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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Αποκατάσταση στην Πνευμονική Ίνωση

ΜΑΤΘΑΙΟΣ ΒΛΑΧΟΣ
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Ευχαριστήριο Σημείωμα

Θα ήθελα να ευχαριστήσω θερμά για τη πολύτιμη βοήθεια, καθοδήγηση και συμβολή τους στη συγγραφή της διπλωματικής μου εργασίας: τον επιβλέπων κύριο Αναπληρωτή Καθηγητή **Ιωάννη Καλομενίδη**, τον κύριο Καθηγητή **Νικόλαο Κουλούρη** και τον κύριο Καθηγητή **Σπυρίδωνα Ζακυνθινό**.

Contents

Abstract

Interstitial lung disease is an umbrella term for 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.

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.

Disorders of any of the physiological mechanisms of exercise or abnormal coordination interaction between them will result in exercise limitation. The processes that involve the function of the lungs in exercise are limited by the negative effects of interstitial lung disease whose role is considered multifactorial due to respiratory, cardiovascular, muscular, and symptom limitations. The main background mechanisms are considered to be hypoxaemia due to the impaired level of gas exchange insufficient increase of alveolar ventilation relative to the oxygen requirements of exercise, ventilation/perfusion inequalities, low mixed venous PaO_2, and diffusion impairment with total ventilation remaining inefficient compared to carbon dioxide production throughout incremental exercise. Parallely, lung fibrosis narrows and distorts the small and larger airways, decreasing laminar airflow and ventilation of gas exchange units while the vascular bed is progressively obliterated impairing alveolar perfusion leading to pulmonary hypertension and cor pulmonale and the protective hypoxic vasoconstriction in areas of lung fibrosis is incomplete. In general, 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. Accumulating evidence demonstrates muscle weakness and fatigue to be a consequence of interstitial lung disease

Studies thus far have proven pulmonary rehabilitation to be effective in relieving dyspnoea and fatigue and improving patient quality of life with increased daily exercise capacity, while being a safe practice for the patients. It has proven most effective when encompassing both aerobic and resistance training, supplemented by educational lectures nutritional and psychosocial support.

Health gains for interstitial lung disease patients appear to be according to the studies similar to those gained from such practices in chronic obstructive pulmonary disease patients but smaller in magnitude. Long-term effects tend to be absent with patient's lung health improvements returning to baseline within 3-6 months suggesting programmes of longer duration then 3 months may be beneficial for more sustainable results with up to 12-30 months of sustained effects in programmes reaching 6-months of duration. Evidence also suggests that maintenance exercise programs may help sustain the attained benefits and that pulmonary rehabilitation can demonstratively decrease severity of symptoms of the disease such as dyspnoea and cough. Results differences should be considered based on specific populations differences.

A large randomised study demonstrated negative effects of early exercise rehabilitation after an exacerbation of chronic respiratory disease with no benefits gained and even a higher rate of mortality observed in the group, considered to be associated with greater degrees of hypoxaemia at rest and greater desaturation on exercise following an acute exacerbation incidence of the disease.

Short-term benefits of pulmonary rehabilitation have been observed in those with more severe functional impairment, while no specific cut-off point was observed at which rehabilitation could be considered ineffective. Additionally, evidence shows that early referral in the disease course may confer greater benefits for the patient overall.

The current recommendations for pulmonary rehabilitation vary across international guidelines and statements. In general, It has been proposed that repetitive stimulus of high ventilatory demands during exercise sessions proved the most beneficial. Furthermore, exercise training was shown to have more evidence suggesting health gains than the non-exercise training component. Pulmonary rehabilitation programmes are proven effective when similar to those commonly employed in chronic obstructive pulmonary disease but with modifications due to the frequent corticosteroid treatment received by Interstitial lung disease patients that limits muscle gains and considering the more fast deteriorating sysmptoms of interstitial compared to obstructive lung disease.

The best balance studies suggest is whole body exercise, where endurance training is combined with resistance (strength) training with additional elements of flexibility training.

Evidence shoes that exercise is proven most effective when accompanied by the nest possible symptom control and other modalities such as oxygen supplementation as well as complication management such as of cardiac arrhythmias and pulmonary hypertension which are associated with interstitial lung disease.

In conclusion, 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, despite some knowledge gaps when considering each

individual type of disease. Pulmonary rehabilitation is supported by current guidelines, as a safe, feasible and worthwhile adjunct therapy.

Περίληψη

Η διάμεση πνευμονοπάθεια είναι ένας όρος ομπρέλας για 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.

Διαταραχές οποιουδήποτε από τους φυσιολογικούς μηχανισμούς άσκησης ή ασυνήθιστης αλληλεπίδρασης συντονισμού μεταξύ αυτών έχουν ως αποτέλεσμα τον περιορισμό της άσκησης. Οι διαδικασίες που περιλαμβάνουν τη λειτουργία των πνευμόνων κατά την άσκηση περιορίζονται από τις αρνητικές επιδράσεις της διάμεσης πνευμονικής νόσου, του οποίου ο ρόλος θεωρείται πολυπαραγοντικός λόγω των αναπνευστικών, καρδιαγγειακών, μυϊκών και συμπτωματικών περιορισμών. Οι κύριοι μηχανισμοί υποβάθρου θεωρούνται υποξαιμία λόγω της μειωμένης στάθμης της ανταλλαγής αερίων ανεπαρκής αύξηση του κυψελιδικού αερισμού σε σχέση με τις απαιτήσεις οξυγόνου για άσκηση, ανεπάρκεια εξαερισμού / διάχυσης, χαμηλή ανάμειξη φλεβικού PaO2 και διαταραχή διάχυσης με συνολικό εξαερισμό που παραμένει αναποτελεσματική σε σύγκριση με παραγωγή διοξειδίου του άνθρακα σε όλη την αυξητική άσκηση. Παράλληλα, η ίνωση των πνευμόνων στενεύει και στρεβλώνει τους μικρούς και μεγαλύτερους αεραγωγούς μειώνοντας τη

στρωτή ροή αέρα και τον εξαερισμό των μονάδων ανταλλαγής αερίων ενώ η αγγειακή κλίνη εξαλείφεται προοδευτικά μειώνοντας την κυψελιδική διάχυση που οδηγεί σε πνευμονική υπέρταση και πνευμονική πνευμονία και η προστατευτική υποξική αγγειοσυστολή σε περιοχές ίνωσης των πνευμόνων ατελής. Γενικά, η παθοφυσιολογία της πνευμονικής κυκλοφορίας έχει αποδειχθεί ότι είναι ακόμη πιο σημαντική από την μηχανική του εξαερισμού για τον περιορισμό της άσκησης σε ασθενείς με διάμεση πνευμονοπάθεια. Τα συσσωρευμένα στοιχεία καταδεικνύουν την μυϊκή αδυναμία και την κόπωση ως συνέπεια της διάμεσης πνευμονικής νόσου.

