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Safety and Efficacy of Exercise Training in various forms of Pulmonary Hypertension

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Abstract

Background: The objective of this prospective study was to assess safety and efficacy of exercise training (ET) in a large cohort of patients with different forms and World Health Organization functional classes (WHO-FC) of chronic pulmonary hypertension (PH).

Methods: 183 patients with PH (pulmonary arterial hypertension (PAH), chronic thromboembolic PH (CTEPH) and PH due to respiratory or left heart diseases (PH) received ET in-hospital for 3 weeks and continued at home. Adverse events have been monitored during the in-hospital training program. Efficacy parameters were evaluated at baseline, after 3 and 15 weeks.

Results: After 3 and 15 weeks, patients significantly improved the distance walked in 6 minutes (6MWD) compared to baseline, scores of quality of life, WHO-FC, peak oxygen consumption, oxygen pulse, heart rate and systolic pulmonary artery pressure at rest and maximal workload. The improvement in 6MWD was similar in patients with different PH-forms and functional classes. Even in severely affected patients (FC-IV) ET was highly effective. Adverse events such as respiratory infections, syncope or presyncope occurred in 13% of patients.

Conclusion: Exercise training in PH is an effective but not a completely harmless add-on therapy even in severely diseased patients and should be closely monitored.

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Introduction

Previous studies in rather small cohorts of patients with idiopathic pulmonary arterial hypertension (IPAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH) have shown beneficial effects of exercise training (ET) as add-on to disease targeted medical therapy by increasing exercise capacity [1, 2, 3] and quality of life.[1] ET also improved peak oxygen consumption and WHO-functional class,[1] and possibly the clinical outcome with 1 and 2-year survival rates of 100 and 95%, respectively.[4] Importantly, no severe adverse events occurred in the previously assessed training groups. The improvement in 6 minute walking distance, reached after 15 weeks ET was unexpectedly high with a mean increase of 96 ± 61 meters [1] and of 84 ± 49 meters, respectively.[4] However, training studies cannot be performed in a blinded design and a selection bias towards highly motivated patients cannot be excluded.[1, 4] Other studies which applied a less intense out-patient training program in small cohorts of PAH-patients did reveal a less pronounced[3] or even no significant [5, 2] improvement in 6MWD or peak oxygen consumption, but an improvement in exercise endurance [5, 2] and muscle capillarization. [2] The effect of training in patients with other etiologies of PH, such as associated PAH (APAH), or out-of-proportion PH with left heart failure or respiratory diseases has not yet been evaluated. Furthermore, it has never been evaluated whether training programs may be harmful especially for patients with severe PH and right heart failure classified in WHO-FC IV. In these patients with end-stage PH prognostic relevant effects of medical treatment are usually very limited and it would be of interest, if such patients may benefit from a careful, low-dose and closely monitored ET as well. Especially in these severely affected patients safety is an important concern, particularly since they would be advised to continue ET. PH-patients sometimes experience presyncope and syncope immediately after exercise. The incidence of sudden

cardiac death due to exercise is unknown, but probably quite low for mild to moderate exercise. However, it is a common clinical experience that at least heavy exercise can be dangerous in PH. In an animal model ET significantly reduced the survival of those rats that received higher monocrotaline dosage representing a progressive form of PH.[6] Thus, ET in PH may possibly be both: a useful and effective additive therapy to disease targeted medication in some patients and a dangerous procedure with severe side effects including the risk of syncope or even sudden cardiac death in others. Therefore, the aim of this study was, to prospectively assess the effects of ET in a large cohort of patients with severe chronic PH of different etiologies and functional classes including end-stage disease with WHO-FC IV. We wanted to monitor the rate of adverse events during the 3 weeks in-hospital ET and to identify patients at risk for adverse events and/or for non-response to training.

Methods

Study Population and Design

This prospective study investigated patients with severe chronic PH who received exercise and respiratory training as add-on to disease-targeted medication between January 2005 and October 2010. The study patients belong to a new cohort and have not been published before. Further inclusion criteria were age between 18 and 80 years and WHO-FC II – IV.[7] Patients had to be stable and compensated with optimized medical therapy (as endothelin-antagonists, inhaled or parenteral prostanoids, sildenafil, anticoagulants, diuretics, and supplemental oxygen) for at least 2 months before entering the study. Six patients who were newly diagnosed with PH had an interval of 2-6 months between initiation of a new PH-targeted medical treatment and the start of exercise training, all other newly diagnosed patients had an interval of > 6 months. All patients in WHO functional class IV had been under maximal medical PH-targeted therapy and were stable even though they were at an unsatisfactory clinically stage.

The diagnosis was established at the participating PH centers according to current guidelines.[8] All patients underwent a detailed clinical work up including right heart catheterization. Left heart catheterization and/or computed tomography of the lungs were performed in all patients with PH due to left heart or respiratory diseases and when clinically indicated. All patients gave written informed consent for this study, which was approved by the Ethics Committee of the University of Heidelberg.

Outcome Measures

Efficacy parameters were prospectively evaluated at baseline, week 3, and week 15 as described previously.[1, 4] Six-minute walking distance (6MWD) was carried out under standardized conditions.[9] Health related quality of life assessment was performed by the Short Form Health Survey (SF-36). [10] The completed SF-36 questionnaire at baseline was compared to the results after 15 weeks. Assessment of 6MWD, SF-36, and of other efficacy parameters were performed by investigators who were blinded to the clinical data. Changes in WHO-FC, Borg dyspnea index (with 6 representing no exertion and 20 maximal exertion),[11] and gas exchange were also analyzed.[12] Cardiopulmonary exercise testing and stress Doppler echocardiography were carried out during supine bicycle exercise without oxygen supply as described previously.[1] Systolic pulmonary artery pressure (PASP), systolic (RRsys) and diastolic (RRdiast) systemic blood pressures, Work load, heart rate, ventilation (VE), oxygen uptake (VO_2), oxygen pulse (VO_2/heart rate), and carbon dioxide output (VCO_2) were measured continuously. The anaerobic threshold (AT) was detected with the V-slope method.[12]

Exercise Training Program

The exercise and respiratory training was performed as described previously[1, 4] in the Rehabilitation Clinic Königstuhl in Heidelberg. We performed a program especially developed for the PH-patients with at least 1.5 h/day ET (in intervals distributed over the day) consisting of interval bicycle ergometer training at low workloads (10-60 Watt) at 7 days a week, walking, dumbbell-training of single muscle

groups using low weights (500-1000g) and respiratory training at 5 days/week. Maximum heart rate during the training corresponded to 60-80% of the heart rate reached during cardiopulmonary exercise testing. Oxygen saturation had to be kept above 85%. The training was continued with at least 30 minutes/day at 5 days a week at home for the following 15 weeks.

