

Author's accepted manuscript (postprint)

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Published in: Medicine & Science in Sports & Exercise

DOI: 10.1249/MSS.0000000000002193

Available online: 04 Nov 2019

Citation:

Karlsen, T., Videm, V., Halle, M., Ellingsen, Ø., Støylen, A., Dalen, H., Delagardelle, C., Larsen, A. I., Hole, T., Mezzani, A., van Craenenbroeck, E. M., Beckers, P., Pressler, A., Christle, J. W., Winzer, E. B., Mangner, N., Woitek, F. J., Höllriegel, R., Snoer, M., Feiereisen, P., Valborgland, T., Linke, A. & Prescott, E. (2020). Baseline and exercise predictors of VO₂peak in systolic heart failure patients: Results from SMARTEX-HF. *Medicine & Science in Sports & Exercise*, 52(4), 810-819. doi: 10.1249/MSS.0000000000002193

This is an Accepted Manuscript of an article published by American College of Sports Medicine in *Medicine & Science in Sports & Exercise* on 04/11/2019, available online: https://journals.lww.com/acsm-msse/FullText/2020/04000/Baseline_and_Exercise_Predictors_of_V_O2peak_in.5.aspx

1 **Baseline and exercise predictors of VO_{2peak} in HF_{rEF}: results from SMARTEX-HF**

2

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59 **Abstract**

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

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

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

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

78 **Conclusion:** Exercise training response ($\Delta\text{VO}_{2\text{peak}}$) correlated negatively with age, LVEF and
79 NYHA class. The ability to increase workload during the training period, and increased
80 $\Delta\text{HR}_{\text{peak}}$ between baseline and the 12-week test were associated with a positive outcome.

81

82 **Word count: 248**

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

85

| 86

87 **Introduction**

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

97 In general, multicenter exercise studies produce smaller outcome effects than single
98 center studies (2, 3, 8, 12). In the HF-ACTION multicenter trial, adherence to target training
99 volume was less than optimal, with only 40% of the patients at or above target exercise
100 minutes per week at three months follow-up (3, 11). In the SMARTEx Heart Failure Study
101 multicenter trial (SMARTEx-HF), adherence to the number of exercise sessions was
102 excellent (96%) during the supervised training period in both the high intensity training group
103 (HIIT) and in the moderate exercise training group (MCT), whereas self-report of exercise
104 training in the recommendation of regular exercise group (RRE) gave less data precision.
105 **Despite excellent adherence to exercise sessions, moderate exercise response and no**
106 **differences in comparative effectiveness were observed between HIIT and MCT for**

107 improvement in VO_{2peak} (13). Hence, it is currently unclear how the magnitude of
108 improvement in VO_{2peak} with exercise training is modified by patient characteristics,
109 adherence, disease severity, co-morbidity, exercise follow-up, or simply by motivation to
110 exercise.

111 To investigate baseline and exercise training predictors of ΔVO_{2peak} from baseline to
112 12-week follow-up in HFrEF patients, we performed a post hoc analysis of data from
113 SMARTEX-HF to address if ΔVO_{2peak} was associated with: 1) one or more of the baseline
114 characteristics. 2) exercise training characteristics, e.g. work-load and heart rate during
115 training sessions, exercise testing characteristics, or clinical characteristics known to affect
116 physical performance, e.g. heart failure pathogenesis, age and smoking. We considered the
117 study too small to investigate whether baseline variables have different effects depending on
118 the three specific training interventions.

119

120

121 **Methodology**

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

124

125 **Participants**

126 In nine European study centers, 261 clinically stable HFrEF patients were randomized from
127 outpatient heart failure clinics, hospital registries, cardiac rehabilitation referrals and public
128 announcements. After withdrawals and appropriate exclusions, 231 started training, and 215
129 patients completed 12 weeks of exercise and clinical baseline and follow-up assessments.

130 Patient flow in the study has been detailed elsewhere (15). At baseline all subjects had stable,
131 symptomatic HFrEF with left ventricular ejection fraction (LVEF) $\leq 35\%$. All subjects were in
132 New York Heart Association (NYHA) functional class II-III and were on optimal medical
133 treatment. Further details of inclusion and exclusion criteria have been described in the
134 rationale and design paper (14).

