Exercise Training-Based Pulmonary Rehabilitation Program Is Clinically Beneficial for Idiopathic Pulmonary Fibrosis

Baruch Vainshelboim^{a, c} Jose Oliveira^c Liora Yehoshua^a Israela Weiss^a
Benjamin Daniel Fox^{a, b} Oren Fruchter^{a, b} Mordechai Reuven Kramer^{a, b}

^aPulmonary Institute, Rabin Medical Center, Beilinson Hospital, Petach Tikva, and ^bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^cResearch Center in Physical Activity, Health and Leisure (CIAFEL), Faculty of Sport, University of Porto, Porto, Portugal

Key Words

Idiopathic pulmonary fibrosis · Cardiopulmonary exercise testing · Exercise tolerance · Functional capacity · Exercise training · Dyspnea

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic, devastating, interstitial lung disease, with few therapeutic options. IPF is characterized by pulmonary restriction, dyspnea, hypoxemia, exercise intolerance and poor quality of life (QOL). **Objectives:** We aimed to examine the effect of exercise training (ET) on clinical outcomes in IPF patients. **Methods:** A randomized controlled study included thirty-two IPF patients (aged 68 ± 8 years) who were allocated either to the ET group ($n = 15$), participating in a 12-week, twice-weekly 60-min supervised ET-based pulmonary rehabilitation program, or to a control group ($n = 17$) continuing with regular medical treatment alone. Cardiopulmonary exercise test, 6-min walking distance (6MWD) test, 30-second chair-stand test, pulmonary function tests, dyspnea and QOL were assessed at baseline and at the end of the 12-week intervention. **Results:** Significant differences were observed between the ET and the control groups in raw mean deltas ($\Delta = \text{post} - \text{pre-intervention}$): $\Delta 6\text{MWD}$, 81 m, $p < 0.001$; ΔVO_2

peak, 2.6 ml/kg/min, $p = 0.002$; $\Delta \text{work rate}$, 22 W, $p < 0.001$; $\Delta \text{anaerobic threshold}$, 3.1 ml/kg/min, $p < 0.001$, and $\Delta \text{FVC \% predicted}$, 6%, $p = 0.038$. Dyspnea, QOL and 30-second chair-stand were also improved significantly following the program. **Conclusions:** ET improves exercise tolerance, functional capacity, pulmonary function, dyspnea and QOL in patients with IPF, suggesting a short-term treatment efficacy for clinical improvement, and should be considered the standard care for IPF.

© 2014 S. Karger AG, Basel

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial lung disease (ILD) with unknown etiology occurring primarily in older adults [1, 2]. IPF has an unpredictable clinical course, usually associated with a poor prognosis [2]. Reports of mean survival rates range from 2 to 5 years from the time of diagnosis [1–3]. Estimates of IPF prevalence have varied from 2 to

This work was presented in the ‘Best Pulmonary Rehabilitation Posters Discussion’ session at the 2013 European Respiratory Society (ERS) congress in Barcelona, Spain.

29 cases per 100,000 in the general population [2]. To date, an effective treatment apart from lung transplantation remains elusive for most IPF patients [1, 2].

IPF is characterized by progressive worsening of dyspnea and lung function, impaired gas exchange and ventilatory capacity, hypoxemia and exercise intolerance [2–4]. Patients with IPF are more breathless and tend to be less physically active [5, 6]. All these manifestations have a significant negative impact on the functional capacity and quality of life (QOL) of IPF patients [3–6].

Pulmonary rehabilitation is an evidence-based standard of care for patients with chronic obstructive pulmonary diseases (COPD) [7–9]. Exercise training (ET) is a major component in these programs, since significant improvements have been reported in exercise and functional capacities, level of dyspnea and QOL among COPD patients [7–9]. As stated, exercise tolerance and QOL are severely impaired in IPF, thus rehabilitative ET may be valuable in order to maintain function in daily living activity [9, 10]. The few randomized controlled studies that have been conducted with IPF patients showed an improvement in 6-min walking distance (6MWD), dyspnea and QOL following ET interventions [11, 12]. Despite these encouraging results, extensive research is lacking with respect to ET on clinical outcomes in IPF, and the level of recommendation for this exercise treatment is weak at present [2, 10]. The aim of this randomized controlled study was to examine the effect of an ET-based pulmonary rehabilitation program on exercise tolerance, functional capacity, pulmonary function, dyspnea and QOL in patients with IPF.

Methods

Patient Recruitment and Selection

This randomized controlled study was conducted at the Rabin Medical Center, Beilinson Campus, Petach Tikva, Israel. The study was approved by the local ethics committee and was registered with clinicaltrials.gov (NCT01499745).

