Effect of respiratory muscle training and pulmonary rehabilitation on exercise capacity in patients with interstitial lung disease: A prospective quasi-experimental study

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Abstract:

BACKGROUND: Interstitial lung diseases (ILDs) are associated with skeletal muscle dysfunction, worsening exercise capacity, and poor health-related quality of life. The clinical relevance of respiratory muscle training (RMT) as part of pulmonary rehabilitation (PR) in patients with ILD largely remains unknown with limited research evidence.

OBJECTIVE: To evaluate the effect of PR on exercise capacity in patients with ILD and to study its relation with the severity of disease.

MATERIALS AND METHODS: Twenty-five patients diagnosed as ILD (clinical, radiological, or histopathological basis as per the American Thoracic Society/European Respiratory Society criteria) and willing for PR were enrolled in this prospective observational study conducted between 2016 and 2017 after obtaining informed consent. All cases were subjected to supervised exercise training thrice weekly for 8 weeks, tailored as per their capacity, in addition to pharmacologic and supportive treatment. Outcome measures including 6-min walk test (6MWT), respiratory muscle pressure, dyspnea (Borg scale), and spirometry were evaluated at baseline and 8 weeks and 6 months following completion of the program and were recorded in a prestructured pro forma.

RESULTS: The mean age of patients was 63.28 ± 10.88 years with majority being nonsmokers (88%) and females (60%). There was a significant improvement in the mean 6MWT distance \( P = 0.02 \), inspiratory muscle pressure \( P = 0.047 \), and dyspnea after exercise training when compared to at 8 weeks from the baseline. The change in spirometry values was nonsignificant. The improvement in outcome parameters was transient with no significant difference from the baseline to at 6 months after stopping PR.

CONCLUSION: Exercise training significantly improves respiratory muscle strength and functional capacity in patients with ILD. Larger studies with multidimensional analysis are required to investigate the promising outcome of PR in such patients.

Keywords: 6-min walk test, dyspnea score, inspiratory muscle pressures, interstitial lung disease, pulmonary rehabilitation, respiratory muscle training

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Kaushal, et al.: Inspiratory muscle training in ILD

Introduction

Pulmonary rehabilitation (PR) is a comprehensive patient-tailored intervention using a structured exercise and education program, designed to improve the physical and psychological condition of people with chronic respiratory diseases. It is a well-established and widely practiced therapeutic tool in chronic obstructive pulmonary disease (COPD) where it has been shown to confer a significant improvement in functional capacity and symptoms of dyspnea. Recent studies have further investigated the role of this modality in other chronic lung diseases such as interstitial lung diseases (ILDs).

ILDs are a group of diverse chronic lung conditions characterized by diffuse inflammation and fibrosis of lung parenchyma resulting in progressive lung stiffness, dyspnea, and decreased functional capacity. The prognosis in ILD is largely dependent on the etiology or subtype, and very few treatments have demonstrated improvements in either health-related quality of life (HRQoL) or community functioning for any of the ILDs. Therapies that can improve dyspnea, fatigue, exercise capacity, and quality of life are highly sought after in ILD with PR being explored as one of the potential modalities.

The provision of PR in ILD poses some unique challenges due to underlying pathophysiology, exercise responses, and symptoms. Exercise limitation is a common feature of ILD with close relation to worst HRQoL. The mechanisms of reduced exercise capacity in ILD are multifactorial and include gas exchange and oxygen diffusion limitation, ventilation-perfusion mismatch, circulatory limitations, pulmonary hypertension, skeletal muscle and respiratory muscle weakness, anxiety or depression, drug-induced myopathy, and a range of associated comorbidities. Two small randomized trials and few cohort studies have demonstrated the beneficial effect of PR on several of these factors, thereby demonstrating clinically significant improvement in functional capacity, HRQoL, and dyspnea in patients with ILD. Despite these promising outcomes, PR is not yet widely recommended for patients with ILD. Only weak recommendations regarding PR are provided in the most recent clinical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis (IPF) and ILD.

There are very few studies in India assessing the role of PR and its outcomes in patients with ILD. There is a wide gap between documented literature evidence regarding the benefits of PR and its clinical application in a resource-poor setup like ours compared to developed world. Hence, the present study was conducted to evaluate the role and feasibility of respiratory muscle training (RMT) and PR with its short- and long-term effects on exercise capacity in patients with ILD.

