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A comparison of high versus low dose of exercise training in exercise-based cardiac rehabilitation: a randomized controlled trial with 12-months follow-up

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Abstract

Objective: To assess if a higher dose of exercise training in exercise-based cardiac rehabilitation could affect improvements in aerobic capacity and muscle strength.
Design: Assessor-blinded randomized controlled trial with 12-months follow-up.
Setting: Aarhus University Hospital, Aarhus, Denmark.
Subjects: A total of 164 cardiac patients referred to exercise-based cardiac rehabilitation were recruited.
Interventions: Patients were randomized to 1-hour exercise sessions either three times weekly for 12 weeks (36 sessions, high-dose group) or twice weekly for 8 weeks (16 sessions, low-dose group). The same standardized exercise and intensity protocol including aerobic and muscle strength training was used in all participants.
Main measures: Primary outcome was changes in VO_{2peak}. Secondary outcomes were changes in maximal workload, muscle strength and power. Measures were obtained at baseline, after termination of the rehabilitation programme and at follow-up after 6 and 12 months.
Results: After the end of intervention, statistically significant between-group differences were seen in favour of the high-dose group in all outcomes: VO_{2peak} 2.6 ($mL\,kg^{-1}\,min^{-1}$) (95% confidence interval (CI):

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0.4–4.8), maximal workload 0.3 W kg^{-1} (95%CI: 0.02–0.5), isometric muscle strength 0.7 N m kg^{-1} (95%CI: 0.1–1.2) and muscle power 0.3 W kg^{-1} (95%CI: 0.04–0.6). After 12 months, a significant between-group difference only persisted in VO_{2peak} and maximal workload.

Conclusion: A higher dose of exercise training had a small effect on all outcomes at termination of intervention. A long-term effect persisted in VO_{2peak} and maximal workload. Although the effect was small, it is an important finding because VO_{2peak} is the most important predictor of all-cause mortality in cardiac patients.

Keywords

Cardiac rehabilitation, exercise training, physical capacity, dose response, randomized controlled trial

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Introduction

Several reviews have consistently identified exercise-based cardiac rehabilitation as a central, safe and effective element of cardiac rehabilitation.[1–4] The scientific data clearly establish that individually tailored exercise-training protocols including both supervised aerobic, endurance and resistance training result in improvements in aerobic capacity, exercise tolerance and physical capacity in cardiac patients.[5–8] Studies have demonstrated that maximal (VO_{2max}) or peak (VO_{2peak}) oxygen uptake defined as the maximum rate of oxygen consumption measured during incremental exercise (exercise of increasing intensity) is the primary factor in influencing prognosis in cardiac patients.[9–11] Furthermore, it has been shown that VO_{2peak} remains an independent and strong predictor of all-cause and cardiovascular-specific mortality after adjustment for relevant covariates, with a risk reduction of 15% with every 1 mL O_2 kg^{-1} min^{-1} increase in VO_{2peak}.[10] Resistance training increases muscle strength and endurance, and positively influences cardiovascular risk factors, metabolism and cardiovascular function in cardiac patients.[6,7,12,13]

Despite the evidence-based recommendations for exercise-based cardiac rehabilitation, the provision of services varies markedly in dose.[2,3] Although studies[14,15] have shown that prolonged duration of exercise-training sessions does not affect physical capacity or cardiovascular disease risk factors, randomized controlled studies with a clearer description of exercise modalities and dose of intervention are requested.[2,16,17]

The purpose of this randomized trial was to investigate if a higher dose of a standardized exercise-based cardiac rehabilitation programme (1-hour exercise sessions three times weekly for 12 weeks) is more effective than a lower dose (1-hour exercise sessions twice weekly for 8 weeks) in improving aerobic capacity and muscle strength. Furthermore, we set out to investigate the overall long-term effects of the two different doses on aerobic capacity, workload and muscle strength.

Methods

Prior to initiation, the study was approved by the Central Denmark Region Committee on Biomedical Research Ethics (ID: M-20100297) and pre-registered at ClinicalTrials.gov (NCT01617850). Written informed consent was obtained from each patient included in the study, and all procedures were in accordance with the Helsinki Declaration. Institute of Clinical Medicine, Aarhus University, and Department of Physiotherapy and Occupational Therapy, Aarhus University Hospital, were responsible for the integrity and conduct of the study. The Central Region Research Foundation, Aarhus University Hospital Research Foundation and the National Funds for Chronic Diseases in Denmark funded the study. The study was carried out between June 2012 and May 2015.

This study was a randomized controlled assessor-blinded parallel-group trial with assessments at baseline (before entering exercise-based cardiac rehabilitation), at the conclusion of intervention

(12 and 8 weeks, respectively) and at follow-up after 6 and 12 months. Patients were consecutively included and randomized to either an exercise-based cardiac rehabilitation programme 1 hour three times weekly for 12 weeks (36 sessions, high-dose group) or an exercise-based cardiac rehabilitation programme 1 hour twice weekly for 8 weeks (16 sessions, low-dose group). Eligible patients were informed about the study and were offered a minimum of two days to consider if they accepted to participate.

