Standardised exercise training is feasible, safe and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension - results from a large European multicentre randomised controlled trial

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Abstract

Aims: This prospective, randomised, controlled, multicentre study aimed to evaluate efficacy and safety of exercise training in patients with pulmonary arterial (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and Results: For the first time a specialised PAH/CTEPH rehabilitation programme was implemented in eleven centres across ten European countries. Out of 129 enrolled patients, 116 patients (58 vs. 58 randomised into a training or usual care control group) on disease-targeted medication completed the study (85 female; mean age 53.6±12.5years; mean pulmonary arterial pressure 46.6±15.1mmHg; World Health Organization (WHO) functional class II 53%, III 46%; PAH n=98; CTEPH n=18). Patients of the training group performed a standardised in-hospital rehabilitation with mean duration of 25 days (95% confidence interval (CI) 17 to 33 days), which was continued at home. The primary endpoint, change of 6-minute walking distance, significantly improved by 34.1±8.3m in the training compared to the control group (95% CI, 18 to 51m; $p<0.0001$). Exercise training was feasible, safe and well tolerated. Secondary endpoints showed improvements in quality of life (short form health survey 36 mental health 7.3±2.5, $p=0.004$), WHO functional class (training vs. control: improvement 9:1, worsening 4:3; chi-square $p=0.027$) and peak oxygen consumption (0.9±0.5ml/min/kg, $p=0.048$) compared to the control group.

Conclusion: This is the first multicentre and so far the largest randomised, controlled study on feasibility, safety and efficacy of exercise training as add-on to medical therapy in PAH and CTEPH. Within this study, a standardised specialised training programme with in-hospital start was successfully established in ten European countries.

Key words: pulmonary rehabilitation, pulmonary hypertension, exercise programme

Words: 249

Introduction

Low-intensity exercise training for patients with pulmonary arterial (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), has been shown to increase quality of life, exercise capacity, lower limb muscle strength and possibly haemodynamics.[1-3] Up to date, six randomised controlled trials have been published[2-7] as well as 14 further controlled trials or cohort studies.[8] Hence, the evidence is mounting that exercise training is a valuable add-on to targeted medical therapy. Currently, specialised low-dose exercise training holds a class IIa level B recommendation in the European Society of Cardiology/ European Respiratory Society (ESC/ERS) pulmonary hypertension (PH) guidelines.[9-11]

Until the ESC/ERS-guidelines had been published, the sample sizes of the 4 randomised controlled studies in precapillary PH-patients considered for recommendations on exercise training were quite small (ranging from 23 to 30 patients). After 2015 two further randomised controlled trials,[2, 5] 3 meta- and one Cochrane analysis[12-15] have shown that exercise training is highly beneficial for precapillary PH patients. In most previous studies the initial training was highly supervised and conducted in an inpatient setting.[8, 9] Therefore, PH guidelines recommended that exercise training programmes should be implemented by centres experienced in both - PAH patient care and rehabilitation of compromised patients. In addition, patients should be treated with the best standard of pharmacological treatment and in a stable clinical condition before embarking on supervised rehabilitation.[9] However, the access to such programmes is very limited and multicentre studies are lacking to assess the effect of exercise training in different countries with different health care systems. Before the start of this trial, rehabilitation was not available for PH patients in most European countries.

Therefore, the objective of this study was to perform a multicentre, randomised, controlled trial across Europe also including countries in which exercise training had so far not been available for PH patients to investigate its feasibility, safety and efficacy. Furthermore, we aimed to develop and

assess standardised settings, monitoring and adjustment of exercise training which would be helpful to implement a validated, high quality programme with a solid scientific evaluation.

Methods

Study population and design

All participating centres were members of a European Respiratory Society Task Force on exercise training in PH.[8] A common protocol was designed to conduct the first multicentre study on exercise training in PH. Eleven centres from ten European countries (Austria, Belgium, Germany, Italy, Lithuania, the Netherlands, Portugal, Scotland, Spain, Switzerland) participated.

Inclusion criteria were precapillary PH (pulmonary arterial hypertension (PAH) or non-operable or recurrent chronic thromboembolic PH (CTEPH)) diagnosed by right heart catheterisation according to the ESC/ERS PH Guidelines.[9] Study participants had to be ≥18 years of age, non-pregnant, in World Health Organization functional class (WHO-FC) II-IV and stable on optimised PAH targeted therapy for at least 2 months prior to study enrolment. Excluded were patients with PAH associated with portal hypertension, complex congenital heart disease,[16] HIV and patients with pulmonary veno-occlusive disease. Further exclusion criteria were clinically relevant lung or left heart disease, active liver disease, acute infection, walking disability, haemoglobin concentration below 75% of lower limit of normal values (individual age and gender adjusted normal values of haemoglobin), systolic blood pressure <85 mmHg, recent syncope and skeletal or muscle abnormalities prohibiting participation in an exercise programme. Patients with sustained supraventricular and ventricular arrhythmias at baseline were not enrolled into the study. Patients with mild non-sustained supraventricular or ventricular arrhythmias or with a history of arrhythmia, e.g. after cardioversion, were able to participate in the study. Targeted PAH or other medication was not to be altered within the training period. The study complies with the Declaration of Helsinki. All patients gave their written informed consent to the study. The study was approved by the ethics committee of the Medical Faculty of Heidelberg University, Germany (S-473/2015) and by each centre's respective ethics committee. The study was registered in clinicaltrials.gov under the identifier NCT03345212.

Randomisation and outcome measures

The study was a 15-week, randomised, controlled multicentre trial. After giving written informed consent for this study, patients were randomly assigned to either a "training group" or a "control group" using a permuted block randomisation procedure with sealed envelopes, stratified by centre. Patients of the training group stayed in-house for the initial 10-30 days of the study period and continued with a programme at home for another 11-12 weeks. Patients of the control group stayed at home with usual daily activity. Efficacy parameters were assessed at baseline and after 15 weeks by investigators who were blinded to the clinical data.

The primary endpoint was the change in six-minute walking distance (6MWD) from baseline to 15 weeks between exercise training and control group. Six-minute walk test was carried out under standardised conditions.[17]

Secondary endpoints were the change from baseline to 15 weeks after rehabilitation in peak oxygen consumption based on a cardiopulmonary exercise testing (CPET), WHO-FC, N-terminal prohormone brain natriuretic peptide (NT-proBNP), quality of life and safety parameters. Echocardiography at rest and during exercise and cardiopulmonary exercise testing were performed in a smaller subset of centres. Assessment and analysis of quality of life (short form health survey 36, SF-36 questionnaire) and of other efficacy parameters were performed as described previously.[2] Adverse events, defined according to International Conference of Harmonization Good Clinical Practice, during the study period were recorded.

