Absence of Fitness Improvement Is Associated with Outcomes in Heart Failure Patients

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Abstract

Purpose. To examine the clinical impact of cardiorespiratory fitness (CRF) and improvements in CRF after cardiac rehabilitation (CR) in heart failure (HF) patients for their risk of all-cause mortality and unplanned hospitalization. Secondly, to investigate possible factors associated with the absence of improvement in CRF after rehabilitation.

Methods. We included 155 HF patients receiving CR between October 2009 and January 2015. Patients performed an incremental bicycle test to assess CRF through peak oxygen uptake (VO_2-peak) before and after CR-based supervised exercise training. Patients were classified as responders or non-responders based on pre-to-post CR changes in VO_2-peak (≥6% and <6%, respectively). Cox proportional hazards models evaluated all-cause mortality and unplanned hospitalization during 5 years of follow-up. Patient characteristics, HF features and co-morbidities were used to predict changes in VO_2-peak using logistic regression analysis.

Results. Seventy HF patients (45%) were classified as responder. Non-responders had a significantly higher risk of all-cause mortality or hospitalization (HR = 2.15, 95% CI = 1.17-3.94) compared to responders. This was even higher in non-responders with low CRF at baseline (HR = 4.88, 95% CI = 1.71-13.93). Factors associated with non-response to CR were age (OR = 1.07/year, 95% CI = 1.03-1.11), baseline VO_2-peak (OR = 1.16/ml/min/kg, 95% CI = 1.06-1.26) and adherence to CR (OR = 0.98/percentage, 95% CI = 0.96-0.998).

Conclusion. Independent from baseline CRF, the inability to improve VO_2-peak by CR doubled the risk of death or unplanned hospitalization. The combination of lower baseline CRF and non-response was associated with even poorer clinical outcomes. Especially older HF patients with higher baseline VO_2-peak and lower adherence have a higher probability of becoming a non-responder.

Key words: exercise, cardiovascular risk, morbidity/mortality, physical fitness, unplanned hospitalization

INTRODUCTION

Heart failure (HF) is diagnosed in 1-2% of the adult population of developed countries and is characterized by a structural or functional impairment of ventricular filling or ejection (1, 2). HF patients typically suffer from dyspnea and fatigue, which may limit their habitual physical activity and contribute to exercise intolerance. Hence, the cardiorespiratory fitness (CRF) of HF patients is lower compared to age- and sex-predicted reference values (3, 4). Previous studies indicated that CRF is an important predictor for the course of disease (5, 6), with lower CRF being related to an increased risk of cardiovascular events. Improvement of CRF through exercise training is therefore recommended in HF patients (1, 2).

Previous studies in HF patients suggest a potential decline in mortality and hospitalization rate after standardized cardiac rehabilitation (CR; involving exercise training) compared to usual care (7, 8). However, significant heterogeneity exists in individual responses to CR, with some demonstrating no change or even a decline in fitness. It has been estimated that only half of the HF patients improve their fitness after standardized CR (9, 10), compared to 86% in non-HF individuals (11). Evidence is limited whether the absence of improvement affects future survival and morbidity. Preliminary work suggests that HF patients with an increased fitness after CR (*responders*) have a lower risk of all-cause mortality and hospitalization compared to patients without such improvements (*non-responders*) (9). Likewise, non-responders demonstrated an increased risk of cardiac events compared to responders (10). These studies were, however, limited by a low adherence (40%) to the exercise training sessions. Moreover, the work related to a specific population of HF patients (i.e. young (systolic) HF patients) and relatively short follow-up (9, 10). Given the overall health benefits of CR-based exercise programs and the high number of non-responders, it is relevant to better understand the clinical impact of being a non-responder and to identify HF patients who are at particular risk of becoming a non-responder.

Therefore, the aim of our study was to compare the risk of morbidity and all-cause mortality between HF patients responding and non-responding in CRF improvement after standardized and supervised exercise training as part of a CR program. We expect that improvement in CRF after rehabilitation is associated with a reduced risk of morbidity and all-cause mortality, whilst this observation is independent of pre-rehabilitation levels of CRF. Furthermore, to better understand the characteristics of a non-responder, we aimed to predict which HF patients will become a non-responder to CR using personal-, health-, disease- and exercise training-related characteristics.

METHODS

Subjects

All HF patients who followed supervised exercise training as part of a CR program at the Radboud university medical center or Isala Clinic between October 2009 and January 2015 were eligible for participation in the study. Both patients with a reduced ejection fraction (HFrEF) and a preserved ejection fraction (HFprEF) were included if they performed a baseline and follow-up fitness test. HF patients with a peak respiratory exchange ratio (RER) <1.00 at baseline and/or post-training exercise test were excluded from the study to guarantee the quality of the included data.