Computer-generated block randomization was performed using block sizes of eight patients. Sequences in permuted blocks with equal numbers of 'intervention' and 'low dose' assignments were obtained using a 'shuffling envelope' procedure before study initiation. A secretary not involved in the study carried out this procedure. At an outpatient visit, before entering the exercise-based cardiac rehabilitation programme, a physiotherapist not involved in the study obtained the sequentially numbered, opaque, sealed envelope containing patient's assigned intervention and informed the patient of the group assignment. The principal investigators and staff involved in collecting outcome data were blinded to randomization.

Patients and procedures

Cardiac patients diagnosed with ischemic heart disease, chronic heart failure or heart valve disease referred to ambulant hospital-based exercise-based cardiac rehabilitation one to six weeks after discharge from hospital (depending on medical treatment and diagnosis) were assessed for eligibility. Exclusion criteria were as follows: age $<$ 18 years, body mass index (BMI) $>$35, inability to speak or read Danish and mental (cognitive) or physical conditions (e.g. amputation or severe paresis) impeding the group-based intervention.

Demographic and clinical data were collected from medical records, patient interviews and clinical tests. Four physiotherapists experienced in exercise testing performed all clinical tests and collected all data. The four physiotherapists were blinded to treatment allocation, and were not involved in the treatment of patients. Outcome measures were collected: prior to intervention, at the conclusion of intervention, respectively, after 8 or 12 weeks, and at follow-up 6 and 12 months after end of intervention. In order to carry out a process analysis, a cardio-pulmonary exercise test was performed in both groups after eight weeks.

Intervention

The exercise-based cardiac rehabilitation programme was group-based, and was supervised by two physiotherapists experienced in exercise-based cardiac rehabilitation. Each training session was based on current recommendations and included aerobic, endurance and muscle strength trainings.[7] All patients followed the same standardized exercise training and intensity protocols. A description of the intervention is presented in Table 1.

The only between-group difference in intervention was exercise dose. In total the high-dose group received 36 1-hour sessions, and the low-dose group received 16 1-hour sessions.

In order to ascertain the safety of exercise training, establish a baseline fitness level and determine maximal heart rate, all participants underwent a symptom-limited breath-by-breath cardio-pulmonary exercise test before initiating the exercise-based cardiac rehabilitation programme.[7,18] Based on test results, exercise intensity was established. During each training session, patients' exercise intensity was monitored either using heart rate or the 6–20 Borg Rate of Perceived Exertion Scale.[7] In addition, all patients received the same educational programme including counselling in behavioural strategies to promote cardio protective lifestyle and modify risk factors.[19] Furthermore, patients were motivated to continue to be physically active after programme conclusion.

Outcome measures

The primary outcome was a change in aerobic capacity between baseline and end of intervention (12 and 8 weeks, respectively), and between baseline and follow-up 6 and 12 months after end of intervention. In order to carry out a process analysis, patients in both groups performed a cardio-pulmonary exercise test after eight weeks of intervention.

Table 1. Exercise modes and intensity of the standardized supervised exercise training and intensity protocols used in all patients participating in the study.

Warm up and cool down	
Modality	Flexibility exercises Stretching for major muscle groups
Intensity	Low intensity aerobic exercises, for example, walking Ballistic and slow static stretching techniques
Duration	15 minutes of each exercise session
Aerobic training	
Modality	Rhythmic motion of large muscle groups in aerobic activities, for example, jogging, treadmill, cycling, ball games
Intensity	First two weeks: 40%–60% of max heart rate ≈ rate of Perceived Exertion Scale 12–14 From week three: 60%–80% of max heart rate ≈ rate of Perceived Exertion Scale 14–16 After week four interval training: 80%–95% of max heart rate ≈ rate of Perceived Exertion Scale 16–19 (3–4 minutes) 60%–70% of max heart rate ≈ rate of Perceived Exertion Scale 14–16 (3–4 minutes)
Duration	20 minutes of each exercise-training session. After week four 10–15 minutes of interval training on ergometer bikes with intensities as described above
Resistance training	
Modality	Lower extremities: leg extensions, leg curls/squats, leg press Upper extremities: bench press, lateral pull-downs, biceps curl, triceps extensions
Intensity	1–3 sets of 12–15 repetitions per exercise was performed in weight training machines at a relative resistance of 40%–60% of 1 repetition maximum. One repetition maximum is defined as the highest weight or load an individual can lift for a given exercise After two weeks, patients increased the number of sets from one to three. Weight was increased if >15 repetitions could be performed
Duration	25 minutes of each exercise session

