Exercise in Interstitial Lung Diseases

7

Baruch Vainshelboim

Abstract

Interstitial lung diseases (ILDs) represent a group of diverse chronic lung conditions characterized by scaring, inflammation, and restrictive pathophysiology. Idiopathic pulmonary fibrosis (IPF) is the most common form of ILDs and is associated with severe signs and symptoms, exercise intolerance, impaired quality of life, and poor prognosis. Exercise training has been shown to be a safe and effective treatment in a variety of ILDs including IPF. Exercise training improves exercise tolerance, functional capacity, dyspnea, and quality of life both in patients with ILDs and IPF. Higher exercise capacity and physical activity levels have been demonstrated to be associated with better survival and enhanced quality of life. The optimal training modalities and the underlining mechanisms with respect to outcome improvements are yet to be well characterized and require further investigation. The existing evidence supports the clinical benefits of exercise in patients with ILDs and thus provides good justification to recommend exercise training as part of standard care for ILDs.

7.1 Introduction

Interstitial lung diseases (ILDs), also known as diffuse parenchymal lung diseases, encompass a wide and diverse group of more than 200 disorders affecting not only the interstitium but also peripheral airways, alveoli, and small blood

B. Vainshelboim (✉)
Master of Cancer Care Program, School of Health Sciences, Saint Francis University, Loretto, PA, USA

Pulmonary Institute, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel

Faculty of Sport, Research Center in Physical Activity, Health and Leisure (CIAFEL), University of Porto, Porto, Portugal

A. Cogo et al. (eds.), *Exercise and Sports Pulmonology*,
https://doi.org/10.1007/978-3-030-05258-4_7

vessels within the lungs. ILDs are characterized by lung inflammation, scarring, and presence of restrictive pathophysiology. ILDs include diseases of underlying systemic processes (i.e., sarcoidosis), connective tissue diseases (i.e., rheumatoid arthritis), occupational exposures (i.e., asbestosis, silicosis), collagen vascular diseases, as well as environmental and drug-related diseases. ILDs also include conditions of unknown etiologies such idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IPF). IPF is the most common form of ILDs and have no established etiology [1, 2].

IPF is a chronic, progressive ILD associated with high morbidity and a median survival of 2–5 years from the time of diagnosis [3–5]. IPF is characterized by progressive pulmonary restriction, ventilatory inefficiency, dyspnea, impaired gas exchange, and hypoxemia, which all lead to diminished exercise capacity [3, 5, 6]. Patients with IPF experience severe breathlessness and tend to be less physically active in order to avoid such symptoms [7, 8]. Manifestations of IPF have a negative impact on functional capacity and quality of life (QOL) and are associated with poorer prognosis [3, 5–8]. Long-term effective treatment apart from lung transplantation is still limited for most IPF patients despite some encouraging recent findings with pharmacotherapies [3, 9–11].

A recent systematic review demonstrated that short-term exercise training in pulmonary rehabilitation settings is a safe and effective treatment for improving exercise capacity, dyspnea, and quality of life in patients with ILDs and IPF [12]. The current chapter comprehensively reviews the existing evidence on physical activity and rehabilitation programs in patients with ILDs and IPF, highlighting important insights concerning exercise in the management of these diseases.

7.2 Pathophysiology

At rest, patients with ILDs and IPF frequently show a restrictive pulmonary physiology characterized by reduced forced vital capacity (FVC) and total lung capacity (TLC), combined with impaired gas exchange [5, 6]. The resting arterial blood gases are usually near normal or may reveal mild hypoxemia; however, breathing pattern is often rapid and shallow. In general, as the disease progresses, lung compliance decreases and lung volumes fall [6]. Dyspnea is a predominant symptom of ILDs and IPF and results clinically significant due to its strong association with exercise intolerance, poor quality of life, and mortality [3, 8, 13–15]. Other symptoms such as leg pain, chest discomfort, and fatigue are also common reasons for exercise test termination [16, 17]. Patients with IPF can be also bothered by a dry cough which interferes with daily activities. The onset of symptoms is slow, despite progressive [5]. Exercise intolerance is a cardinal feature in ILDs and is associated with severe exertional dyspnea and fatigue, as well as poor quality of life [16–18]. Patients with IPF often exhibit reduced peak aerobic capacity (VO_2peak), peak work rate, and sub-maximal exercise endurance (anaerobic threshold) compared to age- and sex-matched healthy controls [16].

