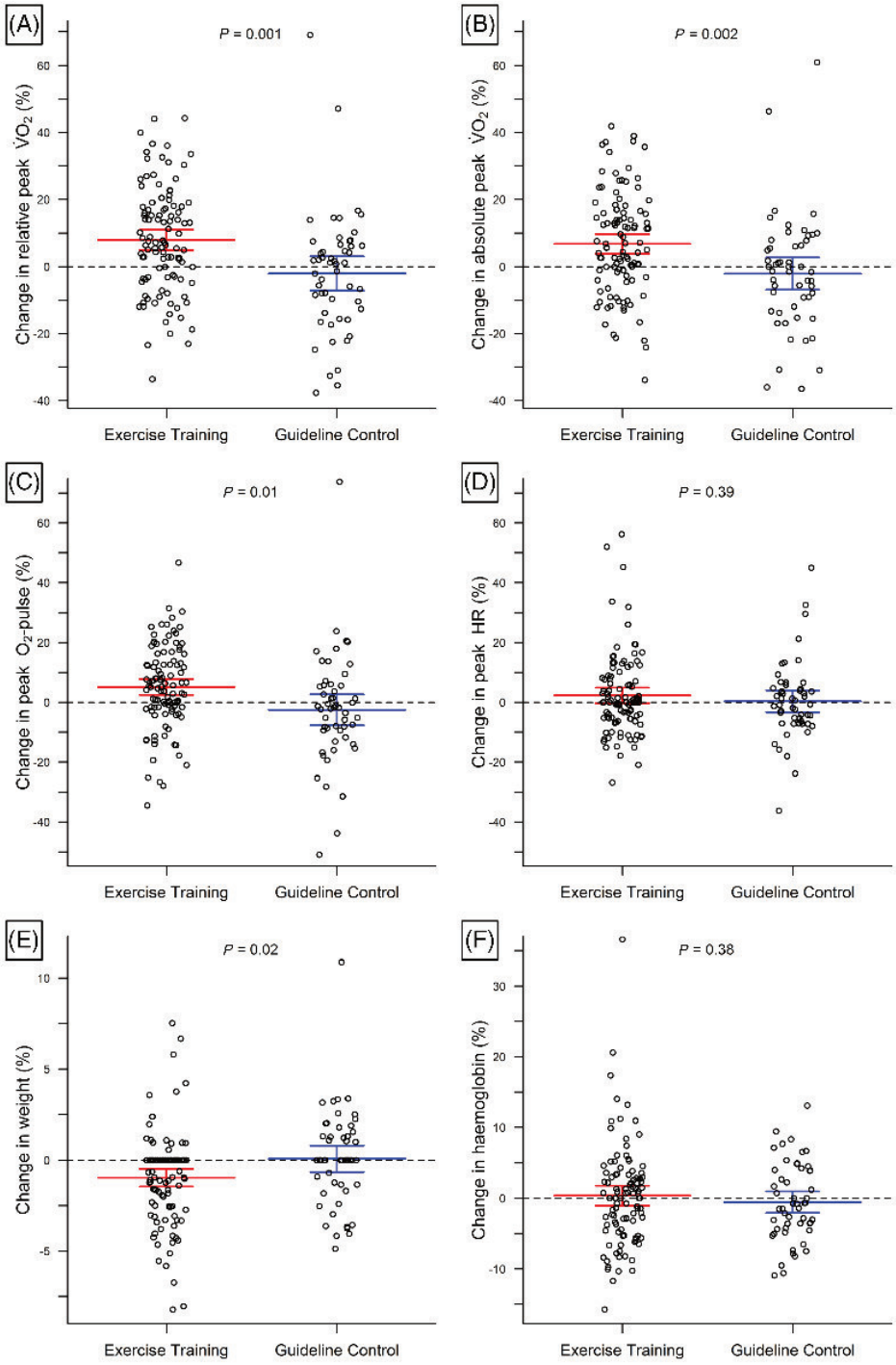
Associations between changes in peak $\dot{V}O_2$ and its determinants

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.



