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Exercise Limitation in IPF Patients: A Randomized Trial of Pulmonary Rehabilitation

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Abstract
Background Patients with idiopathic pulmonary fibrosis (IPF) have severely limited exercise capacity due to dyspnea, hypoxemia, and abnormal lung mechanics. This pilot study was designed to determine whether pulmonary rehabilitation were efficacious in improving the 6-min walk test (6-MWT) distance, exercise oxygen uptake, respiratory muscle strength [maximum inspiratory pressure (MIP)], and dyspnea in patients with IPF. Underlying physiological mechanisms and effects of the intervention were investigated.
Methods Subjects were randomly assigned to a 3-month pulmonary rehabilitation program ($n = 11$) or to a control group ($n = 10$). All subjects initially underwent the 6-MWT and constant load exercise gas exchange studies.
Results Subjects in the rehabilitation group increased treadmill exercise [metabolic equivalent of task-minutes] over the first 14 sessions. Beneficial effects on physical function resulted in those who completed rehabilitation. Subjects who completed the program increased cycle ergometer time and maintained exercise oxygen consumption (exercise VO_2) at the baseline level over 3 months, while the control group suffered a significant decrease in exercise VO_2. Rehabilitation subjects also increased their MIP. Plasma lactate doubled and brain natriuretic peptide levels increased significantly after exercise, as did the plasma amino acids glutamic acid, arginine, histidine, and methionine. These changes were associated with significant decreases in arterial oxygen saturation and increases in 15-F_{2t}-isoprostanes after exercise.
Conclusions Pulmonary rehabilitation effectively maintained exercise oxygen uptake over 3 months and lengthened constant load exercise time in patients with moderately severe IPF. Exercise endurance on cycle ergometry testing was limited by dyspnea and severe hypoxemia associated with systemic oxidant stress.

Keywords Idiopathic pulmonary fibrosis · Exercise · Rehabilitation · Oxidant stress

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Introduction

Idiopathic pulmonary fibrosis (IPF) is an often fatal process characterized by onset in middle age, progressive scarring of the lungs in a usual interstitial pneumonia (UIP) pattern, and the absence of systemic disease that would explain

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Clinical presentation consistent with IPF with onset between 3 and 48 months prior to screening	1. RVSP >55 mmHg based on echocardiography, or TR velocity ≥3.2 m/s
2. Diagnosis made by HRCT scan showing highly probable IPF	2. Severe heart failure (NYHA class III or IV or LVEF <45 %)
3. RVSP ≤55 mmHg based on echocardiography, and absence of decompensated right heart failure (NYHA class I or II acceptable)	3. Six-minute walk distance < 150 m or > 500 m
4. Age 40 through 80 years, inclusive	4. FEV_1/FVC ratio <0.7 at screening (post-bronchodilator)
5. Abnormal pulmonary function tests (FVC 40–90 % predicted or D_LCO 30–90 % predicted or impaired gas exchange with rest or exercise)	5. Residual volume >100 % predicted
6. Six-minute walk distance ≥150 m and ≤500 m	6. Any condition other than IPF likely to result in the death of the patient within the next 2 years
7. Worsening as demonstrated by any one of the following within the past year: >10 % decrease in percent predicted forced vital capacity or worsening dyspnea at rest or upon exertion, based on history	7. History of unstable or deteriorating cardiac or neurological disease
8. Absence of clinical features suggesting infection, neoplasm, sarcoidosis, or collagen-vascular disease	8. Pregnancy or lactation. Patients who are (a) pregnant or (b) breast feeding are excluded from the study
	9. Current treatment with corticosteroids, Cytoxan, azathioprine, colchicine, pirfenidone, antitumor necrosis factor therapy, or endothelin receptor blockers. Prior treatment permitted, but at least 4 weeks of treatment washout prior to inclusion in this study is required
	10. Degenerative arthritis, cerebrovascular accident, or other limitation to mobility preventing completion of the 6-MWT
	11. Oxygen saturation on room air <80 % at rest

lung scarring [1]. No therapies, save lung transplantation, are effective in prolonging lives of IPF patients [2].

Exercise limitation, accompanied by dyspnea, is the cardinal manifestation of IPF [3]. Abnormal lung mechanics limit ventilatory adaptation to exercise and often lead to a less efficient, rapid, and shallow breathing pattern [4]. Pulmonary hypertension is also present in nearly one half of transplant-candidate IPF patients who undergo cardiac catheterization [5]. Increased pulmonary vascular resistance in IPF appears to be poorly amenable to therapy [6].

