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Predictors of benefit following pulmonary rehabilitation for interstitial lung disease

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Pulmonary fibrosis;
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Summary
Background: Pulmonary rehabilitation improves functional capacity and symptoms in the interstitial lung diseases (ILDs), however there is marked variation in outcomes between individuals. The aim of this study was to establish the impact of the aetiology and severity of ILD on response to pulmonary rehabilitation.
Methods: Forty-four subjects with ILD, including 25 with idiopathic pulmonary fibrosis (IPF), underwent eight weeks of pulmonary rehabilitation. Relationships between disease aetiology, markers of disease severity and response to pulmonary rehabilitation were assessed after eight weeks and six months, regardless of program completion.
Results: In IPF, greater improvements in 6-minute walk distance (6MWD) immediately following pulmonary rehabilitation were associated with larger forced vital capacity ($r = 0.49$, $p = 0.01$), less exercise-induced oxyhaemoglobin desaturation ($r_S = 0.43$, $p = 0.04$) and lower right ventricular systolic pressure ($r = -0.47$, $p = 0.1$). In participants with other ILDs there was no relationship between change in 6MWD and baseline variables. Less exercise-induced oxyhaemoglobin desaturation at baseline independently predicted a larger improvement in 6MWD at six month follow-up. Fewer participants with IPF had clinically important reductions in dyspnoea at six months compared to those with other ILDs (25% vs 56%,

Abbreviations: 6MWD, 6-minute walk distance; CRQ, Chronic Respiratory Questionnaire; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MID, minimal important difference; ROC, receiver operating characteristic; RVSP, right ventricular systolic pressure; SpO_2, oxyhaemoglobin saturation measured by pulse oximetry.

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$p = 0.04$). More severe dyspnoea at baseline and diagnosis other than IPF predicted greater improvement in dyspnoea at six months.
Conclusions: Patients with IPF attain greater and more sustained benefits from pulmonary rehabilitation when disease is mild, whereas those with other ILDs achieve benefits regardless of disease severity. Early referral to pulmonary rehabilitation should be considered in IPF.

Introduction

The interstitial lung diseases (ILDs) are characterised by distressing dyspnoea, progressive deterioration in exercise tolerance, poor health-related quality of life and reduced life expectancy. Emerging evidence suggests pulmonary rehabilitation programs that include exercise training may improve functional capacity and symptoms.[1,2] However, the impact of pulmonary rehabilitation on these outcomes is smaller and less consistent than that observed in other populations.[3] This may contribute to the poor uptake of this treatment noted in clinical practice.[4]

Preliminary evidence suggests that response to pulmonary rehabilitation may vary according to diagnosis. Data from a systematic review suggest that patients with idiopathic pulmonary fibrosis (IPF) exhibit a smaller exercise response to pulmonary rehabilitation than those with other ILDs and may not achieve symptomatic benefit.[5] However, this could reflect the impact of more severe disease on exercise responses,[6–8] rather than an effect of IPF itself. To date no studies have evaluated the independent effects of diagnosis and disease severity on response to pulmonary rehabilitation in ILD.

There are few treatment options for many patients with ILD and as a result there is increasing interest in treatments such as pulmonary rehabilitation, which may relieve symptoms without changing disease course.[9,10] There are no guidelines recommending when pulmonary rehabilitation should be offered, although it has been suggested that patients should be referred early in the disease.[11] We hypothesised that (1) in IPF, participants with less severe disease achieve larger and more sustained benefits from pulmonary rehabilitation; and (2) pulmonary rehabilitation is effective across the disease spectrum in those with non-IPF ILDs.

Methods

Patients with documented ILD were recruited from two tertiary hospitals between January 2007 and December 2008. Diagnostic criteria for IPF were consistent with the International Consensus Statement.[12] Patients were eligible to participate if they were ambulant and reported dyspnoea on exertion on stable medical therapy. Exclusion criteria were a history of syncope on exertion; any comorbidities precluding exercise training; or participation in a pulmonary rehabilitation program in the last two years. Participants were consecutive patients who were assessed as suitable for rehabilitation by their treating doctor and referred to the rehabilitation program. Some ($n = 9$) were participants in a study investigating the minimum important difference (MID) for the 6MWD in ILD.[13] All participants gave written informed consent and the study was approved by the human ethics committees at both sites.