ESC Heart Failure 2022; **9**: 3393–3406
DOI: 10.1002/ehf2.14070

Table 2 Mean changes following exercise training and guideline control

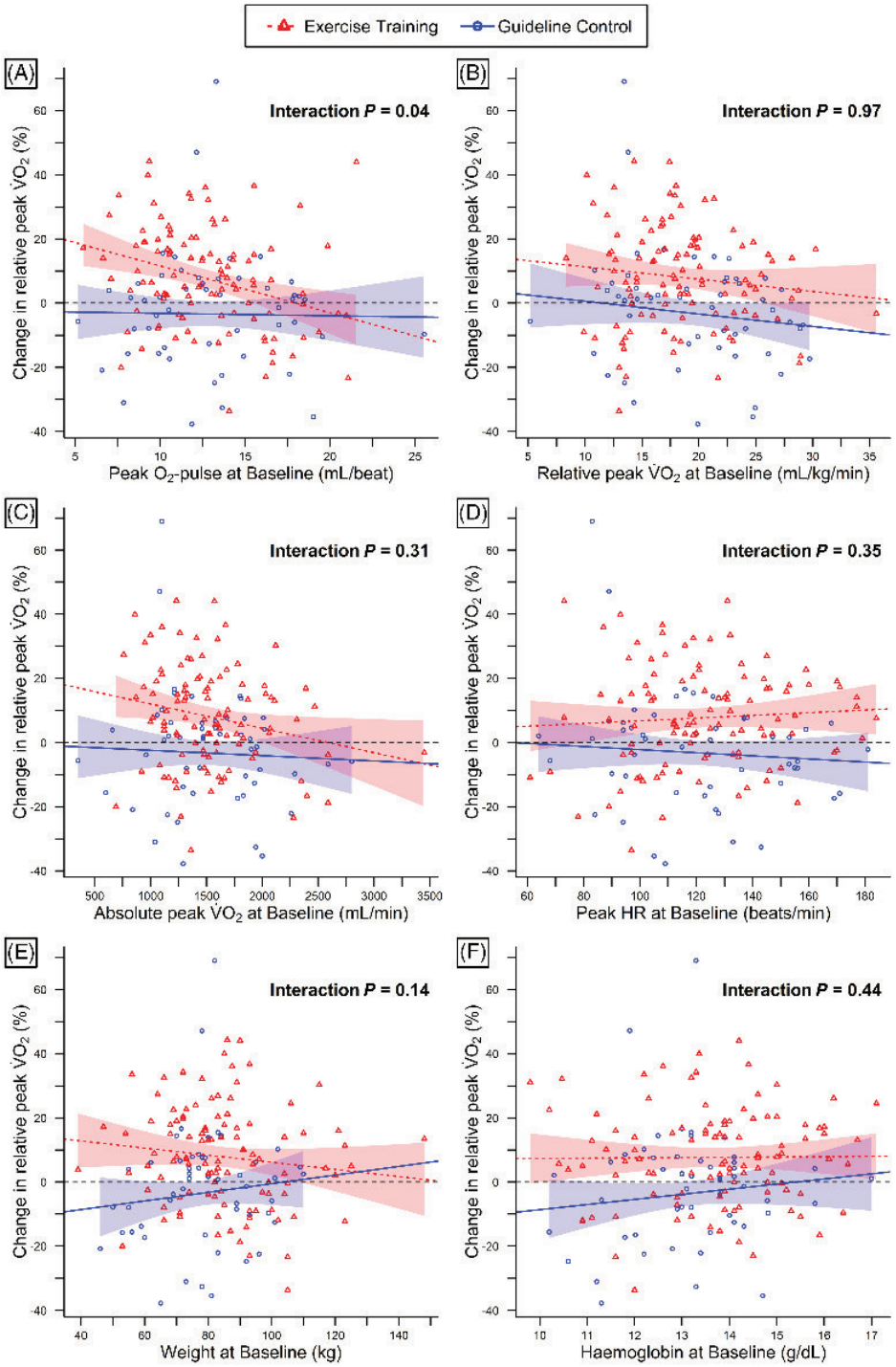
	Mean ± SD						
	Exercise training [N = 106]*			Guideline control [N = 52]*			
	Baseline	3 months	Change	Baseline	3 months	Change	Difference (95% CI), P-value
Relative peak $\dot{V}O_2$, mL/kg/min	18.5 ± 5.1	19.8 ± 5.7	8.0 ± 15.7%	19.5 ± 5.8	18.9 ± 5.7	−2.0 ± 18.3%	10.0% (4.1 to 15.9), P = 0.001
Absolute 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.