Both chronic and intermittent hypoxia impair skeletal muscle function through a number of mechanisms, including oxidative enzyme inhibition, amino acid efflux, and increased production of reactive nitrogen and oxygen species (ROS) [7]. Systemic oxidant stress occurs during low-level exercise in IPF patients, as we have shown by increased urine 15-F_{2t}-isoprostanes (isoprostanes) and decreased plasma total antioxidant capacity [8].

Pulmonary rehabilitation, defined as a variable combination of aerobic and strengthening exercises, quite clearly improves 6-min walk test (6-MWT) distance and well-being in patients with chronic obstructive pulmonary diseases (COPD) [9]. High-quality data showing similar benefits in IPF patients are sparse [10–12]. A recent retrospective study of 402 patients with interstitial lung disease (50 % had IPF) showed that intense inpatient rehabilitation resulted in a 46 ± 3 (SEM)-m average increase in 6-MWT distance [13].

Our goals for this study were to test whether outpatient pulmonary rehabilitation for 12 weeks improved 6-MWT distance, exercise oxygen consumption (exercise VO_2), treadmill exercise [metabolic equivalent of task (MET)-minutes], maximum inspiratory pressure (MIP), and dyspnea (Borg dyspnea index) in subjects who met all contemporary criteria for IPF [14].

Methods

Study Participants

This study was approved by the Miami Veterans Affairs Health System Institutional Review Board. This study is registered as clinicaltrials.gov Identifier: NCT01118221.

IPF cases were defined according to American Thoracic Society–European Respiratory Society (ATS-ERS) clinical diagnostic criteria [14]. Inclusion and exclusion criteria are presented in Table 1. Patients were screened by echocardiography at rest to estimate right ventricular systolic pressure (RVSP) [15]. High-resolution computed tomography (HRCT) scans of the chest were required to show a UIP pattern [16]. The distribution of subjects who were screened and randomized is shown in the CONSORT diagram presented in Fig. 1.

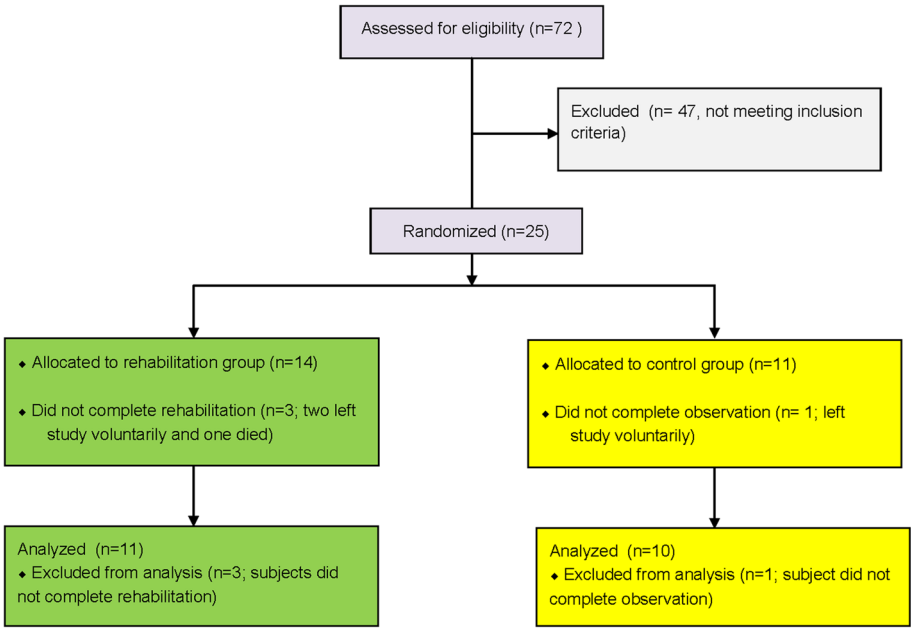

Fig. 1 Selection and disposition of subjects. We screened 72 IPF patients for eligibility and enrolled 25. Fourteen were assigned to rehabilitation and 11 to the control (observation only) group. Two rehabilitation subjects and one control subject chose to leave the trial. One rehabilitation subject died of respiratory failure during the trial. Twenty-one subjects completed the trial and their data are presented here

Experimental Design

The study was designed as a randomized, controlled, nonblinded, pilot study of the effects of pulmonary rehabilitation. The prespecified primary outcome measure of the clinical trial was the 6-MWT distance.

