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Exercise and Respiratory Training Improve Exercise Capacity and Quality of Life in Patients With Severe Chronic Pulmonary Hypertension

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Background—Pulmonary hypertension (PH) is associated with restricted physical capacity, limited quality of life, and a poor prognosis because of right heart failure. The present study is the first prospective randomized study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic PH.

Methods and Results—Thirty patients with PH (21 women; mean age, 50±13 years; mean pulmonary artery pressure, 50±15 mm Hg; mean World Health Organization [WHO] class, 2.9±0.5; pulmonary arterial hypertension, n=23; chronic thromboembolic PH, n=7) on stable disease-targeted medication were randomly assigned to a control (n=15) and a primary training (n=15) group. Medication remained unchanged during the study period. Primary end points were the changes from baseline to week 15 in the distance walked in 6 minutes and in scores of the Short Form Health Survey quality-of-life questionnaire. Changes in WHO functional class, Borg scale, and parameters of echocardiography and gas exchange also were assessed. At week 15, patients in the primary and secondary training groups had an improved 6-minute walking distance; the mean difference between the control and the primary training group was 111 m (95% confidence interval, 65 to 139 m; $P<0.001$). Exercise training was well tolerated and improved scores of quality of life, WHO functional class, peak oxygen consumption, oxygen consumption at the anaerobic threshold, and achieved workload. Systolic pulmonary artery pressure values at rest did not change significantly after 15 weeks of exercise and respiratory training (from 61±18 to 54±18 mm Hg) within the training group.

Conclusions—This study indicates that respiratory and physical training could be a promising adjunct to medical treatment in severe PH. The effects add to the beneficial results of modern medical treatment. (***Circulation*. 2006;114:1482-1489.**)

Key Words: rehabilitation ■ exercise ■ hypertension, pulmonary ■ pulmonary heart disease ■ quality of life

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death.[1,2] Treatment includes supportive therapy (anticoagulants, diuretics, and supplemental oxygen) and disease-targeted therapies, consisting of vasodilators and antiproliferative agents.[3,4] The agents currently approved for treatment of pulmonary arterial hypertension (PAH) in the United States and Europe[3] are intravenous epoprostenol, inhaled iloprost, subcutaneously and intravenously administered treprostinil, the endothelin-receptor antagonist bosentan, and the phosphodiesterase type 5 inhibitor sildenafil.[5] Combinations of these agents might further improve symptoms, exercise capacity, quality of life, and possibly survival rate in PAH.[6–10] Although treatment of PH is advancing rapidly, adverse effects occur with all of the specific agents,[3,4] and most patients remain symptomatic and have reduced exercise capacity, quality of life, and survival rates despite optimized medical treatment. Furthermore, reduced exercise capacity in PH is associated with depression and anxiety disorders.[11] Besides numerous studies for medical therapy, little is known about the effects of lifestyle

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changes such as the amount of physical activity that patients can or should practice. It is commonly believed that physical activity or training may have a negative impact on patients by contributing to the evolution and progression of PH.[12] Therefore, especially in more severely affected patients, many doctors recommend avoidance of physical exercise.[13] Physical exercise has been thought to carry a high risk of sudden cardiac death, increased pulmonary remodeling resulting from the higher shear stress, or worsening of right heart failure. However, there is some evidence from left heart failure that regular physical activity and training may be beneficial even in severe disease. Physical training improved endothelial function, exercise capacity, and quality-of-life parameters in patients with coronary artery disease[14,15] and chronic left heart failure.[16,17] Notably, physical training reduced vascular oxidative stress at least in part via increased activity of endothelial nitric oxide synthase, which could exert beneficial vascular effects.[18] The effect of exercise training in patients with PH has not yet been evaluated systematically. Therefore, the objective of the present study was to evaluate the effectiveness and safety of respiratory and physical exercise training in patients with symptomatic chronic PH.