Μελέτες έχουν μέχρι στιγμής αποδείξει πνευμονική αποκατάσταση για να είναι αποτελεσματικές στην ανακούφιση της δύσπνοιας και της κόπωσης και στη βελτίωση της ποιότητας ζωής των ασθενών με αυξημένη ημερήσια ικανότητα άσκησης, ενώ αποτελούν ασφαλή πρακτική για τους ασθενείς. Έχει αποδειχθεί πιο αποτελεσματικό όταν η αποκατάσταση συμπεριλαμβάνει τόσο αερόβια άσκηση όσο και άσκηση κατάρτισης αντίστασης, συνοδευόμενη απο εκπαιδευτικές διαλέξεις διατροφικής και ψυχοκοινωνικής υποστήριξη.

Τα κέρδη για την υγεία των ασθενών με διάμεση πνευμονοπάθεια φαίνεται να είναι σύμφωνα με τις μελέτες παρόμοιες με εκείνες που αποκτήθηκαν από τέτοιες πρακτικές σε ασθενείς με χρόνια αποφρακτική πνευμονοπάθεια αλλά μικρότερες σε μέγεθος. Τα μακροπρόθεσμα αποτελέσματα τείνουν να απουσιάζουν, καθώς οι βελτιώσεις στην υγεία των πνευμόνων του ασθενούς επιστρέφουν στην αρχική τους βάση εντός 3-6 μηνών, γεγονός που υποδηλώνει ότι προγράμματα μεγαλύτερης διάρκειας από 3 μήνες μπορεί να είναι επωφελής για πιο βιώσιμα αποτελέσματα με έως και 12-30 μήνες συνεχιζόμενων επιπτώσεων σε προγράμματα που φτάνουν

τους 6 μήνες σε διάρκεια. Τα στοιχεία δείχνουν επίσης ότι τα προγράμματα άσκησης συντήρησης μπορεί να συμβάλουν στη διατήρηση των επιτευχθέντων οφέλη και ότι η πνευμονική αποκατάσταση μπορεί να μειώσει επιδεικτικά τη σοβαρότητα των συμπτωμάτων της νόσου, όπως η δύσπνοια και ο βήχας. Οι διαφορές των αποτελεσμάτων πρέπει να λαμβάνονται υπόψη βάσει ειδικών διαφορών πληθυσμού.

Μεγάλη τυχαιοποιημένη μελέτη κατέδειξε αρνητικές επιπτώσεις της πρόωρης αποκατάστασης της άσκησης μετά από επιδείνωση της χρόνιας αναπνευστικής νόσου χωρίς οφέλη και ακόμη υψηλότερο ποσοστό θνησιμότητας που παρατηρήθηκε στην ομάδα και θεωρήθηκε ότι σχετίζεται με μεγαλύτερο βαθμό υποξαιμίας σε κατάσταση ηρεμίας και μεγαλύτερο αποκορεσμό κατά την άσκηση μετά από έντονη εμφάνιση της νόσου.

Βραχυπρόθεσμα οφέλη από πνευμονική αποκατάσταση έχουν παρατηρηθεί σε άτομα με πιο σοβαρή λειτουργική δυσλειτουργία, ενώ δεν παρατηρήθηκε συγκεκριμένο σημείο αποκοπής στο οποίο η αποκατάσταση θα μπορούσε να θεωρηθεί αναποτελεσματική. Επιπλέον, τα στοιχεία δείχνουν ότι η έγκαιρη παραπομπή στην πορεία της νόσου μπορεί να αποφέρει μεγαλύτερα οφέλη για τον ασθενήσυνολικά.

Οι τρέχουσες συστάσεις για πνευμονική αποκατάσταση διαφέρουν σε διεθνείς κατευθυντήριες γραμμές και δηλώσεις. Γενικά, έχει προταθεί ότι το επαναλαμβανόμενο ερέθισμα των υψηλών αναπνευστικών απαιτήσεων κατά τη διάρκεια των συνεδριών άσκησης αποδείχθηκε το πιο ευεργετικό. Επιπλέον, η άσκηση έδειξε ότι έχει περισσότερες ενδείξεις που υποδηλώνουν κέρδη για την υγεία από ότι η συνιστώσα εκπαίδευσης μη άσκησης. Τα προγράμματα πνευμονικής

αποκατάστασης αποδεικνύονται αποτελεσματικά όταν είναι παρόμοια με εκείνα που χρησιμοποιούνται συνήθως στη χρόνια αποφρακτική πνευμονοπάθεια αλλά με τροποποιήσεις λόγω της συχνής θεραπείας με κορτικοστεροειδή που λαμβάνουν ασθενείς με διάμεση πνευμονοπάθεια που περιορίζουν τα μυϊκά οφέλη και εξετάζοντας τα πιο γρήγορα επιδεινούμενα συμπτώματα διάμεσου σε σύγκριση με την αποφρακτική πνευμονοπάθεια.

Οι καλύτερη ισορροπίας, μελέτες υποδεικνύουν, έγκειται στην άσκηση ολόκληρου του σώματος, όπου η εκπαίδευση αντοχής συνδυάζεται με την κατάρτιση αντίστασης (αντοχής) με πρόσθετα στοιχεία άσκησης ευελιξίας.