Exercise training programme

For standardisation of the training programme great effort has been undertaken including several meetings of the participating professionals and the implementation of a train the trainer setting. At least one PH expert and physiotherapist from each centre spent several days at the PH expert centre and rehabilitation clinic in Heidelberg, Germany between November 2014 and April 2018 to

receive first-hand experience on the set-up of the clinical examinations, patients' exercise capacity evaluation, training adjustment, monitoring and exercise training components to assimilate procedures across countries as much as possible. The 6MWD as primary endpoint was performed standardised according to current recommendations.[18] Each centre performed a study entrance examination to assess baseline parameters, enabled an inpatient phase between 10 and 30 days followed by an outpatient phase until the final examination at 15 weeks.

The exercise and respiratory training was based on published procedures[2, 3] and adapted by each country to achieve a feasible set-up which was similar to the described setting. The Heidelberg exercise training program specifically developed for patients with PH was chosen as intervention due to the profound scientific evaluation of the program and safety reasons (low-intensity). The training programme consisted of respiratory therapy, cycle ergometer training, dumbbell training, guided walks and mental training as described previously.[2] During the initiation period, exercise training was performed 5-7 times/week. During the continuation phase at home, training frequency was 3-7 times/week. Training intensity was 40-60% of the patients' achieved maximal workload during ergometer test at baseline. Oxygen saturation, heart rate, right ventricular function at rest and during exercise and subjective perception were considered for initial training intensity and training adjustment. Right ventricular function during exercise was measured by echocardiography as visual estimation of pump function and as change of systolic pulmonary arterial pressure from rest to peak exercise measured during stress echocardiography as described previously.[19] Pump function was classified qualitatively as normal, mildly, moderately or severely impaired. Training was closely supervised by physical therapists and physicians specialised in rehabilitation medicine and PH experts. Transcutaneous oxygen saturation and heart rate were monitored continuously throughout the training. Patients, who were on oxygen therapy 16-24 hours/day before inclusion into this study remained on oxygen during the training programme. At discharge at the end of the inpatient phase, patients received an individualised training manual and organised a cycle ergometer for use at home.

Statistical methods

The analyses were performed by a statistician (NB). The efficacy analysis and subject characterisation were performed by use of the efficacy dataset including all patients with baseline and follow-up assessment of the primary endpoint 6MWD. All patients who were enrolled and randomised into the study were included in the safety analysis. Data are given as mean values ± standard deviations. For the description of effects changes in absolute values were calculated. Differences between changes of the intervention and the control group were calculated and expressed as 'control-group corrected change'

Calculation of sample size was based on the primary efficacy endpoint which was defined as the change in 6MWD between baseline and 15 weeks of exercise training between the training and the control group. To detect a control-group adjusted difference in 6MWD of 30 meters, with an equal standard deviation of 53 meters with a power of 80% and a two-sided significance level of 5%, it was calculated that 50 patients were required in each treatment arm. Under consideration of the assumed dropout rate of 20%, the sample size was increased to 63 patients in each group (total 126). The primary efficacy analysis was performed by a t-test with unequal variances (Welch tests) of changes between groups since the assumption for a covariance analysis was not fulfilled. The frequency of patients with increase of 6MWD ≥10% and the frequency of patients with increase above 440 meters (low risk category according to ESC/ERS risk stratification)[9] was analysed for interpretation of the primary endpoint.

Secondary endpoints were tested with two-sided student's t-tests for unequal variances. For analysis of categorical data, chi-square test was used. No imputation strategy was implemented for missing data. A sensitivity analysis excluding outliers >1.5 of interquartile range was performed for the primary endpoint 6MWD and for peak VO_2.

Safety was analysed descriptively. Adverse events (AEs) during the study period included all AEs that started or worsened from baseline until the last visit (15 weeks). As one centre did not report

AEs for the control group, patients from this centre were excluded from analysis of AEs. All tests were two-sided and p-values <0.05 were considered statistically significant. All analyses were carried out with IBM SPSS V25 (IBM Corp. Armonk, NY, USA).

Results

Study population

From October 2015 until November 2019 a total of 129 patients were enrolled into the study with 61 patients in the control group and 68 patients in the training group (figure 1, suppl. Table 1). Out of them, 116 completed the study with baseline and follow-up assessment of the primary endpoint 6MWD (58 vs. 58 patients; 73.3% female, 53.6±12.5 years, 47.5% WHO-FC ≥3, mean pulmonary artery pressure 47±15 mmHg, pulmonary vascular resistance 8.2±5.0 WU; table 1). One patient in the training group and one patient in the control group had mild impairment of left ventricular function. Right ventricular function was mildly impaired in 13 vs 10, moderately impaired in 5 vs. 5 and severely impaired in 3 vs. 2 patients (training vs. control). Reasons for dropout are given in figure 1. Mean inpatient training duration was 25 days (95% confidence interval 17 to 33 days). PH-specific medication was not changed throughout the study period. Baseline parameters were well balanced between groups (table 1).

Primary endpoint 6MWD

Patients of the training group showed a significant improvement of the primary endpoint 6MWD (30.7±57.9 meters), while the control group slightly decreased in 6MWD (-3.4±25.9 meters; control-group corrected change 34.1±8.3 meters; $p<0.0001$, table 1 and figure 2). In the training group 19 patients (32.3%) had a walking distance improvement ≥10%, compared to two patients (3.4%) in the control group. Twenty-five patients from the training group vs. 1 patient in the control group showed a 6MWD improvement above the threshold of clinically important difference ≥33 metres.

Ten patients of the training group who presented with a walking distance <440 meters at baseline improved their walking distance to ≥440 meters during follow-up (ESC/ERS low risk category), three patients showed deterioration of walking distance below this threshold. In comparison, one

patient from the control group improved walking distance from <440 meters to ≥440 meters, while three patients showed deterioration below the threshold.

Secondary endpoints

Quality of life scores (mental health) significantly improved in the training group, compared to the control group (control-group corrected change 7.3±2.5; p=0.004) and improved in trend for physical functioning (p=0.07) and social functioning (p=0.09; figure 3). With Bonferroni correction, p-values <0.005 remained statistically significant for quality of life data. Other SF-36 scales and subscales did not significantly differ between groups.

In the training group nine patients improved in WHO-FC, compared to one patient in the control group; four patients worsened in WHO-FC, compared to three patients in the control group (chi-square p=0.027).

In cardiopulmonary exercise testing of peak oxygen consumption significantly improved in the training group (control-group corrected change +0.9±0.3 ml/min/kg; p=0.048; figure 4; improvement equals 8.5±17.6% in the training group vs. 1.0±13.8% in the control group (p=0.015)). In the training group 23 patients (41.8%) had a peak oxygen consumption improvement ≥10%, compared to 15 patients (28.3%) in the control group.

