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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Αναπνευστική αποκατάσταση στις διάμεσες πνευμονοπάθειες

ΙΩΑΝΝΑ ΑΥΓΕΡΙΝΟΥ

ΑΘΗΝΑ, 2019

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Ευχαριστήριο Σημείωμα

Θα ήθελα να ευχαριστήσω θερμά τον κύριο Καθηγητή **Νικόλαο Κουλούρη** για την ευκαιρία να συμμετάσχω στο μεταπτυχιακό πρόγραμμα σπούδών.

Ευχαριστώ θερμά για τη πολύτιμη βοήθεια και καθοδήγηση στη συγγραφή της διπλωματικής μου εργασίας: τον επιβλέπων Καθηγητή **Νικόλαο Κουλούρη**, τον Αναπληρωτή Καθηγητή **Πέτρο Μπακάκο και την Επίκουρη Καθηγήτρια Νικολέττα Ροβίνα.**

Contents

Abstract

Interstitial lung diseases (ILDs) comprise a heterogeneous group of more than 300 different chronic conditions that affect primarily and to varying degrees irreversibly the lung parenchyma and whose prognosis heavily depends on their aetiology and type.

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Epidemiologically interstitial lung disease is divided in disease of known aetiology and in disease of unknown aetiology (idiopathic), the most common being the latter. Irrespective of individual category, idiopathic pulmonary fibrosis and sarcoidosis represent together more than 50% of all interstitial lung disease cases.

Pathological, Interstitial lung diseases are characterized by involvement of the lung parenchyma with varying amounts of inflammation and fibrosis leading to restrictive ventilatory syndrom and impaired gas exchange.

Clinically, Interstitial lung diseases are characterized by dyspnea and decreasing exercise capabilities lead to patients developing disabilities and impairments in their health related quality of life.

Treatment are often limited, without proven effect on survival and health related quality of life and associated with significant side effects.

Pulmonary rehabilitation has been defined as an "evidence-based" multidisciplinary and comprehensive intervention for patients with chronic

respiratory disease who are symptomatic and often have decreased daily life activities.

Comprehensive pulmonary rehabilitation programs involve not only exercise training with aerobic conditioning, strength and endurance training and respiratory therapy but also educational lectures, nutritional interventions, behavior modification techniques to improve self-management and physiological support.

The aim of this interview is to determine whether pulmonary rehabilitation in patients with interstitial lung disease has beneficial effects on exercise capacity symptoms, quality of life and survival compared with no pulmonary rehabilitation in patients with interstitial lung disease, to assess the safety of pulmonary rehabilitation in patients with interstitial lung disease.

Περίληψη

Η διάμεση πνευμονοπάθεια είναι μια ετερογενή ομάδα πάνω από 300 διαφορετικών χρόνιων παθήσεων που επηρεάζουν πρωτίστως και σε ποικίλους βαθμούς ανεπανόρθωτα το πνευμονικό παρέγχυμα και των οποίων η πρόγνωση εξαρτάται σε μεγάλο βαθμό από την αιτιολογία και τον τύπο τους.

Η επιδημιολογικά διάμεση πνευμονοπάθεια διαιρείται σε ασθένεια γνωστής αιτιολογίας και σε ασθένεια άγνωστης αιτιολογίας (ιδιοπαθής), με πιο συνηθισμένη κατηγορία την τελευταία. Ανεξάρτητα από την κατηγορία, η ιδιοπαθής πνευμονική ίνωση και η σαρκοείδωση αντιπροσωπεύουν μαζί περισσότερο από το 50% όλων των περιπτώσεων διάμεσης πνευμονικής νόσου.

Παθολογικές, διάμεσες πνευμονοπάθειες χαρακτηρίζονται από εμπλοκή του πνευμονικού παρεγχύματος με ποικίλες ποσότητες φλεγμονής και ίνωσης που οδηγούν σε περιοριστικό αναπνευστικό σύνδρομο και εξασθενημένη ανταλλαγή αερίων.

Κλινικά, οι διάμεσες πνευμονοπάθειες χαρακτηρίζονται από δύσπνοια και μειωμένες ικανότητες άσκησης, οι οποίες οδηγούν σε ασθενείς που αναπτύσσουν αναπηρίες και διαταραχές στην ποιότητα ζωής τους που σχετίζεται με την υγεία.

Η θεραπεία είναι συχνά περιορισμένη, χωρίς αποδεδειγμένη επίδραση στην επιβίωση και σε σχέση με την ποιότητα ζωής και σχετίζεται με σημαντικές παρενέργειες.

Η πνευμονική αποκατάσταση έχει οριστεί ως μια «διεπιστημονική και ολοκληρωμένη παρέμβαση για ασθενείς με χρόνια αναπνευστική νόσο», οι οποίες είναι συμπτωματικές και συχνά έχουν μειωμένες καθημερινές δραστηριότητες.

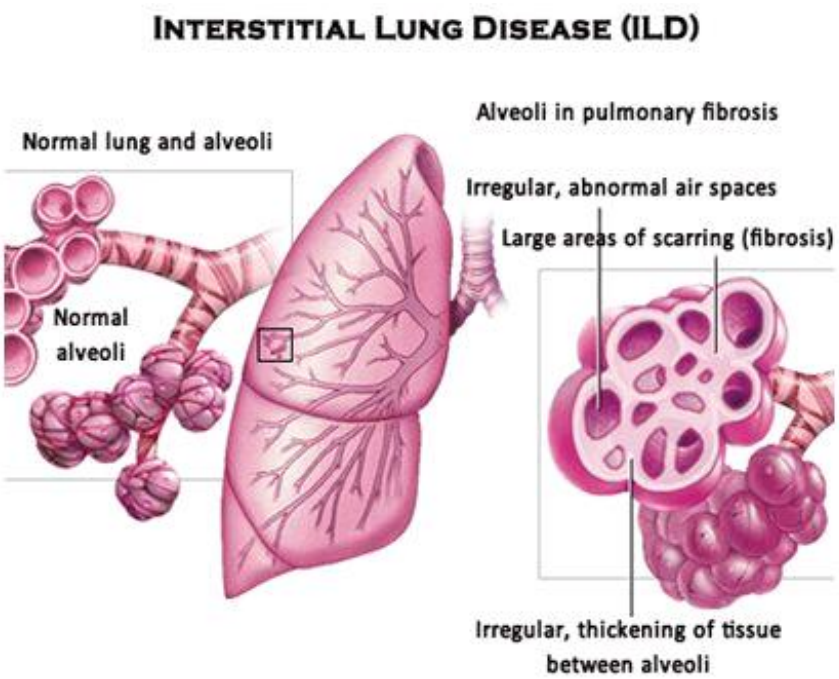
Τα ολοκληρωμένα προγράμματα πνευμονικής αποκατάστασης περιλαμβάνουν όχι μόνο την άσκηση με αερόβια περιποίηση, τη δύναμη και αντοχή και την αναπνευστική θεραπεία, αλλά και εκπαιδευτικές διαλέξεις, διατροφικές παρεμβάσεις, τεχνικές τροποποίησης συμπεριφοράς για τη βελτίωση της αυτοδιαχείρισης και της φυσιολογικής υποστήριξης.

Στόχος αυτής της συνέντευξης είναι να καθοριστεί εάν η πνευμονική αποκατάσταση σε ασθενείς με διάμεση πνευμονοπάθεια έχει ευεργετικά αποτελέσματα στα συμπτώματα της ικανότητας άσκησης, στην ποιότητα ζωής και στην επιβίωση σε σύγκριση με την αποκατάσταση των πνευμόνων σε ασθενείς με διάμεση πνευμονοπάθεια, για την αξιολόγηση της ασφάλειας της πνευμονικής αποκατάστασης ασθενείς με διάμεση πνευμονική νόσο.
αποκατάσταση.

Definition and Classification of Interstitial Lung Disease

Interstitial lung diseases (ILDs) comprise a heterogeneous group of chronic conditions characterized by lung parenchymal involvement with different degrees of inflammation and fibrosis (figure 1) resulting in impaired gas exchange and restrictive physiology. However, depending on the specific disease, other compartments of the lung, including the alveoli, the airways, the blood vessels, and the pleura, may also be affected. In some cases, interstitial lung disease is secondary to systemic diseases such as sarcoidosis or a connective tissue disease, that also affect other organs beyond the lung; this may determine the prognosis to a greater extent than the lung dysfunction.