Experimental design

At baseline and after completion of the exercise-training program, HF patients underwent cardiopulmonary exercise testing to determine changes in CRF. Absolute change in physical fitness was assessed by calculation of the difference in peak oxygen uptake (VO_2-peak) between both exercise tests. Relative change was calculated by dividing the absolute change by the baseline VO_2-peak. HF patients were classified as responder if they demonstrated a relative improvement in VO_2-peak ≥6% and as non-responder if the increase in VO_2-peak was <6%. The threshold of 6% improvement was used to compensate for inter-test variability, and an increase of VO_2-peak ≥6% was considered as a meaningful and reliable difference (12).

Data related to patient characteristics, unplanned hospitalization and all-cause mortality were extracted from electronic patient files at both hospitals. The Local Committee on Research Involving Human Subjects of the region Arnhem and Nijmegen approved the study, and the study adhered to the Declaration of Helsinki.

Exercise training programs

HF patients participated in four different supervised exercise-training programs, depending on year of participation and the available program at the medical center. Patients from the Radboud university medical center participated in: 1) an 8-week exercise program, consisting of 2 sessions/week at a moderate exercise intensity (n=23); or 2) a 12- week exercise program, consisting of 2 sessions/week at moderate (n=10) or high exercise intensity (n=10). Patients from the Isala Clinic participated in 3) a 12-week exercise program, consisting of 2 sessions/week at a moderate exercise intensity (n=36); or 4) a 24-week exercise program (n=76), consisting of 2 sessions/week at a moderate exercise intensity. Moderate intensity was defined as BORG score 11-15. During high intensity training sessions 10 bouts of 1-minute at 90% of the maximal workload were alternated by 2.5 minutes at 30% of the maximal workload. Adherence of HF patients to the exercise program was defined as the total number of training sessions performed by a patient divided by the total number of training sessions in the program. This ratio was multiplied by 100 to obtain a percentage.

Cardiopulmonary exercise test

Standardized exercise testing was performed on a bicycle ergometer with increasing workload until exhaustion. The oxygen consumption was measured by an automated system, which was calibrated before every test with both ambient air and a fixed known gas mixture. During exercise testing, subjects were verbally encouraged to achieve maximum exertion, evidenced by a RER $\geq$1.00. Respiratory gas analysis measured the oxygen uptake, carbon dioxide production, and ventilation. Gas exchange results were used to determine the VO_2-peak, which was defined as the average VO_2 over the last 30 seconds of the exercise test. The maximum heart rate and workload (Watt) were measured during the exercise test.

Data extraction

Electronic patient files were used to collect: 1) baseline patient characteristics including age, sex, body mass index (BMI), current smoking status and co-morbidities (diabetes mellitus, chronic obstructive pulmonary disease and hypertension), and 2) HF characteristics such as disease etiology (ischemic *versus* non-ischemic), New York Heart Association (NYHA) classification, left ventricular ejection fraction, history of atrium fibrillation, medication use (angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta blocker agent, aldosterone receptor antagonist, loop diuretic and statins), and the presence of medical devices (pacemaker, cardiac resynchronization therapy or implantable cardioverter defibrillator). Furthermore, we used all-cause unplanned hospitalization events and all-cause mortality as our end points and obtained these from the electronic patient files.

Data analysis

Kaplan–Meier curves and the log-rank test were used to assess the difference in clinical outcome between responders and non-responders. The end-point was any unplanned hospitalization or all-cause mortality. Patients who did not reach the end-point were censored at the end of the observation period or after 5 years of follow-up. The follow-up started at the baseline cardiopulmonary exercise test prior to CR. The crude hazard rate ratio (HR) with 95% confidence interval (CI) was calculated first by univariable Cox proportional hazards modelling. Subsequently, we compared patient characteristics, HF characteristics, medication use, medical devices and physiological variables between groups using the chi-squared test for categorical variables, Student’s t-test for normally distributed continuous variables and the Mann-Whitney U test for not normally distributed continuous variables. We adjusted the survival analysis with multivariable Cox proportional hazards modelling for the following possible confounding factors: age, sex, BMI, baseline VO_2-peak and a cardiac resynchronization therapy combined with implantable cardioverter defibrillator. The adjusted HR was calculated with a 95% CI.