Beside the physical training patients received mental training to improve their perception of individual physical abilities and limits. Psychological support was offered to all participants. The training program was closely supervised by physical therapists; physicians specialized in rehabilitation medicine and PH-experts by as described before.[1] Adverse events were recorded whenever they occurred. Oxygen saturation and heart rate were monitored continuously throughout the training and used to adjust the training intensity. When patients' oxygen saturation fell below 90% during exercise they received supplemental oxygen (3-10 L/min) throughout the training. Eighty patients, who were on long-term oxygen therapy 16-24 hours/day before inclusion in this study, remained on oxygen throughout the training program. At discharge from the hospital after three weeks, patients received an individualized training manual and ordered a bicycle ergometer for use at home.

Statistical Methods

The analyses were performed by a statistician (C.F.). Data are given as mean ± standard deviation. The inner-group comparisons of baseline and weeks 3 and 15 for 6MWD, workload, Borg dyspnea index, parameters of gas exchange, PASP, systemic blood pressure and heart rate were conducted by paired, Student t-tests and the Mc. Nemar test for WHO-FC class. Summation and subscores of the SF-36 questionnaire were compared by ANOVA, two-tailed Student t-test, and we used the

Kruskall-Wallis test for the comparison of the % changes of the 6MWD among WHO-FC. All tests were two sided and p-values < 0.05 were considered statistically significant. Bonferroni adjustment for multiple comparisons was performed for comparisons of the primary endpoints 6-minute walking distances and quality of life parameters. All analyses were carried out with IBM SPSS V19 (IBM Corp. Armonk, NY, USA).

Efficacy parameters have been available for statistical analysis at baseline and after 3 weeks in all patients. Since there had no adverse events or deaths occurred between week 3 and week 15 we used the last observation (after 3 weeks) carried forward technique as substitution rule for dropouts. To analyse the characteristics of dropouts and the consequences for the results we compared the baseline and 3-weeks data of patients who did not came to the 15-week-visit with the patients who completed the study.

Results

Study Population (Figure 1, Table 1)

We included 194 patients in the study; 11 (5.6%) had to be excluded and did not start the rehabilitation program due to the following reasons: In one patient walking distance was mainly impaired due to peripheral artery occlusive disease, he was referred to further treatment; two patients discontinued due to familial problems; one patient was not included due to severe MRSA infection; one patient couldn't participate due to an acute peroneal palsy after a drop; six patients had to be excluded before entering the ET program because of a clinical instable course and the necessity of additional PH-targeted medication at baseline. Thus, the final study group consisted of 183 patients: 87 patients (47.6%) with IPAH or heritable PAH, 46 patients (25.1%) with APAH, 10.4% with "out-of-proportion" PH due to left heart or lung diseases and 31 patients (16.9%) with inoperable CTEPH (Table 1). Out of proportion PH in left heart disease and lung disease were defined due to current guidelines.[13, 8]

The APAH subgroup consisted mainly of 19 patients with connective tissue disease (CTD-APAH, 41%) and 15 patients with congenital heart defect (CHD-APAH, 33%, table 1). The patients had been referred from 12 centers. Demographic data, diagnosis, functional class, 6-minute walking distance and hemodynamic values are summarized in Table 1. At baseline most patients (74.9%) were in WHO class III, 18 patients (9.8%) were classified in WHO-FC IV. Combination therapies, including 2 to 4 PH-targeted agents, were used in 50.8% of patients (Table 2).

Assessment of training effects

Compared to baseline, mean six-minute walking distance increased significantly after 3 (68±46 meters, p<0.001) and 15 weeks (78±49.5 m, p<0.001) (Figure 1, Table 3). The improvement in 6MWD was similar in the patients with IPAH/HPAH, APAH, inoperable CTEPH or out-of proportion PH in left heart or lung diseases (Figure 2). Patients with APAH had a tendency to a lower improvement of 6MWD as compared to the IPAH/HPAH patients (85±49 vs. 56±49 meters, p=0.086). The patients with inoperable CTEPH showed an improvement in 6MWD of 65±48 meters after 3 weeks (p<0.001) and of 85±50 meters after 15 weeks (p<0.001, Table 3, Figure 2).

The improvement in 6MWD was consistent among different WHO-classes (Figure 3). The mean increase in 6MWD compared to baseline in patients in WHO-FC (FC) IV was 59±51 meters after 3 weeks and 63±61 meters after 15 weeks (Table 3, Figure 3). Compared to WHO FC-II or FC-III patients the percental increase in walking distance was even more pronounced in the WHO FC-IV-patients, although this difference did not reach statistical significance (Table 3). There was a significant improvement of WHO-FC. After 3 weeks ET 22% of the WHO-FC IV patients improved to FC III (p<0.001) and 6% of WHO-FC III to II.

All results remained statistically significant when using the last observation (after 3 weeks) carried forward method. Comparing the patients who completed the study with patients who did not come to the last visit after 15 weeks dropouts had a higher mean body mass index at baseline and improved significantly but approximately 10% less in 6MWD at 3 weeks than patients who completed the study (69 vs. 76 meters, respectively, $p < 0.05$).

