Respiratory Impairment, Limited Activity, and Pulmonary Rehabilitation in Patients with Interstitial Lung Disease

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ABSTRACT. Interstitial lung disease (ILD) is a diverse group of chronic lung conditions characterized by dyspnea, exercise-induced hypoxemia (EIH), and exercise intolerance. Since activity limitations and impaired health-related quality of life (HRQoL) in ILD are similar to those in other chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), pulmonary rehabilitation is also indicated for patients with ILD. This rehabilitation program mainly comprises exercise training and self-management education. Exercise training is the most important component of pulmonary rehabilitation. It significantly improves dyspnea and enhances exercise capacity and HRQoL in patients with ILD. The standard exercise prescription used for COPD is also effective for ILD. However, considering that disease progression and exercise-limiting factors are different in patients with COPD is necessary. Severe EIH, the adverse effects of corticosteroid administration, and comorbidities often lead to difficulty in employing a sufficient exercise intensity. Some modifications in the exercise prescription for individual patients or strategies to minimize EIH and dyspnea are required to optimize training intensity. Since EIH is common and severe in patients with ILD, supplemental oxygen should be provided. In advanced and more severe patients, who have difficulty in performing exercises, energy conservation techniques and the use of energy-saving devices to improve and maintain the patients’ activities of daily living may be effective.

Key words: Interstitial lung disease, Exercise capacity, Dyspnea, Hypoxemia, Exercise training

Interstitial lung disease (ILD) is a diverse group of chronic lung conditions comprising more than 200 disease entities. It is characterized by lung inflammation and/or scarring, inducing restrictive ventilatory disorders. Pulmonary rehabilitation has become an accepted treatment for ILDs because of respiratory impairment, dyspnea on exertion, and exercise-induced hypoxemia (EIH), affecting the patients’ activities of daily living (ADLs) and health-related quality of life (HRQoL). Although significant short-term improvements in patients with ILD following pulmonary rehabilitation have been demonstrated, clinical problems in which the progressive nature of the disease and its characteristics, such as marked EIH, limit the progression of rehabilitation programs have not been elucidated yet. Therefore, this review describes the clinical features of ILD and the consideration and practical guidance for pulmonary rehabilitation, focusing on exercise training.

Clinical Features and Problems of ILD

Disease specificity of ILD

ILD is a heterogeneous group of clinical disorders characterized by inflammation and fibrosis of the lung parenchyma. Pathological images are diverse and classified into various independent disease groups based on the histopathological pattern. Therefore, the clinical course and treatment responsiveness differ depending on the disease group. Specifically, idiopathic pulmonary fibrosis (IPF), the
most common type of idiopathic interstitial pneumonia, is progressive and refractory and has a poor prognosis. The disease trajectory is heterogeneous, including patients who follow a slow and stable course, those who experience an acute exacerbation of IPF, and those who progress rapidly in a short-term period. Recognizing that ILD is a “refractory and progressive disease” is necessary. This is an important factor in not only managing but also considering the patients for selection and evaluation of the effects of exercise training. In addition, we should acknowledge ILD as the most distinct respiratory impairment and activity-limiting disease compared with other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD).

**Respiratory impairment**

In ILD, interstitial fibrosis reduces lung compliance. Restrictive ventilatory disorders, indicated by decreased total lung capacity and vital capacity, are usually observed in pulmonary function tests. Vital capacity significantly declines, and this decline progresses over time. As a result, breathing effort increases, and the patient has a rapid and shallow breathing pattern to ensure ventilation by increasing the respiratory rate. This breathing pattern becomes prominent during exercise, as the dead space ventilation increases.

Gas exchange in ILD is characterized by diffusion limitation (decreased diffusing capacity of the lungs for carbon monoxide [DLCO]), which may be seen before lung capacity decreases. A decreased DLCO is a predictor of EIH owing to their strong correlation. It becomes remarkable when the DLCO decreases to approximately 40% of the predicted value. Oxygen therapy is the control management for diffusion disorders and is essential, especially during exertion.

