Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease

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Abstract: BACKGROUND: The objective of this prospective study was to assess the efficacy of exercise training as add-on to medical therapy in patients with congenital heart disease associated pulmonary arterial hypertension (CHD-APA.H). METHODS: Patients with invasively confirmed CHD-APA.H received in-hospital exercise training for 3 weeks and continued at home. Efficacy parameters were evaluated at baseline, after 3 and 15 weeks. Medical treatment remained unchanged. Worsening events and survival rate were assessed in a follow-up period of 21±14 months. RESULTS: Twenty consecutive CHD-APA.H patients (16 female, 4 male, mean pulmonary arterial pressure 60±23 mmHg) were included. Patients significantly improved the mean distance walked in 6 min compared to baseline by 63±47 m after 3 weeks (p<0.001) and by 67±59 m after 15 weeks (p=0.001). Quality of life score (p=0.05), peak oxygen consumption (p=0.002) and maximal workload (p=0.003) improved significantly by exercise training after 15 weeks. The 1- and 2-year survival rates were 100%, the transplantation-free survival rate was 100% after 1 year and 93% after 2 years. CONCLUSION: Exercise training as add-on to medical therapy may be effective in patients with CHD-APA.H and improved work capacity, quality of life and further prognostic relevant parameters. It was associated with an excellent long-term survival. Further randomized controlled studies are needed to confirm these results.

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Efficacy of Exercise Training in Pulmonary Arterial Hypertension
associated with Congenital Heart Disease

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Key words: Pulmonary Hypertension, Rehabilitation, Exercise Training, Congenital
Heart Disease
**Structured Abstract**

**Background:** The objective of this prospective study was to assess the efficacy of exercise training as add-on to medical therapy in patients with congenital heart disease associated pulmonary arterial hypertension (CHD-APAH).

**Methods:** Patients with invasively confirmed CHD-APAH received in-hospital exercise training for 3 weeks and continued at home. Efficacy parameters were evaluated at baseline, after 3 and 15 weeks. Medical treatment remained unchanged. Worsening events and survival rate were assessed in a follow-up period of 21±14 months.

**Results:** Twenty consecutive CHD-APAH patients (16 female, 4 male, mean pulmonary arterial pressure 60±23mmHg) were included. Patients significantly improved the mean distance walked in 6 minutes compared to baseline by 63±47 meters after 3 weeks (p<0.001) and by 67±59 meters after 15 weeks (p=0.001). Quality of life-score (p=0.05), peak oxygen consumption (p=0.002) and maximal workload (p=0.003) improved significantly by exercise training after 15 weeks. The 1- and 2 year survival rates were 100%, the transplantation-free survival rate was 100% after 1 year and 92% after 2 years.

**Conclusion:** Exercise training as add-on to medical therapy may be effective in patients with CHD-APAH and improved work capacity, quality of life and further prognostic relevant parameters. It was associated with an excellent long-term survival. Further randomized controlled studies are needed to confirm these results.

**Words count:** 209

Total words account: 3.763
Introduction

Congenital heart disease-associated pulmonary arterial hypertension (CHD-APAH) is an important subgroup of associated PAH (APAH) which accounts for approximately 11% of all patients with PAH [1]. In about 0.8-1 of 1000 live births relevant CHD has been diagnosed. Today, in Western countries more than 90% of these children reach adulthood, in some cases with significant pulmonary vascular disease [2]. The prevalence of APAH in CHD in Germany is not known. European registry data suggest a prevalence of APAH in about 4-10% of adult CHD-patients [1, 3, 4]; up to 25-50% develop an Eisenmenger Syndrome (ES) [5]. Patients with CHD-APAH had identical histological findings as idiopathic PAH (IPAH) [6] and revealed a markedly reduced exercise capacity and quality of life [4, 7]. ES had the worst exercise capacity compared to other forms of CHD-APAH [7]. All-cause mortality risk was more than 2-fold higher for CHD-patients with APAH compared with those without [8]. Estimated 1-, 2-, and 3-year survival rates in CHD-APAH-patients were 97%, 89% and 77%, respectively [9].

