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Abstract

Purpose: To investigate baseline, exercise testing, and exercise training-mediated predictors of change in peak oxygen uptake (VO_{2peak}) from baseline to 12-week follow-up (ΔVO_{2peak}) in a post-hoc analysis from the SMARTEX Heart Failure trial.

Methods: We studied 215 patients with heart failure with left ventricular ejection fraction (LVEF) $\leq$35%, and NYHA class II-III, who were randomized to either supervised high intensity interval training (HIIT) with exercise target intensity 90-95% of peak heart rate (HR_{peak}), supervised moderate continuous training (MCT) with target intensity 60-70% of HR_{peak}, or who received a recommendation of regular exercise on their own (RRE). Predictors of ΔVO_{2peak} were assessed in two models; A logistic regression model comparing highest and lowest tertile (baseline parameters) and a multivariate linear regression model (test/training/clinical parameters).

Results: The change in VO_{2peak} in response to the interventions (ΔVO_{2peak}) varied substantially, from -8.50 to +11.30 $mL \cdot kg^{-1} \cdot min^{-1}$. Baseline NYHA (class II gave higher odds vs III, odds ratio (OR) 7.1 (2.0, 24.9), p=0.002), LVEF OR per % 1.1 (1.0, 1.2), p = 0.005), age (OR per 10 years 0.5 (0.3, 0.8)), p=0.003) were associated with ΔVO_{2peak}.

In the multivariate linear regression, 34% of the variability in ΔVO_{2peak} was explained by the increase in exercise training workload, ΔHR_{peak} between baseline and 12-wk post-testing, age, and ever having smoked.

Conclusion: Exercise training response (ΔVO_{2peak}) correlated negatively with age, LVEF and NYHA class. The ability to increase workload during the training period, and increased ΔHR_{peak} between baseline and the 12-week test were associated with a positive outcome.

Key Words: high intensity exercise training, interval training, moderate training, endurance exercise, HFrEF, left ventricle ejection fraction.

Introduction

Peak oxygen uptake (VO_{2peak}) is a strong prognostic factor in heart failure with reduced ejection fraction (HFrEF) (1). Endurance exercise training has a positive impact on VO_{2peak} (2, 3), left ventricular function (4), quality of life (5), mortality, and morbidity (3, 6, 7). Studies evaluating dose and intensity of exercise training show variability in exercise responses from moderate to large (2-4, 8, 9). Absence of improvement in VO_{2peak} following a systematic exercise program was a strong and independent predictor of adverse cardiac events that were not associated with traditional risk factors (10), whereas a modest increase in three-month VO_{2peak} was associated with less all-cause mortality and fewer hospitalizations in the large HF-ACTION trial (3, 11).

In general, multicenter exercise studies produce smaller outcome effects than single center studies (2, 3, 8, 12). In the HF-ACTION multicenter trial, adherence to target training volume was less than optimal, with only 40% of the patients at or above target exercise minutes per week at three months follow-up (3, 11). In the SMARTEX Heart Failure Study multicenter trial (SMARTEX-HF), adherence to the number of exercise sessions was excellent (96%) during the supervised training period in both the high intensity training group (HIIT) and in the moderate exercise training group (MCT), whereas self-report of exercise training in the recommendation of regular exercise group (RRE) gave less data precision. Despite excellent adherence to exercise sessions, moderate exercise response and no differences in comparative effectiveness were observed between HIIT and MCT for improvement in VO_{2peak} (13). Hence, it is currently unclear how the magnitude of improvement in VO_{2peak} with exercise training is

modified by patient characteristics, adherence, disease severity, co-morbidity, exercise follow-up, or simply by motivation to exercise.

To investigate baseline and exercise training predictors of ΔVO_{2peak} from baseline to 12-week follow-up in HFrEF patients, we performed a post hoc analysis of data from SMARTEX-HF to address if ΔVO_{2peak} was associated with: 1) one or more of the baseline characteristics. 2) exercise training characteristics, e.g. work-load and heart rate during training sessions, exercise testing characteristics, or clinical characteristics known to affect physical performance, e.g. heart failure pathogenesis, age and smoking. We considered the study too small to investigate whether baseline variables have different effects depending on the three specific training interventions.

Methodology

Details of the SMARTEX-HF study protocol and the intervention results on primary and secondary endpoints have been published previously (14, 15).

Participants

In nine European study centers, 261 clinically stable HFrEF patients were randomized from outpatient heart failure clinics, hospital registries, cardiac rehabilitation referrals and public announcements. After withdrawals and appropriate exclusions, 231 started training, and 215 patients completed 12 weeks of exercise and clinical baseline and follow-up assessments. Patient flow in the study has been detailed elsewhere (15). At baseline all subjects had stable, symptomatic HFrEF with left ventricular ejection fraction (LVEF) $\leq$35%. All subjects were in New York Heart Association (NYHA) functional class II-III and were on optimal medical

treatment. Further details of inclusion and exclusion criteria have been described in the rationale and design paper (14).

National ethics committees for medical research approved the study in all countries. All patients gave written informed consent. The study was registered in the clinical trial database prior to start (NCT00917046) and conducted in conformity with the policy statement for the use of human subjects of the Declaration of Helsinki and *Medicine & Science in Sports & Exercise*.

Exercise intervention

Patients were randomized 1:1:1 to a 12-week program of HIIT, MCT, or a control group given a recommendation of mainly home-based regular exercise (RRE), stratified by study center, gender and disease pathogenesis (ischemic versus non-ischemic heart failure). Randomization was performed by a web-based randomization system developed and administered by Unit of Applied Clinical Research, The faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway. Patients in the HIIT and MCT groups performed three weekly sessions of supervised exercise training. Briefly, the HIIT group performed a training program with 4x4 minutes of interval training aiming for a target heart rate of 90-95% of peak heart rate (HR_{peak}) (38 minute workout including warm up, active breaks and cool down) and the MCT group a program with 47 minutes of moderate continuous training aimed at 60-70% of HR_{peak}, designed to be isocaloric. RRE patients were advised to exercise at home according to current exercise guidelines, i.e. 30 minutes 5 days per week (16) and attended a session of moderate intensity training every 3 weeks (50-70% HR_{peak}) (14). The exercise training was performed either on a stationary bicycle ergometer or a treadmill (2, 14).

Clinical measurements

Cardiopulmonary exercise testing (CPET), medical history, anthropometrics, physical examination, fasting blood sampling, quality of life questionnaires, and echocardiography were performed at baseline and after 12 weeks of training (14, 15). VO_{2peak} was measured by CPET performed either on a treadmill or a bicycle ergometer, corresponding to the preferred training mode at each study center and was similar at baseline and 12 weeks for each participant. An incremental protocol with 10 or 20 W increase in workload approximately every minute was used. VO_{2peak} was measured using standard equipment for indirect calorimetry. The mean of the three highest 10-second consecutive measurements was used to calculate VO_{2peak}. HR_{peak} and other related values are reported from the time point when this value was reached. Echocardiography data were acquired according to standard operation procedures of the study (15).