**Dyspnea**

Dyspnea on exertion is a common and disabling symptom and is observed in more than 80% of patients with symptomatic ILD. It is also associated with pulmonary function and depression. Moreover, it limits the patient’s physical activity and significantly impairs exercise tolerance and ADL performance, markedly impacting their HRQoL. However, the relationship between dyspnea and EIH often differs among individual patients. In some patients, the sensation of dyspnea is poor even with significant EIH, and thus, assessments of both dyspnea and EIH are required.

**Exercise-induced hypoxemia**

Hypoxemia is often absent at rest in the early stages of ILD (Fig. 1). However, EIH appears relatively early in the course of the disease. EIH is a critical impairment and more advanced than other chronic respiratory diseases, such as COPD. Furthermore, it is identified as a prognostic predictor of mortality.

Since the pulmonary capillary bed is reduced, pulmonary diffusing limitation and ventilation perfusion mismatch show remarkable EIH. Hypoxemia induces a rapid and shallow breathing pattern and, as a result, increases the effort for breathing. Furthermore, it limits the supply of oxygen to peripheral skeletal muscles and causes hypoxic pulmonary vasoconstriction, limiting the cardiac output. The reduction in diffusing capacity and hypoxemia during exercise depends on cardiac output. Thus, the prevalence of pulmonary hypertension is increased in patients with EIH.

**Skeletal muscle dysfunction**

Respiratory impairment, gas exchange disorders, and circulatory limitations are major factors limiting exercise.
tolerance and capacity of patients with ILD. In addition, skeletal muscle dysfunction contributes to exercise intolerance\(^{11}\). Weakness of the quadriceps muscle is associated with reduced functional exercise capacity\(^{13,16}\), and quadriceps force is reduced in patients with ILD, which is significantly lower than in healthy controls\(^{17}\). Moreover, lower muscle strength was associated with a greater activity limitation. Possible causes of skeletal muscle dysfunction include deconditioning due to physical inactivity, malnutrition, oxidative stress, disease-specific systemic inflammation, and adverse drug reactions. Particularly, long-term corticosteroid administration causes skeletal muscle weakness, such as steroid-induced myopathy. Hanada\(^{17}\) has reported that quadriceps and hand grip forces were significantly lower in subjects receiving corticosteroids than those in controls, and muscle weakness is inversely correlated with the total amount of corticosteroids administered. Furthermore, muscle weakness and exercise incapacity in patients with ILD and mild dyspnea were associated with corticosteroid treatment\(^{14}\). The effects of exercise training on patients receiving corticosteroids were less than those on patients not treated with corticosteroids\(^{12}\).

**Impairment of exercise capacity**

Exercise limitation is a common feature of ILD, and its direct causes include dyspnea and deconditioning due to physical inactivity. It contributes to poor functional status and reduced HRQoL. The pathological mechanism of ILD is similar to those in chronic respiratory diseases, such as COPD. However, it differs from other respiratory diseases, in which gas exchange disorders and circulatory limitations are important contributors to exercise limitation in ILD\(^{19}\). Peak oxygen uptake as an indicator of exercise tolerance is better associated with circulatory limitation than respiratory dysfunction in patients with ILD\(^{9,10}\). Oxygen pulse, an indirect marker of stroke volume, is restricted to increasing from the early stage of exercise, and in some patients, it remains at a plateau or decreases even if exercise intensity is increased\(^{10}\). As a result, the heart rate tends to increase for a given exercise intensity compared with healthy individuals. Circulatory limitations promote hypoxia in peripheral tissues, lower mixed venous oxygen saturation, and worsen EIH.

**Basic and Special Considerations for Pulmonary Rehabilitation in Patients with ILD**

In ILD, particularly IPF, reducing symptoms and improving the patients’ HRQoL are difficult even with management, including pharmacological treatment. Pulmonary rehabilitation reduces dyspnea and improves the patients’ HRQoL. Exercise training, a core component of pulmonary rehabilitation, significantly improves dyspnea and enhances exercise capacity and HRQoL of patients with ILD\(^{19}\). However, these effects are short-term and long-term effects longer than six months have not been observed. Studies on exercise training for patients with ILD are based on the rehabilitation program for COPD, indicating that the same program can be implemented in patients with ILD.