In contrast to IPAH, only few randomized controlled trials on advanced, disease-targeted medical therapy have been performed in CHD-APAH including drugs as Bosentan (BREATHE-5 study) [5] and Tadalafil [10] showing significant improvements of pulmonary hemodynamics and exercise tolerance. Positive effects for exercise capacity were also described for sildenafil, epoprostenol and ambrisentan in small, uncontrolled studies [10-13] . Only few data are available on combination therapies, including 2 to or more PAH-targeted drugs [14-16]. However, the effect of advanced medical therapy on exercise capacity and quality of life seems to be very limited in this subgroup. Thus, especially patients with CHD-APAH may need additional therapeutic tools addressing their exercise capacity and quality of life. It is unclear whether and to which extent CHD or CHD-APAH-patients should
perform sports or exercise training, especially with respect that their hypoxemia usually rapidly deteriorates during exercise. In patients with IPAH and other forms of APAH exercise training as add-on to optimized medical treatment has been shown to increase exercise capacity, quality of life, peak oxygen consumption, WHO-functional class (WHO-FC) in a randomized, controlled study [17] and in single arm studies [18-20] and possibly improved clinical outcome [19]. There are only few small uncontrolled studies showing a benefit of exercise training for exercise capacity in CHD-patients without PAH [21-23]. Except one report with 4 CHD-APAH-patients receiving rehabilitation [24] up to now there is no study focusing on the acute and long-term effect of exercise training in this cohort. The aim of this study was to prospectively assess the effects of exercise training on safety and prognostic relevant factors such as exercise capacity and quality of life in a cohort of patients with severe CHD-APAH and to analyze the 1- and 2 year survival rates.
Methods

Study Population and Design

This prospective study included adult patients with invasively confirmed severe chronic CHD-APAH, being stable under disease-targeted medication, who received exercise and respiratory training between September 2008 and October 2011. Patients had to be under optimized advanced medical therapy for PAH (as endothelin-antagonists, inhaled prostanoids, phosphodiesterase-5-inhibitors, diuretics and if useful, supplemental oxygen) for at least 2 months before entering the study. Those with PAH who were newly diagnosed had an interval of at least 6 months between initiation of a new PAH-targeted medical treatment and the start of exercise training. Medication remained unchanged during the study period from baseline to 15 weeks. The diagnosis “CHD-APAH” was established at the participating PH centers according to current guidelines [25, 26]. CHD had been confirmed by specialized centers for congenital heart diseases in each patient. All patients starting the rehabilitation program gave written informed consent for this study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of the University of Heidelberg.

Outcome Measures

At baseline, after 3 weeks and 15 weeks efficacy parameters were prospectively evaluated as previously described [17, 19]. 6-minute walking distance (6MWD) was carried out under standardized conditions. Cardiopulmonary exercise testing and stress-Doppler echocardiography were carried out during supine bicycle exercise as described previously [17]. Workload, heart rate, systolic pulmonary artery pressure (sPAP), systolic (RRsys) and diastolic (RRdias) systemic blood pressures, ventilation...
(VE), oxygen uptake (VO₂), oxygen pulse (VO₂/heart rate), and carbon dioxide output (VCO₂) were evaluated continuously. V-slope method was used to detect the anaerobic threshold (AT). We analyzed gas exchange, Borg dyspnea index (with 6 representing no exertion and 20 maximal exertion) [27] and changes in WHO-FC after 3 and 15 weeks. Health related quality of life was measured by the Short Form Health Survey (SF-36) [28] questionnaire at baseline and was compared to the results after 15 weeks. Serum N-terminal pro brain natriuretic peptide (NTproBNP) was obtained at baseline and after 3 and 15 weeks. 6MWD, SF-36-questionnaire and NT-proBNP have been obtained and analyzed by investigators who have been blinded to clinical data of the patients.

Exercise Training Program

Exercise training was started in-hospital during 3 weeks in the rehabilitation clinic Königstuhl in Heidelberg as previously described [17, 19]. We performed a program especially developed for the PH-patients with at least 1.5 h exercise training per day (in intervals distributed over the day) consisting of interval bicycle ergometer training at low workloads (10-60 Watt) at 7 days a week. Furthermore walking, dumbbell-training of single muscle groups using low weights (500-1000g) and respiratory training were performed at 5 days per week. Maximum heart rate during the training corresponded to 60-80% of the heart rate reached during cardiopulmonary exercise testing and was monitored throughout to adjust the training intensity. Those patients who needed oxygen therapy already at rest remained on supplemental oxygen throughout the whole training program. Exercise training was closely supervised by physical therapists, physicians specialized in rehabilitation medicine and PH-experts and was continued at home for 12 weeks using an individualized training manual for at least 30 minutes per day at 5 days a week and a bicycle ergometer. Beside the
physical training all participants received mental training to improve their perception of individual physical abilities and limits. They were also offered psychological support. Adverse events were recorded whenever they occurred.