ESC Heart Failure 2022; **9**: 3393–3406
DOI: 10.1002/ehf2.14070

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.

Acknowledgements

The authors thank the staff of the University Hospital 'Klinikum rechts der Isar' of the Technical University of Munich, Antwerp University Hospital, Heart Centre Leipzig, Charité Universitätsmedizin Berlin and Norwegian University of Science and Technology Trondheim who were involved in recruitment, evaluations, administration, and support during the conduct of the OptimEx-Clin study. Open Access funding enabled and organized by Projekt DEAL.

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.

Funding

This work was supported by the European Commission, Framework Program 7 [grant number: EU 602405-2]; the German Centre for Cardiovascular Research (DZHK) [grant number: 81Z0600603] [S.M. and M.H.]; and the Deutsche Forschungsgemeinschaft (DFG) through the TUM International Graduate School of Science and Engineering (IGSSE; Garching, Germany) [S.M., A.D., and M.H.]. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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 ≥ 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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ESC Heart Failure 2022; **9**: 3393–3406
DOI: 10.1002/ehf2.14070

Supplementary Material

Supplementary Material

Table S1: Results of the predictor analyses for the inter-individual response variability in $\dot{V}O_2$ at VT1

	Mean change in $\dot{V}O_2$ at VT1 [ß-coefficient (95% CI), p-value]		Interaction p for Exercise Training vs. Guideline Control
	Exercise Training [N = 104]*	Guideline Control [N = 50]*	
Peak O_2-pulse (per 1 mL/beat)	0.09% (-0.87 to -1.04) p = 0.86	0.11% (-1.34 to 1.57) p = 0.88	0.97
Peak $\dot{V}O_2$ (per 1 mL/kg/min)	-0.49% (-1.13 to 0.15) p = 0.13	-0.93% (-1.91 to 0.05) p = 0.07	0.44
Peak $\dot{V}O_2$ (per 100 mL/min)	-0.26% (-1.00 to 0.48) p = 0.49	-0.51% (-1.76 to 0.74) p = 0.42	0.73
Peak heart rate (per 10 beats/min)	-0.68% (-1.94 to 0.57) p = 0.29	-1.74% (-3.73 to 0.25) p = 0.09	0.35
Weight (per 10 kg)	1.39% (-0.42 to 3.20) p = 0.13	2.35% (-1.29 to 5.99) p = 0.19	0.61
Haemoglobin (per 1 g/dL)*	0.07% (-1.92 to 2.06) p = 0.95	0.77% (-3.41 to 4.95) p = 0.73	0.77

*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

	Mean change in peak $\dot{V}O_2$ [ß-coefficient (95% CI), p-value]			Global Interaction p
	High-Intensity Interval Training (N = 52)	Moderate Continuous Training (N = 54)	Guideline Control (N = 52)	
Peak O_2-pulse (per 1 mL/beat)	-1.44% (-2.80 to -0.08) p = 0.04	-1.50% (-2.52 to -0.48) p = 0.007	-0.08% (-1.11 to 0.96) p = 0.88	0.15
Peak $\dot{V}O_2$ (per 1 mL/kg/min)	-0.14% (-1.13 to 0.85) p = 0.78	-0.54% (-1.28 to 0.19) p = 0.15	-0.39% (-1.10 to 0.32) p = 0.28	0.78
Peak $\dot{V}O_2$ (per 100 mL/min)	-0.78% (-1.85 to 0.29) p = 0.16	-0.77% (-1.63 to 0.09) p = 0.08	-0.17% (-1.03 to 0.69) p = 0.70	0.61
Peak heart rate (per 10 beats/min)	0.52% (-1.49 to 2.53) p = 0.61	0.30% (-1.15 to 1.75) p = 0.69	-0.48% (-1.96 to 0.99) p = 0.52	0.61
Weight (per 10 kg)	-2.30% (-4.99 to 0.40) p = 0.10	-0.39% (-2.59 to 1.81) p = 0.72	1.35% (-1.35 to 4.05) p = 0.32	0.15
Haemoglobin (per 1 g/dL)*	-0.80% (-3.63 to 2.03) p = 0.58	0.80% (-1.76 to 3.36) p = 0.54	1.60% (-1.46 to 4.65) p = 0.30	0.48