To calculate the odds of becoming a non-responder, we used univariable logistic regression and examined the following factors: age, sex, BMI, current smoking status, co-morbidities, disease etiology, NYHA classification, ejection fraction, history of atrium fibrillation, medication use and the presence of medical devices (pacemakers, cardiac resynchronization therapy or implantable cardioverter defibrillator), adherence, duration and type of the rehabilitation program, and baseline values of VO_2-peak, maximum achieved heart rate and peak workload. The potential factors were entered into a hierarchical multivariable logistic regression model using different blocks. In all blocks, backward selection was used with stepwise removal at $P = 0.10$ to identify the most predictive variables. The discriminative performance of the model was assessed by calculating the area under the receiver operating characteristic curve (AUC).

To calculate the necessary sample size, we performed a power calculation using a power of 80%, an overall type 1 error of 0.05 (two-sided), and as clinically relevant effect size a hazard ratio of 2. Approximately 145 subjects were needed to obtain the number of required events (n=71)(13). To develop a prediction model, we use the rule of thumb with minimal 10 events per variable for obtaining a good prediction(14, 15). Statistical analyses were performed in SPSS 20.0. A $P < 0.05$ was considered statistically significant.

RESULTS

Study population

A total of 187 HF patients met the inclusion criteria of our study. After inspection for data quality, 32 patients were excluded due to a maximum RER<1.00 during the maximal exercise test. As a result 155 patients were available for analysis (Figure 1), with a median adherence to the supervised training sessions of 88% and inter-quartile range of 79%–96%.

Responders versus non-responders

Seventy HF patients (45%) were classified as responder (Supplemental Figure 1). Non-responders were more frequently men, had a lower adherence to the rehabilitation program, a higher baseline VO_2-peak and a lower post-training VO_2-peak compared to responders (Table 1). Age, BMI, current smoking behavior, and the duration of the rehabilitation program did not differ between the groups. Likewise, no differences in HF characteristics, co-morbidities, medication use, medical devices and other physiological data were found.

All-cause mortality and unplanned hospitalization

143 out of 155 HF patients were included in the survival analysis, as the follow-up data of 12 patients were not accessible for data protection reasons. In total 57 HF patients died or had an unplanned hospitalization: 36 non-responders (46%) and 21 responders (33%). The median follow-up period was 23 months (inter-quartile range 13–47) for non-responders and 30

months (15–50) for responders. Figure 2 shows the Kaplan-Meier curves for time to unplanned hospitalization or death (*P*=0.12). Non-responders had a 52% higher risk of death or unplanned hospitalization than responders (HR = 1.52, 95% CI = 0.89-2.61). The multivariable Cox proportional hazards regression analysis showed that the risk of death or unplanned hospitalization was more than twice as high in non-responders (HR = 2.15, 95% CI = 1.17-3.94) after adjustment for age, sex, BMI, baseline VO_2-peak and a cardiac resynchronization therapy combined with implantable cardioverter defibrillator. Subgroup analyses did not show any difference in results for patients with HFrEF or HFprEF at baseline.

A lower baseline CRF level (VO_2-peak <16.5 ml/min/kg) was associated with a 2.76 (95% CI = 1.52-5.05) increased risk of all-cause mortality and unplanned hospitalization after adjustment for age, sex, BMI and response status. Conversely, after adjustment for age, sex, BMI, and CRF level, non-responders had a 1.80 (95% CI = 1.02-3.18) higher risk of all-cause mortality and unplanned hospitalization. Non-responders with the lowest baseline CRF had a 4.88 (95% CI = 1.71-13.93) higher risk of all-cause mortality or unplanned hospitalization compared to responders with a high baseline CRF level (Figure 3).

Predicting response to exercise training

We identified age, sex, etiology of HF, use of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, loop diuretics, pacemaker, baseline VO_2-peak and adherence to the exercise program as potential factors associated with becoming a non-responder to CR based exercise training (Supplemental Table 1). Multivariable logistic regression analysis revealed that HF patients of higher age (odds ratio [OR] = 1.07/year, 95 % CI = 1.03–1.11), higher baseline VO_2-peak (OR = 1.16/ml/min/kg, 95% CI = 1.06–1.26) and adherence to the exercise program (OR = 0.98/percentage, 95% CI = 0.96–0.998) were associated with being a non-responder. The performance of the prediction model is shown in Figure 4 and demonstrates an AUC of 0.73 (95% CI = 0.65–0.82).

