REVIEW

Best Practice Approach for Interstitial Lung Disease in the Rehabilitation Setting

Leona M. Dowman, PhD[1,2,3,4], Anthony K. May, PhD[1,5]

ABSTRACT

Interstitial lung disease (ILD) is a disabling group of chronic lung conditions comprising over 200 different disease entities that are typically associated with interstitial inflammation and fibrosis. People with ILD almost invariably experience dyspnea, fatigue, anxiety, depression, cough, poor health-related quality of life, and reduced exercise tolerance. Pulmonary rehabilitation (PR) is a comprehensive intervention that includes exercise training as a core and essential component and that aims to improve exercise tolerance and exertional symptoms in people with chronic lung disease. PR is a cornerstone of care for people with chronic obstructive pulmonary disease, where its role and benefits have been well defined. PR offers increasing promise as an equally effective therapy for people with ILD. This review discusses the evidence of PR for ILD, outlines the current exercise training approach for people with ILD, and discusses important areas for future research. *Journal of Clinical Exercise Physiology*. 2020;9(2):67–82.

Keywords: idiopathic pulmonary fibrosis, exercise, pulmonary rehabilitation

INTRODUCTION

The interstitial lung diseases (ILDs) are a debilitating group of chronic lung conditions that are typically characterized by interstitial inflammation and irreversible lung parenchymal fibrosis (1). People with ILD often present with exertional dyspnea and hypoxemia, exercise intolerance, global fatigue, cough, and depression and/or anxiety, significantly reducing health-related quality of life (HRQoL) (2–4). Two effective antifibrotic therapies have been shown to attenuate disease progression in idiopathic pulmonary fibrosis (IPF), the most debilitating ILD; however, there is limited evidence to suggest these treatments can provide convincing benefits for exercise tolerance, HRQoL, or symptoms. Pulmonary rehabilitation (PR) is a promising therapeutic intervention that may effectively address the physical deficits and symptom burden in ILD. There is increasing evidence to suggest PR should be an indispensable factor in the management of ILD. PR includes detailed patient assessment, followed by participation in a supervised exercise training program, a key and essential component, with education and a goal to effect health behavior change (5). The aim of this review article is to present the current best practice approach for PR in ILD and highlight various areas for future investigation.

ILD OVERVIEW

The ILDs represents a diverse, complex, and large group of inflammatory and fibrotic lung conditions (Figure 1) that overlap in their clinical presentations and patterns of lung injury (1). A large number of ILDs, termed idiopathic interstitial pneumonias, have no identifiable cause and include IPF, the most destructive of all ILDs (6). Alternatively, ILD can occur because of occupational or environmental exposures, as in asbestosis or silicosis; as a result of drug-induced lung toxicity (7); or as a result of an aberrant immunological response to the repeated inhalation of organic allergens, as in

[1]Department of Allergy, Clinical Immunology and Respiratory Medicine, Monash University, Melbourne, VIC 3004, Australia
[2]Department of Physiotherapy, Austin Health, Heidelberg, VIC 3084, Australia
[3]Department of Respiratory & Sleep Medicine, Austin Health, Heidelberg, VIC 3084, Australia
[4]Institute for Breathing and Sleep, Heidelberg, VIC 3084, Australia
[5]Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC 3220, Australia

Address for correspondence: Leona Dowman, Department of Allergy, Clinical Immunology and Respiratory Medicine, Monash University, Level 6, The Alfred Centre, 99 Commercial Road, Melbourne 3004, Australia; +61 423 614 218; e-mail: leona.dowman@monash.edu.

Conflicts of Interest and Sources of Funding: None.

hypersensitivity pneumonitis (8). The ILDs are also associated with various connective tissue disorders (CTDs) such as rheumatoid arthritis (RA), Sjogren syndrome, polymyositis/dermatomyositis, and systemic lupus erythematosus (9), and primary diseases and underlying genetic disorders, such as sarcoidosis or lymphangioleiomyomatosis (1,9).

A more recent approach in categorizing ILDs has involved combining those that develop a progressive fibrosing phenotype (1). These patients with fibrotic ILD often have worse impairment and a poorer prognosis. Idiopathic pulmonary fibrosis (IPF) is the most common and prototypical form of chronic progressive fibrotic lung disease. As few as 20% to 30% of people with IPF survive 5 years following diagnosis, a prognosis worse than most malignancies (10). The extent and rate of progression of IPF is heterogeneous and often unpredictable. Patients can experience long stages of stability with slow gradual decline; others can experience rapid dramatic progression whilst others can succumb to acute exacerbation (6). Other fibrotic ILDs that can have clinical, radiological, and histological features similar to IPF can include idiopathic nonspecific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, CTD-ILD (primarily RA-ILD), chronic hypersensitivity pneumonitis, and asbestosis and silicosis (1,9). There is no consensus as to how disease progression should be defined in patients with ILD; typical features include acute deteriorations in

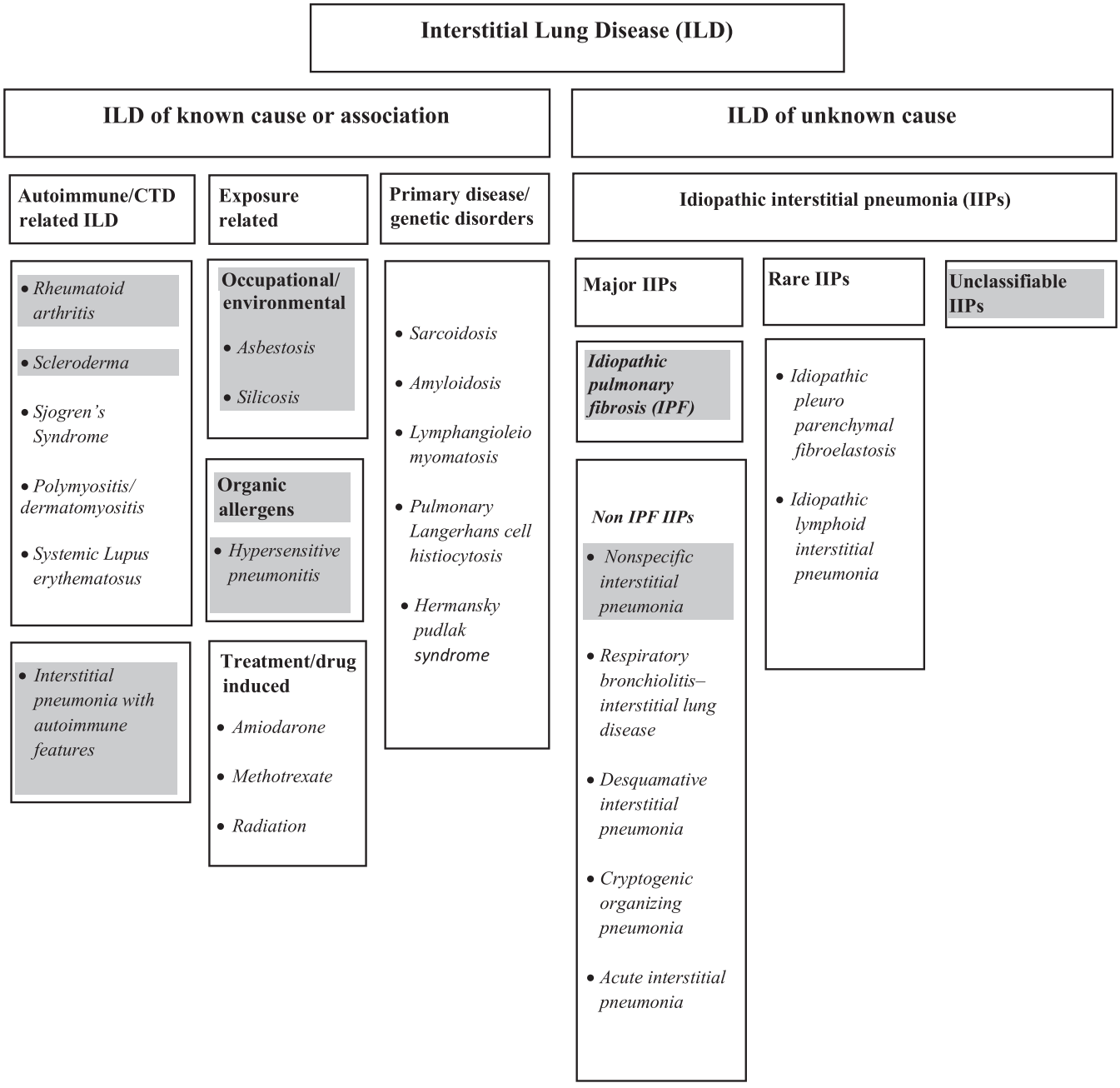

FIGURE 1. Types of interstitial lung disease. Shaded area indicates types of ILD most likely to have progressive–fibrosing phenotypes. CTD = connective tissue disease.

respiratory function, acute exacerbations, evidence of new abnormalities on imaging, decrease in exercise tolerance, worsening of cough, breathlessness and fatigue, increase in hypoxemia, and the initiation of oxygen therapy (1,11).

People with ILD also typically present with a range of comorbidities, further complicating the disease and further negatively impacting patient outcomes and HRQoL (12). Pulmonary hypertension is a frequent complication leading to greater respiratory and functional impairments (13,14). With advancing disease, severe hypoxemia may develop, especially in those with IPF and other fibrotic ILDs, contributing to the development or worsening of pulmonary hypertension and leading to dependence on supplemental oxygen (13). The combination of pulmonary fibrosis and emphysema may occur in up to 10% of patients. These individuals are associated with more severe disease and an increased risk of lung cancer and poor prognosis (12). Gastroesophageal reflux disease is highly prevalent, especially in IPF, and may contribute to the pathogenesis and progression of fibrosis (12,14). There is increased incidence of coronary artery disease, cardiac muscle abnormalities, and lung cancer in IPF, CTD-related ILDs, and exposure-related ILDs (12,14). Anxiety and depression are also common, leading to an overall increase in disease burden (12,15). Systemic manifestations including arthropathy, myopathy, and vasculopathy may also exist as a result of underlying CTD (16).

