European Journal of Physical and Rehabilitation Medicine
EDIZIONI MINERVA MEDICA

Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation

Baptiste CHéHèRE, Valérie BOUGAULT, Cécile CHENIVESSE, Jean-Marie GROSBOIS, Benoit WALLAERT

European Journal of Physical and Rehabilitation Medicine 2018 Jun 14
DOI: 10.23736/S1973-9087.18.05093-1

Article type: Original Article

Article first published online: June 14, 2018
Manuscript accepted: June 13, 2018
Manuscript revised: April 24, 2018
Manuscript received: November 29, 2017

Title: Cardiorespiratory adaptation in a 6-minute walk test by fibrotic idiopathic interstitial pneumonia patients who did or did not respond to pulmonary rehabilitation

Authors:

Baptiste Chéhère[1], Valérie Bougault[1]*, Cécile Chenivesse[2], Jean-Marie Grosbois[3,4], and Benoit Wallaert[2,3]

Affiliations:

[1]University of Lille, EA 7369 - URePSSS - Multidisciplinary Research Unit in Sport Health Society, F-59000 Lille, France; [2]CHU Lille, Department of Immuno-Allergology and Respiratory Diseases, Competence Centre for Rare Pulmonary Diseases, University of Lille, F-59000 Lille, France; [3]Department of Respiratory Medicine, Centre Hospitalier Germon et Gauthier, Béthune, France; [4]FormAction Santé, Pérenchies, France.

Corresponding author:

Valérie Bougault, PhD

URePSSS - Multidisciplinary Research Unit in Sport Health Society

EURASPORT, 413 Avenue Eugène Avinée, 59120 Loos, FRANCE

E-mail: valerie.bougault@univ-lille2.fr

Tel: 0033 (0)3 20 88 73 76

Fax: 0033 (0)3 20 88 73 63

Abstract:

BACKGROUND: Pulmonary rehabilitation (PR) improves performance in the 6-min walk test (6MWT) in a subset of patients with fibrotic idiopathic interstitial pneumonia (f-IIP); however, a large proportion of patients do not respond to PR.

AIM: To investigate the effects of a PR program on cardiorespiratory responses during a 6MWT and to identify the characteristics of patients who do not show improved performance after PR.

DESIGN: An observational study.

SETTING: Patients were recruited from the Competence Centre for Rare Pulmonary Diseases at Lille University Hospital, France and completed an 8-week home-based PR program.

POPULATION: A total of 19 patients with f-IIP; 12 with idiopathic pulmonary fibrosis (IPF) and 7 with fibrotic non-specific interstitial pneumonia.

METHODS: Patients underwent spirometry and completed a 6MWT before and after an 8-week PR program. Gas exchange, heart rate, and pulse O_2 saturation were measured continuously during the 6MWT. Quality of life, dyspnoea, and anxiety/depression were assessed using the Short-Form 36 (SF-36), the baseline/transition dyspnoea index (BDI/TDI), and the Hospital Anxiety and Depression Scale (HADS) questionnaires.

RESULTS: Patients who did and did not improve the distance walked in the 6MWT by at least 30 m after PR were classified as responders (n=9) and non-responders (n=10), respectively. O_2 uptake, ventilation rate, and distance covered during the 6MWT were significantly improved only in the responder group ($p<0.05$). Changes in SF-36, BDI/TDI, and HADS scores did not differ significantly between responders and non-responders. The

non-responder group contained significantly more patients with IPF ($p<0.05$) and experienced greater arterial oxygen desaturation during the 6MWT compared with the responder group.

CONCLUSION: Failure to improve performance in the 6MWT after PR was associated with a diagnosis of IPF, non-improvement in gas exchange, and greater arterial oxygen desaturation.

CLINICAL REHABILITATION IMPACT: Most f-IIP patients who did not respond to PR were diagnosed with IPF and displayed greater hypoxemia during exercise. Clinical practitioners should seek to determine why patients fail to improve exercise performance after PR and propose an alternative exercise regimen to these patients.

Keywords

Responders, Non-responders, 6-min walk test, Interstitial lung disease, Idiopathic pulmonary fibrosis

Introduction

Interstitial lung diseases (ILD) include various disorders characterised by alveolar and interstitial space damage, pulmonary inflammation usually associated with fibrosis, decreased pulmonary capacity, and impaired gas exchange.[1] Patients generally present with exercise intolerance, dyspnoea on exertion, and poor quality of life,[2–4] which can be improved by pulmonary rehabilitation (PR) programs performed at home[5,6] or in outpatient or inpatient settings.[7–11]

ILD patients with fibrotic idiopathic interstitial pneumonia (f-IIP) generally have a poorer exercise tolerance and survival rate compared with non-fibrotic patients.[7,12] In particular, the distance walked during the 6-min walk test (6MWT) is independently associated with mortality in these patients.[13,14] Bajwah *et al.* reviewed the effects of pharmacological and non-pharmacological interventions on changes in the 6MWT distance (6MWD), and only pirfenidone and PR showed strong evidence of a positive impact.[15] Although most studies have reported that PR does improve the 6MWD in f-IIP patients,[5,7–10,16,17] one retrospective study of 599 ILD patients (46% with idiopathic pulmonary fibrosis [IPF]) reported that 40% showed either no clinical improvement or experienced worsening of the 6MWD after PR.[18]