Figure 1



Clinically, the development of irreversible and progressive parenchymal fibrosis leads to ventilatory constraint and abnormal lung mechanics with limited exercise capacity and dyspnea on exertion . In particular, the impaired level of gas exchange seems to be the major cause leading to exercise intolerance in these patients . Consequently, as Interstitial lung disease progresses, the patient's daily activities decline early following symptoms (shortness of breath, tiredness, muscle fatigue). This reduction in everyday performance begins even before that ventilatory limitation with functional impairment occurs . Furthermore Interstitial lung disease patients experience greater physical and social limitations once ventilatory constraint has established, reducing their functional reserves . Finally, due to the progressive exercise limitation, individual's health-related quality of life (HRQoL) is markedly affected.

A practical classification distinguishes interstitial lung disease of known cause from those of unknown aetiology. The most common interstitial lung diseases are idiopathic. The most common types of idiopathic interstitial lung disease are idiopathic pulmonary fibrosis and non-specific interstitial pneumonia accounting for approximately 55% and 25% of all idiopathic interstitial lung diseases, respectively. Overall, idiopathic pulmonary fibrosis and sarcoidosis are the most frequent types of interstitial lung disease and together comprise more than half of all cases (Table 1).

Major ILDs of known aetiology (~35% of all patients with ILDs)
Pneumoconioses
Extrinsic allergic alveolitis
Iatrogenic ILD caused by drugs and/or radiation
Post-infectious ILD
Major ILDs of unknown aetiology (~65% of all patients with ILDs)
Sarcoidosis
Idiopathic interstitial pneumonias, of which the most important are: IPF with a histopathological pattern of usual interstitial pneumonia Nonspecific interstitial pneumonia Respiratory bronchiolitis ILD, occurring in smokers Desquamative interstitial pneumonia Cryptogenic organising pneumonia Lymphoid interstitial pneumonia Acute interstitial pneumonia
ILD in CTDs and in collagen-vascular diseases, of which the most important are: ILD in rheumatoid arthritis ILD in progressive systemic sclerosis

Table 1: Classification of interstitial lung diseases (ILDs). IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; CTDs: connective tissue diseases. Reproduced from: https://www.erswhitebook.org/

Physiological Factors Limiting Exercise Capacity in Interstitial Lung Disease

Interstitial lung disease progresses early, the patients experience breathlessness on exertion, which limits their ability to undertake daily activities and reduces health-related quality of life (1). Reduced exercise tolerance in interstitial lung disease is considered multifactorial due to respiratory, cardiovascular and muscular limitations.

Respiratory Limitations

Respiratory impairment is a major exercise limiting factor in patients with interstitial lung disease. In interstitial lung disease, the partial pressure of oxygen in arterial blood often falls dramatically during exercise leading to profound hypoxaemia (2). In fact, hypoxaemia due to the impaired level of gas exchange, not respiratory mechanics, appears to be the predominant factor leading to exercise intolerance in these patients. This is reflected by the fact that exercising patients with interstitial lung present with reserve in predicted maximum voluntary ventilation at peak exercise. Rather, their total ventilation remains quite inefficient compared to carbon dioxide production (VE/VCO_2 slope) throughout incremental exercise, even at mild workloads (3). Hypoxaemia in interstitial lung disease results from insufficient increase of alveolar ventilation relative to the oxygen requirements of exercise, ventilation/perfusion (V/Q) inequalities, low mixed venous PaO_2, and diffusion impairment (2).

Ventilation of gas exchange units is severely impacted in interstitial lung disease. Lung fibrosis narrows and distorts the small and larger airways, thus decreases laminar airflow and ventilation of gas exchange units (4). In advanced stages, the alveolar architecture is destroyed and, often, the scarring results in multiple air-filled cystic spaces formed by dilated terminal and respiratory bronchioles, the so-called honeycomb lung. On the other hand, obliteration of the vascular bed by progressive parenchymal fibrosis impairs alveolar perfusion. Also, the protective hypoxic vasoconstriction in areas of lung fibrosis is incomplete. These abnormalities of ventilation and perfusion may be dispersed irregularly within the lung whereas, from a physiological point of view, areas with high V/Q cannot counterbalance the deleterious effect produced by areas with low V/Q. As a net result, significant V/Q mismatching develops in interstitial lung disease (5, 6) and in advanced stages, the intrapulmonary shunt fraction increases. In fact, the uneven ventilation and blood flow seems to account for almost all of the resting hypoxaemia in interstitial lung disease, whereas it diffusion impairment becomes of clinical significance during exercise (5).

Cardiovascular Limitations

Interestingly, the pathophysiology of the pulmonary circulation has been shown to be even more important than ventilatory mechanics in limiting exercise in patients with interstitial lung disease (7). Interstitial lung disease is frequently complicated by increased pulmonary vascular resistance leading to

pulmonary hypertension. This is due to obliteration of the vascular bed by progressive parenchymal fibrosis, narrowing of the small pulmonary arteries due to remodeling (5, 8) chronic hypoxic vasoconstriction (8) and reduced operating lung volumes (9). Ultimately, due to the pressure overload that ensues, the right ventricle hypertrophies, dilates and eventually fails (cor pulmonale), resulting in exercise limitation and increased mortality. The overall prevalence of pulmonary hypertension in interstitial lung disease may range up to 40% and it tends to be more frequent and severe at advanced stages of pulmonary fibrosis (8). The most commonly affected patients are those with scleroderma, and sarcoidosis-associated interstitial lung disease (10).

Skeletal Muscle Limitations

Accumulating evidence demonstrates peripheral muscular dysfunction leading to muscle weakness and fatigue in patients with interstitial lung disease (11). Causative factors might include hypoxia, systemic inflammation, negative nutrition balance and corticosteroid myopathy, ageing and sedentarism. In skeletal muscle disuse, in particular, is associated with muscle atrophy (characterized by a decrease in protein content, fiber diameter, force production, and fatigue resistance) through decreases in protein synthesis and increases in proteolysis, downregulation of various genes (12) and activation of alternative-to-cytokines NF-kB pathways (13).

The association of quadriceps performance with exercise capacity was assessed in 41 patients with mild-to-moderate idiopathic pulmonary fibrosis during an incremental symptom-limited exercise test (14). Quadriceps

weakness correlated well with lung function impairment. In stepwise multiple regression analysis that also tested for total lung capacity, diffusion capacity, maximum expiratory pressure and PaO_2 at rest, quadriceps weakness and vital capacity were the only independent predictor of exercise tolerance (VO_{2max}). Interestingly, quadriceps weakness was a significant contributing factor in patients who discontinued exercise, irrespectively of whether their exercise-limiting symptom was leg fatigue or dyspnoea. On the contrary, impaired pulmonary function at the end of exercise significantly correlated with exercise tolerance only in patients who terminated the exercise due to dyspnoea, but not in those who stopped due to leg fatigue (14). Therefore, peripheral muscle force may be a predictor of exercise capacity in interstitial lung disease.

Pulmonary Rehabilitation: Definition

Pulmonary rehabilitation, also known as **respiratory rehabilitation**, is an important part of the management and health maintenance of people with chronic respiratory disease who remain symptomatic or continue to have decreased There is accumulating evidence to support short-term benefits of pulmonary rehabilitation for interstitial lung disease . A Cochrane review analysed nine RCTs of pulmonary rehabilitation in interstitial lung disease , of which three were published in abstract form only (15). Most studies included participants with several types of interstitial lung disease ; however, four studies examined predominantly individuals with IPF, and one, individuals with sarcoidosis. One study was of home-based . These studies had differing

lengths of pulmonary rehabilitation programme, from 5 to 12 weeks. Three studies performed aerobic training and four studies included both aerobic and resistance training. Other interventions such as educational lectures, nutritional and psychosocial support, were provided in most studies. No adverse effects of pulmonary rehabilitation were reported. Meaningful improvements in exercise capacity were seen following , pulmonary rehabilitation with a weighted mean difference (WMD) for change in 6MWD of 44.34 m and 1.24 ml/kg/minute in peak oxygen consumption (VO2). These improvements were confirmed in the subgroup with IPF (WMD 35.63 m and 1.46 ml/kg/min, respectively). Dyspnoea was reduced and HRQL improved, with a similar magnitude of benefit seen in the subgroup with IPF compared with other participants. Most studies were short term, so no data on survival could be presented. The two studies that evaluated effects at 3–6 months following programme completion did not find evidence of sustained benefit for exercise capacity and HRQL.defined by the American Thoracic Society and the European Respiratory Society as an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities (22). In general, pulmonary rehabilitation refers to a series of services that are administered to patients of respiratory disease and their families, typically to attempt to improve the quality of life for the patient (2). Pulmonary rehabilitation may be carried out in a variety of settings, depending on the patient's needs, and may or may not include pharmacologic intervention (23).The potential benefits of pulmonary rehabilitation in patients with interstitial lung disease are presented in figure 2.