Mean peak oxygen consumption, peak oxygen uptake in percent of the predicted value, and mean peak oxygen pulse of all patients increased significantly from baseline to 3 weeks and to 15 weeks (Table 3). The Borg scale remained unchanged

although significantly higher workloads and higher heart rates during exercise were attained (Table 3). After 3 weeks of ET mean heart rate, mean diastolic blood pressure and mean systolic pulmonary artery pressure at rest were significantly reduced (Table 3). Differences in the heart rate after 15 weeks could be influenced by the time point obtaining the ECGs. ECGs after 15 weeks were performed right after the patients had travelled to the hospital usually at noon or afternoon, ECGs at baseline and after 3 weeks have been performed in the morning in patients who stayed in the hospital. It is possible that the higher stress coming to this examination and the later time within the day have lead to a higher mean heart rate at the 15-week-visit.

Furthermore, exercise and respiratory training significantly improved quality of life parameters indicated by the SF-subscale scores for physical functioning ($p<0,001$), role-physical ($p=0.001$), role emotional ($p=0.005$), social functioning ($p=0.037$), mental health ($p=0.006$) and vitality ($p=0.002$; Figure 4; Table 3). Using Bonferroni adjustment p-values below 0.016 (6MWD) and 0.005 (SF-36) remained statistically significant.

Non-Responder

Non-responders have been defined as patients who did not improve the 6-minute walking distance after 3 or 15 weeks ET by > 5% compared to baseline or patients with a decrease in 6-minute walking distance. Twenty-six of the 183 patients (14%) were classified as non-responder. The reasons for non-effective rehabilitation were severe respiratory tract infections (n=4) and orthopedic problems (swelling of the knee due to knee arthrosis, n=4) leading to non-adherence to the training program. In 6 additional patients mental disorders such as depression and anxiety were diagnosed, they needed psychopharmacological treatment. Eleven of the 26 non-

responders had no significant improvement in their 6MWD after 3 weeks although they participated in the training program. One patient had performed training before entering the study at home and reported that the training intensity was possibly too low within the 3 weeks in-hospital rehabilitation. Eight of the remaining 10 non-responders had a 6MWD of > 550 Meters at baseline indicating that the program is less effective in patients who reveal already a near to normal 6MWD. Nevertheless, several of these non-responders, who did not improve during the in-hospital stay due to the reasons mentioned above, improved their 6MWD after 15 weeks ET at home. Their increase in quality of life parameters was not significantly different to the "responding" patients indicating that they did not achieve a significant increase in 6MWD but in quality of life scores. No significant difference between non-responders and the other patients could be found in any parameter listed in table 3. Distribution of WHO-functional class, medication and adverse events were similar in the 26 non-responders and the other patients.

Safety during 3-weeks in-hospital Training

During the 3-weeks in-hospital training 25 patients (13,6%) had adverse events. Two patients had a syncope, which occurred not during the ET itself but a few hours later. In one patient the syncope occurred when standing up at night after she had developed a severe respiratory infection. In one patient a presyncope occurred immediately after the end of the bicycle ergometer training and was therefore most likely linked to the intensity of the ET program. Five other patients experienced a presyncope not directly associated with the ET program. Fourteen patients had to discontinue the training program for 1-2 weeks due to an acute respiratory infection, 12 of them needed antibiotic therapy. Two patients were diagnosed with episodes of supraventricular tachycardia which occurred during the ET and was self-limited. One

patient had an episode of slight hemoptysis which was most likely related to a respiratory infection but did not occur again following successful antibiotic therapy so that she continued the program. All other patients tolerated the ET well. There were no signs of clinical worsening of right heart failure detectable with the non-invasive examinations during the in-hospital program. All patients reported that they had improved their awareness of their physical abilities and limitations. No further severe adverse events have been occurred between the visit after 3 weeks and the last visit after 15 weeks, where the patients continued with the ET at home.

Discussion

This is the first prospective clinical trial investigating the efficacy and safety of respiratory and ET in a large cohort of patients with various etiologies of chronic PH as CTD-APAH, CHD-PAH, PH due to respiratory or left heart diseases and inoperable CTEPH. Furthermore, the study shows that ET can improve prognostic relevant parameters even in patients classified as WHO-FC IV. Quality of life, six-minute walking distance, peak oxygen consumption, WHO-FC, exercise capacity, oxygen pulse, and other parameters of cardiopulmonary exercise testing significantly improved after 3 and 15 weeks compared to baseline in all PH and WHO-FC subgroups.

During the first 3 weeks of the in-hospital-rehabilitation program adverse events occurred in 13.6% of patients, severe events in 4.4% including syncopes in 2 and presyncopes in 6 patients. Thus, the results of this study indicate that ET in PH is an effective, but not a completely harmless add-on therapy and should carefully be supervised and closely monitored.

The study confirms the findings of previous studies in smaller patient cohorts demonstrating a beneficial effect of ET in patients with PAH.[1-5] The magnitude of these effects may vary with different physical therapy regimens and with the condition of the patient at the beginning of rehabilitation. The study suggests that the effect of ET is somewhat independent to the etiology of PH. Even in those subgroups of patients usually responding less well to PH-targeted medication when compared to IPAH like CTD-APAH,[14] CHD-APAH[15-17] and inoperable CTEPH[18] ET markedly improved 6MWD, oxygen consumption and quality of life. In patients with inoperable CTEPH ET may become a new therapeutic option as add-on to medical therapy if this can be proven in further randomized controlled trials.

Exercise Training in PAH associated with congenital heart defects

Data on ET in CHD-APAH are lacking, except one study of two patients with Eisenmenger`s syndrome and two with congenital heart disease that performed low grade ET twice a week for 3 months. This study revealed no adverse events, but no objectively measurable improvement.[19] The 36th Bethesda conference recommended patients with congenital heart disease to perform sport only when pulmonary artery pressures are normal.[20] In our study ET was safe and effective in these patients although all of them had largely elevated pulmonary artery pressures. Nevertheless, ET in patients with CHD-APAH may address special needs and pathophysiological circumstances. Patients with congenital heart disease often tend to overestimate their actual exercise capacity,[21] which has been addressed in our program by offering mental training. Severe progressive cyanosis during exercise in CHD-APAH patients may impair the positive effects of training or even increase the risk for adverse events. Therefore, we tested the possible effect of high-flow oxygen supply in all cyanotic patients.