A clinical assessment was performed for all participants, including medical history, risk factors for IPF, exclusions other forms of ILD and a physical examination. Patients were included if they were diagnosed with IPF according to accepted clinicoradiological criteria based on the current established guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS) and had been clinically stable for the previous 3–6 months [2]. The exclusion criteria were severe comorbid illnesses, unstable cardiac disease, any neurological or orthopedic contraindications for ET, exacerbation of IPF and participation in a pulmonary rehabilitation program in the 12 months prior to recruitment. Patients treated in the Pulmonary Institute were recruited by invitation and volunteered to take part in the study. Randomization

was performed by a study coordinator uninvolved in patient assessment or treatment. Sealed envelopes containing each patient's intervention allocation were randomly opened, and the patient was assigned to the chosen arm. Written informed consent was obtained from all patients prior to participation.

The ET group participated in a 12-week, twice-weekly 60-min supervised group ET as well as continued care in the outpatient pulmonary rehabilitation program, while the control group continued with regular medical care alone. Patients allocated to the control group were allowed to participate in the pulmonary rehabilitation program after the 12-week intervention. At baseline and within 1 week post-intervention, all participants were assessed as described below.

Pulmonary Function Tests

Pulmonary function tests, including spirometry total lung capacity, maximal voluntary ventilation and diffusion capacity for carbon monoxide, were performed according to standard techniques and ATS/ERS guidelines (Zan 530; Oberthulba, Würzburg, Germany) [13–15]. All the measured parameters were presented as the percent of predicted (% pred) values of the European Community for Coal and Steel [16].

Cardiopulmonary Exercise Test

The cardiopulmonary exercise test (CPET) was performed according to established guidelines [17–20]. All tests were supervised by a physician and were held between 8.30 a.m. and 12.30 p.m. Patients were instructed to take their usual medications as prescribed. A 10–15 W/min ramp protocol was performed on an electromagnetically braked cycle ergometer (Ergoline-800S) to the patient's maximal subjective exertion level and respiratory exchange ratio ($RER \geq 1.1$) [17]. During the test, 12-lead electrocardiogram, blood pressure, pulse oximetry (SpO_2) and breath-by-breath respiratory gas exchange were recorded and monitored (Zan 600, Oberthulba). Patients were tested without supplemental oxygen during the test, and oxygen was provided immediately after the CPET as needed. All peak cardiopulmonary data were calculated and the analysis was based on the average of the last 30 s of the test. The anaerobic threshold was determined by the dual methods approach, using the V-slope method combining ventilatory equivalents (VE/VO_2 and VE/VCO_2) [17]. Breathing reserve was calculated in absolute values and also expressed in percentages of maximal voluntary ventilation [17]. Predicted values of peak oxygen consumption (VO_2 peak) and peak work rate (WR) were determined according to Jones et al. [21] based on prospective data of 100 subjects (50 males and 50 females) from the general population aged 15–71 years.

6MWD Test

The 6MWD test was set according to ATS guidelines [22]. Prior to and immediately after the test, measurements of perceived exertion using the dyspnea Borg category ratio (CR) 10 scale, heart rate and SpO_2 % (Pulse Oximeter 2500 30 EM; Nonim Medical, Minneapolis, Minn., USA) were obtained [18]. All tests were conducted without oxygen supplementation. Oxygen was provided immediately following exercise for patients who had desaturated ($SpO_2 < 88\%$), or as needed. Forty-five minutes of rest after completing the CPET was given before conducting the 6MWD test in a 35-meter corridor at the pulmonary unit within the hospital.

30-Second Chair-Stand Test of Leg Strength

At least 20–30 min of rest were allowed after completing the 6MWD test and before performing this test according to guidelines [23]. The subject was encouraged to complete as many full stands as possible from the sitting position on the 43-cm-high chair within the 30 s [23].

Dyspnea and Health-Related QOL

At baseline and after 12 weeks of intervention, prior to the exercise examinations, all patients fulfilled the modified medical research council (mMRC) scale criteria for dyspnea evaluation [24, 25]. In addition, a validated St. George's Respiratory Questionnaire (SGRQ) for IPF was also completed for QOL evaluation [26, 27].

ET Program

The program was conducted according to general ET recommendations for respiratory disease patients [18, 28]. The program continued for 12 weeks, twice-weekly with 60-min group exercise sessions in the pulmonary unit. The exercise sessions were instructed by a clinical exercise physiologist, a physiotherapist and supervised by a respiratory nurse and study physician.

