Resistance Training for Rehabilitation in Patients with Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a debilitating condition that causes severe symptoms, impaired functional capacity and poor quality of life. Exercise training has been shown to be a safe and effective therapy for improving physical function, dyspnea and quality of life in patients with IPF. However, due to pathophysiological limitations and symptom burden, conducting safe and effective exercise interventions is challenging; optimal program components and training modalities are yet to be established. Resistance training (RT) is a well-established exercise modality for combating effects of aging, disuse and chronic diseases, although there are scarce data available among patients with IPF. The current review briefly summarizes the pathophysiology and clinical manifestations of IPF and describes the numerous health and clinical benefits of RT among older adults and patients with respiratory disease. It then explores the potential RT mechanisms for overcoming exercise limitations in IPF, which may provide a therapeutic opportunity for rehabilitation. Finally, the review suggests practical RT recommendations for pulmonary rehabilitation programs in patients with IPF.

Keywords: muscle strength; functional capacity; activity of daily living; physical performance

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease affecting primarily older adults. IPF is associated with a high morbidity and mortality burden with a median survival of 2–5 years from the time of diagnosis. Patients with IPF commonly present with severe signs and symptoms, exercise intolerance and poor quality of life. Despite some advances in pharmacotherapies, long-term effective treatment apart from lung transplantation is still limited for most patients with IPF. Robust evidence supports the safety and efficacy of exercise-based pulmonary rehabilitation (EBPR) in improving exercise tolerance, quality of life and dyspnea in patients with IPF. However, the underlying mechanisms of adaptation to exercise training as well as optimal modalities for outcome improvement are yet to be characterized and require further investigation. Resistance training (RT) is a well-established exercise modality associated with enhanced physical and mental health as well as functional benefits, although few such data are available among patients with IPF. This review briefly summarizes the pathophysiology and the clinical manifestations of IPF, and explores the potential of RT in rehabilitation and therapeutic management of IPF.

Pathophysiology of IPF

Anatomically, IPF manifests over several years by structural scar tissue within the lungs along with pulmonary remodeling and thickening of the alveolar walls, appearing in a form of honeycombing on high resolution computed tomography. In addition, parenchymal damage, interstitial fibrosis, collapse and apposition of alveolar walls resulting in obliteration of alveolar lumina and distortion of normal lung architecture have all been documented in IPF.
Resting physiology

At rest, patients with IPF frequently demonstrate a restrictive pulmonary pattern with diminished forced vital capacity and total lung capacity accompanied by impaired gas exchange. Resting arterial blood gases are usually near normal or mild hypoxemia may be present, although breathing patterns are often rapid and shallow. Dyspnea is a predominant symptom in patients with IPF and this may occur even without physical exertion. As the disease progresses, alveolar wall compliance decreases, lung volumes fall and dyspnea worsens.

Aerobic exercise capacity

Exercise intolerance is a cardinal feature in IPF and associated with severe exertional dyspnea, higher fatigue levels, poor quality of life and increased mortality risk. Direct measure of cardiorespiratory fitness reveals low VO₂ peak, peak work rate and ventilatory threshold compared to age- and sex-matched normal controls. During cardiopulmonary exercise testing, patients with IPF demonstrate multifactorial limitations, including abnormal pulmonary gas exchange, inefficient breathing mechanics, respiratory and circulatory impairments, skeletal muscle dysfunction and exercise-induced hypoxemia. Hypoxemia during exercise measured by the level of desaturation is a hallmark sign in IPF and is closely linked to high mortality risk.

Additionally, most patients with IPF experience severe dyspnea during exercise, which has clinical significance due to its strong association with mortality, poor quality of life and functional limitations. A combination of desaturation and dyspnea during exercise further challenges the ability to exercise in patients with IPF, even when utilizing a well-established moderate intensity continuous aerobic regimen.