All participants took part in a twice-weekly eight-week exercise training program of endurance and strength training which was prescribed and progressed according to a previously described standardised protocol.[1] Supplemental oxygen was provided as required to maintain oxyhaemoglobin saturation (SpO_2) $\geq$85%. An unsupervised home exercise programme was also prescribed with the aim of achieving five exercise sessions per week in total. Those participants who had been prescribed supplemental oxygen ($n = 17$) were instructed to use this during home exercise. Participants were encouraged to record their home exercise in a diary, which was reviewed weekly by the treating clinician. Participants also attended an education and self-management program. At program completion participants were encouraged to continue exercising at least three times per week.

Baseline measurements included spirometry, diffusing capacity (DLCO) and trans-thoracic echocardiogram. Lung function tests were repeated immediately after the intervention and at six months.

Outcomes were assessed in all participants, regardless of program completion, at baseline, eight weeks and six months by an independent assessor who was not involved in delivery of pulmonary rehabilitation. Functional exercise capacity was assessed using the 6-minute walk test (6MWT).[14] Use of oxygen during the test was standardised and the test was stopped if SpO_2 fell below 80%, in accordance with a previously described protocol for ILD.[15] Follow-up walk tests were conducted using the same flow rate of supplemental oxygen as at baseline. Distance walked in six minutes (6MWD) and lowest SpO_2 were recorded. Impact of pulmonary rehabilitation on symptoms was measured using the Chronic Respiratory Questionnaire (CRQ) dyspnoea domain.[16]

The aim of this study was to determine predictors of long-term response to pulmonary rehabilitation in ILD. Primary endpoints for long-term response were defined as: (1) exercise response — change in 6MWD from baseline to six months; and (2) symptom response — change in CRQ dyspnoea domain from baseline to six months. Short-term responses were considered as secondary outcomes, and were defined by comparing the same outcomes at baseline and program completion. The proportion of participants achieving gains exceeding the MID for 6MWD and CRQ dyspnoea, calculated at program completion and at six months, were also secondary endpoints. The MID for 6MWD and CRQ dyspnoea domain were defined as a change of greater than or equal to 34 m[13] and 2.5 points[17] respectively.

Potential physiological markers which may impact on response to pulmonary rehabilitation were defined a priori, based on previously documented markers of disease severity and prognosis in IPF.[18–20] These were forced vital capacity (FVC), DLCO, resting right ventricular systolic pressure (RSVP) and nadir SpO_2 on baseline 6-minute walk test. Baseline 6MWD was also included in the analysis of exercise response as this was associated with response to pulmonary rehabilitation in a retrospective study,[21] while baseline dyspnoea was included in the analysis of symptom response. Change in TLCO over six months was included in the analysis of long-term response to evaluate the effects of disease progression.

Sample size

The pre-specified sample size was 44 participants. This study was powered to detect an association between change in 6MWD following rehabilitation (the dependent variable) and markers of disease severity and prognosis (independent variables). To detect a relationship between baseline DLCO and change in 6MWD with 80% power, 22 subjects with IPF were required. This was based on pilot data which suggested a reduction in 6MWD response to rehabilitation for IPF participants of 1.6 m for every unit reduction in DLCO at baseline, assuming standard deviations of 20.6 for DLCO and 54 m for change in 6MWD. Numbers required to assess the relationship between change in 6MWD and FVC, right ventricular systolic pressure (RVSP) and total lung capacity (TLC) were 18, 16 and 15 subjects respectively. An equivalent number of participants with non-IPF ILDs was recruited as a comparator group, matched for disease severity using FVC and DLCO.