Follow-up Assessment

In 2011 all participating patients were interviewed by telephone or at a control visit in the Thoraxclinic Heidelberg using a half-structured questionnaire. The patients were asked for symptoms according to WHO functional classification, current medication, if and what kind of exercise training they pursued at home, for any adverse events of exercise training and any further cardiac events that have occurred since last observation. If the index patient was deceased, date of death was recorded and their relatives and/or treating physicians were asked for the cause and circumstances of death.

Statistical Methods

The analyses were performed by a statistician (C.F.). Data are given as mean ± standard deviation and as median, 25% and 75% quantiles for more detailed description at baseline. The inner-group comparisons of baseline, weeks 3 and 15 for 6MWD, workload, Borg dyspnea index, parameters of gas exchange, PASP, systemic blood pressure, NT-proBNP and heart rate were conducted by Wilcoxon signed rank test. Also summation and subscores of the SF-36 questionnaire were compared by Wilcoxon rank test. WHO-FC comparisons at different time points were performed by McNemar-Bowden test. 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 such as parameters of quality of life and 6-minute walking distances. All analyses were
carried out with IBM SPSS V20 (IBM Corp. Armonk, NY, USA). We described the 5 patients who did not attend the 15 week measurement in detail. For missing values we performed different imputation strategies and reported the values from the most strict one: 1. multiple imputation using the MCMC method as implemented in SPSS, 2. the last observation carried forward, and 3. a pessimistic imputation, in which 3 week 6MWD was imputed as 15 week measurement if it was lower than baseline, otherwise the baseline 6MWD. Kaplan-Meier estimates have been used for survival-analysis with asymptotic 95% two-sided confidence interval (CI) calculated from Greenwood’s formula. All treated patients were used for the survival analysis. Patients with deaths were counted as endpoints, survivors were regarded as censored.
Results

Study Population (Table 1)

The study group consisted of 20 patients. None of the patients had additional Down syndrome. Demographic data, diagnosis, functional class, hemodynamic values, lung function and medical therapy of the study population are summarized in table 1. Most patients had combined cardiac anomalies. CHD included 9 patients with ventricle septal defect (VSD), 6 patients with atrial septal defect (ASD), 3 patients with ASD and VSD, 5 patients with persistent ductus arteriosus (PDA) (3 of them combined with ASD, VSD and/or PFO) and 2 patients with persistent foramen ovale (PFO). ES was diagnosed in 10 of the 20 patients (50%); 9 patients had been operated years before inclusion into the study (3 VSD patch-closures, 3 ASD-closures, 2 ductus arteriosus-closures and 1 VSD-ASD-closure), whereas in 2 cases a relapse of the septal defect occurred. In all 20 patients severe APAH had been persistent or developed despite heart surgery. The size of the septal defect was not exactly assessed in every patient, but varied in those being sized from 0.5 cm to 2.5 cm. Further additional cardiac anomalies were a common arterial trunk (n=1), a hypoplastic pulmonary artery with major aortopulmonary collateral arteries and tricuspid insufficiency (n=1), tricuspid insufficiency in addition to the VSD (n=2), severe insufficiency of the pulmonary valve (n=1) and a Scimitar syndrome, an anomalous pulmonary venous return and dextrocardia in one patient.

At baseline 6 patients (30%) were in WHO-FC II and 14 patients (70%) were classified in WHO-FC III. Fourteen patients (70%) were treated with an endothelin-receptor-antagonist, 12 (60%) with a phosphodiesterase-inhibitor and 6 (30%) with inhalative or intravenous prostacyclin. Combination therapies, including 2 to 3 PAH-targeted drugs, were used in 55% of patients (Table 1). Eleven patients received supplement oxygen. Cardiac catheterization showed a severe APAH with mean
pulmonary arterial pressures (mPAP) of 60 (±23) mmHg and a mean pulmonary
vascular resistance (PVR) of 855 (±445) dyn*sec*cm⁻⁵.