Methods

Study Population

Patients with severe chronic PH who were stable and compensated under optimized medical therapy (such as endothelin antagonists, iloprost, sildenafil, calcium channel blockers, anticoagulants, diuretics, and supplemental oxygen) for at least 3 months before entering the study were invited to participate. Additional inclusion criteria were age of between 18 and 75 years, World Health Organization (WHO) functional class II to IV,[19] no recent syncope, and no skeletal or muscle abnormalities prohibiting participation in an exercise program. Right heart and left heart catheterization and test for vasoreactivity were performed in all patients before entering the study by the participating centers.

Randomization and Study Design

The study was a 15-week randomized controlled trial, with the control group also entering the training arm after completing the initial protocol. After giving written informed consent for this study, which was approved by the Ethics Committee of the University of Heidelberg, patients were randomly assigned to either a primary training group or a sedentary control group using a permuted block randomization procedure. Patients in each group stayed in the hospital for the initial 3 weeks of the study period and continued with a program at home for another 12 weeks. Medication remained unchanged throughout the study period. After completion of the first 15-week study period, patients in the control group were invited to reenter the study to participate in the exercise training program also. The control subjects who participated in additional exercise training for another 15 weeks made up the secondary training group. The last assessment of the control group after 15 weeks was used as the baseline assessment for the secondary training group. The members of the secondary training group (10 of 15 control subjects) received the same training program as the primary training group. They were assessed again after 3 weeks of training in the hospital and after another 12 weeks of training at home.

Outcome Measures

Patients were evaluated at baseline, week 3, and week 15. Primary end points were the changes from baseline to week 15 in distance walked in 6 minutes and the change in quality of life as measured by the Short Form Health Survey (SF-36) questionnaire. A 6-minute walking test was carried out under standardized conditions[20] and by investigators who were blinded to the clinical data and group assignment of the patients. All patients were familiar with the 6-minute walking test and cardiopulmonary exercise testing. Health-related quality of life was assessed with the SF-36, which consists of 36 items representing 8 subscales that cover the domains of physical functioning, role functioning physical, bodily pain, general health perception, vitality, social functioning, role functioning emotional, and mental health.[21] The 8 subscales range from 0 to 100 (higher scores indicating better quality of life) and are summarized by 2 summation scales, the physical component scale and the mental component scale. The completed questionnaire at baseline was compared with the results after 15 weeks by investigators who were blinded to the patients' clinical data and group assignment.

Secondary end points were changes in WHO functional classification, Borg scale (6=no exertion, 20=maximal exertion)[22] assessed immediately after completion of the stress Doppler echocardiography, and parameters of echocardiography and gas exchange. Stress Doppler echocardiography was carried out at rest and during supine bicycle exercise as described previously.[23,24] Systolic pulmonary artery pressures (PASPs) were estimated from tricuspid regurgitation velocity. The right ventricular and atrial areas were obtained in apical 4-chamber views through planimetry. Cardiopulmonary exercise testing was performed during the stress Doppler echocardiographic examination with cycle ergometer (ER 900, Ergoline GmbH, Bitz, Germany) and a cardiorespiratory diagnosis system (Oxycon Alpha, Erich JAEGER GmbH & Co., Hoechberg, Germany). Workload, heart rate, ventilation ($\dot{V}E$), oxygen uptake, and carbon dioxide output ($\dot{V}CO_2$) were measured continuously. The anaerobic threshold was detected with the V-slope method.[25] All recordings of echocardiography and cardiopulmonary exercise testing were analyzed again offline in random order and in a blinded fashion.