Materials and Methods

This study was a prospective quasi-experimental study conducted in the outpatient department of respiratory medicine of a tertiary care teaching institute. Assuming the prevalence of ILD as 15%, a sample size of 22 was shown to have an 80% power to detect an approximate effect size of 15% (based on the previous unit records) with the level of confidence aimed at 95%. Hence, expecting 10% attrition, a total of 25 patients with stable, moderate-to-severe ILD due to any cause were recruited for the study from April 2016 to March 2017, after obtaining written informed consent. The study was approved by the institutional ethics committee.

Inclusion criteria

All patients >18 years of age of both sexes; diagnosed as ILD on clinical, radiological, and histopathological basis (multidisciplinary approach) as per the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria due to any cause; and willing to participate in the PR program after obtaining informed consent were included in the study. All included patients were clinically stable without exacerbations in the past 3 months.

Exclusion criteria

1. Patients with other significant respiratory disorders such as acute infections, pulmonary tuberculosis, COPD, asthma, bronchiectasis, lung carcinoma, and pneumothorax
2. Patients having other comorbid diseases preventing from exercise training, for example, disability due to orthopedic, neurological, and acute cardiac causes
3. Physically and mentally unwell to attend the hospital for training
4. Already completed or participated in a PR program in the past 1 year

Procedure

All included patients were subjected to detailed history and physical examination, and relevant clinical information was recorded in a prestructured study pro forma. The baseline values of outcome parameters were measured at the time of inclusion to the study. All the patients were then subjected to PR for 8 weeks as per the protocol. The standard pharmacotherapy for ILD including oral and inhaled steroids, bronchodilators, mucolytics, and theophylline was continued in all patients as decided by the treating physician on the primary lung pathology of ILD. The value of outcome parameters was noted again upon completion of the rehabilitation program (8 weeks) and on follow-up at 6 months.

Exercise training

All patients underwent exercise training tailored as per their capacity which was increased or decreased as per the...
protocol. Endurance training (cycle ergometry), flexibility training, strength training, aerobic exercises, and RMT via a Powerbreathe device (a threshold inspiratory muscle trainer) were done as per the ATS/ERS guidelines. The schedule followed was supervised exercise training for a minimum of 60 min over separate sessions each day and 3 days a week for consecutive 8 weeks. Each supervised session had duration between 1 and 4 h tailored according to the capability of the patient. The participants also attended educational sessions on breathing exercises, lung health, stress management, and medications.

**Outcome measures**

The outcome measures were recorded at baseline, after completion of PR for 8 weeks, and on follow-up at 6 months after the exercise training program.

1. **6-min walk test (6MWT)** – Using a spiropolm handheld spirometer by Cosmed
2. **Respiratory muscle pressure (RMP)** – Micro-RMP respiratory pressure meter by care fusion
3. **Dyspnea severity** – Assessed by the Modified Medical Research Council (MMRC) scale and Modified Borg Dyspnoea Scale
4. **Standard spirometry** – which included measurement of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), carbon monoxide transfer factor, and static lung volumes (total lung capacity, functional residual capacity and residual volume); measured via body plethysmography as per ATS/ERS recommendations
5. **Diffusing Capacity of lung for Carbon monoxide (DLCO)** – Diffusion capacity for carbon monoxide was measured in ml/min/kPa, using equipment Master Screen body plethysmography (manufactured by Jaeger, Wuerzberg, Germany)
6. **Pulmonary hypertension** – Assessed by transthoracic echocardiogram with VIVID7 model of GE Healthcare system.

**Statistical analysis**

All the statistical analyses were performed using IBM SPSS performed using IBM SPSS Statistics software for Windows, Version 21.0 (IBM Corp., Armonk, New York, USA). Normally distributed data (6MWT distance and maximum inspiratory pressures) according to Shapiro–Wilk test (P > 0.05) were presented as means and standard deviation or 95% confidence intervals (CIs). Pearson’s Chi-square test was used to evaluate the differences between groups for categorical variables. Unpaired t-test was used to calculate the difference of means for quantitative variables. The subgroup analysis was presented as median and interquartile range as the data was not distributed normally, and compared using related samples Wilcoxon signed rank test. All tests were performed at a 5% level of significance; thus, an association was statistically significant if P < 0.05.