Patients in the training group had a significant decrease in systolic pulmonary arterial pressure (-4 mmHg) compared to the control group (+5.8 mmHg; difference 9.8±3.1 mmHg, p=0.002, table 2). Other echocardiographic parameters did not show significant differences between respective changes compared to baseline.

Other parameters from cardiopulmonary exercise testing and change of NT-proBNP showed no significant differences between groups (table 2).

Sensitivity analysis excluding outliers revealed that the primary endpoint 6MWD (difference 26.3±6.5 metres, p=0.0001) and peak VO_2 (difference 0.75±0.38 ml/min/kg, p=0.05) still remained statistically significant.

Safety

The safety set comprised 99 patients, as AEs from one centre (n=30), which only reported AE data for patients from the intervention group, were excluded. In total, 52 AEs (27 training group, 25 control group) were reported for 21 patients (13 training group and 8 control group). AEs with a frequency ≥5% and serious AEs were comparable between groups (table 3). The most frequent AEs were arrhythmia and respiratory infections. In the training group, three patients experienced a serious AE during the study period, compared to one in the control group (chi square p=0.38). All serious AEs were classified as serious due to occurrence of hospitalisation.

Patients of the training group showed a higher dropout rate for the efficacy dataset (chi square p=0.095), though three patients successfully completed the study, but did not perform a 6MWD due to organisational issues. No patient in the control group vs. four patients in the training group did not complete the study due to AEs, out of which one was a serious AE (decompensated diabetes). However, none of the AEs or serious AEs were evaluated to be related to the study intervention.

Discussion

This is the first randomised controlled multicentre study on exercise training in patients with precapillary PH, performed in eleven centres in ten European countries in a large patient population, showing a significant and clinically meaningful improvement of the primary endpoint 6MWD and of the secondary endpoints WHO-FC, quality of life and peak oxygen consumption. The study showed for the first time that a safe and effective exercise training programme can be standardised and is feasible in different countries with different health care systems. To make this therapy widely available for PH patients participating centres implemented this PH training programme mostly for the first time and successfully adapted it to their local health care system.

Significant improvement of primary endpoint 6MWD

The effects of exercise training have so far been investigated by only a few working groups, which raised the need for larger and multicentre studies to verify the results.[8, 12, 20]

Although the 6MWD as outcome parameter has been criticised, particularly in add-on treatments,[21] we chose this patient-relevant outcome to reflect patients' exercise capacity as it has been shown that the 6MWD highly correlates with daily activity, haemodynamics and prognosis in PH and is thus used for risk assessment. Change in 6MWD has been reported to be below the clinically relevant threshold in several studies, despite significant changes in other relevant outcomes.[21] In a meta-analysis, the 6MWD has shown limitations as surrogate endpoint for clinical worsening events in PAH, but still a difference of 22.4 m favoured active treatment.[22] In our study, clinically relevant improvement in 6MWD was supported by significant improvement of WHO-functional class and peak VO_2, which have both shown to be prognostically important and are included in the ERS/ESC risk stratification model for PAH. Though 6MWD may not be directly linked to clinical worsening events, it does represent physical exercise capacity and may, together with other parameters, be interpreted for risk stratification and quality of life.[23]

Our findings are also in line with previous studies on exercise training in PH[8, 12-15] and confirm the positive results in a multicentre setting with an inpatient start of exercise training. Moreover, this study is the largest trial of PH patients undergoing exercise rehabilitation, substantially increasing the number of patients with scientifically evaluated training effects. The improvement of 6MWD by 34.1±8.3 meters was clinically meaningful and lies above the threshold for clinical importance of 33 meters in PH.[24] Ten patients of the training group (17.2%) improved walking distance to the low risk category, according to ESC/ERS risk stratification. Mean 6MWD improvement was also comparable to results of medication studies in PAH,[25] and lies above the results of add-on medication in PAH with mean improvements of 19.96 meters (95% confidence interval 15.35 to 24.57 m).[26] The improvement of 6MWD is slightly lower than reported from other exercise training studies, which may also be attributed to the multicentricity of this study, the required adaptation of training protocols. It has already been shown that patients with high functional impairment, e.g. WHO-FC III and IV, show the most pronounced benefit by exercise training,[27] which may have influenced the results. As 25/58 patients of the training group and 26/58 patients of the control group already presented with 6MWD values ≥440 meters at baseline, the improvement of walking distance may well be limited by a ceiling effect.[28] Furthermore, exercise training in PH was implemented for the first time in most of the centres, possibly resulting in suboptimal increase of training intensities, likely resulting in a lower training effect. To this end, the low number of AEs does support the focus on safety and tolerability of exercise training in this study.

Improvement of secondary endpoints

Secondary efficacy parameters such as quality of life and peak oxygen consumption significantly improved in the training group compared to the control group. As peak oxygen consumption showed a significant increase, but workload and peak heart rate remained constant, the effect may be attributed to an economisation of oxygen metabolism in the muscles. Patients of the control group improved peak VO_2 >10% in 29% of cases, which may possibly be attributed to the

Hawthorne effect, which describes the change of behaviour that occurs in clinical trials due to the awareness of being observed. The improvement of physical and mental health parameters in this study underlines the holistic approach of exercise training to enable deconditioned PH patients to extend their individual daily activity spectrum. As NT-proBNP was not significantly increased in the training group, the exercise training did also not seem to have a negative impact on right heart insufficiency and ventricular load.

Implementation of exercise training in different countries

To implement the standardised training programme mostly for the first time in the respective European countries new collaborations were initiated between PH expert centres and rehabilitation centres, funding opportunities were sought as the in-hospital rehabilitation was not part of reimbursement schemes of most national insurance systems. Thus, this study was the first step to enable a permanent implementation of an exercise training programme for PH patients in the respective European countries.

Limitations

We cannot exclude a potential inclusion bias whereby patients who are willing to undertake an exercise intervention may reflect a more motivated and adherent group. Another limitation of this study is the amount of missing data including non-invasive haemodynamics. The number of values included for each parameter is reported to indicate parameters which need to be interpreted with caution due to missing data. Especially for haemodynamic changes with exercise training in PH further data, preferably including right heart catheterization, are needed.

It is intrinsically not possible to blind a training study. However, investigators involved in data analysis were blinded as far as possible including clinical data and QoL assessments. Due to organisational reasons, not all centres were, however, able to perform blinded assessments of 6MWD, though the walking distance of previous assessments were not known to the investigators.

Total number of AEs did not differ between groups, though patients of the training group had a higher frequency of serious AEs and a higher dropout rate during the study. None of the AEs or serious AEs were stated to be related to the training intervention.

For safety concerns severely deconditioned patients with very restricted mobility range were not included in this study. Thus, we cannot exclude a selection bias towards more active patients.