The standard expression of aerobic capacity is VO_{2max} or VO_{2peak} commonly expressed as $mLO_2\,kg^{-1}\,min^{-1}$, and it is considered the best measure of cardiovascular fitness.[7,20,21] Aerobic capacity data were collected breath-by-breath using Jaeger Master Screen CPX System (MS-CPX) and JLAB Software Package. Volume was measured by Jaeger patented digital Triple-V sensor. The CPX system has fully automatic calibration of gas-analysers and volume meter. Barometric pressure, humidity and temperature were automatically registered. Before each test, the gas-analysing system was calibrated with a defined gas mixture. Body mass and height were measured under standardized conditions and registered, and a standard 12-lead electrocardiogram was obtained. All cardio-pulmonary exercise tests were performed on a Lode Corival ergometer cycle (Lode Corival Ergometer, Gronningen, The Netherlands), which is a computer-controlled cycle ergometer compatible with the MS-CPX system. A ramping protocol was used in all cases with increases varying from $10\,W\,min^{-1} \approx 2\,W/6$ second to $30\,W\,min^{-1} \approx 4\,W/8$ second. The ramping protocol was individually chosen on the basis of body mass, gender and physical activity level. A test time between 8 and 12 minutes was targeted. Patients were instructed to maintain a cadence between 60 and 70 pedal revolutions per minute, not to talk or stand up in the pedals during test and to keep pedalling until complete exhaustion. During the test, continuous electrocardiographic monitoring was made along with blood pressure measurements. Gas exchange parameters were simultaneously measured breath-by-breath, but averaged for 15-second intervals and expressed as minute values. The test was considered valid when either oxygen uptake or heart rate was levelling off or the respiratory exchange ratio was >1.1.

The secondary outcomes included a change in maximal workload per kg, maximal isometric

muscle strength in Newton per kilogram and muscle power in Watts per kilogram between baseline and all follow-up time points. Maximal workload was measured as the maximal workload reached during the exercise test. The highest measurement in watts was normalized for weight.

Maximal isometric muscle strength was defined as the maximal voluntary contraction at a specific joint angle against a resistance, and muscle power as the product of power generation and speed of a muscle contraction. Maximal voluntary isometric knee extensor strength of the dominant leg was measured using an adjustable dynamometer chair (Good Strength Metitur, Jyvaskyla, Finland).[22] Patients were seated on the dynamometer chair with the hip flexed 90° and arms folded across the chest. The measurement was performed at a knee angle of 60° flexion. The ankle was fastened with a strap to the strain gauge system 5 cm proximal to the lateral malleolus, and straps were applied across the pelvic. Patients were encouraged to extend the leg as fast and forcefully as possible, and to maintain the contraction for 5 seconds. After familiarization with the test, five maximal efforts, each separated by a 30-seconds rest were conducted. Data were gravity corrected with a sampling rate of 100 Hz, digitized into Newton's, normalized for leg length and weight (N m) and stored on a computer using Good Strength Metitur software. For each patient, the best performance with the highest value was accepted as test result.

Leg extensor power of the dominant leg was measured using The Nottingham Leg Extensor Power Rig (The University of Nottingham, Mechanical Engineering Unit, United Kingdom).[23] Patients were seated in an upright position with arms folded across the chest. The foot of the dominant leg was placed on the push pedal attached to a flywheel, and the free leg rested on the floor. Patients were encouraged to push the pedal as hard and as fast as possible. After familiarization to the procedure, the test was repeated with 30-seconds rest between trials until a plateau was reached, defined as two successive measurements below the highest. A maximum of 10 trials were obtained. Data in watt were normalized for weight.

Sample size calculation and statistics

Sample size calculation was based on earlier obtained VO_{2max} data in a population of cardiac patients.[24] Baseline VO_{2max} ($mL\,kg^{-1}\,min^{-1}$) was 17.8 ± 5 (mean $\pm$ SD). The expected difference in effect was defined as a 10% improvement. With a significance level of 0.05 and a power of 80%, the required sample size was 164 (82/82).

Normally distributed data are described by means and SD, and data not normally distributed by medians and interquartile range (IQR). Categorical variables are expressed as numbers and percentage, and compared by chi-square test. All data were tested for the assumption of normality.

An intention-to-treat principle was used including all randomized participants in the analysis. Data were analysed in a mixed effect model for repeated measurements (analysis of variance (ANOVA)) with group and time as systematic factors and patients as random effects. The model takes different random variation over time into account. Post hoc tests were based on the Kenward–Roger approximation in order to test all included patients in spite of missing data. An inspection of the residuals and fitted values did not give cause to doubt the model. The statistical analyses were performed using STATA 14.1 (StataCorp, College Station, TX, United States) software package. The significant level was set at 0.05.