Statistical analysis

The effects of pulmonary rehabilitation on exercise tolerance and dyspnoea in IPF and non-IPF groups were evaluated using repeated measures analysis of variance. The number of participants in IPF and non-IPF groups who achieved benefits exceeding the MID for 6MWD and CRQ dyspnoea was compared using the Pearson Chi Square test. Stepwise multiple linear regression analysis was undertaken to identify independent predictors of 6-month outcome, using change in 6MWD and CRQ dyspnoea domain as dependent variables and diagnosis (IPF or other ILD) as a categorical independent variable. In order to select baseline variables for inclusion in the model, relationships between response to rehabilitation and baseline predictor variables were assessed with Pearson's r or with Spearman's rho (r_S) as appropriate. Baseline variables with a univariate relationship to the dependent variable ($p \leq 0.1$) were entered into the model. Variables that were not significant were removed from the model. For continuous variables, receiver operating characteristic (ROC) curves were used to identify thresholds that discriminated responders from non-responders. A $p < 0.05$ was considered statistically significant. All analyses were undertaken using SPSS version 17.0 (SPSS Inc, Chicago, IL).

Results

Forty-four participants were recruited, 25 of whom had IPF (Table 1). Participants with other ILDs had diagnoses of sarcoidosis ($n = 3$), hypersensitivity pneumonitis ($n = 5$), non-specific interstitial pneumonia ($n = 3$), asbestosis ($n = 5$) and connective tissue disease ($n = 3$). Participants with IPF were well matched for disease severity to those with other ILDs but tended to be younger. Six participants did not complete the rehabilitation program, due to respiratory illness ($n = 1$), other illness ($n = 1$), musculoskeletal pain ($n = 1$) and lack of motivation ($n = 3$). Two of these participants, both with IPF, declined further participation in the study. Diary data indicated that the participants completed 77% of the expected home exercise sessions. One participant was too unwell to complete the 6-minute walk test at 6-months follow-up due to progression of IPF; this participant completed the questionnaires only. One participant with IPF died prior to 6-month follow-up. Data were available for 42 participants immediately following the program and 41 participants at six months. Respiratory function tended to be reduced at six months but this did not reach statistical significance for either FVC (mean − 60ml, 95% confidence interval − 163–45 ml) or DLCO (−0.74 ml/min/mmHg, −2.1–0.62 ml/min/mmHg). Reduction in DLCO tended to be greater in participants with IPF but this did not reach statistical significance ($p = 0.27$).

The 6MWD improved significantly following the program in both IPF and non-IPF groups, however this effect was no longer evident at six months (Fig. 1). The mean improvement in 6MWD for participants with IPF at program completion was 21 (58) m (mean, standard deviation) compared to 43 (56) m in those with other ILDs ($p = 0.21$). Improvements in 6MWD that exceeded the MID occurred in 40% of those with IPF, compared to 52% of those with other ILDs ($p = 0.41$). After six months 35% of those with IPF had maintained gains in 6MWD that exceeded the MID, compared to 41% of the non-IPF group ($p = 0.68$).

Table 1 Baseline demographic characteristics of participants with IPF compared to those with other ILDs.

	IPF, $n = 25$	Other ILD, $n = 19$	p value
Age, years	72.9 (6.8)	68.1 (8.4)	0.05
FVC, %predicted	76.4 (20.3)	72.1 (23.6)	0.53
TLCO, %predicted	48.5 (19.1)	51.7 (19.3)	0.48
TLC, %predicted	74.9 (16.7)	73.2 (16.2)	0.79
RVSP, mmHg	36.5 (15.7)	36.0 (11.4)	0.93
6MWD, m	370 (127)	411 (96)	0.24
Nadir SpO_2, %	85 (7)	88 (5)	0.13
CRQ dyspnoea	15.3 (3.8)	16.5 (5.6)	0.42

Data are mean (standard deviation); p value is comparison between IPF and other ILDs. FVC forced vital capacity; TLCO – diffusing capacity for carbon monoxide; TLC – total lung capacity; RVSP – right ventricular systolic pressure on transthoracic echocardiogram; 6MWD – 6-minute walk distance; nadir SpO_2 – oxyhaemoglobin saturation on baseline 6-minute walk test; CRQ – Chronic Respiratory Questionnaire.