Regardless of etiology, the contribution of comorbidities or the extent of disease, exertional dyspnea, overwhelming fatigue, and poor exercise tolerance are almost invariably present in people with ILD. These symptoms are often debilitating and progressively worsen over time, particularly in IPF and other fibrotic ILDs (2,17). However, treatment options for ILD are limited. Lung transplant is a potentially curative option for a minority of patients with advanced ILD, although medical complications and mortality risk are high (18). Two effective antifibrotic therapies that have been shown to slow disease progression are approved for treatment in IPF; however, they are not recommended for other types of ILD (19). There is also limited evidence to suggest these treatments can provide convincing benefits for exercise tolerance, HRQoL, or symptoms. Therefore, therapeutic interventions such as PR that can lead to improvement in exercise capacity and HRQoL should play an important role in the management of ILD.

EXERCISE LIMITATION: UNDERLYING MECHANISMS AND IMPACT

Impaired exercise tolerance is a well-known, prominent feature of ILD. The contributory mechanisms of exercise limitation are multifactorial (Figure 2); however, the 2 key pathophysiological factors are circulatory dysfunction and gas exchange impairment. Circulatory impairment was found to be the predominant factor limiting exercise in patients with ILD of varying etiology including CTD-ILD, idiopathic interstitial pneumonia, sarcoidosis, systemic sclerosis, and pneumoconiosis (3,20–22). The principal source of circulatory dysfunction appears to be pulmonary hypertension, as a result of pulmonary vascular destruction and hypoxic pulmonary vasoconstriction (3,21,23) resulting in inadequate pulmonary, and therefore systemic, blood flow. Other factors can include impaired heart rate, systolic or diastolic ventricular dysfunction, myocardial conduction defects, or arrhythmias (3,20).

Gas exchange impairment is another major factor limiting exercise performance in ILD. Gas exchange impairment is manifested by reduced diffusing capacity and ventilation perfusion mismatch as a result of thickening of the alveolar capillary membrane and pulmonary capillary bed destruction (24). Reduced diffusing capacity and ventilation perfusion mismatch are the primary cause of arterial hypoxemia in ILD at rest and during exercise (3,20,24). These derangements are likely to impair cardiac output resulting in impaired oxygen delivery, inadequate muscle oxygenation, and reduced oxidative metabolism, thereby impairing muscle function and compromising exercise performance (20,25). Altered respiratory mechanics such as reduced vital capacity, total lung capacity, functional residual capacity, tidal volume, and lung compliance, and increased lung elastic recoil is common in people with ILD. Consequently, people with ILD adopt a rapid and shallow breathing pattern in order to maintain ventilation. This increased work of breathing becomes more pronounced during exercise (3,20,22). These altered respiratory mechanics, however, exert a smaller influence on exercise limitation in patients with ILD compared with circulatory and gas exchange impairments (3).

The extent of exercise-induced desaturation in ILD correlates with the extent of parenchymal abnormality on imaging (3,20), suggesting those with greater degrees of interstitial fibrosis, such as is seen in IPF and other fibrotic ILDs, have greater derangement in gas exchange on exertion (20,22). Similarly, the degree of circulatory dysfunction is correlated with severity of disease as evidenced by greater diffusion limitation, more severe arterial hypoxemia, and increased dead space ventilation. The extent of exercise limitation is also likely to increase in proportion with the severity of pulmonary hypertension (20). Therefore, as disease progresses and fibrosis develops, particular those with a fibrosing phenotype, there is a progressive deterioration in lung function, a tendency to experience more severe diffusion limitation at rest, greater exercise-induced oxyhemoglobin desaturation, and an increase in pulmonary hypertension (1,3,11,24), consequently leading to greater limitation with exercise.

Skeletal muscle dysfunction is another important contributor to exercise limitation in ILD. Quadriceps strength is reduced in ILD and is an independent predictor of reduced exercise capacity (26). The exact cause of skeletal muscle dysfunction is unclear, although several factors may involve malnutrition (27), inflammatory and oxidative stress (27), physical deconditioning due to inactivity and disuse (28), and corticosteroid-induced myopathies resulting in proximal muscle weakness (29). In addition, the frequent occurrence of hypoxemia during exercise often seen in ILD may lead to

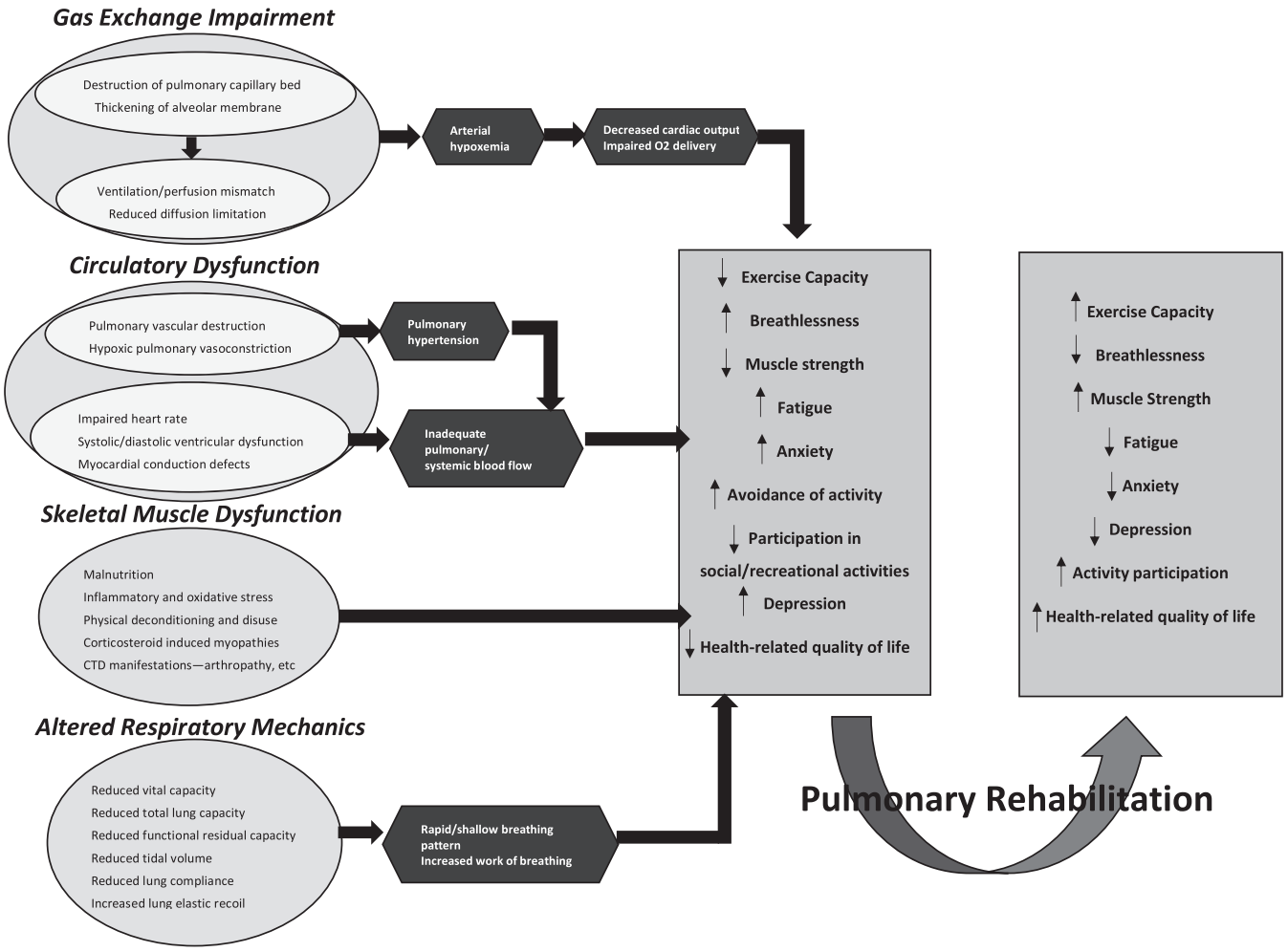

FIGURE 2. Exercise limitation in interstitial lung disease. CTD = connective tissue disease.

adaptive changes in the muscle such as worse quadriceps endurance (30), muscle fiber type redistribution and alteration (31), and enhanced muscle oxidative stress (30) similar to those seen in chronic obstructive pulmonary disease (COPD). The prominent clinical manifestations of proximal skeletal muscle weakness and pain, joint pain, stiffness and swelling, and skeletal muscle vasculopathy seen in CTD-ILD and sarcoidosis may also substantially alter skeletal muscle function.

Irrespective of exact causal mechanisms of impaired exercise tolerance in ILD, this cardinal feature of ILD significantly impacts a patient's HRQoL (3). People with ILD are able to do less physically, limiting their participation in social, recreational, and general activities of daily living, leading to adverse effects on independence, autonomy, and HRQoL. Therefore, interventions such as PR that can positively impact exercise tolerance and in turn assist to improve functional status, reduce the clinical symptoms of fatigue and dyspnea, and restore HRQoL are paramount in this population.

PULMONARY REHABILITATION

PR is defined 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 behavior 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 behaviors" (5). The primary goals of PR are to restore the patient to the highest possible level of independent functioning in the face of chronic lung disease and to facilitate improved self-management (5). Although PR can involve a range of interventions, exercise training is a fundamental component and in some instances is a stand-alone element (5).

PR is a cornerstone of care for people with COPD. There is an enormous amount of evidence highlighting the success of PR in improving exercise capacity, HRQoL, and symptoms in COPD. This benefit for PR in COPD is indisputable, so much so that the Cochrane review of PR in COPD states that additional randomized controlled trials (RCTs) comparing PR and conventional care in COPD are not warranted (32,33). Individuals with ILD often present with similar symptoms to those seen in COPD, despite differences in underlying pathophysiology, such as dyspnea, fatigue, reduced exercise tolerance, anxiety, depression, and poor HRQoL (34). Given these similarities, and that a lot of

these issues have been shown to be modifiable in COPD, it is reasonable to expect PR is equally effective in ILD.