Because changes in the 6MWD over time predict survival in f-IIP patients,[14] there is an urgent need to understand why some patients fail to improve exercise performance after PR. In these patients, exercise limitations may be due to pulmonary and/or gas exchange impairments (diminished lung volume, oxygen desaturation), circulatory limitations (pulmonary hypertension, cardiac dysfunction), and/or muscular dysfunction.[4,19] However, few studies have examined the effects of PR on gas exchange during submaximal exercise tests, such as the 6MWT, in patients with respiratory diseases. Chronic obstructive pulmonary disease (COPD) patients generally show increased peak oxygen uptake (VO_{2peak}) in the post-

PR 6MWT.[20–23] In contrast, several studies have detected no significant change in VO_{2peak} after PR, despite an increase in 6MWD, f-IIP patients.[7,10,24,25] This discrepancy may be due to inter-study differences in the proportion of patients who did or did not show improved 6MWD (i.e., responders and non-responders). For example, patients whose pathology worsened during the PR program may have shown no improvement in either the 6MWD or VO_2. Alternatively, patients with greater arterial desaturation during exercise, reflecting more limited ventilatory function may have benefited less from the PR program.

Based on these possibilities, we hypothesised that f-IIP patients who displayed an increase in exercise performance (i.e., distance walked) during a post-PR 6MWT would show a concomitant increase in VO_2). The aim of the present study was to investigate changes in cardiorespiratory responses during the 6MWT in f-IIP patients after an 8-week home-based PR program, and to identify characteristics that differentiate between responders and non-responders.

Material and Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. Approval for the use of patient data was obtained from the Institutional Review Board of the French Learned Society for Pulmonology (CEPRO 2011-036). Written informed consent was obtained from each participant.

Subjects

Patients with a diagnosis of f-IIP according to established criteria [26,27] and followed at the Competence Centre for Rare Pulmonary Diseases, Lille University Hospital (Lille, France) were recruited by pulmonologists during the patients' routine monitoring visits. Inclusion criteria were: (i) a diagnosis of fibrotic non-specific interstitial pneumonia (f-NSIP) or IPF by high-resolution computed tomography or lung biopsy and (ii) resting pulse O_2 saturation ≥88%. Patients were excluded if they had participated in a PR program in the preceding year, were receiving continuous O_2 therapy, had a comorbidity precluding exercise training or affecting test performance, had a forced vital capacity (FVC) <50% of the predicted value, or had a diffusing capacity of the lung for carbon monoxide (DLCO) <25% of the predicted value.

Thirty-four patients with f-IIP were recruited between September 2014 and June 2016 and offered the home-based PR program. Ten patients declined to participate and 3 were excluded; 1 with a DLCO <25% of predicted and 2 with severe orthopaedic or neurological comorbidities. Finally, a total of 21 patients (12 with IPF, 7 with f-NSIP), were included in the study. A flow diagram outlining patient recruitment is shown in Figure 1.

Study design

Patients completed an 8-week home-based PR program. Once a week, a health professional with specific expertise in exercise training and therapeutic education supervised

a 90-min session in the patient's home. Patients were encouraged to perform the same exercises independently, with a total target of five sessions per week. The supervised sessions included exercise training, therapeutic patient education, and psychosocial support based on an educational needs assessment (see below). Pulmonary function tests and the 6MWT with measurement of gas exchange were performed at the Hospital before and after the PR program. The time between the end of the home-based PR program and the post-PR evaluation was 8±5 days (mean ± standard deviation [SD]).

Exercise training program

Each session included 30 min endurance training on a cycle ergometer (Domyos VM 200, Decathlon, Villeneuve-D'Ascq, France) and/or a stepper (Stepper réglable athlitech, Groupe Go Sport, Sassenage, France), which were set up at the patient's home at the start of the PR program. Training intensity was determined for each individual with a specific functional goal. The exercise intensity for each patient at the start of the program was based on the average heart rate (±5 beats·min^{-1}) obtained during the last 3 min of the pre-PR 6MWT.[28] The cycling workload and stepper movement speed were adjusted to target an exercise rate at perceived exertion scores between 3 and 4 on the 0–10 Borg scale or between 11 and 13 on the Borg 6–20 scale. If patients failed to complete the optimal duration of 30 min continuous exercise, the duration was reduced to 10-min periods of interval training, with a goal of gradually increasing to 30 min continuously over the 8-week program. Strength training of upper and lower limb muscles was performed using body weight, dumbbell, and elastic band exercises, for 15 min per session. Exercise was monitored and modified by an experienced physiotherapist according to a standardised protocol. Supplemental oxygen was provided during the training if pulse O2 saturation <88%. Finally, patients were encouraged to increase their physical activity duration in daily life. Each patient was asked about his/her

adherence to the non-supervised sessions but details of their physical activities and exercise were not recorded.