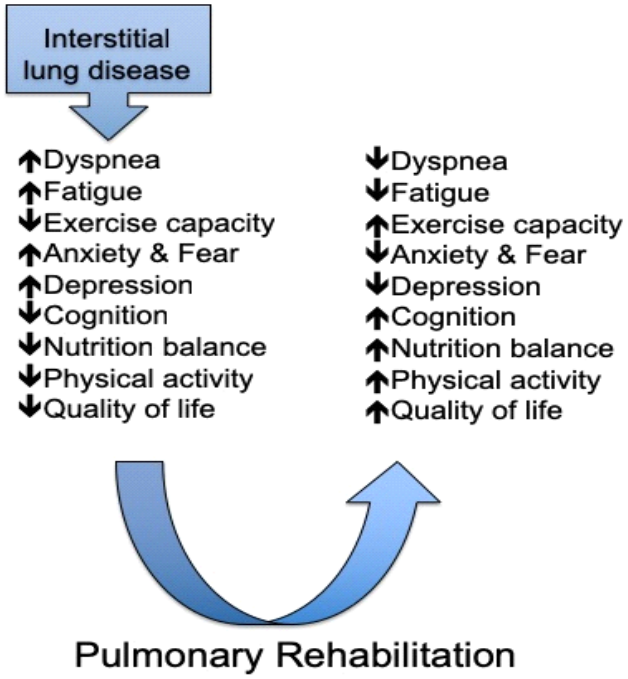


Figure 2: Potential impact of pulmonary rehabilitation in patients with interstitial lung disease. Adapted and modified from (24).

Evidence of pulmonary rehabilitation in interstitial lung disease

There is accumulating evidence to support short-term benefits of pulmonary rehabilitation for interstitial lung disease. A Cochrane review analysed nine RCTs of pulmonary rehabilitation in interstitial lung disease, of which three were published in abstract form only (21).Most studies included participants with several types of interstitial lung disease; however, four studies examined

predominantly individuals with IPF, and one, individuals with sarcoidosis. One study was of home-based pulmonary rehabilitation. These studies had differing lengths of pulmonary rehabilitation programme, from 5 to 12 weeks. Three studies performed aerobic training and four studies included both aerobic and resistance training. Other interventions such as educational lectures, nutritional and psychosocial support, were provided in most studies. No adverse effects of pulmonary rehabilitation were reported. Meaningful improvements in exercise capacity were seen following pulmonary rehabilitation, with a weighted mean difference (WMD) for change in 6MWD of 44.34 m and 1.24 ml/kg/minute in peak oxygen consumption (VO2). These improvements were confirmed in the subgroup with IPF (WMD 35.63 m and 1.46 ml/kg/min, respectively). Dyspnoea was reduced and HRQL improved, with a similar magnitude of benefit seen in the subgroup with IPF compared with other participants. Most studies were short term, so no data on survival could be presented. The two studies that evaluated effects at 3–6 months following programme completion did not find evidence of sustained benefit for exercise capacity and HRQL.

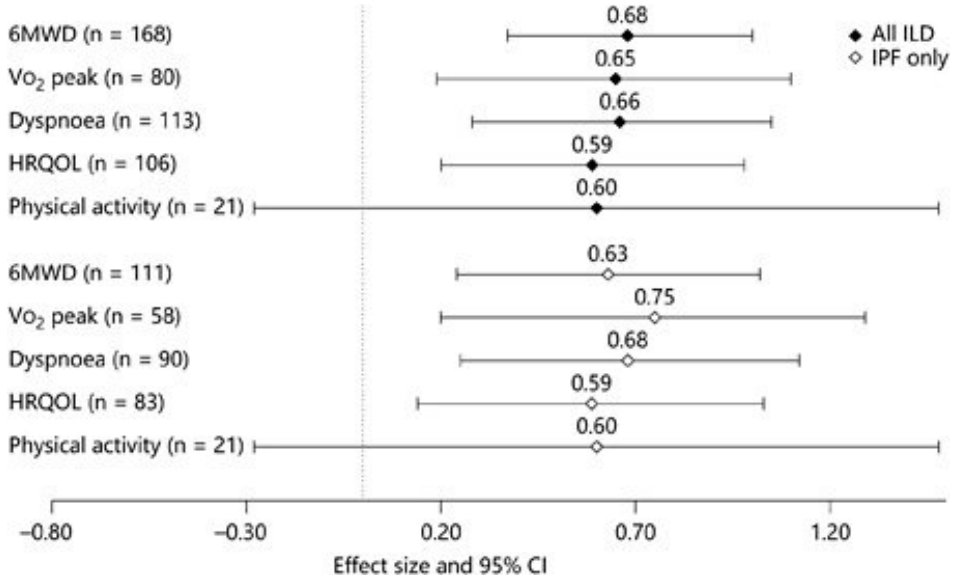


Figure 3: Efficacy of exercise training in interstitial lung disease on clinical outcomes in randomised controlled trials. Data are effect sizes and their 95% CI. HRQOL = Health-related quality of life. From Holland et al (24).

Patient selection and timing of pulmonary rehabilitation in interstitial lung disease

The interstitial lung diseases display differing severity of clinical features and natural history, making prognosis difficult to predict (25) and leading to concerns that some patients with progressive diseases may not benefit (26). However the Cochrane review on this topic showed similar improvements in 6MWD following pulmonary rehabilitation in IPF compared with other interstitial lung diseases (21). Improvements in both groups exceeded the minimum important difference for 6MWD in interstitial lung disease (27). There are fewer data to guide practice in other interstitial lung diseases such

as nonspecific interstitial pneumonia, hypersensitivity pneumonia and connective tissue disease (CTD) interstitial lung disease , despite inclusion of such patients in clinical trials of pulmonary rehabilitation (24). Although robust studies of pulmonary rehabilitation are difficult to conduct in the rarer interstitial lung diseases, consistent evidence of benefit continues to emerge. Recently, beneficial effects of pulmonary rehabilitation in patients with lymphangioleiomyomatosis (LAM) were reported (28). Forty patients with LAM performed 24-exercise training sessions over 12 weeks and received disease-specific education. Significant improvements in 6MWD, endurance time, physical activity, muscle strength, dyspnoea and HRQL were reported. Although not randomized, with participants allocated to groups based on how far they lived from the training centre, effect sizes were consistent with those seen in previous pulmonary rehabilitation studies in interstitial lung disease. In summary, existing studies suggest that pulmonary rehabilitation is effective across the spectrum of interstitial lung disease and could be offered to all patients who are symptomatic on exertion, regardless of underlying diagnosis.

Specific characteristics and features of patients with interstitial lung disease may be associated with a greater response to pulmonary rehabilitation (Table 2) (29;27;30;31) Patients with a higher forced vital capacity, less desaturation on exertion and less disability on commencement of have pulmonary rehabilitation demonstrated greater improvements in exercise capacity (27;29).More severe baseline breathlessness has also been associated with larger improvement in dyspnoea at 6 months after (27) In a prospective cohort study, poorer 6MWD at baseline was an independent predictor of

improvement in 6MWD on pulmonary rehabilitation completion ($r = -0.49$, $p < 0.0005$) (31) In IPF, pulmonary rehabilitation delivered to patients with milder disease might be more likely to produce positive outcomes (27) Although current evidence does not identify the ideal timing of pulmonary rehabilitation for,interstitial lung disease,referral early in the disease course may confer greater benefits.