EVIDENCE FOR PR FOR ILD

In 2008, 2 RCTs of PR in ILD (35,36) provided the first robust scientific evidence that exercise training induces positive changes in exercise tolerance and symptoms. Since then, there has been an encouraging increase in the number, size, and quality of RCTs in ILD. In 2014, a Cochrane review identified 9 RCTs that evaluated the benefit of PR in ILD (37). The meta-analysis, which included 5 of the RCTs, found that PR significantly improved functional capacity, peak exercise capacity, HRQoL, and dyspnea. There have been a further 6 more published RCTs of PR in ILD (38–43), 2 of which were included in abstract form only in the Cochrane review (42,43). All 6 RCTs conferred clinically significant benefits in functional capacity and HRQoL. In addition, the improvements in functional capacity following PR, measured by 6-min walk test distance (6MWD), exceeded the minimal important difference (MID) (44) in 6 out of the 9 RCTs of PR in ILD (Figure 3). A similar response was seen for HRQoL (Figure 4), measured by the St. George's Respiratory Questionnaire (SGRQ) total score, with 5 out of 8 RCTs of PR in ILD reporting an improvement that exceeded the MID (45). This suggests that the benefits achieved from PR are clinically important and meaningful to the patients. PR may also impact other important symptoms in ILD. Significant improvements were also seen in peak exercise capacity (35,39,41,43), endurance time (39), strength (42), fatigue (41), and anxiety (41). This strongly indicates that PR should be part of the standard of care in ILD, just as it has become in COPD.

OPTIMAL TIMING AND PATIENT SELECTION

The ILDs are a complex group of lung disorders that can exhibit substantial variability in disease behavior and progression both between and within subtypes. This led to uncertainty as to whether exercise training would be effective across different etiologies and severities of disease, in particular those with IPF or progressive disease (46,47). The Cochrane systematic review of PR in ILD found that significant improvements in 6MWD following PR were comparable in people with ILD and in those with IPF (37). In addition, both groups exceeded the MID for 6MWD for people with ILD, suggesting both people with ILD and IPF receive clinically meaningful benefits. More recently, a large RCT of exercise training in ILD stratified their randomization and powered their study for specific ILD subgroups (IPF, CTD-ILD, and dust-related ILD) in order to establish if benefits of exercise training varied according to etiology (38). Exercise training exerted a similar positive effect across varying subtypes, including in those with IPF. In addition, greater functional or symptom limitation, not etiology or severity of ILD, predicted functional and symptomatic improvement following PR. This suggest that all types of ILD stand to benefit from PR. On the other hand, markers of disease severity were predictors of improvement at 6 months, suggesting those with the better preserved physiology are more likely to have long-term benefits. This is consistent with an earlier uncontrolled study that found greater and more sustained benefits of exercise training in milder disease (48). Of

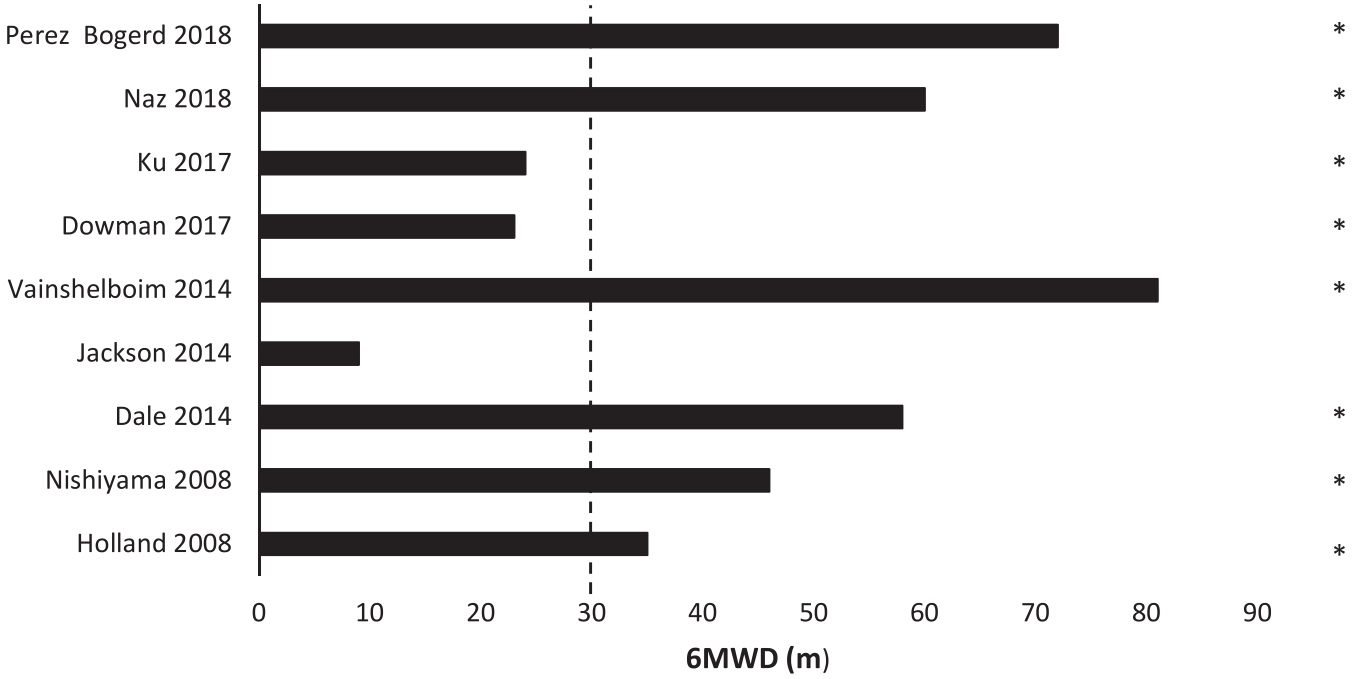

FIGURE 3. Changes in 6-min walk distance (6MWD) in patients with interstitial lung disease (ILD) following pulmonary rehabilitation (PR). *$P < 0.05$, PR versus control group. The dashed line represents the minimal important difference of 30 m in 6MWD in patients with ILD (44).

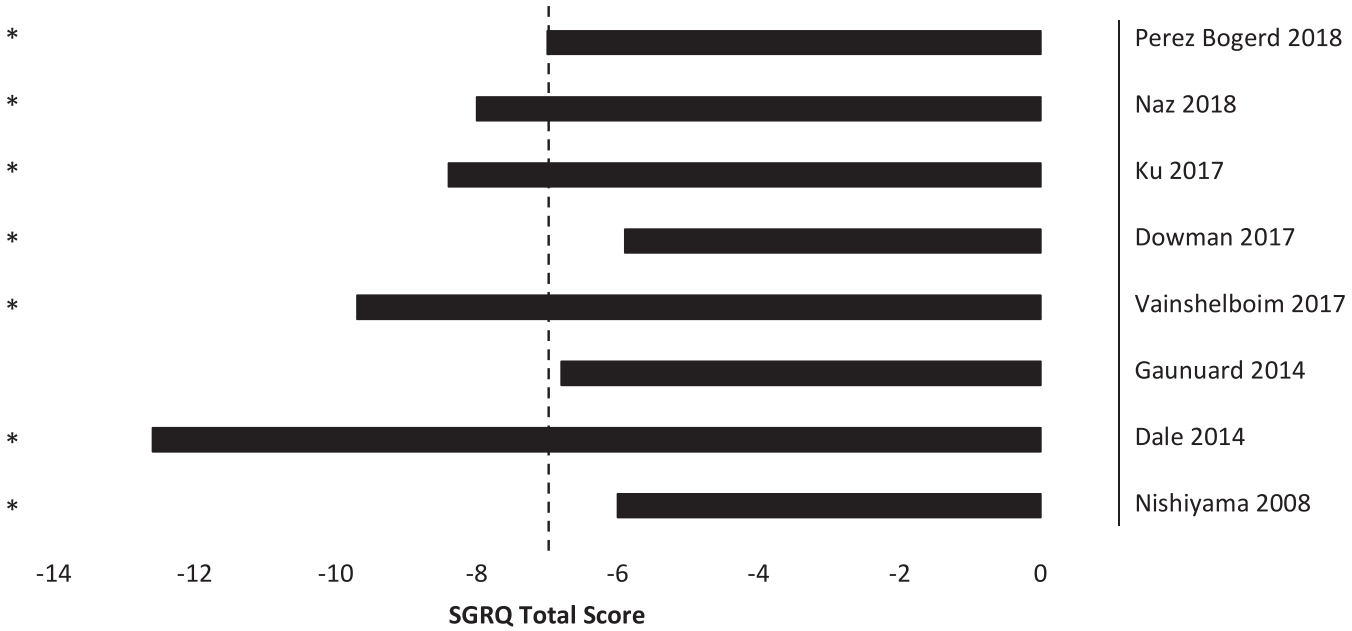

FIGURE 4. Changes in health-related quality of life in patients with interstitial lung disease (ILD) following pulmonary rehabilitation (PR). *$P < 0.05$, PR versus control group. The dashed line represents the minimal important difference of −7 in St. George's Respiratory Questionnaire (SGRQ) total score in patients with ILD (45).

further note, greater decline in lung function, although not a diagnosis of IPF, was a predictor of successful exercise progression during the PR program, which led to much greater change (49). Therefore, all patients with ILD should be provided the opportunity to undertake exercise training, although an early referral is recommended to promote longer lasting effects (38). This may be more relevant, however, in those with IPF and other fibrotic ILDs who tend to exhibit a more progressive disease course.

PROGRAM COMPONENTS

Outcome Assessment

The assessment of the patient and evaluation of outcomes are essential in order to establish the baseline function and health of the individual, guide exercise prescription, and to assess the extent of change following PR.