Therapeutic education program and psychosocial support

An educational assessment was performed at each patient's home before starting the PR program to evaluate his/her existing difficulties and to assess changes required in health-related behaviour. Short, medium and long-term goals were assessed to provide real-life motivation for the PR program. Depending on the patient's needs, the program addressed respiratory diseases and comorbidities (e.g., diabetes, cardiovascular diseases, obesity, depression, anxiety), treatments, prevention and recognition of exacerbations, physical exercise, outings, sleep, sexuality, breathing management, stress management, balanced diet and weight control, smoking cessation, self-image, and self-esteem. This section of the program was administered at each visit (usually in the presence of the patient's spouse or caregiver) in the form of interactive presentations, question and answer sessions, card games, and illustrated printed material.

Assessments

Baseline lung diffusing capacity and volumes were obtained by plethysmography. Forced expiratory volume in 1 s (FEV_1), FVC, total lung capacity (TLC), and DLCO were measured using a BodyBox 5500 (Medisoft Sorinnes, Belgium). Predicted normal values were derived from standard equations recommended by the European Respiratory Society.[29]

Quality of life was assessed using the Medical Outcomes Study Short-Form 36 (SF-36), which is composed of eight domains and two component summary scores (physical and mental).[30] Dyspnoea was assessed using the baseline and transition dyspnoea index (BDI/TDI) and the 10-point Borg scale at the end of the 6MWT.[31,32] Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS).[33]

The 6MWT was performed according to the American Thoracic Society (2002) recommendations using a 30-m corridor, without encouragement.[34] At rest and during the exercise test, gas exchanges and ventilatory responses were measured continuously using a portable spiroergometer (MetaMax 3B, Cortex, Germany). VO_2, carbon dioxide output (VCO_2), minute ventilation (V_E), breathing frequency (Bf), tidal volume (V_T), respiratory exchange ratio, respiratory equivalent ratios for O_2 (V_E/VO_2), and carbon dioxide (V_E/VCO_2) were obtained continuously. Data were recorded every 5 s and the average value per minute was used for statistical analysis. Pulse O_2 saturation (SpO_2) was also recorded every minute using a pulse oximeter (Novametrix 513 Pulse Oximeter, Wallingford, CN, USA), and heart rate (HR) was monitored continuously using a belt compatible with the gas exchange analyser (Polar FS3C, Oy, Finland). Resting (SpO_{2rest}) and minimum SpO_2 during exercise (SpO_{2nadir}) were recorded, and ΔSpO_2 was calculated as ($SpO_{2rest} - SpO_{2nadir}$).

Classification of responders and non-responders

Patients who did or did not show a 6MWD increase of ≥30 m after PR (considered the minimal important difference [MID])[35] were classified as responders or non-responders, respectively.

Statistical analysis

Cardiorespiratory parameters (HR, VO_2, VCO_2, V_E, V_T, Bf, V_E/VO_2, V_E/VCO_2) during the 6MWT performed before (pre-PR) and after (post-PR) the PR program were compared. Values are expressed as the mean ± SD. Data were analysed using SigmaStat (version 3.5). Univariate normality assumptions were verified with the Kolmogorov–Smirnov test, and homogeneity of variances was verified using the Brown–Forsythe variation of Levene's test. A paired t-test and the nonparametric Wilcoxon test were used to compare dyspnoea, and SpO_2 before and after the 6MWT. Repeated measures ANOVA (time and pre/post) was used to compare the change in cardiorespiratory parameters at rest and at each

minute of the 6MWT pre- and post-PR. When ANOVA was significant, Tukey's post hoc test for multiple comparisons was applied. A paired t-test and the nonparametric Wilcoxon test were used to compare the questionnaire scores (HADS, SF-36 and BDI/TDI) pre- and post-PR.

Fisher's test was used to compare the distribution between the responder and non-responder groups of f-IIP patients and of patients who achieved the MID of 30 m for 6MWT. An unpaired t-test and the nonparametric Wilcoxon test were used to compare values at rest and changes following PR for the responders and non-responders. Because the number of subjects was small, the effect size was calculated for p values close to 0.15. Cohen[36] previously suggested that effect sizes of <0.2, 0.2–0.5, 0.5–0.8, and >0.8 reflected trivial, small, moderate, and large effects, respectively.[36] A p-value <0.05 was considered statistically significant.

Results

Twenty-one patients with f-IIP were enrolled and deemed eligible for the study, of whom 19 completed the PR program (Figure 1). A subset of 13 patients had complete (pre- and post-PR) datasets for the gas exchange analysis. Of the 19 patients, 12 (63%) had IPF and 7 (37%) had f-NSIP. The main characteristics and comorbidities of the patients are summarised in Table I.

Following the PR program, the mean 6MWD for the entire cohort (n=19) was significantly increased from 425±57 m to 448±68 m (p=0.01, Table II). Among the eight domains of the SF-36 questionnaire, only the 'physical functioning score' of quality of life was improved post-PR (p=0.004, Table II). The BDI/TDI score showed an improvement of dyspnoea post-PR (p=0.01, Table II). However, the dyspnoea score on the Borg scale assessed at the end of the 6MWT were not significantly different pre- and post-PR (p=0.24, data not shown). Similarly, there was no significant effect of the PR program on the HADS anxiety or depression scores (p=0.53 and p=0.87, respectively; Table II).