Table 2. Major exercise training components in four published randomized controlled trials of pulmonary rehabilitation for interstitial lung disease.

	Training frequency	Endurance training intensity	Endurance training duration	Endurance training modality	Endurance training progression	Resistance training
Holland et al. (2008)	Twice weekly	Initial: walking, 80% of the walking speed achieved on the baseline 6MWT	30 min per session, 8 weeks	Both stationary cycling and walking training	Progressed by an experienced physiotherapist according to a standardized protocol	Upper limb endurance training (free weights) and functional strength training for the lower limbs (e.g. sit to stand)
Nishiyama et al. (2009)	Twice a week	80% of maximal walking speed from 6MWT, 80% of the maximum workload on cycle ergometer test	From weeks 2–9 of a 10-week programme	Treadmill	Not stated	Strength training using elastic bands; exercises included arm raising and knee extensions for 20 min
Vainshelboim et al. (2014)	Twice weekly	Interval training: in the first block, 50–60% of peak WR on CPET for cycling, 70–80% of individual average speed of 6MWT for walking, in the second block, increased up to 60–70% of peak WR in cycling and 80–90% of individual average walking speed	Two 6-week progressive blocks, 30 min; in the second block, further increased up to 20 min	Treadmill walking, leg cycling and step climbing in a continuous, sequential manner	Adding 1 min to the duration of each bout in each session, until reaching 15 min of continuous exercise; in the second block, stair climbing for 3–5 min was added to each session	One set of 12–15 repetitions with 1 min of rest between the sets for 4–6 exercises; in the second block, added two sets of 10–12 repetitions with 45 seconds of rest between the sets
Jackson et al. (2014)	Two sessions per week	Up to 80% maximum heart rate	20/10 min	Treadmill walking/ semi-recumbent cycling	Not stated	Resistance training twice weekly, up to three sets of 15 repetitions using resistance bands

6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test parameters; WR, work rate.

Table 2. Predictors of pulmonary rehabilitation outcome in interstitial lung disease.

Pulmonary Rehabilitation in Specific Types of Interstitial Lung Disease

It remains unclear whether the benefits of pulmonary rehabilitation vary between different types of interstitial lung disease.

The inclusion criteria for most randomised controlled trials of exercise training in interstitial lung disease have been broad and participants have had a wide range of diagnoses (26). Forty percent of trial participants had a diagnosis of idiopathic pulmonary fibrosis (24), which is the most prevalent of the type of interstitial lung disease. Some patients with idiopathic pulmonary fibrosis experience rapid disease progression associated with distressing symptoms and early death, and this has previously raised concerns that pulmonary rehabilitation may not be worthwhile in this group. However, the clinical course of idiopathic pulmonary fibrosis is variable, with most individuals experiencing more gradual disease progression and some experiencing long periods of stability, which offers the opportunity for effective rehabilitation (24). Accordingly, a Cochrane meta-analysis for idiopathic pulmonary fibrosis participants taking part in randomised controlled trials of pulmonary rehabilitation showed effects on clinical outcomes that are clinically meaningful (32) and, of equal magnitude to those in the interstitial lung disease group as a whole (Figure 3) (24). These data are in agreement with the results of recent systematic review of 5 randomised controlled trials of pulmonary rehabilitation in idiopathic pulmonary fibrosis (33) showing improvements in exercise tolerance weighted mean differences (44 m; 95% CI, 5.3-82.8) compared with no exercise. The meta-analyses also showed significant improvement in symptoms, impact, and total score from the St George's Respiratory Questionnaire for participants in pulmonary rehabilitation compared with control (33). Thus, evidence provide reassurance that pulmonary rehabilitation is clinically useful in idiopathic pulmonary fibrosis.

The effect of a specialized, comprehensive, 4-week inpatient pulmonary rehabilitation program on interstitial lung disease as a whole, were examined by a large study that investigated 402 patients with severe disease (including patients with idiopathic pulmonary fibrosis (n=202), cryptogenic organizing pneumonia, hypersensitivity pneumonitis, sarcoidosis, and others) of whom, 299 (74%) were listed for lung transplantation (30). The study found significant and clinically relevant improvements in functional exercise capacity (increase in 6-minute walk distance 46 ± 3 m) as well as health-related quality of life (Short Form-36 physical component score +6 ± 1 points; Short Form-36 mental component score +10 ± 1 points). Those benefits were independent of the underlying disease, albeit no comparisons of benefit between the subgroups were provided (30).

In contrast, Holland et al. (27) found that although improvements in 6-minute walk distance exceeded the minimum important difference in both idiopathic pulmonary fibrosis and other types of interstitial lung disease, the former group tended to improve their functional exercise capacity less than those with other types of interstitial lung disease (6-minute walk distance 21 ± 58 vs. 43 ± 56 m, p = 0.21). Improvements in 6-minute walk distance that exceeded the minimal important difference occurred in 40% of patients with idiopathic pulmonary fibrosis compared to 52% of those with other forms of interstitial lung disease (p = 0.41). A comparable cluster could be found concerning improvements in patients' dyspnoea rating. The Chronic Respiratory Questionnaire dyspnoea domain improved slightly less in idiopathic pulmonary fibrosis patients compared to other types of interstitial lung disease (2.7 ± 5.6 vs. 4.6 ± 5.2 points, p = 0.25). Accordingly, the authors

hypothesized that patients with idiopathic pulmonary fibrosis would generally demonstrate greater abnormalities of exercise-induced hypoxaemia and tend to improve less following pulmonary rehabilitation (27).

In the study by Dowman et al.(34) there were larger improvements in 6-minute walk distance, health-related quality of life and dyspnoea in patients with asbestosis and idiopathic pulmonary fibrosis compared with patients with connective tissue disease-related interstitial lung disease. The authors attributed the lack of improvement in 6-minute walk distance the 6-minute walk test's ceiling effect as the subgroup of patients with connective tissue disease-related interstitial lung disease had higher baseline 6-minute walk distance and a greater percentage of participants above the test's threshold. They also argued that the common systemic manifestations such as joint pain, joint swelling, muscle weakness and muscle pain that associate with connective tissue diseases may had limited the benefits in health-related quality of life (34).

There are fewer disease-specific data to guide practice in other interstitial lung disease such as nonspecific interstitial pneumonia, hypersensitivity pneumonia and connective tissue disease-interstitial lung disease, and other, rarer types of the disease, despite inclusion of such patients in clinical trials of pulmonary rehabilitation (24). This is largely due to smaller numbers of participants in trials or inadequate reporting. However, recently, beneficial effects of pulmonary rehabilitation in patients with lymphangioleiomyomatosis were reported (28). Forty patients with lymphangioleiomyomatosis performed 24 exercise training sessions over 12 weeks and received disease-specific

education. Significant improvements in 6-minute walk distance, endurance time, physical activity, muscle strength, dyspnoea and health-related quality of life were reported. Although not randomized, with participants allocated to groups based on how far they lived from the training centre, effect sizes were consistent with those seen in previous pulmonary rehabilitation studies in interstitial lung disease (28).

The contradictory data to date, suggest that lumping interstitial lung disease together in trials to evaluate pulmonary rehabilitation runs a risk of obscuring effects in specific populations. Patients, of course, have the disease that they have, so the comparisons between conditions are of limited relevance for guiding clinical practice (35). Nonetheless, existing studies suggest that pulmonary rehabilitation is effective across the spectrum of interstitial lung disease and could be offered to all patients who are symptomatic on exertion, regardless of underlying diagnosis.