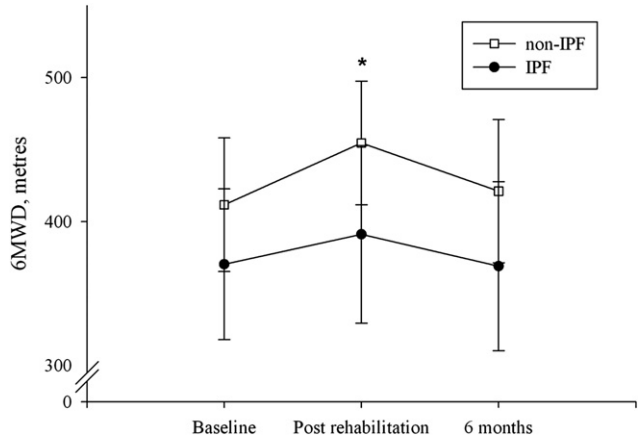

Figure 1 Comparison of exercise response to pulmonary rehabilitation in participants with IPF and other ILDs. IPF — idiopathic pulmonary fibrosis, 6MWD — 6-minute walk distance. $^{*}p < 0.05$ vs baseline for both groups.

Dyspnoea improved immediately following pulmonary rehabilitation, with a mean improvement of 2.7(5.6) points in those with IPF compared to 4.6 (5.2) points in those with other ILDs ($p = 0.25$, Fig. 2). No effect on dyspnoea was evident after six months. At program completion 59% of those with IPF achieved improvements in dyspnoea that exceeded the MID, compared to 67% of those with other ILDs ($p = 0.62$). After six months a significantly lower proportion of those with IPF had clinically important improvements in dyspnoea (24% vs 56%, $p = 0.04$).

There were no significant associations between baseline characteristics and improvement in 6MWD when the entire group was analysed together either at program completion ($n = 42$) or six months later ($n = 41$). However, in participants with IPF, univariate analysis suggested that larger changes in 6MWD immediately following rehabilitation were associated with a greater FVC, lower RVSP and less oxyhaemoglobin desaturation on baseline 6MWD (Table 2).

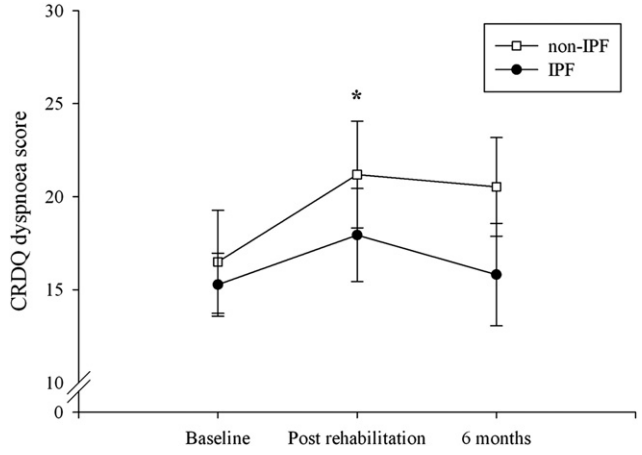

Figure 2 Comparison of symptoms response to pulmonary rehabilitation in participants with IPF and other ILDs. IPF — idiopathic pulmonary fibrosis, CRDQ — chronic respiratory disease questionnaire. $^{*}p < 0.05$ vs baseline for both groups.

Similar relationships were seen at six months, with the exception of RVSP. In those with other ILDs, baseline characteristics had no relationship to exercise response at either timepoint. In a stepwise multiple regression model that included nadir SpO_2 on baseline 6-minute walk test and baseline FVC, the only significant predictor of long-term exercise response was nadir SpO_2 (Table 3). This model explained 18% of the variation in exercise response at six months. Nadir SpO_2 was also the best predictor of short-term exercise response, however this model did not reach statistical significance ($p = 0.08$). Post-hoc analysis using the ROC curve method indicated that a SpO_2 threshold of 86% differentiated long-term 6MWD responders from non-responders with a sensitivity of 80%, however specificity was 56% and the area under the curve was 64%.

There were no significant associations between baseline physiology and change in dyspnoea immediately after the pulmonary rehabilitation program, either in the group as a whole or in subgroups of IPF and non-IPF participants. However, those with worse baseline dyspnoea had significantly greater improvements in dyspnoea at six months, both for IPF and non-IPF groups (Table 2). In a stepwise multiple regression model, the baseline CRQ dyspnoea score and a diagnosis of IPF were predictors of symptom response at six months (Table 4). This model explained 43% of the variation in symptom response at six months, with IPF participants less likely to achieve improvements (Table 4). This model explained 31% of the variation in symptom response at six months. Post-hoc analysis could not identify a suitable threshold for baseline CRQ dyspnoea score to predict long-term symptom outcome.