Exercise Training Program

For the first 3 weeks, all patients stayed in the hospital. Patients in the control group received a common rehabilitation program based on healthy nutrition, physical therapy such as massages, inhalation, counseling, and muscular relaxation without exercise and respiratory training but were allowed to perform daily activity as usual. All patients were advised to avoid heavy exercise. Patients in the primary and secondary training groups participated in an additional exercise program 7 days a week at low workloads (10 to 60 W) that was supervised by physical therapists and physicians. The training consisted of an interval bicycle ergometer training with a lower workload for ½ minute and a higher workload for 1 minute (eg, 20 to 35 W) for 10 to 25 min/d, corresponding to 60% to 80% of the heart rate they had reached during peak oxygen uptake in the initial exercise test. The training intensity was increased (eg, up to 35 to 50 W) with respect to the individual tolerability and improvement. Training intensity was limited by peak heart rate (not more than 120 bpm), oxygen saturation >85%, and subjective physical exertion. Furthermore, 60 minutes of walking was performed 5 days a week and consisted of flat-ground and uphill walking. During this training, patients were accompanied by a physiotherapist and received additional "mental training" to improve their perception of their individual physical abilities and limits to keep physical exercise safe even in demanding situations (eg, walking with higher speed but perceiving the right breathing rhythm). Five days a week, 30 minutes of dumbbell training of single muscle groups with low weights (500 to 1000 g) and 30 minutes of respiratory training, including stretching, breathing techniques such as pursed lip breathing, body perception, Yoga, and strengthening of respiratory muscles, were performed. Oxygen saturation and heart rate

TABLE 1. Baseline Characteristics of the Patients

Characteristic	Control Group (n=15)	Primary Training Group (n=15)	P
Gender, M/F	5/10	5/10	...
Age, y	53±14	47±12	0.39
Height, cm	166±5	171±11	0.24
Weight, kg	78±18	75±13	0.91
WHO functional class	...	...	0.50
I	0	0	...
II	2	4	...
III	12	10	...
IV	1	1	...
Cause of pulmonary hypertension, n (%)	...	...	0.54
PAH	11 (73.3)	13 (86.6)	...
Chronic thromboembolic	4 (26.7)	2 (13.3)	...
Walking distance at 6 min, m	411±86	439±82	0.38
Cardiac catheterization			
Mean pulmonary artery pressure, mm Hg	49.6±12.3	49.5±17.6	0.98
Pulmonary vascular resistance, dyne · s · cm^{-5}	901.8±358.0	968.7±444.1	0.66
Cardiac index, L · min^{-1} · m^{-2}	2.1±0.5	2.3±0.5	0.61
Right atrial pressure, mm Hg	7±5	6±4	0.74

Values are mean±SD.

were monitored continuously throughout the training and were used to adjust the training intensity. When patients' oxygen saturation fell to <85%, training was reduced. Three patients who were on oxygen therapy 16 h/d before inclusion in this study kept the oxygen even through the training program.

At hospital discharge, patients in the primary and secondary training groups received an individualized training manual and arranged to receive a bicycle ergometer for use at home. They were asked to continue the bicycle exercise training close to their target heart rate once daily for a total of 15 to 30 minutes for 5 days a week. Furthermore, they were asked to continue the respiratory exercise and dumbbell training for 15 to 30 minutes every other day according to the manual. In addition, they were to walk twice a week. The amount of training at home was supervised by phone every 2 weeks by physiotherapists and/or physicians. During the home-based respiratory and exercise training, all patients were asked to keep in close contact with the physicians of the training program. Furthermore, the general practitioners and specialized centers that admitted the patients were informed and kept involved in the monitoring of the patients at home.