The ET program consisted of two 6-week progressive blocks. In the first block participants exercised using the interval training method by increasing the duration of work to rest ratio. Each session began with 5- to 8-min warm-up exercises (calisthenics), short active stretching and deep breathing exercises. The main part of the exercise session comprised 30 min of aerobic interval training (treadmill walking, leg-cycling and step climbing in a continuous sequential manner). The program began with bouts of 5 min, followed by 1 min of passive rest (interval), for 5 repetitions (5 min bout + 1 min rest, repeated 5 times). The progression of the training program included adding 1 min to the duration of each bout in each session, until reaching 15 min of continuous exercise, thus maintaining the time frame of 30 min of aerobic activity. Exercise intensity in the first block for cycling was set at 50–60% of peak WR achieved during the CPET, and 70–80% of individual average walking speed measured during the 6MWD test. In addition, during the first sessions the workload was adjusted individually using the Borg CR 10 scale on the level of 3–5 [18]. Additionally, a specific bout of self-paced walking for 5–8 min in a 35-meter corridor within the pulmonary unit was conducted in each session for functional transfer adaptation. Ten minutes of resistance training with dumbbells and training for the upper and lower body were also included. One set of 12–15 repetitions was performed at moderate intensity (3–5 on Borg CR 10 scale) with 1 min of rest between the sets for 4–6 exercises (wall push-ups, chair squat, dumbbells shoulder press, dumbbells biceps curls, dumbbells arm extension and abdominal curl-ups). In addition, 5 min of flexibility training was conducted at the end of each session. One set of 4–5 stretching exercises was performed for 15–30 s (seated single leg hamstring stretch, standing quadriceps stretch, chest stretch, overhead reach stretch and wall cat stretch) [18].

In the second block the duration of the exercise bouts was maintained and further increased up to 20 min of continuous aerobic endurance training. The intensity was increased up to 60–70% of peak WR in cycling and 80–90% of individual average walking speed for treadmill walking and corridor walking. Stair climbing for 3–5 min within the hospital was added to each session. In addition, resistance and flexibility training were maintained and the

overall load was increased. Two sets of 10–12 repetitions with 45 s of rest between the sets for resistance and 2 sets of 15–30 s for stretching exercises at Borg CR 10 scale 4–6 perceived exertion level were conducted [18].

During all exercise sessions patients were monitored for blood pressure, SpO₂, heart rate and symptoms. Oxygen supplementation was provided for patients on request or following desaturation (SpO₂ <88%) during exercise. During the sessions patients were also educated for symptom management and encouraged to increase their physical activity levels beyond the program on non-training days.

Primary and Secondary Outcomes

The primary outcomes were changes in 6MWD and VO₂ peak. The secondary outcomes were changes in pulmonary function, ventilatory responses, dyspnea, 30-second chair-stand test and SGRQ. A power analysis was performed to calculate the sample size with 95% probability and 80% power for detecting the mean difference ≥ 50 m in one primary outcome (6MWD) between the groups and time effect based on previous IPF data [29]. The analysis revealed that a total of 30 participants (15 in each group) was needed [30].

Statistical Analysis

All clinical and physiological parameters were presented as mean $\pm$ SD. Patient baseline characteristics, including all primary and secondary parameters and delta changes from baseline (Δ = post- – pre-intervention) were compared between the ET and control groups by independent two-sample t test and χ^2 test for nonparametric variables. Exploratory data analysis used Pearson's correlation coefficient for deltas between primary and secondary outcomes in the ET group. The statistical analyses were conducted using SPSS v.17 software (SPSS, Chicago, Ill., USA). The significance level was set at $p < 0.05$.

Results

Between January and December 2012, 38 IPF patients were screened and 34 were recruited and randomly assigned to the ET group ($n = 18$) or control group ($n = 16$). During the 12-week intervention, 1 patient in the ET group dropped out due to an acute IPF exacerbation. In the control group, 1 patient withdrew consent (fig. 1).

Thirty-two patients completed the study with baseline and post-12-week measurements. All patients in the ET group participated in at least 18 exercise sessions (75% of the program; mean 22.5 ± 2.2) with an overall adherence rate of 90%. There were no serious adverse events during the program. Five patients from the ET group required supplemental oxygen during the exercise sessions. Baseline characteristics and physiological data of the ET ($n = 15$) and the control groups ($n = 17$) are shown in table 1. At baseline there were no differences between the groups with respect to patient characteristics, comorbidities,

Fig. 1. Flowchart of the study design.

physiological and clinical parameters or medication. Thirteen patients in the control group and 9 patients in the ET group were treated with corticosteroids, without differences between the groups ($p = 0.316$). Two patients from the control and 1 patient from the ET group were pirfenidone users, and there was no change in medication during the study period.

Following the intervention, the primary and the secondary outcomes were achieved in our study. Compared to the control group, the ET group improved their exercise tolerance (mean differences of raw deltas): ΔVO_2 peak, 2.6 ml/kg/min (95% CI 1–4.1, $p = 0.002$); functional capacity: $\Delta 6\text{MWD}$, 81 m (95% CI 39–124, $p < 0.001$); leg strength: $\Delta 30\text{-second chair-stand test}$, 4.1 stands (95% CI 2.3–5.9, $p < 0.001$); pulmonary function: $\Delta\text{FVC \% pred}$, 6% (95% CI 0.4–12, $p < 0.038$); dyspnea levels: ΔmMRC , –1.1 units (95% CI –1.6 to –0.5, $p < 0.001$), and QOL: ΔSGRQ , –9.7 points (95% CI –13 to –6, $p < 0.001$; table 2; fig. 2, 3). In addition, 9 out of 15 patients in the ET group improved both their VO_2 peak and mMRC. Exploratory analysis, including exercise, pulmonary and QOL parameters among the ET group, revealed significant associations between several outcomes (table 3).