Characterisation of responders and non-responders

Of the 19 patients, 9 (47%) showed a 6MWD improvement of at least 30 m (the MID for this test[35]) and were considered responders; the remaining 10 patients were designated non-responders. The two groups showed no significant differences in the baseline (pre-PR program) 6MWD or other characteristics (Table III). However, the proportion of f-NSIP and IPF patients was significantly different between the groups, with the non-responder group containing only 1 of the 7 f-NSIP patients but 9 of the 12 IPF patients (14% *vs.* 75%; p=0.02). Notably, changes of FEV_1 and TLC values for the responder and non-responder groups were different (Table IV). Whereas, the responders showed increased (or at least the maintenance) FEV_1 and TLC following the PR program, both parameters were decreased in the non-responder group (p=0.04 for ΔFEV1, p=0.08 for ΔTLC; Table IV). However, there were no

significant differences between the responder and non-responder groups in the changes in quality of life, anxiety, depression, or dyspnoea from pre- to post-PR.

Cardiorespiratory adaptation during the 6MWT

Of the 19 patients who completed the PR program, 13 were analysed for gaseous exchange during the 6MWT (6 responders and 7 non-responders; Figure 1). The mean cardiorespiratory values (HR, VO_2, VCO_2, V_E, V_T, and Bf) for the group of 13 were not significantly different before *vs.* after the PR program or at rest *vs.* during the 6MWT. The change in the 6MWD from pre- to post-PR correlated with the changes in VO_2 ($r=0.59$, $p=0.03$), in V_E ($r=0.69$, $p=0.01$) and in Bf ($r=0.55$, $p=0.05$).

In the responder group (n=6), the post-PR 6MWT showed significantly increased VO_2 and VCO_2 during the last 3 min and significantly increased V_E throughout compared with the pre-PR 6MWT (Figure 2A). In contrast, HR and ventilatory patterns were not significantly affected by the PR program. In the non-responder group (n=7), none of the cardiorespiratory parameters evaluated were significantly changed between the pre- and post-PR 6MWT (Figure 2B).

Discussion

In this study, we showed that more than half (10/19, 53%) of f-IIP patients who underwent an 8-week home-based PR program did not reach the MID of 30 m in the 6MWD. We found that responders had higher VO_2, VCO_2, and V_E during the post-PR 6MWT, but no differences in cardiorespiratory parameters were detected in non-responders before vs. after the PR program. The two patient groups also showed no significant differences in pre- *vs.* post-PR changes in dyspnoea, quality of life, or anxiety/depression scores. The non-responder group was notable for the predominance of IPF patients (9/10) and the greater arterial oxygen desaturation during exercise.

Characterisation of responders and non-responders

Our findings are consistent with previous studies showing the beneficial effects of a PR program for f-IIP patients in the 6MWT.[5,7,8,10,11,25,37] However, we also observed a 53% non-responder rate, which matches previous reports that 58–60% of IPF patients failed to attain a MID of 28–34 m in a post-PR 6MWT.[25,38] One exception to this trend was the study of Vainshelboim *et al.*, who reported that 13 of 15 IPF patients reached a MID of 25 m in a post-PR 6MWT.[10] This difference could be partly explained by the shorter MID selected in the latter study.

The baseline severity of lung disease (FVC, SpO_{2nadir}),[38] dyspnoea grade,[37] and 6MWD[11,39] have been reported to predict post-PR changes in the 6MWD in ILD patients. In our study, the non-responder group contained more patients with IPF and with severe lung diffusion impairment, as reflected by baseline DLCO level and arterial oxygen desaturation during the 6MWT, compared with the responder group. These results are consistent with the study of Holland *et al.*, who found that exercise-induced desaturation was a significant predictor of the change in 6MWD in ILD patients after a 6-month PR program.[38] This result should be interpreted with caution, however, since a similar study of ILD patients by

Dowman *et al.* found that SpO_{2nadir} did not predict short- or long-term changes in 6MWD post-PR.[11] This discrepancy could be due to the higher proportion of patients with connective tissue disease-related ILD and the small number of patients requiring long-term or exertional oxygen therapy in the study of Dowman *et al.*[11] As yet unidentified factors may also contribute to post-PR changes in 6MWD in ILD patients. For example, Holland *et al.* reported that desaturation may limit exercise intensity during PR in ILD patients, thus reducing the potential beneficial effect of the program on the 6MWD.[38] Patients in that study—as in ours—were permitted O_2 therapy to maintain a SpO_2 ≥88% during the PR program. Moreover, a recent study found no difference in pre-6MWT SpO_{2nadir} between ILD patients who did or did not improve their exercise intensity during a PR program.[11]