As most of the patients in the control group were offered to participate in the exercise training programme after having finished their final examination, long-term data for comparison between exercise training and control group were not available. No daily physical activity measurements were part of the protocol. Thus, it is not possible to quantify whether general activity increased after the exercise training.

Conclusions

This is the first multicentre and the largest randomised, controlled study so far, reporting the beneficial effects of exercise training on 6MWD, quality of life and oxygen consumption in patients with PH. Study results are in line with previous studies. Exercise training was successfully implemented in all participating centres, including PH expert centres as well as experienced rehabilitation facilities. Further large multicentre studies are needed to investigate the haemodynamic effects of this intervention on different subtypes of PH.

Conflicts of interest:

E Grünig reports speaker fees from Actelion, Bayer/MSD, Bial, OrphaSwiss GmbH, Medscape and research grants from Actelion, Bayer/MSD, GSK, United Therapeutics, Novartis, Bellerophon, OMT, Pfizer and Reat outside of the submitted work.

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Figure Legends

Figure 1 Study flow-chart

This flow-chart gives the course of the study, patient randomisation, assessments and definition of dropouts. 6MWD: 6-minute walking distance, AE: adverse event, CI: confidence interval, CO: cardiac output, CTEPH: chronic thromboembolic pulmonary hypertension, FU: follow-up, mPAP: mean pulmonary artery pressure, PAH: pulmonary arterial hypertension.

Figure 2 Primary endpoint 6-minute walking distance

Patients of the training group significantly improved in 6MWD compared to the control group by 34.1±8.3 meters ($p<0.0001$).

Figure 3 Secondary endpoints: Quality of life

The secondary endpoint quality of life (QoL) significantly improved in the subscale mental health in the training group compared to the control group ($p=0.004$). Two further subscales were significant in trend (physical function $p=0.07$, social function $p=0.09$).

Figure 4 Secondary endpoints: peak oxygen consumption/kg

Peak oxygen consumption (VO_2)/kg body weight significantly improved by 0.9±0.5 ml/min/kg in the training group compared to the control group ($p=0.048$).

Table 1 Demographics and clinical characteristics of patients

Characteristic	Control group (n=58)			Training group (n=58)			Efficacy dataset (n=116)		
	Mean ± SD or n and %	95% confidence interval	n	Mean ± SD or n and %	95% confidence interval	n	Mean ± SD or n and %	95% confidence interval	n
Age [years]	55.0 ± 12.7	(51.6 to 58.3)		52.3 ± 12.4	(49.1 to 55.6)		53.6 ± 12.5	(51.3 to 55.9)	
Height [cm]	164.6 ± 8.4	(162.4 to 166.8)		167.2 ± 9.9	(164.6 to 169.8)	57	165.9 ± 9.2	(164.2 to 167.6)	115
Weight [kg]	73.4 ± 12.9	(70.0 to 76.8)		77.7 ± 19.8	(72.4 to 82.9)	57	75.5 ± 16.8	(72.4 to 78.6)	115
Female sex number [%]	45	(77.6%)		40	(69.0%)		85	(73.3%)	
Pulmonary hypertension diagnosis									
Idiopathic or heritable PAH	34	(58.6%)		39	(67.2%)		73	(62.9%)	
Congenital heart disease associated PAH	4	(6.9%)		5	(8.6%)		8	(6.9%)	
Connective tissue disease associated PAH	8	(13.8%)		4	(6.9%)		12	(10.3%)	
Other type of PAH	1	(1.7%)		2	(3.4%)		3	(2.6%)	
PH due to lung disease	0			1	(1.7%)		1	(0.9%)	
Chronic thromboembolic pulmonary hypertension	11	(19.0%)		7	(12.1%)		18	(15.5%)	
PH-targeted drugs									
Calcium channel blockers	3	(5.2%)		9	(15.5%)		12	(10.3%)	
Phosphodiesterase 5-Inhibitors	43	(74.1%)		45	(77.6%)		88	(75.9%)	
Endothelin Receptor antagonists	49	(84.5%)		46	(79.3%)		95	(81.9%)	
Soluble guanylate cycle stimulator	8	(13.8%)		6	(10.3%)		14	(12.1%)	
Prostacyclin	10	(17.2%)		18	(31.0%)		28	(24.1%)	
IP receptor agonist	2	(3.5%)		2	(3.5%)		4	(3.5%)	

Medication combination treatment												
One drug	14	(24.1%)			12	(20.7%)			26	(22.4%)		
Two drugs	29	(50.0%)			24	(41.4%)			53	(45.7%)		
Three drugs	15	(25.9%)			21	(36.2%)			36	(31.0%)		
Four drugs	0				1	(1.7%)			1	(0.1%)		
Right heart catheterization												
Right atrial pressure [mmHg]	7.9 ± 4.5		(6.6 to 9.2)	51	6.5 ± 4.1		(5.4 to 7.7)	51	7.2 ± 4.3		(6.4 to 8.1)	102
Mean pulmonary arterial pressure [mmHg]	46.7 ± 14.9		(42.7 to 50.6)		46.5 ± 15.5		(42.4 to 50.6)	57	46.6 ± 15.1		(43.8 to 49.4)	115
Cardiac Output [l/min]	5.2 ± 1.4		(4.8 to 5.6)	52	5.1 ± 1.5		(4.7 to 5.5)	53	5.2 ± 1.5		(4.9 to 5.45)	105
Cardiac Index [l/min/m²]	2.8 ± 0.7		(2.6 to 3.0)	52	2.7 ± 0.7		(2.5 to 2.9)	54	2.8 ± 0.7		(2.6 to 2.9)	106
Pulmonary arterial wedge pressure [mmHg]	9.9 ± 3.4		(9.0 to 10.9)	53	9.1 ± 3.7		(8.1 to 10.1)	55	9.5 ± 3.6		(8.8 to 10.2)	108
Pulmonary vascular resistance [WU]	7.7 ± 4.5		(6.4 to 9.0)	49	8.6 ± 5.5		(7.1 to 10.2)	52	8.2 ± 5.0		(7.2 to 9.2)	101
WHO FC class number [%]												
I	0				1	(1.7%)			1	(0.9%)		
II	34	(58.6%)			26	(44.8%)			60	(51.7%)		
III	24	(41.4%)			30	(51.7%)			54	(46.6%)		
IV	0				1	(1.7%)			1	(0.9%)		
Laboratory												
NTproBNP [ng/l]	332.5 ± 480.6		(184.6 to 480.4)	43	686.0 ± 1031.0		(342.2 to 1029.7)	37	460.0 ± 799.2		(318.2 to 673.8)	80
6-minute walking test												
6MWD [m]	447.4 ± 120.2		(415.8 to 479.0)		447.2 ± 117.7		(416.2 to 478.1)		447.3 ± 118.4		(425.5 to 469.1)	
Cardiopulmonary exercise test (CPET) with stress echocardiography												
Heart rate at rest [/min]	78.7 ± 14.3		(74.3 to 83.2)	42	83.9 ± 14.0		(79.7 to 88.2)	44	81.4 ± 14.3		(78.3 to 84.4)	86
SaO_2 at rest [%]	95.4 ± 4.6		(93.9 to 96.8)	41	93.2 ± 11.8		(89.6 to 96.9)	42	94.3 ± 9.0		(92.3 to 96.2)	83