*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

	ß-coefficient (95 % CI), p-value			Interaction p
	All patients [N = 158]	Exercise Training [N = 106]	Guideline Control [N = 52]	
Mean change in peak $\dot{V}O_2$ for every 1% change in peak heart rate	0.64% (0.47 to 0.81) p < 0.001	0.61% (0.40 to 0.81) p < 0.001	0.67% (0.40 to 0.95) p < 0.001	0.77
Mean change in peak $\dot{V}O_2$ for every 1% change in peak O_2-pulse	0.80% (0.69 to 0.91) p < 0.001	0.78% (0.61 to 0.94) p < 0.001	0.77% (0.61 to 0.93) p < 0.001	0.80
Mean change in peak $\dot{V}O_2$ for every 1% change in weight	-2.39% (1.46 to 3.32) p < 0.001	-2.14% (-3.31 to -0.97) p < 0.001	-1.77% (-3.24 to -0.30) p = 0.02	0.70
Mean change in peak O_2-pulse for every 1% change in peak heart rate	-0.36% (-0.52 to -0.20) p < 0.001	-0.38% (-0.57 to -0.19) p < 0.001	-0.36% (-0.65 to -0.08) p = 0.02	0.95
Mean change in peak heart rate for every 1% change in weight	-0.56% (-1.17 to 0.05) p = 0.08	-0.38% (-1.18 to 0.43) p = 0.39	-0.71% (-1.68 to 0.26) p = 0.14	0.59
Mean change in peak O_2-pulse for every 1% change in weight	-0.34% (-1.21 to 0.52) p = 0.45	-0.02% (-1.06 to 1.02) p = 0.97	-0.06% (-1.59 to 1.46) p = 0.94	0.96

$\dot{V}O_2$ = oxygen consumption

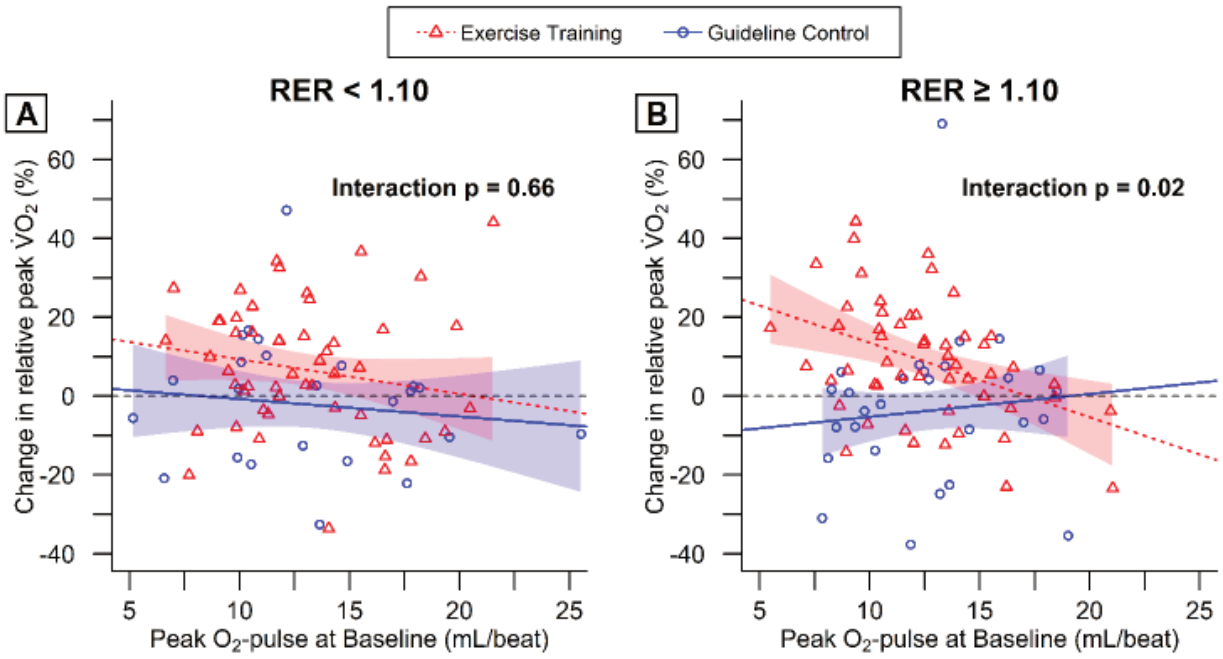

Figure S1: Relationships between baseline peak O_2-pulse and change in peak $\dot{V}O_2$, separated by median baseline peak respiratory exchange ratio (RER). In patients with baseline peak RER < 1.10 (A), there was no significant interaction between baseline peak O_2-pulse × group on change in peak $\dot{V}O_2$ (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 ≥ 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 (-△-) and Guideline Control (—○—). Black dashed lines (- - -) represent null lines