DISCUSSION

As many as 55% of 155 HF patients did not increase VO_2-peak following supervised exercise training sessions in a CR program. More importantly, HF patients classified as non-responders to CR had a 2.15 times higher risk of all-cause mortality or unplanned hospitalization compared to responders after adjustment for possible confounders. The increased risk of all-cause mortality or unplanned hospitalization for non-responders was independent of pre-rehabilitation CRF levels. In addition, non-responders with lower CRF levels had the worst prognosis for unplanned hospitalization and all-cause mortality. Taken together, our data reinforce the clinical importance of baseline CRF levels and the ability to improve fitness after exercise training. In order to predict non-response to CR, we found that higher age, lower adherence and higher baseline VO_2-peak were significant associated with of non-response status.

Non-response, all-cause mortality and unplanned hospitalization

We found that 85 HF patients (55% of study population) were classified as non-responders to exercise training. Although this prevalence is remarkably high, our findings are in line with most (50-56% non-responders) (9, 10), but not all (0.9% non-responders) (16), studies assessing changes in VO_2-peak following CR. The conflicting outcomes are probably related to the definition of being a non-responder. For example, the study of Leifer et al. with a prevalence of 0.9% non-responders defined non-response as a decrease in VO_2-peak ≥5 ml/min/kg (16), whereas we and others (9, 10) defined non-response as a lack of increase in VO_2-peak after exercise training. Nonetheless, our data provides further evidence that the presence of non-responders in HF patients who participate in CR programs is larger than typically observed in a healthy patient cohort.

In line with our observations, previous work found that HF patients benefit from exercise training (7, 17-19). Data from the HF-ACTION trial revealed a 5% higher risk for all-cause mortality or all-cause hospitalization in non-responders compared to responders after 3 years of follow-up (9). The benefits of VO_2-peak improvement were much larger in our study population as we found a 2.15 higher risk (HR = 2.15, 95% CI = 1.17–3.94) for all-cause mortality or unplanned hospitalization in non-responders versus responders after 5 years of follow-up. However, comparison between the HF-ACTION trial and this study is limited since HF-ACTION only included HFrEF patients and this study included both HFrEF and HRprEF. In addition, apart from a longer follow-up time, the difference in risk reduction between our study and HF-ACTION may also relate to study cohort characteristics. Compared to the HF-ACTION trial, our HF patients were more often classified as NYHA classification I or II, showed a lower prevalence of ischemic etiology, a higher baseline peak-VO_2 (16.5 versus 15.0 ml/min/kg), and had a relatively high adherence (median, 88%). These factors (i.e. lower NYHA classification, non-ischemic etiology (20), higher CRF (6)) are typically associated with better survival in HF patients. This suggests that less severe HF patients may have greater health benefits from CRF improvements following CR. Future studies are required to better understand this relation.

In examining the benefits of cardiac rehabilitation it is important to take pre-rehabilitation levels of fitness into consideration since previous work found that fitness may represent the strongest predictor for (all-cause) mortality and morbidity in HF patients (5, 6). In agreement with this previous research, we found that baseline fitness levels are strongly and independently related to mortality or hospitalization. Taking both baseline fitness and change in fitness post-rehabilitation into consideration, we found that non-responders with lower fitness levels had the highest risk of adverse clinical outcomes. These data show for the first time that, both, lower baseline fitness levels and non-response to CR are independently and in combination associated with an increased risk of adverse events in HF patients.

Prediction of non-response

In this study we tried to identify factors that predict non-response to exercise training in HF patients, since this response is related to future adverse events. We demonstrated that older HF patients with a relatively high baseline VO_2-peak and lower adherence were more often non-responders. These findings align with observations from other studies. A meta-analysis in HF patients showed that lower age was associated with larger improvements of VO_2-peak (21). Also, HF patients higher VO_2-peak (22, 23) had smaller improvements in fitness following exercise training. Medication use was not associated with response status and did not significantly change during CR within both groups. Therefore, we do not expect an interaction of medication in relation to performance outcomes. Our prediction model had an AUC of 0.73, which indicates that the discriminative power of our model is not sufficient for direct implementation in clinical practice. Nonetheless, we have identified factors that significantly contribute to the prediction whether CRF improves after training. The addition of chonotropic incompetence (24) and parameters reflecting severe hemodynamic dysfunction (25, 26) and cardiac dimensions (27, 28) may further improve its predictive capacity and warrant further investigation.