Peak heart rate [/min]	123.0 ± 23.3	(115.8 to 130.1)	43	134.1 ± 22.9	(127.2 to 141.1)	44	128.6 ± 23.6	(123.6 to 133.6)	87
Peak SaO_2 [%]	90.0 ± 7.2	(87.7 to 92.2)	41	90.5 ± 7.1	(88.3 to 92.7)	43	90.2 ± 7.1	(88.7 to 91.8)	84
Peak VO_2 [ml/min/kg]	15.3 ± 4.3	(14.2 to 16.5)	53	14.2 ± 5.2	(12.8 to 15.6)		14.7 ± 4.8	(13.8 to 15.6)	111
Peak VO_2 % predicted [%]	68.5 ± 20.8	(61.9 to 75.0)	41	68.7 ± 51.5	(52.9 to 84.6)	43	68.6 ± 39.4	(60.1 to 77.2)	84
Peak workload [W]	81.6 ± 30.2	(71.9 to 91.2)	40	81.2 ± 27.1	(79.3 to 89.4)	44	81.4 ± 28.4	(75.2 to 87.5)	84
Workload % predicted [%]	74.8 ± 30.4	(65.0 to 84.5)	40	65.3 ± 29.0	(56.4 to 74.2)	43	69.9 ± 29.9	(63.4 to 76.4)	83
$V'E/VCO_2$ slope	45.4 ± 11.1	(41.6 to 49.3)	35	46.2 ± 12.9	(41.6 to 50.7)	33	45.8 ± 11.9	(42.9 to 48.7)	68
Echocardiography									
sPAP [mmHg]	59.1 ± 23.3	[51.3 to 66.8]	37	27.8 ± 4.3	[56.8 to 74.3]	41	62.5 ± 25.8	[56.7 to 68.3]	78
TAPSE [mm]	2.1 ± 0.4	[2.0 to 2.3]	41	2.1 ± 0.4	[2.0 to 2.2]	43	2.1 ± 0.4	[2.0 to 2.2]	84
RA area [cm^2]	21.1 ± 9.0	[18.1 to 24.0]	38	21.6 ± 8.6	[18.9 to 24.3]	41	21.4 ± 8.8	[19.4 to 23.3]	79
RV area [cm^2]	23.3 ± 6.1	[21.0 to 25.6]	29	26.0 ± 7.9	[23.2 to 28.7]	33	24.7 ± 7.1	[22.9 to 26.5]	62
Quality of life [SF-36 Questionnaire]									
Physical summation score	45.6 ± 19.5	(40.1 to 51.1)	55	45.4 ± 19.0	(40.3 to 50.6)	50	45.5 ± 19.1	(41.8 to 49.2)	105
Mental summation score	56.9 ± 18.7	(51.6 to 62.2)	55	57.7 ± 21.3	(51.9 to 63.4)	50	57.3 ± 20.0	(53.4 to 61.2)	105
Physical functioning	53.7 ± 22.6	(47.5 to 59.9)	57	46.3 ± 24.5	(39.8 to 52.8)	53	49.9 ± 23.8	(45.4 to 54.4)	110
Physical role functioning	50.5 ± 40.9	(39.2 to 61.7)	57	39.9 ± 41.2	(29.0 to 50.8)	53	45.0 ± 45.0	(37.2 to 52.8)	110
Bodily pain	69.2 ± 29.6	(61.1 to 77.4)	57	71.0 ± 27.0	(63.8 to 78.2)	53	70.2 ± 70.2	(64.8 to 75.5)	110
General health perceptions	40.7 ± 19.7	(35.2 to 46.1)	57	46.6 ± 21.4	(41.0 to 52.3)	53	43.8 ± 20.7	(39.9 to 47.7)	110
Vitality	52.9 ± 20.2	(47.4 to 58.5)	57	54.7 ± 22.9	(48.7 to 60.8)	53	53.9 ± 21.6	(49.8 to 57.9)	110
Social role functioning	72.9 ± 25.6	(65.6 to 80.2)	57	69.8 ± 28.3	(62.2 to 77.3)	53	71.3 ± 27.4	(66.1 to 76.4)	110
Emotional role functioning	71.7 ± 37.8	(61.3 to 82.1)	57	66.1 ± 43.0	(54.7 to 77.5)	53	68.8 ± 40.5	(61.1 to 76.4)	110
Mental health	72.5 ± 17.6	(67.6 to 77.3)	57	72.0 ± 21.1	(66.4 to 77.6)	53	72.2 ± 19.4	(68.6 to 75.9)	110

In case of missing values, sample sizes are given in the column of n; SD: standard deviation. WHO FC: world health organisation functional class, NTproBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-minute walking distance, PH: pulmonary hypertension, SaO_2: oxygen saturation, VO_2: oxygen consumption, $V'E/VCO_2$: minute ventilation / carbon dioxide production, sPAP: systolic pulmonary arterial pressure, RA: right atrial, RV: right ventricular, TAPSE: tricuspid annular plane systolic excursion.