**Assessment of training effects**

Exercise training significantly improved mean 6MWD by 63±47 meters after 3 weeks
(p<0.001) and by 67±59 meters after 15 weeks (p=0.001) (Figure 1, Table 2). All
except two patients improved in 6MWD (Figure 1) about more than 5% compared to
baseline. The reason for non-response to exercise training in 2 of the 20 patients was
in one patient that she could not perform most parts of the rehabilitation program due
to a long-lasting respiratory infection. However, she improved in oxygen uptake and
quality of life parameters. The other patient had no significant improvement in 6MWD
although she participated in the complete program. After cardiac surgery she had
been suffering from a chronic thoracic pain syndrome before she participated in the
rehabilitation program.

Exercise training also significantly improved the mean maximal workload during
cardiopulmonary exercise testing from baseline to 3 weeks (p<0.012) and to 15
weeks (p<0.003, Table 2). Mean peak oxygen uptake (peak VO₂, Figure 2), as well
as peak VO₂/kg per kg body weight increased in trend after 3 weeks (p=0.066 and
p=0.063) and significantly after 15 weeks (p=0.002 and p=0.008, respectively, table
2). Mean maximal workload during cardiopulmonary exercise testing increased
significantly after 3 and 15 weeks whereas Borg scales remained unchanged (Table
2, Figure 3).

SF-36 quality of life parameters were significantly impaired compared to an
assessment of German standard population (Figure 4). Scores did not significantly
improve by exercise training except in one subscale “bodily pain” with borderline
significant improvement (p=0.05, Figure 4).
Although in 5 patients WHO-FC has improved from III to II, the change in WHO-FC compared to baseline after 3 and 15 weeks was not significant, possibly due to the small sample size (p=0.157). Mean NTproBNP serum-levels slightly decreased after 3 weeks of exercise training and significantly increased after 15 weeks (Table 2). Mean oxygen saturation was reduced at rest (93±5%), decreased during cardiopulmonary exercise test (84±10%), and remained unchanged during 3 and 15 weeks of exercise training (Table 2). The other parameters as mean systolic and diastolic systemic blood pressures and oxygen pulse remained unchanged.

**Missing values, results of imputation role**

Five patients (25%) did not attend the visit after 15 weeks (all referred from other PH-centers than Heidelberg) mainly due to the long travel distance, but were reached during the follow-up assessment after 22±14 months. Results remained significant after imputation of missing values for the 6 MWD at 15 weeks using multiple imputations rules as described in the methods. Multiple imputation revealed a mean improvement of 6 MWD at 15 weeks of 67.2±50.6, p<0.001; last observation carried forward strategy 60.9±51.9 meters, p<0.001, and the pessimistic strategy of baseline observation carried forward 50.3±58.4 meters, p<0.001. The SF-36 subscore pain scale was significantly better after 15 Weeks, p=0.017. Comparing all variables at baseline and after 3 weeks the 5 patients who missed the visit after 15 weeks did not significantly differ from the other 15 patients. Dropouts had a similar mean age and improved with their 6MWD after 3 weeks (Figure 1). According to the statistical analysis it is unlikely that drop outs did not come to the visit after 15 weeks due to a reduced effect of the exercise training.
Worsening events during follow-up and survival

Follow-up data were obtained after a mean period of 21±14 months (Figure 5). The 1- and 2-years overall-survival rate was 100%. After 3 years 95% of our patients were still alive. One patient, aged 23 years, died due to right heart decompensation in a severe acute respiratory infection 2.5 years after rehabilitation. A female 65-years old patient received double-lung transplantation 14 months after exercise training due to disease progression. After transplantation her clinical status rapidly improved. Therefore, transplant-free survival rate after 1 year was 100%, after 2 years 93%. Overall during the follow-up period 12 worsening events were noticed: 1 patient died, 1 lung transplantation, 6 patients required in-hospital treatment (because of pneumonia, hysterectomy, arrhythmia and orthopedic problems). In 1 patient an additional PAH-targeted drug was started due to clinical worsening. In 3 patients WHO-FC had worsened from II to III.

In 18 of the 20 patients information on the exercise training program at home could be obtained. All reported to continue at least some parts of the exercise training program, 74% had continued with walking and dumbbell-training, 68% bicycle ergometer training and 58% respiratory training. Two patients performed additional outdoor bicycle training. Sixty-five percent of patients reported to practice exercise training at least 3 days per week, 50% almost every day.