135

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

141 **Exercise intervention**

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

157

158 ***Clinical measurements***

159 Cardiopulmonary exercise testing (CPET), medical history, anthropometrics, physical
160 examination, fasting blood sampling, quality of life questionnaires, and echocardiography

161 were performed at baseline and after 12 weeks of training (14, 15). VO_{2peak} was measured by
162 CPET performed either on a treadmill or a bicycle ergometer, corresponding to the preferred
163 training mode at each study center and was similar at baseline and 12 weeks for each
164 participant. An incremental protocol with 10 or 20 W increase in workload approximately
165 every minute was used. VO_{2peak} was measured using standard equipment for indirect
166 calorimetry. The mean of the three highest 10-second consecutive measurements was used to
167 calculate VO_{2peak} . HR_{peak} and other related values are reported from the time point when this
168 value was reached. Echocardiography data were acquired according to standard operation
169 procedures of the study (15).

170

171 *Statistical analysis*

172 In the first post-hoc analysis, data were analyzed using logistic regression comparing the
173 highest versus the lowest tertile of ΔVO_{2peak} (high tertile, ≥ 1.5 mL· kg· min and low tertile \leq -
174 1.5 mL· kg· min). In the second analysis we used multivariate linear regression with ΔVO_{2peak}
175 as continuous dependent variable. Data are given as frequencies with percentage in
176 parenthesis, or median with 95 % confidence interval (c.i.) of the median in parenthesis, if
177 otherwise is not stated. P-values <0.05 were considered significant.

178

179 **Association of baseline variables with ΔVO_{2peak}**

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

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

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

199 group (MCT, RRE or HIIT). In addition, creatinine clearance and LVEDD were included in
200 an additional sensitivity analyses.

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

208

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

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

218 $\Delta\text{VO}_{2\text{peak}}$ was analyzed as a continuous variable using a multivariate linear regression
219 model including the following explanatory/adjustment variables **selected per protocol**:
220 $\text{VO}_{2\text{peak}}$ at baseline (CPET1), difference in peak heart rate between baseline and follow-up test
221 at 12 weeks ($\Delta\text{HR}_{\text{peak}}$), peak respiratory **ratio** at CPET2, change in ΔWatt after 12 weeks of
222 exercise training, and training group (MCT or HIIT). Based on clinical knowledge on
223 suspected influence, heart failure pathogenesis, age, and smoking were also included in the
224 model for adjustment. Robust standard errors were used and model fit was evaluated using
225 residual plots. The analysis was performed in 106 patients (data for Δwatt missing in n=20
226 (31%) in MCT and n=15 (19%) in HIIT).

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

230

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234

235 **Results**

236 *Changes in VO_{2peak}*

237 One patient in the MCT group had missing values for the baseline CPET and was excluded
238 from the analysis, leaving 214 patients for investigation. Characteristics of these patients are
239 shown in Table 1 and in Supplemental Table 1, **showing additional patient characteristics.**

240 There was large variability in ΔVO_{2peak} after the 12-week intervention (from $-8.50 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
241 $\text{L}\cdot\text{min}^{-1}$ to $+11.30 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The distribution of ΔVO_{2peak} in each intervention group is
242 illustrated in Figure 1.

243 The percentage of patients in the high versus the low tertile was 39% vs. 31% in the HIIT
244 group, 40% vs. 25% in the MCT group and 19% vs. 49% in the RRE group. The number of
245 responders in the two training groups were significantly higher than in the RRE group ($p =$
246 0.003). The median change in VO_{2peak} in each of the tertiles is displayed in Figure 2.

247

248 *Associations of ΔVO_{2peak} with baseline values*

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

253

254 The analysis indicated 7.1 higher odds for an exercise response (Highest $\Delta\text{VO}_{2\text{peak}}$ tertile) if
255 classified in NYHA II vs. NYHA III at baseline. In the SMARTEX-HF dataset (i.e. without
256 bootstrapping), 58 of 70 (82.9%) of the patients with a positive change in $\text{VO}_{2\text{peak}}$ (above the
257 tertile cutoff) were in NYHA class II. (Mean baseline $\text{VO}_{2\text{peak}}$ (\pm SD) for NYHA II was $18.7 \pm$
258 $4.8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and for NYHA III, $15.0 \pm 3.8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Compared to control (RRE),
259 the proportion that were responders (i.e. highest $\Delta\text{VO}_{2\text{peak}}$ tertile) was higher in the two
260 exercise groups (HIIT and MCT), with no statistically significant difference between HIIT
261 and MCT ($p = 0.71$).