Exercise training in patients with connective tissue disease

In patients with CTD-APAH the effect of medication therapy on 6MWD was significantly lower compared to IPAH-patients[14] possibly due to existing co-morbidities as concomitant musculoskeletal problems, which we addressed in our program by increased physiotherapy. Therefore, in our study ET in CTD-APAH was as effective as in patients with IPAH or other forms of PH.

Effect of Exercise Training in patients classified in WHO-functional class IV

Another interesting finding was the high beneficial effect of ET in the most severely impaired patients classified in WHO-FC IV. These patients usually have very limited medical options[8] and even with combination therapy a severely impaired quality of life and survival rate.[22] The data of our study suggest, that the more patients have been impaired in their physical abilities at baseline, the better was the effect of ET in improving 6MWD. The incidence of adverse events has not been higher, when compared to the patients in WHO-FC II and III. However, these results need to be interpreted with caution due to the quite small number of patients (n=18) in this group. Further studies may clarify whether ET improves time to clinical worsening and survival in patients with PH in WHO-FC IV.

Adverse events and non-responders

The overall rate of severe acute adverse events occurred during the in-hospital stay (2 syncopes, 6 presyncopes) and has been quite low (4.34 %) and is comparable or even lower than that of patients in rehabilitation programs for left heart failure.[23] However, this study documented the potential for acute adverse events occurring during the first 3 weeks of in-hospital rehabilitation program. We cannot exclude that further or more severe adverse events occur when the ET is continued at home. ET should definitely not be initiated in a non-supervised and not adequately monitored setting. The patients need to be trained how to perform a safe ET at home.

The analysis of patients who were not able to improve their 6MWD during the 3-weeks in hospital training (14.2% of the 183 patients cohort) did not reveal any differences in the assessed clinical parameters when compared to the 85.8% of patients who did improve. Most often the mechanism of non-response was simply the inability to perform any training within the 3 weeks in-hospital stay due to varying reasons. Furthermore, patients with a 6MWD > 550 meters did improve less than

patients with impaired 6MWD at baseline. Obviously, training is only effective if it is adequately performed and if there is a limited physical capacity in the beginning. Nevertheless, non-responder patients may have improved by other parameters (as quality of life, hemodynamic) than in the 6MWD. In a previous study changes of functional class and hemodynamic indices were more sensitive in detecting treatment effects of PAH-targeted medication [24].

Clinical and pathophysiological mechanism of action

The precise mechanism through which exercise-based interventions benefit PH patients remains unclear. Besides improving endothelial dysfunction, muscular blood supply, gas exchange and strength,[25, 2] ventilatory efficiency, and ventricular contractility[26] as described in left heart failure,[27] ET may reduce adrenergic tone and increase vagal tone. After 3 weeks heart rate at rest, peak oxygen consumption and oxygen pulse all significantly improved in PH-patients of this cohort. Further studies including right heart catheterization are necessary e.g. to analyse whether ET improves right ventricular contractile reserve. In this study we performed a combined strength and endurance training program which has been described as the optimal exercise prescription in left heart failure.[28]

Limitations

Although we believe this to be the largest prospective study analysing the impact of ET in patients with pulmonary hypertension, we acknowledge a number of limitations. The study had no randomized control group and was conducted by a single centre. Our data provide a good rationale for future studies of ET in PH-patients and assessed this therapy in various aetiologies of PH for the first time. However a large controlled randomized, multicentric study should be performed to confirm these

results especially in patients with inoperable CTEPH, CTD-APAH, CHD-APAH and in patients with WHO-FC IV. The effects of ET after 15 weeks may be overestimated due to the missing values of about 40% of patients who did not perform the last follow-up visit and who gained approximately 10% less in 6MWD after 3 weeks than the others. Unfortunately, we did not have funding to provide transportation for patients who live more than 400 km from Heidelberg and therefore often missed the last visit. Analysis of the data of the participating centres showed that there was no dropout due to side effects of the training or due to deaths. In addition, we cannot exclude that patients who had less training effect may have been less willing to perform the last visit. Furthermore, it is a general issue of rehabilitation programs that the therapy cannot be performed in a blinded fashion and that a referral bias towards highly motivated patients with a better outcome may occur.

Baseline 6MWD in our cohort of class IV patients was higher than previously reported.[29] We cannot exclude that patients with less exercise limitations have been selected. However, higher values for 6MWD at baseline could at least in part be due to the fact, that the test was performed in a large sports hall, in which the patients could walk without any time delay by turns or stops and that some patients younger age had a comparatively high 6-minute walking distance though they are in WHO IV as described before (24).

Further studies are necessary to determine the effects of training programs on outcome in patients with pulmonary hypertension.

Conclusion

The results of this study suggest that low-dose exercise and respiratory training as add-on to medical therapy is safe in a closely supervised setting and may improve exercise capacity and quality of life in patients with various forms of PH. Further randomized trials are required to determine whether there is any survival benefit.

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References

1. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth F, Wilkens H, Katus HA, Olschewski H, Grunig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation. 2006;114:1482-89.
2. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, Grotjohan HP, Twisk JW, Bogaard HJ, Boonstra A, Postmus PE, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2009;34:669-75.
3. Wilkinson A, Elliot CA, Condliffe R, Mawso S, .Armstrong IJ, Billings C, Kiely DG A randomised-controlled trial of a physiotherapist-led rehabilitation programme in patients with pulmonary hypertension. ERS Congress 2008, P1004, epub http://www.ersnet.org/learning_resources_player/abstract_print_08/main_frameset.htm, data last accessed 14.07.2011.
4. Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, Opitz CF, Klose H, Wilkens H, Rosenkranz S, Olschewski H, Halank M. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration. 2011;81:394-401.
5. Boutet K, Garcia G, Degano B, Gonzalves-Tavares M, Tcherakian C, Jaïs X, Humbert M, Escourrou P, Simonneau G, Sitbon O. Results of a 12-week outpatient cardiovascular rehabilitation in patients with idiopathic pulmonary arterial hypertension (iPAH). ERS Congress 2008, E1413, epub http://www.ersnet.org/learning_resources_player/abstract_print_08/main_frameset.htm, data last accessed 14.07.2011.

