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ORIGINAL ARTICLE

Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis

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Background and objective: Although pulmonary rehabilitation is effective for patients with COPD, its efficacy in patients with IPF is unknown. The purpose of this study was to evaluate the effects of pulmonary rehabilitation in IPF.

Methods: Thirty patients diagnosed with IPF, according to the consensus statement, were randomly assigned to the rehabilitation group or the control group. The pulmonary rehabilitation mainly consisted of a 10-week programme of exercise training. Pulmonary function, blood gas analysis, 6MWD, dyspnoea rating with the baseline dyspnoea index and health-related quality of life score on the St George's Respiratory Questionnaire were evaluated at baseline and after the programme.

Results: Assessment of efficacy was carried out on 13 patients who completed the programme and 15 patients in the control group. There were no significant effects of the programme on measures of pulmonary function, values of arterial blood gas analysis or dyspnoea rating. Although there were some differences in the baseline 6MWD and total health-related quality of life score which were not statistically significant, marked improvements were observed in the 6MWD (mean difference 46.3 m (95% CI: 8.3–84.4), $P < 0.05$) and the total health-related quality of life score (–6.1 (95% CI: –11.7 to –0.5), $P < 0.05$).

Conclusions: Pulmonary rehabilitation improves both exercise capacity and health-related quality of life in patients with IPF.

Key words: exercise, interstitial, lung disease, pulmonary fibrosis, rehabilitation.

INTRODUCTION

IPF is a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histological feature of usual interstitial pneumonia.[1] The criteria for the diagnosis of IPF were stated by the American Thoracic Society and the European Respiratory Society (ATS/ERS) consensus statement, and the definition of IPF has been clarified.[2,3]

Although IPF is progressive with significant morbidity and mortality, the clinical course is considered to be chronic. Some treatment options have been reported, including corticosteroids, immunosuppressive/cytotoxic agents (e.g. azathioprine, cyclophosphamide) and antifibrotic agents (e.g. colchicines, D-penicillamine, interferon-gamma, and acetylcysteine) alone or in combination.[2,4–7] The effects of these treatments, however, are considered to be marginal.[8,9] New strategies for treating IPF patients are needed.

Pulmonary rehabilitation programmes have been shown to be effective in improving exercise capacity, dyspnoea and health-related quality of life in patients with COPD,[10–12] and are recommended in the recent

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treatment guideline.[13] Although the effects of pulmonary rehabilitation for non-COPD patients have been reported in some non-randomized studies,[14–16] no evidence has been reported for the efficacy of the programme in patients with IPF. The present study investigated the effects of a pulmonary rehabilitation programme compared with usual care in patients with IPF. Those effects were assessed in terms of pulmonary function, functional exercise capacity and health-related quality of life.

METHODS

Study subjects

Subjects were consecutive patients referred to the outpatient clinic between 2000 and 2004. Inclusion criteria were as follows: (i) age less than 75 years; (ii) a diagnosis of IPF; (iii) shortness of breath on effort; and (iv) a stable clinical condition with no infection or exacerbation in the previous 3 months. Exclusion criteria were severe comorbid illnesses, collagen vascular diseases, the need for long-term oxygen therapy and previous treatment with corticosteroids or immunosuppressives. The diagnosis of IPF was made in accordance with the ATS/ERS statement[3] using the following major criteria: (i) exclusion of other known causes of interstitial lung disease (ILD); (ii) abnormal pulmonary function with restriction and impaired gas exchange; (iii) bi-basilar reticular abnormalities on high-resolution CT (HRCT); and (iv) transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis. Minor criteria included: (i) age >50 years; (ii) insidious onset of otherwise unexplained dyspnoea; (iii) duration of illness >3 months; and (iv) bi-basilar inspiratory crackles. All the major and at least three of the four minor criteria had to be satisfied. For those with a surgical lung biospy specimen showing usual interstitial pneumonia,[2,3] only the major criteria were considered relevant. Patients included in the study were randomly assigned to either the rehabilitation or control group using sealed envelopes that had been prepared prior to the study. No patients received any treatment with corticosteroids or immunosuppressives during the study period. Informed consent was obtained from all who participated.