'Ερευνες αποδεικνύουν ότι η άσκηση αποδεικνύεται πιο αποτελεσματική όταν συνοδεύεται από τον έλεγχο των συμπτωμάτων και άλλες μορφές παρέμβασης όπως η συμπλήρωση οξυγόνου καθώς και η διαχείριση επιπλοκών όπως καρδιακές αρρυθμίες και πνευμονική υπέρταση που σχετίζονται με τη διάμεση πνευμονοπάθεια.

Συμπερασματικά, οι συνεπείς αποδείξεις για το όφελος από τυχαιοποιημένες ελεγχόμενες και άλλες δοκιμές παρέχουν ένα σκεπτικό για την ενσωμάτωση της πνευμονικής αποκατάστασης ως μέρος της συνήθους φροντίδας για διάμεση πνευμονοπάθεια, παρά τα μερικά κενά γνώσης κατά την εξέταση κάθε ξεχωριστού τύπου νόσου. Η πνευμονική αποκατάσταση υποστηρίζεται από τις τρέχουσες κατευθυντήριες γραμμές, ως μια ασφαλής, εφικτή και αξιόλογη συμπληρωματική θεραπεία.

Definition, Classification and Epidemiology of Interstitial Lung Disease

Interstitial lung disease is an umbrella term for a large, heterogeneous group of more than 300 different chronic conditions. These conditions are classified together because they affect primarily the lung parenchyma leading to varying degrees of irreversible interstitial inflammation and fibrosis (Figure 1) resulting in impaired gas exchange and restrictive pulmonary 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.

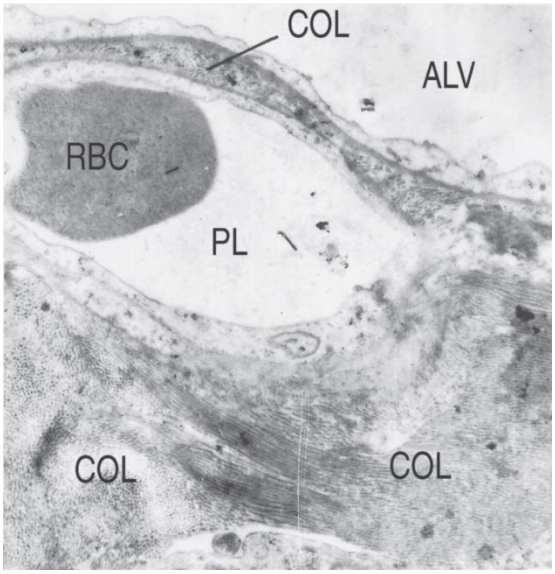

Figure 1: Electron Micrograph from a Patient with Diffuse Interstitial Fibrosis. Note the thick bundles of collagen. *COL*, collagen; *ALV*, alveolar space; *RBC*, red blood cell; *PL*, plasma. Compare Figure 5-1. (From West, John B. Pulmonary pathophysiology: the essentials. 8th ed. 2013).

The classification of causes and the terminology in interstitial lung disease has been subject to numerous changes over the years, which reflects the diversity and heterogeneity of the encompassed diseases. For epidemiological purposes, 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/

Exercise Physiology in Brief

The systemic integration of physiologic mechanisms underlying exercise response was described by Wasserman et al. in 1967 (Figure 2) (1). Physiological systems directly involved in the response to maximal aerobic exercise include: 1) coupling of muscle metabolism to mechanical power output; 2) gas transport between muscle capillary and mitochondria; 3) matching of muscle blood flow to its requirement; 4) oxygen and carbon dioxide carrying capacity of the blood; 5) cardiac output; 6) pulmonary vascular function; 7) pulmonary oxygen and carbon dioxide transport; 8) control of ventilation; and 9) pulmonary mechanics and respiratory muscle function (2).

Exercise prompts the mounting of the appropriate amount of oxygen from the external environment to the haemoglobin molecules of red blood cells (ventilation and alveolar-capillary diffusion: the function of the pulmonary system). Oxygen is then transported to the muscle cells (cardiac output and blood flow: the function of the heart and cardiovascular system, but also the concentration of haemoglobin and the shape and position of the oxygen dissociation curve; the function of the blood). In the muscle cells, aerobic oxidative phosphorylation takes place to produce energy in the form of adenosine triphosphate (diffusive oxygen transport from the microcirculation to the mitochondria and utilization of oxygen for energy production; the function of the muscles). Carbon dioxide which is also co-produced, should then flow in the opposite direction through the same organ systems until it is exhaled to the external environment. Disorders of any of these organ systems or abnormal coordination interaction or between them will result in exercise limitation, i.e., inability to achieve the predicted maximum exercise capacity for a given individual. Such is

the level of complexity of this cascade that exercise limitation is rarely ascribable to any single structural or functional abnormality, either in health or in disease (2).

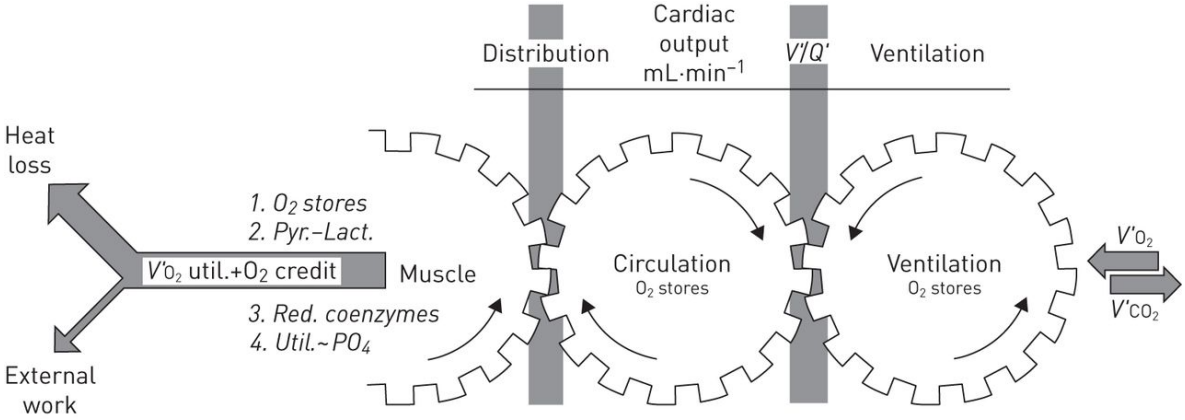

Figure 2: The interaction of physiological mechanisms during exercise based on the classic 1967 conceptualisation of Wasserman et al. (1). The ability to perform exercise is dependent on the performance of a number of linked systems, each of which is subject to deterioration with ageing. V′O2: oxygen uptake; V′/Q′: ventilation/perfusion ratio; V′CO2: carbon dioxide production. Pyr.: pyruvate; lact.: lactate; util.: utilisation. Reproduced from (3).