Statistical analysis

In the first post-hoc analysis, data were analyzed using logistic regression comparing the highest versus the lowest tertile of ΔVO_{2peak} (high tertile, $\geq$ 1.5 mL· kg·min and low tertile $\leq$ -1.5 mL· kg·min). In the second analysis we used multivariate linear regression with ΔVO_{2peak} as continuous dependent variable. Data are given as frequencies with percentage in parenthesis, or median with 95 % confidence interval (c.i.) of the median in parenthesis, if otherwise is not stated. P-values <0.05 were considered significant.

Association of baseline variables with ΔVO_{2peak}

To investigate whether the overall moderate changes after exercise training in the SMARTEX-HF study was due to demographics or other characteristics at baseline, we compared the highest versus lowest tertile of ΔVO_{2peak}. The middle tertile was not included in the analysis to increase the contrast between groups, thereby better permitting differences to be identified. The analysis was done for the patient population as a whole, without considering treatment group (i.e. RRE, MCT or HIIT). VO_{2peak} at baseline and treatment group were included as adjustment variables in the analysis.

Additional variables were selected applying no additional a priori hypothesis for an unbiased selection of predictors and to avoid overfitting the analysis model. To this end, a pre-defined selection of baseline variables (see below) was pre-screened using Random Forest analysis with bootstrapping (n=2000), using the "party" package in the R statistical environment (version 3.0.2, R Foundation, http://www.r-project.org).

The baseline variables screened included; study center, heart failure pathogenesis (ischemic versus non-ischemic), height, sex, age, LVEF, NYHA class, VO_{2peak}, sinus rhythm, systolic and diastolic blood pressure, body mass index, duration of HFrEF, cardiac device therapy, chronic obstructive pulmonary disease, smoking (never vs. ever smoker), concentrations of N-Terminal Brain Natriuretic Peptide (NT-proBNP), high sensitive C-reactive protein (CRP) and Thyroxin (T4). The following baseline variables were identified as giving a strong signal of association in the Random forest model: NYHA class, LVEF, age, smoking and treatment group (MCT, RRE

or HIIT). In addition, creatinine clearance and LVEDD were included in an additional sensitivity analyses.

The final main endpoint analysis was logistic regression modeling using the selected baseline variables indicated above, as well as baseline VO_{2peak}. The standard errors of the final logistic regression model were bootstrapped (n=1000) in order to get less biased results. Linearity of logits was tested using restricted cubic splines. As a sensitivity analysis to examine whether omittance of the middle delta VO_{2peak} tertile influenced the results, a linear regression model including all patients was also fitted, using ΔVO_{2peak} as dependent variable and the same predictors as in the logistic regression model.

Association of test- and training-related variables with ΔVO_{2peak}

We then investigated whether exercise test- and training-related variables were associated with the variability in VO_{2peak}, adjusting for relevant baseline variables. ΔVO_{2peak} was analyzed as a continuous variable using multivariate linear regression. Training and exercise test values in the model each represent measures of test and training quality, which are expected to be associated with ΔVO_{2peak}. For instance, significant improvements in both change in exercise training work load (ΔWatt) and ΔVO_{2peak} are typically seen after HIIT (2, 17). Only data from MCT and HIIT patients were included in this analysis as training data were recorded to a limited degree in the mainly home-based RRE group.

ΔVO_{2peak} was analyzed as a continuous variable using a multivariate linear regression model including the following explanatory/adjustment variables selected per protocol: VO_{2peak} at

baseline (CPET1), difference in peak heart rate between baseline and follow-up test at 12 weeks (ΔHR_{peak}), peak respiratory ratio at CPET2, change in ΔWatt after 12 weeks of exercise training, and training group (MCT or HIIT). Based on clinical knowledge on suspected influence, heart failure pathogenesis, age, and smoking were also included in the model for adjustment. Robust standard errors were used and model fit was evaluated using residual plots. The analysis was performed in 106 patients (data for Δwatt missing in n=20 (31%) in MCT and n=15 (19%) in HIIT).

As a supplementary secondary analysis, we removed □Watt from the model to avoid case loss due to missing exercise work load data. This analysis was performed in 134 patients (HR_{peak} missing in 3 MCT patients and 4 HIIT patients, i.e. 5% missing in both groups).

Results

Changes in VO_{2peak}

One patient in the MCT group had missing values for the baseline CPET and was excluded from the analysis, leaving 214 patients for investigation. Characteristics of these patients are shown in Table 1 and in Supplemental Table 1 (see Table, Supplemental Digital Content 1, additional patient characteristics).

There was large variability in ΔVO_{2peak} after the 12-week intervention (from -8.50 $mL \cdot kg^{-1} \cdot min^{-1}$ to +11.30 $mL \cdot kg^{-1} \cdot min^{-1}$). The distribution of ΔVO_{2peak} in each intervention group is illustrated in Figure 1.

The percentage of patients in the high versus the low tertile was 39% vs. 31% in the HIIT group, 40% vs. 25% in the MCT group and 19% vs. 49% in the RRE group. The number of responders in the two training groups were significantly higher than in the RRE group (p = 0.003). The median change in VO_{2peak} in each of the tertiles is displayed in Figure 2.

Associations of ΔVO_{2peak} with baseline values

In the final logistic regression model, NYHA class, age, LVEF and treatment group were significantly associated with ΔVO_{2peak}. VO_{2peak} at baseline (p=0.34 or ever being a smoker (p=0.09), were not associated with ΔVO_{2peak}. Table 2 shows the multivariate model (as well as univariate associations, even if they were not used for explanatory variable selection).

The analysis indicated 7.1 higher odds for an exercise response (Highest ΔVO_{2peak} tertile) if classified in NYHA II vs. NYHA III at baseline. In the SMARTEX-HF dataset (i.e. without bootstrapping), 58 of 70 (82.9%) of the patients with a positive change in VO_{2peak} (above the tertile cutoff) were in NYHA class II. (Mean baseline VO_{2peak} (± SD) for NYHA II was 18.7 ± 4.8 $mL \cdot kg^{-1} \cdot min^{-1}$ and for NYHA III, 15.0 ± 3.8 $mL \cdot kg^{-1} \cdot min^{-1}$). Compared to control (RRE), the proportion that were responders (i.e. highest ΔVO_{2peak} tertile) was higher in the two exercise groups (HIIT and MCT), with no statistically significant difference between HIIT and MCT (p = 0.71).