Assessment and rehabilitation programme

Patients were assessed at enrolment and 10 weeks after the start of the programme. Pulmonary function tests were assessed using a spirometer (CHESTAC-55V; Chest, Tokyo, Japan) according to the method described in the American Thoracic Society 1994 update.[17] Single-breath DL_{CO} was also measured (CHESTAC-55V; Chest, Tokyo, Japan). Results were compared with the predicted normal values.[18] Functional exercise capacity was measured by 6-min walking test, according to the ATS statement.[19] All patients underwent the tests twice at each evaluation, and the longer distance was used to minimize training effects. The baseline dyspnoea index (BDI)[20] and the St George's Respiratory Questionnaire (SGRQ)[21] were used to assess the dyspnoea rating and health-related quality of life, respectively. The BDI score comprises three categories: functional impairment, magnitude of task and magnitude of effort. Each category recognizes five grades (0–4), and the total BDI score ranges from 0 to 12.[20] The higher BDI score denotes milder dyspnoea in everyday living. The SGRQ score comprises three component scores (symptoms, activity and impacts) which sum to a total score.[21] Each component of the SGRQ score can range from 0 to 100 with a lower score denoting a better health-related quality of life. The BDI and SGRQ have been validated in Japanese subjects.[22] The SGRQ was validated for patients with ILD including IPF.[5,23,24] The pulmonary rehabilitation programme, a general programme, not one specifically for IPF, involved a twice-a-week outpatient programme of exercise training integrated with peripheral muscle training. In the first week, a baseline assessment was made that included the 6-min walking test and assessments of the BDI and SGRQ scores. Maximal exercise tests on a cycle ergometer were also performed by some patients. From the second to the ninth week, exercise training was performed on a treadmill at 80% of the patient's maximal walking speed assessed at the baseline 6-min walking test. In some patients who underwent the baseline cycle ergometer test, exercise intensity was also targeted at 80% of the initial maximum workload. Supplemental oxygen was given to maintain oxygen saturation above 90% if desaturation was observed. Strength training for the limbs was conducted using elastic bands; exercises included arm raising and knee extensions for about 20 min. The assessment was repeated in the final week to evaluate the effect of the pulmonary rehabilitation programme. Some educational lectures were also held during the programme.

Statistical analysis

The baseline characteristics between the two groups were compared using unpaired *t*-tests. Differences in the values for each subject before and after treatment were evaluated using the paired *t*-test. To account for differences between the two groups at baseline, comparisons between the rehabilitation and control groups were conducted using an analysis-of-variance model including the baseline values as covariates (ANCOVA). Changes in the total score for the SGRQ and changes in the 6MWD and the BDI were correlated using Pearson's correlation coefficient. A P-value < 0.05 was considered significant. Values are expressed as mean ± SD.

RESULTS

Thirty consecutive patients who satisfied the eligibility criteria were randomly assigned to either the rehabilitation group ($n = 15$) or the control group ($n = 15$). Two patients assigned to the rehabilitation group who refused to participate in the programme did not

Table 1 Baseline characteristics of patients

	Control group (n = 15)	Rehabilitation group (n = 13)
Sex (male/female)	9/6	12/1
Age (years)	64.5 ± 9.1	68.1 ± 8.9
Height (cm)	159.1 ± 10.3	161.1 ± 7.6
Weight (kg)	58.0 ± 9.6	60.0 ± 11.6
BMI (kg/m^2)	22.9 ± 2.8	23.0 ± 3.8
FVC (L)	2.0 ± 0.8	2.1 ± 0.4
FVC (% predicted)	68.7 ± 19.5	66.1 ± 13.2
FEVI (L)	1.7 ± 0.6	1.6 ± 0.2
FEV_1 (% predicted)	78.3 ± 19.4	73.3 ± 15.0
FEV_1/FVC (%)	85.2 ± 6.1	78.8 ± 8.2
TLC (L)	3.1 ± 1.0	3.2 ± 0.7
TLC (% predicted)	66.6 ± 16.1	64.1 ± 13.1
DLco (%)	48.6 ± 16.7	59.4 ± 16.7
PaO_2 (mm Hg)	83.0 ± 12.3	79.8 ± 11.5
$PaCO_2$ (mm Hg)	39.5 ± 6.0	33.6 ± 6.5*
6MWD (m)	476 ± 128	385 ± 116
BDI score	8.4 ± 1.5	6.7 ± 1.4**
SGRQ score		
Symptoms	38.0 ± 25.8	56.4 ± 22.3
Activity	50.4 ± 26.2	64.7 ± 17.1
Impacts	29.9 ± 23.7	39.7 ± 17.6
Total	37.8 ± 22.7	50.2 ± 16.3