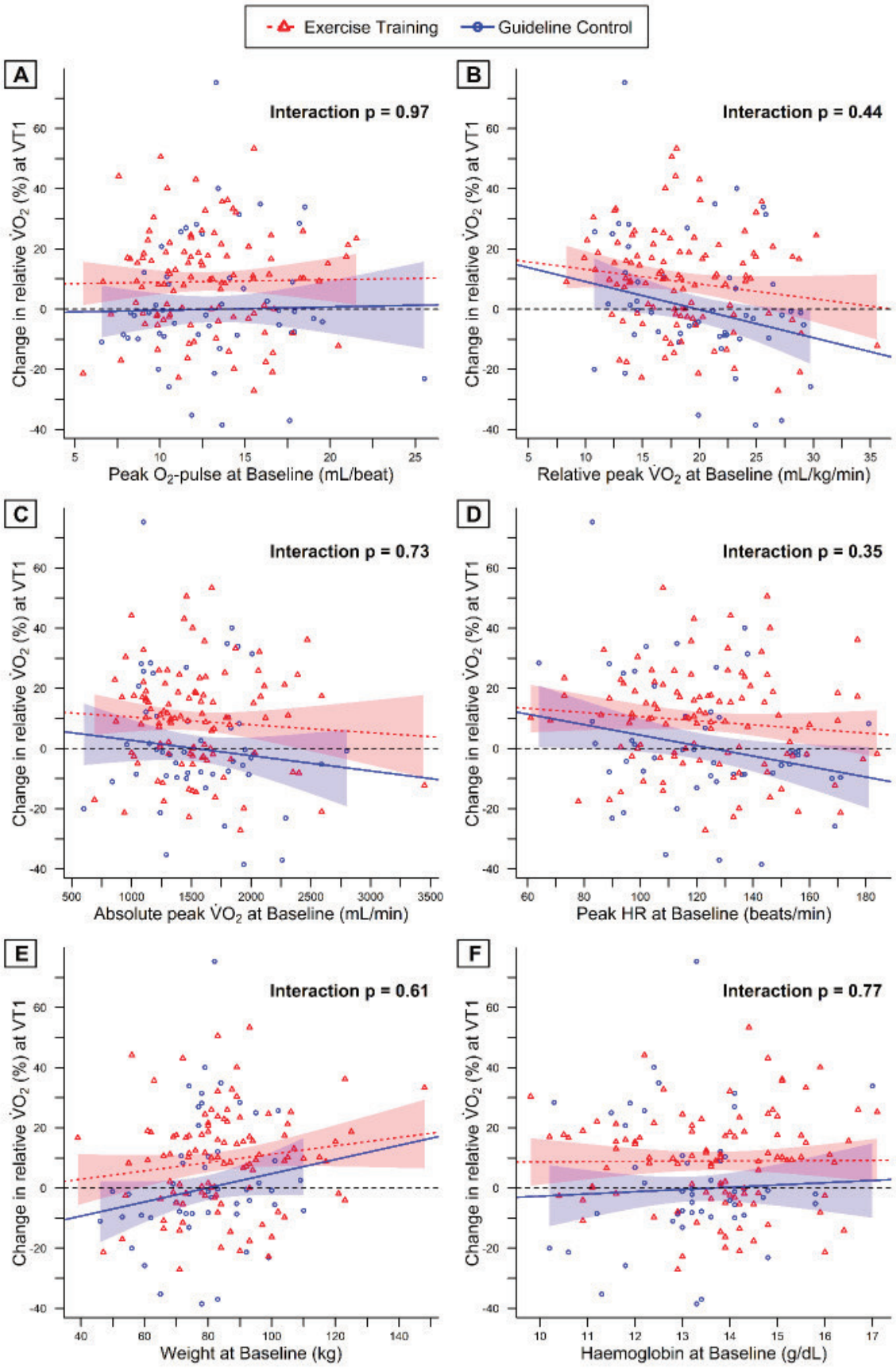

Figure S2: Predictors of change in $\dot{V}O_2$ at VT1. Relationships between changes in relative $\dot{V}O_2$ at VT1 and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak $\dot{V}O_2$ at baseline (C), peak heart rate at baseline (D), baseline weight (E), and baseline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