**Results**

A total of 85 cases of ILD attending the outpatient department were screened for exercise training program, and, as per the inclusion and exclusion criteria, 52 cases were selected. Of these, only 33 were willing to join the program and they were recruited after obtaining written informed consent. Of these, four cases opted out due to traveling issues, two were lost to follow-up, and two did not complete the schedule due to deteriorating disease. Twenty-five patients completed the 8-week PR schedule, and the outcome measures were evaluated for these patients after 8 weeks and 6 months of completion.

**Demographic profile**

The mean age of patients was 63.28 ± 10.88 years. The gender-wise distribution included 40% males (n = 10) and 60% females (n = 15). Majority of patients were nonsmokers (n = 22, 88%), three patients were former smokers, and none were active smokers. The mean DLCO value at baseline was 8.46 ± 4.29 ml/min/kPa. The severity of ILD was categorized on the basis of percentage of DLCO (predicted for age and height) at baseline with mild (DLCO >60%), moderate (DLCO between 40% and 60%), and severe (DLCO <40%) subgroups. The patients were also subgrouped as IPF and non-IPF-ILD and those with or without pulmonary hypertension.

The mean value of DLCO at 8 weeks was 9.07 ± 3.94 and at 6 months was 8.61 ± 4.2 with no significant change from the baseline (P = 0.18 and 0.77, respectively, when compared with baseline). The severity categorization also changed only marginally with 7, 4, and 14 patients of mild, moderate, and severe category, respectively, at the end of 6 months.

Majority of the patients (n = 19) were on oral steroid therapy at the initiation of the program which was essentially continued in tapering doses in 18 patients at 8 weeks and 16 patients at 6 months, respectively. During the study period, only antifibrotic drug available was pirfenidone with 6 patients on this therapy at the beginning. At 8 weeks, seven patients were on pirfenidone which decreased to 6 again at six months in view of drug intolerance by one patient. Nintedanib was introduced in the last quarter of the study period and therefore none of our patients were on nintedanib.

The baseline demographic characteristics, etiological diagnosis of ILD, and associated comorbidities are summarized in Table 1.

**Change in 6-min walk test distance**

There was a statistically significant improvement in the mean 6MWT distance after 8 weeks of exercise training.
However, this effect was transient with deterioration in the mean distance between 8 weeks and 6 months (mean difference 31.34, \( P = 0.021 \)) and returned to almost baseline values at the end of 6 months [Table 2]. The test results also showed less fall in minimum SpO\(_2\) values and percentage of desaturations at 8 weeks compared to baseline (83.48% vs. 86.32 and 9.08% vs. 11.04%, respectively). On subgroup analysis, the mean 6MWT distance was found to improve at 8 weeks in all categories of ILD with maximum improvement in the severe category (\( P = 0.014 \)), non-IPF group (\( P = 0.003 \)), and those without pulmonary hypertension (\( P = 0.001 \)) [Table 3]. However, the study was highly underpowered to reliably comment on the level of significance on subgroup analysis owing to small sample size.

### Change in dyspnea scale and respiratory muscle pressures

The dyspnea was assessed using both MMRC scale and BORG scale. On MMRC scale, the number of patients in the severe category (Grade 3 or 4 MMRC) decreased from 15 (60%) at the baseline to 7 (28%) at the end of 8 weeks (\( P = 0.014 \)) with category changing from severe to mild (Grade 1 or 2) for 8 patients with PR. The effect was partially sustained at 6 months with 13 (52%) patients falling in mild to moderate group and 12 (48%) in severe subgroup on MMRC classification.

There was a significant decrease in the BORG scale for dyspnea and fatigue after 8 weeks of PR (median values decreased from 7 to 5 for dyspnea and from 9 to 5 for fatigue, respectively). However, the effect was short-lasting with values returning to almost baseline at 6 months after completion.

The mean value of peak inspiratory muscle pressure also improved significantly with exercise training (62.68 ± 25.84 at baseline and 79.92 ± 27.20 at 8 weeks, respectively, \( P = 0.00 \), 95% CI = −23.0−11.3). Moreover, a significant negative correlation was established between BORG scale for dyspnea and inspiratory muscle pressure (\( P = 0.047 \)), indicating an improvement in dyspnea scale with an increase in muscle strength due to training. However, all these effects were reversed at 6 months after completion of PR.

### Changes in spirometry

The mean values of FEV\(_1\) and FVC showed insignificant changes when compared at baseline, 8 weeks, and 6 months. Despite no change in lung volume parameters, there was an improvement in 6MWT and dyspnea scales.