*$P < 0.05$, **$P < 0.01$ compared with the control group (unpaired t-test).

Values are mean ± SD.

BDI, baseline dyspnoea index; SGRQ, St George's Respiratory Questionnaire.

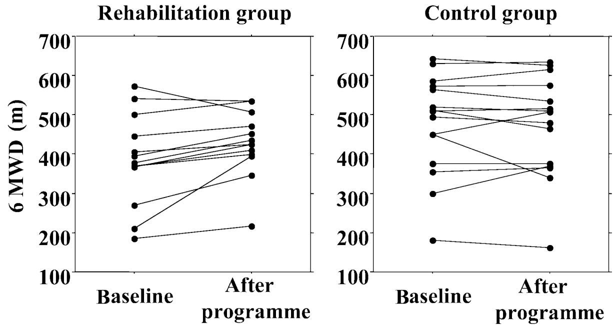

Figure 1 Improvement in 6MWD for the rehabilitation group and the control group. Statistically significant improvement from baseline was observed in the rehabilitation group ($P < 0.05$) but not in the control group.

undergo initial evaluations. The other 28 patients completed the initial assessments. The baseline characteristics of patients in both groups are shown in Table 1. Although the $PaCO_2$ value was lower, as was the BDI score in the rehabilitation group, there were no other significant differences between the groups.

All patients in the rehabilitation group who commenced the programme completed the programme, and all patients in both groups underwent the second evaluation. After the programme, 6MWD (Fig. 1) and the total SGRQ score, but not the other variables, had significantly improved compared with baseline values (Table 2). The programme appeared to have no significant effect on measures of pulmonary function, respiratory muscle strength, values of arterial blood gas analysis or dyspnoea rating compared with baseline. However, significant improvements in the 6MWD and the total SGRQ score were observed after the rehabilitation programme (Table 2).

For all 28 patients, the changes in the total SGRQ score were significantly correlated with changes in the 6MWD but not with changes in the BDI score ($r = -0.43$, $P = 0.02$ and $r = -0.29$, $P = 0.13$, respectively) (Fig. 2).

DISCUSSION

The efficacy of pulmonary rehabilitation in COPD has been proven in many clinical studies,[10] and rehabilitation programmes have been widely adopted for treating patients with COPD. Although the effectiveness of pulmonary rehabilitation in non-COPD patients has been reported,[13–15] most studies were not randomized controlled trials. In addition, in most of the preceding studies IPF was not distinguished from other restrictive lung diseases, such as bronchiectasis, scoliosis and neuromuscular disease.[14,15] Therefore, a randomized controlled trial was conducted and demonstrated the efficacy of pulmonary rehabilitation in patients with IPF.

In previous studies of patients with COPD, improvements in exercise capacity, dyspnoea rating and health-related quality of life were demonstrated after pulmonary rehabilitation programmes.[10] In the current study of IPF patients, significant improvements were observed in functional exercise capacity assessed by a 6-min walking test and in the health-related quality of life score, but not in the BDI score. Although these results suggest that it is difficult to improve dyspnoea ratings in IPF patients, the improvement in the 6-min walking test seems comparable with that of patients with COPD as previously reported.[25] Moreover, it is important to note that the total score for the health-related quality of life also significantly improved.