6. Handoko ML, de Man FS, Happé CM, Schalij I, Musters RJ, Westerhof N, Postmus PE, Paulus WJ, van der Laarse WJ, Vonk-Noordegraaf A. Opposite effects of training in rats with stable and progressive pulmonary hypertension. Circulation. 2009;120:42-9.
7. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, Gine S. Diagnosis and Differential Assessment of Pulmonary Arterial Hypertension. J Am Coll Cardiol 2004;43:40-47.
8. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34:1219-63.
9. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. Thorax 1984;39:818-822.
10. Ware JE, Sherbourne CD. The MOS 36-item Short-Form health survey (SF-36). Med Care 1992;304:73-83.
11. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-381.
12. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Caseburi R. Measurements during integrative cardiopulmonary exercise testing. In: Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R, eds. Principles of Exercise Testing and Interpretation. Philadelphia: Lea & Febiger, 1994;53-79.

13. Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J; Task Force. Guidelines on diagnosis and treatment of pulmonary arterial hypertension Eur Heart J 2004;25:2243–2278
14. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR, Zamanian RT. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest. 2010;138:1383-94.
15. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest. 2010;137:52S-61S.
16. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M; Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114:48-54.
17. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart. 2009;95:312-7.
18. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. Eur Respir Rev. 2010;19:59-63.
19. Martínez-Quintana E, Miranda-Calderín G, Ugarte-Lopetegui A, Rodríguez-González F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension.Congenit Heart Dis. 2010 Jan-Feb;5:44-50.

20. Graham TP Jr, Driscoll DJ, Gersony WM, Newburger JW, Rocchini A, Towbin JA. Task Force 2: congenital heart disease. J Am Coll Cardiol. 2005;45:1326-33.
21. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J. 2009;30:497-504.
22. Humbert M, Sitbon O, Simmoneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004;351:1425-36.
23. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439-50.
24. Degano B, Sitbon O, Savale L, Garcia G, O'Callaghan DS, Jaïs X, Humbert M, Simonneau G. Characterization of pulmonary arterial hypertension patients walking more than 450 m in 6 min at diagnosis. Chest. 2010;137:1297-303.
25. Hambrecht R, Niebauer J, Fiehn E, Kalberer B, Offner B, Hauer K, Riede U, Schlierf G, Kübler W, Schuler G. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239–1249.
26. Belardinelli R, Georgiou D, Ginzton L, Cianci G, Purcaro A. Effects of moderate ET on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 1998;97:553–561.
27. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. Am J Med. 2004;116:693-706.

28. Davies EJ, Moxham T, Rees K, Singh S, Coats AJ, Ebrahim S, Lough F, Taylor RS. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. Eur J Heart Fail. 2010;12:706-15
29. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023-30.

Figure Legend

Figure 1: Individual changes in Six-Minute-Walking Distance (6MWD) after 3 and 15 weeks exercise training. With the use of a two-sample t-test stratified according to baseline walking distance, P<0.001 was obtained for the comparison to baseline with week 3 and week 15. In this intention to treat analysis after 3 weeks of exercise training the data from 183 patients, after 15 weeks of 103 patients were available and included. The coloured line indicates the mean change from baseline in 6MWD.

Figure 2: Individual changes in the Six-Minute Walking Distance in PH subgroups with different etiologies from baseline to week 3 and 15. IPAH: idiopathic pulmonary arterial hypertension-, HPAH: hereditary pulmonary arterial hypertension, APAH: associated pulmonary arterial hypertension, CTEPH: chronic thromboembolic PH , PH: pulmonary hypertension due to respiratory or left heart diseases. The change in 6MWD was not significantly different between the subgroups (p=0.086). The dashed line indicates the mean change in 6MWD from baseline with 95 Percent confidence Intervals.

Figure 3: Change in 6MWD after 3 and 15 weeks according to WHO-functional class, indicated as mean (*), median (solid line), interquartile range (box) and minimum and maximum.

Figure 4: Mean SF-36 scores of Quality of life Subscales (SF-36 questionnaire) at baseline and after 15 weeks of Exercise Training.

At baseline (green line), mean SF-36 scores were significantly reduced in comparison to respective values of a normal population (lilac line). After 15 weeks (red line), 6 scales of the SF-36 questionnaire improved significantly: physical functioning, role-physical, role emotional, social functioning, mental health and vitality. P-values are indicated vs. baseline. No significant improvement was found for for bodily pain (BP), and general health perception (GH) after training. With Bonferroni adjustment, values of $p < 0.05$ preserve statistical significance. At baseline data of 183 patients, after 15 weeks of 103 patients were available and included.

Table 1: Baseline Characteristics of the patients

Patients		n = 183	
Gender, F/M	126	/	57
Age, y	53	±	15
Height, cm	168	±	9
Weight, kg	75	±	17
WHO-functional class – no. (%)			
I		2	(1,1%)
II		26	(14,2%)
III		137	(74,9%)
IV		18	(9,8%)
Cause of pulmonary hypertension – no. (%)			
IPAH		83	(45.4%)
HPAH		4	(2.2%)
APAH		46	(25.1%)
Drug or toxin induced		3	
connective tissue disease		19	
HIV		4	
portal hypertension		5	
congenital heart defect		15	
PH due to left heart disease		8	(4.4%)
PH due to lung disease		11	(6.0%)
Obstructive lung disease		2	
Restrictive lung disease		8	
sleep apnoea syndrome		1	
CTEPH		31	(16.9%)
Walking distance at 6 min, m	425	±	106
Cardiac catheterization			
Pulmonary artery pressure- mmHg	49	±	16
Pulmonary Vascular Resistance, dyn·sec·cm^{-5}	806	±	405
Right atrial pressure, - mmHg	7	±	7
Arterial oxygen saturation (%)	92	±	5
PCWP – mmHg	9	±	5
Cardiac output, (L/min)	4.5	±	1.3
Cardiac index, (L/min/m²)	2.4	±	0.6

PCWP=pulmonary capillary wedge pressure, Values are mean ± SD.