Adverse events and non-responders

During the 3-weeks in-hospital training 4 patients had adverse events and suffered from respiratory infections; 2 patients received an antibiotic therapy. Three of the 4 patients were able to continue the training program after one or two weeks. In one patient the respiratory infection was long-lasting, so that she could not perform effective exercise training over several weeks. None of the patients had signs of
clinical worsening of heart failure or cyanosis during the in-hospital program. All patients tolerated exercise training well without severe adverse events, especially no syncope or presyncope occurred. Every patient reported that exercise training improved the awareness of physical abilities and limitations and was overall satisfied with the 3-weeks in-hospital program.
Discussion

This is the first prospective clinical trial investigating short- and long-term effects of exercise training as add-on to PAH-targeted medication in patients with severe CHD-APAH. The results of the study suggest that exercise training can significantly improve exercise capacity and oxygen consumption in this condition and has an excellent long-term overall-survival of 100% after 2 years and 95% after 3 years.

The results represent an important source of data on survival and exercise capacity in patients with CHD-APAH treated by exercise training. Mean 6MWD significantly improved by almost 16%, mean peak oxygen consumption by ≈11%, and mean maximal workload by ≈29% during 15 weeks intensive exercise training program. The positive effect of exercise training was also documented by the feed-back of 18 patients who continued the program at home during the follow-up period of 21±14 months. However, these data must be confirmed in further randomized, controlled studies.

Assessment of efficacy parameters and setting of exercise training in CHD

The results of this study are in line with previous studies of exercise training in patients with other forms of PH/PAH [17-20]. These studies showed similar effects in patients with various forms of PH and right heart insufficiency in a randomized controlled [17] and in a single-arm, non-controlled design [18-20]. However, in these studies only few patients with CHD-APAH have been included [17, 19, 20]. Thus, there are almost no previous data on the effect of exercise training in patients with CHD-APAH. The promising results of this study suggest that in experienced hands exercise training may be an important add-on therapy for these patients especially in regard of their impaired exercise capacity and peak VO₂.
The data of this study support previous findings in CHD-patients without PAH. Dua et al. reported improved exercise capacity and quality of life by regular walking training in 61 CHD-patients [21]. Winter et al. showed that step aerobics 3 times per week improved peak VO₂ in 28 patients with transposition of the great arteries WHO-FC II [23]. There is only one previous study with CHD-APA showing an improved oxygen saturation and WHO-FC by exercise training in 4 patients [24] using an out-patient program twice a week.

The effects of training may vary between different programs and settings, the results of our study suggest that it can improve clinically relevant parameters. However, an in-hospital start of the rehabilitation program has the advantage of a closely supervised setting which might be beneficial especially in patients with CHD-APA, since they tend to overestimate their exercise capacity [29] and show severe hypoxemia during exercise. A profound understanding of the pathophysiology of the underlying cardiac anomaly on the part of the trainers and the treating physicians is deeply required.

**Improvement in 6-Minute walking distance and peak oxygen uptake**

It is well established that patients with CHD, especially those developing pulmonary hypertension and ES have limitation of their exercise capacity [30]. Patients with ES had the most impaired exercise capacity compared to other cyanotic patients [7]. Reduced peak VO₂ and 6MWD were the main predictors of mortality in patients with CHD-APA [30]. Therefore, improvement of 6MWD and peak VO₂ by exercise training as reached in this study might be of prognostic relevance. In this study we show for the first time that CHD-APA patients can improve their peak VO₂ by exercise training although severe hypoxemia occurred in all patients during the program.
Quality of life parameters

Although patients with CHD are severely affected with reduced exercise capacity especially in psychosocial aspects quality of life parameters seem to be less impaired as in IPAH-patients [29]. This might be due to the fact that CHD-patients live with the disease from childhood on and might be better adapted to exercise limitations [31]. In our study only the SF-36 subscale “bodily pain” improved in trend by exercise training although exercise capacity and peak VO₂ markedly improved. Possibly in this disease general questionnaires such as the SF-36 are not completely appropriate. Previous studies found that quality of life parameters in ES-patients were mainly reduced in physical scales [7].

Survival rate

Adults with CHD-APAH seem to have a better survival than those with IPAH [9]. This might be due to a slower progression of CHD-APAH [31] and to an almost normal cardiac output resulting from associating shunts. Hopkins et al. reported a survival rate of 89% at 2 years and 77% at 3 years in patients with CHD-APAH [9]. The development of ES increased mortality about 10- to 12-fold [32] and was estimated by 20.6% in 5 years [4]. Lowe et al. showed in a retrospective cohort study that the diagnosis of P(A)H in CHD increased mortality rate more than 2-fold. Heart failure and arrhythmia occurred 3-fold more often in CHD-APAH than in CHD-patients without P(A)H [8]. Compared to the previous reported survival rates [4, 9, 32] and considering the severely impaired hemodynamic compromise of the patients assessed in this study the documented overall 2-year survival rate of 100% and transplantation-free 2-year survival rate of 93% suggest that exercise training did at least not reduce but rather improve clinical worsening and long-term survival.
However, for further assessment of long-term effects further randomized, controlled trials in a larger patient population are needed.