Exercise Testing

We used an Oxycon^{TM} Mobile portable unit (CareFusion, San Diego, CA, USA) to measure sustained exercise VO_2 and other gas exchange variables, while subjects exercised to their volitional limit at a constant load on an exercise cycle (Life Cycle 65R, Life Fitness, Schiller Park, IL, USA) [17]. This approach has been used to assess the effects of nonpharmacological interventions in patients with respiratory disease [18–20]. V_E/VCO_2 slope values, acquired from the initiation to peak exercise, were calculated using least-squares linear regression [21]. Heart rate reserve (HRR) was calculated as maximum predicted heart rate (220 − age in years/min) minus the actual peak heart rate recorded during exercise [3, 4]. Before (resting) and immediately after (post-exercise) constant-load cycle ergometry at 50 W, plasma (15-F_{2t}-isoprostanes, lactate, NT-proBNP, and AA) and urine (15-F_{2t}-isoprostanes and creatinine) samples were collected, processed, and frozen at −80 °C.

Pulmonary Function Tests

The maximum voluntary ventilation (MVV) was calculated as 35× FEV_1 [in L (liters)] [3, 4]. Maximum inspiratory (MIP) and expiratory (MEP) pressures were measured as previously described [22].

6-Min Walk Test Protocol

The 6-MWT was done and monitored as previously described [23]. Before and after the test, we recorded heart rate, oxygen saturation, and the Borg Dyspnea Index (BDI) [24].

Rehabilitation Program

Subjects in the rehabilitation group completed 24 twice-weekly 2-h rehabilitation sessions over 12 weeks. Control subjects did not participate in a rehabilitation program. Supplemental nasal oxygen was provided from a compressed gas source during exercise training to maintain SpO_2 above 88 %. Treadmill and cycling exercises were initiated at 60–80 % of the predicted maximum heart rate based on age. MET-minutes for each session were estimated and recorded [25]. Details of the rehabilitation program are presented in Table 2. Perceived breathlessness on exertion was recorded using the modified BDI before and after each exercise modality [24].

Biochemical Analyses

We quantified 15-F_{2t}-isoprostanes in plasma and urine using high-performance liquid chromatography (HPLC) tandem mass spectroscopy (MS–MS), as previously described [26, 27]. We assayed plasma free amino acids (AA) by liquid chromatography–mass spectroscopy (LC–MS) using the EZ:faast Assay (Phenomenex®, Torrance, CA, USA). The concentration of lactate in plasma samples obtained before

Table 2 Description of pulmonary rehabilitation program

Intervention	Mode	Intensity	Protocol	Duration	Frequency
Educational lectures	PowerPoint presentation and handouts		Topics included medication use, breathing techniques, exercise strategies, proper nutrition, pulmonary physiology, psychological coping mechanisms	15 min	1 session biweekly
Cardiopulmonary endurance training	Treadmill walking	Up to 80 % maximum heart rate		20 min	2 sessions/ week
Cardiopulmonary endurance training	Semirecumbent cycling	Up to 80 % maximum heart rate		10 min	2 sessions/ week
Flexibility exercises	Self-administered standing or seated	3 sets × 30 s	*Upper body* bilateral horizontal abduction pectoral stretch; lower cervical and upper thoracic stretch; thoracolumbar side bends *Lower body* knee extension stretch; knee flexion stretch; standing forward lunge	15 min	2 sessions/ week
Strength training	Self-administered standing or seated with home exercise program	Up to 3 sets × 15 repetitions Theraband (yellow, red, green, and blue)	*Session 1* biceps curls, midback row, and shoulder flexion *Session 2* chest press and triceps extension *Session 3* standing hip abduction and extension *Session 4* knee flexion and extension Then repeated.	15–30 min	2 sessions/ week

Table 3 Baseline characteristics of study participants by group

Variable	Rehabilitation group[a] ($n = 11$)	Control group[b] ($n = 10$)	*P* value
Age (years)	71 ± 6	66 ± 7	0.094
Weight (kg)	97 ± 20	92 ± 21	0.583
Height (cm)	175 ± 10	166 ± 12	0.076
FVC (% predicted)	60 ± 11	61 ± 14	0.857
FEV_1/FVC (ratio)	0.84 ± 0.04	0.86 ± 0.05	0.691
TLC (% predicted)	58 ± 8	60 ± 12	0.655
DLCO (% predicted)	44 ± 11	43 ± 11	0.837
MVV (L/min)	69 ± 16	75 ± 26	0.527
SpO_2 (%)	95 ± 3	96 ± 2	0.385
6-MWT distance (m)	361 ± 55	339 ± 109	0.575
RVSP (mmHg)	33 ± 17	37 ± 18	0.607

Data are means ± SD

[a] The exercise group completed a 12-week twice-weekly pulmonary rehabilitation program

[b] The control group did normal activities for 3 months

and after exercise was measured using standard techniques [28]. Amino terminal pro-brain natriuretic peptide (NT-proBNP) was assayed in plasma using the procedure described by Elin and Winter [29].