Rehabilitation After Exacerbation of Interstitial Lung Disease

Exacerbations are common in the natural history of interstitial lung diseases. For idiopathic pulmonary fibrosis, historical criteria for acute exacerbation have included an unexplained worsening of dyspnoea within 1 month, evidence of hypoxaemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure (25). To date, there has been no study devoted specifically in the investigation of pulmonary rehabilitation following an episode of acute exacerbation of idiopathic pulmonary fibrosis or other

interstitial lung disease. Although pulmonary rehabilitation has been recommended after an acute exacerbation of chronic obstructive lung disease, no recommendation is made for interstitial lung disease (15, 26). To date, a large randomised study demonstrated negative effects of early exercise rehabilitation after an exacerbation of chronic respiratory disease (36). This study included 389 subjects, of which 320 (82%) with chronic obstructive pulmonary disease and 21 (5%) with interstitial lung disease. Patients performed 6 weeks of exercise training, starting in hospital and carrying over to the outpatient setting. There were no beneficial effects on physical function or hospital readmission, and the rehabilitation group had higher mortality at 12-month follow up. Therefore, although early mobilization following an exacerbation may contribute to early hospital discharge and recovery of the ability to perform activities of daily living, a cautious approach might be required for commencement of pulmonary rehabilitation in the early stages following an exacerbation of interstitial lung disease. It has been postulated that the risks associated with exercise rehabilitation could be higher in this subgroup of patients due to greater hypoxaemia at rest and greater desaturation on exercise following an acute exacerbation, as well as associated comorbidities (36).

Current Guideline Recommendations for Pulmonary Rehabilitation in Interstitial Lung Disease

The current recommendations for pulmonary rehabilitation vary across international guidelines and statements. The ATS/ERS statement on pulmonary rehabilitation supports pulmonary rehabilitation in interstitial lung

disease as an intervention for meaningful short-term benefits (15). The international statement on the diagnosis and management of idiopathic pulmonary fibrosis (25) makes a weak positive recommendation for pulmonary rehabilitation in this particular form of interstitial lung disease, due to the low quality of evidence on the real achievable gain. This recommendation acknowledges that the uncertainty regarding the duration of benefit means that some patients may reasonably choose not to undertake pulmonary rehabilitation, depending on their personal circumstances. The National Institute of Health and Care Excellence (NICE) guideline suggests that pulmonary rehabilitation is likely to be cost effective in idiopathic pulmonary fibrosis when offered every 6–12 months (37). Conversely, British guidelines for pulmonary rehabilitation do not make any specific recommendation, citing the wide variation in patient presentation, lack of comprehensive pulmonary rehabilitation studies (as opposed to exercise only) and the likelihood of rapid deterioration in some patients that potentially makes pulmonary rehabilitation futile (26). The latter reflects the considerable interstitial lung disease inter- and intra-type variability in terms of severity of clinical features and natural history, which makes the prognosis difficult to predict and leads to concerns on the feasibility and benefit of pulmonary rehabilitation in certain patients with interstitial lung disease. The differencechallenges in the application of pulmonary rehabilitation to this diverse patient group, particularly with regard to patient selection, programme components and duration of benefits (38).

Mechanisms of Benefit for Exercise Training in Interstitial Lung Disease

The effect of exercise training on physiological and clinical outcomes in interstitial lung disease is poorly explored and understood. In theory, it can be explained by several mechanisms. Patients with interstitial lung disease usually present with impaired lung compliance and inefficient breathing patterns as part of their restrictive pathophysiology. It has therefore been proposed that repetitive stimulus of high ventilatory demands during exercise sessions, chest expansion during deep-breathing exercises and stretching of the thoracic muscles that are frequently used in pulmonary rehabilitation result in a more efficient breathing pattern, improved strength of respiratory muscles, enhanced pleural elasticity and pulmonary compliance within the lung tissue, and decreased dyspnoea perception (39). In support, data suggest that most of the improvement in VO_{2peak} after pulmonary rehabilitation in patients with interstitial lung disease occurs due to an enhancement in peak tidal volume as suggested by the high correlations between a) improvements in VO_{2peak} and improvement in peak tidal volume, and b) change in 6-minute walk distance and change in forced vital capacity % predicted (39). The same line of work also suggests that the improvement in exercise tolerance may also be facilitated to some extent by skeletal muscle and cardiovascular adaptations, as evidenced by an improvement in the 30-second chair-stand test and O2 pulse, respectively, although, significant correlations between these parameters and VO_{2peak} or 6-minute walk distance were not detected (39).

Elsewhere, Keyser et al (40), examined the effect of a 10-week multimodal pulmonary rehabilitation program in patients with interstitial lung disease with moderate-to-severe exercise limitation. By employing cardiopulmonary exercise testing, bioimpedance cardiography and near infrared spectroscopy, they observed significant improvements in cardiorespiratory function after exercise training. The improvements included higher work rates at any given oxygen uptake, higher anaerobic threshold, and higher peak oxygen uptake and they were attributed to increases in the limb muscle oxygen extraction rather than cardiopulmonary oxygen delivery or muscle oxygen availability (40). Supporting data that improvements in muscle performance may be a fruitful area for further investigation were provided by a non-randomised study showed significant improvement in quadriceps force after a 12-week exercise-based rehabilitation program in people with restrictive lung disease (18). It is possible that these alterations are mediated by exercise-induced enhanced mitochondrial oxidative capacity, increased muscle vascularization and alterations in the muscle fiber types in analogous way to patients with chronic obstructive pulmonary disease (41). However, initial benefits of exercise training in muscle force in patients with advanced idiopathic pulmonary fibrosis, were reported to be less sustainable (not maintained at 6-months) compared with patients with chronic obstructive pulmonary disease who continued to benefit at 6-month follow-up (29).

Pulmonary rehabilitation: programme components

Pulmonary rehabilitation comprises of exercise training and non-exercise components, all of which must work smoothly together to achieve optimal outcomes for people with interstitial lung disease (38) (Figure 4).

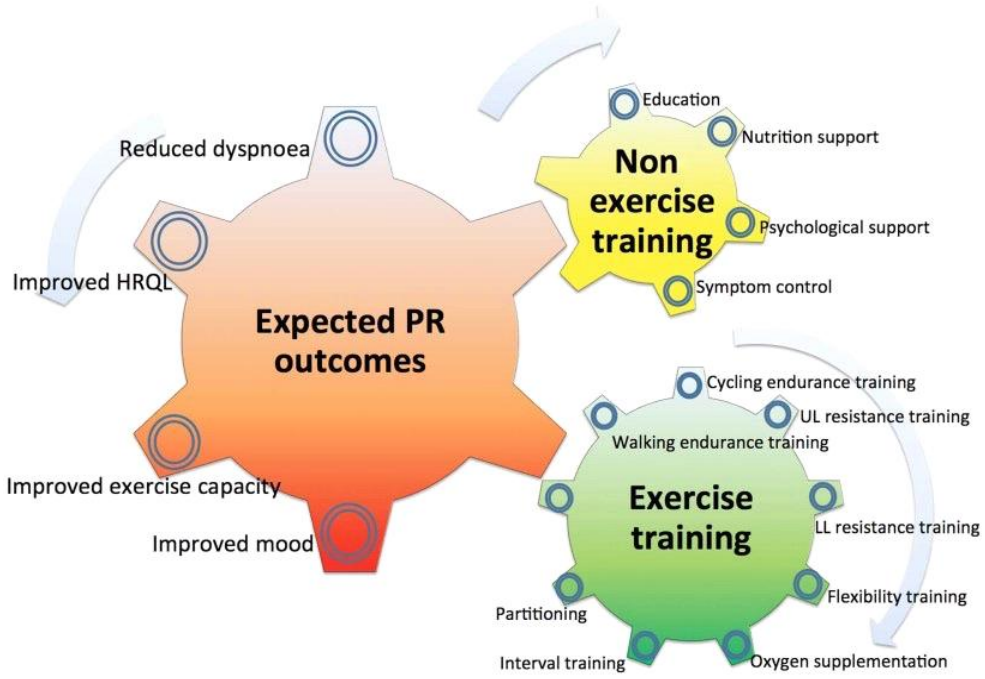


Figure 4: Comprehensive pulmonary rehabilitation for interstitial lung disease. The gears with red, green and yellow colour present expected PR outcomes, exercise training and non-exercise training, respectively. The green gear is bigger than the yellow gear, because exercise training has more evidence than non-exercise training. The cogs of gears indicate their components. Comprehensive intervention in PR can be accomplished when the gears mesh together and cogs work well. Cooperation and smooth connection of all gears are vital to make pulmonary rehabilitation successful. HRQL, health-related quality of life; UL, upper limb; LL, lower limb; PR, pulmonary rehabilitation. From (50).