Results

A total of 416 cardiac patients referred to hospital-based exercise-based cardiac rehabilitation between 2012 and 2015 were assessed for eligibility. Eligible patients who gave informed consent were consecutively randomized and enrolled in the study. The participant flow through the phases of the study is shown in Figure 1.

In total, 164 were randomized to either high-dose or low-dose group ($n = 82/82$). After randomization, six patients in the high-dose group and eight patients in the low-dose group dropped out. Reasons for discontinuing interventions are described in Figure 1.

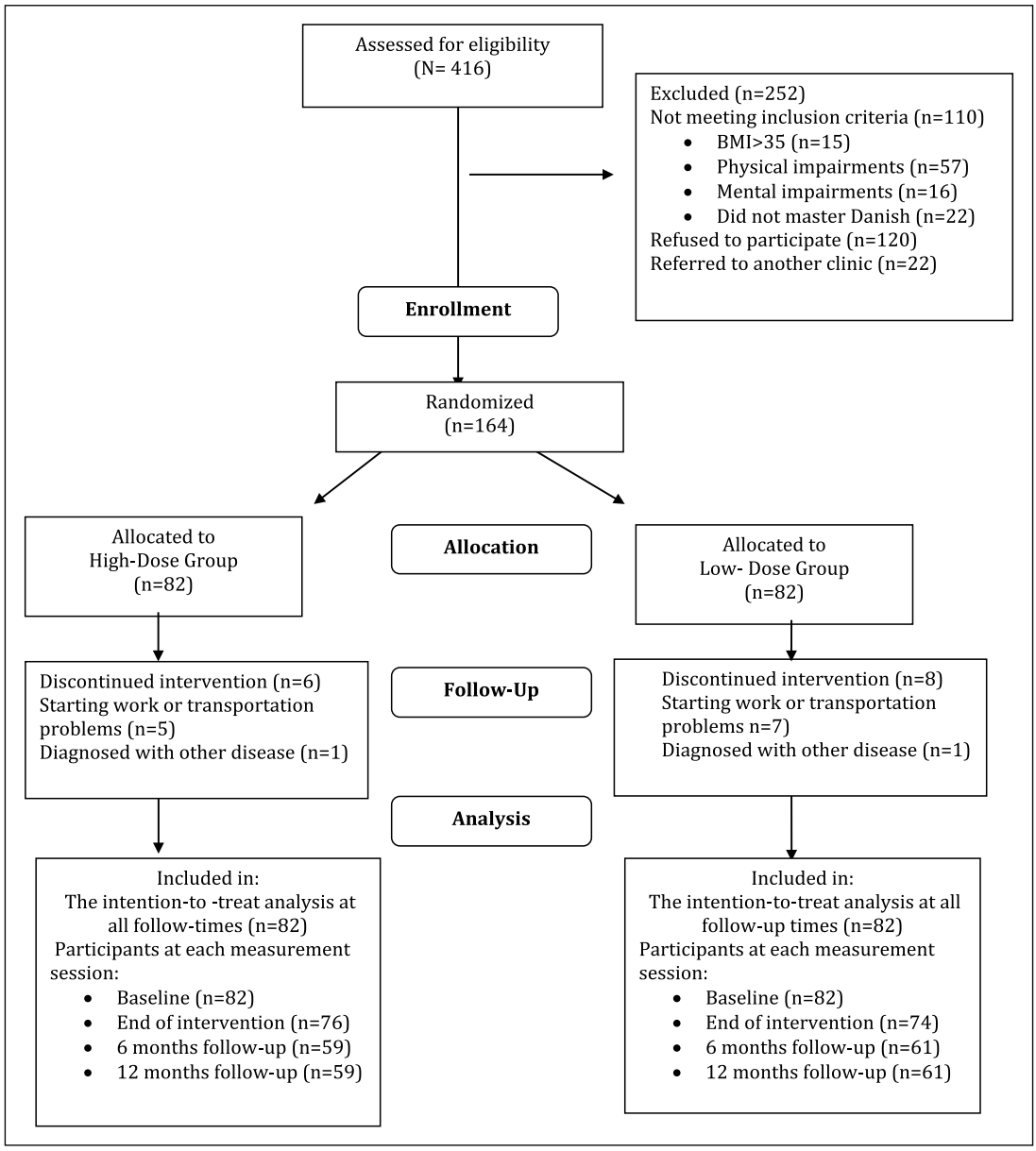

Figure 1. Participant flow throughout the phases of the study.

Baseline measurement data were available from all included patients, and data on all randomized patients ($n = 164$) were included in the intention-to-treat analysis. A drop out analysis revealed no differences in baseline characteristics between patients who fulfilled the study protocol and patients who dropped out.

Compliance was defined as participation in 60% or more of the exercise sessions. Patients in the high-dose group attended a median of 31 out of 36 planned exercise sessions (IQR: 28–34), and patients in the low-dose group attended a median of 14 out of 16 planned exercise sessions (IQR: 13–15). Completion rates were 86% (IQR: 75%–

94%) in the high-dose group and 87% (IQR: 74%–94%) in the low-dose group.