The sensitivity analysis using ΔVO_{2peak} as a continuous dependent variable and including all patients. Table 3 confirmed the direction and significance of the associations from the main model for NYHA class (p=0.002), age (p=0.001), and training group (HIIT or MCT vs. RRE:

p<0.01, HIIT vs. MCT: p=0.93), but not for LVEF (p=0.10). Sensitivity analyses including estimated creatinine clearance (p=0.84) or left ventricular end diastolic diameter (LVEDD) (p=0.17) showed that these variables were not significant.

Associations of ΔVO_{2peak} with test- or training-related variables (HIIT and MCT groups)

In a multivariate linear regression model with ΔVO_{2peak} as a continuous outcome variable the significant variables were: ΔHR_{peak} between baseline and 12-week test (p = 0.007), change in training workload between baseline and follow-up (p = 0.003), age (negative coefficient, p < 0.001) and ever smoker (p = 0.001). R-squared for this model was 0.34. The following variables were not significant: HIIT versus MCT (p = 0.47), peak RQ at 12-week test (p = 0.53), heart failure pathogenesis (p = 0.92), VO_{2peak} at baseline (p = 0.55). The model is given in supplementary table 2 (see Table, Supplemental Digital Content 2, Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: primary model), and illustrated in Figure 3A, showing results for an increase or decrease in HR_{peak} of 20 BPM.

In the secondary model given in supplementary table 3, (see Table, Supplemental Digital Content 3, Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: secondary model), excluding ΔWatt (due to lower n for this variable) 29% of the variation in ΔVO_{2peak} was explained and the significant variables were: ΔHR_{peak} from baseline to 12-weeks test (p<0.001), age (negative coefficient, p = 0.002) and ever smoker (p = 0.02, Figure 3B). There were still no differences between HIIT and MCT (p = 0.42, Figure 3C). The initial model explained more of the variance in the VO_{2peak} response than the second model (34% vs.

29%). When including the same patients in the two models (n = 106), the explained variation was 34% and 29% for the initial and secondary model, respectively.

Both a logistic regression- and a linear regression analysis excluding the RRE group gave the same results as analyses reported in the manuscript (unpublished data).

Discussion

Associations of ΔVO_{2peak} with baseline values

The main finding of this study was that the baseline characteristics NYHA class, LVEF, age, and treatment group were associated with ΔVO_{2peak} after 12 weeks of exercise training. Older age, poorer left ventricular function and higher NYHA class were associated with a less favorable 12-week change in VO_{2peak}. As illustrated in figure 2, a large part of the study participants in all three groups had neutral or negative changes in VO_{2peak} over the 12-week intervention. This does not necessarily mean that they were negative responders to exercise. It could also be due to a negative fitness trajectory caused by advancing severity of heart failure. VO_{2peak} and NYHA class are closely related, with higher VO_{2peak} (18, 19) and lower number of long-term cardiac events (10) in NYHA II versus NYHA III-IV HFrEF patients (18). We confirmed that baseline NYHA class and ΔVO_{2peak} are associated as well, with the ΔVO_{2peak} response independent of baseline VO_{2peak}.

Each 1% higher baseline LVEF was associated with 10% greater odds of being in the highest delta VO_{2peak} tertile, independent of exercise intensity or exercise group. The overall group response in LVEF at 12 weeks was moderate (15). Our logistic regression analysis shows

that baseline LVEF might indicate the left ventricular exercise recovery potential in HFrEF-patients. To the best of our knowledge, the baseline LVEF – exercise response association adds new knowledge about individual exercise responses, with improved exercise recovery prognosis in HFrEF patients with higher baseline contractile function.

In HFrEF, older age is associated with lower VO_{2peak} (18, 20), more severe symptoms and worse prognosis compared with younger patients (20). Our study confirms an age-dependent effect in ΔVO_{2peak} as well, with higher odds for increasing VO_{2peak} in the youngest HFrEF patients (median age 56 and 65 years in high and low VO_{2peak} tertile, respectively). In comparison, some have reported a larger training response in HFrEF patients above 70 years of age (2), while others report an age-independent response in HFrEF patients below and above 65 years of age (5, 21, 22). The differences between studies could be due to patient selection, physiological aging, which reduces HR_{peak} and VO_{2peak} (20), clustering of comorbidities, medication, age-dependent deteriorating heart failure that may affect the ability or motivation to exercise (11), different training quality or continuous versus categorical statistical analysis. The age dependent exercise response was confirmed in the secondary analyses as well. HFrEF duration was classified above and below 12 months in our study, making interaction analysis between age and years with symptomatic HFrEF impossible. In addition, the study sample was too small to study this association; however, heart failure duration was far from significant in the main logistic regression model.

Associations of ΔVO_{2peak} with test- or training-related characteristics (HIIT and MCT groups)

According to the multivariable linear regression analysis a total of 34% of the variability in ΔVO_{2peak} was explained by the test and training quality variables ΔHR_{peak} (CPET2 minus CPET1) and ΔWatt (exercise training workload from exercise week 1 to 12), in addition to the baseline variables age and ever being a smoker.

Challenges for long-term adherence to exercise training in patients with chronic symptomatic heart failure include dyspnea, medication, muscle and physiological deconditioning (3). Peak heart rate rarely changes in apparently healthy individuals, and ΔHR_{peak} seldom changes from baseline to follow-up testing in HIIT studies (2, 23, 24). In HFrEF patients, both no change, and increasing HR_{peak} are reported after exercise training (2, 25-27). A positive ΔHR_{peak} and ΔVO_{2peak} could indicate a transition from peripheral (muscle) to central (heart) limitations to maximal exercise performance throughout the training period (9, 28). A negative ΔHR_{peak} and ΔVO_{2peak} may indicate deteriorating heart failure and decreased exercise tolerance (11), or could indicate some variability in test quality in the study. Maximal RQ values indicated similar levels of effort during testing at all timepoints (13). As there were only minor changes in medication throughout the training intervention, change in medication does not explain ΔHR_{peak} from CPET1 to CPET2.

In addition to the moderate increase in exercise training workload (Δ workload was 21 watt and 15 watt in HIIT and MCT, respectively), the lack of difference in intensities (mean training intensity in HIIT and MCT was 88% and 80%, respectively) between groups is most likely also responsible for the VO_{2peak} response (15).