Statistical Analysis

Data are given as mean±SD. The null hypothesis of the study was that there was no difference between patients receiving rehabilitation program including exercise training and those receiving rehabilitation without training in the distribution of changes from baseline in exercise capacity. To reject the null hypothesis, a sample of 15 patients in each group was required if the means of the distribution with equal SDs of 55 m differed by at least 50 m (≈12% change) according to the Mann-Whitney *U* test, with a type I error of 0.05 (2 sided) and 90% power. Baseline characteristics were compared by 2-tailed Student *t* test. For comparison of categorical variables, the χ^2 test was performed. Comparisons of both groups for the 6-minute walk test, workload, WHO functional class, Borg dyspnea index, gas exchange, PASP, heart rate, and cardiac output were performed by the Mann-Whitney *U* test. For the intergroup comparison of baseline with 3 weeks and baseline with 15 weeks, the Wilcoxon signed rank test was used. Summation and subscores of the SF-36 questionnaire were compared by ANOVA and 2-tailed Student *t* test. Bonferroni adjustment for multiple comparisons was made for comparisons of 6-minute walking distances (probability values given later in Results) and for comparison of quality-of-life parameters. Values of $P<0.05$ were considered statistically significant.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Thirty-two consecutive patients with PH were assessed. Patients who had an alteration in their medication were excluded to avoid changes in the evaluated parameters resulting from modification of medication. Thus, the study group consisted of 30 patients with severe PH (PAH, n=24; inoperable chronic thromboembolic pulmonary hypertension, n=6; 21 women; mean age, 50±13 years; range, 19 to 72 years). Diagnosis was confirmed by a cascade of clinical examinations, including right and left heart catheterization, and was made according to the WHO criteria.[2] Diagnosis and treatment in these patients had been performed by at least 1 experienced PH center. The patients were randomly assigned to the control group (15 patients) or the primary training group (15 patients).

Baseline Characteristics

At baseline, patients in the 2 groups did not differ in their demographic data, 6-minute walking distance, and hemodynamic values (Table 1) or in their medical treatment (Table 2). Six patients received supplemental oxygen during the night. Only 1 of the 30 patients responded to calcium channel blocker and received amlodipine 15 mg/d; the other patients received calcium channel blockers at low dosage. According to the WHO classification, 20% of

TABLE 2. Medical Treatment With PH-Targeted Agents

	Control Group (n=15)	Primary Training Group (n=15)	*P*
Agent	...	...	0.22
Bosentan	11	8	...
Sildenafil	5	5	...
Iloprost inhaled	4	1	...
Epoprostenol	1	2	...
Beraprost	1	0	...
Calcium channel blockers	4	7	...
Drug combination therapy			1.0
Monotherapy	7	6	...
Dual therapy	5	5	...
Triple Therapy	3	4	...

The 2 groups did not differ with respect to medical therapy. Values represent mean±SD. Probability values were adjusted by χ^2 test.

patients were in class II (with no discomfort at rest but mild physical limitations such as dyspnea when walking 2 stairs), 73% in class III (no discomfort at rest, marked limitation of physical activities such as flat-ground walking), and 7% class IV (patients who have symptoms at rest and during each physical activity). Combination therapy, including 2 or 3 PH-targeted agents, were given to 57% of patients (Table 2). The 10 of 15 patients in the control group who reentered the study were classified as the secondary training group and performed the exercise training as well. The remaining 5 patients in the control group were not willing (n=1) or were not able to take part in the training program because of disease progression and a change in medication (n=4).

Exercise Capacity

After 3 weeks of treatment, the 6-minute walking distance increase was significantly larger in the primary training group (85±56 m) than in the control group (12±37 m; $P=0.0003$; Figure 1). After 15 weeks of treatment, the distance walked in 6 minutes decreased in the control group (−15±54 m), whereas patients in the primary training group revealed a further improvement (96±61 m; $P<0.0001$; Figure 1); the mean difference between groups was 111 m (95% CI, 65 to 139; $P<0.001$). Patients in the secondary training group improved similarly to the patients in the primary training group and showed a significantly higher increase in the 6-minute walking test after 3 weeks (mean, 75±41 m) and after 15 weeks (mean 74±49 m) compared with baseline (after 3 weeks, $P<0.05$; after 15 weeks, $P=0.001$; Figure 1).

Quality of Life

At baseline, all 30 patients had significantly compromised quality-of-life scores compared with the general population[26] and showed a >40% score reduction in the 2 summation scores (the physical and mental component scales; not shown) and in 3 of 8 SF-36 scales (Figure 2). Exercise and respiratory training significantly improved the physical ($P=0.013$) and mental ($P=0.027$) component