Table 2: Pulmonary Hypertension targeted Medication

Endothelin Receptor Antagonists	108	(59%)
Phosphodiesterase -5 Inhibitors	107	(58.5%)
Prostanoids inhaled	32	(17.5%)
Calcium channel blockers	20	(10.9%)
Prostanoids iv.	6	(3.3%)
Beraprost	5	(2.7%)
Soluble guanyl cyclase -Stimulator	5	(2.7%)
Imatinib	2	(1.1%)
Combination Therapy		
No PH-targeted medication*	10	(5.5%)
Mono	80	(43.7%)
Dual	71	(38.8)
Triple	21	(11.5%)
Quadruple	1	(0.5%)

*in patients with PH due to left heart disease or lung disease

Table 3: Efficacy parameters

Characteristic	Baseline (n= 183)				3 weeks (n= 183)					15 weeks (n=103)					
6MWD PH-Etiology Subgroups; Meter				**95% CI**				**95% CI**	**p-value**				**95% CI**	**p-value**
all	425	±	106	[410;441]	493	±	110	[478;510]	<0.001	506	±	104	[486;528]	<0.001
IPAH/HPAH (n=87/87/53)	448	±	89	[429;467]	523	±	89	[503;542]	<0.001	543	±	74	[522;563]	<0.001
APAH (n= 46/46/18)	427	±	113	[393;461]	482	±	123	[445;518]	<0.001	454	±	132	[392;516]	<0.001
CTEPH (n= 31/31/18)	417	±	110	[377;457]	482	±	126	[436;528]	<0.001	512	±	81	[473;551]	0,001
PH (n=19/19/11)	327	±	100	[279;375	403	±	86	[362;444]	<0.001	407	±	118	[328;486]	<0.001
6MWD PH-Etiology Subgroups, Difference from baseline; Meter														
all					68	±	46	[61;75]	<0.001	78	±	49,5	[68;88]	<0.001
IPAH/HPAH (n=87/53)					75	±	43	[69;92]	<0.001	85	±	48,9	[71;98]	<0.001
APAH (n= 46/18)					54	±	44	[36;80]	<0.001	56	±	48,8	[32;80]	<0.001
CTEPH (n= 31/18)					65	±	48	[52;100]	<0.001	85	±	49,8	[60;110]	0,001
PH (n=19/11)					76	±	55	[44;118]	<0.001	72	±	48	[41;105]	<0.001
6MWD in WHO-FC-Subgroups, Meter														
WHO-FC II (n= 26/26/13)	507	±	100	[466;548]	572	±	100	[532;613]	<0.001	588	±	57	[554;623]	<0.001
WHO-FC III (n= 137/137/76)	424	±	86	[410;439]	494	±	93	[478;510]	<0.001	511	±	85	[492;530]	<0.001
WHO-FC IV (n= 18/18/10)	239	±	95	[190;291]	298	±	90	[253;342]	<0.001	287	±	108	[209;364]	0.010
6MWD, in WHO-FC-Subgroups, Difference from baseline; Meter														
all (n= 183/103)					68	±	46	[61;75]	<0.001	78	±	50	[68;88]	<0.001
WHO-FC II (n= 26/13)					65	±	41	[49;82]	<0.001	85	±	53	[53;117]	<0.001
WHO-FC III (n= 137/76)					70	±	46	[62;78]	<0.001	79	±	48	[68;90]	<0.001
WHO-FC IV (n= 18/10)					59	±	51	[33;84]	<0.001	63	±	61	[19;107]	0.010
6MWD, WHO-FC-Subgroups Improved (in %)*							**Median**						**Median**	
WHO-FC II (n= 26/13)					14.3	±	11.1 12.9	[9.8; 18.7]	<0.001	18.5	±	14.1 16.1	[10.0;27.0]	<0.001
WHO-FC III (n= 137/76)					17.5	±	13.5 14.7	[15.2;20.0]	<0.001	19.3	±	13.3 14.6	[16.3;22.4]	<0.001
WHO-FC IV (n= 18/10)					25.0	±	27.0 17.4	[11.5;38.4]	<0.001	26.3	±	30.1 17.8	[4.8;47.8]	0.010
* Kruskall Wallis test showed no significance in intergroup comparison, p (3 weeks) = 0.446 and p (15 weeks) = 0.993.														
Cardiopulmonary exercise testing														
peak VO2/kg; mL/Min/kg	12.2	±	3.5		13.6	±	4		<0,001	13.9	±	3.8		<0,001
peak VO2; ml/min	907	±	276		1006	±	308		<0,001	1011	±	292		<0,001
EqCO2 at AT	45.2	±	9.6		43.6	±	10.6		0,249	44.3	±	10.8		0,225
VO2 at AT; ml/min	692	±	214		712	±	236		0,216	790	±	261		0,007
oxygen pulse	7.5	±	2.1		7.9	±	2.4		<0,001	7.7	±	2.4		0,001
PASP rest, mmHg	59	±	20		57	±	20		0,028	56	±	20		0,016
PASP max, mmHg	91	±	26		91	±	26		0,542	95	±	26		0,512
HR rest, min-1	77	±	13		74	±	11		<0,001	80	±	13		0,009
HR max, min-1	122	±	19		127	±	22		<0,001	133	±	20		<0,001
RR sys rest, mmHg	117	±	17		114	±	15		0,016	113	±	14		0,019
RR dia rest, mmHg	78	±	14		75	±	9		<0,001	77	±	9		0,128
RR sys max, mmHg	150	±	26		151	±	24		0,615	150	±	24		0,719
RR dia max, mmHg	86	±	14		86	±	12		0,617	87	±	12		0,667
Borg scale	15.6	±	2		15.6	±	2		0,896	15.7	±	2		0,100
Workload max, W	64	±	24		77	±	28		<0,001	80	±	27		<0,001

Values are mean±SD. § p < 0.05; # p < 0.01; * p < 0.001 in comparison to baseline, p-values are the same for absolute values and differences in 6MWD; CI= confidence interval
6MWD: two-sided Student t-test, Cardiopulmonary Exercise Testing : Wilcoxon
6-MWD = 6-minute walking distance, VO2/kg = max. oxygen consumption/kg, HR= heart rate,

Figure 1: Change from Baseline in the Six-Minute Walking Distance (6MWD) after 3 and 15 weeks exercise training.