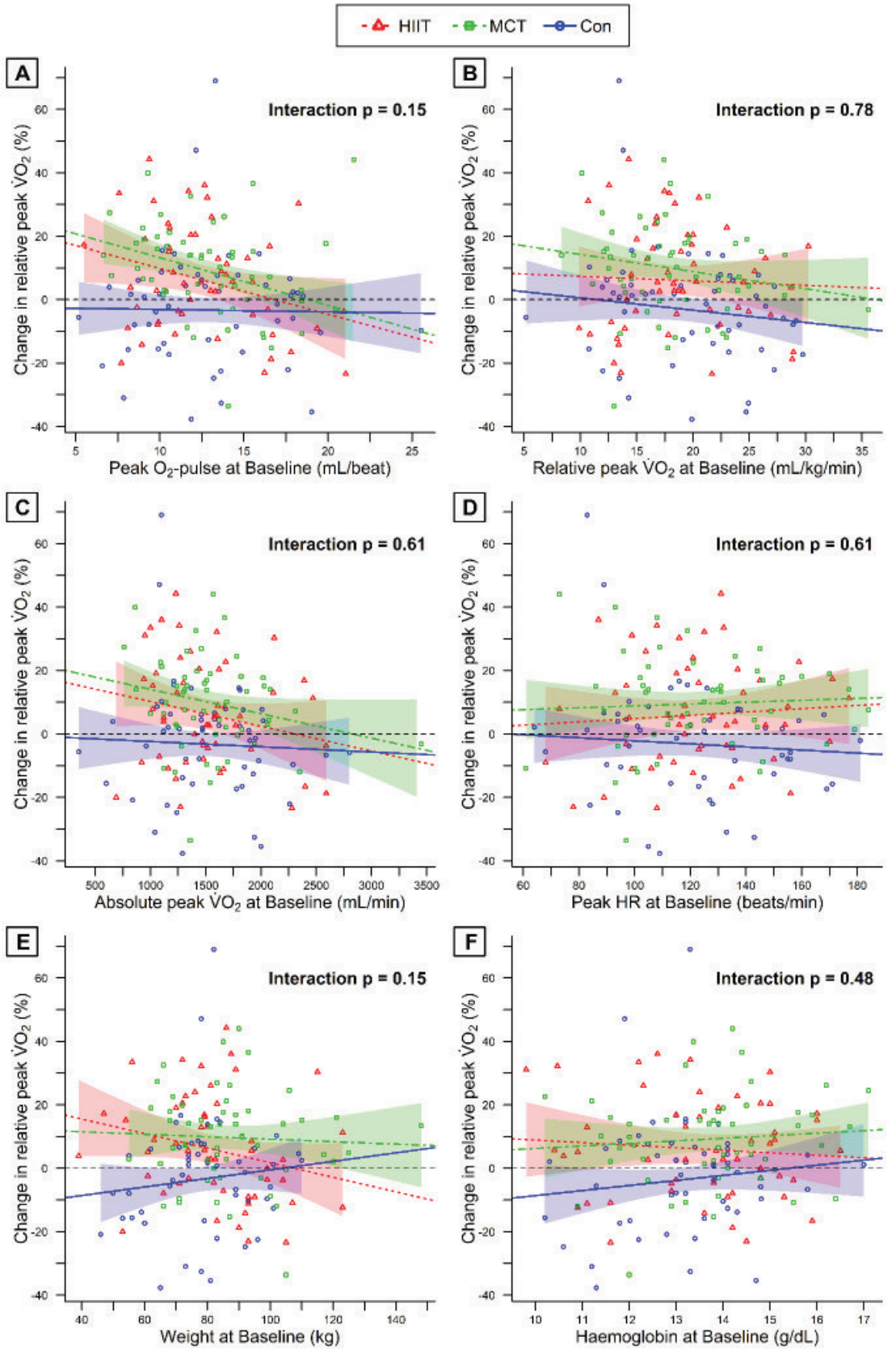

Figure S3: Predictors of change in peak $\dot{V}O_2$ following High-Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control (Con). Relationships between changes in relative peak $\dot{V}O_2$ and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (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 (-△-), MCT (··⊟··) and Con (—○—). Black dashed lines (- - -) represent null lines.

