ABSTRACT

Inspiratory muscle training (IMT) has been described as one of the components of the treatment of chronic lung conditions such as obstructive and restrictive lung diseases. Although the number of studies showing results of IMT in patients with interstitial lung disease (ILD) is scarce when compared with studies in patients with COPD, evidence points to benefits of IMT in this population. This scoping review aimed to explore the role and the rationale of IMT in patients with ILD and to gather recent evidence on the effects of IMT in this population. The studies included in this review showed improvements in respiratory muscle function, quality of life, exercise capacity and dyspnea after ILD patients participated in programs that included stand-alone IMT or combined with pulmonary rehabilitation. There is still a gap in the literature to allow a clear conclusion on the indications of IMT as part of ILD treatment because of poor research design and small numbers of participants. Therefore, although IMT seems to have a positive effect in patients with ILD, current evidence prevents us from drawing a definite conclusion. Further studies need to be conducted using better research methodology to demonstrate and confirm the positive effects of IMT.

Keywords: Respiratory muscles; Lung diseases, interstitial; Rehabilitation.

BACKGROUND

Respiratory muscles are responsible for creating air flow to the lungs by elevating the ribs and increasing the chest wall dimensions, as well as decreasing airway resistance and intrathoracic pressure. During breathing, the activation of respiratory muscles can be very different from the activation of other skeletal muscles. However, the capability of adaptation to different conditions and functional demands is comparable between those two muscle groups, hence having a similar response to training stimulus. A literature review conducted by Powers & Criswell described an increase in the number of fibres and mitochondrial activity in respiratory muscles after specific endurance respiratory training. That study showed positive effects of training, with the reduction of oxidative stress and a delay in respiratory muscle fatigue. Three different fibre types can be found in respiratory muscles and are the same encountered in peripheral skeletal muscles: type I, type IIA and type IIB. However, the proportion and distribution of these fibres across the diaphragm muscle, for example, are different from those across other peripheral muscles, such as the quadriceps. The diaphragm presents 80% of oxidative fibres (types I and IIA), that is, fatigue resistant fibres, whereas the quadriceps shows only 35-45% of oxidative fibres.

The role of respiratory muscles has been poorly investigated in patients with interstitial lung disease (ILD). Nevertheless, the mechanisms of inspiratory muscle training (IMT) have been extensively studied and its effects could possibly be extended to people with lung parenchymal disorders.

A recent brief review by Jensen et al. investigated the physiological mechanisms of exertional breathlessness in patients with ILD and suggested that it is related to increased neural respiratory drive. In patients with ILD, the ability to answer to an increased ventilatory demand is mainly impaired because of reduced lung compliance. In this case, the respiratory system is forced to work in a non-ideal pressure-volume relationship, contributing to weakness of the inspiratory muscles. Consequently, the breathing frequency increases to abnormal levels as a result of a constrained expansion of $V_{\text{t}}$, leading to increased respiratory muscle effort and breathlessness rating.

A literature review published in 2013 explored the connection between weakness of inspiratory muscles and poor exercise tolerance in people with sarcoidosis. Evidence of decreased MIP and inspiratory muscle endurance in that population was shown and was related to decreased exercise tolerance and respiratory muscle failure.

Currently, several studies have described the use of IMT as part of the treatment of patients with lung conditions such as COPD, asthma and ILD. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have recommended that IMT be an additional intervention to pulmonary rehabilitation (PR) programs as part of the treatment of patients with chronic lung
Interstitial lung diseases, especially in the presence of inspiratory muscle weakness.

The rationale behind the recommendation of IMT to patients with chronic lung diseases can be related to a very common symptom to most of the patients: dyspnea. Diaphragm work increases during exercise, and patients with chronic lung diseases use a larger proportion of their MIP than do healthy subjects. Because of this different breathing pattern, there is an increase in dyspnea during exercise, leading to fatigue of the respiratory muscles and restriction of exercise capacity. In addition, when there is an increase in respiratory work, a competition between peripheral muscles and respiratory muscles can take place. In patients with COPD, a consumption of blood supply from the respiratory muscles during exercise can go up to 35%, whereas that consumption is 15% in healthy subjects.

IMT is also associated with structural changes in muscle fibre types and fibre distribution in inspiratory muscles. After five weeks of IMT, patients with COPD showed an increase in the number of type I fibres, as well as an increase in fibre II size in external intercostal muscle. IMT was able to improve inspiratory muscle work capacity by decreasing the relative work (percentage of maximal muscle work capacity). After IMT, there is a decrease in the amount of cardiac output consumed by the inspiratory muscles; consequently, a bigger portion of cardiac output can be redirected to peripheral muscles and increase exercise capacity.