In CVD patients, superior exercise response was found in the higher part of the HIIT workload zone (29). In comparison to Wisløff et al (Δ workload HIIT = 95 watt) (2), and Iellamo et al (Δ workload HIIT = 70 watt) (17), the increase in exercise training workload and the ability to maintain exercise intensity within the target range were moderate in the SMARTEX-HF study (9). Maintaining target exercise intensity is challenging (30), and the limited increase in exercise training workload may be due to physiological, pathological, psychological factors or patient and/or coaching motivation (9). Heart failure deterioration is associated with a negative exercise response (11, 31), and may explain part of the modest improvement in VO_{2peak} and LVEDD in the SMARTEX-HF study (14, 15). Similarly, others have reported a moderate exercise outcome even in coronary patients, with a neutral outcome of HIIT versus MCT in a large multicenter study (32), whereas combining endurance and strength training was not associated with improved cardiac function (4). A subgroup of patients with advanced chronic heart failure improved exercise capacity and reversed LV remodeling after daily, long-term moderate exercise training (6 and 12 months) (33). As patients with the poorest left ventricular function responded the least to exercise training in our study, further investigation of whether daily exercise and longer duration of the intervention is necessary to gain a positive exercise response, or if this may lead to deterioration of CHF. With both positive and negative exercise responders in our study, tailor-made programs and follow-up may be highly warranted in deconditioned CHF patients. The findings in the primary statistical model suggests that both physiological and pathological factors may limit the ability to exercise at moderate and high intensity, and we acknowledge that our model leaves 66% of the variability in the exercise response unexplained. As the change in VO_{2peak} is influenced by several central and peripheral factors (7, 26, 27, 34) that were not measured in the present study, we are unable to conclude which of them are the

most important, except to confirm the importance of chronotropic incompetency. It may be argued that inclusion of non-baseline variables precludes prediction of the exercise response, but this was not the focus of the secondary analyses. As we have no data on exercise motivation, this factor could also not be discussed.

Study strengths and limitations

Study strengths includes the explorative statistical design using random forest-based analysis to select among a substantial number of potential explanatory factors without overfitting the model, close supervision of exercise training and thorough documentation of clinical and physiological patient data. Patient adherence to exercise training sessions was excellent. In addition, the multicenter study probably reflects a wider and more representative patient selection compared to single-center studies. The patients included in the present study represented approximately 10% of the heart failure population screened for inclusion. We believe that the study participants are representative for stable HFrEF with LVEF ≤ 35% under optimal medical care. However, a majority of the screened patients had LVEF above 35%, indicating less representativeness of the overall HFrEF population.

It is a limitation that exercise-related data on intensity and duration could not be studied in the RRE group due to their per protocol unsupervised and unrecorded home-based exercise. Furthermore, we did not assess training motivation and thus could not tell whether there were differences between the intervention groups**.** Of note, the confidence intervals for the exercise group effects were wide and the precision of the OR should be interpreted with caution.

Conclusion

Exercise training response (ΔVO_{2peak}) correlated negatively with age, LVEF and NYHA class. The ability to increase workload during the training period, and a positive ΔHR_{peak} between baseline and 12-week test were associated with a positive outcome.

Clinical implications

Exercise training is an important and recommended treatment for heart failure, and this study indicates that individualized approaches may be warranted, as different patients experience exercise tolerance and "exercise intolerance" with a limited or negative response to exercise training. Our analyses suggest that age, LVEF, NYHA classification and the ability to improve VO_{2peak} might be considered when advising exercise training and evaluating exercise response in HFrEF, as data point to a gradient towards a poor exercise response in the oldest and most symptomatic HFrEF-patients. An exercise response evaluation by exercise testing might indicate if exercise is an individual treatment of choice, or not. Furthermore, it is important to focus on a systematic increase in exercise workload and maintaining exercise target exercise intensity, as individual patients have different ability and/or motivation to increase exercise workload during a training period.

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Conflict of Interests Disclosures

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References

1. Corra U, Giordano A, Mezzani A, et al. Cardiopulmonary exercise testing and prognosis in heart failure due to systolic left ventricular dysfunction: a validation study of the European Society of Cardiology Guidelines and Recommendations (2008) and further developments. *Eur J Prev Cardiol*. 2012;19(1):32-40.

2. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115(24):3086-94.

3. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1439-50.

4. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. *J Am Coll Cardiol*. 2007;49(24):2329-36.

5. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301(14):1451-9.

6. Vanhees L, Rauch B, Piepoli M, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (Part III). *Eur J Prev Cardiol*. 2012;19(6):1333-56.

7. Tucker WJ, Lijauco CC, Hearon CM, Jr., et al. Mechanisms of the Improvement in Peak VO2 With Exercise Training in Heart Failure With Reduced or Preserved Ejection Fraction. *Heart Lung Circ*. 2018;27(1):9-21.

8. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99(9):1173-82.

9. Karlsen T, Aamot IL, Haykowsky M, Rognmo O. High Intensity Interval Training for Maximizing Health Outcomes. *Prog Cardiovasc Dis*. 2017;60(1):67-77.

10. Tabet JY, Meurin P, Beauvais F, et al. Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure. *Circulation Heart failure*. 2008;1(4):220-6.

11. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circulation Heart failure*. 2012;5(5):579-85.

12. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol*. 2018;261:134-41.

13. Ellingsen O, Halle M, Conraads V, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation*. 2017;135(9):839-49.

14. Stoylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen O. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF--rationale and design. *Eur J Prev Cardiol*. 2012;19(4):813-21.

15. Ellingsen O, Halle M, Conraads VM, et al. High Intensity Interval Training in Heart Failure Patients with Reduced Ejection Fraction. *Circulation*. 2017.

16. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-200.

17. Iellamo F, Manzi V, Caminiti G, et al. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. *Int J Cardiol*. 2013;167(6):2561-5.

18. Russell SD, Saval MA, Robbins JL, et al. New York Heart Association functional class predicts exercise parameters in the current era. *Am Heart J*. 2009;158(4 Suppl):S24-30.

19. Pina IL, Lin L, Weinfurt KP, et al. Hemoglobin, exercise training, and health status in patients with chronic heart failure (from the HF-ACTION randomized controlled trial). *Am J Cardiol*. 2013;112(7):971-6.

20. Forman DE, Clare R, Kitzman DW, et al. Relationship of age and exercise performance in patients with heart failure: the HF-ACTION study. *Am Heart J*. 2009;158(4 Suppl):S6-S15.

21. Wielenga RP, Huisveld IA, Bol E, et al. Safety and effects of physical training in chronic heart failure. Results of the Chronic Heart Failure and Graded Exercise study (CHANGE). *Eur Heart J*. 1999;20(12):872-9.

22. Wielenga RP, Huisveld IA, Bol E, et al. Exercise training in elderly patients with chronic heart failure. *Coronary artery disease*. 1998;9(11):765-70.

23. Storen O, Helgerud J, Saebo M, et al. The Effect of Age on the V O2max Response to High-Intensity Interval Training. *Med Sci Sports Exerc*. 2017;49(1):78-85.

24. Helgerud J, Hoydal K, Wang E, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc*. 2007;39(4):665-71.

25. Jonsdottir S, Andersen KK, Sigurosson AF, Sigurosson SB. The effect of physical training in chronic heart failure. *Eur J Heart Fail*. 2006;8(1):97-101.

26. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA*. 2000;283(23):3095-101.

27. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995;25(6):1239-49.