Adverse events and non-responder

Although no severe adverse effects occurred during the in-hospital exercise training program of this study, in our opinion those programs should be closely monitored by PH-experts. Exercise training in CHD-APAH seems to be an effective add-on therapy but it is not completely harmless. During exercise training severe deterioration of oxygen saturation occurred in almost all patients. In addition the severely impaired right heart function needed to be monitored. Especially exercise training in patients with CHD-APAH has to address special needs and pathophysiological circumstances.

Limitations

The results of this prospective study are limited by the small number of patients with CHD-APAH and the lack of randomization. Because of this, there could be a referral bias that patients doing well have been selected. Nevertheless, the study provides a good rationale for future randomized-controlled studies. The effects of exercise training after 15 weeks may be further biased due to the missing values of 25% of patients who did not perform the last follow-up visit. However, the efficacy after 3 weeks exercise and respiratory therapy and the high proportion of patients who continued with the program suggest a positive effect in this cohort. The significant effect and high compliance of exercise training in CHD-APAH-patients might also be due to the closely supervised in-hospital rehabilitation program, which probably cannot be simply translated to an out-patient program. This limits the application of this program in other countries which cannot provide in-hospital rehabilitation care.
Therefore, further studies are necessary using ambulatory training programs. Furthermore, it is a general problem of rehabilitation programs that the therapy cannot be performed double-blinded. Further prospective, randomized studies are necessary to determine the effects of training programs on long-term outcome in patients with CHD-APA-H.

**Conclusion**

This is the first trial investigating short- and long-term effects of exercise training in CHD-APA-H as add-on to optimized medical therapy. The results indicate that exercise training is effective in CHD-APA-H and may improve work capacity, quality of life and further prognostic relevant parameters. Exercise training possibly improves survival rate. Further randomized studies are needed to confirm these promising results.

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**Conflict of interest disclosures:** None
Contributors

TBG, EG, NE, ML and CF were responsible for designing, conducting and analysing the present study and were directly involved in data collection. EG, CN, MG, HT, DS, AH, AK, OM, SU, RS, and SU were principle investigators directly involved in data collection. All authors were involved in the writing of the manuscript and saw and approved the final version of the paper.
References:


Figure Legend

Figure 1: Individual changes in Six-Minute-Walking Distance (6MWD) after 3 and 15 weeks exercise training. With the use of Wilcoxon Test according to baseline walking distance, p<0.001 was obtained for the comparison to baseline with week 3 and p=0.001 with week 15. For the analysis after 3 weeks of exercise training the data from 20 patients, after 15 weeks of 15 patients were available and included. The coloured line indicates the mean change from baseline in 6MWD (63 meters and 67 meters).

Figure 2: Peak oxygen uptake (peak VO₂) at three time points. The figure represents significant improvements after 3 and 15 weeks exercise training (p= 0.063 and p=0.002). Peak VO₂ increased continuously in mean change from 831±220 to 902±267 after 3 weeks (n=16) and to 925±264 ml/min after 15 weeks (n=14). Minimum and maximum are indicated.

Figure 3: Workload compared to Borg Scale. The figure shows an increase in workload after 3 and 15 weeks (p=0.012 and p=0.003) without significant change in Borg Scale (p=0.964 and p=0.877, respectively). Both are indicated as median and statistical minimum and maximum. The coloured columns represent workload (measured in Watt) and the dotted line Borg Scale.

Figure 4: Mean SF-36 scores of Quality of life Subscales (SF-36 questionnaire) before and after Exercise Training. The figure shows no significant differences in quality of life, but in the subscale “pain” with p=0.05 after 15 weeks. The dotted line represents the quality of life of a healthy standard population.

Figure 5: One- and 2-year Survival Rate.