Physiological Factors Limiting Exercise Capacity in Interstitial Lung Disease

As interstitial lung disease progresses, the patient's exercise capacity declines early (4) and, this is correlated with poor health-related quality of life (5). Reduced exercise tolerance in interstitial lung disease is considered multifactorial due to respiratory, cardiovascular, muscular, and symptom 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 (3). 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 (6). 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 (3).

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 (7). 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 (8, 9) 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 (8).

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 (10). 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 (8, 11) chronic hypoxic vasoconstriction (11) and reduced operating lung volumes (12). 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 (11). The most commonly affected patients are those with scleroderma, and sarcoidosis-associated interstitial lung disease (13).

Skeletal Muscle Limitations

Accumulating evidence demonstrates peripheral muscular dysfunction leading to muscle weakness and fatigue in patients with interstitial lung disease (14). 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 (15) and activation of alternative-to-cytokines NF-kB pathways (16).

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 (17). 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 (17). Therefore, peripheral muscle force

may be a predictor of exercise capacity in interstitial lung disease.

Symptom Limitations

It is important to appreciate the fact that patients with interstitial lung disease often present with severe symptoms including debilitating dyspnoea, cough and muscle fatigue, all of which are intensified by exercise. Therefore, in contrast to normal subjects, in whom physiologic limitation to oxygen transport may be evident, patients with interstitial lung disease are often symptom limited and may stop exercise before reaching limits of metabolic or gas transport capacity (3, 6).

Pulmonary Rehabilitation: Definition

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) define pulmonary rehabilitation as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours” (18).

Pulmonary rehabilitation programs have been widely assessed and validated in patients with chronic obstructive pulmonary disease, for which they have been proved to be unequivocally effective in relieving dyspnoea, improving exercise to bera and fatigue and improving emotional function, and enhancing the sense of control that individuals have over their condition, health-related quality of life and exercise capacity in a moderately large and clinically significant fashion (19). In fact, pulmonary rehabilitation may improve health-related quality of life and exercise capacity more than usual care in chronic obstructive pulmonary disease (20) and it already serves as a core component of the management of the disease (18).

In line with the paradigm of chronic obstructive pulmonary disease, a growing body of evidence suggests that pulmonary rehabilitation could improve outcomes such as dyspnoea, functional capacity, and quality of life also in patients with interstitial lung disease (4). The potential benefits of pulmonary rehabilitation in patients with interstitial lung disease are presented in Figure 3.

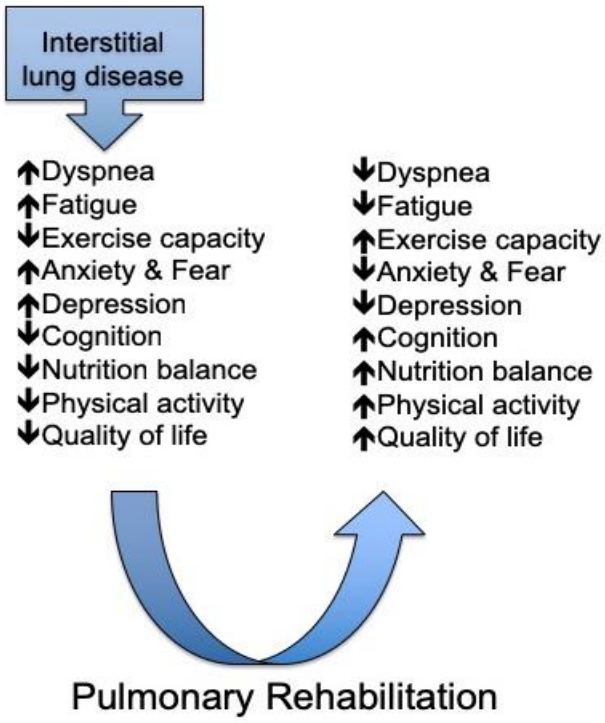

Figure 3: Potential impact of pulmonary rehabilitation in patients with interstitial lung disease. Adapted and modified from (21).

Evidence of Benefit for Pulmonary Rehabilitation in Interstitial Lung Disease

Short-Term Benefit

The evidence base for pulmonary rehabilitation in interstitial lung disease is small but growing. In 2014, a Cochrane meta-analysis (22) of 5 randomized control trials of pulmonary rehabilitation including 86 patients with interstitial lung disease and 82 control participants concluded that pulmonary rehabilitation seems to be safe in interstitial lung disease patients as no adverse effects were reported. Most studies included participants with several types of interstitial lung disease; however, four studies examined predominantly individuals with idiopathic pulmonary fibrosis, 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. Improvements in functional exercise capacity (weighted mean difference of 44.34 meters (95% CI 26.04 to 66.64 metres, n=168 in 6-minute walk distance),maximal exercise capacity (1.24 mL/kg/min-1, 95% CI 0.46 to 2.03 mL/kg/min- 1, n=50, in peak oxygen consumption (VO2peak)), dyspnoea (standardised mean difference for change in dyspnoea - 0.66 in favour of the pulmonary rehabilitation group (95% CI -1.05 to -0.28). and quality of life (standardised mean difference for change 0.59 in favour of the pulmonary rehabilitation group (95% CI 0.20 to 0.98)) were seen immediately following pulmonary rehabilitation. In the meta-analysis, there was also a significant effect of pulmonary rehabilitation across all of the above domains seen in the subgroup of participants with idiopathic pulmonary fibrosis (Figure 3). However, because of inadequate reporting of methods and small numbers of participants, the quality of evidence was deemed low to moderate. The available data were also deemed insufficient to allow examination of the impact of disease severity or exercise training modality (22). Nonetheless, the mean improvement in the six-minute walk test following pulmonary rehabilitation was similar to the mean improvement of 43.93 meters seen in people with chronic obstructive pulmonary disease who have undergone pulmonary rehabilitation (19) suggesting that people with interstitial lung disease receive comparable benefit from pulmonary rehabilitation, and this improvement exceeds the minimal important difference for six-minute walk distance among people with interstitial lung disease, which ranges from 30 to 33 metres (23).