Exercise Capacity

The assessment of exercise capacity is a critical element of PR. It determines the level of functional impairment and exercise intolerance, identifies the presence of exertional desaturation, identifies the presence of comorbidities that may require modifications to the exercise program, provides information necessary for prescription of exercise intensity, and assesses the effectiveness of PR in improving exercise tolerance and exertional symptoms.

Laboratory/Cycle-Based Exercise Tests

The cardiopulmonary exercise test (CPET) is a progressive incremental exercise test to symptom-limited exhaustion with continuous breath-by-breath gas analysis and electrocardiogram rhythm monitoring. It is considered the "gold standard" measurement of exercise capacity, and exercise can be described as a direct percentage of measured peak exercise capacity. The CPET may be less sensitive in detecting exercise-induced desaturation (50). In addition, the CPET is a complex test requiring specialized equipment and staff; therefore, it may not be available in all settings. The cycle endurance test is another test that is emerging as an effective measure of exercise performance. This test involves the patient pedaling continuously at a constant work rate, at a percent of peak work rate from a CPET, until volitional or symptom-limited exhaustion. The cycle endurance test, when compared with the CPET, 6MWD, and incremental shuttle walk test (ISWT), was found to be the most responsive exercise measurement for evaluating improvement in exercise performance following PR (51). The limitation of the cycle endurance test is it requires a CPET to be completed first to set the percentage of achieved peak work rate, therefore limiting the accessibility in a lot of clinical settings.

Field Walking Tests

The 6-min walk test (6MWT) is a valid, reliable, reproducible, and responsive measure of exercise tolerance in ILD (52). The 6MWT is also sensitive for identifying exercise-induced desaturation (52). Despite its excellent reliability, there is strong evidence of a learning effect (52). Therefore, 2 tests are recommended, particularly when it is used to evaluate response to treatment or change over time (52). The 6MWT may be less sensitive, though, in detecting change in those with high baseline walk distances (38). The ISWT is emerging as a robust and useful test of functional exercise capacity. The ISWT requires the patient to progressively increase their walk speed along a 10-meter course until the patient is unable to maintain speed, provoking a similar physiological response to a CPET (52). The distance walked

during ISWT has been shown to strongly correlate with VO_{2peak} in IPF (53). It is also recommended that 2 ISWTs be performed (52). The ISWT could be a useful measure of peak exercise capacity, particularly in those with high functional capacity; however, it has not yet been widely used in ILD.

The 6MWD is affected by methodological factors such as the track length used, encouragement, supplemental oxygen, and walking aids (52). Supplemental oxygen also affects ISWT performance (52). Therefore, it is important these factors be kept constant with repeat assessments (52). Supplemental oxygen and wheeled walkers can be used during testing where indicated. Wheeled walkers should be used in patients who use walkers for day-to-day activities or if the perceived exercise training will involve the use of walker. Similarly, oxygen therapy is provided for those who use exertional or long-term oxygen therapy, or in cases where supplemental oxygen is clinically indicated during the assessment. It is worth noting that progression of disease over time may lead to changes in oxygen flow rate or the addition of a walking aid. Therefore, if follow-up tests are performed with a new walking aid or on a higher oxygen setting because of changes in oxygen prescription and/or disease deterioration, this change must be clearly indicated on the test report and considered in the test interpretation.

The execution of both the 6MWT and ISWT should follow the official European Respiratory Society/American Thoracic Society Technical Standard: field walking tests in chronic respiratory disease (52,54).

Functional Tests

The 6MWT and ISWT are considered surrogate measures of day-to-day physical functioning (55). In addition, the 6MWT is the most widely used outcome measure of functional capacity in PR programs (52,54). However, it may not be feasible to perform these tests in some clinical settings or in home-based PR. Simple functional tests such as step up, sit-to-stand (STS), gait speed, or timed up and go tests can provide valid, reliable, and easily administered assessments of physical function. They can also be used to provide additional complementary information to the 6MWD (56), or an indirect measure of lower limb strength and function.

The 3-min step test, which involves stepping for 3 min at a rate guided by an audio signal, has been shown to have excellent reproducibility in monitoring exertional dyspnea and estimating functional exercise capacity in people with COPD (57,58), although there are limited data in patients with ILD. The 6-min step test, which is modelled from the 6MWT and involves stepping as many times as possible on a 20-cm step, has been shown to be a reliable measure of functional capacity and exertional desaturation in ILD (59), and responsive to PR in people with COPD (59). The timed up and go test, the time taken to stand up from a chair, walk 3 meters, turn around, walk back to the chair, and sit down, is a reliable and simple test to assess balance and functional mobility. Its validity has not been assessed in ILD; however, it has been shown to be valid and responsive to PR in patients with COPD (56,58,60). The STS tests involve either the time taken to stand from a sitting position 5 times (5-repetition STS test), or the number of STS in a set time (typically 30 s to 3 min) (61). The STS test in 1 min and the 5-repetition STS have both been shown to be valid, reliable, correlate strongly with 6MWT or ISWT, responsive to PR, and have an established MID of 3 repetitions or 1.7 seconds, respectively (62,63). In addition, the 1-min STS was successful in detecting exercise-induced gas exchange impairment in ILD (64). STS tests of longer duration (e.g., 3 min) are less ideal as they may be less feasible in patients with severe ILD. Overall, the STS tests are limited in those who have difficultly standing unaided because of poor functional ability or lower limb impairment (61). The 4-meter gait speed test, the time taken to walk 4 meters at one's usual walking speed, is widely used in older adults as a measure of frailty and functional and lower limb performance (65). In IPF, it has been shown to be valid, reliable, responsive to PR, and strongly correlated with exercise performance, respiratory disability, and HRQoL (65). There is an associated ceiling effect; therefore, it may be more suited to those with more severe ILD or limited functional capacity (65).

Muscle Function

Skeletal muscle strength, although not the most sensitive measure, is an accessible and clinically applicable method to assess skeletal muscle function (66). Isokinetic dynamometry provides accurate assessments of dynamic and static strength through a range of movements and is the preferred option for the quantification of muscle strength in laboratory-based settings (67). This method has also successfully identified an increase in quadriceps force following PR (42,51), suggesting it may be responsive to therapy. Limitations of the isokinetic dynamometer are its large size, nonportability, and cost; therefore, it is impractical in most clinical settings. Another reliable assessment of strength and the "gold standard" for assessing muscle strength in nonlaboratory situations is the 1-repetition maximum (1RM) (68). The 1RM was shown to be well tolerated in patients undertaking PR, and it has been used successfully to evaluate muscle strength in patients with COPD (68); however, there is no clear evidence regarding its effectiveness in patients with ILD. The advantage of 1RM testing is resistance training exercise can be prescribed as a direct percentage of the 1RM. The limitations of 1RM testing are that it can be time consuming and it requires appropriately experienced personnel and suitable equipment with a sufficiently large range of resistance (68). The use of the 3RM, 5RM, or 10RM may be more feasible with regard to accessibility of equipment as well as being more suited to those with severe disease. The handheld dynamometer is a potential alternative for measuring skeletal muscle strength in ILD. The handheld dynamometer is placed into the palm of the hand, direct resistance is applied to movement of the extremity, and the force output of the muscle movement is measured. The handheld dynamometer is small, portable, inexpensive, and shown to have good reliability in people with ILD (69). Measurement of isometric quadriceps force using a fixed strain gauge is another viable strength

testing procedure (66,70). It has been shown to produce reliable results that are comparable to those from computerized isokinetic dynamometry in people with COPD (70), and it is a recommended technique in the American Thoracic Society/European Respiratory Society Statement update on Limb Muscle Dysfunction in COPD (66). Finally, the STS test may provide an indirect measure of muscle strength when there is limited access to the required testing equipment. Both the 30-second and 1-min STS tests have been shown to significantly correlate with 1RM in people with COPD. The STS test has been successfully used in the assessment of skeletal muscle dysfunction in advanced ILD (28) and to evaluate improvements in muscle strength following PR in patients with IPF (43), suggesting it may be responsive to therapy.

Symptom Evaluation

Dyspnea and fatigue are common symptoms in people with ILD, and the reduction of these symptoms is an important aim in PR. Dyspnea and fatigue are also frequently measured using questionnaires and scales. The Modified Medical Research Council Dyspnea Scale, which grades breathlessness from 0 to 4, where 0 indicates no restriction and 4 represents severe impairment to activities due to breathlessness, is commonly used to assess the perception of overall physical limitation due to breathlessness (71). Two more dyspnea-specific instruments include the Dyspnea-12 and the University of California, San Diego Shortness of Breath Questionnaire. Both questionnaires have been used to assess dyspnea in patients with ILD following PR (72,73). Fatigue assessment instruments include the Fatigue Severity Scale, which is valid, sensitive, and responsive to change following exercise training in ILD (74).

HRQoL and Mood

The chronic respiratory disease questionnaire and the SGRQ are the most widely used disease-specific HRQoL measures. The chronic respiratory disease questionnaire and the SGRQ are both sensitive to change and have defined MID thresholds (2,45,75). The SGRQ has a standard and IPF-specific version (SGRQ-I). The SGRQ-I IPF version has similar psychometric properties to the original SGRQ, but it has been designed to be more relevant for patients with IPF (76). Due to its more recent development, it has not been as widely used; however, it has successfully detected HRQoL improvements following exercise training in a recent RCT of PR in patients with ILD (38). Anxiety and depression are also prevalent in ILD. The Hospital Anxiety and Depression Scale, the Center for Epidemiologic Studies Depression Score, and the Geriatric Depression Scale are reliable measures of mood that have been used to evaluate effectiveness of PR (4). The Hospital Anxiety and Depression Scale is the most widely used tool (15,77), and a key benefit is it gives a measure of anxiety and depression as opposed to just depression.