Within a follow-up period of 21±14 months 1 patient died and 1 patient received a lung-transplantation. Thus, the 1-year and 2-year overall survival rate was 100%. The transplantation-free survival after 2 years was 93%. The dashed lines represent the 95th percentile of the overall- and transplantation- free survival rates.
<table>
<thead>
<tr>
<th><strong>Table 1: Baseline Characteristics</strong></th>
<th><strong>Quantile [25-75%]</strong></th>
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<tr>
<td><strong>Mean 6MWD [meters]</strong></td>
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<td>RA pressure [mmHg]</td>
<td>6 ± 5 5 3-9</td>
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<tr>
<td>SaO₂ [%]</td>
<td>86 ± 13 89 80-91</td>
</tr>
<tr>
<td>PCWP [mmHg]</td>
<td>10 ± 7 8 6-12</td>
</tr>
<tr>
<td>CI [L/min/m²]</td>
<td>2.9 ± 0.7 2.9 2.2-3.2</td>
</tr>
<tr>
<td><strong>PAH-targeted medication</strong></td>
<td></td>
</tr>
<tr>
<td>Endothelin Receptor Antagonist</td>
<td>14 70%</td>
</tr>
<tr>
<td>Phosphodiesterase-5-Inhibitor</td>
<td>12 60%</td>
</tr>
<tr>
<td>Prostanoids inhaled</td>
<td>4 20%</td>
</tr>
<tr>
<td>Prostanoids intravenous</td>
<td>1 5%</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>1 5%</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>9 45%</td>
</tr>
<tr>
<td>Dualtherapy</td>
<td>8 40%</td>
</tr>
<tr>
<td>Tripletherapy</td>
<td>3 15%</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD, 25 and 75 Quantiles [Quantile 25-75%] or as n and %.
mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, RA = right atrium, SaO₂ = arterial oxygen saturation, PCWP = pulmonary capillary wedge pressure, CI = Cardiac Index.
Table 2: Efficacy parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline (n=20)</th>
<th>3 weeks (n=20)</th>
<th>p-value</th>
<th>15 weeks (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6MWD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking distance [meters]</td>
<td>423 ± 90</td>
<td>486 ± 93</td>
<td>&lt;0.001  *</td>
<td>486 ± 102</td>
<td>&lt;0.001  *</td>
</tr>
<tr>
<td>mean change [meters]</td>
<td>63 ± 47</td>
<td>67 ± 59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for the difference to baseline</td>
<td>41 - 85</td>
<td>35 - 99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of life Questionnaire SF-36</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>41.2 ± 23</td>
<td>45.0 ± 19.4</td>
<td>0.206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role-physical</td>
<td>45.8 ± 40</td>
<td>45.3 ± 42</td>
<td>0.631</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>62.2 ± 33</td>
<td>82.4 ± 20</td>
<td>&lt;0.05   *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health perception</td>
<td>40.6 ± 15</td>
<td>43.3 ± 11</td>
<td>0.366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>50.3 ± 20</td>
<td>53.8 ± 14</td>
<td>0.431</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>75.0 ± 24</td>
<td>80.8 ± 21</td>
<td>0.842</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role-emotional</td>
<td>70.4 ± 43</td>
<td>81.3 ± 36</td>
<td>0.194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>73.6 ± 13</td>
<td>72.2 ± 11</td>
<td>0.713</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiopulmonary exercise testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peak VO₂/kg [mL/Min/kg]</td>
<td>11.4 ± 2.2</td>
<td>12.4 ± 2.2</td>
<td>0.066</td>
<td>12.3 ± 2.4</td>
<td>0.008   *</td>
</tr>
<tr>
<td>peak VO₂ [mL/min]</td>
<td>831 ± 220</td>
<td>902 ± 267</td>
<td>0.063</td>
<td>925 ± 264</td>
<td>0.002   *</td>
</tr>
<tr>
<td>EqCO₂ at AT [mL/min]</td>
<td>42.2 ± 10.3</td>
<td>43.9 ± 12.3</td>
<td>0.116</td>
<td>44.3 ± 11.6</td>
<td>0.285</td>
</tr>
<tr>
<td>VO₂ at AT [mL/min]</td>
<td>683 ± 208</td>
<td>665 ± 203</td>
<td>0.271</td>
<td>777 ± 196</td>
<td>1.00</td>
</tr>
<tr>
<td>O₂-pulse [(mL/min)/min-1]</td>
<td>7.0 ± 2.0</td>
<td>7.2 ± 2.1</td>
<td>0.345</td>
<td>6.8 ± 2.1</td>
<td>0.08</td>
</tr>
<tr>
<td>HR rest [min-1]</td>
<td>81 ± 15</td>
<td>79 ± 13</td>
<td>0.064</td>
<td>87 ± 18</td>
<td>0.065</td>
</tr>
<tr>
<td>HR max [min-1]</td>
<td>119 ± 18</td>
<td>122 ± 24</td>
<td>0.155</td>
<td>138 ± 15</td>
<td>0.004   *</td>
</tr>
<tr>
<td>RR sys rest [mmHg]</td>
<td>114 ± 14</td>
<td>115 ± 15</td>
<td>0.598</td>
<td>115 ± 12</td>
<td>0.687</td>
</tr>
<tr>
<td>RR dia rest [mmHg]</td>
<td>75 ± 9</td>
<td>73 ± 9</td>
<td>0.109</td>
<td>74 ± 8</td>
<td>0.951</td>
</tr>
<tr>
<td>RR sys max [mmHg]</td>
<td>140 ± 16</td>
<td>141 ± 21</td>
<td>0.552</td>
<td>150 ± 25</td>
<td>0.061</td>
</tr>
<tr>
<td>RR dia max [mmHg]</td>
<td>80 ± 12</td>
<td>83 ± 12</td>
<td>0.305</td>
<td>86 ± 11</td>
<td>0.116</td>
</tr>
<tr>
<td>Oxygen saturation rest [%]</td>
<td>92 ± 6</td>
<td>93 ± 4.4</td>
<td>0.704</td>
<td>93 ± 4.3</td>
<td>0.193</td>
</tr>
<tr>
<td>Oxygen saturation max [%]</td>
<td>83 ± 9.7</td>
<td>84 ± 10.6</td>
<td>0.461</td>
<td>83 ± 9.9</td>
<td>0.723</td>
</tr>
<tr>
<td>sPAP rest [mmHg]</td>
<td>71 ± 28</td>
<td>66 ± 28</td>
<td>0.553</td>
<td>60 ± 29</td>
<td>0.202</td>
</tr>
<tr>
<td>sPAP max [mmHg]</td>
<td>106 ± 30</td>
<td>105 ± 28</td>
<td>0.285</td>
<td>99 ± 26</td>
<td>0.799</td>
</tr>
<tr>
<td>Workload max [Watt]</td>
<td>58 ± 20</td>
<td>72 ± 28</td>
<td>0.012   #</td>
<td>75 ± 23</td>
<td>0.003   *</td>
</tr>
<tr>
<td>Borg Scale</td>
<td>16 ± 2</td>
<td>16 ± 3</td>
<td>0.964</td>
<td>16 ± 2</td>
<td>0.877</td>
</tr>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP [pg/mL]</td>
<td>493 ± 471</td>
<td>450 ± 397</td>
<td>0.981</td>
<td>651 ± 565</td>
<td>0.031   #</td>
</tr>
</tbody>
</table>