262

263 The sensitivity analysis using $\Delta\text{VO}_{2\text{peak}}$ as a continuous dependent variable and including all
264 patients. **Table 3** confirmed the direction and significance of the associations from the main
265 model for NYHA class ($p=0.002$), age ($p=0.001$), and training group (HIIT or MCT vs. RRE:
266 $p<0.01$, HIIT vs. MCT: $p=0.93$), but not for LVEF ($p=0.10$). Sensitivity analyses including
267 estimated creatinine clearance ($p=0.84$) or left ventricular end diastolic diameter (LVEDD)
268 ($p=0.17$) **showed that these variables were not significant.**

269

270 *Associations of $\Delta\text{VO}_{2\text{peak}}$ with test- or training-related variables (HIIT and MCT groups)*

271 In a multivariate linear regression model with $\Delta\text{VO}_{2\text{peak}}$ as a continuous outcome variable the
272 significant variables were: $\Delta\text{HR}_{\text{peak}}$ between baseline and 12-week test ($p = 0.007$), change in
273 training workload between baseline and follow-up ($p = 0.003$), age (negative coefficient, $p <$

274 0.001) and ever smoker ($p = 0.001$). R-squared for this model was 0.34. The following
275 variables were not significant: HIIT versus MCT ($p = 0.47$), peak RQ at 12-week test ($p =$
276 0.53), heart failure pathogenesis ($p = 0.92$), VO_{2peak} at baseline ($p = 0.55$). The model is given
277 in supplementary table 2, with linear regression model for associations of delta VO_{2peak} with
278 test- or training-related variables: primary model, and illustrated in Figure 3A, showing
279 results for an increase or decrease in HR_{peak} of 20 BPM.

280

281 In the secondary model given in supplementary table 3, with linear regression model for
282 associations of delta VO_{2peak} with test- or training-related variables, excluding $\Delta Watt$ (due to
283 lower n for this variable) 29% of the variation in ΔVO_{2peak} was explained and the significant
284 variables were: ΔHR_{peak} from baseline to 12-weeks test ($p < 0.001$), age (negative coefficient, p
285 = 0.002) and ever smoker ($p = 0.02$, Figure 3B). There were still no differences between HIIT
286 and MCT ($p = 0.42$, Figure 3C). The initial model explained more of the variance in the
287 VO_{2peak} response than the second model (34% vs. 29%). When including the same patients in
288 the two models ($n = 106$), the explained variation was 34% and 29% for the initial and
289 secondary model, respectively.

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

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296

297 **Discussion**

298 *Associations of ΔVO_{2peak} with baseline values*

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

310 Each 1% higher baseline LVEF was associated with 10% greater odds of being in the
311 highest delta VO_{2peak} tertile, independent of exercise intensity or exercise group. The overall
312 group response in LVEF at 12 weeks was moderate (15). Our logistic regression analysis
313 shows that baseline LVEF might indicate the left ventricular exercise recovery potential in
314 HFrEF-patients. To the best of our knowledge, the baseline LVEF – exercise response
315 association adds new knowledge about individual exercise responses, with improved exercise
316 recovery prognosis in HFrEF patients with higher baseline contractile function.

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

332

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

335 **According to the multivariable linear regression analysis** a total of 34% of the variability in
336 ΔVO_{2peak} was explained by the test and training quality variables ΔHR_{peak} (CPET2 minus

337 CPET1) and Δ Watt (exercise training workload from exercise week 1 to 12), in addition to
338 the baseline variables age and ever being a smoker.

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

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

355 In CVD patients, superior exercise response was found in the higher part of the HIIT
356 workload zone (29). In comparison to Wisløff et al (Δ workload HIIT = 95 watt) (2), and

357 Iellamo et al (Δ workload HIIT = 70 watt) (17), the increase in exercise training workload and
358 the ability to maintain exercise intensity within the target range were moderate in the
359 SMARTEX-HF study (9). Maintaining target exercise intensity is challenging (30), and the
360 limited increase in exercise training workload may be due to physiological, pathological,
361 psychological factors or patient and/or coaching motivation (9). Heart failure deterioration is
362 associated with a negative exercise response (11, 31), and may explain part of the modest
363 improvement in VO_{2peak} and LVEDD in the SMARTEX-HF study (14, 15). Similarly, others
364 have reported a moderate exercise outcome even in coronary patients, with a neutral outcome
365 of HIIT versus MCT in a large multicenter study (32), **whereas combining endurance and**
366 **strength training was not associated with improved cardiac function (4). A subgroup of**
367 **patients with advanced chronic heart failure improved exercise capacity and reversed LV**
368 **remodeling after daily, long-term moderate exercise training (6 and 12 months) (33). As**
369 **patients with the poorest left ventricular function responded the least to exercise training in**
370 **our study, further investigation of whether daily exercise and longer duration of the**
371 **intervention is necessary to gain a positive exercise response, or if this may lead to**
372 **deterioration of CHF. With both positive and negative exercise responders in our study, tailor-**
373 **made programs and follow-up may be highly warranted in deconditioned CHF patients. The**
374 findings in the primary statistical model suggests that both physiological and pathological
375 factors may limit the ability to exercise at moderate and high intensity, **and we acknowledge**
376 **that our model leaves 66% of the variability in the exercise response unexplained. As the**