Exercise Training

Currently, exercise training for people with ILD is prescribed according to the guidelines for exercise prescription in COPD, and the majority of RCTs of PR in ILD have used this approach. While this strategy may not provide the most optimal training stimulus, there is no evidence to suggest that the exercise prescription should vary from that provided to patients with COPD (32).

Settings

Pulmonary rehabilitation can occur in several settings. Outpatient PR, which typically involves hospital outpatient departments and community health centers, tends to be the most widely available setting and makes up the majority of studies evaluating the benefits of PR in COPD and ILD (5,37,78). Exercise training is conducted under the supervision of experienced health clinicians, such as physiotherapists, clinical exercise physiologists, and nurses. Inpatient PR programs provide supervised exercise training either as a special inpatient rehabilitation center to which a patient is directly admitted, or as part of standard inpatient care provided during an admission (78). Inpatient PR may prove useful in the recovery of an acute exacerbation and for those with severe function limitation, or those who require daily medical or nursing care (5,78). Accessibility to hospital or community-based PR, however, can be challenging, with travel as one of the main barriers (32,79). Home-based PR has been shown to produce short-term clinical outcomes that were equivalent to center-based PR in people with COPD (5,79). It is reasonable to suggest that similar outcomes could occur in ILD. However, it is recommended that the home-based PR includes regular contact by health personnel to facilitate exercise participation and progression (32,46). Telerehabilitation is emerging as a promising method of PR delivery with preliminary evidence in COPD suggesting it provides equivalent outcomes for exercise capacity and HRQoL (5,80). Further study is currently underway to compare the clinical outcomes of telerehabilitation and traditional center-based PR for people with COPD and ILD (anzctr.org.au identifier: ACTRN12616000360415).

Duration

A duration of 6 to 12 weeks (46) and a training frequency of at least 2 supervised sessions a week is recommended. A third session is advised, either supervised or formalized unsupervised, a prescribed exercise session to be performed at home (5,46). The majority of RCTs of PR in ILD have had program durations ranging from 5 to 12 weeks, with one lasting 6 months with 2 to 3 sessions per week (37,42). These trials were all associated with improvements in a range of outcomes, suggesting the standard 8-week PR program might be effective for participants with ILD. It is worth noting that a longer PR program may assist with the maintenance of benefits. Two recent RCTs of PR in ILD, both of which employed a longer PR duration, are the first to report long-term benefits of PR. Vainshelboim and colleagues (43) found sustained improvements in leg strength and HRQoL 11 months after a 12-week PR program. Perez and colleagues (42) found a 6-month PR program results in sustained improvements in exercise capacity and HRQoL at 1-year follow-up.

Endurance Training

Endurance exercise training is a core component of a PR program. Endurance training aims to increase aerobic exercise capacity and exercise endurance, leading to an increase in physical activity tolerance that is associated with a reduction in dyspnea and/or fatigue (5). Endurance training can be comprised of walking, either on the treadmill or along a corridor, and/or cycling. Both these modalities are ideal if tolerated. Walking is a functional exercise that can lead to improvement in walking capacity (5). Cycling results in less exertional desaturation yet places a greater training stimulus on quadriceps muscles than walking (5). The aim is to complete 30 min of endurance training per exercise session. This can be divided into smaller bouts (e.g., 10 to 15 min) if patients are unable to tolerate a single bout of 30 min (46). The initial exercise intensity corresponding to 60% peak work rate is considered the minimum required for physiological change, with a goal of progressively increasing the training intensity over the course of the program.

Initial walking training intensity is set at a speed that is 80% of the peak walking speed ($km \cdot h^{-1}$) achieved on the 6MWT. This approach has shown to achieve the recommended training intensity of 60% VO_2peak (81). Initial intensity for cycling is set at a workload equivalent to 60% peak work rate on CPET. Equations do exist that estimate peak work rate from 6MWD; however, caution should be applied when using these equations as they were subject to substantial variation across a range of works rates (82). In addition, they were developed for people with COPD and may be less accurate in those with ILD.

Regular progressions (e.g., increase in walking speed or cycle resistance) in the intensity of exercise should occur weekly if tolerated after 1 to 2 weeks. Participants should be encouraged to rate their dyspnea and fatigue (e.g., according the Borg scale) during endurance training, aiming for moderate levels (3-4 on 0-10 Borg score) of breathlessness throughout. Intermittent monitoring of oxyhemoglobin saturation and pulse rate via pulse oximetry is also recommended (4). Participants should be encouraged to exercise at home for an additional 1 to 3 sessions, aiming for an overall total of 3 to 5 sessions per week (46). Ideally, participants should aim to exercise at a similar intensity and duration as the PR program.

Although this approach for endurance training appears applicable, it may not provide optimal exercise stimuli for patients in ILD. There is currently no evidence in ILD comparing the efficacy of one form of exercise prescription type with another or investigating effectiveness of alternative endurance training strategies.

Alternative Endurance Training Strategies

Interval Training

Interval training could be a feasible and effective training alternative to the traditional form of exercise training in PR of moderate-intensity continuous training, particularly in those patients who have difficulty adhering to continuous training or the prescribed target exercise intensity or duration required to provide a physiological benefit. Interval training involves repeated intermittent bursts of relatively high-intensity exercise, interspersed by periods of rest or low-intensity exercise (83). The duration of the exercise bout and recovery can vary from a few seconds to up to several minutes, as can the number of intervals performed. In COPD, interval training has been shown to produce equivalent improvements in peak exercise capacity, 6MWD, quadriceps cross-sectional muscle size, fatiguability, and HRQoL compared with continuous training (84). In addition, 2 studies reported significantly reduced perceptions of dyspnea and leg discomfort during interval training and reported greater adherence to interval training protocol (84). In contrast, 2 studies reported no difference in symptoms between the 2 training modes. However, those studies associated with better adherence and less dyspnea and leg fatigue included shorter intervals with the interval durations ranging from 20 to 40 seconds. Therefore, it is possible that using intervals <1 min at 100% peak is better tolerated than continuous exercise (84). In ILD, high-intensity interval training has been shown to provide comparable benefits in both patients with ILD and COPD preparing for lung transplantation (85). A recent study comparing the effects of a single bout of continuous training with high-intensity interval training with a work-recovery ratio of 30 seconds:30 seconds and maximum intensity of 80% to 100% peak work found that interval exercise was the preferred exercise modality in 90% of participants and was associated with less dyspnea, leg fatigue, and effort in individuals with advanced ILD (86). This preliminary evidence suggests interval training could be a feasible and effective training strategy. Whether interval training produces equivalent or superior physiological improvements following a PR program remains unknown, although 1 RCT is currently underway which may provide insight in this area (Clinicaltrials.gov identifier: NCT03800914).

Downhill Training

Downhill walking may also be an attractive and feasible alternative to traditional endurance training. Downhill walking involves the repeated eccentric contraction, and elongation of the muscle during contraction (87), of the quadriceps. The alluring characteristic of this eccentric training is the lower metabolic cost coupled with a high force production (87). Therefore, ILD patients who have difficulty sustaining continuous training or interval protocols with standard walking due to excessive dyspnea or exercise desaturation may be able to tolerate an exercise regime of downhill walking. However, the efficacy of downhill walking in ILD has not been investigated. The evidence in COPD is also small, although promising. Downhill walking produced greater improvements in 6MWD and HRQoL compared with level walking in 45 patients with COPD. The results of this study are likely overestimated since the downhill walking training was supervised with planned clinician-led progressions whereas the standard level walking training was a self-progressed and unsupervised home routine (88). Another study found equivalent

improvements in 6MWD and HRQoL following a 12-week PR program comparing level walking and downhill walking in 34 patients with COPD (89). Downhill walking, however, had a significantly greater proportion of patients that exceeded the MID for 6MWT (89). Downhill walking may be an appropriate training strategy for ILD patients whose exercise tolerance is severely reduced. Further research studies are warranted to evaluate the effectiveness of downhill walking in ILD. However, current exercise training approaches could include adding a decline of 5% to the initial walking intensity. Progressions could involve gradual increases in speed until the peak walk speed of the 6MWT is reached followed by gradual reductions in the decline towards 0%.

Water-Based Training

Water-based training may provide a viable alternative in ILD patients with significant physical limitations, particularly in those with CTD-ILD who are commonly affected with joint pain, joint swelling, and limited range of motion. Water-based exercise uses warm water to relieve pain and induce muscle relaxation, and buoyancy to reduce the mechanical impact on the body (90). Water-based training is an effective alternative to land-based training in patients with COPD with physical comorbidities (91). The effectiveness of water-based exercise training has not been tested in ILD; therefore, it is an important target of future research, especially for those with CTD-ILD who commonly experience systemic manifestations of arthropathy, myopathy, and vasculopathy. A small feasibility study of water-based exercise training in ILD is currently underway which may provide insight in this area (anzctr.org.au identifier: ACTRN12619000308190).

Partitioned Exercise Training

Another alternative training strategy that may allow ILD patients to adhere to continuous exercise or adhere to the recommended higher intensity is partitioned exercise training. Partitioned exercise involves exercising a single limb at a time, for example cycling with a single leg, then the contralateral leg (92) for 15 min each, as opposed to cycling for 30 min with both legs (93,94). Partitioned exercise places the same metabolic and functional demands on the targeted muscle but reduces the overall ventilatory requirement (95). In COPD, single-legged cycling has produced greater improvement in VO_2peak and peak work rate (94) with lower minute ventilation and dyspnea compared with 2-legged cycling (93,94). It was successfully implemented into a PR program as the principal aerobic activity with significant improvements in VO_2peak, 6MWD, and HRQoL with no significant barriers, safety issues, or noncompliance (92). While partitioned exercise training could be a reasonable option for ILD, there is no research into the benefits for ILD, although 1 RCT is currently underway (ClinicalTrials.gov Identifier: NCT03752892).

Strength Training

Skeletal muscle dysfunction is a common maladaptation in ILD. In addition, reductions in muscle force correlate with the level of lung impairment and reduced peak exercise capacity (26,96). Therefore, improving muscle strength and function is an important goal of PR. However, the specific benefit of resistance training alone in people with ILDs is unclear as no study has evaluated resistance training as a standalone element.