Discussion

In the present randomized controlled study we examined the effect of a 12-week ET-based pulmonary rehabilitation program on clinical and physiological outcomes in IPF patients. The results show that supervised group ET improves exercise tolerance, functional capacity, leg strength, pulmonary function, ventilatory responses, dyspnea and QOL in patients with IPF, while a worsening trend was observed in the control group. With our program we achieved improvements beyond the minimal clinically important difference for 6MWD (24–45 m) and SGRQ (5–8 points), as was previously described in IPF patients (fig. 2, 3) [27, 31]. These data have important clinical significance and practical implications, since proven and efficient treatments for IPF are limited.

To the best of our knowledge this is the first randomized controlled study of ET with IPF patients showing significant improvements in VO_2 peak measured by CPET, which is considered the gold-standard measurement for cardiorespiratory capacity [19, 20]. Additionally, the results show that patients who completed the program demonstrated improvements in resting and exercise pulmonary function, reduced dyspnea levels, im-

Table 1. Baseline characteristics of the study population (n = 32)

	Control (n = 17)	ET (n = 15)	p value
Age, years	66±9	68.8±6	0.337
Male/female	11/6 (65/35)	10/5 (67/33)	0.907
BMI	28.8±3.8	28.3±3.5	0.686
Time from the diagnosis of IPF, years	1.9±3.1	3±3.7	0.379
Patients with smoking history	9 (53)	10 (67)	0.430
<i>Supplemental oxygen users</i>			
Rest	1 (6)	2 (13)	0.471
Exertion	4 (24)	5 (33)	0.538
<i>Comorbidities</i>			
Pulmonary hypertension according to echocardiography	6 (35)	5 (33)	0.907
Coronary arterial disease	6 (35)	7 (47)	0.513
Systemic hypertension	11 (65)	12 (80)	0.337
COPD emphysema	5 (29)	2 (13)	0.272
Type 2 diabetes	4 (24)	7 (47)	0.169
Osteoporosis	3 (18)	2 (13)	0.093
<i>Resting cardiopulmonary parameters</i>			
FVC % pred	70.1±17.4	66.1±14.8	0.487
FEV ₁ % pred	71.8±20.1	68.5±15.8	0.607
FEV ₁ /FVC % pred	107.5±11.4	109.3±10.5	0.635
TLC % pred	68.5±14	64.3±13	0.231
DLCO % pred	53.2±12.2	48.6±17.2	0.393
MVV, l/min	78.9±28.6	69.8±18.3	0.301
Systolic pulmonary arterial pressure, mm Hg	32.4±9.2	32.5±7	0.994
Heart rate, beats/min	70.4±15	74.8±12	0.373
Systolic blood pressure, mm Hg	112.8±17.5	113.4±13.7	0.911
Diastolic blood pressure, mm Hg	78.3±10.6	70.7±11	0.054
SpO ₂ , %	97.1±1.7	96.5±2.3	0.419
<i>Exercise capacity, dyspnea and QOL</i>			
Peak WR, W	83.7±33.1	71.5±27.9	0.265
VO ₂ peak, ml/kg/min	14.3±3.1	13.6±3.4	0.539
30-second chair stand, number of stands	13.7±4.5	11.5±2.8	0.117
6MWD, m	513±108	471±108	0.283
SpO ₂ after 6MWD test, %	85.2±8.4	83.7±8	0.609
Borg dyspnea CR 10 scale after 6MWD test	4.3±1.9	4.4±2.5	0.864
mMRC dyspnea scale (0–4)	1.7±0.9	1.9±0.9	0.684
SGRQ total score	18±4.8	20.6±6.7	0.204

Values are presented as means ± SD or n (%). TLC = Total lung capacity; DLCO = diffusion capacity for carbon monoxide; MVV = maximal voluntary ventilation.

proved QOL and functional exercise capacity. These are novel and unexpected findings among IPF subjects, especially since pulmonary function and VO₂ peak do not typically improve with exercise interventions in other respiratory diseases, such as COPD [32].

Previous randomized controlled studies with ILD and IPF patients using an ET program showed improve-

ments only in the 6MWD test, which is a test performed at submaximal intensity [11, 12]. In the present study, patients were tested with CPET, 6MWD test and 30-second chair-stand test, and those who participated in supervised ET improved both their submaximal (anaerobic threshold and 6MWD) and maximal exertion (VO₂ peak and peak WR) levels, and leg strength. Our find-

Table 2. Mean changes from baseline to 12 weeks (raw differences) and mean differences of changes between the ET and the control groups for primary and secondary parameters in IPF patients