Statistical Analyses

Paired *t*-tests or Wilcoxon signed-rank tests were used for within-group comparisons, whereas independent-sample *t*-tests or Mann–Whitney tests were used for between-group comparisons. A generalized linear model was used to analyze trends in treadmill MET-minutes [30]. Statistical significance was defined as $P < 0.05$.

Results

Characteristics and Disposition of the Subjects

The participants' baseline characteristics are presented in Table 3. At the time of enrollment, subjects had mild to moderate restriction of lung volumes (mean ± SD FVC = 61 ± 12 % of predicted) and moderate to severe diffusion impairment (mean D_LCO = 44 ± 10 % of predicted). Eight of 11 rehabilitation and 3 of 10 control subjects were taking empirical *N*-acetyl-L-cysteine (600 mg orally three times daily) at the time of enrollment [1].

Baseline Response to Cycle Ergometry Testing

During the initial cycle ergometry, the 21 subjects achieved on average 63 ± 3 (SEM) % of their predicted MVV. The average maximum heart rate during cycle ergometry testing at baseline evaluation reached 68 ± 3 (SEM) % of

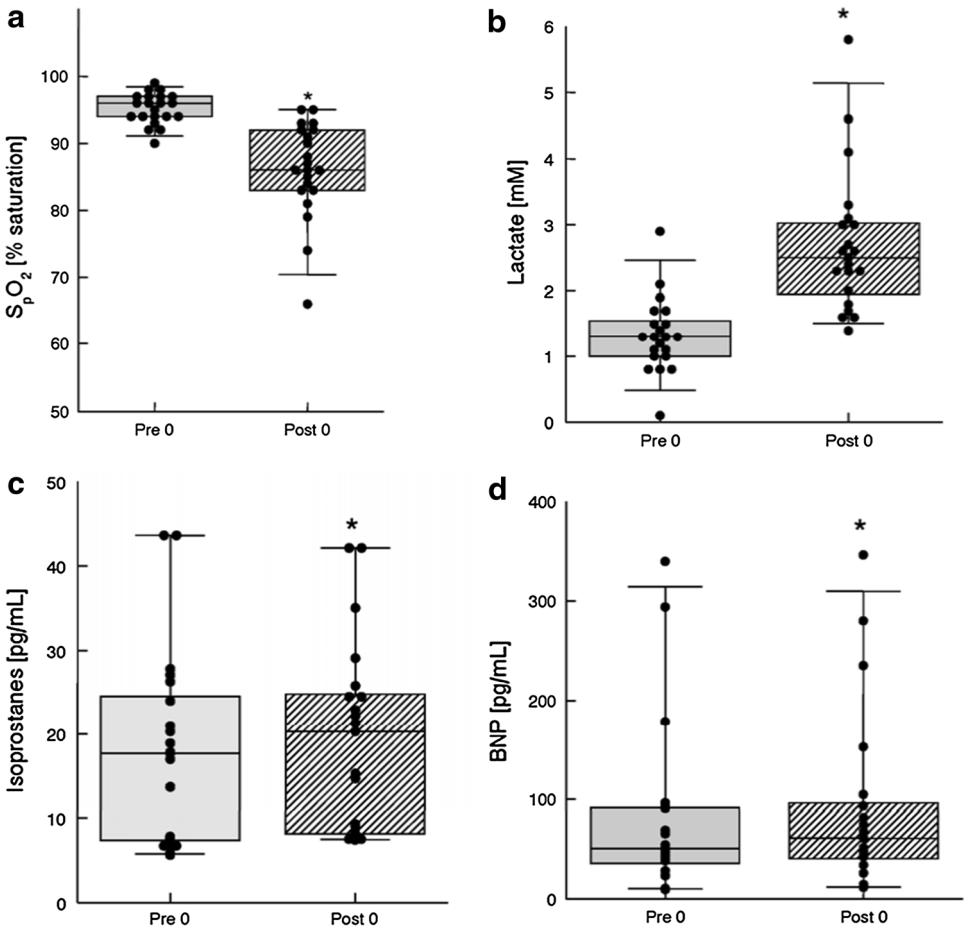

Fig. 2 Overall effects of cycle ergometry exercise testing (~50-W exercise) on arterial oxygen saturation, plasma lactate, 15-F_{2t}-isoprostanes, and NT-proBNP at baseline. Data shown were obtained at baseline (i.e., before any intervention) from all subjects who completed the 3-month study. **a** S_pO_2. **b** Plasma lactate. **c** Plasma 15-F_{2t}-isoprostanes. **d** NT-proBNP. Box-whisker plots display distribution of the data as the median (*line in box*), 25th and 75th percentiles (*box*), and 5th and 95th percentiles (*error bars*) for all subjects before (Pre 0) and after (Post 0) the baseline cycle ergometry test. $*P < 0.05$ for the pre-ergometry data compared to the post-ergometry data

predicted, and the HRR at maximum achieved exercise averaged 49 ± 2/min.