A small number of RCTs of PR in ILD have incorporated resistance training, with the majority resulting in improvements in exercise tolerance and HRQoL (35,36,38,41–43). The American Thoracic Society/European Respiratory Society and British Thoracic Society PR guidelines recommend the inclusion of resistance training in PR to ensure strength and endurance benefits (5,46), and resistance training is often incorporated in clinical PR programs. There are no specific guidelines for the prescription of resistance training for people with ILD or for PR in general. Instead, recommendations (5) follow the American College of Sports Medicine principles for healthy adults or older adults (97). Single-joint and multiple-joint exercises may be performed at a slow-to-moderate velocity, 1 to 3 sets (8 to 12 repetitions per set), 60% to 70% 1RM, 1 to 3 min rest, for 2 to 3 $d \cdot wk^{-1}$ (97). A load that evokes fatigue after 8 to 12 repetitions or a rating of perceived exertion score of 12 to 14 (Borg 6-20 scale) or 4 to 6 (Borg category ratio CR-10 scale) can also be used to determine resistance training intensity (43,98). For those who are very deconditioned or frail, less physically demanding initial workloads are recommended: a lower intensity (40% to 50% 1RM or a rating of perceived exertion score of 11 to 12 (6-20 scale) or 3 to 4 (CR-10 scale)) and volume (1 set of 10 to 20 reps) (97). A longer rest period may also be required. Resistance training with lower loads may also reduce the likelihood of patients performing the Valsalva maneuver during efforts. Functional movements that use large muscle groups that are active during everyday activities, such as chair squats or step-ups, are recommended. However, an individualized approach, guided by the participant's capability, should be adopted when selecting resistance training exercises and the initial load. Modifications should also be made where appropriate to manage and improve musculoskeletal comorbidities and limitations. For continuing adaptations to muscle strength and endurance, regular individualized progressions are required. This overload can be achieved by increasing the weight, number of repetitions per set, number of sets of each exercise, or decreasing the rest (5). A recommended approach includes focusing on the patient achieving 2 to 3 sets of each exercise, at which point the number of repetitions per set can be increased. Once the patient achieves the desired maximum number of repetitions per set, the weight can be increased (46,99).

Role of Oxygen Therapy

Exertional desaturation is common in people with ILD, with approximately 54% demonstrating a decrease in oxygen saturation of $SpO_2 < 88\%$ during the 6MWT with the prevalence increasing to 86% to 93% with severe impairment (FVC < 50% predicted or TLCO < 35% predicted) (100).

While the exact benefit of oxygen during exercise is unclear, the American Thoracic Society/European Respiratory Society PR guidelines recommend the use of oxygen during exercise training in those who fulfil the assessment criteria for ambulatory oxygen (46), and supplemental oxygen is commonly used following these criterion in clinical practice (34,46) to ensure safety, to provide relief in the presence of profound desaturation, and to improve exercise tolerance.

There is emerging evidence to suggest supplemental oxygen may be a beneficial adjunct to exercise training by optimizing physiological improvements through increased endurance training time. Two small studies in IPF evaluating the provision of oxygen during constant load cycling found that oxygen significantly increased endurance time and reduced exertional dyspnea (101,102). In addition, 1 study found that oxygen was associated with a reduction in xanthine levels, an indirect marker of ATP deletion and impaired muscle metabolism (101), suggesting oxygen therapy may improve muscle metabolism through increased oxygen delivery to skeletal muscle. Further research is required to determine whether the provision of supplemental oxygen during exercise training consistently enables patients with ILD, limited by exertional desaturation, to achieve the recommended training intensity and the desired progression of exercise intensity. Importantly, further studies would need to establish whether this would lead to enhanced cardiovascular and muscular adaptations and whether such adaptations would successfully result in improved exercise capacity, physical activity in daily life, and HRQoL upon completion of a PR program. A 2-arm double-blind randomized placebo-controlled trial of supplemental oxygen during 8 weeks of thrice-weekly aerobic exercise training in 88 IPF patients is currently underway (103) and may shed some light on these important questions (ClinicalTrials.gov identifier: NCT02551068). Given the high prevalence of profound exercise-induced desaturation that patients with ILD experience, it is currently recommended that supplemental oxygen should be available at all centers providing exercise training for people with ILD (32). The usual practice would be to deliver oxygen therapy for any patient who desaturates to $SpO_2 < 85\%$ during training, with the aim of maintaining SpO_2 at greater than 88% (4). If the patient is asymptomatic, able to safely tolerate training load, and prefers to exercise without the use of oxygen, it would be appropriate to reduce this SpO_2 threshold by 2% to 3%. In addition, in patients who prefer not to use supplemental oxygen, alternate training strategies such as interval training or downhill walking can be employed to manage desaturation.

Role of PR After Exacerbation of IPF

Acute exacerbation (AE) of ILD is defined as a "clinically significant respiratory deterioration developing within typically less than 1 month, accompanied by new radiologic abnormalities on HRCT, and the absence of other obvious clinical causes like fluid overload, left heart failure, or pulmonary embolism" (104). The clinical presentation of AE-ILD is similar in non-IPF ILD and IPF, but AE-ILD in non-IPF ILD is less common and the clinical course is less fatal compared with IPF (104). There is little evidence for treatment of AE in ILD and optimal approach is not known (11,105). In contrast, acute exacerbations in COPD have been long identified, with greater knowledge and evidence regarding treatment (105). PR is recommended following an acute exacerbation in COPD, with commencement advised 1 month after discharge (46), due to evidence that it reduces the risk of future hospital admission and improves HRQoL and exercise capacity (46). There is no recommendation provided for ILD (46). The role of PR may involve restoring function and reducing symptoms, leading to greater day-to-day functioning and allowing for improved HRQoL. A cautious approach, with confirmation that clinical stability of disease has occurred, might be required for commencement of PR following an exacerbation for IPF since risks could be higher in this subgroup because of greater desaturation on exercise, greater hypoxemia at rest, and associated comorbidities (4).

Nonexercise Components of PR

Many PR programs often incorporate education, nutrition counselling, and psychological support, which may help to improve emotional and physical wellbeing in this population (4,5). The education component of PR has been geared primarily toward patients with COPD. While people with ILD are willing and value the opportunity to attend standard PR education sessions (106,107), they expressed a desire for inclusion of ILD-specific content. Key topics included disease behavior and prognosis, managing cough, how to manage medications and their side effects, clinical tests, autonomy, and end of life counseling (106,107). While the existing education curriculum may provide relevant information, this highlights the need for PR to incorporate an ILD-specific curriculum.

There are no specific recommendations regarding nutritional depletion or nutritional support for people with ILD. However, a higher body mass index is associated with better survival in IPF, and low baseline body mass index is associated with poor prognosis and increased disease severity in IPF and other fibrotic ILDs (108). In addition, a healthy body weight is often a consideration for transplant eligibility (109). Therefore, adequate nutritional intake is important in maintaining health status and HRQoL in patients with ILD (110). It seems reasonable to provide general advice on maintaining a healthy and well-balanced diet, and in addition to incorporate general dietary screening within the PR program and provide dietary counseling and nutritional intervention (e.g., supplementation when malnutrition is identified).

People with ILD suffer a high symptom burden including dyspnea, fatigue, and cough. Anxiety and depression are also prevalent symptoms, particularly in those with more pronounced dyspnea and comorbidities, leading to an overall increase in disease burden (15). PR plays an important role in symptom control. It has been shown to significantly reduce dyspnea in patients with ILD (37) and is strongly recommended in British Thoracic Society PR guidelines for

all patients functionally limited by dyspnea (46). PR proved beneficial in alleviating fatigue in people with IPF (74) and sarcoidosis (41). Anxiety and depression may also improve following PR. Exercise training improved anxiety in people with sarcoidosis (41) and trended towards a reduction in anxiety in people with IPF and ILD of varying etiology (38). PR improved depression in 52% of participants and this benefit was sustained for 6 months in a nonrandomized study of PR (111). Considering the prevalence of anxiety and depression in ILD, providing advice on effective strategies to manage mood may also be appropriate and the contribution of a psychologist is desirable (16).

POSSIBLE FUTURE DIRECTIONS

Despite this growing evidence for the benefit of PR in ILD, there are a number of important challenges that lie ahead. Two key challenges include: (a) *defining the optimal exercise training strategy that results in maximal physiological benefit*s. The majority of the evidence into the benefit of PR in ILD has used the standard exercise prescription principles of exercise training for COPD. Although this approach appears applicable, it may not provide optimal exercise stimuli for patients with ILD and investigation into alternative exercise strategies is required; and (b) *investigating ways to promote longer lasting improvements in outcomes following exercise training*. There is little evidence to suggest benefits of exercise training extend beyond or reach 6 months. Only 2 RCTs have reported sustained benefits in the longer term (42,43). Strategies such as a longer PR program, or a maintenance exercise training program, or repeating PR at regular intervals may prove useful in ILD, but further research is needed in this area.

CLINICAL IMPLICATIONS

PR is an effective and key intervention in people with ILD. There is increasing evidence to suggest it should be a crucial element in the clinical management of all people with ILD, with all patients regardless of etiology or severity afforded the opportunity to undertake exercise training. An early referral, however, may assist in sustaining the benefits in the longer term. An initial and follow-up assessment should be performed to assess the effectiveness of PR and to guide prescription of exercise intensity. Exercise prescription can follow the standard exercise training guidelines for PR. This approach may not provide optimal exercise stimuli for all people with ILD; therefore, alternative training strategies such as high-intensity interval training, water-based exercise training, downhill walking, or partitioned exercise can be used. However, the clinician should be aware that while these methods can be useful, there is limited evidence for the benefit of these strategies in people with ILD. Supplemental oxygen may be required to manage the effects of exercise-induced desaturation. There are a number of nonexercise components to PR that can assist with improving the wellbeing of the patient.