### Radiological changes

The radiological features on high resolution computerized tomography (HRCT) chest, were compared at baseline and at 6 months. Fourteen patients showed no changes, 7 had worsening in fibrosis, 1 patient each showed exacerbation and increase in number of lung cysts with 3 patients refusing for a repeat scan.

### Table 1: Baseline characteristics of the study participants

| Variable                      | Data     |
|-------------------------------|----------|
| Age, years*                   | 63.28±10.88 |
| Age of symptom onset, years*  | 60.08±10.88 |
| Height, cm*                   | 143±8.07  |
| Weight, kg*                   | 43±12.87  |
| BMI, kg/m\(^2\)*              | 26.03±4.99|
| Diagnosis*                    |          |
| CTD-ILD                       | 12 (48)  |
| HSP                           | 5 (20)   |
| IPF                           | 3 (12)   |
| Idiopathic NSIP               | 2 (8)    |
| LIP                           | 1 (4)    |
| CPFE                          | 1 (4)    |
| Sarcoidosis                   | 1 (4)    |
| Comorbidities*                |          |
| Diabetes                      | 20 (80)  |
| Hypertension                  | 10 (40)  |
| Hypothyroidism                | 6 (24)   |
| CKD                           | 1 (4)    |
| OSAHS                         | 1 (4)    |
| Osteoporosis                  | 4 (16)   |
| Pulmonary hypertension        | 4 (16)   |
| Long-term oxygen therapy*     | 3 (12)   |
| Severity of ILD*              |          |
| Mild (DLCO >60%)              | 6 (24)   |
| Moderate (DLCO 40%-60%)       | 5 (20)   |
| Severe (DLCO<40%)             | 14 (56)  |

*Mean±SD, *n*(%). CTD-ILD: Connective tissue disease-associated interstitial lung disease, HSP: Hypersensitivity pneumonitis, IPF: Idiopathic pulmonary fibrosis, NSIP: Nonspecific interstitial pneumonia, LIP: Lymphocytic interstitial pneumonia, CPFE: Combined pulmonary fibrosis and emphysema, CKD: Chronic kidney disease, OSAHS: Obstructive sleep apnea-hypopnea syndrome, DLCO: Diffusing capacity of lung for carbon monoxide, SD: Standard deviation, BMI: Body mass index

### Table 2: Comparison of primary objectives at various intervals (n=25)

| Variable                          | Mean±SD | Mean difference/increase in distance | \( P \) |
|-----------------------------------|---------|--------------------------------------|--------|
|                                  | Baseline 8 weeks 6 months 8 weeks-baseline 6 months-baseline 8 weeks-baseline 6 months-baseline |
| 6MWT distance (m)                 | 295.68±81.99 335.36±72.15 304.12±78.92 39.68 8.44 0.002 0.421 |
| Peak inspiratory muscle pressure (cm H\(_2\)O) | 62.68±25.84 79.92±27.20 72.64±28.37 17.44 9.96 0.03 0.016 |

SD: Standard deviation, 6MWT: 6-min walk test
Table 3: Subgroup analysis of 6-min walk test distance (metres)

| Variable                  | Baseline | 8 weeks | 6 months | P      |
|---------------------------|----------|---------|----------|--------|
| **Severity**              |          |         |          |        |
| 1. Mild (n=6)             | 363 (168)| 371 (147)| 394 (108)| 0.043  |
| 2. Moderate (n=5)         | 312 (126)| 306 (113)| 324 (54) | 0.141  |
| 3. Severe (n=14)          | 264 (129)| 324 (100)| 254 (131)| 0.014  |
| **Pulmonary Hypertension**|          |         |          |        |
| 1. With (n=4)             | 228 (107)| 243 (98) | 225 (131)| 0.465  |
| 2. Without (n=21)         | 312 (129)| 350 (89) | 324 (101)| 0.001  |
| **Etiology**              |          |         |          |        |
| 1. IPF group (n=3)        | 270      | 308     | 306      | 0.109  |
| 2. Non-IPF (n=22)         | 301 (138)| 333 (96) | 324 (114)| 0.003  |

IPF: Idiopathic pulmonary fibrosis, IQR: Interquartile range

Discussion

The present study demonstrates that an 8-week exercise training-based PR program in patients with ILD showed a significant improvement in functional capacity (as indicated by improvement in 6MWT distance), exercise capacity and dyspnea (improvement in BORG and MMRC scale), and RMPs. This benefit was seen regardless of age, severity (more marked in severe group), etiology (IPF or non-IPF), or presence and absence of pulmonary hypertension. Although there was an effective treatment for clinical improvements in patients with ILD, these benefits were unpreserved in the long term (6 months after stopping PR). Nevertheless, the results of the study strongly suggest that PR is safe and feasible for patients with ILD and can be recommended as part of standard care in this population.