Table 2 Changes in exercise testing and quality of life parameters

Characteristic	Control group (n=58)			Training group (n=58)				Control-group corrected change		
	Mean ± SD or n and %	95% confidence interval	n	Mean ± SD or n and %	95% confidence interval	n	p-value*	Mean ± SD or n and %	95% confidence interval	n
Laboratory										
NTproBNP [ng/l]	79.4 ± 195.5	(15.1 to 143.6)	38	16.5 ± 297.8	(-90.9 to 123.9)	32	0.31	62.9 ± 59.4	(-55.6 to 181.3)	70
6MWT										
6-minute walking distance [m]	-3.4 ± 25.9	(-10.2 to 3.4)		30.7 ± 57.9	(15.4 to 45.9)		<0.0001	34.1 ± 8.3	(-50.6 to -17-5)	
Cardiopulmonary exercise test (CPET)										
Heart rate at rest [/min]	-1.4 ± 12.4	(-5.3 to 2.4)	42	-0.1 ± 14.1	(-4.5 to 4.4)	39	0.64	1.4 ± 2.9	(-7.2 to 4.4)	83
SaO_2 at rest [%]	-0.1 ± 2.7	(-1.0 to 0.8)	39	2.3 ± 10.4	(-1.1 to 5.6)	41	0.17	2.4 ± 1.7	(-5.9 to 1.1)	78
Peak heart rate [/min]	4.9 ± 19.1	(-1.0 to 10.8)	43	3.6 ± 12.5	(-0.4 to 7.5)	40	0.70	-1.4 ± 3.5	(-5.6 to 8.3)	83
Peak SaO_2 [%]	-0.8 ± 5.7	(-2.7 to 1.1)	38	-0.5 ± 3.2	(-1.6 to 0.5)	38	0.80	0.3 ± 1.1	(-2-4 to 1.8)	78
Peak VO_2 [ml/min/kg]	0.0 ± 2.3	(-0.7 to 0.6)	53	0.9 ± 2.5	(0.3 to 1.6)	55	0.05	0.9 ± 0.5	(-1.9 to 0.0)	108
Peak VO_2 % predicted [%]	2.3 ± 8.0	(-0.2 to 4.9)	39	4.6 ± 10.2	(1.3 to 7.9)	39	0.28	-2.3 ± 2.0	(-6.4 to 1.9)	78
Peak workload [Watt]	3.7 ± 13.7	(-0.7 to 8.1)	40	4.6 ± 15.3	(-0.3 to 9.4)	41	0.80	0.8 ± 3.2	(-7.3 to 5.6)	81
Peak workload % predicted [%]	3.7 ± 12.5	(-0.3 to 7.7)	40	2.4 ± 10.8	(-1.1 to 5.8)	40	0.61	1.3 ± 2.6	(-3.9 to 6.5)	80
$V'E/VCO_2$ slope	-0.1 ± 5.6	(-2.1 to 1.9)	33	-1.9 ± 15.9	(-7.7 to 3.8)	32	0.55	1.8 ± 3.0	(-4.2 to 7.8)	65
Echocardiography										

	sPAP [mmHg]	5.8 ± 14.2	[1.0 to 10.6]	36	-4.0 ± 12.5	[-8.1 to 0.1]	38	0.002	9.8 ± 3.1	[3.6 to 16.0]	74
	TAPSE [mm]	3.2 ± 29.2	[-0.1 to 0.1]	41	5.5 ± 41.7	[-0.1 to 0.2]	38	0.77	-2.4 ± 8.2	[-18.6 to 13.9]	79
	RA area [cm²]	-0.2 ± 6.7	[-2.5 to 2.1]	36	0.4 ± 6.0	[-1.6 to 2.3]	39	0.70	-0.6 ± 1.5	[-3.5 to 2.4]	75
	RV area [cm²]	0.3 ± 2.1	[-0.5 to 1.1]	29	-0.3 ± 3.1	[-1.5 to 0.9]	28	0.41	0.6 ± 0.7	[-0.8 to 2.0]	57
Quality of life											
	Physical summation score	3.9 ± 13.2	(0.2 to 7.7)	50	6.4 ± 14.4	(8.1 to 18.1)	49	0.37	2.5 ± 2.8	(-8.0 to 3.0)	99
	Mental summation score	2.2 ± 11.6	(-1.1 to 5.5)	50	4.3 ± 11.7	(20.6 to 38.6)	49	0.38	2.1 ± 2.4	(-6.8 to 2.5)	99
	Physical functioning	4.3 ± 13.2	(0.5 to 8.1)	48	8.1 ± 18.1	(3.0 to 13.3)	50	0.23	3.8 ± 3.2	(-10.2 to 2.5)	104
	Physical role functioning	6.1 ± 42.2	(-5.5 to 17.8)	53	20.6 ± 38.6	(9.7 to 31.5)	51	0.07	14.5 ± 7.9	(-30.2 to 1.3)	104
	Bodily pain	0.7 ± 26.7	(-6.7 to 8.1)	53	3.4 ± 18.3	(-1.8 to 8.5)	51	0.55	2.7 ± 4.5	(-11.6 to 6.2)	104
	General health perceptions	3.0 ± 14.1	(-0.9 to 6.9)	53	0.6 ± 16.6	(-4.1 to 5.3)	51	0.23	-2.4 ± 3.0	(-3.6 to 8.4)	98
	Vitality	2.5 ± 14.2	(-1.5 to 6.4)	53	4.6 ± 11.3	(1.4 to 7.8)	51	0.39	2.2 ± 2.5	(-7.2 to 2.9)	104
	Social role functioning	0.1 ± 21.1	(-5.8 to 5.9)	53	6.6 ± 17.8	(1.6 to 11.6)	51	0.09	6.6 ± 3.8	(-14.1 to 1.0)	104
	Emotional role functioning	4.7 ± 35.5	(-5.6 to 1.4)	53	8.5 ± 34.5	(1.7 to 8.7)	51	0.58	3.8 ± 6.9	(-17.4 to 9.8)	104
	Mental health	-2.1 ± 12.8	(-5.6 to 1.4)	53	5.2 ± 12.5	(1.7 to 8.7)	51	0.004	7.3 ± 2.5	(-12.2 to -2.4)	104

In case of missing values, sample sizes are given in the column of n; SD: standard deviation. NTproBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-minute walking distance, RV: right ventricular, O_2: oxygen, HR: heart rate, SaO_2: oxygen saturation, VO_2: oxygen consumption, $EqCO_2$: respiratory equivalent for CO_2, $V'E/VCO_2$: minute ventilation / carbon dioxide production, sPAP: systolic pulmonary arterial pressure, RA: right atrial, RV: right ventricular, TAPSE: tricuspid annular plane systolic excursion. N is given in case of missing values. *p-value: significance of changes compared to baseline between groups

Table 3 Adverse events with occurrence ≥5%

	group		
Adverse Events	**control (n=47)**	**training (n=52)**	**Total**
Arrhythmia of any kind	5	3	8
Respiratory infection	3	4	7
	8	7	15
Serious adverse events			
diabetes, decompensated	0	1	1
edema, generalised	0	1	1
haemoptysis	1	0	1
stroke	0	1	1
Total	1	3	4