The two groups were comparable in demographic and clinical baseline variables (Table 2). Although equally distributed between groups, more men than women participated in the study, and a large number of patients were over-weighted, and suffered from one or more comorbidities (Table 2).

Effect of intervention

Data on primary and secondary outcomes at all measurement time points are shown in Table 3, and the overall within-group progression over time is presented in Figure 2.

In both groups, significant improvements in all outcome variables were achieved after attending the exercise-based cardiac rehabilitation programme at all follow-up measurement time points (Table 3 and Figure 2), and the achieved within-group improvements persisted 12 months after termination of the exercise-based cardiac rehabilitation programme. At the end of intervention, a statistically significant between-group difference in favour of the high-dose group was seen in all outcome measures (Table 3 and Figure 2).

The between-group differences at termination of intervention were VO_{2peak} 2.6 (0.4–4.8) $mL\,kg^{-1}\,min^{-1}$ ($P=0.01$), maximal workload 0.3 (0.03–0.5) $W\,kg^{-1}$ ($P\leqslant 0.02$), isometric muscle strength 0.7 (0.1–1.2) $N\,m\,kg^{-1}$ ($P\leqslant 0.02$) and muscle power 0.3 (0.03–0.6) $W\,kg^{-1}$ ($P\leqslant 0.03$).

The statistically significant effect in favour of the high-dose group persisted in VO_{2peak} and in maximal workload at 12-months follow-up, whereas no between-group effect was observed for muscle strength and muscle power (Table 3 and Figure 2). In both groups, only minor changes in all outcomes between 6- and 12-months follow-up were observed.

A stratified analysis adjusting for diagnosis (ischemic heart disease, heart failure and heart valve disease) did only reveal minor insignificant changes compared to the unadjusted analysis (data not shown). A process analysis of improvements in exercise capacity after eight weeks exercise training showed a mean difference between the two groups of $1.7\,mL\,kg^{-1}\,min^{-1}$ (−0.4 to 3.9) ($P=0.1$) in favour of the high-dose group.

Discussion

The main finding of this randomized controlled trial was a small but statistically significant short- and long-term effects in VO_{2peak} and maximal workload of a higher dose of exercise sessions (36 1-hour exercise session) compared to a lower dose (16 1-hour exercise session). An effect of the high-dose programme on muscle strength and muscle power was only found after end of intervention. A stratified analysis adjusting for differences in diagnosis only revealed minor insignificant changes, which did not affect study results.

A process analysis after eight weeks of intervention showed a small effect ($1.7\,mL\,kg^{-1}\,min^{-1}$ (−0.4 to 3.9, $P=0.1$)) in favour of the high-dose group. The result of this study, demonstrating effect on aerobic capacity of a higher dose of exercise sessions in exercise-based cardiac rehabilitation, is in accordance with what has been shown by others.[25,26] In a meta-analysis by Almodhy et al.,[26] a sub-group analysis showed that although there was a trend towards a difference in improved aerobic capacity according to programme length, the only significant moderator of exercise capacity was number of exercise sessions. Furthermore, a meta-regression analysis revealed that the number of exercise sessions prescribed was positively associated with improved aerobic capacity.[26] Findings from another meta-analysis[25] demonstrated that changes in exercise capacity did not vary according to overall programme length (less or more than 12 weeks), but according to number of exercise sessions. A sub-group analysis revealed that patients receiving more than 36 sessions had larger changes in fitness compared to those receiving fewer than 36 sessions. Data from this review suggested that 36 sessions were sufficient to promote clinically relevant gains in exercise capacity close to the overall mean differences presented for the group receiving more than 36 sessions. A large variation (4–28 sessions) in the group receiving less than 36 exercise sessions made it impossible to identify the dose of exercise that could produce meaningful changes in exercise capacity.[25] In contrast to this trial, a meta-regression analysis by Uddin et al.[27] examining different factors that could predict differences in exercise capacity following exercise-based cardiac rehabilitation did not find strong evidence for the effect of dose.

Table 2. Demographic and clinical baseline characteristics of 164 heart patients allocated to exercise-based cardiac rehabilitation for either 1-hour sessions three times weekly for 12 weeks (high-dose group) or 1-hour sessions biweekly for 8 weeks (low-dose group).