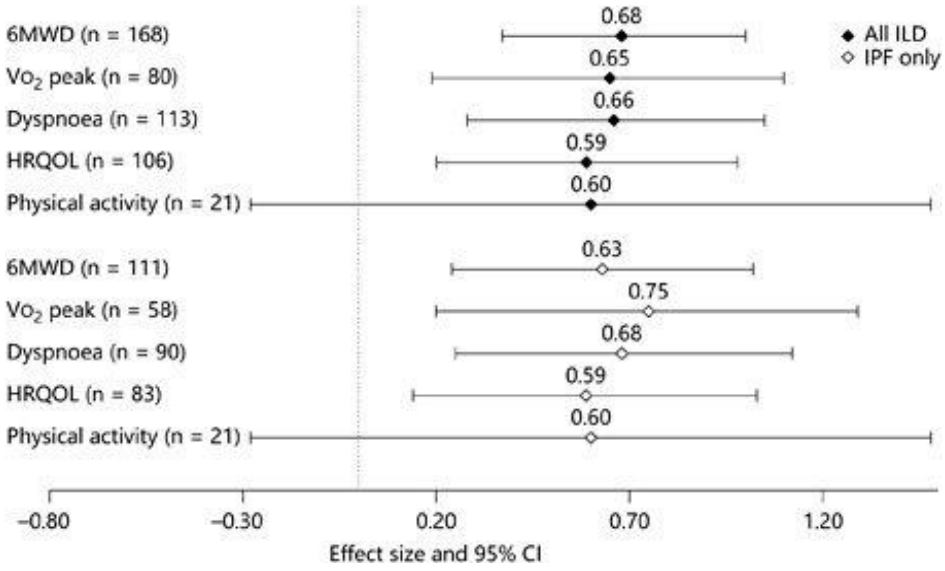

Figure 4: Efficacy of exercise training in interstitial lung disease on clinical outcomes in randomised controlled trials. Data are effect sizes and their 95% CI. HRQOL = Health-related quality of life. From Holland et al (24).

However, evidence from a randomised controlled trial comparing head-to-head the responses in subjects with idiopathic pulmonary fibrosis to rehabilitation to those seen in a cohort with chronic obstructive pulmonary disease suggests that the attained benefits from pulmonary rehabilitation in patients with interstitial lung disease, may be relatively smaller in magnitude (25). Although significant improvements in dyspnoea, muscle force, exercise capacity and activities of daily living were observed in both groups, the magnitude of improvement in all outcomes was less in the idiopathic pulmonary fibrosis group (mean (95% CI) improvement in 6-minute walk distance, idiopathic pulmonary fibrosis 16.2 (7.1–25.4); chronic obstructive pulmonary disease 53.1 (44.9–61.2)). All domains of Short Form-36, with the exception of social function, improved in the chronic obstructive pulmonary disease group; however, there were no changes in Short Form-36 scores in the idiopathic pulmonary fibrosis group (25).

Nonetheless, the current data suggest that it is feasible and effective on important patient-centred clinical outcomes and should be considered as standard therapy in people with symptomatic disease.

Long-Term Benefit

One aim of pulmonary rehabilitation is to sustain the acute effects. This is becoming more relevant in the context of advances in pharmacological management and, perhaps, survival improvement in interstitial lung disease. Few studies have reported on longer-term outcomes of pulmonary rehabilitation in interstitial lung disease. In an already discussed study (25), the benefits from pulmonary rehabilitation were well maintained in the chronic obstructive pulmonary disease group at 6 months, but, they were no longer present in the idiopathic pulmonary fibrosis group (25). In a randomised trial of 57 patients with interstitial lung disease, there were no significant effects on exercise capacity, symptoms and quality of life at 6 months after an 8-weeks pulmonary rehabilitation programme (26). More recently, in the largest randomised controlled study of exercise training in interstitial lung disease, 142 subjects with various pathologies (61 idiopathic pulmonary fibrosis, 22 asbestosis, 23 connective tissue disease-related interstitial lung disease and 36 with other aetiologies) who received either 8 weeks of supervised exercise training or usual care, were followed up for 6 months (27). After the completion of pulmonary rehabilitation, there were significant improvements in health-related quality of life and exercise training (6-minute walk distance, 25 m, 95% CI 2 to 47 m) but, by 6 months, these benefits had returned to baseline in the pulmonary rehabilitation arm. Of note, the control arm had deteriorated further with a 21 meters difference in exercise capacity (27). Elsewhere, patients with restrictive impairment due to occupational

asbestosis and silicosis, not only received smaller immediate benefits but did not maintain exercise capacity benefits beyond 3 months, in comparison with patients with occupational asthma and chronic obstructive pulmonary disease, who sustained benefits at 12 months (28). It has been suggested that the loss in the beneficial effects of pulmonary rehabilitation in the long-term may be due in part to the fact that interstitial lung disease is a chronic and progressive disease (26).