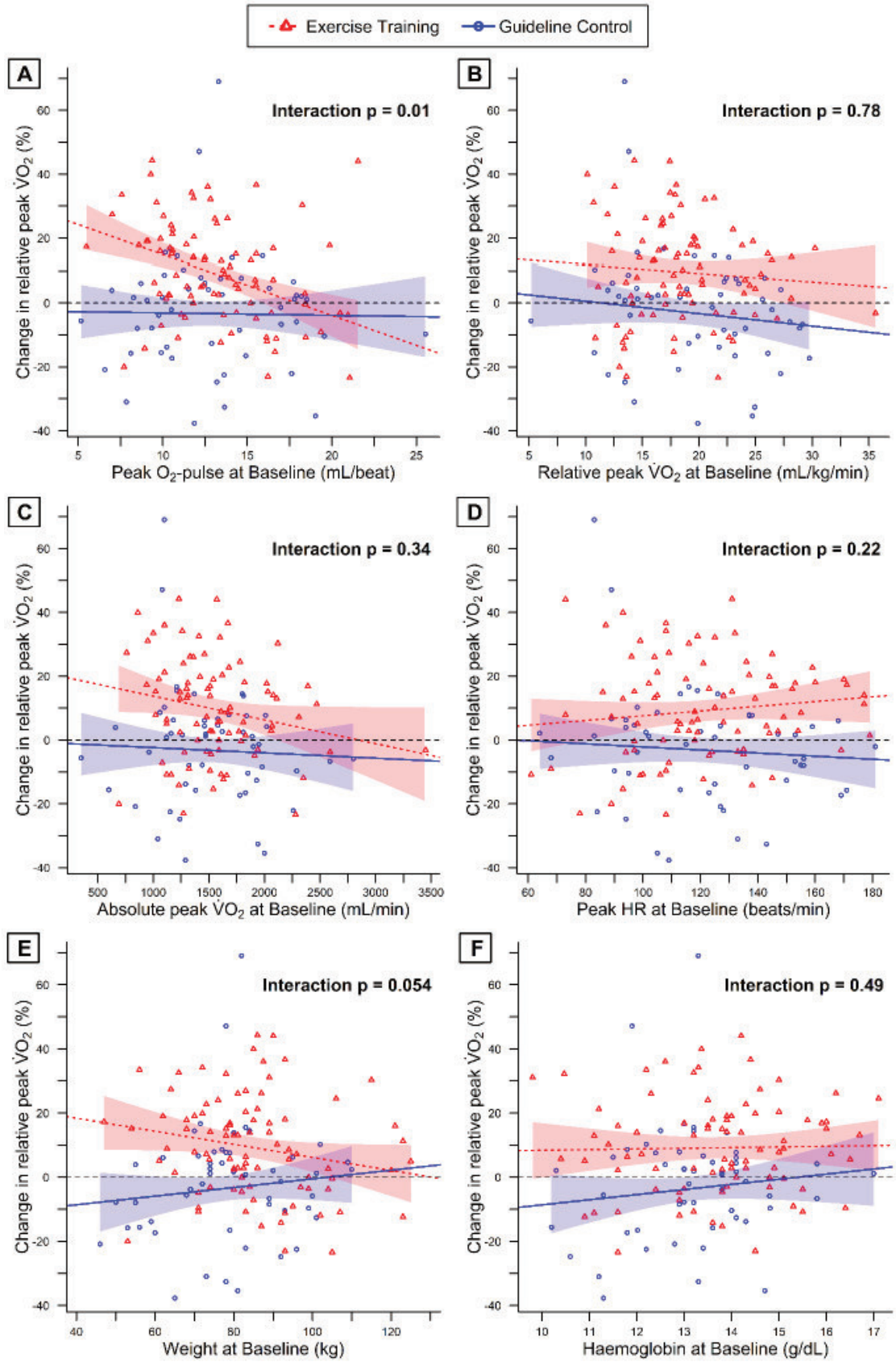

Figure S4: Predictors of change in peak $\dot{V}O_2$ (excluding patients with adherence < 70%). Relationships between changes in peak $\dot{V}O_2$ and peak O_2-pulse at baseline (A), relative peak $\dot{V}O_2$ at baseline (B), absolute peak VO2 at baseline (C), peak heart rate at baseline (D), baseline 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 (- △ -) and Usual Care (—○—). Black dashed lines (- - -) represent null lines.