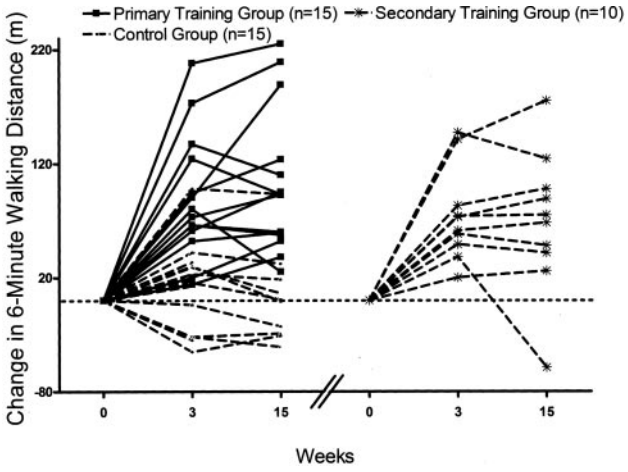

Figure 1. Mean (±SE) change in 6-minute walking distance from baseline to week 15 in the primary training, control, and secondary training groups (10 members of the control group reentered the study and received 15 weeks of exercise training). *$P=0.0003$ for primary training vs control group after 3 weeks of training; **$P<0.0001$ for primary training vs control group after 15 weeks of training; ■$P<0.05$ for secondary training group vs control group after 3 weeks of training; ■■$P=0.001$ for secondary training group vs control group after 15 weeks of training.

scale summation scores and the subscale scores for physical functioning ($P=0.018$), role-physical ($P=0.003$), social functioning ($P=0.002$), mental health ($P=0.017$), and vitality ($P=0.001$) compared with the control group, in which these parameters remained virtually unchanged (Figure 2). In the primary training group, the largest increase occurred in the score for physical functioning (45±16.5 to 62.8±13.6 versus 29.3±23.1 to 35.7±24.3 for the control group; $P=0.001$) and vitality (41.3±11.3 to 60.0±17.0 versus 51.7±17.1 to 56.0±16.7; $P=0.025$). No significant changes occurred in the subscales role functioning emotional, bodily pain, and general health perception (Figure 2). With Bonferroni adjustment, values of $P<0.005$ preserve statistical significance.

Secondary End Points

WHO Functional Class

At baseline, 80% of patients were in WHO functional class III or IV.[19] By week 15, all patients in the primary training group perceived a noticeable improvement in their symptoms; 6 patients improved from class III to II during the exercise training, and 1 improved from class IV to III. In contrast, none of the patients in the control group improved. Thus, mean WHO functional class improved significantly from 2.8±0.6 to 2.4±0.5 after 3 weeks and to 2.3±0.4 after 15 weeks in the primary training group; it remained unchanged in the control group after 3 weeks (training versus control; $P=0.02$) and progressed from 2.9±0.5 to 3.0±0.3 after 15 weeks (training versus control, $P<0.001$).

Workload

After exercise training, patients in the primary training group reached significantly higher workloads than at baseline and patients in the control group (Table 3). The