Values are mean±SD; #p<0.05; *p<0.01 in comparison to baseline, p-values are the same for absolute values and differences; 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, RR = Blood pressure sPAP = systolic Pulmonary arterial pressure;
Figure 1:

Mean: +63 m
p < 0.001
p = 0.001
Mean: +67 m

Change in 6MWD [meters]

Baseline (n=20)  3 weeks (n=20)  15 weeks (n=15)
Figure 2:

![Bar chart showing peak VO2 (mL/min) at baseline, 3 weeks, and 15 weeks with significant p-values.]

- Baseline: 831±221 mL/min (n=20)
- 3 weeks: 902±267 mL/min (n=20)
- 15 weeks: 925±264 mL/min (n=15)

Significance levels:
- Baseline vs. 3 weeks: p=0.063
- Baseline vs. 15 weeks: p=0.002
- 3 weeks vs. 15 weeks: p=0.002

Note: p-values indicate significance in changes at 15 weeks compared to baseline and 3 weeks.
Figure 3:

- Baseline: 58±20 W (n=20)
- 3 weeks: 72±27 W (n=20)
- 15 weeks: 75±23 W (n=15)

Mean Borg Score:
- p=0.012
- p=0.003

Workload [Watt] vs. Borg Score
Figure 4:
Figure 5:

Survival

Overall survival

Transplantation-free survival

100% 1- and 2-year-survival

Transplantation-free survival:
100% 1- and 93% 2-year-survival

Patients at risk

<table>
<thead>
<tr>
<th>years</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>