Exercise Training

The optimal exercise prescription for people with interstitial lung disease remains unknown. In general, large variations exist in the described exercise modalities, duration, and intensity used in this setting. The majority of studies of pulmonary rehabilitation in interstitial lung disease have used exercise prescriptions similar to those commonly employed in chronic obstructive pulmonary disease, with the assumption that the recommendations are applicable to subjects with other lung diseases. This seems intuitively plausible because, despite the differences in underlying pathophysiology, several disease manifestations of interstitial lung disease, including those related to exercise intolerance such as severe and disabling dyspnoea, fatigue and exhaustion, muscle dysfunction, deconditioning and impaired quality of life are similar to those seen in chronic obstructive pulmonary disease (15). This constellation of symptoms and impairments is familiar to healthcare professionals in pulmonary rehabilitation (42).

However, the pathophysiology and exercise limitation in interstitial lung disease differs from chronic obstructive pulmonary disease. In chronic obstructive pulmonary disease, ventilatory limitation and skeletal muscle dysfunction are the predominant factors contributing to exercise limitation [14], whereas, as already discussed, impaired pulmonary gas exchange and circulatory factors may be the primary limitations to exercise in interstitial lung disease. In general, patients with interstitial lung disease more frequently than those with chronic obstructive pulmonary disease have severe or rapidly progressive disease with debilitating symptoms, develop pulmonary hypertension and manifest profound exercise-induced hypoxaemia. Also, patients with interstitial lung disease may require higher doses and more

extended treatment with oral corticosteroids than those with chronic obstructive pulmonary disease, which impairs the function of skeletal muscle function and prevents gains in muscle performance from exercise training (29). Therefore, patients with interstitial lung disease may require modifications to the standard approach in pulmonary rehabilitation. With these in mind, next follows a discussion on the exercise programs currently used in pulmonary rehabilitation in interstitial lung disease.

Whole body exercise training is the core of pulmonary rehabilitation for people with interstitial lung disease. Principles of exercise training in chronic respiratory diseases are similar to those in healthy individuals, including individualized exercise prescription and gradual progression of the training load. As with chronic obstructive pulmonary disease, endurance training is an essential component of exercise training for interstitial lung disease and it is, almost invariably, combined with resistance (strength) training. Flexibility training and stretching are also used.

Endurance Training

The majority of published studies in pulmonary rehabilitation in interstitial lung disease used protocols of endurance exercise training. The exercise training is commonly delivered in the form of treadmill walking, leg cycling, and step climbing either in isolation or in variable combinations depending on the local resources and expertise, and patient preferences and ability. Endurance training aims to improve aerobic capacity, increase exercise endurance, and improve daily function and physical activity with less breathlessness and fatigue. Initial endurance training intensity is usually set at 60–80% of

maximum exercise capacity, such as walking speed on baseline 6-minute walk distance (for walking exercise) or peak work rate on cardiopulmonary exercise test (for cycling). A minimum frequency of two supervised sessions per week is suggested. The target duration of endurance exercise in each session should be 30 minutes in participants, broken into shorter intervals if needed (e.g. 15 minutes stationary cycling and 15 minutes of walking, either on a treadmill or in a corridor). Most participants achieve this duration of exercise within 1–2 weeks of training, with appropriate support from an experienced clinician. Participants should be encouraged to rate their breathlessness and fatigue regularly during exercise, aiming for moderate levels of breathlessness throughout (e.g 3-5 or 4-6 on the Borg 10 scale, for the initial and late stages of training, respectively). Once a duration of 30 minutes is achieved, progression occurs by regular increases in the intensity of exercise (e.g. weekly increase in walking speed or cycle work rate). Participants should also be encouraged to adopt a home exercise programme, with the aim of completing 3–5 sessions of endurance exercise each week (38).

Interval training may provide an alternative exercise modality to endurance training in interstitial lung disease. High intensity interval training utilizes repeated short (e.g. 30 s) to longer bouts of relatively high-intensity exercise (e.g. 75% VO_{2max}) alternated with recovery periods of either low-intensity exercise or rest. The aim of interval training is to allow patients to achieve the required training dose through repeated bouts rather than continuous exercise, which may reduce dyspnoea and fatigue. In fact, a greater total exercise duration and greater volume of higher intensity exercise can be

accumulated during a single exercise session with significantly lower and more stable metabolic and ventilatory responses compared with compared to energy expenditure-matched steady state traditional moderate-intensity continuous exercise training**.** Accordingly, the interval training mode may be appropriate for patients such those with idiopathic pulmonary fibrosis who perceive higher degrees of dyspnoea on exertion (43) and thus a more pronounced limitation in endurance capacity compared to patients with chronic obstructive pulmonary disease (39). Few published studies have included interval training in patients with interstitial lung disease, although others are currently underway. In a study by Vainshelboim et al. (39) interval exercise training improved significantly exercise tolerance, functional capacity, pulmonary function, dyspnoea and quality of life in patients with idiopathic pulmonary fibrosis. Preliminary results also showed a tendency that interval training is effective and feasible also in patients with severe interstitial lung disease listed for lung transplantation, with the attained benefits in functional and maximal exercise capacity being comparable to those in patients with chronic obstructive pulmonary disease (43). However, interim results of a randomised study of high intensity interval training versus moderate intensity continuous training in patients with interstitial lung disease showed that, both being statistically and clinically beneficial in functional exercise capacity, there was no difference between groups to suggest that high intensity interval training is superior to moderate intensity continuous training (44).

Resistance Training

Resistance training improves local muscle strength and endurance. Resistance can be generated against gravity, body weight or through the use of fixed or free weights and applied to both upper and lower limbs. There are no specific guidelines for prescribing resistance training in pulmonary rehabilitation, and the principles of the American College of Sports Medicine (ACSM) position stand for healthy adults or older persons (45) are usually applied. The ACSM recommends training 2–3 days per week, with 10–15 repetitions and a single set for older persons. For intensity, the ACSM recommends 40–50% of the 1 repetition maximum (very light to light intensity) to improve strength and 20–50% of the 1 repetition maximum to improve power. Modalities include resistance bands and free weights (45).

Progression of resistance training may involve increasing the weight, number of repetitions per set, number of sets of each exercise or decreasing the rest period between sets (15).The best modality for limb training is not known; however, ACSM suggests emphasizing functional activities (e.g. stair climbing, sit-to-stand) as these are directly relevant to daily activities and can be easily reproduced in the home setting (45).

Flexibility Training and Stretching

Flexibility training aims to increase the range of motion of joints and muscles of both upper and lower limbs. Examples include seated single leg hamstring stretch, standing quadriceps stretch, chest stretch, overhead reach stretch and wall cat stretch. There are no specific guidelines for flexibility training in interstitial lung disease and its contribution to pulmonary rehabilitation outcomes is unknown. The ACSM recommends flexibility exercise on at least

2–3 days per week, with 30–60-second stretches repeated two-to-four times for older people (45).

Non-Exercise Components

Participants in pulmonary rehabilitation programs may benefit from the input of an interdisciplinary team, including physicians and other health care professionals such as physiotherapists, respiratory therapists, nurses, psychologists, behavioural specialists, exercise physiologists, nutritionists, occupational therapists, and social workers (15). Apart from of tailored and supervised training on aerobic and resistance exercises, individuals with interstitial lung disease may therefore receive multiple benefits from the standard, non-exercise components of pulmonary rehabilitation. Therefore, pulmonary rehabilitation may serve as a point of respiratory physiotherapy, disease education, advance care planning, self-management of symptoms, optimising activities of daily living and management of mood disorders.

Education

Education on interstitial lung disease was a component of pulmonary rehabilitation programs in several studies. However, disease education has been documented as an unmet need for people with idiopathic pulmonary fibrosis (46). Early disease education may increase knowledge of the disease so that patients and their caregivers can have a better understanding of the effect and consequences of disease and engage in active self-management. Most educational programs in interstitial lung disease provided information on

breathing techniques, coping strategies, pacing during activities of daily living, and energy conservation but none of the trials to date had offered detailed information on the specific content of these education sessions (39).