REFERENCES

1. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev. 2019;28(151):180100.
2. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. Chest. 1999;116(5):1175–82.
3. Holland AE. Exercise limitation in interstitial lung disease—mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101–11.
4. Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. Ther Adv Respir Dis. 2017;11(2):115–28.
5. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Mölken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13–64.
6. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
7. Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. Open Respir Med J. 2012;6:63–74.
8. Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. Am J Respir Crit Care Med. 2012;186(4):314–24.
9. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, Skowasch D, Park JS, Poonyagariyagorn HK, Wuyts W, Wells AU. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150):180076.
10. King TE, du Bois RM. Elucidating the causes and examining the latest clinical findings in pulmonary fibrosis. Eur Respir Rev. 2008;17(109):105–7.
11. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20(1):57.
12. Margaritopoulos GA, Kokosi MA, Wells AU. Diagnosing complications and co-morbidities of fibrotic interstitial lung disease. Expert Rev Respir Med. 2019;13(7):645–58.

13. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J. 2008;31(6):1357–67.
14. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. Curr Opin Pulm Med. 2013;19(5): 466–73.
15. Holland AE, Fiore JF, Bell EC, Goh N, Westall G, Symons K, Dowman L, Glaspole I. Dyspnea and comorbidity contribute to anxiety and depression in interstitial lung disease. Respirology. 2014;19(8):1215–21.
16. Holland AE, Dowman LM, Hill CJ. Principles of rehabilitation and reactivation: interstitial lung disease, sarcoidosis and rheumatoid disease with respiratory involvement. Respiration. 2015;89(2):89–99.
17. De Vries J, Drent M. Quality of life and health status in interstitial lung diseases. Curr Opin Pulm Med. 2006;12(5): 354–8.
18. Alalawi R, Whelan T, Bajwa RS, Hodges TN. Lung transplantation and interstitial lung disease. Curr Opin Pulm Med. 2005;11(5):461–6.
19. Richeldi L, Varone F, Bergna M, de Andrade J, Falk J, Hallowell R, Joutnea S, Kondoh Y, Morrow L, Randerath W, Strek M, Tabaj G. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev. 2018;27(150):180074.
20. Bonini M, Fiorenzano G. Exertional dyspnea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. Eur Respir Rev. 2017;26(143):160099.
21. Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. Chest. 1996;109(6):1566–76.
22. Markovitz GH, Cooper CB. Exercise and interstitial lung disease. Curr Opin Pulm Med. 1998;4(5):272–80.
23. Ryu JH, Krowka MJ, Swanson KL, Pellikka PA, McGoon MD. Pulmonary hypertension in patients with interstitial lung diseases. Mayo Clin Proc. 2007;82(3):342–50.
24. Agusti AG, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1991; 143(2):219–25.
25. Vogiatzis I, Zakynthinos G, Andrianopoulos V. Mechanisms of physical activity limitation in chronic lung diseases. Pulm Med. 2012;2012:634761.
26. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, Arizono S. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. Chest. 2005;127(6):2028–33.
27. Panagiotou M, Polychronopoulos V, Strange C. Respiratory and lower limb muscle function in interstitial lung disease. Chron Respir Dis. 2016;13(2):162–72.
28. Mendes P, Wickerson L, Helm D, Janaudis-Ferreira T, Brooks D, Singer LG, Mathur S. Skeletal muscle atrophy in advanced interstitial lung disease. Respirology. 2015;20(6):953–9.
29. Mitsui T, Azuma H, Nagasawa M, Iuchi T, Akaike M, Odomi M, Matsumoto T. Chronic corticosteroid administration causes mitochondrial dysfunction in skeletal muscle. J Neurol. 2002;249(8):1004–9.
30. Koechlin C, Maltais F, Saey D, Michaud A, LeBlanc P, Hayot M, Préfaut C. Hypoxemia enhances peripheral muscle oxidative stress in chronic obstructive pulmonary disease. Thorax. 2005;60(10):834–41.
31. Kim HC, Mofarrahi M, Hussain SN. Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008;3(4):637–58.
32. Alison JA, McKeough ZJ, Johnston K, McNamara RJ, Spencer LM, Jenkins SC, Hill CJ, McDonald VM, Frith P, Cafarella P, Brooke M, Cameron-Tucker HL, Candy S, Cecins N, Chan AS, Dale MT, Dowman L, Granger C, Halloran S, Jung P, Lee AL, Leung R, Matulick T, Osadnik C, Roberts M, Walsh J, Wootton S, Holland AE. Australian and New Zealand pulmonary rehabilitation guidelines. Respirology. 2017;22(4): 800–19.
33. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015(2): Cd003793.
34. Holland AE, Wadell K, Spruit MA. How to adapt the pulmonary rehabilitation programme to patients with chronic respiratory disease other than COPD. Eur Resp Rev. 2013; 22(130):577–86.
35. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax. 2008;63(6):549–54.
36. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, Watanabe F, Arizono S, Nishimura K, Taniguchi H. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13(3):394–9.
37. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014(10):Cd006322.
38. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, Glaspole I, Goh NSL, Southcott AM, Burge AT, Gillies R, Martin A, Holland AE. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax. 2017;72(7):610–9.
39. Dale MT, McKeough ZJ, Munoz PA, Corte P, Bye PTP, Alison JA. Exercise training for asbestos-related and other dust-related respiratory diseases: a randomised controlled trial. BMC Pulm Med. 2014;14:180.
40. Ku V, Janmej AK, Aggarwal D, Sood P. Pulmonary rehabilitation in patients with interstitial lung diseases in an outpatient setting: a randomised controlled trial. Indian J Chest Dis Allied Sci. 2016;59:75–80.
41. Naz I, Ozalevli S, Ozkan S, Sahin H. Efficacy of a structured exercise program for improving functional capacity and quality of life in patients with stage 3 and 4 sarcoidosis: a randomized controlled trial. J Cardiopulm Rehabil Prev. 2018;38(2):124–30.
42. Perez-Bogerd S, Wuyts W, Barbier V, Demeyer H, Van Muylem A, Janssens W, Troosters T. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. Respir Res. 2018;19(1):182.
43. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, Kramer MR. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. Respiration. 2014;88(5):378–88.
44. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Small changes in six-minute walk distance are important in diffuse parenchymal lung disease. Respir Med. 2009; 103(10):1430–5.
45. Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, Wamboldt FS. The SF-36 and SGRQ: validity and first

look at minimum important differences in IPF. Respir Med. 2010;104(2):296–304.
46. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, Greening NJ, Heslop K, Hull JH, Man WD, Morgan MD, Proud D, Roberts CM, Sewell L, Singh SJ, Walker PP, Walmsley S. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;68 Suppl 2:ii1–30.
47. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6): 788–824.
48. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. Respir Med. 2012;106(3):429–35.
49. Nakazawa A, Dowman LM, Cox NS, McDonald CF, Hill CJ, Lee AL, Holland AE. Factors predicting progression of exercise training loads in people with interstitial lung disease. ERJ Open Res. 2019;5(4):00245–2018.
50. Holland AE, Dowman L, Fiore J, Brazzale D, Hill CJ, McDonald CF. Cardiorespiratory responses to 6-minute walk test in interstitial lung disease: not always a submaximal test. BMC Pulm Med. 2014;14(1):136.
51. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Watanabe F, Nishiyama O, Nishimura K, Kozu R, Tabira K. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. Respir Care. 2014;59(7):1108–15.
52. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, Wanger J, MacIntyre N, Kaminsky DA, Culver BH, Revill SM, Hernandes NA, Andrianopoulos V, Camillo CA, Mitchell KE, Lee AL, Hill CJ, Singh SJ. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428–46.
53. Moloney ED, Clayton N, Mukherjee DK, Gallagher CG, Egan JJ. The shuttle walk exercise test in idiopathic pulmonary fibrosis. Respir Med. 2003;97(6):682–7.
54. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, Lee AE, Camillo CA, Troosters T, Spruit MA, Carlin BW, Wanger J, Pepin V, Saey D, Pitta F, Kaminsky DA, McCormack MC, MacIntyre N, Culver BH, Sciurba FC, Revill SM, Delafosse V, Holland AE. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6): 1447–78.
55. Bui KL, Nyberg A, Maltais F, Saey D. Functional tests in chronic obstructive pulmonary disease, part 1: clinical relevance and links to the international classification of functioning, disability, and health. Ann Am Thorac Soc. 2017;14(5):778–84.
56. Johnston KN, Potter AJ, Phillips A. Measurement properties of short lower extremity functional exercise tests in people with chronic obstructive pulmonary disease: systematic review. Phys Ther. 2017;97(9):926–43.
57. Beaumont M, Losq A, Péran L, Berriet A-C, Couturaud F, Le Ber C, Reycler G. Comparison of 3-minute step test (3MStepT) and 6-minute walk test (6MWT) in patients with COPD. COPD. 2019;16(3-4):266–71.
58. Bui KL, Nyberg A, Maltais F, Saey D. Functional tests in chronic obstructive pulmonary disease, part 2: measurement properties. Ann Am Thorac Soc. 2017;14(5):785–94.
59. Dal Corso S, Duarte SR, Neder JA, Malaguti C, de Fuccio MB, de Castro Pereira CA, Nery LE. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29(2):330–6.
60. Mesquita R, Wilke S, Smid DE, Janssen DJ, Franssen FM, Probst VS, Wouters EF, Muris JW, Pitta F, Spruit MA. Measurement properties of the Timed Up & Go test in patients with COPD. Chron Respir Dis. 2016;13(4):344–52.
61. Maddocks M, Nolan CM, Man WD-C. Simple functional tests in COPD: stand up and be counted! Eur Respir J. 2017;49(3): 1700104.
62. Crook S, Büsching G, Schultz K, Lehbert N, Jelusic D, Keusch S, Wittmann M, Schuler M, Radtke T, Frey M, Turk A, Puhan MA, Frei A. A multicentre validation of the 1-min sit-to-stand test in patients with COPD. Eur Respir J. 2017;49(3):1601871.
63. Jones SE, Kon SSC, Canavan JL, Patel MS, Clark AL, Nolan CM, Polkey MI, Man WD. The five-repetition sit-to-stand test as a functional outcome measure in COPD. Thorax. 2013; 68(11):1015–20.
64. Briand J, Behal H, Chenivesse C, Wémeau-Stervinou L, Wallaert B. The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. Ther Adv Respir Dis. 2018;12:1753466618793028.
65. Nolan CM, Maddocks M, Maher TM, Canavan JL, Jones SE, Barker RE, Patel S, Jacob J, Cullinan P, Man WD. Phenotypic characteristics associated with slow gait speed in idiopathic pulmonary fibrosis. Respirology. 2018;23(5):498-506.
66. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, Dekhuijzen PN, Franssen F, Gayan-Ramirez G, Gea J, Gosker HR, Gosselink R, Hayot M, Hussain SN, Jannssens W, Polkey MI, Roca J, Saey D, SChols AM, Spruit MA, Steiner M, Taivassalo, Troosters T, Vogiatzis, Wagner PD. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 2014;189(9):e15–62.
67. Baltzopoulos V, Brodie DA. Isokinetic dynamometry. Applications and limitations. Sports Med. 1989;8(2):101–16.
68. Zanini A, Aiello M, Cherubino F, Zampogna E, Azzola A, Chetta A, Spanevello A. The one repetition maximum test and the sit-to-stand test in the assessment of a specific pulmonary rehabilitation program on peripheral muscle strength in COPD patients. Int J Chron Obstruct Pulmon Dis. 2015;10:2423–30.
69. Dowman L, McDonald C, Hill C, Lee A, Barker K, Boote C, Glaspole I, Goh N, Southcott A, Burge A, Ndongo R, Martin A, Holland AE. Reliability of the hand held dynamometer in measuring muscular strength in people with interstitial lung disease. Physiotherapy. 2016;102(3):249–55.
70. Machado Rodrigues F, Demeyer H, Hornikx M, Camillo CA, Calik-Kutukcu E, Burtin C, Janssens W, Troosters T, Osadnik C. Validity and reliability of strain gauge measurement of volitional quadriceps force in patients with COPD. Chron Respir Dis. 2017;14(3):289–97.