Behavioral manifestation

Many patients with IPF become physically inactive and highly sedentary as a consequence of disease manifestations. Severe signs and symptoms (desaturation and dyspnea) occurring during physical effort lead to the avoidance of discomfort associated with exercise, a fact that further deteriorates patients’ health condition and quality of life. A study by Wallaert et al. using step counter accelerometers found a 65% lower daily physical activity level in patients with IPF compared to healthy sedentary controls. This study also demonstrated that physical activity < 3287 steps/day was associated with poor survival rates. Consistent with these findings, our group employed a physical activity questionnaire and demonstrated that physical activity ≤ 417 METS-min/week (corresponding to 100–105 min of moderate intensity physical activity/week) was associated with a nearly 10-fold increased mortality risk in patients with IPF. Emerging data also suggests that prolonged sitting time is associated with poorer clinical outcomes in patients with IPF. Secondary analysis of our cohort revealed that patients who sat ≥ 10 hours/day compared to those who sat < 5 hours/day exhibited 6- and 21-fold higher hospitalization and mortality risks, respectively.

Muscular fitness

Muscle strength and endurance are important health-related fitness components, which have strong associations with functional capacity, the ability to perform activities of daily living, and mortality. Due to the low physical activity levels and prolonged sedentary time that patients with IPF exhibit, there is a high probability of developing secondary behavioral manifestations. These include accelerated muscle atrophy (sarcopenia) and decreased muscular fitness (dynamopathy). These pathophysiological alterations can negatively affect physical performance and activities of daily living, which further deteriorate a patient’s condition and increase the risk for poor clinical outcomes. This was recently demonstrated by marked declines in performance on the 30-s chair-sit-to-stand and 8-foot-up-and-go tests among patients with IPF. Additionally, poor performance on the 8-foot-up-and-go test was associated with significantly higher hospitalization and mortality risks, suggesting the importance of maintaining physical function and muscular fitness for these patients.

Resistance training

Resistance training (RT) is a well-established and highly effective form of exercise aimed to improve muscle fitness and mass. During this type of exercise, external loads (resistance) are applied to challenge muscle contraction using specific machines, free weights, elastic bands or body weight in an intermittent fashion (sets comprised of repetitions followed by resting periods). The total volume of effort that is associated with benefits is usually based upon the intensity of effort that brings a given muscle group close to failure. While there lacks a strong evidence base in IPF specifically, the exercise prescription that is similar to that for elderly patients is generally considered appropriate in IPF. Sets with fewer repetitions (1–5) and high loads (≥ 85% of 1 repetition maximum (RM)) usually target maximal muscle strength; whereas sets with higher numbers of repetitions (> 12) and relatively low loads (40%–60% of 1RM) are generally effective for improving local muscle endurance. A medium range of repetitions (6–12) with moderate loads (60%–80% of 1RM) are recommended for increasing muscle hypertrophy, whereas explosive movements (power) using low to moderate intensities (30%–60% of 1RM) are effective in enhancing functional performance. Additionally, RT exercises that simu-
late activities of daily living such as chair sit-to-stand exercise help to optimize improvements in function and health outcomes in older adults and in rehabilitation of patients with chronic diseases.  

Health benefits of resistance training for older adults

Robust evidence supports numerous physiological, psychological and health benefits of RT among older adults. RT can effectively improve functional performance, thus playing an important role in prevention and rehabilitation of chronic diseases and reduce the risk for adverse events. A recent meta-analysis demonstrated enhanced survival among those who engaged in RT. The study comprised 11 prospective cohorts with a total of 370,256 participants, who were followed for a mean of 8.9 years. The analysis showed that compared to no exercise, RT was associated with 21% [hazard ratio = 0.79, 95% CI (0.69–0.91)] and 40% [hazard ratio = 0.60, 95% CI (0.49–0.72)] lower all-cause mortality risks in those who practiced RT alone and in combination with aerobic exercise, respectively. Although this meta-analysis found only a borderline association between RT and cardiovascular mortality, participation in RT among men was associated with a 23% reduced risk [risk ratio = 0.77, 95% CI (0.61–0.98)] of coronary heart disease events. In agreement with the latter findings in men, the Women’s Health study showed that women who engaged 60–120 min/week in RT had 45% and 32% reduced risks of incident type 2 diabetes and cardiovascular disease, respectively. Incidence of cardiometabolic diseases is closely related to their risk factors. The health benefits of RT on cardiometabolic risk factors were robustly demonstrated in a meta-analysis of 173 randomized controlled trials (RCTs) involving 6169 participants (2840 control and 3329 RT). The study showed that RT reduced systolic and diastolic blood pressures and decreased fasting insulin levels. The effect of RT was more pronounced among individuals with cardiometabolic risk factors and diseases compared to young healthy adults. Other studies have similarly reported beneficial effects of RT on cardiometabolic health and reduced risk of diabetes. Short-term RT interventions have been shown to decrease hemoglobin A1c (HbA1c), increase glucose transporter type 4, improve insulin sensitivity and decrease low density lipoprotein cholesterol and triglycerides and increase high density lipoprotein cholesterol.