377 change in VO_{2peak} is influenced by several central and peripheral factors (7, 26, 27, 34) that
378 were not measured in the present study, we are unable to conclude which of them are the most
379 important, except to confirm the importance of chronotropic incompetency. It may be argued
380 that inclusion of non-baseline variables precludes prediction of the exercise response, but this
381 was not the focus of the secondary analyses. As we have no data on exercise motivation, this
382 factor could also not be discussed.

383

384 *Study strengths and limitations*

385 Study strengths includes the explorative statistical design using random forest-based analysis
386 to select among a substantial number of potential explanatory factors without overfitting the
387 model, close supervision of exercise training and thorough documentation of clinical and
388 physiological patient data. Patient adherence to exercise training sessions was excellent. In
389 addition, the multicenter study probably reflects a wider and more representative patient
390 selection compared to single-center studies. The patients included in the present study
391 represented approximately 10% of the heart failure population screened for inclusion. We
392 believe that the study participants are representative for stable HFrEF with LVEF \leq 35%
393 under optimal medical care. However, a majority of the screened patients had LVEF above
394 35%, indicating less representativeness of the overall HFrEF population.

395 It is a limitation that exercise-related data on intensity and duration could not be
396 studied in the RRE group due to their per protocol unsupervised and unrecorded home-

397 based exercise. Furthermore, we did not assess training motivation and thus could not
398 tell whether there were differences between the intervention groups. Of note, the
399 confidence intervals for the exercise group effects were wide and the precision of the OR
400 should be interpreted with caution.

401

402

403 **Conclusion**

404 Exercise training response ($\Delta\text{VO}_{2\text{peak}}$) correlated negatively with age, LVEF and NYHA class.

405 The ability to increase workload during the training period, and a positive $\Delta\text{HR}_{\text{peak}}$ between

406 baseline and 12-week test were associated with a positive outcome.

407

408

409 **Clinical implications**

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

421

422

423 **Acknowledgements**

424 We greatly acknowledge the time and the effort of the participating patients and the entire
425 study staff. Jennifer Adam, Elena Bonanomi, Silvia Colombo, Christian Have Dall, Ingrid
426 Granøien, Kjersti Gustad, Anne Haugland, Julie Kjønnørød, Marit Kristiansen, Jorunn Nilsen,
427 Maren Redlich, Anna Schlumberger, and Kurt Wuyts performed exercise testing and training;
428 Rigmor Bøen, Marianne Frederiksen, Eli Granviken, Loredana Jakobs, Adnan Kastrati,
429 Nadine Possemiers, Hanne Rasmusen, Liv Rasmussen, and Johannes Scherr performed
430 patient screening, inclusion, and clinical assessments; Volker Adams, Ann-Elise Antonsen,
431 Wim Bories, Nadine Possemiers, Malou Gloesner, Vicky Hoymans, and Hielko Miljoen,
432 collected data; Hanna Ellingsen and Maria Henningsen performed data monitoring; Lars
433 Kjøber, Christian Torp-Pedersen, John Kjekshus, Rainer Hambrecht and Stephan Gielen
434 monitored safety. Together these contributors and the authors comprise the SMARTEX Heart
435 Failure Study Group.

436

437 **Funding Sources**

438 This work was supported by St. Olavs Hospital; Faculty of Medicine and Health Sciences,
439 NTNU – Norwegian University of Science and Technology; Norwegian Health Association;
440 Danish Research Council; Central Norwegian Health Authorities/NTNU; Western Norway
441 Health Authorities; Simon Fougner Hartmanns Familiefond; Else-Kröner-Fresenius-
442 Stiftung, and Société Luxembourgeoise pour la recherche sur les maladies cardio-vasculaires.