Few studies attempted to identify components for optimal of disease education in interstitial lung disease. In a qualitative study of the perspectives of patients and clinicians related to the ideal content of an educational component of pulmonary rehabilitation for interstitial lung disease, participants expressed the need for disease-specific information, as well as information about end-of-life planning and most were happy to discuss this in a group (24). Semi-structured interviews of patients with interstitial lung disease by healthcare professionals with expertise in interstitial lung disease and/or pulmonary rehabilitation also identified key topics to be in pulmonary rehabilitation-based education programs: disease education, symptom management, clinical tests, autonomy, oxygen use, medications, and end-of-life counselling (47).

Psychological Support

Depression and anxiety are prevalent in interstitial lung disease. In a study of 118 patients with idiopathic pulmonary fibrosis, significant depressive symptoms were evident in 58 (49%) patients had but only 9 were taking antidepressant medication. Interestingly, depression was not significantly correlated with disease severity, age, duration since diagnosis and number of co-morbidities (48). Depression was also among the most common comorbidities in a study of 272 patients with idiopathic pulmonary fibrosis, whom had a mean number of comorbidities of 2.68 ± 1.83 (0–7) per patient

(49). In a study of 124 patients with interstitial lung disease of mixed aetiology, the prevalence of anxiety and depression were 31% and 23%, respectively (24). Of note, high levels of dyspnoea were an independent predictor of anxiety, and more dyspnoea and comorbidities were independent predictors of depression (24). Apart from dyspnoea, other causes of psychological distress may include loss of independence, feelings of social isolation and inadequate sleep (50).

The impact of pulmonary rehabilitation on mood in interstitial lung disease has not been studied in randomised controlled studies. However, non-randomised studies have reported significant improvements in quality of life, anxiety and depression (31, 50, 51) and fatigue (57) in a significant proportion of patients. Also, the benefits of 6–9 weeks of pulmonary rehabilitation on depression were maintained at the 6-month follow up, in one study (31). The mechanism by which pulmonary rehabilitation improves mood is not clear, but may be related to improved symptoms and sense of control over the disease.

Nutritional Support

Nutritional depletion and the effectiveness of nutritional support, within or out of the frame of pulmonary rehabilitation, has seldom been investigated interstitial lung disease. In idiopathic pulmonary fibrosis, survival was significantly associated with body mass index (BMI) (hazard ratio, 0.93 for each 1-U increase in BMI; 95% CI, 0.89 to 0.97; p = 0.002) with increased BMI being associated with better survival, as opposed to a low BMI (72). A multimodal nutritional rehabilitation programme in 122 patients with chronic respiratory failure (including 11 with restrictive diseases) encompassing

education, oral nutritional supplements, exercise and oral testosterone found improved exercise tolerance in all participants and health-related quality of life in females (59).

Symptom Control

Many people with interstitial lung disease have a high symptom burden including dyspnoea, cough and fatigue. Pulmonary rehabilitation may contribute to symptom control in patients with interstitial lung disease. Specialists in symptom management, including palliative care teams, may have a key role to play in addressing the substantial unmet needs of people with interstitial lung disease for symptom control and psychosocial support (52).

Respiratory physiotherapists are key members of the pulmonary rehabilitation multidisciplinary team. Generic goals of respiratory physiotherapy management in chronic lung disease are to optimize alveolar ventilation, lung volumes and capacities and, reduce the work of breathing in order to maximize exercise capacity, reduce respiratory symptoms and maximize the patient's quality of life, general health and wellbeing. Patient monitoring includes assessment for dyspnoea and respiratory distress, breathing pattern (depth and frequency) and arterial saturation. Breathlessness is most commonly accessed using a modified version of the Borg scale of perceived exertion. For research purposes, other patient-reported questionnaires such as the Medical Research Council Scale and Baseline Dyspnoea Index Respiratory are used. Respiratory physiotherapy in interstitial lung disease may include breathing retraining, chest wall mobility exercises, body

positioning, coughing, relaxation techniques, pacing and energy and energy conservation. Thoracic expansion exercises or stretching of the thoracic muscles may be beneficial since many since many patients with interstitial lung disease develop rigid rib cage structures (39).

The British guidelines strongly recommend pulmonary rehabilitation for all patients with Medical Research Council Dyspnoea score of 3–5 and functional limitation (26). Chronic exertional dyspnoea is characteristic of idiopathic pulmonary fibrosis (25). The Cochrane review confirmed reduced dyspnoea after pulmonary rehabilitation in a subgroup of patients with idiopathic pulmonary fibrosis (32). A statistically significant effect for reduced dyspnoea was also seen in patients who desaturated on exertion. These benefits may be mediated by breathing retraining, which is one of the most highlighted parts of the pulmonary rehabilitation programs. In interstitial lung disease, the emphasis in breathing retraining should be on teaching those techniques for breathing control and diaphragmatic effort to prevent tachypnea and anxiety and to improve gas exchange (39). Pursed-lip breathing is one of the most favoured and beneficial breathing techniques in patients with chronic obstructive pulmonary disease (27). This technique has also been used in most of the studies that provided breathing retraining to patients with interstitial lung disease. However, since patients with interstitial lung disease do not suffer from obstructed airways, it is not likely that positive expiratory pressure breathing via pursed-lips would be helpful primarily (39). More so, the use of an intense pursed-lip breathing technique could actually increase the work of breathing in patients with restrictive lung diseases (39). However, pursed-lip breathing may be more helpful in a significant proportion of patients

with interstitial lung disease who develop an unnecessary degree of hyperventilation, especially during physical activity. In these patients, a slight pursed-lip breathing technique could be helpful to adjust the breathing frequency to an appropriate level and regain breathing control (29, 39).

Cough may exert a marked impact on daily life in patients with interstitial lung disease, especially, idiopathic pulmonary fibrosis. It is often among the first symptoms, often preceding exertional dyspnoea, sometimes by years, it is usually recurrent and refractory to therapeutic attempts, and it is considered an independent predictor of disease progression (53). Qualitative studies have shown that discussion of strategies to manage cough is a priority for patients with interstitial ling disease undertaking pulmonary rehabilitation (24, 47); however, the ideal components of such an intervention are not known. Recently, a randomised controlled trial showed the efficacy of a combination of nonpharmacological interventions, grouped under the term “physiotherapy, and speech and language intervention” (PSALTI), in patients with refractory chronic cough (54); this approach remains to be proven in idiopathic pulmonary fibrosis, but highlights the potential benefit of physiotherapy and nonpharmacological interventions (53).

Pulmonary rehabilitation may also be important in ameliorating fatigue in patients with chronic respiratory disease including interstitial lung disease (15). A 12-week exercise supervised training program improved subjective fatigue in people with interstitial lung disease and sarcoidosis at 3 months (55). Elsewhere, an intense aerobic exercise-training regimen (24-30 sessions at a target heart rate of 70-80% of the heart rate reserve, 30 min per session,

3 times per week for 10 weeks), improved objective muscle fatigability in 13 subjects with interstitial lung disease of heterogeneous aetiology (56).

Special Considerations for Exercise Training in Interstitial Lung Disease

Oxygen supplementation

Oxygen therapy is commonly delivered during exercise training for patients who exhibit significant desaturation, despite limited evidence for this practice. Management guidelines strongly recommend long-term oxygen therapy in IPF patients with resting hypoxaemia (25). The ATS/ERS statement for pulmonary rehabilitation recommends supplemental oxygen during exercise training for interstitial lung disease (15) Supplemental oxygen would routinely be administered to such patients during exercise training in pulmonary rehabilitation, to ensure safety in the presence of profound desaturation. To date, there is no evidence to indicate that this practice results in better pulmonary rehabilitation outcomes, such as greater improvements in exercise capacity or HRQL. Retrospective studies evaluating the administration of oxygen during acute bouts of exercise in interstitial lung disease have reported improvements in walking distance with oxygen therapy, suggesting there may be beneficial effects on exercise performance (60) However, interpretation of these findings is limited by the retrospective nature of the studies and lack of participant blinding. More evidence is needed to improve our understanding of the role of oxygen therapy during exercise training. Currently, usual practice would be to deliver oxygen therapy for any patient

who desaturates to less than 85% during training, with the aim of maintaining SpO2 at greater than 88%.