In a systematic review, Gosselink at al. reported that IMT used as a stand-alone intervention is able to increase inspiratory muscle strength and endurance significantly as well as improving exercise capacity and quality of life and decreasing dyspnea in patients with COPD. Studies included in that review showed that patients presenting with inspiratory muscle weakness are better responders to IMT when compared with patients without it. IMT has also been shown to improve inspiratory muscle strength and exercise capacity in patients with ILDs such as idiopathic pulmonary fibrosis (IPF), although there is less evidence in the literature.

ILDs are a group of heterogeneous disorders that affect the lung parenchyma and are mostly associated with poor morbidity and high mortality rates. Most of ILDs involve common features and symptoms, such as dyspnea, cough, gas exchange deficiency, hypoxemia and decreased lung volumes that could lead to respiratory failure. ILDs can also be defined as diffuse parenchymal lung diseases, which could be classified by the presence of a known cause, as idiopathic interstitial pneumonia, as granulomatous pneumonia, or others. Chart 1 shows the classification of ILDs in accordance with the ATS/ERS.

Diagnosis and treatment of ILDs require a multidisciplinary approach and a comprehensive evaluation through history combined with physical examination and tests. The use of additional testing is quite often needed, and HRCT is a valuable tool to reach a specific diagnosis with confidence. Most of the times HRCT is enough for a definitive diagnosis, avoiding further invasive testing such as bronchoscopy or surgical lung biopsy. In 2014, Meyer published an interesting diagnostic approach to ILDs.

Once a definitive diagnosis is reached, there are essential elements to be considered for the treatment of ILDs, such as pharmacological agents, lung transplantation, supportive therapies, symptom relief management and treatment of comorbidities.

Corticosteroids, immunosuppressive agents and anti-inflammatory agents are medications that are most frequently prescribed for ILDs; more recently, anti-fibrotic medications have also been recommended for the treatment of patients with not only IPF, but also with other fibrotic ILD, such as rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, connective tissue disease-associated ILD, hypersensitivity pneumonitis and unclassifiable idiopathic pneumonitis. Anti-fibrotic medications have been shown to decrease disease progression (decrease in FVC) with a similar magnitude of effects for the overall population of ILD patients.

It is important to consider measurements of disease progression and symptom relief in patients with ILDs. Dyspnea measurements and lung function tests evaluating FVC and DLCO are routinely performed to monitor the disease. The six-minute walk test is also part of the routine evaluation of disease progression and provides valuable information regarding functional capacity.

PR is one of the non-pharmacological therapies that should be considered in the management of ILDs. Some studies have been conducted in order to evaluate the effects of PR in patients with ILD, such as functional capacity, breathlessness and quality of life. The ATS/ERS have defined PR as an intervention to reduce symptoms and improve functional status and performance of activities of daily living, contributing to reduce healthcare costs.

A Cochrane systematic review published in 2008 evaluated the safety of physical training for patients with ILD. Randomised and quasi-randomised studies were searched in the literature, and five studies were included in the analysis; a subanalysis was performed for IPF. Physical training was shown to be safe and improve functional exercise capacity, dyspnea and quality of life in patients with ILD, including those with IPF, although long-term effects of physical training could not be demonstrated.

In 2013, Holland et al. described ways to adapt PR programs for patients with IPF. In summary, the PR program for patients with fibrotic ILD should include the same components as does that for those with other severe lung conditions, such as aerobic and strength exercising as well as an educational component addressing depression and anxiety, which are usually present in this population. The PR
program, however, should consider that the incidence of pulmonary hypertension in ILD patients is greater and that decreased exercise tolerance and disabling dyspnea might be present. Different exercise protocols or exercise modalities such as interval training, water exercise and neuromuscular stimulation should be considered, because these patients are prone to presenting with more severe limitations.\(^{(25)}\)

IMT is one of the components of PR and has been extensively described in the literature in patients with COPD and asthma. One of the first studies to investigate IMT was described by Leith & Bradley in 1976.\(^{(26)}\) That was the first study to demonstrate that inspiratory muscles could be trained, strength and endurance being increased. The first IMT protocol described in the literature used non-linear resistance devices and showed inconsistent results.\(^{(27)}\) Then, a linear resistance device combined with a pressure threshold breathing device (Threshold-IMT; Respironics, Andover, MA, USA) was introduced,\(^{(28)}\) and, in 1988, the effects of IMT in patients with COPD who used such devices for two months were evaluated.\(^{(29)}\) The pressure threshold breathing device provides a resistance from \(-7\) cmH\(_2\)O to \(-41\) cmH\(_2\)O. Larson et al.\(^{(30)}\) compared the differences between IMT using a resistance from 15% to 30% of MIP for training and two different protocols. Their results showed better improvements in inspiratory muscle strength, endurance and exercise tolerance evaluated with the 12-minute walk test in patients who trained using higher resistance.\(^{(30)}\)