	Control (n = 17)	ET (n = 15)	Mean difference (95% CI)	p value
<i>Pulmonary function test</i>				
ΔFVC % pred	-3±7.6	3±8.4	6 (0.35 to 11.9)*	0.038
ΔFEV ₁ % pred	-0.9±11.5	6.3±11.3	7.2 (-1 to 15.5)	0.085
ΔFEV ₁ /FVC % pred	0.12±6	0.66±6.1	0.55 (-3.8 to 4.9)	0.799
ΔTLC % pred	-0.2±83	2.4±10	2.6 (-4.1 to 9.3)	0.439
ΔDLCO % pred	-1.5±10.6	-0.1±6.8	1.38 (-5.3 to 8.1)	0.676
ΔMVV, l/min	-6±11.5	8.2±13.9	14.2 (5 to 23.4)*	0.003
ΔSpO ₂ rest, %	-0.9±1.6	0.13±1.7	1 (-0.17 to 2.2)	0.092
<i>Cardiovascular parameters</i>				
ΔHeart rate rest, beats/min	4.4±10	-2.4±9.1	-6.8 (-13.8 to -0.16)	0.055
ΔSystolic blood pressure rest, mm Hg	-1.3±19.2	-2.9±13.6	-1.6 (-13.9 to 10.6)	0.786
ΔDiastolic blood pressure rest, mm Hg	1±14.4	1.5±7.1	0.5 (-7.8 to 8.9)	0.897
ΔPeak heart rate, beats/min	0.7±9.1	4.2±9.3	3.6 (-3.1 to 10.2)	0.283
ΔPeak systolic blood pressure, mm Hg	-5±23	7.3±24.6	12.3 (-4.9 to 29.5)	0.154
ΔPeak diastolic blood pressure, mm Hg	5.6±21.6	5.9±14.4	0.3 (-13.1 to 13.8)	0.959
ΔPeak O ₂ pulse, ml/beat	-0.18±1.2	0.93±1.5	1.1 (0.12 to 2.1)*	0.028
<i>Exercise tolerance</i>				
ΔPeak WR, W	-6.7±9.5	15.4±9.8	22.1 (15.1 to 29.1)**	<0.001
ΔVO ₂ peak, ml/kg/min	-0.5±2	2.1±2.3	2.6 (1 to 4.1)*	0.002
ΔVO ₂ peak % pred	-1.8±9.2	8.9±9.3	10.7 (4 to 17.4)*	0.003
ΔAnaerobic threshold, ml/kg/min	-0.72±1.8	2.4±2.4	3.1 (1.6 to 4.6)**	<0.001
<i>Respiratory parameters</i>				
ΔPeak tidal volume, l/breath	-0.94±0.1	0.16±0.2	0.25 (0.13 to 0.37)**	<0.001
ΔPeak breathing frequency, breaths/min	0.35±5.9	1.4±6.2	1 (-3.3 to 5.4)	0.629
ΔVE peak, l/min	-4.5±6.7	7±6.9	11.6 (6.7 to 16.5)**	<0.001
ΔBreathing reserve (MVV - VE peak), l	-1.4±11.8	1.2±14.7	2.6 (-6.9 to 12.2)	0.580
ΔBreathing reserve % (VE peak/MVV)	0.3±13.7	3.4±15.7	3.1 (-7.5 to 13.7)	0.558
ΔPeak VE/VO ₂ (ratio)	-2.2±5.7	3.2±6.2	5.5 (1.2 to 9.7)*	0.014
ΔPeak VE/VCO ₂ (ratio)	0.5±3.6	0.4±4.8	-0.1 (-3.1 to 2.9)	0.947
ΔPeak VD/VT, %	0.76±3.2	-0.7±2.2	-1.4 (-3.4 to 0.6)	0.155
ΔPeak SpO ₂ , %	-1.4±5.4	-0.73±4.3	0.7 (-2.9 to 4.2)	0.700
<i>Functional capacity, dyspnea and QOL</i>				
Δ6MWD, m	-10.6±35.4	70.4±77	81 (38.7 to 123.5)**	<0.001
ΔBorg dyspnea CR 10 scale after 6MWD test	0.47±2	0.4±1.7	-0.7 (-1.4 to 1.3)	0.916
ΔSpO ₂ after 6MWT, %	-0.3±6	-1.6±3.6	-1.3 (-4.9 to -2.3)	0.465
Δ30-second chair stand, number of stands	-0.4±2.5	3.7±2.6	4.1 (2.3 to 5.9)**	<0.001
ΔmMRC (0-4)	0.35±0.7	-0.73±0.8	-1.1 (-1.62 to -0.54)**	<0.001
<i>ΔSGRQ</i>				
Total score	2.8±3.6	-6.9±6.5	-9.7 (-13.4 to -5.9)**	<0.001
Symptoms	8.9±15	-14.7±22.8	-23.5 (-37.4 to -9.7)*	0.002
Impact	2.5±3.7	-7.6±5.4	-10.1 (-13.7 to -6.5)**	<0.001
Activity	-0.04±1.4	-1.4±3.3	-1.34 (-3.1 to 0.45)	0.137

Values are presented as means ± SD. Significant differences between the groups: * p < 0.05; ** p < 0.001. TLC = Total lung capacity; DLCO = diffusion capacity for carbon monoxide; VE = minute ventilation; MVV = maximal voluntary ventilation; VE/VO₂ = ventilatory equivalent for oxygen consumption; VE/VCO₂ = ventilatory equivalent for carbon dioxide; VD/VT = dead space-to-tidal volume ratio.