Plasma and Urine Isoprostanes

The baseline mean plasma concentration of 15-F_{2t}-isoprostanes was 16.5 ± 2.3 (SEM) pg/mL. Immediately after cycle ergometry to measure exercise VO_2, the concentration of 15-F_{2t}-isoprostanes increased significantly to 18.0 ± 12.2 pg/mL ($P = 0.028$). At baseline, the mean concentration of 15-F_{2t}-isoprostanes in urine (normalized to creatinine) was 336 ± 43 (SEM) pg/mg creatinine. Urine isoprostane concentration did not change significantly after cycle ergometry from baseline (post exercise testing, 345 ± 46; $P = 0.746$).

Plasma Lactate

Plasma lactate increased significantly, more than doubling (+108 %), after ergometry from baseline (pre-exercise test, 1.3 ± 0.1 [SEM] mM; post-exercise test, 2.7 ± 0.2; $P = 0.001$).

Brain Natriuretic Peptide

NT-proBNP also increased significantly (+11 %) after the baseline cycle ergometry exercise test (pre-exercise test, 81 ± 19 [SEM] pg/mL; post-exercise test, 90 ± 20; $P = 0.012$).

Oxygenation

At baseline, mean SpO_2 in the subjects was 95 ± 1 (SEM) %. SpO_2 decreased uniformly and significantly to 86 ± 2 % ($P < 0.001$) at the conclusion of exercise testing while breathing room air. Plasma oxygen saturation, plasma lactate, 15-F_{2t}-isoprostanes, and NT-proBNP data are summarized in Fig. 2 for subjects before and after the 3-month protocol.

Plasma Amino Acid Concentrations

Glutamic acid (GLU) concentration in the plasma more than doubled (+113 %). This increase was accompanied by significant but smaller increases in the concentrations of arginine (ARG) (+10 %), aspartic acid (ASP) (+47 %),

Table 4 Effects of exercise testing on plasma AA

	Pre-exercise test ($n = 21$)	Post-exercise test ($n = 21$)	P value*
ARG	98 ± 5	108 ± 6	0.005
ASP	1.9 ± 0.1	2.8 ± 0.2	<0.001
GLU	207 ± 30	441 ± 52	<0.001
HIS	50 ± 6	66 ± 4	0.015
MET	17 ± 1	21 ± 1	0.005

Data are means ± SEM in micromoles/liter (μM/L) for all subjects at the initial evaluation

* P values calculated by paired t test

Table 5 Effect of exercise on [cysteine]/[cystine]

	Pre-exercise test	Post-exercise test	P value*
All subjects ($n = 21$)	1.23 ± 0.51	0.49 ± 0.07	0.190
Subjects not taking NAC ($n = 10$)	1.79 ± 0.68	0.51 ± 0.11	0.037

Data are means ± SEM (unitless)

NAC *N*-acetyl-L-cysteine

* P value determined by Wilcoxon signed-rank test

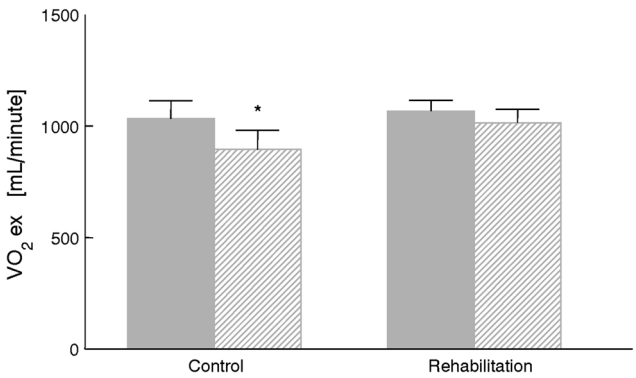

Fig. 3 Subjects in rehabilitation program maintained exercise VO_2 at baseline. We measured exercise oxygen uptake (exercise VO_2) during cycle ergometry exercise testing at baseline (*solid gray bars*) and again after 3 months (*cross hatched bars*) of rehabilitation (Rehabilitation) or observation (Control). Data shown are the mean ± SEM exercise oxygen consumption (mL/min) measurements in the rehabilitation and control groups at baseline and at 3 months. Exercise VO_2 did not change over 3 months in the rehabilitation group, while it decreased significantly in controls; *$P < 0.05$

histidine (HIS) (+32 %), and methionine (MET) (+24 %). These data are summarized in Table 4. Importantly, among those subjects who were not taking *N*-acetyl-L-cysteine, the [cysteine]/[cystine] ratio decreased by 72 % after exercise. These data are summarized in Table 5.