Clinical relevance

The observation that non-response to CR training is related to increased all-cause mortality or hospitalization has important clinical consequences. Independent of baseline fitness levels, the inability to improve fitness after exercise training increases the risk for adverse events. Especially non-responders with lower baseline fitness are at high risk for adverse events. This further emphasizes the importance of non-response in CR. Non-modifiable factors (age, baseline VO_2-peak) contribute to early identification, which may lead to the prescription of a different type of CR. For example, non-responders might benefit from other types of exercise interventions such as high intensity interval training or resistance training to improve their physical fitness. Literature revealed that HF patient performing high or vigorous intensity exercise programs have an higher increase in the peak VO_2 compare to moderate intensity programs (17, 29) and are less likely to show a non-response to training. Resistance exercise improves muscle mass, strength and muscular fitness in HF patients (30-32) and therefore might increase cardiovascular fitness by optimizing the response to aerobic conditioning. In fact, the combination of aerobic and resistance exercise training appeared to be superior for improving submaximal exercise capacity and health-related quality of life compared to aerobic exercise only (33). In addition, HF patients who remain to be non-responders, may have to increase training frequency (34). Such approaches may contribute to a reduction of future adverse events in this vulnerable group. Finally, strong adherence to exercise training should be encouraged in HF patients, since adherence is a significant and, more importantly, modifiable factor for being a non-responder to CR.

Strengths and limitations

This study included typical HF outpatients, which increases the external validity of our study. In addition, there were no drop-outs during follow-up which means that all censoring was non-informative and therefore unrelated to patient prognosis. A limitation of our study may relate to the exclusion of 17% of eligible HF patients due to an insufficient RER during the exercise test. However, to guarantee the quality of the achieved maximal VO_2 and thereby the stratification into responder versus non-responder, it was inevitable to exclude those patients. Furthermore, it was not feasible to use standardized meals before exercise testing. Also, no data was available about diet or water consumed before the exercise test, which may influence the VO_2-peak.

CONCLUSIONS

Non-responders to exercise training had a 2.15 higher risk of all-cause mortality or unplanned hospitalization compared with responders after adjustment for possible confounders, a finding independent from other prognostic markers for adverse events (including baseline levels of fitness). This observation is of clinical importance since half of the HF patients participating in a CR-based supervised exercise training program was unable to significantly improve VO_2-peak. Higher age and baseline VO_2-peak, and lower adherence were identified as independent factors associated with non-response to CR-based exercise training in HF patients.

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Conflict of interest disclosure

The authors declare that there is no conflict of interest.

The results of the study do not constitute endorsement by ACSM and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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TABLES

Table 1. Characteristics of 155 heart failure patients according to their response to cardiac rehabilitation.

	Responders N=70	**Non-responders N= 85**	***P*-value**
Patient characteristics			
Age (years)	61 (53−67)	63 (55−71)	.09
Sex (male)	47 (67%)	69 (81%)	.045
BMI (kg/m^2)	28 (SD 5.8)	29 (SD 5.0)	.40
Smoking (current)	16 (23%)	16 (19%)	.54
Diabetes mellitus (yes)	12 (17%)	9 (11%)	.24
COPD (yes)	6 (9%)	9 (11%)	.67
Hypertension (yes)	26 (37%)	38 (45%)	.34
Heart failure characteristics			
Aetiology, ischemic	24 (34%)	40 (47%)	.11
Baseline NYHA			.66
I-II	47 (67%)	63 (74%)	
III-IV	16 (23%)	18 (21%)	
Baseline LVEF			.79
worse (<30%)	20 (28%)	21 (25%)	
moderate (30-45%)	14 (20%)	19 (22%)	
reasonable (45-55%)	3 (4%)	3 (4%)	
good (>55%)	18 (26%)	27 (32%)	
Atrium fibrillation (yes)	20 (29%)	27 (32%)	.67

Medication use			
ACEI or ARB	64 (93%)	83 (98%)	.15
Beta blocker agent	64 (91%)	75 (88%)	.52
Aldosteron receptor antagonist	14 (20%)	18 (21%)	.86
Loop diuretic	61 (87%)	68 (80%)	.23
Statin	41 (58%)	52 (61%)	.74
Medical devices			
ICD-CRT	13 (19%)	22 (25%)	.26
Pacemaker	10 (14%)	16 (19%)	.44
CRT	1 (1%)	1 (1%)	.90
ICD	15 (21%)	19 (22%)	.87
Rehabilitation program			
Type of rehabilitation			.36
MIT	64 (91%)	81 (95%)	
HIT	6 (9%)	4 (5%)	
Duration of rehabilitation (weeks)	20 (12-26)	13 (12-26)	.79
Adherence to exercise program (%)*	91 (81-100)	83 (75-96)	.028
Physiological parameters			
Baseline VO_2-peak (ml/min/kg)	15.2 (13.1−18.6)	16.9 (14.1−20.9)	.025
Post VO_2-peak (ml/min/kg)	18.8 (15.5−21.9)	15.9 (12.8−19.7)	.017
Difference VO_2-peak(ml/min)	224 (162−359)	-43 (-136−31)	<.001