7.3 Exercise Tolerance Assessment

7.3.1 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is the gold-standard procedure to objectively assess cardiorespiratory fitness (VO_2 peak/VO_2 max), ventilatory, electrocardiographic, and metabolic responses to exercise [19–24]. Treadmill and cycle ergometers are the most commonly adopted CPET protocols among patients with chronic heart and lung diseases. CPET provides a comprehensive evaluation of exercise tolerance and functional capacity, detecting limiting factors during exercise; it also aids in establishing diagnosis and in reliably assessing responses to interventions [19–24]. In addition, variables obtained from CPET provide powerful prognostic information that has been shown to be more sensitive than traditional measures among patients with cardiopulmonary diseases [21–23]. Table 7.1 shows prognostic markers in patients with IPF.

Table 7.1 Selected prognostic markers in ILDs and IPF

Variables	Studies/thresholds	Hazard ratio (95% confidence intervals) for mortality
Low 6-min walk distance	du Bois et al. 2014 [25]<250 m	2.1 (1.2–3.9)
	Kawut et al. 2005 [26]<350 m	4.6 (1.5–14.2)
	Lederer et al. 2006 [27]<207 m	4.7 (2.5–8.9)
	Caminati et al. 2009 [28]<212 m	Not reported
Desaturation during 6-min walk test	Lama et al. 2003 [29] SpO_2 < 88%	4.5
	Vainshelboim et al. 2016 [30] Δ SpO_2 ≥ 10%	23.3 (1.5–365)
Low exercise capacity	Fell et al. 2009 [31] VO_2 peak <8.3 mL/kg/min	3.2 (1.1–9.6)
	Triantafillidou et al. 2013 [32] VO_2 peak >14.2 mL/kg/min per one unit increase	0.75 (0.6–0.95)
	Vainshelboim et al. 2016 [33] work rate < 62 watts	9.2 (1.9–42.6)
	Layton et al. 2017 [34] peak work rate %predicted<35%	4.7 (2.6–8.4)
Ventilatory inefficiency	Triantafillidou et al. 2013 [32] VE/VCO_2 at anaerobic threshold per one unit increase	1.15 (1.04–1.26)
	Vainshelboim et al. 2016 [33] VE/VCO_2 at anaerobic threshold>34	4.6 (1.2–17.3)
Physical activity	Vainshelboim et al. 2016 [30] ≤417 METS-min/week	9.7 (1.3–72)
	Vainshelboim et al. 2018 [35]	
	Walking 100 to <150 vs. <100 min/week	0.38 (0.16–0.88)
	Walking ≥150 vs. <100 min/week	0.14 (0.03–0.53)
Prolonged sitting time	Vainshelboim et al. 2018 [35]	
	5 to <10 vs. <5 h/day	4.6 (1.3–16.3)
	≥10 vs. <5 h/day	21.2 (4.1–32.6)

Reviews and research studies utilizing CPET in ILDs usually show multifactorial limitations during exercise. These include abnormal pulmonary gas exchange, inefficient breathing mechanics, exercise-induced hypoxemia, circulatory impairments, and respiratory and skeletal muscle dysfunctions [6, 16, 17, 36]. A hallmark clinical sign in patients with ILDs is hypoxemia, which manifests as a decline in arterial O_2 pressure and arterial O_2 saturation in response to exercise. This phenomenon mainly relates to abnormalities in pulmonary gas exchange, due to alveolar ventilation-perfusion (VA/Q) mismatching, oxygen diffusion limitation, and low mixed venous oxygen content [16, 17]. Ventilatory pattern is also seen abnormal in patients with ILDs; however breathing reserve in most cases is kept within normal values [16, 17]. In particular, part of the raised ventilatory drive during exercise is related to the increased dead space ventilation, which may also relate to underlying pulmonary vascular diseases, especially chronic pulmonary emboli or associated emphysema [6, 16, 17].