Recent data from the Health Survey for England and the Scottish Health Survey involving over 80,000 participants demonstrated that engaging in RT alone was associated with 21% lower all-cause mortality and 34% lower cancer mortality risks. Representative US data from the National Health Interview Survey (NHIS) of older adults (≥ 65 years) showed that individuals who were meeting the national physical activity guidelines on RT (≥ 2 sessions/week) had an enhanced survival profile. Meeting the RT physical activity guidelines was associated with 36%, 28% and 17% lower all-cause, cardiovascular disease-related and cancer-related mortality risks, respectively. Among cancer survivors, regular RT has been shown to be associated with 33% lower all-cause mortality risk even after adjusting for physical activity levels. Finally, strong evidence from the National Institutes of Health (NIH)–American Association of Retired Persons (AARP) Diet and Health Study also supported the preventive benefit of regular RT against developing several cancers. This large prospective study of 215,122 individuals (121,001 men and 94,121 women) demonstrated that a moderate volume (5–90 min/week) of RT was associated with 26%, 35% and 12% reduced incidence of colon, rectum and lung cancers, respectively.

RT as part of multicomponent exercise program has also been shown to be an effective tool for reducing the risk of falls and injuries in older adults. Three meta-analyses have demonstrated that physical exercise including RT was associated with 17%–23% lower falling rates among older adults. Most effective programs for incident fall reduction included a combination of functional RT and balance exercises. Physiologically, RT has a profound effect on improving muscle mass and muscular fitness, particularly muscle strength. Collective evidence shows 1%–21% gains in muscle hypertrophy, 14%–97% improvements in muscle power and 9%–174% improvements in maximal strength after RT in older adults. RT also increases resting metabolic rate, reduces body and visceral fat and promotes bone mineral density. As mentioned above, RT has a profound effect on increasing muscle strength, which is a powerful predictor of mortality, physical function and falls in older adults. In contrast, poor muscle strength is strongly associated with higher risk of mortality, falls and functional limitations in older adults. Additionally, RT is highly effective in combating physical limitations and disability, the preservation of quality of life and increasing activities of daily living. The cumulative incidence of disability affecting activities of daily living is significantly lower for older adults who practice RT and/or aerobic training than non-exercisers. Psychologically, RT provides a variety of cognitive and mental health benefits for older adults. Regular exercise including RT has shown powerful neuroprotective effects against cognitive decline, dementia and Alzheimer’s disease. RT in combination with aerobic training is an effective therapy for improving executive tasks of attention, memory, verbal fluency and global cognitive function in older adults. Randomized controlled trials have demonstrated that RT is effective in reducing depression symptoms, improving overall mood, positive
changes in confusion and anger, reducing trait anxiety, enhancing sleep quality, decreasing tension, improving vigor, spatial awareness and visual and physical reaction times, and increasing self-efficacy. Taken together, robust observational and experimental evidence has established numerous health benefits of RT for older adults, suggesting that RT is a powerful, safe and effective tool for chronic disease prevention and rehabilitation. Table 1 summarizes the benefits of RT in older adults.