Baseline max. heart rate (beats/min)	125 (110−143)	127 (109−144)	.98
Post max. heart rate (beats/min)	129 (113−149)	126 (110−139)	.13
Baseline max. cycle load (Watt)	107 (77−142)	116 (89−149)	.08
Post max. cycle load (Watt)	130 (87−165)	120 (88−150)	.35
Baseline RER	1.16 (1.09−1.22)	1.16 (1.08−1.25)	.90
Post RER	1.15 (1.08−1.22)	1.17 (1.09−1.25)	.22

Data is presented in n (%) unless indicated as mean (SD) and median (Q_{25}−Q_{75}).

*Data was only available in 135 patients.

BMI = body mass index, COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association functional classification, LVEF = left ventricular ejection fraction, ACEI = angiotensin-converting enzyme inhibitor, ARB=angiotensin II receptor blocker, ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronization therapy, MIT= moderate intensity training, HIT=high intensity training, VO_2-peak = peak oxygen consumption max.=maximal and RER=respiratory exchange ratio.

FIGURES

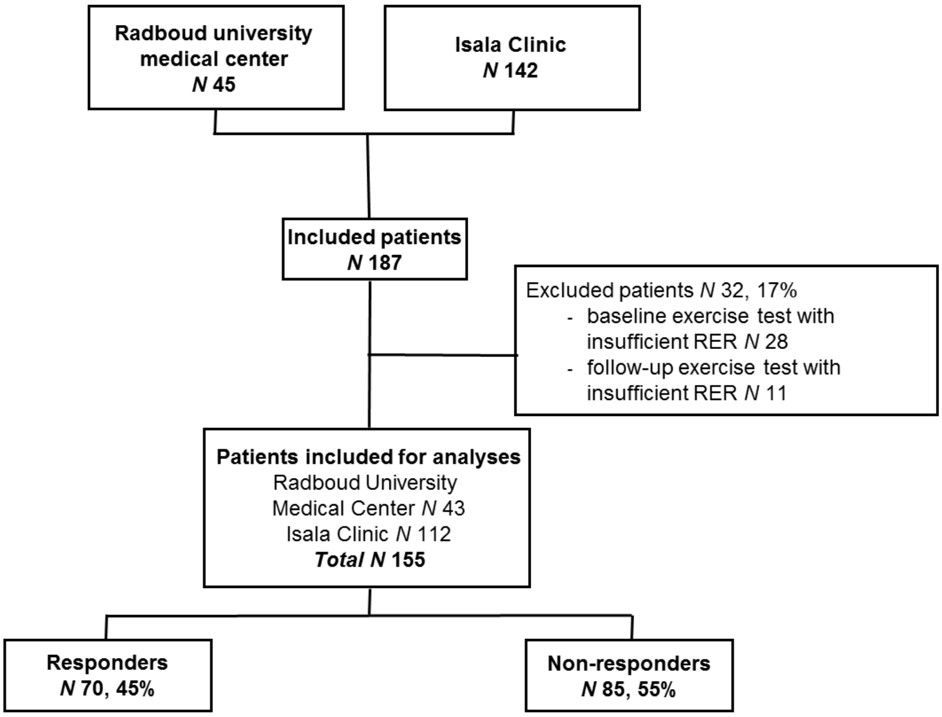


Figure 1. Flowchart of the inclusion of 155 heart failure patients from Radboud university medical center and Isala Clinic. The study population consisted of 187 HF patients who met the inclusion criteria. After inspection for data quality, 32 patients were excluded due to a maximal respiratory exchange ratio <1.00 during the exercise test. The final study population comprised 70 responders and 85 non-responders.