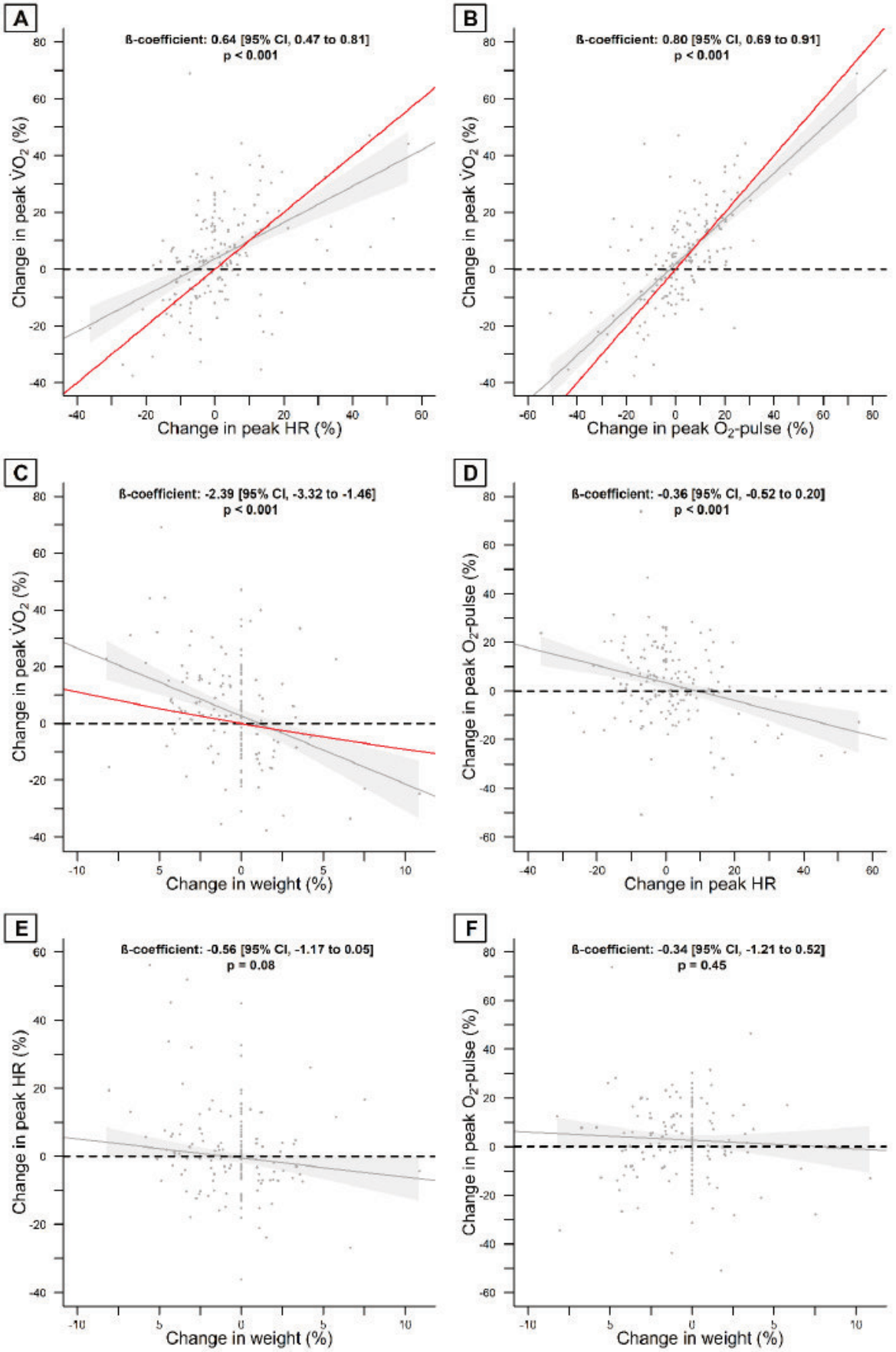

Figure S5: Associations between the changes in peak $\dot{V}O_2$ and its determinants including regression lines and 95% confidence bands. Red lines (—) in A-C represent the predicted associations if all other determinants remain constant. Black dashed lines (- - -) represent null lines.

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