7.3.2 6-Min Walk Test

The 6-min walk test (6MWT) is a well-established test for assessing functional capacity in elderly subjects and in patients with cardiopulmonary diseases [37]. The primary outcome of the 6MWT is the 6-min walk distance (6MWD), a metric that provides a valid and reliable estimate of exercise capacity for people with chronic lung diseases. The 6MWD is associated with peak work rate capacity, physical activity, and VO_2 peak, supporting its role as a functional endpoint of exercise performance [38, 39]. The 6MWD has a good sensitivity to detect significant changes in pre-post exercise-based rehabilitation interventions. The minimal clinical important difference for the 6MWD ranges from 25 m to 33 m in adults with chronic respiratory diseases, and most of the trials performed in ILDs and IPF patients show clinical improvement by meeting or exceeding this threshold [12, 18, 38–40]. Desaturation during 6MWT in patients with ILDs and especially IPF has been shown to be an important clinical sign. The nadir SpO_2 during 6MWT aids in determining disease severity and providing prognostic values, such as the need for lung transplantation [3, 29]. The distance completed during the 6MWT has been also consistently proven to be associated with mortality among patients with IPF and has been used as an important marker of Lung Allocation Score for lung transplantation (Table 7.1) [25–28, 41].

7.4 Exercise Training in ILDs

In the past decade, growing body of evidence revealed the safety and efficacy of exercise training interventions for patients with ILDs and IPF [15, 42–55]. This was confirmed by a recent Cochrane systematic review and meta-analysis from Dowman et al. [12]. The analysis included five randomized controlled trials (86 subjects who took part in pulmonary rehabilitation programs and 82 controls). Significant

improvements in 6MWD [44.3 m 95% CI (26.04–62.64)] and in VO_2 peak [1.24 mL/kg/min 95% CI (0.46–2.03)] were shown for all ILD patients. Similar findings were reported in the subgroup of IPF patients with significant improvements of 36 m, 95% CI [16–55], and 1.5 mL/kg/min, 95% CI (0.5–2.4), respectively. The results from this meta-analysis also showed a reduced dyspnea and improved quality of life both in ILD and IPF patients with comparable efficacy [12, 56]. These findings are consistent with the previous Cochrane review by Holland et al. demonstrating clinical benefits of exercise training in ILD and IPF [56]. Of note, both meta-analyses showed an average improvement of 6MWD exceeding the minimal clinical important difference of 25 m generally set for chronic respiratory patients [12, 18, 38, 39, 57].

In general, exercise programs were undertaken for 4–12 weeks utilizing 2–3 weekly exercise sessions of 30–60 min duration. All training programs included aerobic endurance exercises, such as walking and cycling, whereas some programs combined also resistance and flexibility training, respiratory muscle training, and breathing exercises [16, 52].

7.5 Skeletal Muscle Strength and Endurance

Muscular strength and endurance are important health-related fitness components due to their associations with functional capacity and daily life activities [58, 59]. However, only few studies of exercise training investigated the strength and endurance of peripheral muscles in patients with ILDs [53, 54]. Available findings showed beneficial effect of exercise training on muscular strength and endurance. In particular, Arizono et al. showed significant improvements in handgrip and quadriceps strength following 10 weeks of a pulmonary rehabilitation program in patients with IPF [53]. Vainshelboim et al. [54] demonstrated a significant improvement in a 30-s chair-stand test (suggestive of the functional strength-endurance capacity of lower limb muscles) after 12-week exercise program in patients with IPF [54]. However, the data are still limited, and future studies are needed to fully address the muscular fitness component in ILDs and IPF patients.

7.6 Physical Activity

Physical inactivity has been identified by the World Health Organization as the fourth leading risk factor for global mortality [60]. Approximately 31% of adults are estimated to be physically inactive, contributing to 6% of all deaths [60, 61]. Physical activity has not been studied extensively in patients with ILDs. The manifestation of ILDs and the presence of signs and symptoms, especially during physical exertion, may mechanistically explain the high prevalence of inactivity in order to avoid breathless, fatigue, and other related respiratory symptoms [5, 7]. In general, inactivity among chronic respiratory disease patients is associated with poorer outcomes including higher mortality risk [18].