Interestingly, we did not observe significant differences between the responders and non-responders in pre- *vs.* post-PR quality of life, dyspnoea, or anxiety and depression scores. Spielmanns *et al.* similarly found no significant differences in SF-36 scores between responders and non-responders in their study.[18] These findings indicate that PR can have major benefits for f-IIP patients, independently of improvements in 6MWD. The educational therapy aspect of the program is likely to have played a part in the improved symptom and quality of life scores, supporting the previous recommendation[40] that educational therapy and exercise training should be combined to optimise the benefits of PR. Arizono *et al.* compared the effects of a PR program on the performance of f-IIP patients in various exercise tests, and they found that duration of the endurance shuttle walk test (ESWT) was a more sensitive readout of PR efficacy than the distance walked in the 6MWT.[25] We note, however, that improvement in the 6MWD, but not the ESWT, requires the patient to walk faster after PR. It seems likely that it would be easier for a deconditioned patient to increase the duration, rather than intensity, of physical activity during a home-based program, given the lack of involvement of medical staff. In our study, for example, the non-responders may have shown

improvements in exercise duration, following the PR program, but this would not be detected by the 6MWT. Future studies should include a more detailed investigation of the responders and non-responders, which could provide valuable information for clinicians to design different training regimens for patients who are 'non-responders' using a particular exercise test.

Cardiorespiratory adaptation during the 6MWT

To the best of our knowledge, this is the first study to describe the effects of a PR program on cardiorespiratory adaptation during a 6MWT in patients with pulmonary disease. Similar to the study of IPF patients by Jackson *et al.*, we observed no differences in cardiorespiratory adaptation following the PR program,[41] despite significant differences in performance. But, the responders and non-responders differed in their VO_2, VCO_2, and V_E during the post-PR 6MWT. Our results also suggest that f-IIP patients with lower DLCO and greater desaturation are less likely to show improved 6MWD and cardiorespiratory performance after a PR program. However, we note that the number of subjects compared is small. As proposed for COPD patients,[42] it is possible that the greater hypoxia observed in non-responders may limit muscular adaptation, and thus the post-PR 6MWD. Therefore, for ILD patients and especially f-IIP, further studies are warranted to explore the mechanisms, including muscular adaptation, underlying the post-PR differences between responders and non-responders.

Limitations of the study

One limitation of this study is the mild to moderate disease severity of the cohort. We excluded patients who required oxygen supplementation at rest for technical reasons related to the gas exchange analyser. The fact that the pre- and post-PR 6MWT were performed without oxygen may also explain the failure of some patients to show overt improvement in the response. Even if some muscular adaptation had occurred, it may have been masked by a

worsening of pathology and consequent need for oxygen therapy post-PR. In addition, the sample size was small, and our results should be verified on a larger cohort. In particular, the small number of subjects per responder and non-responder group limits the interpretation of the cardiorespiratory outcomes of the 6MWT. However, we did observe evidence of differences in respiratory adaptation between the responders and non-responders with moderate to large effect sizes.

Conclusions

More than 50% of the f-IIP patients in our cohort did not show an improvement in the 6MWD following a PR program. Further studies should focus on the underlying mechanisms that explain the observed differences between responders and non-responders, especially the role of chronic hypoxemia. This is a crucial point, because patients who are non-responsive to the 6MWT may have poorer prognoses and survival rates compared with responders. Nevertheless, non-responders and responders showed similar benefits in quality of life and dyspnoea, suggesting that these parameters, or other exercise metrics, may be more sensitive to PR than the 6MWD MID for some patients. For example, since our patient cohort was asked to prioritise an increase in exercise duration over intensity during the 8-week program, it is possible that the non-responders in the 6MWT may have been responders in endurance tests performed at submaximal intensity.

Notes:

Authors' contribution statement:

BC made substantial contributions to study conception and design; acquisition, analysis, and interpretation of the data; and drafting of the manuscript. VB made substantial contributions to study conception and design, analysis and interpretation of the data, and drafting of the manuscript. CC made substantial contributions to acquisition of the data and drafting of the manuscript. JMG made substantial contributions to study conception and design, acquisition of the data, and drafting of the manuscript. BW made substantial contributions to study conception and design, analysis and interpretation of the data, and drafting of the manuscript.

Conflict of interest:

All authors declare no conflicts of interest relevant to this study.

Acknowledgements:

We would like to thank the rehabilitation team (G Tywoniuk, S Duriez, F Urbain, V Wauquier, and M Lambinet) and the staff of the Competence Centre for Rare Pulmonary Diseases who managed the patients during the home-based PR program and routine monitoring. The authors would also like to thank Adair, France Oxygène, Homeperf, LVL Medical, Orkyn, Santélys, SOS Oxygène, Sysmed, VitalAire, and ARS Nord-Pas-de-Calais for their support during the home-based PR program.

References

1. King TE. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268-79.

2. Markovitz GH, Cooper CB. Exercise and interstitial lung disease. *Curr Opin Pulm Med* 1998;4:272-80.

3. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. *Chest* 1999;116:1175-82.

4. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. *Chron Respir Dis* 2010;7:101-11.

5. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Multidiscip Respir Med* 2010;5:31-7.

6. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois J-M. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Rev Mal Respir* 2011;28:52-7.