ILDs are a serious cause of morbidity and mortality around the world with very few treatment options available. Patients with ILD have various disease-related restrictions, in view of which exercise training seems to be an easy approach to bring the positive outcomes in them, and the same was observed in the present study. The patient profile in this study included female predominance (male-to-female ratio 1:1.5) with about 50% of patients having connective tissue disease-associated ILD; patients with IPF and with pulmonary hypertension comprised 12% and 16% of the study group, respectively.

The primary outcome measure was an improvement in the 6MWT distance, which has been recommended by the ATS as a valid and well-accepted tool to assess exercise capacity in lung disease patients. Recently, this test was also validated for IPF, and the minimal clinical important difference (MCID) was established as 24–45 m. The results of our study showed a significant improvement in the mean 6MWT distance (39.68 m, \( P = 0.002 \)), which corresponds to average increase (44.34 m) seen in Cochrane meta-analysis of five randomized controlled trials on PR in ILD. There have been several small studies of PR in patients with ILD published to date, and all of them demonstrate a significant improvement in 6MWT distance with exercise training. Moreover, our study shows that patients with major limitation in 6MWT, initially, benefitted the most with PR (46.86 m in the severe group vs. 24 m in the mild group), suggesting that even those patients who are severely impaired can substantially improve their functional status without any side effects. These results verified similar findings of previous studies by Spielman et al., Ferreira et al., and Boutou et al. who also observed a higher probability of significant improvement in patients with lowest initial distance walked in 6MWT.

Our exercise training program was also effective in improving dyspnea and quality of life as measured by MMRC and BORG scale, which is consistent with previous reports in ILD and IPF patients. The MCID for BORG dyspnea scale has been well established, and our study shows that, on average, the patients on PR achieved improvement equal or greater than the MCID. The increase in inspiratory muscle pressures could be a possible reason for improved perception of dyspnea in these cases despite no improvement in PFTs. Maria Koulopoulou et al. demonstrated that inspiratory muscle strength and dyspnea improve significantly, when evaluated after 8 weeks of high-intensity inspiratory muscle training program in patients with ILD.

The effects of PR on pulmonary function tests are largely controversial, unlike COPD where a definite improvement in PFT has been demonstrated with exercise training. The study by Vonbank et al. concluded a significant improvement in FVC values after endurance and RMT in patients with ILD whereas Ozalevli et al. described no improvement in FVC values. In our study, also, no significant change was noted in FEV1 and FVC values when evaluated at 8 weeks and 6 months.

Limited evidence is available regarding long-term effects of PR. In Cochrane meta-analysis, only two studies reported long-term outcomes, with no significant effects of PR on clinical variables or survival at 3 or 6 months.
In our study, also, most of the parameters including 6MWD and dyspnea scales showed a decline when reassessed at 6 months from the baseline after stopping PR. The progressive nature of disease process itself could be a possible reason for such deterioration.

Most of these studies have been published from developed countries where PR program is already well established for COPD patients and now its utility is increasingly being recognized for patients with ILD. Literature evidence regarding this issue is lacking from the Indian subcontinent. A pilot Indian study by Gupta et al. demonstrated similar benefits in dyspnea and quality of life scales after 6 weeks of domiciliary PR program. The results of our study combined with this pilot study provide an opportunity for the establishment of PR as a cheap yet effective treatment modality in reducing health-care costs of chronic lung condition patients in a resource-poor country like ours.

The major limitations of this study are that it is an uncontrolled clinical study and the clinical improvement cannot be solely attributed to exercise training program as the role of confounders was not evaluated. The sample size was also less and ILD being a disease with wide spectrum can have different clinical presentations per se. The strengths of this study include properly conducted PR program under trained personnel and long-term follow-up done for all patients.

Conclusion

The findings of this study strengthen the existing evidence for the beneficial effects of supervised exercise training-based PR on clinical outcomes in patients with ILDs, especially in those with severe disease. It is recommended to be a safe and effective treatment with low concerns of side effects and could be practiced as standard care for patients with ILD. Larger scale studies with a more robust follow-up are required to assess the long-term effect of continued PR in these patients.

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Conflicts of interest

There are no conflicts of interest.

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