Few observational studies among patients with IPF have shown that low physical activity levels are associated with higher mortality rates [30, 62–64]. The study of Wallaert et al. [63], by using accelerometers for step counting, found a 65% lower daily physical activity in patients with IPF compared to healthy sedentary controls [63]. This study also showed that among these patients, physical activity <3287 steps/day was associated with poorer survival rates [63]. In align, Nakayama et al. [62] showed that low physical activity was associated with disease severity, as measured by blood biomarkers, extent of honeycombing, 6MWD, and dyspnea levels among stable IPF patients [62]. Vainshelboim et al. [30] using an international physical activity questionnaire reported that physical activity levels ≤417 METS-min/week (corresponding to 100–105 min of moderate-intensity physical activity per week) were associated with almost 10 times higher risk for mortality during a 40-month follow-up in patients with IPF [30]. More recently, Bahmer et al. [64] relying on step counters accelerometers showed that physically active patients with IPF exhibited significant lower risk of mortality (hazard ratio = 0.46) compared to inactive individuals during a median of 34-month follow-up [64].

Nonetheless, the effects of participating in supervised exercise training or pulmonary rehabilitation programs on physical activity were not extensively studied among patients with ILDs and IPF. In fact, only three prospective studies examined the effect of short-term exercise-based pulmonary rehabilitation programs on physical activity levels in IPF, with some conflicting results in the follow-up reassessment [50, 65, 66]. These studies consistently reported a short-term increase in physical activity after completion of the exercise-based interventions [50, 65, 66]. However, during follow-up while Gaunaurd [66] and Vainshelboim [65] showed reduction in physical activity levels, assessed by the international physical activity questionnaire, Ryerson [50] demonstrated conservation of physical activity levels, based on the rapid assessment of physical activity questionnaire scores. Interestingly, while the average physical activity levels in Vainshelboim's study [65] declined during the 11-month follow-up, at individual level 57% of the patients who participated in the exercise training were still above the baseline with preserved minimal clinically important difference of 200 METs-min/week (50 min/week at moderate intensity). This may provide a preliminary support for long-term positive effects of supervised exercise programs on home-based physical activity [65].

Taken together, preliminary data suggest benefits and better survival in active compared to inactive patients with IPF. Limited data also suggest the potential for pulmonary rehabilitation and supervised exercise programs to increase activity levels among patients with IPF. However, the existing evidence is confined to small sample sizes and lacks validation with objective devices (step counters/accelerometers), thus requiring further research. In addition, large prospective cohorts are warranted to characterize the role of physical activity in ILDs prognosis, and the long-term effects of exercise interventions on physical activity need to be explored more in depth.

7.7 Sedentary Behaviors

Population-based studies have found that more than half of an average person's waking hours involve sedentary activity, mainly prolonged sitting, such as watching television and using computer [67]. Prolonged sitting time was also recently acknowledged as independent risk factor from physical inactivity for incidence of many chronic diseases, hospitalizations, and mortality [68, 69]. While sedentary behaviors got little scientific attention in patient with ILDs and IPF, few available data demonstrated that sedentary lifestyle were associated with poorer outcomes [35, 70, 71]. Atkins et al. [70] found a trend toward significant association between prolonged sitting and mortality at 1 and 2 years of follow-up in IPF patients [70]. Vainshelboim et al. [35] showed that compared to patients with IPF who reported sitting time < 5 h/day, patients who sat ≥5 h/day experienced an increased risk of hospitalizations and mortality [35]. These preliminary findings support the potential clinical significance of sedentary behaviors in patients with IPF that need to be further addressed in future large prospective studies.

7.8 Possible Physiological Mechanisms of Exercise Training Effect in ILDs

ILDs are complex chronic lung diseases which result in intra- and extrapulmonary impairments that often worsen over time [1–3, 5, 16, 17]. Exercise training in healthy population has been shown to positively impact on cardiovascular, respiratory, and musculoskeletal systems [72]. Chronic appropriate stimuli with exercise may result in beneficial training effects and physiological adaptation for patients with ILDs, despite the existence of pathophysiological abnormalities and impairments [16, 17, 59]. Figure 7.1 illustrates possible mechanisms for the beneficial effects of exercise training in patients with ILDs.