Discussion

This study is the first to prospectively evaluate predictors of long-term benefit from pulmonary rehabilitation in people with IPF and other ILDs using an intention-to-treat analysis. Improvements in functional exercise capacity for people with IPF were related to markers of disease severity and prognosis, with greatest and most sustained treatment effects achieved in those with milder disease. In contrast, people with other ILDs attain benefits from pulmonary rehabilitation regardless of disease severity and are more likely than those with IPF to achieve sustained reductions in dyspnoea.

Consistent with previous reports, there was a significant improvement in 6MWD following pulmonary rehabilitation in both IPF and non-IPF groups.[1,2,21–23] However there was marked variability in response between individuals and only a minority of participants with IPF achieved the MID. Our data indicate that this may be explained by disease severity, with greater gains evident in those with a higher FVC %predicted and less exercise-induced desaturation. Similarly, a recent study in IPF found short-term benefits of pulmonary rehabilitation occurred only in less disabled participants.[24] In a previous retrospective study[21] there was no relationship between improvement in 6MWD and disease severity in a large group with mixed ILDs. This is consistent with our results, where the relationship between response to pulmonary rehabilitation and markers of disease severity only became evident when the subgroup of patients with

Table 2 Relationship between baseline characteristics and response to pulmonary rehabilitation.

	Short-term response				Long-term response			
	Change in 6MWD		Change in CRQ dyspnoea		Change in 6MWD		Change in CRQ dyspnoea	
	IPF	Non-IPF	IPF	Non-IPF	IPF	Non-IPF	IPF	Non-IPF
FVC %pred	0.49*	−0.07	−0.01	−0.09	0.40†	0.16	−0.04	−0.26
DLCO %pred	0.29	−0.31	0.03	−0.26	0.08	−0.05	−0.06	−0.34
RVSP, mmHg	−0.47†	0.03	−0.42	0.33	−0.18	−0.09	−0.006	0.21
Nadir SpO_2, %	0.43*	−0.21	0.16	−0.14	0.55*	−0.02	0.29	−0.21
Baseline 6MWD, m	0.20	−0.39	0.18	−0.14	−0.31	−0.28	−0.03	0.07
Baseline CRQ dyspnoea	0.25	−0.12	−0.34	−0.39	0.08	0.17	−0.52*	−0.60*

Data are Pearson's *r*, except for short-term 6MWD response in non-IPF which are Spearman's rho. †$p < 0.1$, *$p < 0.05$.
FVC forced vital capacity; TLCO — diffusing capacity for carbon monoxide; TLC — total lung capacity; RVSP — right ventricular systolic pressure on trans-thoracic echocardiogram; 6MWD — 6-minute walk distance; nadir SpO^2 — oxyhaemoglobin saturation on baseline 6-minute walk test; CRQ — Chronic Respiratory Questionnaire.

IPF was analysed separately. The current study suggests that accurate diagnostic information may assist with appropriate referral to pulmonary rehabilitation in ILD. Although the natural history of IPF is unpredictable, the majority of patients experience a gradual decline in pulmonary function over many years.[25] Our data suggest that for such patients, early referral to pulmonary rehabilitation may be required in order to maximise its benefits.

A smaller degree of exercise-induced desaturation was the only independent predictor of exercise benefits at six months following the pulmonary rehabilitation program. Desaturation on 6-minute walk test has a strong relationship to other markers of disease severity in IPF, including FVC,[26] and thus other markers of disease severity were not retained in the model. Diagnosis of IPF did not remain an independent predictor of response when desaturation was included, suggesting that the effect of IPF on exercise response is mediated by the degree of desaturation during exercise.[27] This is supported by the greater degree of desaturation evident in participants with IPF, despite matching for other measures of disease severity (Table 1) and likely reflects the greater degree of gas exchange impairment during exercise.[28] It is possible that greater desaturation during exercise may limit the training intensity that can be achieved in pulmonary rehabilitation, resulting in less favourable outcomes for IPF participants, however this has not yet been tested. It should be noted that our model explained only a small proportion of the variance in 6MWD, suggesting that other unidentified factors also contribute to longer-term outcomes. Post-hoc analysis indicated that a nadir SpO_2 during the 6-minute walk test of 86% or less could distinguish responders from non-responders; however an area under the curve of only 0.64 suggests that caution should be exercised in applying this threshold to clinical practice.