Variables	High-dose group ($n=82$)	Low-dose group ($n=82$)	P-values[a]
Gender (n/%)			
Male	66 (80%)	64 (78%)	0.8
Female	16 (20%)	18 (22%)	
Age in years (mean/95%CI)	61 (59–64)	60 (57–62)	0.3
BMI in $kg\,m^{-2}$ (mean/95%CI)	28 (27–29)	27 (26–28)	0.4
Current smoker (n/%)	5/82 (6%)	11/82 (11%)	0.2
Treatment (n/%)			
Coronary artery bypass grafting (CABG)	30 (37%)	29 (35%)	0.7
Percutaneous coronary intervention (PCI)	20 (24%)	19 (23%)	
Heart valve surgery	18 (22%)	16 (20%)	
Heart failure medical treated	14 (17%)	18 (22%)	
Ejection fraction $<50\%$ (n/%)			
Coronary artery bypass grafting (CABG)	10/30 (33%)	7/29 (24%)	0.5
Percutaneous coronary intervention (PCI)	9/20 (45%)	10/19 (53%)	
Heart valve surgery	4/18 (22%)	5/16 (31%)	
Heart failure medical treated	7/14 (50%)	7/18 (39%)	
Number of comorbidities (n/%)			
None	5 (6%)	13 (16%)	0.5
1	24 (29%)	21 (26%)	
2	25 (30%)	18 (22%)	
3	18 (22%)	20 (24%)	
>3	10 (12%)	10 (12%)	
Type of comorbidities			
Hypertension	50 (61%)	47 (57%)	0.7
Hyper cholesterol	44 (54%)	34 (41%)	
Claudication	5 (6%)	5 (6%)	
Cancer	7 (8%)	7 (8%)	
Renal insufficiency	5 (6%)	4 (5%)	
Stroke – transient ischemic attack	12 (15%)	6 (7%)	
Diabetes	16 (19%)	14 (17%)	
Chronic obstructive lung disease	11 (13%)	8 (10%)	
VO_{2peak} ($mL\,kg^{-1}\,min^{-1}$)	22.4 (20.8–24.0)	21.2 (19.6–22.8)	0.2
Max workload ($W\,kg^{-1}$)	1.7 (1.5–1.8)	1.6 (1.4–1.7)	0.3
Muscle strength ($N\,m\,kg^{-1}$)	5.2 (4.9–5.6)	5.2 (4.8–5.5)	0.9
Muscle power ($W\,kg^{-1}$)	2.1 (1.9–2.2)	2.0 (1.8–2.2)	0.9

BMI: body mass index.

Numbers and percentages describe categorical data, mean and 95% confidence intervals (CIs) continuous data.

[a]Statistical differences between groups were analysed with Fischer's exact two-sided chi-square test, Kruskal–Wallis rank sum test or Student's unpaired t-test.

The magnitude of the observed improvement in VO_{2peak} in the high-dose group of $3.1\,mL\,kg^{-1}\,min^{-1}$ (95% confidence interval (CI): 2.5–3.5) in our study is in line with data from previous reviews and meta-analysis in both chronic heart disease and heart failure patients presenting improvements of $3.3\,mL\,kg^{-1}\,min^{-1}$ (95%CI: 2.6–4.0),[27–31] but lower than the VO_{2peak} improvements of $5.2\,mL\,kg^{-1}\,min^{-1}$

Table 3. Data on primary and secondary outcome measures in the high-dose and low-dose groups at all measurement times.

Primary outcome	Baseline Mean (95%CI)	Week 12/8 Mean (95%CI)	6-months follow-up Mean (95%CI)	12-months follow-up Mean (95%CI)	Mean differences (95%CI) between groups Baseline – week 12/8	Mean differences (95%CI) between groups Baseline – month 12	P1 Overall within-group progression over time	P2 Overall between-group effects
VO_{2peak} ($mL\,kg^{-1}\,min^{-1}$)								
High-dose group	22.4 (20.8–24.0)	25.5 (23.9–27.0)	25.0 (23.4–26.6)	25.2 (23.7–26.9)	2.6 (0.4–4.8)	2.5 (0.3–4.8)	0.03	0.03
Low-dose group	21.2 (19.6–22.8)	22.8 (21.3–24.4)	22.6 (21.0–24.1)	22.8 (21.2–24.3)				
Secondary outcome								
Max workload ($W\,kg^{-1}$)								
High-dose group	1.7 (1.5–1.8)	2.1 (1.8–2.2)	1.9 (1.7–2.0)	1.9 (1.7–2.0)	0.3 (0.03–0.5)	0.3 (0.04–0.3)	0.02	0.04
Low-dose group	1.6 (1.4–1.7)	1.8 (1.5–1.9)	1.6 (1.5–1.7)	1.6 (1.5–1.8)				
Muscle strength ($N\,m\,kg^{-1}$)								
High-dose group	5.2 (4.9–5.6)	6.2 (5.8–6.6)	6.1 (5.7–6.5)	6.1 (5.7–6.6)	0.7 (0.1–1.2)	0.3 (−0.3 to 0.9)	0.01	0.3
Low-dose group	5.2 (4.8–5.5)	5.6 (5.2–6.0)	5.8 (5.4–6.2)	5.8 (5.4–6.2)				
Muscle power ($W\,kg^{-1}$)								
High-dose group	2.1 (1.9–2.2)	2.6 (2.4–2.9)	2.6 (2.4–2.8)	2.5 (2.3–2.7)	0.3 (0.03–0.6)	0.01 (−0.3 to 0.3)	0.01	0.4
Low-dose group	2.0 (1.8–2.2)	2.3 (2.1–2.5)	2.4 (2.2–2.6)	2.5 (2.2–2.6)				