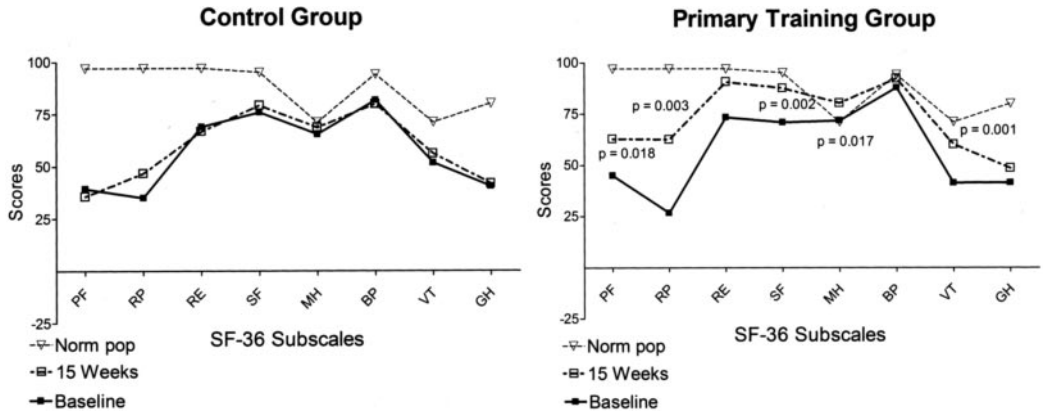

Figure 2. Mean (±SE) SF-36 scores at baseline and after 15 weeks of rehabilitation in the control and primary training groups. At baseline, mean SF-36 scores were similar in both groups. After 15 weeks, 7 scales of the SF-36—physical component scale (PCS), mental component scale (MCS), physical functioning (PF), role limitations due to physical limitation (RP), social functioning (SF), mental health (MH), and vitality (VT)—improved significantly in the primary training group (*P* values are indicated) vs the control group. No significant differences between groups were measured in the scores for role limitations caused by emotional problems (RE), bodily pain (BP), and general health perception (GH) after training. The respective values of a normal population (Norm pop; n=906)[26] are shown for comparison. With Bonferroni adjustment, values of $P<0.005$ preserve statistical significance.

Borg scale remained unchanged in the primary training group, although higher workloads had been reached, whereas the Borg scale increased significantly in the control group within the same workloads (Table 3).

Hemodynamics and Gas Exchange

Hemodynamic parameters did not change significantly within the groups during the study period (Table 3). PASP values at rest and during exercise, however, were significantly lower after 3 and 15 weeks of exercise and respiratory training compared with the values of the control group (Table 3). Peak oxygen consumption, peak oxygen consumption in percent of the predicted value, oxygen consumption at the anaerobic threshold, and the achieved workload at the anaerobic threshold significantly improved

TABLE 3. Respiratory and Hemodynamic Variables at Baseline and After Intervention

	Control Group (n=15)			Primary Training Group (n=15)		
	Baseline	3 wk	15 wk	Baseline	3 wk	15 wk
$Workload_{max}$, W	64±22	60±24	67±20	70±17	85±26*†	90±25*†
Borg scale	15±2	15±1	16±1*	15±2	15±2	15±2
HR_{rest}, bpm	71±17	74±11	72±11	72±11	73±11	75±11
HR_{max}, bpm	108±19	107±22	110±20	118±16	125±15*†	132±17*†
VE_{max}, L · min	41.6±14.6	40.5±14.1	43.4±15.3	44.2±13.8	47.1±15.1	48.5±15.1
$\dot{V}o_{2\ peak}$, mL · min^{-1} · kg^{-1}	11.9±3.1	11.6±3.4	11.4±3.3	13.2±3.1	14.5±3.5*†	15.4±3.7*†
$\dot{V}o_{2\ \%\ predicted}$, %	46.3±10.7	45.9±14.6	49.8±12.7	51.6±16.3	56.5±18.0*	60.3±19.6*
Workload at AT, W	35±17	31±16	36±17	45±14	56±21*†	65±19*†
$\dot{V}o_2$ at AT, mL/min	640.7±187.4	613.4±206.6	610.4±200.4	736.6±210.3	802.3±229.8†	865.4±264.7*†
$Eqco_2$ at AT	42.4±11.3	50.7±10.8*	43.5±10.5	44.4±11.5	42.6±9.8†	42.9±10.4
Echocardiography						
$PASP_{rest}$, mm Hg	68±21	71±23	70±25	61±18	57±18†	54±18†
$PASP_{max\ exercise}$, mm Hg	98±28	104±29	102±30	89±17	84±23†	89±20
Cardiac $index_{rest}$, L · min^{-1} · m^{-2}	1.4±0.3	1.5±0.4	1.6±0.5	1.5±0.5	1.6±0.3	1.6±0.4
Cardiac $index_{max}$, L · min^{-1} · m^{-2}	1.9±0.7	1.8±0.7	1.9±0.7	2.3±0.6	2.3±0.7	2.5±1.1
RV $area_{rest}$, cm^2/m^2	16.2±5.8	16.0±4.3	13.3±4.7	13.0±3.9	14.2±4.3	12.2±3.8
RV $area_{max}$, cm^2/m^2	17.0±6	17.2±4.8	16.4±4.8	13.7±4.0	14.2±4.3	14.0±2.7
RA $area_{rest}$, cm^2/m^2	13.5±4.4	15.5±5.7	13.8±3.3	12.7±3.9	13.2±4.1	12.8±3.8
RA $area_{max}$, cm^2/m^2	15.3±4.8	15.0±5.9	14.7±3.9	13.9±4.5	14.8±4.3	12.3±3.3