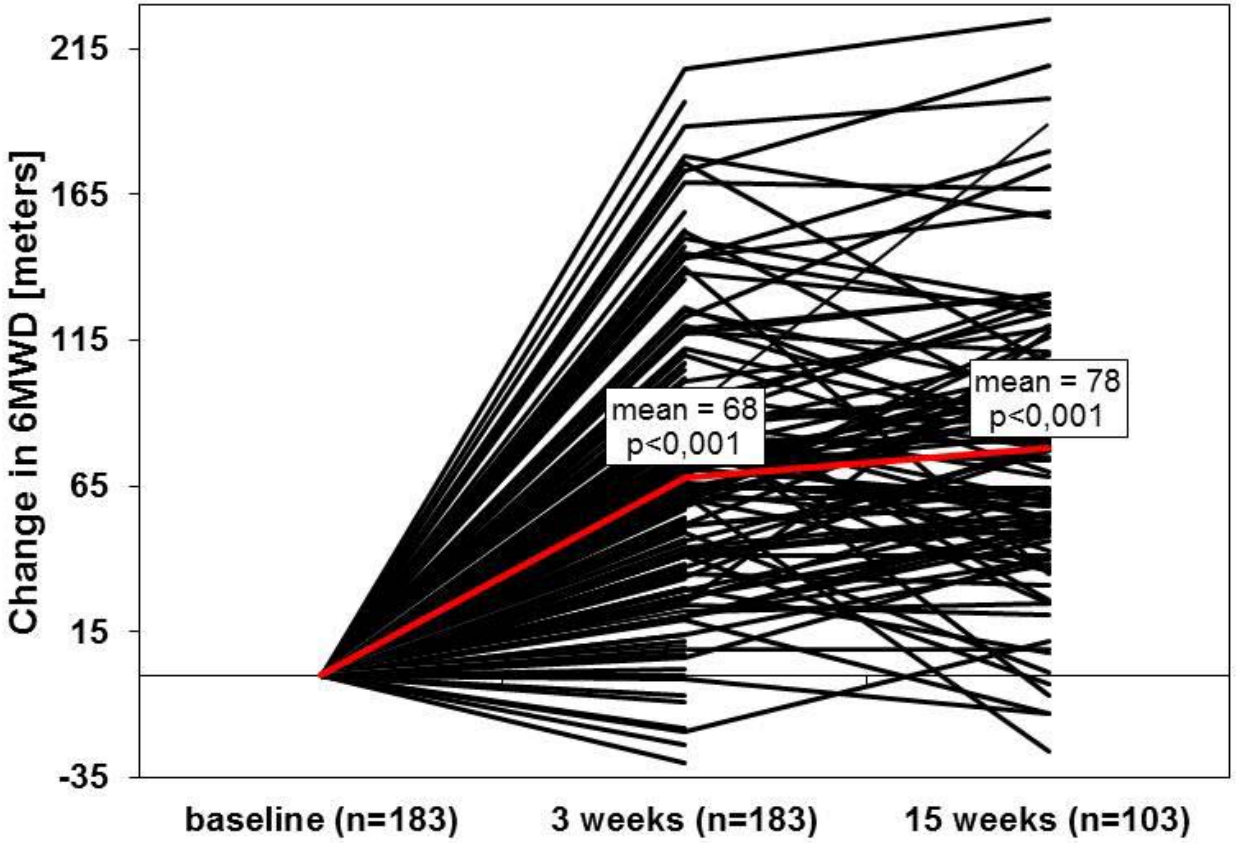

Figure 2: Change from Baseline in the Six-Minute Walking Distance (6MWD) in different PH- subgroups after 3 weeks exercise training, dashed lines indicate the mean difference and the 95% confidence interval of the mean