The basis of exercise intolerance in ILD and COPD is complex and multifactorial.[26,27] Ventilatory limitation, gas exchange abnormalities, diffusion limitation and circulatory limitation have been reported as some of the causes of exercise intolerance in ILD.[26] On the other hand, increased airway resistance, ineffective ventilation, hyperinflation and increased elastic load to breathing, gas exchange abnormalities and a mechanical disadvantage of the respiratory muscles have all been reported to contribute to ventilatory limitation during exercise in patients with COPD.[27] In addition, skeletal muscle dysfunction has been reported as an important contributor to exercise limitation in COPD.[28,29] Although there seem to be some differences in the mechanisms of exercise intolerance between ILD and COPD, the rehabilitation programme reported to be beneficial for patients with COPD has also proven effective in enhancing the exercise capacity of patients with IPF. Reductions in exercise lactic acidosis and ventilation along with a more

Table 2 Change in pulmonary function comparing baseline values with those 10 weeks after enrolment, by intervention status

Variables	Absolute values after programme		Difference between groups in change from baseline (95% CI)
	Control group ($n = 15$)	Rehabilitation group ($n = 13$)	
FVC (L)	2.0 ± 0.8	2.1 ± 0.4	0.03 (–0.13–0.19)
FEV_1 (L)	1.7 ± 0.6	1.6 ± 0.2	0.04 (–0.17–0.08)
TLC (L)	3.3 ± 1.0	3.3 ± 0.6	0.03 (–0.18–0.24)
PaO_2 (mm Hg)	75.2 ± 5.4	79.5 ± 9.7	5.5 (–5.0–16.0)
$PaCO_2$ (mm Hg)	42.3 ± 2.9	35.4 ± 5.6	–1.0 (–5.8–3.9)
6MWD (m)	472 ± 130	427 ± 84*	46.3 (8.3–84.4)‡
BDI score	8.0 ± 2.2	6.7 ± 1.3	0.4 (–0.6–1.4)
SGRQ score			
Symptoms	40.6 ± 21.2	53.4 ± 25.8	–5.7 (–18.7–7.2)
Activity	54.0 ± 22.6	62.5 ± 16.9	–5.8 (–14.7–3.1)
Impacts	32.9 ± 23.5	36.5 ± 17.5	–6.2 (–12.8–0.3)
Total	40.9 ± 20.7	47.3 ± 17.4*	–6.1 (–11.7–0.5)†

*$P < 0.05$ for comparison with baseline values (unpaired *t*-test).
†$P < 0.05$, ‡$P < 0.01$ for comparison of difference in change from baseline between groups (ANCOVA).
Values are mean ± SD.
BDI, baseline dyspnoea index; SGRQ, St George's Respiratory Questionnaire.

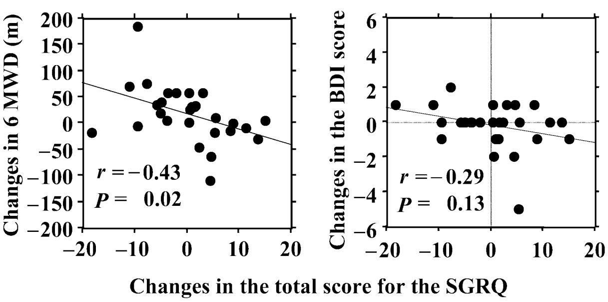

Figure 2 Scatterplots of the change in 6MWD and the baseline dyspnoea index (BDI) score against the total score for the St George's Respiratory Questionnaire (SGRQ). A significant relationship was observed between the change in the 6MWD and the total SGRQ score but not between change in the BDI score and total SGRQ score.

efficient exercise breathing pattern have been demonstrated after patients with COPD completed a pulmonary rehabilitation programme. These effects are considered to be associated with the improved exercise tolerance of those patients.[30,31] Further studies are needed to confirm whether the same mechanisms that improve the exercise capacity of patients with COPD are associated with the improvement in exercise tolerance in patients with IPF. Recently, the importance of training the muscles of ambulation has been emphasized in improving the exercise tolerance of patients with COPD.[32] Similarly, it has become evident that quadriceps force is related to exercise capacity in patients with IPF.[33] The fact that a rehabilitation programme mainly consisting of exercise training of the muscles of the lower extremities improved exercise tolerance in IPF strongly suggests the importance of the muscles of ambulation in IPF as well, although the strength of the ambulatory muscles was not specifically evaluated in this study.