7. 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;63:549-54.

8. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirol Carlton Vic* 2008;13:394-9.

9. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med* 2014;108:203-10.

10. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014;88:378-88.

11. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017;72:610-9.

12. Travis WD, Matsui K, Moss J, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol* 2000;24:19-33.

13. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM: Six-Minute-Walk Distance Predicts Waiting List Survival in Idiopathic Pulmonary Fibrosis. *Am. J. Respir. Crit Care Med* 2006;174:659-64.

14. Caminati A, Bianchi A, Cassandro R, Rosa Mirenda M, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. *Respir Med* 2009;103:117-23.

15. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. *Thorax* 2013;68:867-79.

16. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G et al. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. *J Cardiopulm Rehabil Prev* 2015;35:47-55.

17. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2014;10:CD006322.

18. Spielmanns M, Gloeckl R, Schmoor C, Windisch W, Storre JH, Boensch M et al. Effects on pulmonary rehabilitation in patients with COPD or ILD: A retrospective analysis of clinical and functional predictors with particular emphasis on gender. *Respir Med* 2016;113:8-14.

19. Troy LK, Young IH, Lau EM, Corte TJ. Exercise pathophysiology and the role of oxygen therapy in idiopathic interstitial pneumonia. *Respirol Carlton Vic* 2016;21:1005-14.

20. Gigliotti F, Coli C, Bianchi R, Romagnoli I, Lanini B, Binazzi B et al. Exercise training improves exertional dyspnea in patients with COPD: evidence of the role of mechanical factors. *Chest* 2003;123:1794-802.

21. Puente-Maestu L, Abad YM, Pedraza F, Sánchez G, Stringer WW. A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. *Lung* 2006;184:159-67.

22. Skumlien S, Skogedal EA, Bjørtuft O, Ryg MS. Four weeks' intensive rehabilitation generates significant health effects in COPD patients. *Chron Respir Dis* 2007;4:5-13.

23. Ramponi S, Tzani P, Aiello M, Marangio E, Clini E, Chetta A. Pulmonary Rehabilitation Improves Cardiovascular Response to Exercise in COPD. *Respiration* 2013;86(1):17-24.

24. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. *Eur J Phys Rehabil Med* 2017;53:209-18.

25. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K et al. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respir Care* 2014;59:1108-15.

26. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was

adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277-304.

27. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733-48.

28. Fabre C, Chéhère B, Bart F, Mucci P, Wallaert B, Grosbois JM. Relationships between heart rate target determined in different exercise testing in COPD patients to prescribe individualized exercise training. *Int J Chron Obstruct Pulmon Dis* 2017;16:1483-9..

29. 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.

30. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

31. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85:751-8.

32. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377-81.

33. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.

34. 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;166:111-7.

35. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Small changes in six-minute walk distance are important in diffuse parenchymal lung disease. *Respir Med* 2009;103:1430-5.

36. Cohen J. *Statistical Power Analysis for the Behavioural Sciences, 2nd Edition.* New York: Lawrence Erlbaum Associates; 1988.

37. Kozu R, Senjyu H, Jenkins SC, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. *Respir Int Rev Thorac Dis* 2011;81:196-205.

38. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. *Respir Med* 2012;106:429-35.

39. Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. *Chest* 2009;135:442-7.

40. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester 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;188:13-64.

41. Jackson RM, Gómez-Marín OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. *Lung* 2014;192:367-76.

42. Costes F, Gosker H, Feasson L, Desgeorges M, Kelders M, Castells J et al. Impaired exercise training-induced muscle fiber hypertrophy and Akt/mTOR pathway activation in hypoxemic patients with COPD. *J Appl Physiol (1985)* 2015;118:1040-9.

Tables:

Table I. Characteristics of the 19 patients with fibrotic idiopathic interstitial pneumonia

Variable	All (n=19)	IPF (n=12)	f-NSIP (n=7)	P value
Men/women, n	15/4	10/2	5/2	0.60
Age, years	65 ± 9	66 ± 7	62 ± 12	0.53
BMI, $kg \cdot m^{-2}$	30 ± 6	30 ± 3	30±9	0.90
FVC, % predicted	75 ± 13	79 ± 12	70±13	0.13
TLC, % predicted	78 ± 19	83 ± 20	69 ± 14	0.11
FEV_1, % predicted	73 ± 12	75 ± 10	71 ± 15	0.44
DLCO, % predicted	40 ± 8	39 ± 8	42 ± 10	0.43
Exercise O_2 therapy support, n (%)	15 (79)	9 (75)	6 (86)	1.00
BDI, score	7 ± 2	7 ± 2	6 ± 2	0.18
6MWT				
6MWD, m	425 ± 57	438 ± 59	401 ± 49	0.18
SpO_{2nadir}, % #	85 ± 5	84 ± 6	88 ± 4	0.12
Comorbidities, n (%)				
Arterial hypertension, %	11 (58)	8 (67)	3 (43)	0.37
Type 2 diabetes, %	8 (42)	7 (58)	1 (14)	0.17
Cardiovascular disease, %	7 (37)	6 (50)	1 (14)	0.15
Sleep-disordered breathing, %	6 (32)	3 (25)	3 (43)	0.62
Gastroesophageal reflux, %	2 (11)	1 (8)	1 (14)	1.00

Values are expressed as the mean ± SD, number (n) and percentage of patients, or number (n) of patients. #The effect size for the SpO_{2nadir} was 0.75 (moderate). 6MWD: 6-min walk test distance; 6MWT: 6-min walk test; BDI: baseline dyspnoea index; BMI: body mass index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; f-NSIP: fibrotic non-specific interstitial pneumonia; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; SpO_{2nadir}: minimum SpO_2 recorded; TLC: total lung capacity.