There are many different protocols varying in number of weeks and resistance during training. In 2006, Hill et al.\(^{(31)}\) innovated by proposing a high-intensity interval IMT for patients with COPD. The study compared high-intensity interval training resistance (\(\geq 60\%\) of MIP) with constant training resistance at 10% of MIP.
The protocol consisted of eight weeks of IMT, three times per week, for 21 min (Figure 2). The study showed that high-resistance interval training allowed participants to achieve higher training resistance with a significant increase in strength, endurance and quality of life, as well as a significant decrease in dyspnea during activities of daily living when compared with low-intensity constant training. The role of IMT as an additional therapy to PR or as a stand-alone intervention in patients with ILD has yet to be established, and the number of studies in the literature is scarce.

SCOPE OF THE SYSTEMATIC SEARCH

As described by Arksey & O’Malley,(32) a scoping review aims to explore a research area and to provide coverage of the literature available on a specific topic. This scoping review aimed to explore the effects of IMT in patients with ILD.

A systematic search using the Ovid MEDLINE platform and PubMed was performed to identify interventional studies in English including the terms “interstitial lung disease” and “inspiratory muscle training” and their variations. Additional hand searching was performed following reference lists from included articles and grey literature (Figure 3).

Sixty-three studies were identified, and only four studies have reported the effects of IMT alone or combined with PR in patients with ILD. Figure 3 shows the flow chart of the literature search.

EFFECTS OF IMT ALONE OR IN COMBINATION WITH PR

Jastrzebski et al.(33) evaluated the effects of PR in patients with pulmonary fibrosis. The six-week PR program included cycling for 15 min, general exercise and IMT performed using a threshold device (six cycles of five breaths twice a week). The results of that study showed improvement in dyspnea (Borg scale) and quality of life (Medical Outcomes Study 36-item Short-Form Health Survey and Saint George’s Respiratory Questionnaire).

In 2019, Kaushal et al.(34) also evaluated the effects of respiratory muscle training and PR in patients with ILD. The PR program included exercise training for 60 min—endurance training (cycle ergometry), flexibility training, strength training and respiratory muscle training (threshold IMT)—three days a week for eight weeks. All the sessions were supervised, and the participants also attended educational sessions on breathing exercises, lung health, medication and stress management. Outcome measurements—six-minute walk distance (6MWD), respiratory muscle pressure, severity of dyspnea and lung function parameters—were taken at baseline, at the end of the PR program and at a follow-up visit six months after the end of the program. After eight weeks of PR, the participants with ILD (IPF and non-IPF) showed statistically significant improvement in functional capacity (increase in 6MWD), which decreased at the end of the follow-up period. Dyspnea changed from severe to mild according to the modified Medical Research Council (mMRC) scale after PR. Inspiratory muscle pressure significantly increased after exercise training and was negatively correlated with Borg scale scores for dyspnea, which indicates that increased muscle strength could have led to improvements in dyspnea. However, those effects were not sustained after completion of the PR program and reversed after six months of follow-up.(33)

An interventional study(32) investigated the effects of an IMT program on patients with advanced lung disease. The sample included 22 participants with ILD (IPF or hypersensitivity pneumonitis). Although there were patients with restrictive and/or obstructive disease and no control group, the results showed the benefits of IMT regarding dyspnea during activities of daily living and quality of life, as well as improvements in respiratory muscle strength and endurance. In that study,(32) IMT was defined as a high-intensity interval training program performed during eight weeks using a tapered flow resistive loading device, proving to be more feasible and leading to better adherence to training.(35,36) In 2018, the same group used the same program to evaluate the effects of IMT based on the perception of the patients with advanced lung disease.(37) The authors interviewed the patients, including two participants with IPF, after the completion of high-intensity IMT for eight weeks. The patients reported that there was an improvement in mobility and breathlessness after IMT, leading to better performance on activities of daily living and communication.(37)