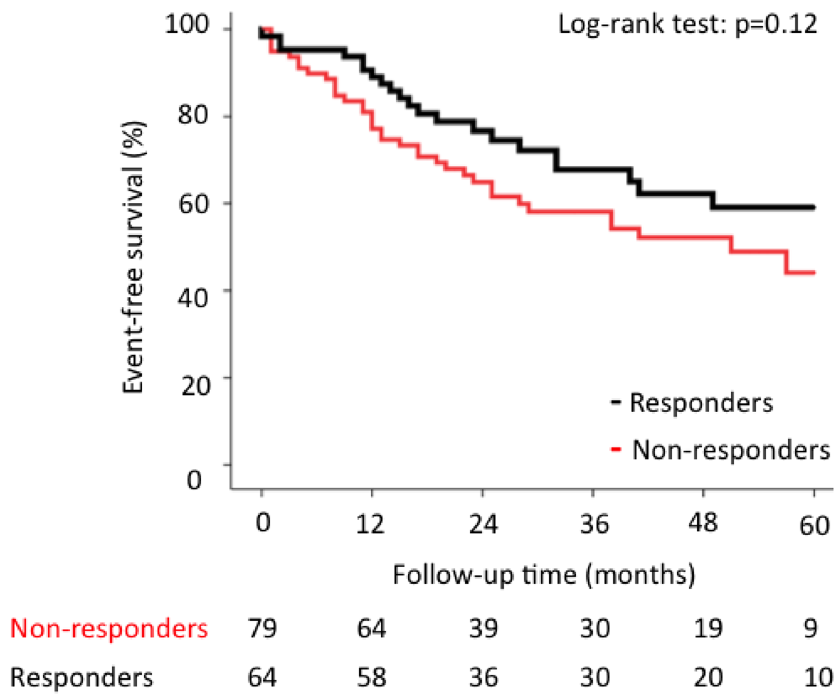
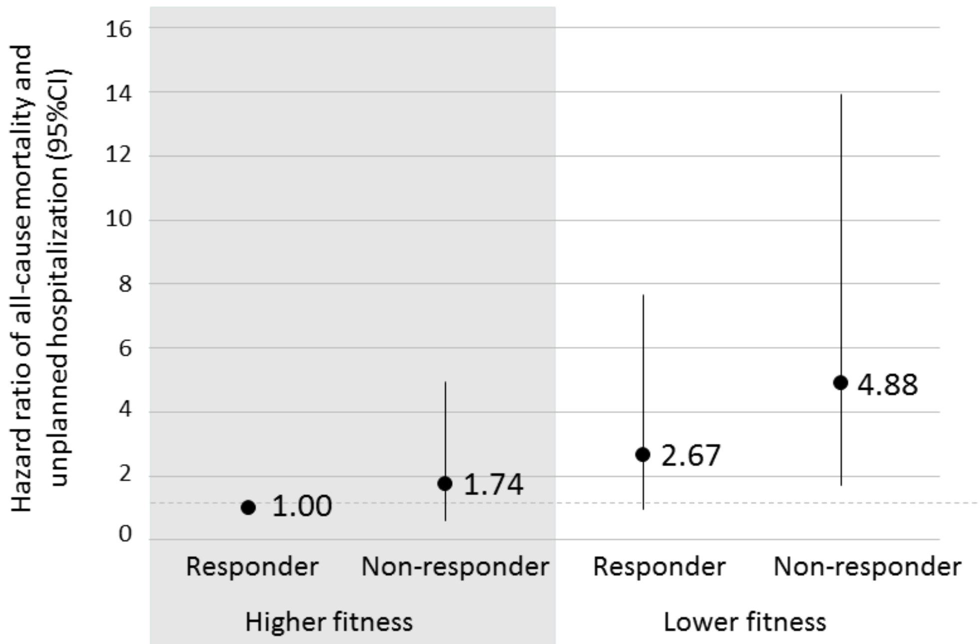


Figure 2. Kaplan-Meier curves of the time to death or unplanned hospitalization in 143 heart failure patients. In total 57 HF patients were hospitalized or died during follow-up: 36 non-responders (46%) and 21 responders (33%). The crude 5-year probability for all-cause mortality or unplanned hospitalization was 41% for responders and 56% for non-responders (log-rank test *P*=.12).



No. of cases	5	14	16	22
N (%)	23 (16%)	43 (30%)	41 (29%)	36 (25%)

Figure 3. Hazard ratios of all-cause mortality or unplanned hospitalization by baseline fitness levels and response to CR. The dots present hazard ratios (95% confidence intervals). Higher fitness was defined as baseline VO_2-peak >16.5 ml/min/kg and lower fitness as VO_2-peak ≤16.5 ml/min/kg. Hazard ratios were adjusted for age, sex and BMI.