Table 1 Beneficial effects of resistance training for older adults

| Disuse and/or aging and (or) chronic disease | Effect of resistance training | Type of evidence |
|---------------------------------------------|-------------------------------|-----------------|
| All-cause mortality risk                     | Increases                     | Decreases       | II   |
| Cardiovascular disease risk                  | Increases                     | Decreases       | I    |
| Cancer risk                                  | Increases                     | Decreases       | II   |
| Type 2 diabetes risk                         | Increases                     | Decreases       | I    |
| Obesity risk                                 | Increases                     | Decreases       | III  |
| Sarcopenia (low muscle mass)                 | Progresses                   | Reverses        | I    |
| Dynapenia (muscle weakness)                  | Progresses                   | Reverses        | I    |
| Falls, fractures and injury risk             | Increases                     | Decreases       | I    |
| Frailty risk                                 | Increases                     | Decreases       | I    |
| Physical function and performance            | Deteriorates                 | Improves        | I    |
| Mobility                                     | Deteriorates                 | Improves        | II   |
| Disability                                   | Increases                     | Decreases       | II   |
| Independence                                 | Deteriorates                 | Improves        | II   |
| Activity of daily living                     | Decreases                    | Increases       | I    |

**Physiological and metabolic changes**

| Muscle strength                              | Decreases                     | Increases       | I    |
| Muscle power                                 | Decreases                     | Increases       | I    |
| Muscle hypertrophy                           | Decreases                     | Increases       | II   |
| Bone mass density                            | Decreases                     | Increases       | III  |
| Cardiorespiratory fitness                    | Decreases                     | Increases       | II   |
| Glycemic control                             | Decreases                     | Increases       | I    |
| Dyslipidemia                                 | Progresses                    | Reverses        | III  |
| Blood pressure                               | Increases                     | Decreases       | II   |
| Chronic inflammation                         | Progresses                    | Reverses        | III  |
| Immune system function                       | Deteriorates                  | Improves        | IV   |
| Oxidative stress                             | Progresses                    | Reverses        | III  |

**Psychological and well-being**

| Cognitive function                           | Deteriorates                  | Improves        | IV   |
| Anxiety and depression symptoms and risk     | Increases                     | Decreases       | IV   |
| Pain                                         | Worsening                     | Relieves        | IV   |
| Fatigue                                      | Increases                     | Decreases       | III  |
| Quality of life                               | Deteriorates                  | Improves        | II   |

Note: Level I : High quality randomized controlled trials or prospective studies; Level II : Lesser quality randomized controlled trials or prospective studies; Level III : Case control studies or retrospective comparative studies; Level IV : Case series or case control studies, poor reference standard.
Health benefits of resistance training in patients with respiratory diseases

During the past few decades, RT has been added to pulmonary rehabilitation programs among patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), bringing beneficial effects on clinical outcomes. A meta-analysis of 18 studies (14 RCTs and 4 controlled trials) demonstrated that short-term RT moderately increased muscle strength in patients with COPD. A more recent meta-analysis of 18 RCTs including 750 patients with COPD showed that compared to non-exercise controls, RT improved dyspnea, muscle strength and % predicted forced expiratory volume in one second. In addition, the combination of resistance and aerobic training significantly improved quality of life, symptoms and muscle strength. No adverse events related to RT were reported.

In patients with ILD and IPF, RT has been utilized as part of comprehensive exercise interventions along with aerobic, functional and breathing exercises. In general, robust scientific evidence supports the safety and efficacy of exercise-based pulmonary rehabilitation interventions for patients with IPF. Five RCTs and five meta-analyses of RCTs have demonstrated significant improvement in exercise capacity, quality of life and dyspnea in patients with IPF. Several studies have also demonstrated beneficial effects on muscle fitness and function—strength-endurance capacity. For example, Arizono et al. showed significant improvements in handgrip and quadriceps strength following a 12 week exercise-based pulmonary rehabilitation program in patients with IPF. These encouraging findings support the potential rehabilitative benefits of RT for patients with IPF, although future studies are needed to explore other RT responses and its impact on clinical outcomes.