In contrast, evidence suggests that programmes of longer duration may be beneficial for more sustainable results. Recently, Perez-Bogerd et al (29) published on short and long-term effects (at 1-year follow-up) of a 6-month outpatient pulmonary rehabilitation program in 60 patients with interstitial lung disease (64 ± 11 years; 62% males; 23% with IPF). This constitutes, by far, the longer pulmonary rehabilitation program reported in interstitial lung disease. In that randomised trial, functional and maximal exercise capacity, health status and muscle force improved significantly after pulmonary rehabilitation. Importantly, the benefits were maintained after 1 year in those patients that completed the program (6-minute walk distance−73, (28 to 118) m; peak work rate 23, (10 to 35)%predicted; St George's Respiratory Questionnaire−11,(− 18 to – 4) points; quadriceps force 9.5, (1 to 18) %predicted) (29). Another randomised trial of 12-week exercise training or usual care also showed that pulmonary rehabilitation may assist with maintenance of some benefits for up to a year (30). Although differences between groups in 6-minute walk distance were no longer evident at 11 months following exercise training, significant differences were maintained for 30-second chair stand and St George's Respiratory Questionnaire, suggesting sustained improvement in leg strength and health-related quality of life following pulmonary rehabilitation. At 30 months, the survival analysis showed no significant differences between the exercise training group and control

group (30). Elsewhere, pulmonary rehabilitation over 3 months (24 twice-weekly 2-hour sessions over 12 weeks) maintained effectively the exercise oxygen uptake over 3 months and lengthened the constant load exercise time in patients with moderately severe idiopathic pulmonary fibrosis as opposed to the controlled group, who did not achieve any benefits (6). An uncontrolled trial of 50 patients with interstitial lung disease who completed six- to nine-week pulmonary rehabilitation programs also showed that improvements in 6-minute walk distance and quality of life were maintained at 6 months, although the high dropout rate (28%) may have influenced this finding (31). Finally, some evidence suggests preservation of pulmonary rehabilitation benefits in the subgroup of patients with severe disease, who had significantly improved quality of life compared with controls at six-month follow-up (standardized mean difference 14.93, 95% CI 0.54 to 29.32, one study, 23 participants) (22).

Evidence also suggests that maintenance exercise programs may help sustain the attained benefits. In a retrospective, observational study of 79 patients, the initial benefits from a 6-week pulmonary rehabilitation program in functional exercise capacity (mean improvement in incremental shuttle walk of 29.5 m) and health-related quality of life (mean improvement in the chronic respiratory disease questionnaire of 11,6, exceeding minimal clinically important difference of 10 points) were not sustained at 6 or 12 months (32). However, the subgroup of patients who continued with home exercise prescription, or continued to attend a weekly supervised exercise session after the completion of the original program, were less likely to experience a fall in their incremental shuttle walk at 6 months, compared with those who did not continue with maintenance exercise (32). The latter corresponds with findings in pulmonary rehabilitation in occupational respiratory

diseases, where patients with asbestosis who followed a 3-month maintenance program after a 3-week intensified outpatient pulmonary rehabilitation program maintained the beneficial effects of rehabilitation in quadriceps muscle strength and 6-minute walk distance, while the those who did not follow a maintenance program returned to baseline within 6 months (28, 33, 34). Nevertheless, the possibility that some improvements in the exercise tolerance might be related to the placebo effect of regular medical visits to rehabilitation centres has been acknowledged (35).

In summary, further work is required to define the optimal duration of pulmonary rehabilitation for people with interstitial lung disease, define the related longer-term impacts of exercise training, to ensure that the benefits can be sustained over time reduces mortality. Growing evidence suggests that pulmonary rehabilitation programmes of longer duration (beyond 12 weeks), as well as maintenance exercise programs may be beneficial for more sustainable results.

Effect in Daily Physical Activity

An important aim of pulmonary rehabilitation is to improve physical activity in daily life (36). In interstitial lung disease the impact of pulmonary rehabilitation on daily physical activity has not yet been adequately defined although objective activity monitoring has showed a severe reduction in daily physical activity in patients with fibrotic idiopathic interstitial pneumonia (37, 38) and a moderate reduction in patients with lymphangioleiomyomatosis (39).

In the study by Perez-Bogerd et al. (29) a 6-month pulmonary rehabilitation program failed to enhance daily physical activity (in terms of daily steps and moderate intense physical activity as measured objectively by activity monitors) at 1-year follow-up. A small randomised trial examining an estimate of this outcome through the patient-

reported International Physical Activity Questionnaire in 21 patients with idiopathic pulmonary fibrosis also found no statistically significant findings, in the 3-month follow-up period (40). Similar outcomes were produced by another study (38), where a group of 72 patients with fibrotic idiopathic interstitial pneumonia patients failed to improve their daily physical activity immediately after completion of the 8-week pulmonary rehabilitation programme, despite the benefits attained in exercise tolerance (assessed using 6-minute stepper test). In contrast, by the end of a pulmonary rehabilitation programme, 18 younger patients with lymphangioleiomyomatosis, demonstrated an improvement in daily physical activity (39).

Further study is therefore needed to address this matter. It is possible that pulmonary rehabilitation of longer duration that is also applied early in disease course is required to render patients with interstitial lung disease more physically active in their daily life.

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 (41). 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 (22) 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 (42) 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 (42). 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 (43). 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 (43).

In contrast, Holland et al. (44) 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 (44).

In the study by Dowman et al.(27) 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 (27).

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 (39). 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 (39).

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 (45). 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 (46). 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 (18, 41). To date, a large randomised study demonstrated negative effects of early exercise rehabilitation after an exacerbation of chronic respiratory disease (47). 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 (47).

Early versus Late Pulmonary Rehabilitation in Interstitial Lung Disease.

For patients with interstitial lung disease as a group, several studies suggest that the short-term benefits of pulmonary rehabilitation may be more pronounced in those with more severe functional impairment. Dowman et al. (27). found that baseline clinical variables of interstitial lung disease were poorly predictive of the response to exercise training. This finding provides no basis for using pulmonary function markers of severity to exclude individuals with interstitial lung disease from exercise training (45). In fact, those most limited at baseline tended to have the greatest short-term benefit from pulmonary rehabilitation, a pattern that is also recognised in chronic obstructive pulmonary disease (48).