Fig. 2. Exercise tolerance and functional capacity after the 12-week intervention in IPF patients. Data are presented as means and SD. Significant differences between the groups: * $p < 0.05$; ** $p < 0.001$.

Table 3. Correlations between the changes from baseline to 12 weeks for primary and secondary outcomes in the ET group

	$\Delta 6\text{MWD}$ (m)	ΔVO_2 peak (ml/kg/min)	$\Delta 30$ -second chair stand test (number of stands)	ΔSGRQ total score	ΔFVC % pred	$\Delta \text{Peak VT}$ (l/breath)
$\Delta 6\text{MWD}$ (m)	1	$r = 0.534^*$ $p = 0.04$	$r = 0.411$ $p = 0.128$	$r = -0.543^*$ $p = 0.018$	$r = 0.722^*$ $p = 0.002$	$r = 0.444$ $p = 0.097$
ΔVO_2 peak (ml/kg/min)	$r = 0.534^*$ $p = 0.04$	1	$r = 0.145$ $p = 0.605$	$r = -0.067$ $p = 0.407$	$r = 0.513$ $p = 0.051$	$r = 0.775^*$ $p = 0.001$
$\Delta 30$ -second chair stand test (number of stands)	$r = 0.411$ $p = 0.128$	$r = 0.145$ $p = 0.605$	1	$r = -0.175$ $p = 0.532$	$r = 0.094$ $p = 0.739$	$r = 0.132$ $p = 0.639$
ΔSGRQ total score	$r = -0.543^*$ $p = 0.018$	$r = -0.067$ $p = 0.407$	$r = -0.175$ $p = 0.532$	1	$r = -0.683^*$ $p = 0.005$	$r = -0.334$ $p = 0.223$
ΔFVC % pred	$r = 0.722^*$ $p = 0.002$	$r = 0.513$ $p = 0.051$	$r = 0.094$ $p = 0.739$	$r = -0.683^*$ $p = 0.005$	1	$r = 0.404$ $p = 0.135$
$\Delta \text{Peak VT}$ (l/breath)	$r = 0.444$ $p = 0.097$	$r = 0.775^*$ $p = 0.001$	$r = 0.132$ $p = 0.639$	$r = -0.334$ $p = 0.223$	$r = 0.404$ $p = 0.135$	1

* Significant correlation. VT = Tidal volume.

ings are consistent with those of Holland et al. [11] but extend further with additional outcomes they did not observe, such as improved VO_2 peak and pulmonary function. In the study by Holland et al. [11] the ET program duration was only 8 weeks compared to 12 weeks in our study, and at baseline the patients had more severe levels of dyspnea (mMRC = 3 vs. <2 among our patients) and lower functional capacity (6MWD = 354 vs. 493 m, respectively) [11]. Possibly the shorter program duration and severity of the IPF patients in their study had an impact on patient ability to adapt to the same extent after the ET program. This was previously demonstrated among COPD and ILD patients, suggesting greater improvement in longer pulmonary rehabilitation programs [7, 10], and supported by Kozu et al. [33], who showed that the dyspnea severity and disability level of IPF patients at baseline has a negative impact on the degree of improvement following pulmonary rehabilitation. In contrast, Huppmann et al. [34] and Ryerson et al. [35] showed higher improvement rates in 6MWD following pulmonary rehabilitation programs in the most deconditioned ILD patients and those with low baseline values, respectively [34, 35]. Our findings are also in concordance with a recent report by Arizono et al. [36], who also showed significant improvements of CPET parameters in IPF patients, but not VO_2 peak. Following the intervention we also found significant improvements in pulmonary and ventilatory parameters in the

ET group (table 2). Despite the fact that these enhancements seem to be beneficial for restrictive pulmonary pathophysiology of IPF, the MCID for these variables is unknown at present.

To date the prognostic value of pulmonary rehabilitation among IPF patients is unknown. Only one randomized controlled study included a follow-up period after an 8-week exercise program, and did not find benefits in survival [11]. We speculate that ET might have an additional benefit on IPF prognosis, since our intervention caused significant improvements in FVC % pred, VO_2 peak, 6MWD and dyspnea levels, which have been proposed as prognostic parameters for increased risk of mortality in IPF patients [2, 37–41]. Enhancement in these parameters may increase physiological reserves, delay the clinical course and slow the progression of the disease. This issue must be ascertained in long-term studies.