No significant improvement in the dyspnoea rating was observed in the current study. That is quite interesting because pulmonary rehabilitation generally improves the dyspnoea rating in COPD.[10] Dyspnoea in patients with COPD can be partially due to the overinflation of the lung and over-expansion of the thorax, which are characteristics of COPD,[34] but are not found in IPF. This hypothesis seems to be consistent with a previous report which demonstrated that only O_2 saturation at the end of the 6MWD was an independent predictor of dyspnoea in IPF, whereas FEV_1 was the only predictor in COPD.[35] However, further research is necessary to better define the factors contributing to dyspnoea in patients with IPF and to identify possible treatments.

In the present study, the change in the health-related quality of life score was significantly correlated with the change in the 6MWD but not with the change in the BDI score. Although exercise capacity and the dyspnoea rating are the two main factors determining health-related quality of life in COPD,[22,36] it is the latter not the former that is predictive of quality of life in IPF.[24] However, it is interesting that the relationship between the changes in the 6MWD and the changes in the SGRQ score were statistically significant. Results from the current study suggest that, although it seems difficult to ameliorate dyspnoea in IPF patients by pulmonary rehabilitation, improving their exercise capacity can lead to improvements in their health-related quality of life. What specific exercise training might best enhance their exercise capacity should be investigated in further studies. Furthermore, elucidation of the mechanisms underlying dyspnoea and the development of methods to relieve its impact on IPF patients are required.

An improvement in the total SGRQ score of more than four is recognized as being the minimum to achieve a clinically important difference in patients with COPD.[37] The fact that the difference in the change in the total SGRQ score from baseline between groups was –6.1 in the current study indicates that the pulmonary rehabilitation programme was clinically effective in IPF. Strictly speaking, however, the minimum clinically important difference in the SGRQ score in IPF has not been determined and should be investigated further.

In the present study, there were significant baseline differences between the two groups in the $PaCO_2$ value and the BDI score. Moreover, the 6MWD and the total SGRQ score were relatively worse in the rehabilitation than in the control group, although no statistically significant difference was observed. Patients with lower values in study indices may have a greater capacity to achieve a measurable improvement. However, as the analysis of covariance model allows for such baseline inequalities, the true effect of pulmonary rehabilitation was considered to have been demonstrated. There are still some limitations to the study. First, the study was based on a small number of patients, and a larger study will be needed to confirm the results. Second, patients included had relatively mild impairments with mean FVC being 68.7% and 66.1% of predicted in the control and rehabilitation groups, respectively. Possible effects of pulmonary rehabilitation in patients with more severe disease could not be guaranteed. Third, the transient dyspnoea index (TDI)[20] was not used to evaluate the changes in dyspnoea. As the TDI seems to be more sensitive to changes in dyspnoea, a smaller improvement might have been detected had the TDI been used.

This study was confined to examining the short-term benefits of pulmonary rehabilitation. Those effects can reportedly be maintained for several years in COPD.[38–41] Thus, it would be interesting to observe the longer-term effects of pulmonary rehabilitation in patients with IPF, although their relatively shorter survival may not allow assessments of such long-term effects. Because exercise capacity has recently been recognized as an important prognostic factor in IPF,[42–44] it is significant that the 6MWD was improved in the current study. Whether pulmonary rehabilitation can improve survival in IPF should be evaluated. However, short-term effects were clearly demonstrated in this study despite the relatively small number of patients, indicating that pulmonary rehabilitation should be integrated into the treatment of patients with IPF.

In conclusion, pulmonary rehabilitation improves functional exercise capacity and health-related quality of life in patients with IPF.

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