A randomized controlled study by Vainshelboim et al. [54] revealed a significant improvement in ventilatory functions, including peak minute ventilation and peak tidal volume, after 12 weeks of an exercise training intervention in patients with IPF [54]. The improvement in peak tidal volume was significantly correlated ($r = 0.78$, $p = 0.001$) with an improvement in VO_2peak values, a gold-standard marker of cardiorespiratory fitness associated with better survival and overall health [19, 22, 23, 54, 73]. This underlying mechanism is poorly understood but may be related to a repetitive stimulus of high ventilatory demands, chest expansion during breathing exercises and stretching of the thoracic muscles during exercise sessions. These could result in a more efficient breathing pattern, improved strength of respiratory muscles, enhanced pleural elasticity, and pulmonary compliance [6, 16, 54, 74]. The abovementioned is consistent with a review paper suggesting beneficial effects of thoracic expansion and stretching on pulmonary restriction for IPF [74]. In addition, patients included in the study of Vainshelboim et al. [54] also showed improvements

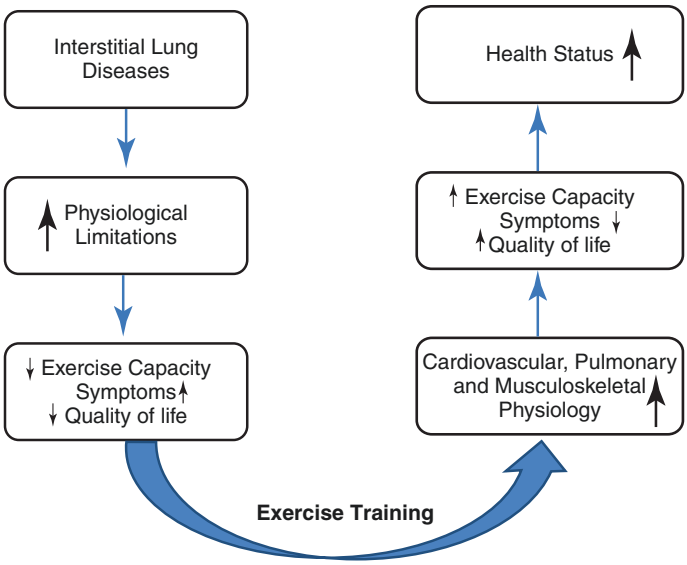

Fig. 7.1 Potential physiological mechanisms of exercise training in patients with interstitial lung diseases

in dyspnea, a phenomenon that further supports the relationship between cardiorespiratory fitness, ventilatory capacities, and exertional dyspnea [54]. These findings are consistent with data provided by Manali et al. [75] who found a significant correlation between dyspnea and VO_2peak in patients with IPF [75]. It also may be that the improvement in exercise capacity and ventilatory function results in reduced dyspnea at sub-maximal exercises, such as activities of daily living, as demonstrated by declined dyspnea scale rating after the program. This enhancement could determine an increase in alveolar oxygen tension and improvements in alveoli ventilation/perfusion (VA/Q) mismatch, resulting in an improved VO_2peak [5, 6, 16].

Furthermore, the study conducted by Keyser et al. [76] found significant peripheral adaptation after 10-week aerobic treadmill exercise program among ILD patients [76]. The authors used a near-infrared spectroscopy of peripheral oxygen extraction, suggesting it as primary physiological mechanism of increase in aerobic capacity in ILD [76]. In addition, Vainshelboim et al. [77] found a significant improvement in cluster of noninvasive exercise cardiovascular indexes, representing cardiac power and heart contractility among patients with IPF. This improvement was significantly correlated with improvements in functional capacity (6MWD) [77]. Given a considerably high (66%) prevalence of coronary artery disease in patients with IPF, the improvement in exercise cardiovascular function is potentially clinically important for cardiac disease prognosis and risk reduction in patients with IPF [77, 78].

Taken together, physiological studies in patients with ILDs and IPF suggest a significant improvement in ventilatory, cardiovascular, and skeletal muscle functions. However, the exact underlying mechanisms of training adaption in patients

with ILDs and IPF are yet to be understood and require future research utilizing low-dose computed tomography, stress echocardiography, and near-infrared spectroscopy to clearly address the intra- and extrapulmonary anatomical and physiological adaptations to exercise interventions.

7.9 Conclusions

Interstitial lung diseases, especially IPF, are associated with significant morbidity and mortality, exercise intolerance, dyspnea, and poor quality of life. Exercise training is feasible, safe, and clinically effective for improving exercise capacity, dyspnea, and quality of life in patients with ILDs and IPF. Higher exercise capacity and physical activity levels in patients with IPF were associated with better survival. Long-term effects of exercise training and fitness, as well as the physiological mechanisms, are yet to be determined.