The effect of ET on improvement of physiological and clinical outcomes in IPF can be explained by several mechanisms. IPF patients usually present impaired lung compliance and inefficient breathing patterns as part of the restrictive pathophysiology [3, 4, 42]. It is possible that repetitive stimulus of high ventilatory demands during exercise sessions, chest expansion during deep-breathing exercises and stretching of the thoracic muscles that were used in our program resulted in a more efficient breathing pattern, improved strength of respiratory muscles, enhanced pleural elasticity and pulmonary compli-

ance within the lung tissue, and decreased dyspnea perception following the ET program [4, 10, 42]. This is consistent with a recent review suggesting a beneficial effect of thoracic expansion and stretching on pulmonary restriction in IPF [10]. Part of these physiological changes may have occurred as a result of our treatment since improvements in pulmonary function, ventilatory responses, anaerobic threshold, VO_2 peak, mMRC dyspnea scale and QOL were indeed demonstrated among the ET group, although pulmonary morphological adaptations were not tested objectively in the current study and need to be ascertained in future studies.

Most patients in the ET group had improvements in exercise tolerance, ventilatory responses and mMRC, which were strengthened by the relationship between exercise and ventilatory capacities and exertion dyspnea, respectively. This is in line with Manali et al. [43] who reported a significant correlation between mMRC and VO_2 peak in IPF patients. The increase in exercise capacity probably resulted in less dyspnea in submaximal exercises such as daily living activities which were demonstrated by a declined mMRC after the program. The enhancement in ventilatory responses that occurred after the exercise program could have increased alveolar oxygen tension and improvements in alveoli ventilation-to-perfusion mismatch, resulting in an increase in VO_2 peak [3, 4, 42]. This was partially supported by the trend of decline in dead space-to-tidal volume ratio in the ET group. Although most of our patients were not limited by ventilation and had a normal breathing reserve, ventilatory enhancements seem to be closely related to the improvements in aerobic capacity. In the exploratory analysis of the ET group we noted that improvements in VO_2 peak were highly correlated with the improvement in peak tidal volume (table 3). Furthermore, $\Delta 6\text{MWD}$ was significantly associated with ΔFVC % pred and with ΔSGRQ total score, which is consistent with the results of Nishiyama et al. [12], who showed improvement in SGRQ associated with the improvement in 6MWD. In addition, ΔFVC % pred was significantly associated with ΔSGRQ total score, which is in agreement with Tzanakis et al. [44], who also demonstrated a significant correlation between FVC and SGRQ.

Thus, our data suggest that most of the improvement in VO_2 peak occurred due to an enhancement in peak tidal volume, although it is also likely that improvement in skeletal muscle and cardiovascular adaptations contributed to some extent to this improvement, evident by an improvement in the 30-second chair-stand test and O_2

pulse, respectively [5]. However, significant correlations between these parameters and VO_2 peak or 6MWD were not detected. Improvements in walking functional capacity might have a beneficial effect on pulmonary function (FVC % pred) and QOL (SGRQ total score), which were closely related to the improvement in 6MWD. Furthermore, our data indicates that improvement in FVC % pred may play a role as a potential mediator for other clinical outcomes (both exercise and QOL) in IPF and should be further examined. Nevertheless, it is also important to acknowledge that some improvements among the ET group might be related to the placebo effect of regular medical visits (twice a week) to the pulmonary unit.

Our study has several limitations. Firstly, sample size was relatively small for each group of patients and somewhat heterogeneous; nevertheless, the study was adequately powered. The number of participants yielded enough statistical power for detecting significant changes in one primary outcome (6MWD). Secondly, most of our participants had moderate pulmonary restriction (mean FVC% pred 68 ± 16) and our results are possibly applicable only to patients with this degree of IPF severity.

In conclusion, our results strengthen the evidence for the role of an ET-based pulmonary rehabilitation program in IPF patients. ET improves exercise tolerance, functional capacity, leg strength, pulmonary function, ventilatory responses, dyspnea and QOL in patients with IPF. Short-term supervised group ET can clinically improve several IPF manifestations. We suggest including supervised group ET for IPF patients as part of the standard comprehensive treatment. More research is warranted regarding the long-term prognostic impact of this treatment on IPF.

Financial Disclosure and Conflicts of Interest

All authors have no financial or other potential conflicts of interest to disclose.

Acknowledgements

The authors thank the study coordinators and nurses of the Pulmonary Institute for their help in the recruitment process, and the pulmonary function technicians for their professional assistance in the study. Finally, the authors extend thanks to Mr. Mike Garmise and Ms. Dalia Dawn Orkin for their important English language contributions and to Dr. Michal Arnon for her statistical assistance.