Although activity limitation in patients with ILD is similar to that in patients with COPD, disease progression and exercise-limiting factors are different among these patients. In severe EIH, the adverse effects of corticosteroid administration and comorbidities often make sufficient exercise intensity difficult to employ. Patients with ILD present with various comorbidities that may also affect exercise capacity. Therefore, disease-specific and/or individual differences, including comorbidities, should be considered in developing exercise programs. In addition, the timing of exercise training should be considered. Early referral to exercise training should be considered in all patients, particularly those with IPF, because of the difficulty in implementing exercises in advanced or severe patients with uncontrollable symptoms. Exercise training may be more effective when offered earlier in the disease trajectory.

In patients with advanced and severe ILD, considering the referral to palliative care and trying to reduce the burden in performing ADLs by teaching the patients’ energy conservation techniques and using energy-saving devices are necessary\(^{20}\).

**Practical Approach of Pulmonary Rehabilitation**

**Patient selection, assessment, and program component**

Several studies have examined the effects of exercise training on patients diagnosed with ILD. A diagnosis is not an indication for exercise training. In patient selection, disease severity and progression rate are the most important criteria for patient selection. Patients with ILD show several disease trajectories, including long periods of stability, gradual or rapid progression, and acute exacerbation. Implementing exercise training programs and obtaining its effects on patients with severe or advanced disease or rapid progression are difficult. The feasibility, safety, and benefits of exercise training during and early after acute exacerbation of ILD are unclear.

Patient assessment is required when employing exercise training. Symptoms (e.g., dyspnea and cough), exercise capacity, and the patients’ HRQoL are the main elements of pulmonary rehabilitation (Table 1) and are similar to those of COPD. Assessment of desaturation (EIH) with dyspnea is essential for evaluating exercise capacity. In some patients with ILD, a discrepancy exists between dyspnea and the degree of EIH, and identifying these patients is necessary because of safety management for exercise training. Many patients with ILD have various comorbidities, which may also impact exercise capacity, functional status, and HRQoL. These comorbidities include ischemic heart dis-
Effects of exercise training on ILD are limited, a systematic review that patients with ILD. Efficacy and characteristics of exercise training for patients with ILD are currently unknown. Moreover, the effects of inspiratory muscle training on breathing have not been investigated in patients with ILD. Breathing retraining or controlled breathing techniques are difficult for patients with ILD and have not been shown to be useful. Pursed lip breathing, proven to be useful in patients with COPD, did not acutely improve dyspnea on exertion, walking distance, and gas exchange in patients with ILD. The effects of chest wall mobilization techniques and respiratory muscle relaxation to reduce the effort of breathing have not been investigated in patients with ILD. Moreover, the effects of inspiratory muscle training on these patients are currently unknown.

Efficacy and characteristics of exercise training for patients with ILD

Although randomized controlled trials examining the effects of exercise training on ILD are limited, a systematic review has shown that exercise training improves exercise capacity, dyspnea, and the patients' HRQoL. In addition, no significant adverse events have been reported, and exercise training can be safely performed in this patient group. These programs are based on those employed in patients with COPD. However, many studies did not have a detailed description of exercise prescription, and the disease-specific program and progress criteria remain unclear. Dowman et al. have examined the effects of an 8-week exercise training program as a randomized controlled trial involving 142 patients with ILD by disease classification. As a result, although the effects of the program were observed in all disease groups, they were particularly larger in patients with IPF and asbestosis than those with connective tissue disease-related ILD. These results indicate that exercise training is effective regardless of ILD disease classification.

Obtaining the effects of exercise training is difficult in severe patients, and exercise training should be started earlier in the disease course for all patients, particularly in patients with IPF. A major cause of the poor efficacy of exercise training in severe patients is the inability to adequately increase the exercise intensity due to severe dyspnea and EIH, and controlling these symptoms is essential in exercise training. Furthermore, in exercise training, understanding the pathophysiology and characteristics of impairment in each subject is important; furthermore, observing the changes in symptoms during the clinical course is crucial as well. The dynamic changes in the respiratory status during exercise compared with during rest may lead to early detection of complications, such as acute exacerbation, pneumothorax, and progression of pulmonary hypertension in clinical practice.