A recent study investigated prospectively whether baseline exercise capacity, disease severity or underlying aetiology might affect outcomes in 40 patients (idiopathic pulmonary fibrosis 63%, age 66.9 ± 11 ys) who completed successfully a standard pulmonary rehabilitation course (4). It found that patients with lower baseline 6-minute walk distance showed greater improvement in 6-minute walk distance (Spearman r score = −.359, p = .034) and symptoms relief at St George's Respiratory Questionnaire (r = −.315, p = .025) regardless of underlying disease. Thus, the baseline submaximal exercise capacity inversely correlated with both functional and symptom gains in this heterogeneous population with interstitial lung disease (4). This is in line with a previously mentioned prospective study of 402 patients with severe interstitial lung disease, in which the improvement in 6-minute walk distance after a 4-week inpatient pulmonary rehabilitation program was smaller

the higher the baseline 6-minute walk distance was ($p<0.01$) (43). Of note, of all the variables tested (age, sex, body mass index, smoking history, use of long-term oxygen therapy, baseline forced vital capacity, baseline 6-minute walk distance and baseline visual analogue score), only the baseline 6-minute walk distance was a significant predictor of change in 6-minute walk distance. Also, patients with signs of pulmonary hypertension showed a decreased baseline 6-minute walk distance (277 ± 12 vs. 322 ± 8 m) and, although the improvement in 6-minute walk distance remained significant and clinically meaningful, it was significantly less than that of patients without pulmonary hypertension (36 ± 6 vs. 48 ± 3 m, $p = 0.045$). The latter suggests that pulmonary hypertension may be a negative predictor of response to pulmonary rehabilitation in interstitial lung disease (43). Accordant results were produced by another prospective study in patients with interstitial lung disease of various aetiologies, where the baseline 6-minute walk distance was the only independent predictor of improvement in 6-minute walk distance during rehabilitation ($r = -0.49$, $p < 0.0005$) (31). In detail, for every 10-meter greater 6-minute walk distance pre-rehabilitation, the change in 6-minute walk distance post-rehabilitation declined by 2.63 m (95%CI 1.31 to 3.95, $p < 0.0005$), however, there was no specific threshold of baseline 6-minute walk distance at which rehabilitation could be considered ineffective. In a retrospective study (35), baseline 6-minute walk distance was also a significant predictor of change in 6-minute walk distance ($p < 0.0001$), with increasing baseline 6-minute walk distance predicting a smaller improvement after pulmonary rehabilitation; a post hoc analysis was unable to identify a baseline 6-minute walk distance value above which pulmonary rehabilitation was ineffective (35).

In contrast, some evidence support that referral early in the disease course for

pulmonary rehabilitation may confer greater benefits. A prospective study by Holland et al. (44), concluded that patients with idiopathic pulmonary fibrosis have greater improvements in functional exercise capacity when pulmonary rehabilitation is delivered early in the course of disease (as evidenced by larger forced vital capacity, less exercise-induced oxyhaemoglobin desaturation and lower right ventricular systolic pressure), thus supporting early referral to pulmonary rehabilitation for patients with idiopathic pulmonary fibrosis. Of note, patients with other interstitial lung diseases achieved significant gains in exercise capacity regardless of disease severity and were more likely than those with idiopathic pulmonary fibrosis to achieve sustained improvements in dyspnoea (44).

Thus, the current evidence on the ideal timing of pulmonary rehabilitation for interstitial lung disease is not unanimous. It is possible that the discrepancy in evidence reflects, at least to some extent, the heterogeneity in the underlying diagnosis. However, it remains that pulmonary rehabilitation benefits at any point in the disease course, and as such, it should to be offered, as a standard aspect of care, in the management of stable patients with interstitial lung disease who are limited by their condition.

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 (18). The international statement on the diagnosis and management of idiopathic pulmonary fibrosis (46) 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 (49). 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 (41). 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 differences in recommendations between major international guidelines emphasize the challenges in the application of pulmonary rehabilitation to this diverse patient group, particularly with regard to patient selection, programme components and duration of benefits (50).

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 (51, 52). 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 (51). 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 (51).

Elsewhere, Keyser et al (53), 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 (53). 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 (17). 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 (36). 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 (25).

Components of Pulmonary Rehabilitation in Interstitial Lung Disease

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 (50) (Figure 4).

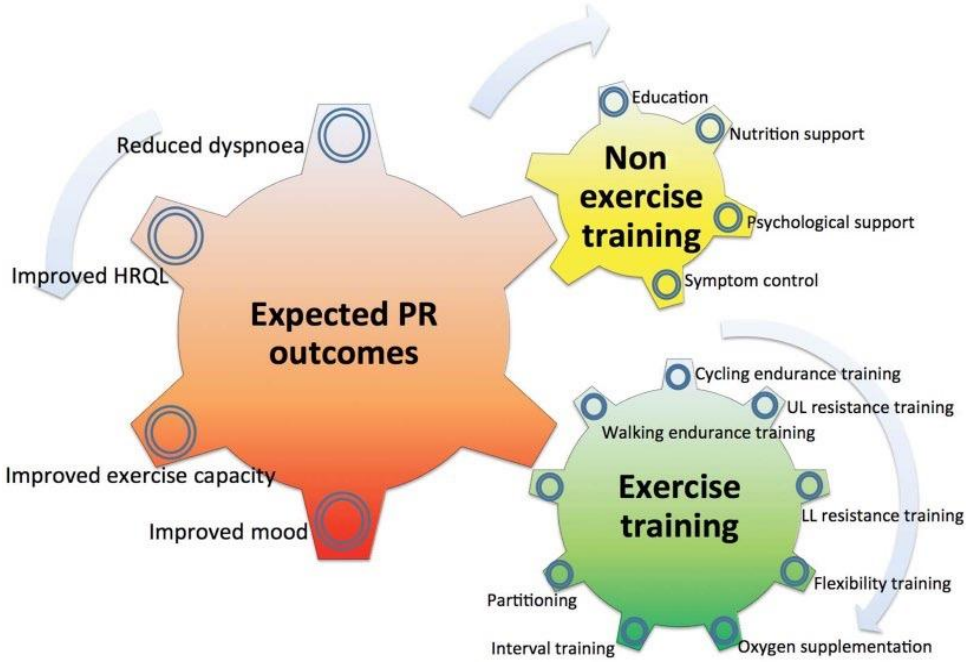

Figure 4: Comprehensive pulmonary rehabilitation for interstitial lung disease. The gears with red, green and yellow colour present expected PR outcomes, exercise training and non-exercise training, respectively. The green gear is bigger than the yellow gear, because exercise training has more evidence 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 (18). This constellation of symptoms and impairments is familiar to healthcare professionals in pulmonary rehabilitation (54).