References

- Frankel SK, Schwarz MI: Update in idiopathic pulmonary fibrosis. *Curr Opin Pulm Med* 2009;15:463–469.
- Raghu G, Collard HR, Egan JJ, et al: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- Meltzer EB, Noble PW: Idiopathic pulmonary fibrosis. *Orphanet J Rare Dis* 2008;3:8.
- American Thoracic Society (ATS), European Respiratory Society (ERS): Idiopathic pulmonary fibrosis: diagnosis and treatment – international consensus statement. *Am J Respir Crit Care Med* 2000;161:646–664.
- Swigris JJ, Brown KK, Make BJ, Wamboldt FS: Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. *Respir Med* 2008;102:1675–1680.
- Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK: Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. *Thorax* 2005;60:588–594.
- Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, Make B, Rochester CL, Zuwallack R, Herreras C: Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest* 2007;131:4S–42S.
- Nici L, Donner C, Wouters E, et al: American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390–1413.
- Spruit MA, Singh SJ, Garvey C, et al: An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13–e64.
- Kenn K, Gloeckl R, Behr J: Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis: a review. *Respiration* 2013;86:89–99.
- Holland AE, Hill CJ, Conron M, Munro P, McDonald CF: Short-term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008;63:549–554.
- Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H: Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008;13:394–399.
- Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720–735.
- Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J: General considerations for lung function testing. *Eur Respir J* 2005;26:153–161.
- Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D, Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G: Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows: report working party standardization of lung function tests, European Community for Steel and Coal. Official statement of the European respiratory society. *Eur Respir J Suppl* 1993;16:5–40.
- American Thoracic Society, American College of Chest Physicians: ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
- Pescatello LS, et al (eds): ACSM's guidelines for exercise testing and prescription, ed 8. Philadelphia, Lippincott Williams & Wilkins, 2010, pp 60–271.
- Ferrazza AM, Martolini D, Valli G, Palange P: Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. *Respiration* 2009;77:3–17.
- Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, O'Donnell DE, Puente-Maestu L, Schols AM, Singh S, Whipp BJ: Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007;29:185–209.
- Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N: Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;131:700–708.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
- Rikli RE, Jones CJ: The Senior Fitness Test Manual. Champaign, Human Kinetics, 2001, pp 111–151.
- Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. *Chest* 1988;93:580–586.
- Papiris SA, Daniil ZD, Malagari K, Kapotsis GE, Sotiropoulou C, Milic-Emili J, Roussos C: The medical research council dyspnea scale in the estimation of disease severity in idiopathic pulmonary fibrosis. *Respir Med* 2005;99:755–761.
- Peng S, Li Z, Kang J, Hou X: Cross-sectional and longitudinal construct validity of the Saint George's Respiratory Questionnaire in patients with IPF. *Respirology* 2008;13:871–879.
- Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, Wamboldt FS: The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med* 2010;104:296–304.
- Jenkins S, Hill K, Cecins NM: State of the art: how to set up a pulmonary rehabilitation program. *Respirology* 2010;15:1157–1173.
- Swigris JJ, Wamboldt FS, Behr J, du Bois RM, King TE, Raghu G, Brown KK: The 6-minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. *Thorax* 2010;65:173–177.
- Florey CD: Sample size for beginners. *BMJ* 1993;306:1181–1184.
- du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE Jr: Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2011;183:1231–1237.
- Casaburi R, ZuWallack R: Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *N Engl J Med* 2009;360:1329–1335.
- Kozu R, Jenkins S, Senjyu H: Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2011;16:1196–1202.
- Huppmann P, Szczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, Behr J, Kenn K: Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J* 2013;42:444–453.
- Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C: Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med* 2014;108:203–210.
- Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K: Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respir Care* 2014;59:1108–1115.
- Lee SH, Shim HS, Cho SH, Kim SY, Lee SK, Son JY, Jung JY, Kim EY, Lim JE, Lee KJ, Park BH, Kang YA, Kim YS, Kim SK, Chang J, Park MS: Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic, and molecular aspects. *Sarcoidosis Vasc Diffuse Lung Dis* 2011;28:102–112.

- 38 Fell CD, Liu LX, Motika C, Kazerooni EA, Gross BH, Travis WD, Colby TV, Murray S, Toews GB, Martinez FJ, Flaherty KR: The prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:402–407.
- 39 Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, Taglieri A, Mezzasalma F, Rottoli P, Saltini C, Rogliani P: Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. *Eur Respir J* 2012;40:101–109.
- 40 Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S: Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. *Respir Med* 2009;103:117–123.
- 41 du Bois RM, Albera C, Bradford WZ, Costabel U, Leff JA, Noble PW, Sahn SA, Valeyre D, Weycker D, King TE Jr: 6-Min walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2014;43:1421–1429.
- 42 Lama VN, Martinez FJ: Resting and exercise physiology in interstitial lung diseases. *Clin Chest Med* 2004;25:435–453.
- 43 Manali ED, Lyberopoulos P, Triantafyllidou C, Kolilekas LF, Sotiropoulou C, Milic-Emili J, Roussos C, Papiris SA: MRC chronic dyspnea scale: relationships with cardiopulmonary exercise testing and 6-min walk test in idiopathic pulmonary fibrosis patients: a prospective study. *BMC Pulm Med* 2010;10:32.
- 44 Tzanakis N, Samiou M, Lambiri I, Antoniou K, Siafakas N, Bouros D: Evaluation of health-related quality-of-life and dyspnea scales in patients with idiopathic pulmonary fibrosis: correlation with pulmonary function tests. *Eur J Intern Med* 2005;16:105–112.