443

444 **Conflict of Interests Disclosures**

445 MH reports grants from the Else-Kröner-Fresenius Foundation for the present work and is on
446 the advisory board of Novartis, Sanofi-Aventis and MSD outside of the present study. AL
447 reports grants and personal fees from Medtronic and from Claret Medical, and personal fees
448 from Edwards, SJM, Bard, and Symetis, all outside of the present study. The results of this
449 study do not constitute endorsement by ACSM. The results of the study are presented clearly,
450 honestly, and without fabrication, falsification, or inappropriate data manipulation.

451

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570 Supplemental table 1, additional patient characteristics

571 **Supplemental table 2, Linear regression model for associations of delta VO_{2peak} with test- or**

572 **training-related variables: primary model**

573 **Supplemental table 3, Linear regression model for associations of delta VO_{2peak} with test- or**

574 **training-related variables: secondary model**

575

576 **Figure legends**

577 **Figure 1.**

578 Distribution of ΔVO_{2peak} after 12 weeks of exercise training in the HIIT, MCT and RRE

579 groups. The dotted line marks zero change in VO_{2peak} , with positive and negative changes in

580 VO_{2peak} to the right and left side of zero. HIIT, high intensity exercise training; MCT,

581 moderate continuous training; RRE, recommendation of regular exercise; VO_{2peak} , peak

582 oxygen uptake

583 **Figure 2.**

584 Median ΔVO_{2peak} in $mL \cdot kg^{-1} \cdot min^{-1}$ after 12 weeks of exercise training in the three tertiles of

585 high (H), medium (M) and low (L) VO_{2peak} responders (all patients). The medium tertile: -1.5

586 mL·kg·min⁻¹ to 1.5 mL·kg·min⁻¹. Open bars: range. Grey shading: 95% confidence interval of
587 the medians.

588

589

590 **Figure 3.**

591 Prediction of $\Delta\text{VO}_{2\text{peak}}$ differences after 12 weeks of supervised exercise training (data from

592 HIIT and MCT) versus: A) Effect of change in exercise training work load in patients with

593 either a positive or a negative $\Delta\text{HR}_{\text{peak}}$ from CPET1 to CPET2. **The multivariable linear**

594 **regression model also includes delta workload, age, ever smoking, exercise training group,**

595 **peak RQ at 12 weeks, heart failure pathogenesis, and $\text{VO}_{2\text{peak}}$ at baseline.** B) Effect of

596 $\Delta\text{HR}_{\text{peak}}$ from CPET1 to CPET2 in ever vs. never smokers. **The multivariable linear**

597 **regression model also includes age, delta HRpeak from CPET1 to CPET2, exercise training**

598 **group, peak RQ at 12 weeks, heart failure pathogenesis, and $\text{VO}_{2\text{peak}}$ at baseline.** C) Effect

599 of change in $\Delta\text{HR}_{\text{peak}}$ from CPET1 to CPET2 in HIIT vs MCT, **same model as B.** Data are

600 means with 95% confidence intervals (CI); HR, heart rate; $\text{VO}_{2\text{peak}}$, peak oxygen uptake,

601 CPET, cardiopulmonary exercise testing, HIIT, high intensity interval training, HR_{peak} , peak

602 heart rate.

603

Table 1. Baseline characteristics

Characteristic	Low (n=72)			Medium (n=72)			High (n=70)		
$\Delta\text{VO}_{2\text{peak}}$ 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/m ²	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·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·kg·min ⁻¹	15.9 (13.4,19.1)	15.8 (14.6,19.3)	18.3 (16.5,20.3)	15.9 (13.9,17.9)	15.5 (14.3,19.6)	17.3 (14.6,19.0)	17.5 (16.1,19.7)	18.4 (15.0,19.7)	20.4 (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 ₂ puls, 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; CRPs, high sensitive C-reactive protein; HR_{peak}, peak heart rate; RQ, Respiratory quotient; peak O₂puls, peak oxygen puls.