28. Keteyian SJ, Levine AB, Brawner CA, et al. Exercise training in patients with heart failure. A randomized, controlled trial. *Ann Intern Med*. 1996;124(12):1051-7.

29. Moholdt T, Madssen E, Rognmo O, Aamot IL. The higher the better? Interval training intensity in coronary heart disease. *Journal of science and medicine in sport*. 2014;17(5):506-10.

30. Aamot IL, Forbord SH, Karlsen T, Stoylen A. Does rating of perceived exertion result in target exercise intensity during interval training in cardiac rehabilitation? A study of the Borg scale versus a heart rate monitor. *Journal of science and medicine in sport*. 2014;17(5):541-5.

31. Jones LW, Douglas PS, Khouri MG, et al. Safety and efficacy of aerobic training in patients with cancer who have heart failure: an analysis of the HF-ACTION randomized trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(23):2496-502.

32. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol*. 2015;179:203-10.

33. Hollriegel R, Winzer EB, Linke A, et al. Long-Term Exercise Training in Patients With Advanced Chronic Heart Failure: SUSTAINED BENEFITS ON LEFT VENTRICULAR PERFORMANCE AND EXERCISE CAPACITY. *J Cardiopulm Rehabil Prev*. 2016;36(2):117-24.

34. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014;48(16):1227-34.

Supplemental table 1, additional patient characteristics

Supplemental table 2, Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: primary model

Supplemental table 3, Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: secondary model

Figure legends

Figure 1.

Distribution of ΔVO_{2peak} after 12 weeks of exercise training in the HIIT, MCT and RRE groups. The dotted line marks zero change in VO_{2peak},with positive and negative changes in VO_{2peak} to the right and left side of zero. HIIT, high intensity exercise training; MCT, moderate continuous training; RRE, recommendation of regular exercise; VO_{2peak}, peak oxygen uptake

Figure 2.

Median ΔVO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$after 12 weeks of exercise training in the three tertiles of high (H), medium (M) and low (L) VO_{2peak} responders (all patients). The medium tertile: -1.5 $mL \cdot kg \cdot min^{-1}$ to 1.5 $mL \cdot kg \cdot min^{-1}$. Open bars: range. Grey shading: 95% confidence interval of the medians.

Figure 3.

Prediction of ΔVO_{2peak} differences after 12 weeks of supervised exercise training (data from HIIT and MCT) versus: A) Effect of change in exercise training work load in patients with either a positive or a negative ΔHR_{peak} from CPET1 to CPET2. The multivariable linear regression model also includes delta workload, age, ever smoking, exercise training group, peak RQ at 12 weeks, heart failure pathogenesis, and VO_{2peak} at baseline. B) Effect of ΔHR_{peak} from CPET1 to CPET2 in ever vs. never smokers. The multivariable linear regression model also includes age, delta HRpeak from CPET1 to CPET2, exercise training group, peak RQ at 12 weeks, heart failure pathogenesis, and VO2peak at baseline. C) Effect of change in ΔHR_{peak} from CPET1 to CPET2 in HIIT vs MCT, same model as B. Data are means with 95% confidence intervals (CI); HR, heart rate; VO_{2peak}, peak oxygen uptake, CPET, cardiopulmonary exercise testing, HIIT, high intensity interval training, HR_{peak}, peak heart rate.