Table II. Pre- *vs.* post-PR changes in dyspnoea and quality of life scores in the f-IIP patients.

	Pre-PR	Post-PR	P value	Effect Size
6MWD, m	425 ± 57	448 ± 68	**0.01**	0.37
SF-36				
Physical summary score	54 ± 19	60 ± 18	0.10	0.33
Physical functioning score	55 ± 23	63 ± 24	**0.004**	0.33
Mental summary score	60 ± 21	66 ± 21	0.14	0.28
BDI/TDI score	6.8 ± 2.1	+0.9 ± 1.3	**0.01**	0.39
HADS				
Anxiety score	7.6 ± 4.8	6.7 ± 4.1	0.53	
Depression score	5.2 ± 3.5	5.3 ± 3.0	0.87	

Values are expressed as the mean ± SD. 6MWD: 6-min walk test distance; BDI/TDI: baseline/transition dyspnoea index; HADS: hospital anxiety depression scale; PR, physical rehabilitation; SF-36: short-form 36.

Table III. Baseline characteristics of the responder and non-responder groups.

Variable	Responders (n=9)	Non-responders (n=10)	P value	Effect Size
Pulmonary function				
FVC, % predicted	73 ± 13	77 ± 12	0.48	
TLC, % predicted	70 ± 12	82 ± 20	0.16	
FEV_1, % predicted	73 ± 14	74 ± 10	0.77	
DLCO, % predicted	44 ± 9	38 ± 7	0.15	0.73
6WMT				
6MWD, m	422 ± 66	428 ± 51	0.83	
SpO_{2nadir}, %	87 ± 4	83 ± 6	0.14	0.69
Dyspnoea end, Borg 0–10	6 ± 3	5 ± 2	0.21	
BDI score	6 ± 2	7 ± 2	0.45	
SF-36 physical component score	50 ± 21	58 ± 18	0.41	
SF-36 mental component score	54 ± 18	65 ± 22	0.27	
HADS anxiety score	9 ± 4	6 ± 5	0.14	0.68
HADS depression score	7 ± 4	4 ± 5	0.10	0.77

Values are expressed as the mean ± SD. 6MWD: 6-min walk test distance; 6MWT: 6-min walk test; BDI: baseline dyspnoea index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; HADS: hospital anxiety depression scale; SF-36: short-form 36; SpO_{2nadir}: minimum SpO_2 recorded; TLC: total lung capacity.

Table IV. Pre- *vs.* post-PR changes in the responder and non-responder groups.

Variable	Responders (n=9)	Non-responders (n=10)	P value	Effect Size
ΔFVC, mL	2 ± 119	-55 ± 119	0.31	
ΔTLC, mL	131 ± 305	-347 ± 711	0.08	0.82
ΔFEV1, mL	26 ± 66	-85 ± 131	**0.04**	0.94
ΔDLCO, $mL \cdot min^{-1} \cdot mmHg^{-1}$	0.10 ± 0.94	-0.09 ± 0.13	0.47	
ΔTDI score	1 ± 1	1 ± 1	0.93	
ΔSF-36 physical component score	9 ± 17	4 ± 16	0.47	
ΔSF-36 mental component score	6 ± 17	5 ± 15	0.86	
ΔHADS anxiety score	-2 ± 4	0 ± 3	0.23	
ΔHADS depression score	-1 ± 3	1 ± 2	0.41	

Values are expressed as the mean ± SD. DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; HADS: hospital anxiety depression scale; SF-36: short-form 36; TLC: total lung capacity; TDI: transition dyspnoea index.

Titles of figures:

Figure 1. Patient flow diagram.

Δ6MWD: pre- *vs.* post-PR change in 6MWT distance; 6MWT: 6-min walk test; PR: pulmonary rehabilitation.

Figure 2. Change in cardiorespiratory parameters during the 6MWT performed before and after a PR program.

(A and B) Results for the 6 responders (A) and 7 non-responders (B) who underwent gas exchange analysis. 6MWT: 6-min walk test; HR: heart rate; VCO_2: carbon dioxide output; VO_2: O_2 uptake; V_E: minute ventilation. Data are presented as the mean±SD. *p<0.05, **p<0.01 by repeated measures ANOVA.

Table 1. Characteristics of the 19 patients with fibrotic idiopathic interstitial pneumonia.