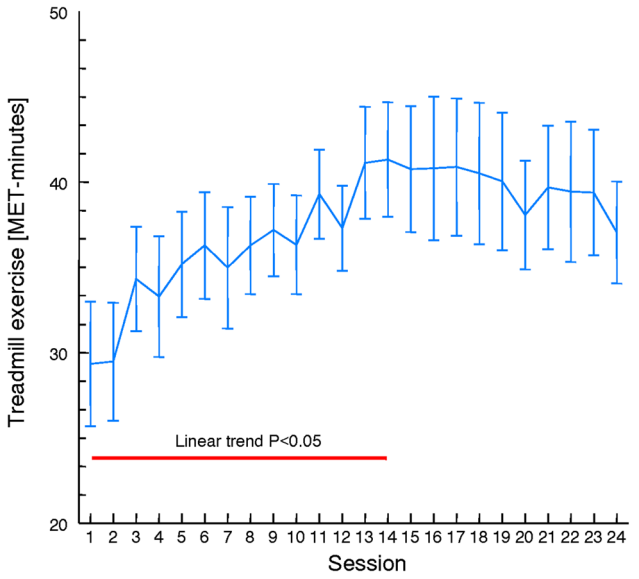

Fig. 4 Treadmill exercise MET-minutes during the 24 rehabilitation sessions. We recorded MET-minutes of treadmill exercise (shown by the *solid blue line*) for each rehabilitation subject ($n = 11$) at each of the 24 sessions. Data shown are arithmetic means ± SEM (MET-minutes) for the subjects during each rehabilitation session. Sessions occurred twice weekly over 3 months. The subjects increased treadmill exercise as reflected by mean MET-minutes during the initial 14 sessions (linear trend $P < 0.05$), but they appeared to reach a plateau in the latter sessions (15–24) of rehabilitation

Effects of Rehabilitation on Cycle Ergometry Exercise Testing

After 3 months, VO_2 during exercise, a prospectively chosen end point, remained stable in the rehabilitation group, whereas it decreased significantly (−13 %; $P = 0.027$) over that time in the control group. These data are shown in Fig. 3. Completion of the rehabilitation program significantly increased exercise time from 184 ± 28 (SEM) to 302 ± 62 s ($P = 0.036$) among those subjects who did not reach a steady state exceeding 10 min during cycle ergometry testing at 50 W. In contrast, exercise time did not change in controls over the 3-month observation period (baseline, 141 ± 29 s, 3-month, 137 ± 36 s; $P = 0.762$).

Effects of Rehabilitation on Treadmill Walking and Exercise Cycling

Rehabilitation subjects ($n = 11$) achieved 65 ± 2 (SEM) % of their predicted maximum heart rate on the treadmill and 66 ± 2 % on the exercise cycle during the twice-weekly rehabilitation sessions. The intensity of treadmill exercise increased significantly during the initial 14 rehabilitation sessions. These data are summarized graphically in Fig. 4.

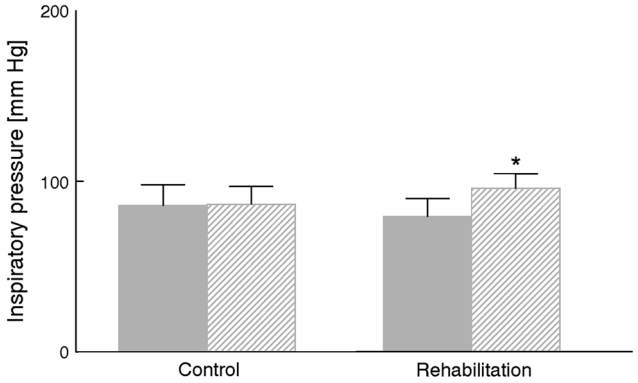

Fig. 5 Rehabilitation increases MIP. We measured MIP at baseline (*solid gray bars*) and again after 3 months (*cross hatched bars*) of rehabilitation (Rehabilitation) or observation (Control). Data shown are the mean ± SEM MIP (mmHg) measurements in the rehabilitation and control groups at baseline and at 3 months. MIP did not change after 3 months in the control group, while it increased significantly in the rehabilitation group; $*P < 0.05$. The maximum expiratory pressure (MEP) did not change significantly in either group

Table 6 6-MWT distances at baseline and 3-month evaluations

	Control ($n = 10$)	Rehabilitation ($n = 11$)
0-month	339.4 ± 34.4	360.6 ± 16.5
3-month	324.1 ± 35.5	354.4 ± 37.2
P value*	0.289	0.818

Data are means ± SEM in meters

* *P* value for 0-month compared to 3-month by paired *t*-test

Effects of Rehabilitation or Observation on Maximum Inspiratory and Expiratory Respiratory Pressures

The MIP increased significantly after 3 months compared to that at 0-month baseline in subjects in the rehabilitation group. These data are summarized in Fig. 5.