$Workload_{max}$ indicates maximal workload; HR, heart rate; $Eqco_2$, respiratory equivalent of carbon dioxide at the anaerobic threshold (AT; $\dot{V}E/\dot{V}co_2$); $PASP_{rest}$, PASP at rest, $PASP_{max\ exercise}$, maximal PASP; RV, right ventricular; and RA, right atrial. Values are mean±SD. $P<0.05$ by Mann-Whitney rank sum test for the comparison between both groups and Wilcoxon signed rank test for the intergroup comparison.

*$P<0.05$ vs baseline.

†$P<0.05$, primary training group vs control group.

after 3 and 15 weeks in the primary training group compared with baseline and values of the control group (Table 3). Ventilatory equivalent of carbon dioxide at the anaerobic threshold decreased in the primary training group after 3 weeks and increased significantly in patients without exercise training.

Safety

All patients in the primary and secondary training groups tolerated the exercise training well and had no adverse events such as progression of symptoms, progression of PH, or right heart failure. Two patients perceived a short episode of dizziness without fainting immediately after bicycle ergometer training. In 1 patient, oxygen saturation dropped from 88% to 74% during exercise, although the training was performed with an oxygen mask.

Efficacy and Compliance of Training Methods

During the first 3 weeks in the hospital, patients in the primary and secondary training groups participated in exercise sessions almost every day. During the 12 weeks of the home-based study period, the patients were to continue their training program 5 days a week; compliance was monitored by phone contact every 2 weeks and by an open unstructured questionnaire at the final assessment in week 15. Patients were asked which exercise technique they had continued at home. Of the 25 patients in the primary and secondary training groups, 23 reported continuing regular exercise at home (3 to 6 times per week). The best results, a 29±21% ($P<0.001$) increase in the 6-minute walking distance, was reached in the 17 patients who continued with regular exercise and respiratory training. Six patients who continued only exercise training attained significantly smaller training effects, with a mean increase of 12±11% ($P=0.125$) in 6-minute walking distance after 15 weeks. The lowest 6-minute walking improvement (6±2%; $P=0.5$) was reached by the 2 patients who had not performed exercise or respiratory training at home regularly (<3 times a week).

Discussion

The present study is the first prospective, controlled, randomized study investigating the effect of respiratory and exercise training in patients with severe chronic PH and right heart failure. Low-dose exercise and respiratory training significantly improved exercise capacity, 6-minute walking test, quality of life, WHO functional class, and peak oxygen consumption. Thus, the exercise and respiratory training program shows promise as a safe and powerful potential adjunct therapy in patients with advanced PH.

The 6-minute walking test has been used as the primary end point in most clinical trials involving patients with PH.[3] The treatment-related increase in walking distance of 96 m (22%) observed in this study was higher than the increases observed with the use of sildenafil,[5] intravenous epoprostenol,[27] inhaled iloprost,[28] and oral bosentan.[29] A similar effect of training has been shown in patients with chronic left heart failure,[30] whereas angiotensin-converting enzyme inhibitors in these patients improved exercise capacity by only ≈10%.[31] However, the present findings are limited by the small number of patients and the general impossibility for a placebo-controlled, double-blind design in training studies. To avoid bias as far as possible in this study, all measurements and/or offline readings were performed by investigators who were blinded to patient data and group assignment. Furthermore, the effects of training were reevaluated by the secondary training group; similar effects were seen in the control group patients after training compared with the patients in the primary training group.