Interval training

Interval training may provide an alternative exercise modality to endurance training in interstitial lung disease. Interval training consists of periods of relative high-intensity exercise interspersed with periods of low-intensity exercise with or without rest. The aim of interval training is to allow patients to achieve the required training dose through repeated bouts rather than continuous exercise, which may reduce dyspnoea and fatigue. The ATS/ERS statement for pulmonary rehabilitation suggests that interval training can be performed with fewer symptoms than continuous training(16). With regard to interstitial lung disease, few published studies have included interval training, although several are currently underway. Authors of a systematic review of interval training in COPD reported a variety of interval training regimens in this group, including: two studies with 1-minute intervals of higher intensity [>90% peak power (Ppeak)], alternating with 2 minutes of low intensity (<75% Ppeak); three trials with 30-second intervals (100/45% Ppeak); one study with high (50% Ppeak) and low (10% Ppeak) intervals of 20 and 40 seconds; and one study with 2-minute intervals of high intensity (90% Ppeak) and 1 minute of low intensity (50% Ppeak) (61) There was no significant difference in exercise capacity and HRQL between interval training and continuous training. Further study of interval training in interstitial lung disease is required.

Musculoskeletal disorders

Musculoskeletal disorders are prevalent in people with interstitial lung disease and may affect pulmonary rehabilitation participation. For example, patients with CTD might experience joint pain and stiffness, limiting their ability to undertake pulmonary rehabilitation. It is important that practitioners modify the exercise component of pulmonary rehabilitation appropriately for people with musculoskeletal disorders, to avoid pain or exacerbation of chronic conditions. For instance, it might be necessary to avoid weight-bearing exercises like walking in some patients; stationary cycling may be more appropriate. Similarly, care should be taken with prescription of resistance training. In some cases, it may be necessary to seek the advice of a rheumatologist or musculoskeletal physiotherapist, to directly address underlying causes of musculoskeletal pain and dysfunction.

Rehabilitation after exacerbation of IPF

The ATS/ERS definition of an acute exacerbation in IPF incorporates unexplained worsening of dyspnoea, evidence of hypoxaemia, new radiographic alveolar infiltrates, in the absence of an alternative diagnosis (25). Delivery of pulmonary rehabilitation after an episode of acute exacerbation of IPF has not been described. Although pulmonary rehabilitation has been recommended after an acute exacerbation of COPD, no recommendation is made for IPF (16;26). Recently, a large study demonstrated negative effects of exercise rehabilitation after an exacerbation of chronic respiratory disease (62). This study included 21 interstitial lung disease patients (total n = 389). Patients performed 6 weeks of exercise

training, starting in hospital and carrying over to the outpatient setting. There were no beneficial effects on physical function or hospital readmission, and the rehabilitation group had higher mortality at 12-month follow up. Although early mobilization following an exacerbation may contribute to early hospital discharge and recovery of the ability to perform activities of daily living, a cautious approach might be required for commencement of pulmonary rehabilitation in the early stages following an exacerbation for IPF. It is possible that the risks associated with exercise rehabilitation following an acute exacerbation could be higher in this subgroup of patients due to greater desaturation on exercise, greater hypoxaemia at rest and associated comorbidities.

Knowledge Gaps and Research Considerations for Pulmonary Rehabilitation in Interstitial Lung Disease

The application and investigation of the attained benefits of pulmonary rehabilitation in interstitial lung disease is hindered by various elements. First, interstitial lung disease is an extremely heterogeneous disease. Despite their similarities, their numerous conditions encompassed under the umbrella term of interstitial lung disease do not share identical pathophysiology. For example, there can be great variation in the period prior to presentation and the trajectory of lung function decline with variable time for deconditioning to develop. Conditions such as scleroderma or sarcoidosis, may have important systemic effects including direct insult of the respiratory and/or peripheral skeletal muscles. Accordingly, some patients will be receiving systemic corticosteroid therapy known to impair muscular function. Similarly, the

development or intersecting pulmonary hypertension occurs more frequently in certain conditions such as scleroderma than other connective tissue disease-associated interstitial lung disease. These all may limit the potential for gains in function. It is therefore, unlikely that all diseases share the same systemic and local determinants of muscle performance, and this may underlie the absence of agreement between the studies on which type of interstitial lung disease form could benefit the most from a pulmonary rehabilitation program (see earlier discussion). Second, the rarity of some of the subtypes of interstitial lung disease poses an essential obstacle in the recruitment of sufficient numbers of patients for clinical trials. The recruitment of study patients may also be further compromised by the natural history of interstitial lung disease. In idiopathic pulmonary fibrosis the progression of the disease may be rapid or intercepted by exacerbations and acute deteriorations, thus further limiting the available patient study sample. As a result, the lack of appropriately empowered studies does not allow to sufficiently assess the effect of potentially confounding factors in exercise capacity and response to exercise training including age, sex, disease severity and the use of oral corticosteroids. Finally, because the patients with advanced interstitial lung disease tend to be highly symptomatic and/or develop hypoxaemia during exercise, the study participants are commonly carefully selected to be clinically stable with only non-advanced lung disease and reasonable baseline exercise capacity. Thus, more often than not, the evidence on the effect of pulmonary rehabilitation refers to the patient the population with non-advanced interstitial lung disease. For these reasons, it remains unclear and difficult to conclude whether aetiology and/or disease

severity might impact on the benefits of pulmonary rehabilitation in patients with interstitial lung disease. The latter would help define the optimum timing of initiation of pulmonary rehabilitation in interstitial lung disease.

The optimum exercise training method for participants with interstitial lung disease has not been established. To this end, large studies are required to determine whether the benefits of pulmonary rehabilitation vary according to disease severity and whether pulmonary rehabilitation may lead to longer-term effects in interstitial lung disease. Regarding the latter, further study is needed to look specifically into weather longer training periods (i.e. more than 3 months) can increase the duration of benefit for pulmonary rehabilitation in interstitial lung disease. Further research is also needed to enable better understanding of the mechanisms by which pulmonary rehabilitation improves outcomes for people with interstitial lung disease, and, perhaps, more targeted interventions.

In the setting of severe dyspnoea, strategies that may enhance the training effect on peripheral muscle may also have a role, but this has not yet been tested in randomised controlled trials in interstitial lung disease. Neuromuscular electrical stimulation involves applying an intermittent electrical current to a superficial peripheral muscle, most commonly the quadriceps femoris, in order to provide a training stimulus to muscle with minimal ventilatory demands respiratory symptoms. In patients with severe chronic obstructive pulmonary disease, and severe functional impairment, addition of neuromuscular electrical stimulation to an exercise training program resulted in better peripheral muscle function and reduced dyspnoea

(63). Therefore neuromuscular electrical stimulation may be a useful strategy for the most severely debilitated or symptomatic patients, either alone or combined with whole body exercise (24).

Conclusions

clinical gain.Patients with interstitial lung disease represent a very heterogeneous population with significant morbidity. Exercise tolerance in interstitial lung disease is significantly impaired and this is most due to a combination of respiratory, cardiovascular, muscular, and symptom limitations.

Pulmonary rehabilitation comprises structured exercise training and non-exercise components and offers to patients with interstitial lung disease the opportunity to benefit from a multidisciplinary, patient-centred approach. Despite some gaps in our knowledge, consistent evidence of benefit from randomised controlled and other trials provides a rationale for including pulmonary rehabilitation as part of usual care for interstitial lung disease. This is supported by current guidelines, as a safe, feasible and worthwhile adjunct therapy. The evidence suggests that the main benefits from pulmonary rehabilitation extend to immediate gains in functional and maximal exercise capacity, dyspnoea and health-related quality of life. The benefits seem to apply in varying degree to all the underlying diagnoses, including idiopathic pulmonary fibrosis, which is the most prevalent and debilitating type of interstitial lung disease, as well as to all stages of disease severity. However, there is less evidence on the sustainability of the benefits after the completion of pulmonary rehabilitation. Nonetheless, further research is needed to bridge

the knowledge gaps regarding the optimal individual pulmonary rehabilitation prescription in interstitial lung disease in order to maximise its effectiveness and clinical gain.

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