Effects of Rehabilitation on 6-Minute Walk Tests

The 6-MWT distance did not change significantly as a result of the 3-month rehabilitation program, nor did it change significantly in controls after the observation period. These data are summarized in Table 6.

Effects of Rehabilitation on BDI and Ventilatory Efficiency

Completion of the rehabilitation program did not decrease the level of dyspnea experienced after the 6-MWT, nor did it change after the observation period. These data are summarized in Table 7. Consistent with its lack of effect on dyspnea, rehabilitation had no effect on the subjects' ventilatory efficiency, represented by VE/VCO_2 slope [3, 4]. These data are given in Table 8.

Table 7 Dyspnea before and after 6-MWT at 0- and 3-month evaluations

	Control ($n = 10$)		Rehabilitation ($n = 11$)	
	Pre-walk	Post-walk	Pre-walk	Post-walk
0-month	0.2 ± 0.2	2.7 ± 0.6	0.5 ± 0.3	1.1 ± 0.3
3-month	0.6 ± 0.2	2.4 ± 0.4	0.6 ± 0.3	2.6 ± 0.6
P value*	0.039	0.273	0.406	0.281

Data are means ± SEM in BDI units

* *P* value of 0-month compared to 3-month by Wilcoxon signed-rank test

Table 8 V_E/VCO_2 slope at baseline and 3-month evaluations

	Rehabilitation ($n = 11$)	Control ($n = 10$)
0-month	43 ± 3	46 ± 5
3-month	45 ± 3	47 ± 5
P value*	0.577	0.868

Data are means ± SEM (unitless)

* *P* value of 0-month compared to 3-month by paired *t*-test

Discussion

Mechanisms of Exercise Limitation on Cycle Ergometry

Moderate-intensity constant-load exercise testing has been used successfully to test the effects of selected interventions such as exercise training and pharmacologic therapies [18–20]. IPF subjects did not usually reach predicted maximum or heart rates or minute ventilation, because symptoms restricted their ability to exercise at predicted maximum levels [3, 4]. On average, subjects reached 63 ± 3 (SEM) % of the predicted MVV (group mean baseline MVV was 71.7 ± 4.6 L/min), indicating that subjects exercised submaximally because of other factors such as dyspnea, hypoxemia, and oxidant stress. Total ventilation remained quite inefficient compared to carbon dioxide production (V_E/VCO_2 slope) throughout the test [3, 4]. The V_E/VCO_2 slope was markedly elevated during exercise, demonstrating an inability to optimize respiratory function even at these mild workloads [4].

Despite the low level of work (50 W) and the often brief exercise testing time (<10 min), subjects had uniformly increased plasma lactate levels after exercise testing, indicating a physiologically important shift to anaerobic energy production [4]. Concomitant with severe hypoxemia and increased plasma lactate, we found that IPF subjects also had an increase in plasma 15-F_2-isoprostanes after exercise, a highly reliable (when measured by mass spectroscopy) marker of systemic oxidant stress and lipid peroxidation [26, 27]. This is likely because both exercise and cellular hypoxia

increase the production of ROS [7, 31]. The increased plasma isoprostane concentrations we found here reflect increased oxidation of arachidonic acid [8].

Activation of phospholipase A2 leads to further increased intracellular ROS and release of oxidized arachidonic acid products, which result in isoprostane production [32]. ROS produced during exercise impair calcium metabolism and myofilament function in skeletal muscle cells, resulting in the lack of endurance that we observed [7, 31].

NT-proBNP, a putative marker of pulmonary hypertension in interstitial lung diseases [33], increased significantly after cycle ergometry testing, suggesting increased pulmonary artery pressure. Patients with IPF are at risk of developing worsened pulmonary hypertension with exercise because of fixed vascular resistance [34]. Brain natriuretic peptide levels correlate well with pulmonary hypertension determined by right heart catheterization in interstitial lung diseases [33]. In addition, 15-F_{2t}-isoprostanes are potent vasoconstrictors in pulmonary circulation [32]. The plasma concentration of thromboxane B_2, which might also increase pulmonary resistance, increased during exercise in a previously studied group of IPF patients [34].