Potential beneficial effects and mechanisms of resistance training for patients with IPF

Although most exercise intervention studies included some form of RT combined with aerobic exercise, optimal training modalities and exercise regimens have yet to be established in patients with IPF. RT is performed in an intermittent manner (sets with 6–15 repetitions followed by rest periods), thus providing a lower work to rest ratio. RT also places a relatively lower cardiorespiratory demand, resulting in a lower dyspnea level, a primary limiting symptom during exercise in IPF. Additionally, by performing intermittent rather than continuous exercise, RT can potentially overcome the severe hypoxemia and drop in oxygen saturation that commonly occurs during exercise in IPF. The rest periods following each weight lifting set provide a sufficient time for re-oxygenation and re-saturation, preserving the overall oxygenation level, while stimulating muscles to induce a training effect. RT, compared to traditional endurance, continuous aerobic exercise, potentially overcomes at least some of the pathophysiological limitations in IPF, potentially leading to higher compliance and fewer barriers to participation in exercise programs. These issues require further research exploration. Figure 1 presents the potential mechanisms and benefits of resistance training for patients with IPF.
Resistance training recommendations for exercise-based pulmonary rehabilitation programs in patients with IPF

In general, RT programs for patients with IPF should include 2–3 sessions/week, 8–10 exercises involving major muscle groups; 1–3 sets per exercise with 10–15 repetitions per set at 30%–50% of 1RM are recommended for beginners and frail individuals, and 8–12 repetitions per set at 60%–80% of 1RM are recommended for more fit or advanced individuals. Power exercises, functional movements and balance training are also encouraged as components of the program. Using one to three minute rest periods is recommended between sets for recovery and re-oxygenation. Table 2 summarizes the RT variables recommended for pulmonary rehabilitation of patients with IPF.

Future research directions

Future research should focus on comparisons between RT and aerobic training in terms of program design, utilizing self-reported rates of discomfort and satisfaction among patients with IPF. Additional studies on the effects of RT on overall program adherence and levels of improvements in physiological, psychological and clinical outcomes are needed. These metrics are very valuable for prioritizing and optimizing program components. Finally, cost-effective analyses of combined RT and other training modalities could be beneficial for optimizing patient and program outcomes of pulmonary rehabilitation programs in patients with IPF.

Summary

RT is a well-established exercise modality that has an excellent safety profile, which provides numerous physiological, psychological and clinical benefits against disuse, aging and disease processes. Due to the intermittent manner of RT, it potentially provides a powerful tool that overcomes the pathophysiological limitations during exercise in IPF. Given the profound therapeutic effects of RT to improve functional performance, symptoms and quality of life, as well as to reduce the risk of many adverse events including mortality, robust evidence supports the utilization of RT as a standard of healthcare practice in pulmonary rehabilitation programs among patients with IPF.

Table 2 Resistance training recommendations for exercise-based pulmonary rehabilitation programs in patients with IPF

| Fitness components | Frequency | Number of exercises per session | Number of sets per exercise | Number of repetitions per set | Load (Intensity) | Rest periods between the sets (min) |
|--------------------|-----------|---------------------------------|-----------------------------|-------------------------------|------------------|------------------------------------|
| Strength-endurance-hypertrophy | 2–3 sessions/week | 8–10 exercises targeting major muscle groups | 1–3 | 10–15 for beginners and frail individuals | 30%–50% of 1RM or Borg 5–6 for beginners and frail individuals | 1–3 |
| Power | 2–3 sessions/week | Include few power exercises each session | 1–3 | 6–10 using movement with high velocity | 30%–60% of 1RM | 1–3 |
| Functional movements | 2–3 sessions/week | Include few exercises that simulate activities of daily living such as the sit-to-stand and stair-climbing | 1–3 | 10–15 for easy movement 8–12 for complexed movements | | Moderate |
| Balance | 2–3 sessions/week | Include several exercises stimulating balance such as line walking, tandem foot standing, standing on one leg, heel-toe walking, stepping practice, and weight transfers from one leg to the other | 1–3 | 8–12 | Light to moderate | 1–3 |
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