Quality of Life

The effect of respiratory and exercise training on exercise capacity was associated with a significant improvement in quality of life, as measured by the SF-36 questionnaire. Factors that may lead to impaired quality of life in PH include dyspnea, functional limitations, adverse effects of therapy, social isolation, and emotional issues such as anxiety and depression.[11] In this study, we have shown for the first time that exercise training in patients with severe PH provides beneficial psychological and physical effects, leading to a better health-related quality of life.

Effects on Hemodynamics and Gas Exchange

Although the PASP response to exercise tended to be lower after training, there was no significant effect on the pulmonary artery pressures within the primary training group and no improvement in cardiac output or other hemodynamic parameters. Therefore, the improvements in exercise capacity and peak $\dot{V}O_2$ in the primary and secondary training groups were most likely due to other effects, as also demonstrated in chronic left heart failure. These effects include the efficacy of muscular gas exchange and metabolism, ventilatory efficiency,[32] and reversal of skeletal muscle atrophy[33] and might include the attenuation of endothelial dysfunction[16] and inflammatory mediators.[34–36] Furthermore, exercise training improved exercise tolerance in patients, as documented by an unchanged Borg scale despite higher workloads and higher heart rates. $\dot{V}O_2$ and workload at the anaerobic threshold improved significantly in the primary training group; an improved oxygen uptake also may have occurred. The observation that patients who continued with respiratory exercise in addition to the physical training methods had the best outcome may lead to the suggestion that this therapeutic component is essential and might improve the weakness of respiratory muscles that has been described in patients with PAH.[37] Because patients received a mixture of different training methods, however, the findings of this study cannot be attributed to a single training component.

Safety

Although patients included in the study had severe PH with right heart failure (5 patients had pericardial effusion at start of rehabilitation, 1 patient was under continuous intravenous prostacyclin, 1 was on a list for lung transplantation), no adverse effects or complications of low-

dose physical training occurred in the present study. Nevertheless, we cannot exclude the possibility that exercise training may have serious adverse effects. To avoid adverse effects in the present study, exercise training was started in the hospital, where close monitoring was possible. Furthermore, the training was performed at a low-dose level. Because the therapeutic range for efficient but safe exercise training is probably small in these patients, close supervision of the exercise training seems necessary. All patients included in the present study were clinically stable for at least 3 months under advanced medical therapy, which was adjusted by medical professionals at experienced PH centers. The results of the present study indicate that respiratory and exercise training may add to an optimized medical therapy.

The results of the present study may be limited because most patients in exercise programs do not perform daily exercise, as was done in this study. The high compliance to the training program in this study may be due to the close monitoring during the 15-week study period. Furthermore, most patients with severe PH want to exercise more than they are allowed to do and used to exercise more before their diagnosis. Nevertheless, we expect that compliance to this therapy will be reduced without home-based or ambulatory-based monitoring.

Further research is required to determine the effects of exercise training on PH at earlier or later stages (WHO functional class I/II or III/IV), on the time to clinical worsening, and on survival in patients with PH, as well as to evaluate the relative efficacy of the components of the program, particularly respiratory training.

Conclusions

This prospective randomized study demonstrates the efficacy of low-dose exercise and respiratory training as add-on treatment of severe chronic PH. The effects add to the beneficial results of modern medical treatment.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Patients with severe chronic pulmonary hypertension suffer from a life-threatening disease with restricted physical capacity, impaired quality of life, and poor prognosis because of right heart failure. The present study is the first randomized prospective study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic pulmonary hypertension who were stable under medical therapy. Low-dose exercise and respiratory training were well tolerated and significantly improved scores of quality of life, 6-minute walking distance, World Health Organization functional class, peak oxygen consumption, and exercise capacity. The mean increase in walking distance observed in this study was 96 m after 15 weeks, resembling the effect of the medication specific for pulmonary hypertension. For safety reasons, exercise training should be started in the hospital and should be closely monitored in an outpatient setting. Therefore, cooperation between specialized centers for pulmonary hypertension, rehabilitation clinics and general practitioners is necessary.