Figure 1

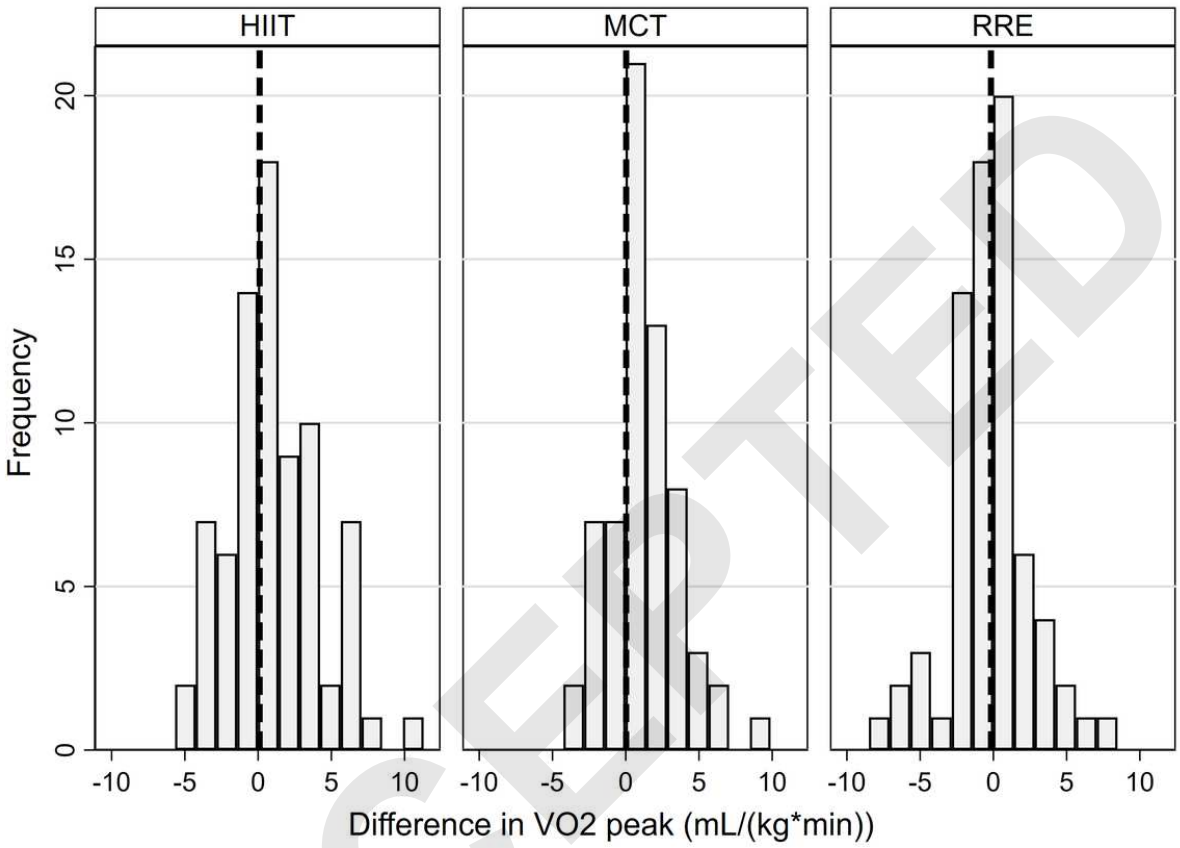

Figure 2

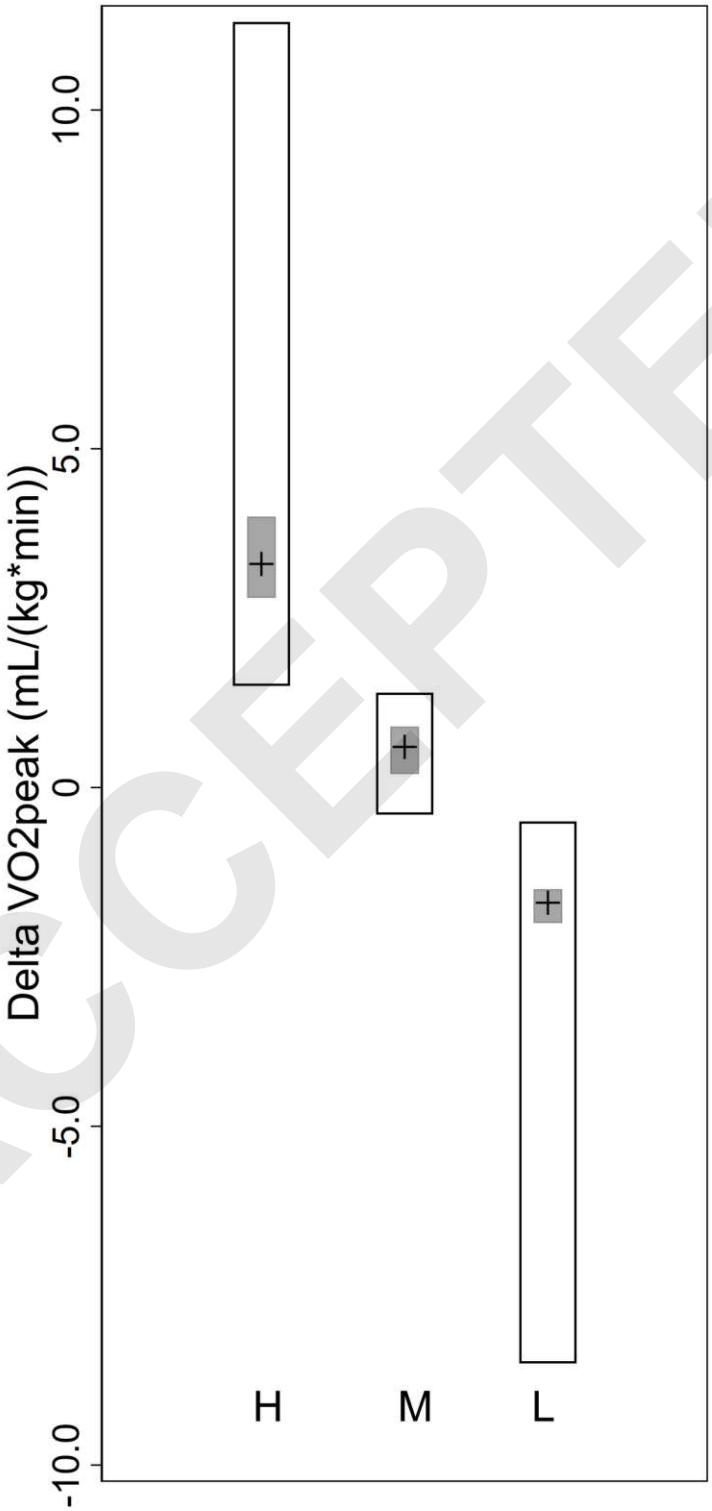

Figure 3

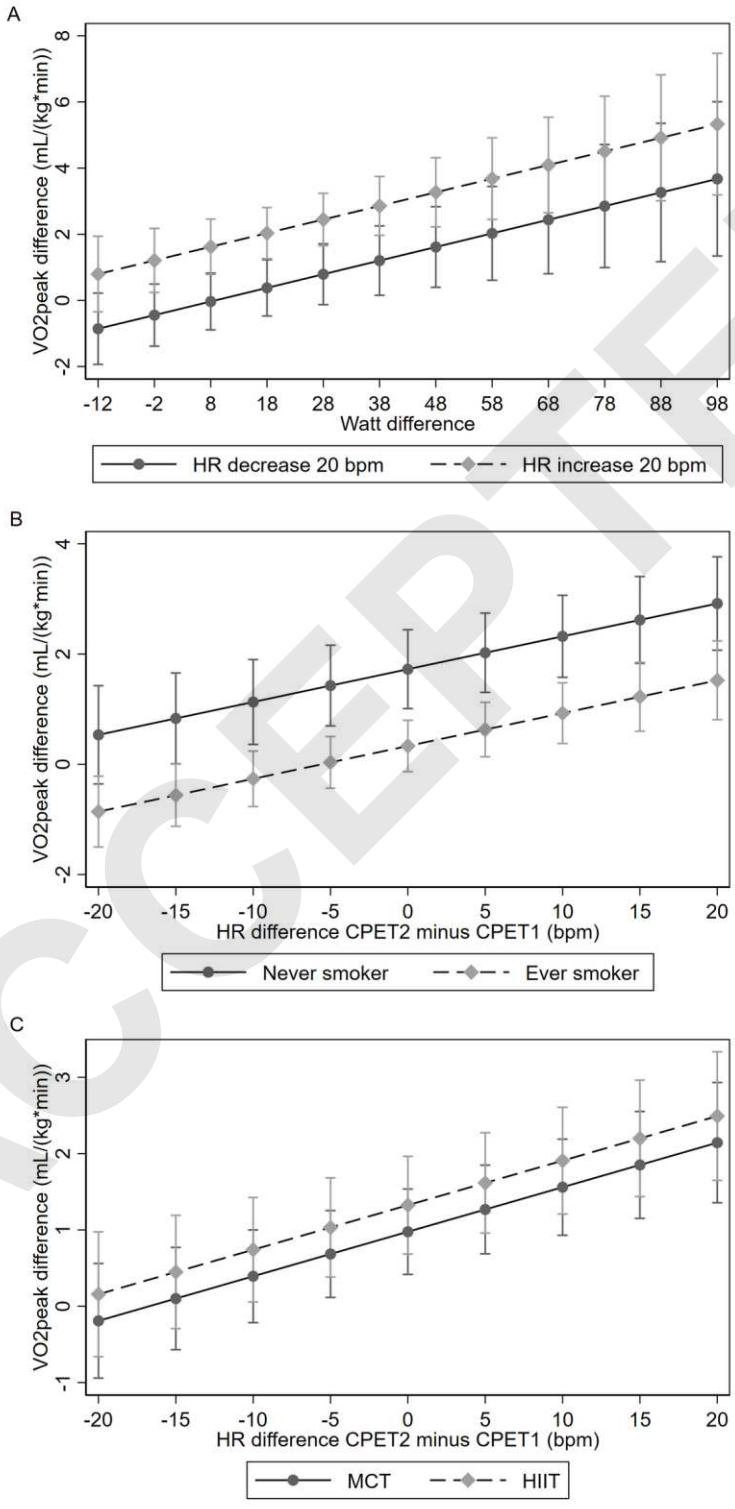

Table 1. Baseline characteristics

Characteristic									
ΔVO_{2peak} tertiles	Low (n=72)			Medium (n=72)			High (n=70)		
Study groups	HIIT (n =24)	MCT (n =16)	RRE (n = 32)	HIIT (n =23)	MCT (n =22)	RRE (n =27)	HIIT (n=30)	MCT (n =26)	RRE (n =14)
Age	68 (61,75)	63 (57,70)	56 (53,67)	65 (54,73)	65 (56,67)	63 (55,66)	58 (54,67)	58 (51,63)	56 (49,70)
Women, n (%)	2 (8)	1 (6)	5 (16)	5 (22)	6 (27)	5 (19)	7 (23)	5 (19)	4 (29)
BMI, kg/m2	28.0 (26.0,32.4)	27.6 (23.8,31.3)	27.4 (25.6,29.2)	27.8 (25.2,30.8)	28.1 (26.7,32.3)	27.5 (24.9,30.1)	27.4 (24.9,28.9)	26.9 (25.5,31.1)	27.9 (24.4,30.2)
SBP, mmHg	116 (110,123)	114 (110,130)	117 (110,120)	115 (108,122)	121 (117,135)	125 (115,130)	117 (110,125)	115 (110,123)	122 (114,134)
DBP, mmHg	73 (70,78)	78 (64,80)	70 (70,79)	70 (65,74)	70 (68,80)	78 (74,82)	77 (67,80)	76 (69,80)	78 (64,86)
Alcohol drinks per week, n	1 (0,1)	3 (2,7)	2 (0,3)	2 (0,7)	1 (1,3)	2 (1,4)	2 (1,6)	2 (0,5)	1 (0,3)
Current smoking, n (%)	3 (13)	1 (6)	12 (38)	6 (26)	4 (18)	4 (15)	5 (17)	1 (4)	2 (14)

Heart Failure < 12 mo, n (%)	21 (88)	13 (81)	25 (78)	19 (83)	20 (91)	23 (85)	23 (77)	24 (92)	10 (77)
NYHA class, n (%)									
II	16 (67)	7 (44)	23 (72)	14 (61)	14 (64)	18 (67)	25 (83)	20 (77)	13 (93)
III	8 (33)	9 (56)	9 (28)	9 (39)	8 (36)	9 (33)	5 (17)	6 (23)	1 (7)
LVEF, %	26 (24,30)	27 (23,33)	30 (27,32)	30 (24,34)	31 (28,34)	28 (23,31)	30 (29,33)	28 (22,33)	33 (30,36)
LVEDD	69 (64,74)	72 (65,74)	69 (67,71)	69 (63,77)	67 (62,73)	68 (63,70)	65 (63,70)	69 (65,74)	67 (64,71)
NT-proBNP, ng/L	2289 (1051,3175)	1133 (731,1758)	1056 (685,1130)	871 (737,1670)	910 (437,1864)	1025 (558,1853)	894 (395,1221)	853 (586,1059)	458 (365,987)