Practice of exercise training for ILD

Exercise training for patients with ILD mainly consists of whole-body endurance and upper and lower limb resistance exercises, similar to that for patients with COPD. Endurance training includes cycling and walking. The standard exercise prescription used for COPD is also effective on ILD, including 8-12 weeks of the training. The exercise intensity should be 60-80% of the maximum oxygen consumption, maximum work rate, or maximum walking speed obtained from various exercise tests. The target exercise duration should be set to more than 20 min. However, patients with ILD are heterogeneous and require modifications in exercise prescriptions according to each individual patient.

Limb resistance training was performed using a free weight, an elastic band, and a training machine. The exercise intensity started low, which gradually increased. All these should be performed three times a week, preferably daily. During exercise training, percutaneous oxygen saturation (SpO2) and dyspnea should be monitored. If controlling EIH or dyspnea is difficult, the following strategies or methods of training should be considered. Several strategies to minimize EIH and dyspnea and to optimize training intensity have been proposed for patients with COPD and ILD.
1) Interval training

Interval training is a type of discontinuous exercise involving a series of high-intensity exercises interspersed with rest or recovery periods. A systematic review comparing interval training compared with continuous training in patients with varying degrees of COPD has shown that functional capacity, dyspnea, and HRQoL significantly improved in both groups, with no significant difference between the groups\(^\text{25}\). In the clinical setting, few patients with ILD can perform continuous training for 20 min; thus, discontinuous training is often indicated. Interval training was demonstrated to be well tolerated and preferred by patients with advanced ILD\(^\text{26}\) and may be considered an alternative to continuous training in patients with ILD, especially in those with severe EIH or dyspnea.

2) Supplemental oxygen

In patients with ILD, the use of supplemental oxygen during exercise training may lead to optimization or superior training outcomes. If the patients who experience marked desaturation during exercise have difficulty achieving the required training intensity, instead of reducing the training intensity, a necessary and sufficient amount of oxygen should be administered. It may be useful to help patients achieve effective training intensity\(^\text{27}\).

Since high-flow rates of oxygen are often required in this patient group, selecting appropriate oxygen delivery devices (e.g., nasal cannula and simple face mask) is important. When a higher concentration of oxygen is needed, a simple face mask or non-rebreather mask should be indicated according to relevant institutional protocols. However, during the coronavirus disease 2019 (COVID-19) pandemic, the combined use of a surgical mask over the nasal cannula is empirically useful in maintaining adequate SpO\(_2\) in some patients (Fig. 2).

Therefore, evaluating the effects of supplemental oxygen on each subject is necessary, rather than uniformly administering oxygen only due to the presence of EIH and dyspnea\(^\text{27}\). The purposes of supplemental oxygen are to assess exercise tolerance (6-minute walk test and constant-load exercise test) with and without oxygen administration; to compare changes in indicators, such as dyspnea, walking distance, and exercise duration; and to evaluate the patients’ response. Exercise endurance time is sensitive to changes due to these interventions\(^\text{28}\). Moreover, it is also suitable for assessing the effects of oxygen use.

Although exercise capacity was increased, a systematic review evaluating the impact of supplemental oxygen on training outcomes in patients with ILD has shown that oxygen therapy has no effects on dyspnea during exercise\(^\text{29}\). Future trials are warranted to evaluate whether improvements in exercise capacity with oxygen use can affect the HRQoL and physical activity of patients with ILD.

3) High-flow nasal cannula oxygen therapy

High-flow nasal cannula (HFNC) oxygen therapy is a recently introduced high-flow oxygen delivery system. This consists of an air-oxygen blender and heated humidification system and generates a gas flow up to 60 L/min and fraction of inspired oxygen (FIO\(_2\)) up to 100%, allowing the administration of oxygen at accurate concentrations. In addition, HFNC has several effects such as washout of anatomical dead space and improved gas mixing in large airways, high nasal inspiratory flow, and generation of a low-level positive airway pressure. It is expected that these effects are useful for preventing severe EIH and reducing the effort of breathing during exercise (Fig. 3).

Cirio et al.\(^\text{31}\) have evaluated the effects of the administration of oxygen using HFNC in patients with COPD during exercise and reported that EIH and dyspnea were sig-
significantly reduced and oxygen therapy using HFNC allowed the patients to exercise for a longer time with a higher exercise intensity.