Figure 1

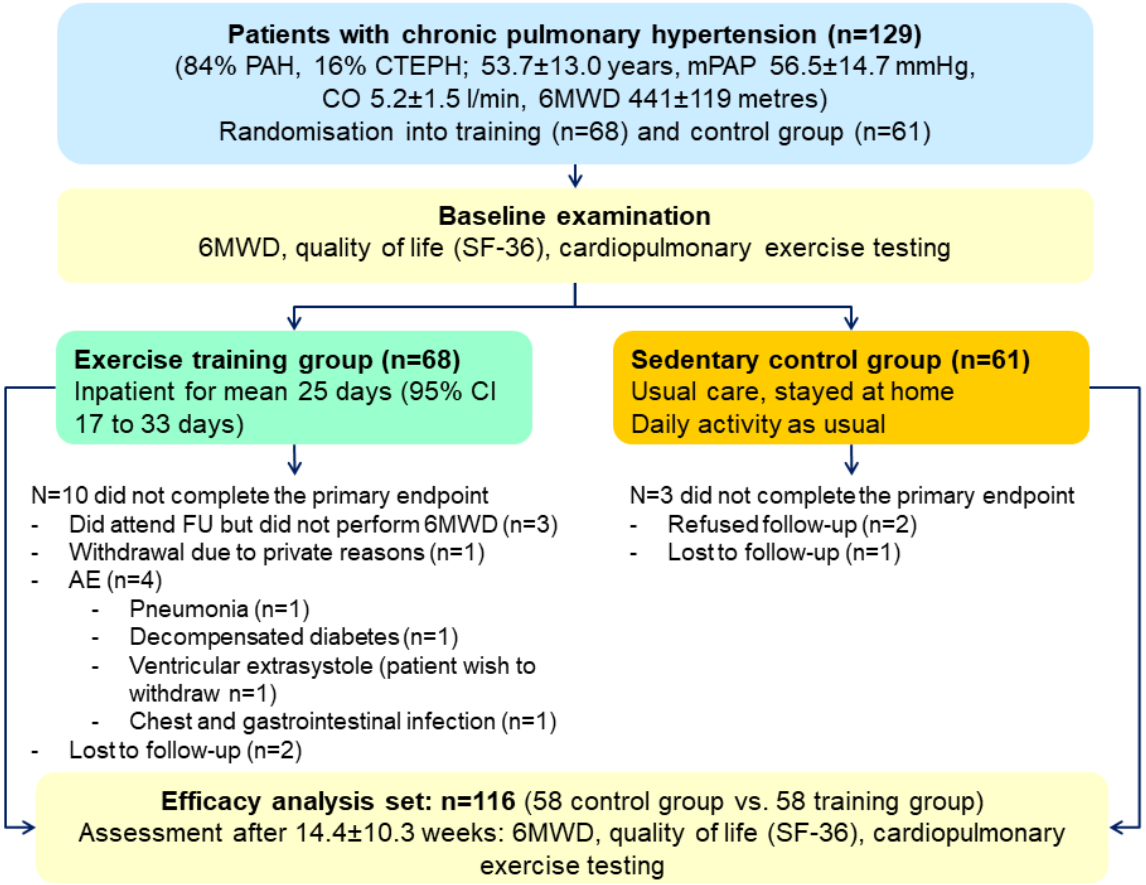

Patients with chronic pulmonary hypertension (n=129)
(84% PAH, 16% CTEPH; 53.7±13.0 years, mPAP 56.5±14.7 mmHg,
CO 5.2±1.5 l/min, 6MWD 441±119 metres)
Randomisation into training (n=68) and control group (n=61)
Baseline examination
6MWD, quality of life (SF-36), cardiopulmonary exercise testing
Exercise training group (n=68)
Inpatient for mean 25 days (95% CI 17 to 33 days)
Sedentary control group (n=61)
Usual care, stayed at home
Daily activity as usual
N=10 did not complete the primary endpoint
- Did attend FU but did not perform 6MWD (n=3)
- Withdrawal due to private reasons (n=1)
- AE (n=4)
  - Pneumonia (n=1)
  - Decompensated diabetes (n=1)
  - Ventricular extrasystole (patient wish to withdraw n=1)
  - Chest and gastrointestinal infection (n=1)
- Lost to follow-up (n=2)
N=3 did not complete the primary endpoint
- Refused follow-up (n=2)
- Lost to follow-up (n=1)
Efficacy analysis set: n=116 (58 control group vs. 58 training group)
Assessment after 14.4±10.3 weeks: 6MWD, quality of life (SF-36), cardiopulmonary exercise testing

Figure 2

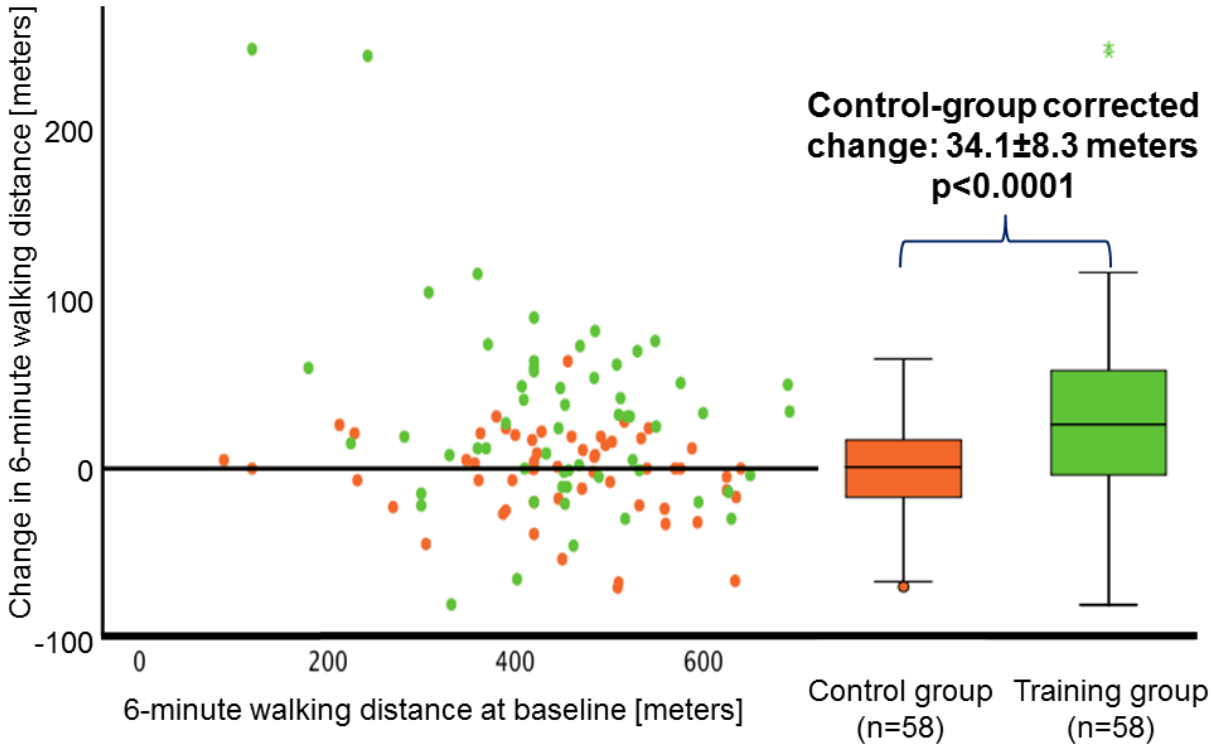

Control-group corrected change: 34.1±8.3 meters p<0.0001
Change in 6-minute walking distance [meters]
200
100
0
-100
0
200
400
600
6-minute walking distance at baseline [meters]
Control group (n=58)
Training group (n=58)