hs-CRP	2.2 (1.3,4.6)	1.7 (1.0,3.2)	2.0 (1.3,2.7)	2.4 (1.7,5.4)	1.9 (0.9,4.4)	2.7 (1.7,3.8)	1.1 (0.9,1.6)	2.3 (0.9,4.1)	1.9 (1.4,5.9)
History of Diabetes mellitus, n (%)	7 (29)	8 (50)	8 (25)	3 (13)	7 (32)	6 (22)	6 (20)	6 (23)	0
Peak exercise testing									
VO_{2peak}, $L \cdot min^{-1}$	1.48 (1.22, 1.68)	1.35 (1.18,1.55)	1.52 (1.42,1.77)	1.44 (1.05,1.63)	1.39 (1.18,1.62)	1.35 (1.12,1.56)	1.45 (1.27,1.64)	1.42 (1.31,1.82)	1.83 (1.35,2.12)
VO_{2peak}, $ml \cdot kg \cdot min^{-1}$	15.9	15.8	18.3	15.9	15.5	17.3	17.5	18.4	20.4

	(13.4,19.1)	(14.6,19.3)	(16.5,20.3)	(13.9,17.9)	(14.3,19.6)	(14.6,19.0)	(16.1,19.7)	(15.0,19.7)	(16.3,24.4)
Workload peak, Watt	100 (83,121)	90 (75,107)	110 (90,120)	100 (70,110)	90 (80,141)	110 (80,121)	105 (90,120)	100 (90,140)	130 (88,143)
HR_{peak}, beats·min^{-1}	124 (116,136)	128 (106,151)	130 (120,138)	127 (114,137)	125 (105,142)	137 (128,149)	126 (115,135)	125 (99,134)	129 (114,142)
RQ	1.15 (1.11,1.21)	1.11 (1.03,1.22)	1.11 (1.07,1.15)	1.09 (1.03,1.15)	1.15 (1.09,1.18)	1.14 (1.09,1.18)	1.14 (1.10,1.19)	1.16 (1.10,1.20)	1.11 (1.01,1.16)
Peak O_2puls, mL·beats^{-1}	11.8 (9.7,14.1)	9.7 (9.2,12.7)	12.5 (12.1,14.2)	11.5 (9.5,13.8)	10.8 (9.6,15.2)	10.2 (8.4,12.8)	11.9 (9.6,12.7)	12.3 (10.4,14.4)	13.3 (10.3,18.5)

Baseline patient demographics by study group and exercise response (tertiles of change in VO_{2peak} from baseline to 12-weeks of exercise training). Continuous variables are given as median with 95% confidence interval of the median. $VO_{2peak,}$ peak oxygen uptake; HIIT, high intensity exercise training; MCT, moderate continuous training; RRE, recommendation of regular exercise; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain factor; CRPhs, high sensitive C-reactive protein; HR_{peak}, peak heart rate; RQ, Respiratory quotient; peak O_2puls, peak oxygen puls.