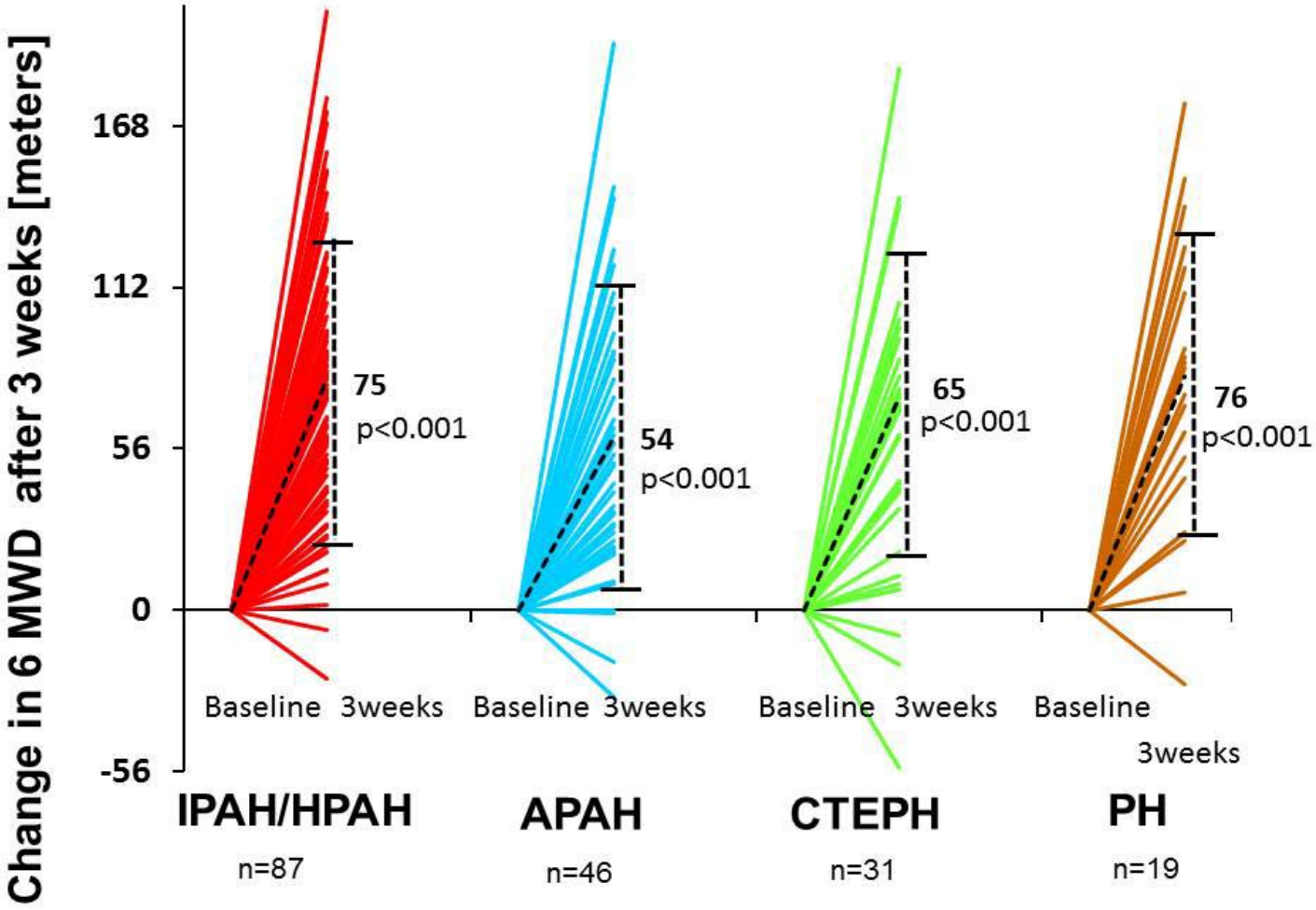

Figure 3: Change in 6MWD according to WHO-functional class after 3 and 15 weeks of exercise training

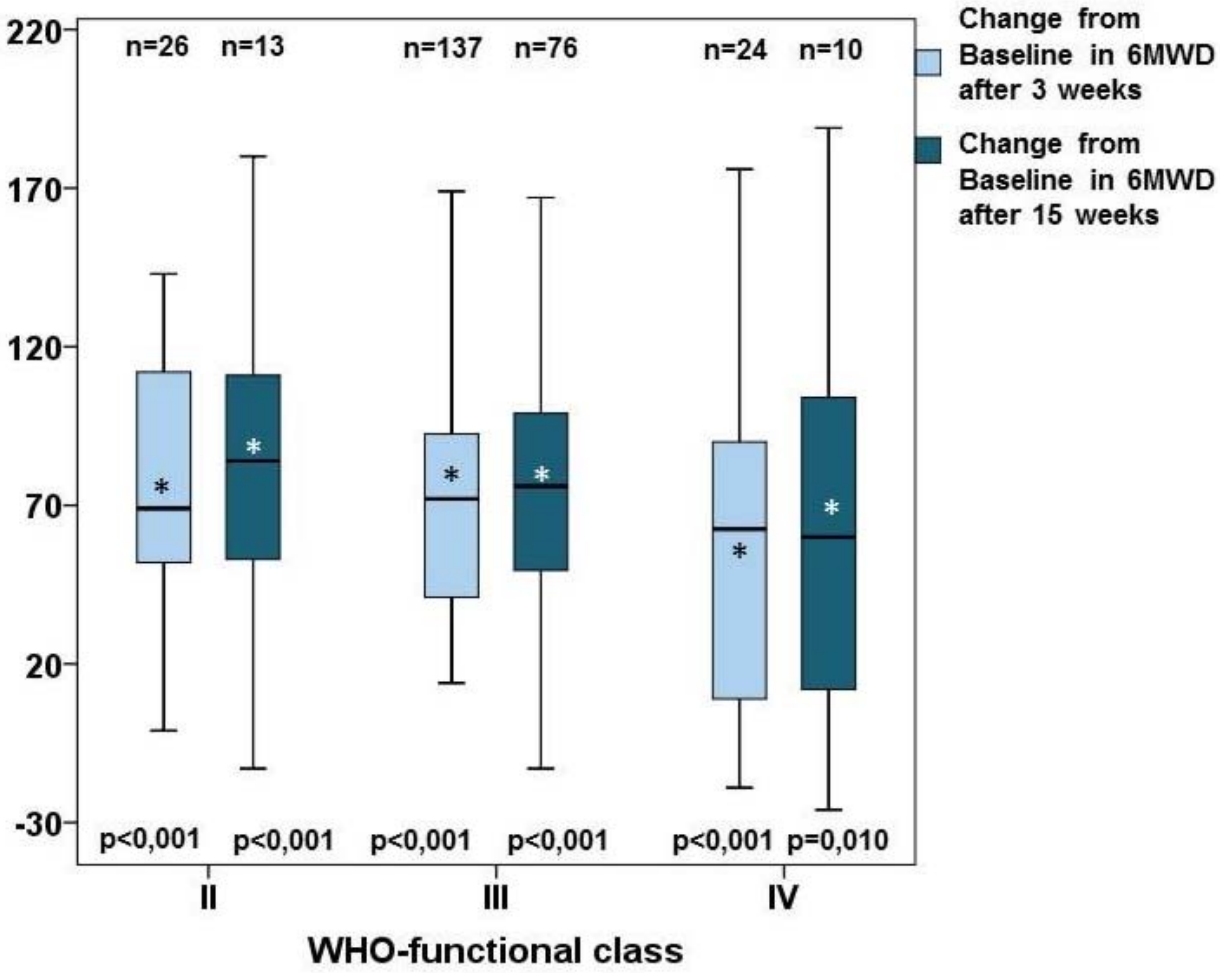

Figure 4: Mean SF-36 scores of Quality of life Subscales (SF-36 questionnaire) at baseline and after 15 weeks of Exercise Training.