Blood glutamine increases with power output during exercise in normal men and the increase parallels the blood ammonia concentration [35]. Muscle glutamate concentration decreases after short-term exercise in COPD patients, and this has been attributed to oxygen deprivation [36]. We detected a large (twofold) increase in plasma GLU after exercise in patients with IPF, suggesting its release from muscle stores. Glutamate may enhance energy production in hypoxic tissue by conversion to succinate [37]. Increased ARG might modulate increases in pulmonary artery pressure otherwise occurring with exercise [38].

We found (in those subjects not taking *N*-acetyl-L-cysteine, a common empiric therapy for IPF) that the ratio of cysteine to cystine decreased significantly in plasma after exercise. This change in [cysteine]/[cystine] signals a shift in the reduction–oxidation state to a more oxidized milieu after exercise.

Effects of Pulmonary Rehabilitation on Exercise Capacity of IPF Patients

A clear and important training effect was evident in increased endurance time at 50-W exercise, maintenance of exercise VO_2 during constant-load testing, increase in treadmill MET-minutes, and improvement in respiratory muscle strength (MIP) after rehabilitation [22].

Pulmonary rehabilitation as applied in our program (see Table 2) did not significantly change the 6-MWT distance in these strictly defined IPF patients. Rehabilitation and control groups both experienced significant increases in dyspnea after the 6-MWT, and 3 months of rehabilitation did not ameliorate the increase in the BDI. IPF patients likewise did not improve ventilatory work efficiency (V_E/VCO_2 slope) as a result of rehabilitation. Similarly, Nishiyama et al. [11] reported that a 10-week exercise program did not improve pulmonary function or dyspnea in IPF patients, but, in contrast, it did increase the 6-MWT distance by 46 m (95 % confidence interval = 8–84 m), which du Bois et al. [39] interpreted as clinically important. Salhi et al. [12] reported that patients with various restrictive lung diseases demonstrated improved 6-MWT distance and quadriceps strength after a 12-week rehabilitation program, although their study had no control group and the enrolled population differed greatly from ours. On the whole, the benefit of pulmonary rehabilitation on exercise capacity is not as clear in IPF as it is in COPD, although it may enhance quality of life [40, 41]. Mean 6-MWT distance decreased 6 m in the rehabilitation group, while it decreased by 15 m in controls. Neither mean change is considered clinically important (i.e., 24–45 m) for patients with IPF [39].

In patients with end-stage lung diseases awaiting transplantation, the 6-MWT distance correlated with maximum oxygen uptake [42]. We found no such correlation between exercise VO_2 and 6-MWT distance in this trial. Exercise VO_2 more precisely represents moderate to maximum exercise capacity, while 6-MWT distance reflects the ability to do sustained, low-level exercise [43].

Limitations of the Study

Because the effects of pulmonary rehabilitation on 6-MWT distance and perception of dyspnea are small, a larger number of subjects would be required to definitively demonstrate an effect on those variables. Subjects all had clinically diagnosed IPF according to ATS-ERS criteria [14]. Only 2 of 21 subjects had undergone surgical lung biopsy to definitively diagnose UIP, so it remains formally possible that some subjects may have been misclassified [1]. We did not do right heart catheterizations to measure pulmonary artery pressures, and it remains possible (since we used echocardiography) that some subjects with severe pulmonary hypertension, which would by itself limit exercise, may have been included [15].

Conclusions

We did not design this study to develop clinical guidelines, although its results suggest that clinical benefits and improvements in quality of life may accrue to patients with IPF as a result of pulmonary rehabilitation. We also found (Gaunaurd et al., unpublished observations) that subjects

who completed the pulmonary rehabilitation program experienced improvements in the symptom domain of the St. George's Respiratory Questionnaire for IPF [44]. The 12-week rehabilitation program tested here is comparable to that recently recommended [40], and it is practical for enrolled subjects in regard to time and effort commitment. Rehabilitation programs are not, however, standardized and vary widely based on local practice and reimbursement schemes [9]. We did not specifically test the premise that extended periods of rehabilitation might provide additional benefits by delaying declines in functional status of patients with IPF, which is often relentlessly progressive. Our program clearly increased endurance time (cycle ergometry) and maintained exercise capacity (oxygen uptake) and skeletal muscle strength (MIP) during rehabilitation. Pulmonary rehabilitation is clearly not harmful, and thus it may be a useful therapeutic modality in patients with IPF.

We conclude that although patients with IPF are limited by symptoms and have a relentlessly progressive disease, a pulmonary rehabilitation program like that we describe produces measurable benefits in maintaining exercise capacity and increasing endurance time and respiratory muscle strength. Mechanisms of exercise limitation, including oxidant stress related to hypoxemia, warrant further study so that more targeted exercise regimens can be designed.

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Conflict of interest The authors have no conflicts of interest to declare.

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