A randomized controlled crossover trial was conducted to compare the effects of HFNC (50 L/min; FIO₂ 0.5) on exercise endurance time, SpO₂, and dyspnea with those of oxygen therapy using a Venturi mask (15 L/min; FIO₂ 0.5) in patients with fibrotic ILD. They reported no significant differences in endurance time, SpO₂, and dyspnea between HFNC and Venturi mask. In this study, the FIO₂ setting may have been insufficient during exercise. The effects of HFNC with FIO₂ may be shown according to the degree of EIH in each patient. This may be due to the benefit of using this device in patients with severe EIH. Further large-scale studies are needed.

4) Noninvasive ventilation

The combination of exercise training and noninvasive positive pressure ventilation (NPPV) enables high exercise load and improves exercise tolerance in patients with moderate to severe COPD. In patients with IPF, the use of NPPV during exercise reduced EID and dyspnea, improved exercise tolerance, and decreased the heart rate, indicating its usefulness. However, tachypnea is likely to occur during exercise in patients with ILD, which often makes synchronization with the ventilator difficult. Oxygen administration using HFNC is more tolerated than NPPV in patients with synchrony.

5) Alternative exercise interventions

Some strategies have been proposed to optimize training intensity and decrease dyspnea in patients with COPD during exercise training. These interventions in clinical settings include single-limb partitioning, Nordic walking, and downhill walking. These strategies may be useful in patients who cannot tolerate high-intensity exercises due to EIH or dyspnea. In patients with COPD, these strategies showed some positive effects on exercise capacity and/or HRQoL compared with conventional training. However, the feasibility and outcomes of these interventions have not been investigated in patients with ILD. Further research is required to compare the effects of these interventions with those of conventional training.

Energy conservation techniques and the use of energy-saving devices in performing ADLs

Improving and maintaining a patient’s ADL is crucial, which is conducted for patients with COPD. This intervention aims to reduce energy expenditure and includes methods such as pacing, coordinating breathing with tasks, sitting to perform activities, performing ADLs slowly, using lightweight equipment, and regular rest breaks. Although energy conservation techniques and the use of energy-saving devices may be useful for improving ADL performance, their effectiveness has not been proven in patients with ILD.

First, essential or important activities to the patient are restricted due to dyspnea and EIH should be identified. In addition, the physiotherapist and patient should consider the pace of movement and timing of breaks in performing activities in burden.

Patients with advanced ILD often develop severe dyspnea and EIH, even in performing basic ADLs. The living environment at home should be set to reduce the physical burden by using self-help tools and equipment to facilitate the performance of activities, installing handrails for standing up, and reducing steps. Because indoor walking is also limited in patients with severe ILD, placing a few
chairs to take a break while moving from the living room to
the toilet or bedroom is beneficial. In addition, being careful
not to entangle or get caught in the oxygen extension
tube is important.

A fundamental intervention for reducing the burden in
the performance of ADLs is to slowly perform activities,
and reviewing how to spend the day and establishing rou-
tines are also important. Daytime activities are often con-
centrated in the morning after waking up; thus, distributing
activities throughout the day should be considered. In addi-
tion, planning ADLs is crucial.

These interventions are empirically useful for patients
with advanced ILD who have difficulty performing exer-
cise training. Strategies to enhance and maintain the per-
formance of ADLs as part of patient education and self-
management in pulmonary rehabilitation programs should
be provided.

**Conclusion**

Pulmonary rehabilitation is an important component of
comprehensive care for patients with ILD. Exercise training
can improve exercise capacity, symptoms, and HRQoL of
these patients. Although the standard exercise prescription
for patients with COPD is also effective in patients with
ILD, the mechanism of exercise limitation and clinical course of ILD is different from that of COPD; therefore, special consideration is required. Particularly, EIH is common; therefore, supplemental oxygen is recommended, and other methods for reducing EIH should be considered.

An approach that considers disease specificity and the
clinical course is important. Hence, understanding the char-
acteristics of the subject’s dysfunction, disease severity,
progression rate, and clinical course is essential. Moreover,
to constantly discuss the role and potential of pulmonary re-
habilitation, exercise training is important. In clinical prac-
tice, the effects of antifibrotic treatment on patients with
IPF and progressive fibrosing ILD are expected; thus, the
timing, roles, and significance of pulmonary rehabilitation
may change in the future.

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