7.10 Tips and Pitfalls

Despite the emerging scientific evidence with respect to safety and efficacy of exercise training in patients with ILDs and IPF, specific set of guidelines are yet to be published [74, 79]. Although exercise training studies in patients with ILDs show a good safety profile, these patients tend to have additional comorbidities, such as coronary arterial disease, systemic and pulmonary hypertension, as well as significant symptoms during exercise [3, 5, 6, 16, 78]. Thus, baseline comprehensive evaluation would be beneficial before starting an exercise training program. This may include a respiratory physician evaluation, pulmonary function test, 6MWT, "30-second chair sit to stand test," and "8-foot up and go test" [18, 23]. In addition, ILD patients present multifactorial limitations during exercise; integrative CPET would be therefore valuable to assess the electrocardiographic, hemodynamic, respiratory, and gas exchange responses to exercise [16, 17]. CPET can also serve to optimize personal training program prescriptions and necessary adjustments in oxygen supplementation during exercise sessions [18].

Oxygen supplementation seems to be necessary for hypoxemic patients during exercise as has been recommended by the American Thoracic Society/European Respiratory Society guidelines [3]. $SpO_2 > 90\%$ was previously recommended as appropriate oxygenation threshold for ILD patients [80], based on COPD data [81]. However, ILD patients tend to desaturate to much lower levels compared to COPD patients and practically may require different thresholds for oxygen supplementation delivery [82, 83]. In this regard, SpO_2 thresholds <88% [54] and <85% [49] were previously reported for oxygen supplementation during exercise sessions and seem to be reasonable and safe [49, 54]. A specific set of guidelines on oxygen supplementation during exercise in ILDs are yet to be published, and suggestions provided in this chapter are based on observational reports [15, 42–50, 54] and the pulmonary rehabilitation documents of leading respiratory organizations [18, 84, 85].

7.11 Practical Recommendations for Supervised Exercise Training Program

- Identify an appropriate space for conducting the exercise training program.
- Rely on staff specialized in exercise rehabilitation and familiar with signs and symptoms of ILDs.
- Address safety requirements in terms of emergency plans, oxygen delivery, and necessary monitoring during exercise sessions.
- Assess patients at baseline and after the intervention with at least medical evaluation, 6MWT, "30-second chair sit to stand test," "8-foot up and go test," dyspnea scale, and QOL questionnaire.
- Deliver at least two supervised exercise sessions per week over 6–12 weeks (longer is better).
- Include in exercise sessions 20–45 min of aerobic exercise (can start using an interval training of 5 min*4–6 bouts with 1 min rest between the bouts), 15–25 min of resistance/strength activities, and 10–15 min of flexibility and breathing exercises.
- Close monitoring of SpO_2, heart rate, blood pressure, Borg dyspnea scale, and clinical symptoms during exercise sessions.
- Incorporate educational sessions and psychological support with the exercise training as recommended for comprehensive pulmonary rehabilitation program.
- Encourage patients for home-based physical activity on other days of the week and consult to reduce sedentary behaviors.
- Develop a maintenance plan in order to sustain the improvement in outcomes.

Key Points

- Interstitial lung diseases (ILDs), especially idiopathic pulmonary fibrosis (IPF), are associated with significant morbidity, mortality, exercise intolerance, dyspnea, and poor quality of life.
- Interventional studies demonstrate that exercise training is feasible, safe, and clinically effective for improving exercise capacity, dyspnea, and quality of life in patients with ILDs.
- Preliminary observational data show that higher exercise capacity and physical activity levels are associated with better survival in IPF.

References

1. Kebbe J, Abdo T. Interstitial lung disease: the diagnostic role of bronchoscopy. J Thorac Dis. 2017;9(Suppl 10):S996–S1010.
2. 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.
3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. 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.

4. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med. 2007;176(3):277–84.
5. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis. 2008;3:8.
6. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161(2 Pt 1): 646–64.
7. Swigris JJ, Brown KK, Make BJ, Wamboldt FS. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. Respir Med. 2008;102(12):1675–80.
8. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax. 2005;60(7): 588–94.
9. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92.
10. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760–9.
11. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
12. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014;10:CD006322.
13. Ryerson CJ, Donesky D, Pantilat SZ, Collard HR. Dyspnea in idiopathic pulmonary fibrosis: a systematic review. J Pain Symptom Manag. 2012;43(4):771–82.
14. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40(1):101–9.
15. Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16(8):1196–202.
16. Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. Clin Chest Med. 2004;25(3):435–53.. v
17. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101–11.
18. Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C, et al. 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.
19. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211–77.
20. Arena R, Sietsema KE. Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. Circulation. 2011;123(6):668–80.
21. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191–225.
22. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2012;126(18):2261–74.
23. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription, vol. xxiv. 9th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014. p. 456.
24. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873–934.
25. du Bois RM, Albera C, Bradford WZ, Costabel U, Leff JA, Noble PW, et al. 6-minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2014;43(5):1421–9.

26. Kawut SM, O'Shea MK, Bartels MN, Wilt JS, Sonett JR, Arcasoy SM. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. Respir Med. 2005;99(11):1431–9.
27. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(6):659–64.
28. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med. 2009;103(1):117–23.
29. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168(9):1084–90.
30. Vainshelboim B, Kramer MR, Izhakian S, Lima RM, Oliveira J. Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis. J Clin Med. 2016;5(8):E73.
31. Fell CD, Liu LX, Motika C, Kazerooni EA, Gross BH, Travis WD, et al. The prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179(5):402–7.
32. Triantafillidou C, Manali E, Lyberopoulos P, Kolilekas L, Kagouridis K, Gyftopoulos S, et al. The role of cardiopulmonary exercise test in IPF prognosis. Pulm Med. 2013;2013:514817.
33. Vainshelboim B, Oliveira J, Fox BD, Kramer MR. The prognostic role of ventilatory inefficiency and exercise capacity in idiopathic pulmonary fibrosis. Respir Care. 2016;61(8):1100–9.
34. Layton AM, Armstrong HF, Kim HP, Meza KS, D'Ovidio F, Arcasoy SM. Cardiopulmonary exercise factors predict survival in patients with advanced interstitial lung disease referred for lung transplantation. Respir Med. 2017;126:59–67.
35. Vainshelboim B, Oliveira J, Izhakian S, Unterman A, Kramer MR. Lifestyle behaviors and clinical outcomes in idiopathic pulmonary fibrosis. Respiration. 2018;95(1):27–34.
36. Vainshelboim B, Oliveira J, Fox BD, Adir Y, Ollech JE, Kramer MR. Physiological profile and limitations in exercise in idiopathic pulmonary fibrosis. J Cardiopulm Rehabil Prev. 2016;36(4):270–8.
37. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
38. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. 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.
39. Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, et al. 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.
40. Vainshelboim B, Fox BD, Oliveira J, Kramer MR. Exercise training in idiopathic pulmonary fibrosis. Expert Rev Respir Med. 2016;10(1):69–77.
41. Tuppin MP, Paratz JD, Chang AT, Seale HE, Walsh JR, Kermeeen FD, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. J Heart Lung Transplant. 2008;27(7):729–34.
42. Jastrzebski D, Gumola A, Gawlik R, Kozielski J. Dyspnea and quality of life in patients with pulmonary fibrosis after six weeks of respiratory rehabilitation. J Physiol Pharmacol. 2006;57(Suppl 4):139–48.
43. Ozalevli S, Karaali HK, Ilgin D, Ucan ES. Effect of home-based pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2010;5(1):31–7.
44. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, et al. Beneficial effects of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56(6):783–9.
45. Rammaert B, Leroy S, Cavestri B, Wallaert B, Grosbois JM. Home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis. Rev Mal Respir. 2011;28(7):e52–7.

46. Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. Chest. 2009;135(2):442–7.
47. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J. 2013;42(2):444–53.
48. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13(3):394–9.
49. 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.
50. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med. 2014;108(1):203–10.
51. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax. 2017;72(7):610–9.
52. Tonelli R, Cocconcelli E, Lanini B, Romagnoli I, Florini F, Castaniere I, et al. Effectiveness of pulmonary rehabilitation in patients with interstitial lung disease of different etiology: a multicenter prospective study. BMC Pulm Med. 2017;17(1):130.
53. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, et al. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. Respir Care. 2014;59(7):1108–15.
54. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. Respiration. 2014;88(5):378–88.
55. Jackson RM, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung. 2014;192:367.
56. Holland A, Hill C. Physical training for interstitial lung disease. Cochrane Database Syst Rev. 2008;4:CD006322.
57. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. 6-minute walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med. 2011;183(9):1231–7.
58. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. 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 Exerc. 2011;43(7):1334–59.
59. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 2009;41(7):1510–30.
60. World Health Organization. Global recommendations on physical activity for health. 2010. http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf.
61. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380(9838):247–57.
62. Nakayama M, Bando M, Araki K, Sekine T, Kurosaki F, Sawata T, et al. Physical activity in patients with idiopathic pulmonary fibrosis. Respirology. 2015;20(4):640–6.
63. Wallaert B, Monge E, Le Rouzic O, Wemeau-Stervinou L, Salleron J, Grosbois JM. Physical activity in daily life of patients with fibrotic idiopathic interstitial pneumonia. Chest. 2013;144(5):1652–8.
64. Bahmer T, Kirsten AM, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Prognosis and longitudinal changes of physical activity in idiopathic pulmonary fibrosis. BMC Pulm Med. 2017;17(1):104.
65. Vainshelboim B, Fox BD, Kramer MR, Izhakian S, Gershman E, Oliveira J. Short-term improvement in physical activity and body composition after supervised exercise training program in idiopathic pulmonary fibrosis. Arch Phys Med Rehabil. 2016;97(5):788–97.

66. Gaunaurd IA, Gomez-Marin OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, et al. Physical activity and quality of life improvements of patients with idiopathic pulmonary fibrosis completing a pulmonary rehabilitation program. Respir Care. 2014;59(12):1872–9.
67. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. Am J Epidemiol. 2008;167(7):875–81.
68. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med. 2015;162(2):123–32.
69. Bouchard C, Blair SN, Katzmarzyk PT. Less sitting, more physical activity, or higher fitness? Mayo Clin Proc. 2015;90(11):1533–40.
70. Atkins C, Baxter M, Jones A, Wilson A. Measuring sedentary behaviors in patients with idiopathic pulmonary fibrosis using wrist-worn accelerometers. Clin Respir J. 2018;12(2):746–53.
71. Leuchte HH, Mernitz P, Baezner C, Baumgartner RA, von Wulffen W, Neurohr C, et al. Self-report daily life activity as a prognostic marker of idiopathic pulmonary fibrosis. Respiration. 2015;90(6):460–7.
72. Kenney WL, Wilmore JH, Costill DL. Physiology of sport and exercise, vol. xvii. 5th ed. Champaign, IL: Human Kinetics; 2012. p. 621.
73. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation. 2016;134(24):e653–e99.
74. Kenn K, Gloeckl R, Behr J. Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis—a review. Respiration. 2013;86(2):89–99.
75. Manali ED, Lyberopoulos P, Triantafillidou C, Kolilekas LF, Sotiropoulou C, Milic-Emili J, et al. MRC chronic dyspnea scale: relationships with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients: a prospective study. BMC Pulm Med. 2010;10:32.
76. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, et al. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. J Cardiopulm Rehabil Prev. 2015;35(1):47–55.
77. Vainshelboim B, Kramer MR, Fox BD, Izhakian S, Sagie A, Oliveira J. Supervised exercise training improves exercise cardiovascular function in idiopathic pulmonary fibrosis. Eur J Phys Rehabil Med. 2017;53(2):209–18.
78. Nathan SD, Basavaraj A, Reichner C, Shlobin OA, Ahmad S, Kiernan J, et al. Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. Respir Med. 2010;104(7):1035–41.
79. Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. Ther Adv Respir Dis. 2017;11(2):115–28.
80. Garvey C. Interstitial lung disease and pulmonary rehabilitation. J Cardiopulm Rehabil Prev. 2010;30(3):141–6.
81. Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–46.
82. Kozu R, Senjyu H, Jenkins SC, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81(3):196–205.
83. Holland AE, Dowman L, Fiore J Jr, 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;14:136.
84. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;131(5 Suppl):4S–42S.
85. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med. 2006;173(12):1390–413.