Variable, unit	All (n=19)	IPF (n=12)	f-NSIP (n=7)	P
Men/women, n	15/4	10/2	5/2	0.60
Age, years	65 ± 9	66 ± 7	62 ± 12	0.53
BMI, $kg.m^{-2}$	30 ± 6	30 ± 3	30±9	0.90
FVC, % predicted	75 ± 13	79 ± 12	70±13	0.13
TLC, % predicted	78 ± 19	83 ± 20	69 ± 14	0.11
FEV_1, % predicted	73 ± 12	75 ± 10	71 ± 15	0.44
DLCO, % predicted	40 ± 8	39 ± 8	42 ± 10	0.43
Exercise O2 therapy support, n (%)	15 (79)	9 (75)	6 (86)	1.00
BDI, score	7 ± 2	7 ± 2	6 ± 2	0,18
6MWT				
6MWD, mètres	425 ± 57	438 ± 59	401 ± 49	0.18
$SpO_{2\ nadir}$, % [#]	85 ± 5	84 ± 6	88 ± 4	0.12
Comorbidities, n (%)				
Arterial hypertension, %	11 (58)	8 (67)	3 (43)	0.37
Type 2 diabetes, %	8 (42)	7 (58)	1 (14)	0.17
Cardiovascular disease, %	7 (37)	6 (50)	1 (14)	0.15
Sleep-disordered breathing, %	6 (32)	3 (25)	3 (43)	0.62
Gastroesophageal reflux, %	2 (11)	1 (8)	1 (14)	1.00

Values are expressed as the mean ± SD or except for the number of mens and womens and for the comorbidities expressed as the number of patients (percentage). BMI: body mass index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; f-NSIP: fibrotic non-specific interstitial pneumonia; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; SpO_{2nadir}: minimum SpO_2 recorded; TLC: total lung capacity; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test. [#]The effect-size for the SpO_{2nadir} was moderate with 0.75.

Table 2. Baseline characteristics of the responders and non-responders patients to the 6MWT.

Variable, unit	Responders (n=9)	Non-responders (n=10)	p	ES
Pulmonary function				
FVC, % predicted	73 ± 13	77 ± 12	0.48	
TLC, % predicted	70 ± 12	82 ± 20	0.16	
FEV_1, % predicted	73 ± 14	74 ± 10	0.77	
DLCO, % predicted	44 ± 9	38 ± 7	0.15	0.73
6WMT				
6MWD, m	422 ± 66	428 ± 51	0.83	
SpO_{2nadir}, %	87 ± 4	83 ± 6	0.14	0.69
Dyspnoea end, Borg 0-10	6 ± 3	5 ± 2	0.21	
BDI	6 ± 2	7 ± 2	0.45	
SF-36 physical component score	50 ± 21	58 ± 18	0.41	
SF-36 mental component score	54 ± 18	65 ± 22	0.27	
HAD anxiety score	9 ± 4	6 ± 5	0.14	0.68
HAD depression score	7 ± 4	4 ± 5	0.10	0.77

Values are expressed as the mean ± SD. BDI: baseline dyspnoea index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; HAD: hospital anxiety depression scale; SF-36: short-form 36; SpO_{2nadir}: minimum SpO_2 recorded; TLC: total lung capacity; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test.

Table 3. Changes between pre- and post-PR program in responders and non-responders to the 6MWT.

Variable, unit	Responders (n=9)	Non-responders (n=10)	p-value	ES
ΔFVC, mL	2 ± 119	-55 ± 119	0.31	
ΔTLC, mL	131 ± 305	-347 ± 711	0.08	0.82
ΔFEV1, mL	26 ± 66	-85 ± 131	**0.04**	0.94
ΔDLCO, $mL.min^{-1}.mmHg^{-1}$	0.10 ± 0.94	-0.09 ± 0.13	0.47	
ΔTDI, score	1 ± 1	1 ± 1	0.93	
ΔSF-36 physical component score	9 ± 17	4 ± 16	0.47	
ΔSF-36 mental component score	6 ± 17	5 ± 15	0.86	
ΔHAD anxiety score	-2 ± 4	0 ± 3	0.23	
ΔHAD depression score	-1 ± 3	1 ± 2	0.41	

DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; HAD: hospital anxiety depression scale; SF-36: short-form 36; TLC: total lung capacity; TDI: transition dyspnoea index.

Table 4. Changes following PR program in 19 f-IIP patients.

	Pre-PR	Post-PR	p-value	ES
6MWD, m	425 ± 57	448 ± 68	**0.01**	0.37
SF-36				
Physical summary score	54 ± 19	60 ± 18	0.10	0.33
Physical functioning score	55 ± 23	63 ± 24	**0.004**	0.33
Mental summary score	60 ± 21	66 ± 21	0.14	0.28
BDI-TDI, score	6.8 ± 2.1	+0.9 ± 1.3	**0.01**	0.39
HAD				
Anxiety score	7.6 ± 4.8	6.7 ± 4.1	0.53	
Depression score	5.2 ± 3.5	5.3 ± 3.0	0.87	

6MWD: 6-min walk distance; BDI/TDI: baseline/transition dyspnoea index; HAD: hospital anxiety depression scale; SF-36: short-form 36.