Figure 3

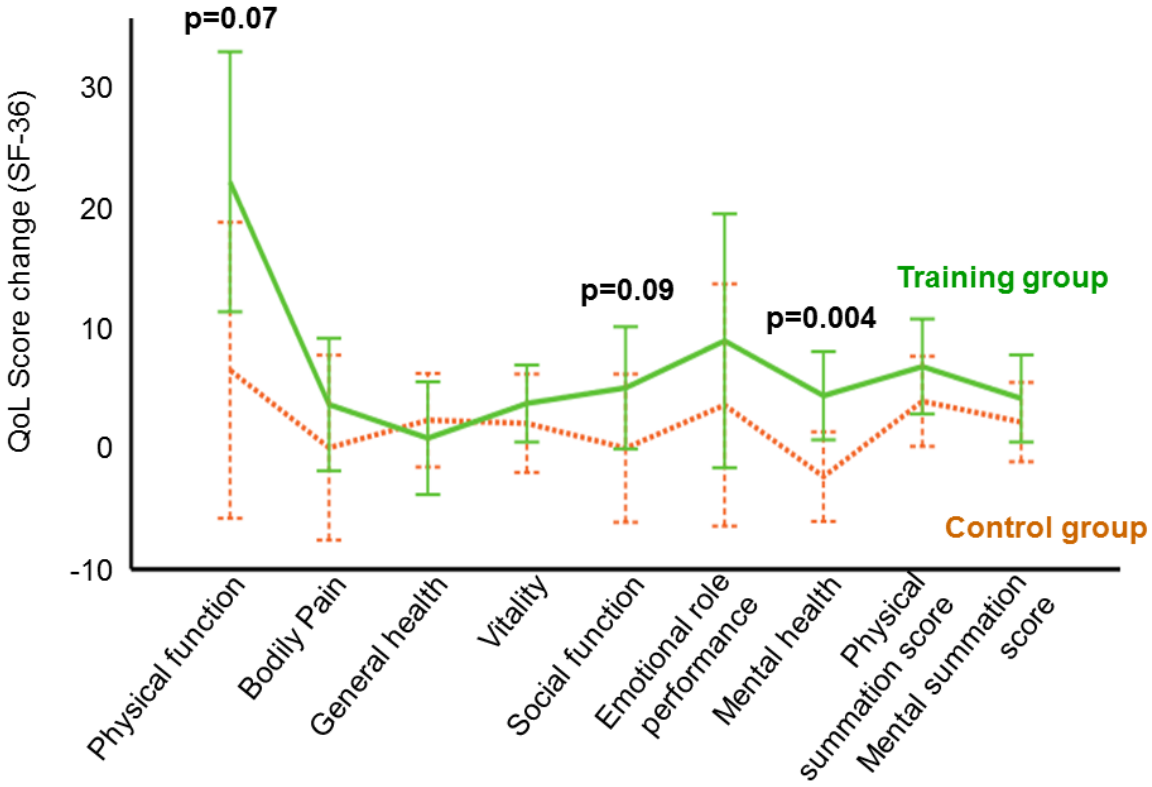
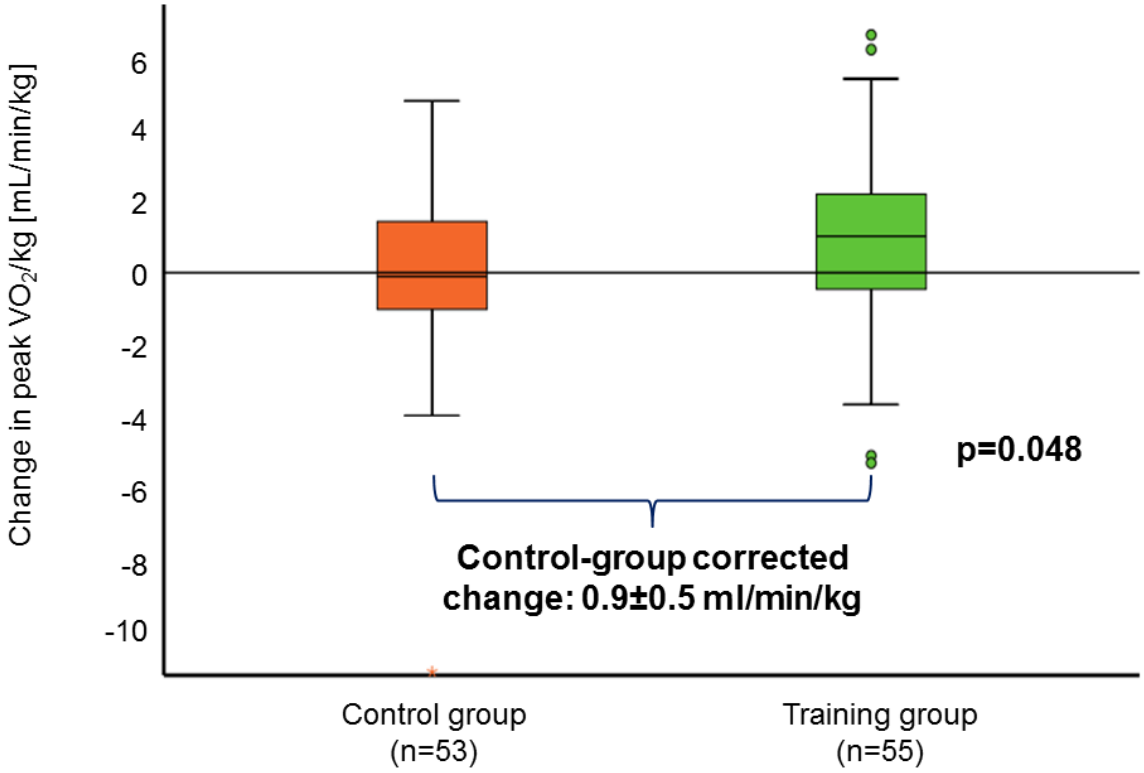

p=0.07
p=0.09
p=0.004
Training group
Control group
QoL Score change (SF-36)
30
20
10
0
-10
Physical function
Bodily Pain
General health
Vitality
Social function
Emotional role performance
Mental health
Physical summation score
Mental summation score

Figure 4


Change in peak VO_2/kg [mL/min/kg]
6
4
2
0
-2
-4
-6
-8
-10
p=0.048
Control-group corrected
change: 0.9±0.5 ml/min/kg
Control group
(n=53)
Training group
(n=55)