Three case reports about PR in sarcoidosis, combined pulmonary fibrosis and emphysema, and IPF were included in the present review. Herrera-Olivares et al.(38) reported the case of a female patient with sarcoidosis who performed an exercise program, including high-intensity interval training, high-load resistance training and IMT using a mechanical threshold loading device for 4.5 years. The results showed improvements in cardiorespiratory fitness and functional capacity.(38) De Simone et al.(39) also reported the effects of a PR program that included interval training, high-load resistance...
training and IMT using a mechanical threshold loading device in a 65-year-old male patient with combined pulmonary fibrosis and emphysema syndrome. There were improvements in exercise capacity (6MWD), depression levels, health-related quality of life (Saint George's Respiratory Questionnaire) and dyspnea.\(^{(39)}\)

Another case report demonstrated that long-term combined interval aerobic training, resistance training and IMT helped maintain functional independence, walking capacity, and tolerance to resistance training in a 56-year old man before he experienced a decline in functional capacity due to IPF.\(^{(40)}\)

Three abstracts that reported the effects of IMT on ILD were included in this scoping review. Kerti et al.\(^{(41)}\) aimed to investigate the effects of IMT in association with PR on functional parameters and quality of life in patients with ILD. No control group seemed to be used; however, the results showed improvements in functional capacity (6MWD), quality of life, dyspnea (mMRC) and inspiratory muscle strength. Nykvist et al.,\(^{(42)}\) using the same idea, evaluated the effects of IMT in combination with physical exercising on patients with IPF. Improvements in 6MWD, inspiratory muscle strength, dyspnea (mMRC), fatigue and quality of life (chronic respiratory disease questionnaire) were reported in the group that performed IMT and exercising when compared with the group only performing IMT.\(^{(42)}\)

Koulopoulou et al.\(^{(43)}\) showed the results of a pilot study investigating the effects of high-intensity IMT on exercise capacity, dyspnea, inspiratory muscle function and health-related quality of life. The study included 17 patients with ILD who performed a high-intensity IMT program (n = 9) or a low-intensity IMT program (n = 8) for eight weeks. Quality of life, dyspnea and inspiratory muscle strength were evaluated. The results revealed a significant increase in inspiratory muscle strength in the intervention group, but no differences were found between the intervention and control groups regarding quality of life, dyspnea or exercise capacity.\(^{(43)}\)

The results of this scoping review show that the role of inspiratory muscles and IMT has been poorly investigated in patients with ILD. Studies vary in methodology and lack control groups to prove the benefits of IMT on top of recommended PR. Nevertheless, the mechanisms of IMT have been extensively studied, and their effects could possibly be extended to patients with pulmonary parenchymal disorders. A recent review by Álvarez-Herms et al.\(^{(44)}\) investigated the role of IMT in hypoxia and showed that IMT is an effective therapy to enhance strength and endurance of the respiratory muscles in healthy athletes, contributing to improved ventilatory function. The authors concluded that IMT would possibly have effects on factors that limit the respiratory system under stress, including premature fatigue, delay of respiratory muscle metaboreflex, perception of dyspnea, increased peripheral oxygen saturation and positive blood redistribution to locomotor muscles.\(^{(44)}\) These results could potentially explain how IMT could benefit patients with ILD when acting towards a decrease in exercise fatigue, dyspnea and delay of metaboreflex.

A recent study by O’Connor et al.\(^{(45)}\) evaluated the feasibility of IMT as an acceptable treatment option for patients with COPD who declined PR. The study showed that there was a lack of motivation, lack of information regarding the benefits of PR programs and barriers for attendance, such as transportation to the PR centre. It is likely that the same barriers would be faced by patients with ILD, and further studies are needed in this area. In that study,\(^{(45)}\) IMT proved to be acceptable and feasible to be performed and the investigated participants showed good adherence to the therapy, thus becoming a possible option in the management of patients with ILD who decline participation in PR.

**FINAL CONSIDERATIONS**

Inclusion of IMT in the treatment of patients with ILD needs to be better explored, because there is a limited number of articles in the literature that confirm...
its benefits to this population. There is an evident gap in the literature regarding the effects of IMT on patients with ILD, although published studies tend to demonstrate benefits in terms of improvement in quality of life, activities of daily living and exercise capacity. Evidence of effects of IMT on ILD is poor, and studies exploring this therapy included a small number of subjects or had a poor research methodology.

Consequently, it is not possible to draw definitive conclusions regarding the potential benefits of IMT to this population. Further well-designed studies should be conducted for the evaluation of the effects of IMT on patients with ILD and the possibility of inclusion of IMT as part of ILD patient management, as a component of PR programs or even as an additional option for patients who refuse PR.

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