Sustained improvements in dyspnoea following pulmonary rehabilitation were significantly more likely in non-IPF participants with worse dyspnoea scores at baseline. Although short-term improvements in dyspnoea have previously been documented in randomised controlled trials[1] and observational studies,[23] longer-term gains following rehabilitation have not been demonstrated.[5,22] These data indicate that dyspnoeic patients with non-IPF ILDs are more likely than those with IPF to achieve long-term symptomatic benefit from pulmonary rehabilitation, with significant improvements in dyspnoea still evident in over half of the non-IPF participants at six months following the program. To our knowledge this is the first report of sustained benefits following pulmonary rehabilitation for ILD. These results are encouraging for a patient group with few treatment options. Further investigation of these effects in a randomised controlled trial is warranted.

Many patients with IPF are not routinely referred to pulmonary rehabilitation as physicians feel that its benefits are unproven.[4] Existing randomised controlled trials are small[1,2] and no previous prospective study has evaluated predictors of response related to diagnosis and disease severity. Only low grade recommendations regarding exercise training for ILD are provided in guidelines for clinical practice in pulmonary rehabilitation[29] and ILD[25,30]. This may be due in part to lack of certainty regarding which patients will benefit and how long any positive effects will

Table 3 Stepwise multiple linear regression model for change in 6MWD from baseline to six months following pulmonary rehabilitation.

	B	SE of *B*	Standardised beta	*p* value
Constant	−496.456	179.601		0.009
Nadir SpO_2 at baseline	5.699	2.058	0.424	0.009
R^2 for model				18%

6MWD — 6-minute walk distance; nadir SpO_2 — lowest oxyhaemoglobin saturation on baseline 6-minute walk test; *B* — unstandardised coefficient; SE standard error; R^2 — proportion of variation in change in 6MWD at six months explained by the model.

Table 4 Stepwise multiple linear regression model for change in dyspnoea from baseline to six months following pulmonary rehabilitation.

	B	SE of *B*	Standardised beta	*p* value
Constant	16.655	4.048		0.001
CRDQ dyspnoea score at baseline	−0.776	0.2189	−0.518	0.001
IPF diagnosis	−4.442	1.960	−0.328	0.031
R^2 for model				31%

CRDQ — chronic respiratory disease questionnaire; *B* — unstandardised coefficient; SE — standard error; R^2 — proportion of variation in change in CRDQ score explained by the model.

last. Data from the current study confirm the clinically important effects of pulmonary rehabilitation for patients across the spectrum of ILDs and indicate that for patients with IPF, the timing of treatment matters. Our results support the contention of previous authors that pulmonary rehabilitation should be considered the standard of care for people with ILD[21] and add evidence supporting early referral for patients with IPF.

Weaknesses of this study include the relatively small numbers of participants and the small number of predictors evaluated. However, the study was adequately powered to assess relationships of interest which were specified a priori. Only small numbers of independent variables were included in the regression models to ensure stability of the estimates. Our study numbers compare favourably with recently published prospective studies in this area.[1,2,22,23] Strengths of this study are its prospective design and the use of intention-to-treat analysis, making the likelihood of overestimation of treatment effect low. An additional strength is the inclusion of a six month follow-up period, providing data regarding the sustained effects of pulmonary rehabilitation.

In conclusion, this study demonstrates that patients with IPF have greater improvements in functional exercise capacity when pulmonary rehabilitation is delivered early in the course of disease. Patients with other ILDs achieve significant gains in exercise capacity regardless of disease severity and are more likely than those with IPF to achieve sustained improvements in dyspnoea. Admission criteria for pulmonary rehabilitation programs should support the inclusion of patients with ILD and facilitate early participation in those with IPF.

Conflict of interest

The authors have no conflicts of interest to declare in relation to this work.

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