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 (25). 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 (50).

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 (55) and thus a more pronounced limitation in endurance capacity compared to patients with chronic obstructive pulmonary disease (51). 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. (51) 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 (55). 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 (56).

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 (57) 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 (57).

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 (18).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 (57).

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 (57).

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 (18). 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.

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 ILD for symptom control and psychosocial support (58).

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 (52).

The British guidelines strongly recommend pulmonary rehabilitation for all patients

with Medical Research Council Dyspnoea score of 3–5 and functional limitation (41). Chronic exertional dyspnoea is characteristic of idiopathic pulmonary fibrosis (46). The Cochrane review confirmed reduced dyspnoea after pulmonary rehabilitation in a subgroup of patients with idiopathic pulmonary fibrosis (22). 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 (52). Pursed-lip breathing is one of the most favoured and beneficial breathing techniques in patients with chronic obstructive pulmonary disease (59). 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 (52). More so, the use of an intense pursed-lip breathing technique could actually increase the work of breathing in patients with restrictive lung diseases (52). 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 (25, 52).

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 (60). Qualitative studies have shown that discussion of strategies to manage cough is a priority for patients with interstitial ling disease undertaking pulmonary rehabilitation (61, 62); 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 (63); this approach remains to be proven in idiopathic pulmonary fibrosis, but highlights the potential benefit of physiotherapy and nonpharmacological interventions (60).

Pulmonary rehabilitation may also be important in ameliorating fatigue in patients with chronic respiratory disease including interstitial lung disease (18). A 12-week exercise supervised training program improved subjective fatigue in people with interstitial lung disease and sarcoidosis at 3 months (64). 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 (65).

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 (66). 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 (52).

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 (61). 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 (62).

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 (67). 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 (68). In a study of 124 patients with interstitial lung disease of mixed aetiology, the prevalence of anxiety and depression were 31% and 23%, respectively (69). Of note, high levels of dyspnoea were an independent predictor of anxiety, and more dyspnoea and comorbidities were independent predictors of depression (69). Apart from dyspnoea, other causes of psychological distress may include loss of independence, feelings of social isolation and inadequate sleep (38).

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, 38, 70) and fatigue (71) 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 (73).

Special Considerations for Exercise Training in Interstitial Lung Disease

Given the prevalence of severe exertional oxyhaemoglobin desaturation and pulmonary hypertension in interstitial lung disease (74, 75), intermittent monitoring of oxy-haemoglobin saturation and pulse rate via pulse oximetry is recommended and, supplemental oxygen should be available at all centres providing exercise training for people with interstitial lung disease (18). In patients with systemic sclerosis, a forehead probe may provide more accurate oximetry measures than a finger probe, due to cutaneous involvement. Supplemental oxygen has been used during many exercise training studies to maintain blood oxygen saturation at acceptable levels, which has been defined as above 85%, above 88% or above 90% (24). Supplemental oxygen may result in better oxygen delivery to the tissue, but it does not appear to impact on exercise-induced elevation in pulmonary artery pressures (76). Patients with severe disease, in whom desaturation may be difficult to control even with supplemental oxygen, will require close supervision during exercise. Where adherence to the exercise protocol is limited by intolerable symptoms, interval training protocols may be considered (see earlier discussion).

For patients with connective tissue-related interstitial lung disease such as scleroderma, joint pathology and pain are important disease manifestations (77) that warrant consideration when establishing an exercise programme. It is possible that alternative approaches such as water-based exercise programme may be better suited than land-based training in some of these individuals in order to minimise joint loading, similar to that found effective in chronic obstructive pulmonary disease (78).

Patients with interstitial lung disease may develop frequent cardiac arrhythmias, both

during both daily life and exercise testing, most commonly atrial premature contractions or ventricular premature contractions. Although ventricular arrhythmia is potentially harmful, they have not been reported to occur more frequently in hypoxaemic than normoxaemic conditions, to be symptomatic and to require specific treatment (79).

Pulmonary hypertension is common in interstitial lung disease at rest and may also be induced or aggravated by exercise but there have been no reports of pulmonary hypertension-related adverse effects in exercising patients with interstitial lung disease. In the study by Huppmann et al. (43), following inpatient pulmonary rehabilitation, 286 patients not affected by pulmonary hypertension had significant improvements in the physical and mental health sub-scores of Short Form-36, while 111 patients with signs of pulmonary hypertension only had significant improvements in the mental health sub-scores. Six-minute walk distance on admission was significantly lower in patients with signs of pulmonary hypertension compared to those without signs of pulmonary hypertension (277±12 m versus 322±8 m; $p = 0.001$). On discharge, both groups showed a significant improvement ($p<0.001$) (PH: 313±12 m versus non-PH: 370±7 m). However, patients with signs of pulmonary hypertension had a smaller absolute increase in 6-minute walk distance compared to patients without signs of pulmonary hypertension (36±6 m versus 48±3 m; $p = 0.045$). Therefore, patients with signs of pulmonary hypertension also benefited from an inpatient pulmonary hypertension, albeit, to a smaller extent (43).

Safety of Exercise Training in Interstitial Lung Disease

Despite the marked physiological abnormalities, and limiting symptoms, exercise testing and training for interstitial lung disease has an excellent safety profile. For the

6-min walk testing, no clinical adverse events have been reported, despite profound oxygen desaturations (80). For pulmonary rehabilitation, a Cochrane review found no reports of adverse events during exercise training for interstitial lung disease (22). One study reported the death of one pulmonary rehabilitation participant during the intervention period; however, this was believed to be unrelated to the intervention received, and the data were not included in the analysis (6, 22). Likewise, a recent systematic review of pulmonary rehabilitation in idiopathic pulmonary fibrosis did not identify any serious adverse effects (42).

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 (81). 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

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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