Table 2 - Logistic regression model for associations of delta VO_{2peak} with baseline values[1]

Baseline variable	Multivariable model (n=142)				Univariable associations		
	OR	95% CI	p-value		OR	95% CI	p-value
NYHA class II vs. class III	7.1	2.0, 24.9	0.002		2.7	1.2, 6.1	0.01
Age per 10 years	0.5	0.3, 0.8	0.003		0.7	0.5, 0.9	0.02
LVEF	1.1	1.0, 1.2	0.005		1.0	1.0, 1.1	0.14
HIIT vs. MCT	0.4	-0.8, 1.6	0.71		1.3	0.6, 3.1	0.55
HIIT vs. RRE	1.7	0.1, 3.4	0.03		2.9	1.2, 6.8	0.02
MCT vs. RRE	2.1	0.4, 3.9	0.001		3.7	1.4, 9.7	0.007
VO_{2peak}	1.0	0.9, 1.1	0.34		1.0	1.0, 1.1	0.34
Ever smoker	0.4	0.2, 1.1	0.09		0.3	0.1, 0.7	0.002

[1]Odds ratio for being in the upper tertile vs. the lower tertile

Table 3 - Sensitivity analysis: Linear regression model for associations of delta VO_{2peak} with baseline values

Baseline variable	Multivariable model (n=214)					Univariable associations			
	Coefficient	95% CI	t	p-value		Coefficient	95% CI	t	p-value
NYHA class III vs. class II	-1.18	-1.92, -0.44	-3.17	0.002		-0.84	-1.55, -0.13	-2.32	0.021
Age per 10 years	-0.57	-0.91, -0.23	-3.30	0.001		-0.43	-0.74, -0.11	-2.67	0.008
LVEF	0.04	-0.01, 0.09	1.64	0.10		0.02	-0.03, 0.08	0.82	0.41
HIIT vs. MCT	0.04	-0.81, 0.88	0.09	0.93		0.05	-0.88, 0.97	0.10	0.92
HIIT vs. RRE	1.47	0.56, 2.39	3.18	0.002		1.35	0.41, 2.30	2.82	0.005
MCT vs. RRE	1.44	0.59, 2.28	3.35	0.001		1.40	0.53, 2.26	3.18	0.002

VO_{2peak}	-0.07	-0.17, 0.02	-1.47	0.14		0.00	-0.09, 0.10	0.09	0.93
Ever smoker	-0.59	-1.29, 0.12	-1.63	0.10		-0.75	-1.51, 0.01	-1.94	0.053

Characteristic									
ΔVO_{2peak} tertiles	Low (n=72)			Medium (n=72)			High (n=70)		
Study groups	HIIT (n =24)	MCT (n =16)	RRE (n = 32)	HIIT (n =23)	MCT (n =22)	RRE (n =27)	HIIT (n=30)	MCT (n =26)	RRE (n =14)
HF pathogenesis, n (%)									
Non- Ischemic	12 (50)	4 (25)	11 (34)	5 (22)	12 (55)	11 (41)	14 (47)	10 (38)	10 (71)
Ischemic	12 (50)	12 (75)	21 (66)	18 (78)	10 (45)	16 (59)	16 (53)	16 (62)	4 (29)
Previous MI	9 (38)	11 (69)	13 (41)	18 (78)	9 (41)	15 (56)	17 (57)	15 (58)	4 (29)
Previous CABG	6 (25)	6 (38)	7 (22)	8 (35)	4 (18)	9 (33)	6 (20)	3 (12)	1 (7)
Previous PCI	10 (42)	8 (50)	16 (50)	12 (52)	5 (23)	13 (48)	10 (33)	10 (38)	4 (29)
Device therapy, n (%)									
Pacemaker	0	0	0	0	0	2 (7)	2 (7)	0	0
ICD	7 (29)	11 (69)	15 (47)	9 (39)	9 (41)	11 (41)	11 (37)	17 (65)	5 (38)
CRT	6 (25)	0	6 (19)	5 (22)	0	5 (19)	3 (10)	4 (15)	2 (14)
Medication									

ACE inhibitor/ARB	22 (92)	14 (88)	31 (97)	21 (91)	21 (95)	26 (96)	28 (93)	24 (92)	12 (93)
β-blocker	23 (96)	15 (94)	31 (97)	22 (96)	21 (95)	26 (96)	28 (93)	24 (92)	14 (100)
Aldosterone receptor antagonist	18 (75)	9 (56)	20 (63)	11 (48)	9 (41)	12 (44)	20 (67)	16 (62)	7 (50)
Diuretic	19 (79)	14 (88)	23 (72)	18 (78)	14 (64)	18 (67)	21 (70)	20 (77)	10 (71)
Digoxin or digitoxin	6 (25)	2 (13)	3 (9)	6 (26)	2 (9)	1 (4)	5 (17)	4 (15)	2 (14)
Statin	15 (63)	14 (88)	22 (69)	19 (83)	15 (68)	18 (67)	16 (53)	17 (65)	5 (36)

Supplementary table 1.

Baseline patient demographics by study group and exercise response (tertiles of change in VO_{2peak} from baseline to 12-weeks of exercise training). Continuous variables are given as median with 95% confidence interval of the median. $VO_{2peak,}$ peak oxygen uptake; HIIT, high intensity exercise training; MCT, moderate continuous training; RRE, recommendation of regular exercise; HF, heart failure; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ICD, implanted cardiac device; CRT, cardiac resynchronization therapy; ACE inhibitor/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; β-blocker, beta blockers.

Supplementary table 2 – Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: primary model

Baseline variable	Multivariable model (n=106)					Univariable associations			
	Coefficient	95% CI	t	p-value		Coefficient	95% CI	t	p-value
Delta HR_{peak}	0.04	0.01, 0.07	2.78	0.007		0.06	0.03, 0.09	3.86	<0.001
Delta workload	0.03	0.01, 0.05	3.01	0.003		0.04	0.02, 0.06	3.40	0.001
Age per 10 years	-0.69	-1.04, -0.33	-3.85	<0.001		-0.82	-1.16, -0.48	-4.83	<0.001
Ever smoker	-1.66	-2.63, -0.69	-3.39	0.001		-1.67	-2.76, -0.59	-3.06	0.003
HIIT vs. MCT	0.34	-0.59, 1.27	0.72	0.47		0.14	-0.90, 1.18	0.26	0.79
Peak RQ at 12-	-1.47	-6.04,	-	0.53		-0.36	-5.47,	-	0.89

weeks test		3.10	0.64				4.76	0.14	
Heart failure pathogenesis	0.05	-0.92, 1.02	0.10	0.92		-0.71	-1.80, 0.39	-1.28	0.20
VO_{2peak} at baseline	-0.04	-0.16, 0.09	-0.60	0.55		0.11	-0.01, 0.23	1.90	0.06

Supplementary table 3 – Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: secondary model

Baseline variable	Multivariable model (n=134)			
	Coefficient	95% CI	t	p-value
Delta HR peak	0.06	0.03, 0.08	4.37	<0.001
Age per 10 years	-0.65	-1.05, -0.25	-3.23	0.002
Ever smoker	-1.28	-2.31, -0.25	-2.46	0.02
HIIT vs. MCT	0.35	-0.50, 1.20	0.81	0.42
Peak RQ at 12-weeks test	-4.28	-9.97, 1.41	-1.49	0.14
Heart failure pathogenesis	-0.02	-1.01, 0.96	-0.05	0.96
VO_{2peak} at baseline	-0.02	-0.13, 0.08	-0.38	0.70