71. Rajala K, Lehto JT, Sutinen E, Kautiainen H, Myllärniemi M, Saarto T. mMRC dyspnea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. ERJ Open Res. 2017;3(4).
72. Collard HR, Pantilat SZ. Dyspnea in interstitial lung disease. Curr Opin Support Palliat Care. 2008;2(2):100–4.
73. Swigris JJ, Yorke J, Sprunger DB, Swearingen C, Pincus T, du Bois RM, Brown KK, Fischer A. Assessing dyspnea and its impact on patients with connective tissue disease-related interstitial lung disease. Respir Med. 2010;104(9):1350–5.
74. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56(6): 783–9.
75. Redelmeier DA, Guyatt GH, Goldstein RS. Assessing the minimal important difference in symptoms: a comparison of two techniques. J Clin Epidemiol. 1996;49(11):1215–9.
76. Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. Thorax. 2010;65(10):921–6.
77. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69–77.
78. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltias F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T. American Thoracic Society/ European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006;173(12): 1390–413.
79. Holland AE, Mahal A, Hill CJ, Lee AL, Burge AT, Cox NS, Moore R, Nicolson C, O'Halloran P, Lahham A, Gillies R, McDonald CF. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. Thorax. 2017;72(1):57–65.
80. Tsai LL, McNamara RJ, Moddel C, Alison JA, McKenzie DK, McKeough ZJ. Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD: the randomized controlled TeleR Study. Respirology. 2017;22(4):699–707.
81. Zainuldin R, Mackey MG, Alison JA. Prescription of walking exercise intensity from the 6-minute walk test in people with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev. 2015;35(1):65–9.
82. Holland AE, Hill K, Alison JA, Luxton N, Mackey MG, Hill CJ, Jenkins SC. Estimating peak work rate during incremental cycle ergometry from the 6-minute walk distance: differences between reference equations. Respiration. 2011;81(2):124–8.
83. Gibala MJ, Little JP, Macdonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol. 2012;590(5):1077–84.
84. Beauchamp MK, Nonoyama M, Goldstein RS, Hill K, Dolmage TE, Mathur S, Brooks D. Interval versus continuous training in individuals with chronic obstructive pulmonary disease—a systematic review. Thorax. 2010;65(2):157–64.
85. Gloeckl R, Halle M, Kenn K. Differences in feasibility of interval training between patients with end stage COPD and interstitial lung disease before transplantation. A pilot study. Am J Respir Crit Care Med. 2012;185:A2390.
86. Wickerson L, Brooks D, Granton J, Reid WD, Rozenberg D, Singer LG, Mathur S. Interval aerobic exercise in individuals with advanced interstitial lung disease: a feasibility study. Physiother Theory Pract. 2019:1–9.
87. Roig M, Shadgan B, Reid WD. Eccentric exercise in patients with chronic health conditions: a systematic review. Physiother Can. 2008;60(2):146–60.
88. Moezy A, Erfani A, Mazaherinezhad A, Mousavi SAJ. Downhill walking influence on physical condition and quality of life in patients with COPD: a randomized controlled trial. Med J Islam Repub Iran. 2018;32:49.
89. Camillo CA, Osadnik C, Loeckx M, Rodrigues FMM, Hornikx M, Demeyer H, Everaerts S, Maes K, Burtin C, Janssens W, Troosters T. Effects of a training program including downhill walking in COPD: a randomized controlled trial. Eur Respir J. 2016;48(suppl 60):OA1517.
90. McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Water-based exercise training for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013(12): Cd008290.
91. McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Water-based exercise in COPD with physical comorbidities: a randomised controlled trial. Eur Respir J. 2013;41(6): 1284–91.
92. Evans RA, Dolmage TE, Mangovski-Alzamora S, Romano J, O'Brien L, Brooks D, Goldstein RS. One-legged cycle training for chronic obstructive pulmonary disease. A pragmatic study of implementation to pulmonary rehabilitation. Ann Am Thorac Soc. 2015;12(10):1490–7.
93. Dolmage TE, Goldstein RS. Response to one-legged cycling in patients with COPD. Chest. 2006;129(2):325–32.
94. Dolmage TE, Goldstein RS. Effects of one-legged exercise training of patients with COPD. Chest. 2008;133(2):370–6.
95. Vaes AW. Partitioning strength exercises as an alternative training modality for patients with COPD. Respirology. 2017;22(7):1243–4.
96. Watanabe F, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, Ogawa T, Arizono S, Nishiyama O, Hasegawa Y. Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia. Respir Med. 2013;107(4): 622–8.
97. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Ex. 2011;43(7):1334–59.
98. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Ex. 2009;41(7):1510–30.
99. Australian Lung Foundation and Australian Physiotherapy Association. Pulmonary rehabilitation toolkit. http://www.pulmonaryrehab.com.au. Accessed November 4, 2019.
100. Khor YH, Goh NS, Glaspole I, Holland AE, McDonald CF. Exertional desaturation and prescription of ambulatory oxygen therapy in interstitial lung disease. Respir Care. 2019;64(3):299–306.
101. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, Hill CJ, Goh NSL, Holland AE. Greater endurance capacity and improved dyspnea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxemia. Respirology. 2017;22(5):957–64.

102. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG, Guenette, JA. Effects of hyperoxia on dyspnea and exercise endurance in fibrotic interstitial lung disease. Eur Respir J. 2017;49(5):1602494.
103. Ryerson CJ, Camp PG, Eves ND, Schaeffer M, Syed N, Dhillon S, Jensen D, Maltais F, O'Donnell DE, Raghavan N, Roman M, Stickland MK, Assayag D, Bourbeau J, Dion G, Fell CD, Hambly N, Johannson KA, Kalluri M, Khalil N, Kolb M, Manganas H, Moran-Mendoza O, Provencher S, Ramesh W, Rolf JD, Wilcox PG, Guenette JA. High oxygen delivery to preserve exercise capacity in patients with idiopathic pulmonary fibrosis treated with nintedanib. Methodology of the HOPE-IPF Study. Ann A. Thorac Soc. 2016;13(9):1640–7.
104. Leuschner G, Behr J. Acute exacerbation in interstitial lung disease. Front Med. 2017;4:176.
105. Kreuter M, Cottin V. The threat in chronic lung diseases: acute exacerbations. Eur Respir Rev. 2017;26(145):170075.
106. Holland AE, Fiore JF Jr, Goh N, Symons K, Dowman L, Westall G, Hazard A, Glaspole I. Be honest and help me prepare for the future: what people with interstitial lung disease want from education in pulmonary rehabilitation. Chron Respir Dis. 2015;12(2):93–101.
107. Morisset J, Dube BP, Garvey C, Bourbeau J, Collard HR, Swigris JJ, Lee JS. The unmet educational needs of patients with interstitial lung disease. Setting the stage for tailored pulmonary rehabilitation. Ann Am Thorac Soc. 2016;13(7): 1026–33.
108. Alakhras M, Decker PA, Nadrous HF, Collazo-Clavell M, Ryu JH. Body mass index and mortality in patients with idiopathic pulmonary fibrosis. Chest. 2007;131(5):1448–53.
109. Jo HE, Troy LK, Keir G, Chambers DC, Holland A, Goh N, Wilsher M, de Boer S, Moodley Y, Grainge C, Whitford H, Chapman S, Reynolds PN, Glaspole I, Beatson D, Jones L, Hopkins P, Corte TJ. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia. Respirology. 2017;22(7): 1436–58.
110. Spagnolo P, Tzouvelekis A, Bonella F. The management of patients with idiopathic pulmonary fibrosis. Front Med. 2018;5:148.
111. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med. 2014;108(1):203–10.