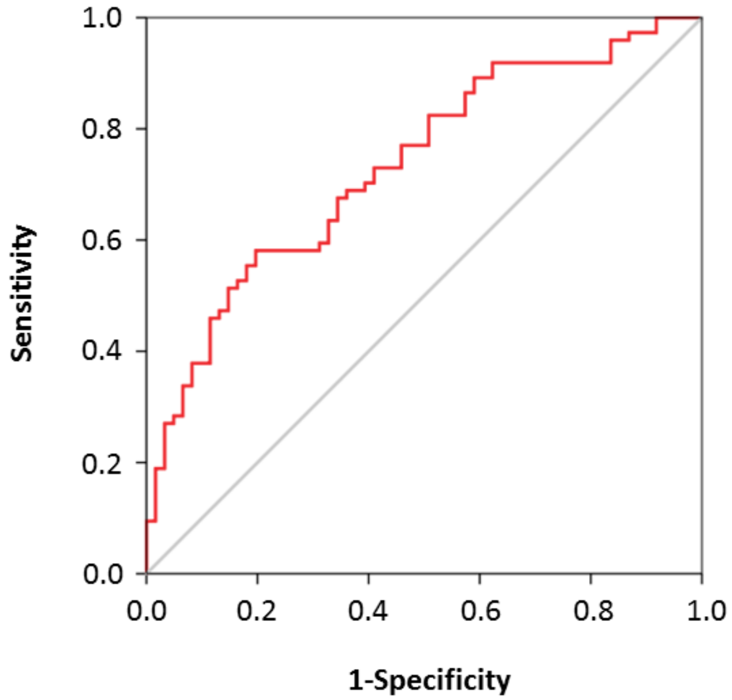


Figure 4. Discriminative performance of the prediction model for non-response to exercise training. The prediction model included age, baseline peak-VO_2 and adherence to the exercise program. The receiver operating characteristic curve had an area under the curve of 0.73 (95% CI = 0.65–0.82).

SUPPLEMENTAL MATERIAL MSSE

Supplemental Table 1. Predictors of non-response to exercise training in 155 heart failure patients using univariate logistic regression.

Parameters	**Odds ratio**	**95% CI**	***P*-value**
Patient characteristics			
Age (median, years)	1.03	1.00-1.05	.07
Sex (male)	0.47	1.01-4.41	.05
BMI (kg/m^2)	1.03	0.97-1.09	.40
Smoking (current)	0.78	0.34-1.71	.54
Diabetes mellitus (yes)	0.57	0.23-1.45	.24
COPD (yes)	1.26	0.43-3.74	.67
Hypertension (yes)	1.37	0.72-2.61	.34
Heart failure characteristics			
Aetiology, ischemic	1.70	0.89-3.27	.11
Baseline NYHA (I-II)	1.19	0.55-2.58	.66
Baseline LVEF			
worse (<30%)	0.70	0.30-1.65	.41
moderate (30-45%)	0.91	0.36-2.25	.83
reasonable (45-55%)	0.67	0.12-3.68	.64
good (>55%)	REF		
Atrium fibrillation (yes)	1.16	0.58-2.32	.67
Medication use			

ACEI or ARB	3.24	0.61-17.25	.17
Beta blocker agents	0.58	0.19-1.80	.35
Aldosteron receptor antagonist	1.06	0.48-2.31	.89
Loop diuretics	0.53	0.21-1.30	.16
Statins	1.07	0.56-2.06	.83
Medical devices			
ICD-CRT	1.55	0.72-3.38	.27
Pacemaker	1.71	0.89-3.28	.11
CRT	1.51	0.71-3.22	.29
ICD	1.46	0.77-2.79	.25
Rehabilitation program			
Type of rehabilitation*			
MIT	1.90	0.51-7.01	.34
HIT	REF		
Duration of rehabilitation (weeks)	0.99	0.95-1.04	.76
Adherence to exercise program (%)†	0.98	0.97-1.00	.06
Physiological parameters			
Baseline VO_2-peak (ml/min/kg)	1.07	1.01-1.14	.03
Baseline max. heart rate (beats/min)‡	1.00	0.99-1.01	.91
Baseline max. cycle load (Watt)‡	1.01	0.99-1.01	.07

*excluded in multivariable model due to low numbers.

†data was only available in 135 patients.

‡excluded in multivariable model due to high correlation with VO_2-peak.

BMI = body mass index, COPD = chronic obstructive pulmonary disease, NYHA= New York Heart Association classification, LVEF = left ventricular ejection fraction, ACEI = angiotensin-converting enzyme inhibitor, ARB=angiotensin II receptor blocker, ICD = implantable cardioverter defibrillator, CRT = cardiac resynchronization therapy, MIT= moderate intensity training, HIT=high intensity training, REF= reference, VO_2-peak = peak oxygen consumption, max.= maximal and RER=respiratory exchange ratio.

Supplemental Figure 1. Relative difference in VO2-peak (%) between baseline and post exercise training values. Responders are presented in dark grey and non-responders in light grey. The dashed line represents a 6% improvement in VO2-peak, which was the cut-point for being a responder or non-responder.