Data are described by means and 95% confidence intervals (CIs). Data analyses are based on the intention-to-treat principle in a mixed effect model for repeated measurements.
Mean differences with 95%CI between baseline and end of intervention (respectively week 12/8) and between baseline and 12-months follow-up are presented.
P-values are presented for the comparison of overall progression over time within groups (P1) and for the comparison of the overall between-group effects (P2).

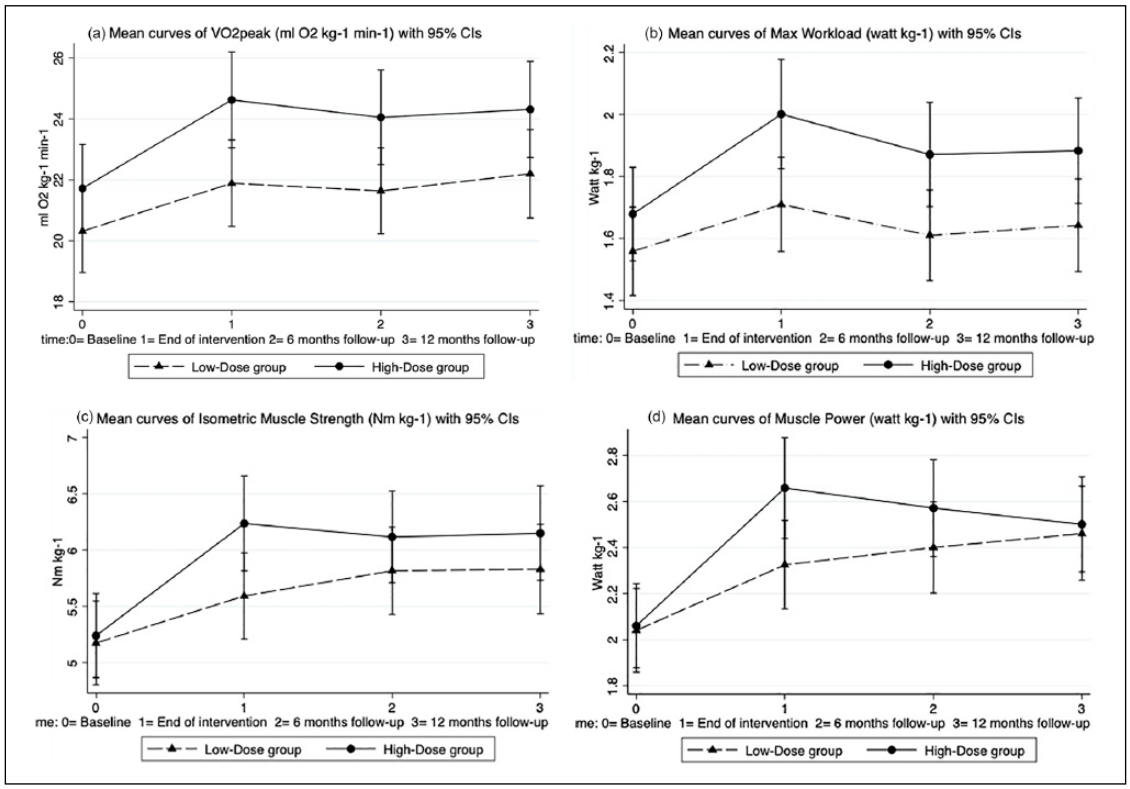

Figure 2. (a–d) Mean curves with 95% confidence intervals (CIs) of the progression over time within high-dose and low-dose group in all outcome measures (a = VO_{2peak}, b = maximal workload, c = isometric muscle and d = muscle power) at all measurement time points.

(95%CI: 4.1–6.4) presented by Sandercock et al.[25] In comparison to this, an improvement in VO_{2peak} of 1.6 mL kg^{-1} min^{-1} (95%CI: 0.7–1.7) in the low-dose group was rather modest, but in line with data reported in a retrospective multicentre study with between 8 and 16 exercise sessions.[32] Patients in our study suffered from different diagnoses (ischemic heart disease, chronic heart failure and heart valve disease). The difference in clinical condition is not likely to have influenced our study results, because the different diagnoses were equally distributed between groups and the stratified analysis did not affect study results.