Table 2 - Logistic regression model for associations of delta VO_{2peak} with baseline values¹

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

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

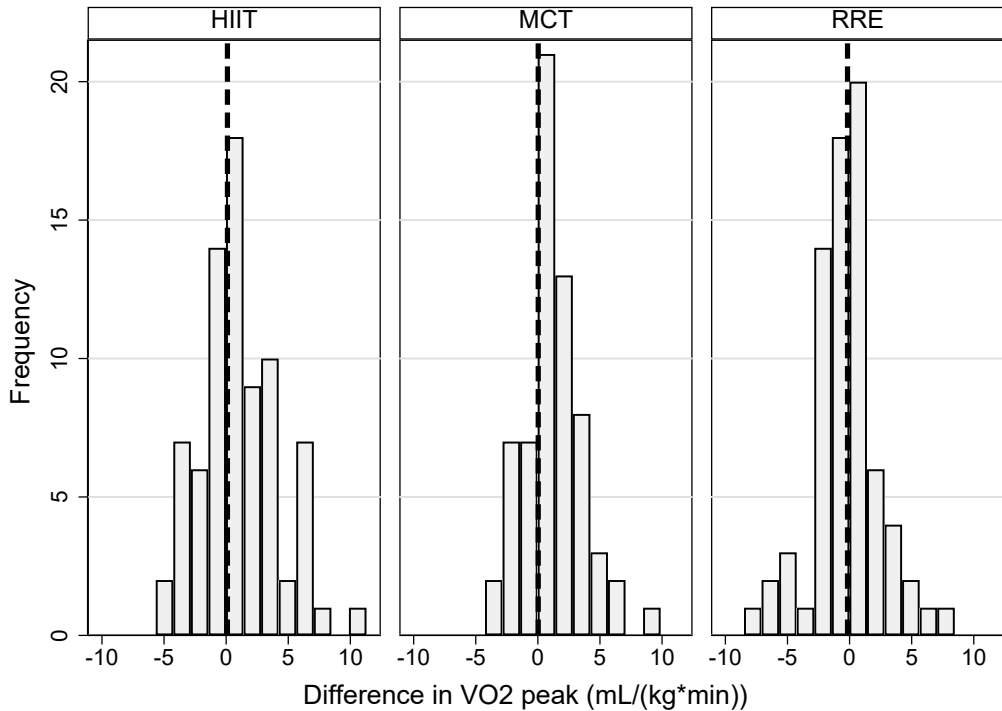
Table 3 - Sensitivity analysis: Linear regression model for associations of delta VO_{2peak} with baseline values

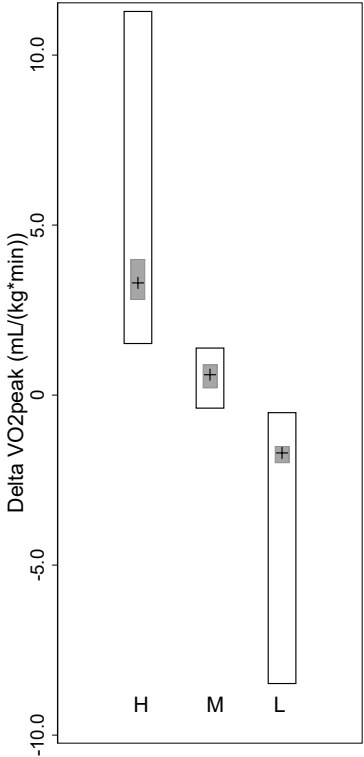
Baseline variable	Multivariable model (n=214)				Univariable associations			
	Coefficient	95% CI	t	p-value	Coefficient	95% CI	t	p-value
NYHA class III vs. class II	-1.18	-1.92, -0.44	-3.17	0.002	-0.84	-1.55, -0.13	-2.32	0.021
Age per 10 years	-0.57	-0.91, -0.23	-3.30	0.001	-0.43	-0.74, -0.11	-2.67	0.008
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

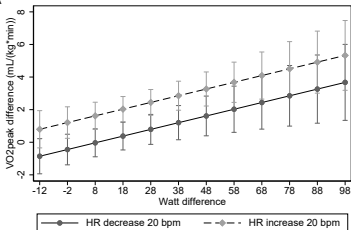
Supplementary table 3 – Linear regression model for associations of delta VO_{2peak} with test- or training-related variables: secondary model

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

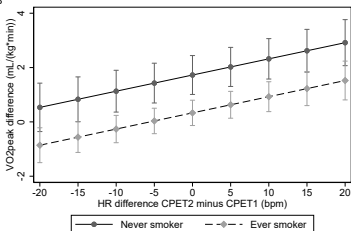




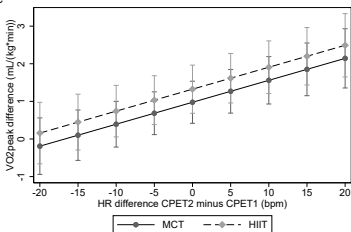
A



B



C



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-weeks test	-1.47	-6.04, 3.10	- 0.64	0.53	-0.36	- 5.47, 4.76	- 0.14	0.89
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