A limitation of our study is that, although we used a gold standard symptom-limited exercise test with direct cardio-respiratory assessment of VO_{2peak}, we performed the test on a cycle ergometer. A comparison between cycle ergometer and treadmill testing has demonstrated that maximal oxygen uptake is 10%–20% higher when the test is performed on a treadmill. Especially untrained subjects are at risk of terminating the cycle ergometer test due to quadriceps fatigue.[20]

Although exercise test protocols were individually chosen based on an assessment of each patient's body mass, gender and physical activity level, the use of ergometer cycle instead of treadmill could have biased the assessments of the absolute improvements in exercise capacity in our study due to fatigue limitation. It has also been demonstrated that exercise test protocols with larger stage-to-stage increments in energy requirements (workload) have a weaker relationship between measures of VO_2 and work rate, and individually tailored ramping protocols with modest increase in work rates are recommended

in order to avoid fatigue-limited exercise test duration time.[20]

In this study, we used ramping protocols with increments of work rates between 2 and 4 W every 6-8 seconds. Although effort was made to choose a test protocol that fulfilled the recommendations, the use of an ergometer cycle instead of a treadmill may have biased the assessments of the absolute improvements in exercise capacity due to fatigue limitation. However, we set some easy definable criteria for evaluating if the individual test was a valid test (either oxygen uptake or heart rate levelling off), and controlled these after test termination. Furthermore, a group-wise post hoc comparison of respiratory-exchange-ratio (data not shown) did not give cause to believe that fatigue-limitations influenced the group comparison. Using an ergometer cycle therefore is not likely to have biased study results.

In our sample size calculation, we expected the high-dose group to improve 10% more than the low-dose group. However, we only found a 6% higher improvement in the high-dose group compared to the low-dose group. An explanation could be that the study was underpowered. Although we included the estimated number of patients ($n = 164$ (82/82)), six patients in the high-dose group and eight patients in the low-dose group discontinued intervention ($n = 150$ (76/74)), and only 120 patients (59/61) fulfilled follow-up tests.

Accordingly, the lack of a significant difference in the long-term effect of the high-dose programme on muscle strength and muscle power could be due to a type 2 error. Primarily, because the power calculation was based on VO_2 data, and second, because, as described above, the estimated number of participants were reduced during the progress of the study.

Another criticism of our study is the use of an isometric muscle test to measure changes in muscle strength. Because the resistance training programme in our study mainly consisted of dynamic (isotonic) exercises, the use of an isometric muscle test could be argued to lack specificity. Based on this, it would have been more appropriate to use an isokinetic test to evaluate changes in muscle strength.

Although we followed recommendations for resistance training in exercise-based cardiac rehabilitation,[7] the number of repetitions per set was rather high, and further studies are needed to investigate the effects of resistance training with higher weights (<12–15 repetitions). The quality of this study includes the assessor-blinded randomized design, inclusion of all groups of cardiac patients and a standardized intensity and exercise-training programme. The high compliance to exercise-based cardiac rehabilitation attendance in both groups (86% (IQR: 75–94) in the high-dose group and 87% (IQR: 74%–94%) in the low-dose group) verifies that the intended exercise intervention was successfully implemented.

Patients in the extended group improved VO_{2peak} 2.6 mL kg^{-1} min^{-1} more than patients in the low-dose group after termination of the exercise-based cardiac rehabilitation programme, and the gained overall effect almost persisted after 12 months. The clinical relevance of this improvement can be argued; it is smaller than the 10% difference that we expected in the sample size calculation, and smaller than what is generally considered to be a clinically relevant difference. However, it has been documented that aerobic capacity is a strong predictor of cardiovascular and all-cause mortality,[33] and Martin et al.[34] demonstrated that improvements in cardio-respiratory fitness after a 12 week exercise-based cardiac rehabilitation programme was associated with an overall reduction in mortality of 13% per metabolic equivalent increase in VO_{2peak}, and a 30% reduction in patients who entered the programme with a low fitness level. Furthermore, Keteyian et al.[10] in a study including 2812 cardiac patients demonstrated a cardiovascular-specific mortality risk reduction of 15% per 1 mL O_2 kg^{-1} min^{-1} increase in VO_{2peak}. Accordingly, an achieved overall effect of the high-dose programme of 2.6 mL kg^{-1} min^{-1} could be of clinical importance, as it can be translated into a relevant improvement in survival in cardiac patients.

Because patients in our study represented different diagnoses, were rather unfit and overweighed and with a majority of patients suffering one or more comorbidities, we believe that our study has high generalizability to clinical practice. In order to investigate if the extended exercise-based cardiac rehabilitation programme is cost-effective, an economic evaluation will be carried out.

Clinical messages

- In patients undergoing cardiac rehabilitation, a higher dose (36 sessions in 12 weeks) of exercise training has a small, statistically significant short- and long-term effect on improvements in aerobic capacity compared with 16 sessions in 8 weeks.
- It also has a small, statistically significant short-term effect on improvements in muscle strength and power.

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