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REVIEWS

The usefulness of respiratory rehabilitation in patients with idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis is a disease that affects the interstitial space of the lungs and its cause is unknown. This pathology is considered to be the most common in the group of idiopathic interstitial pneumonias. Nowadays we can see an increase both in its prevalence and its incidence among Western countries, which should be a reason for concern as there is no known curative medical treatment.

Generally, patients presenting with idiopathic pulmonary fibrosis have a dry cough, breathlessness, weight loss, fatigue and can later develop clubbing of the fingers. Before a definitive diagnosis can be made, we must take into account the risk factors of the more common pulmonary fibrosis such as: cigarette smoking, occupational exposure to harmful substances, radiotherapy and chemoterapy and asthma, and we should rule out other similar interstitial pathologies.

The treament used consists of mostly supportive and symptomatic therapies, the only known curative treament being lung transplantation. Therefore, pulmonary rehabilitation can become an alternative solution given the fact that it has proved effective in other lung diseases and has been included in COPD therapeutic guidelines for some time now.

So far, resistance improving, stretching and breathing exercises are considered, as well as other cardiorespiratory(aerobic) exercises such as walking and cycling which have been used for a long time in the manangement of dyspnea and they have a positive impact on the functional capacity, mental health and overall quality of life that cannot be contested.

Therefore, these types of therapies should be applied and further studied in order to see their efficiency in patients suffering from idiopathic interstitial fibrosis, as well as in those with other types of idiopathic interstitial pneumonias. Recently, it has been discovered that a large number of patients infected with the SARS-CoV-2 virus later develop this type of disease, making its treatment even more relevant on a global scale.

Keywords: idiopathic pulmonary fibrosis, respiratory rehabilitation, SARS-COV-2 rehabilitation, improved quality of life.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic disease belonging to the interstitial lung disease category which affects the tissue surrounding the lung alveoli and has the histological appearance of interstitial pneumonia. Interstitial lung diseases are a group of pulmonary parenchymal disorders that can occur as a result of a precipitating factor such as drugs, autoimmune diseases of the connective tissue, sarcoidosis, hypersensitivity upon inhaling certain allergens, although some have no known causes, which makes them an idiopathic lung disease (1); (***, 2000).

Some studies state that there is an abnormal activation of the alveolar epithelial cells that leads to a process in which fibroblasts and myofibroblasts within the tissue become activated as they start producing an excessive amount of extracellular matrix that eventually leads to disarray within the lung architecture (King et al., 2011). This process is caused in turn by a somatic mutation of some genes (Vassilakis et al., 2000; Mori et al., 2001).

Epidemiology

IPF (idiopathic pulmonary fibrosis) is considered to be the most common within the group of idiopathic interstitial

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pneumopathies. Data from existing registers suggest that between 17-37% of idiopathic lung diseases are due to IPF (Thomeer el al., 2001; Tinelli et al., 2005).

Global studies show a growth in prevalence and a stable increase in IPF incidence in Western countries. By analyzing the population subgroups of certain studies, it can be seen that this disease is more frequently encountered in men, especially those who are over 75 years old (Sgalla et al., 2016).

The mortality of IPF is closely related to the fact that the disease tends to be underdiagnosed, therefore suggesting that available data could be underestimated (Coultas et al., 1994). Consequently, certain studies have shown that the mortality linked to IPF is higher in older men and tends to increase over time as more cases are being diagnosed globally (Mannino et al., 1996; Johnston et al., 1990). One American study of records between 1992-2003 calculated that the mortality related to IPF after being adjusted for age and gender is 50.8/100,000/year. The same study shows that the main cause of death in patients suffering from idiopathic pulmonary fibrosis is respiratory failure (60%), followed by cardiovascular diseases (8.5%) and lung cancer (2.9%) (Olson et al., 2011).

In spite of this, a more recent study states that a large proportion of patients (40%) die from acute exacerbations of idiopathic pulmonary fibrosis (Natsuizaka et al., 2014).

Idiopathic pulmonary fibrosis is a serious illness with an average life expectancy of just 2-3 years, which seems to be linked to the patients' remaining forced vital capacity (FVC) (Raghu et al., 2011). As a result, those that have a FVC under 55% live on an average just 27.4 months, while those having >70% of their FVC have a better prognosis of 55.6 months (Nathan et al., 2011).

The risk factors of pulmonary fibrosis

Understanding the conditions that lead to pulmonary fibrosis is helpful as some authors consider that IPF develops most likely due to multiple concurrent processes, so the aim is to find a treatment that covers multiple pathophysiological pathways. Cystic fibrosis, a disease determined by a genetic mutation that occurs primarily in Caucasian people, is among the known risk factors of common pulmonary fibrosis. Furthermore, we could mention the main risk factors of secondary pulmonary fibrosis: cigarette smoking, asthma, radiotherapy, chemotherapy, exposure to asbestos particles or metallic dust. Moreover, we should not forget that the chain of events which causes fibrosis within the lung is as follows: an injury leads to inflammation, which in turn determines the repair of that tissue, which leads to fibrosis (Maher et al., 2007).

In secondary pulmonary fibrosis, avoiding the factor that has initially led to inflammation could stop the process from evolving, but in some cases like in idiopathic pulmonary fibrosis which is the subject of this article, the element that causes an inflammatory response is unknown, making the process very hard to stop or even slow down (Wynn & Ramalingam, 2012). Fibrosis can be found in many places within the human body, the most problematic areas being within the lungs, liver, heart and kidneys, or it could be widespread throughout the body as systemic sclerosis (Wynn, 2004).

Symptoms and the diagnosis of idiopathic pulmonary fibrosis

The main symptom of IPF is dyspnea. Because this occurs frequently in most lung diseases, until proper recognition, these patients are usually evaluated and misdiagnosed by other medical facilities (Hewson et al., 2018). The persistent hypoxia favors the appearance of characteristic clinical findings such as clubbing of the fingers which should aid the doctor in reaching a diagnosis. Some patients can present with a persistent cough, fatigue and loss of appetite (2).

All these non-specific symptoms unfortunately delay the diagnosis of IPF, the average being 2.2 years from the onset of dyspnea to reaching a facility that correctly makes the diagnosis, and this leads to a higher mortality among patients affected by this disease (Lamas et al., 2011). Other risk factors that could delay the diagnosis are male sex and old age (Hoyer et al., 2019). More than often, IPF is misdiagnosed as an obstructive pulmonary disease and patients are treated with inhalation drugs with no effect on symptoms (Cosgrove et al., 2018).

Reaching a diagnosis is difficult and involves a multidisciplinary team of clinicians, radiologists and pathologists (Flaherty et al., 2004). The gold standard is high resolution computed tomography (HRCT), ideally with confirmation by a pulmonary biopsy. Eventually, once the diagnosis has been reached, staging of the disease is done with typical respiratory function investigations such as: TLCO, 6MWT and PFTs (3). This biopsy is often risky and could cause an increase in mortality; as such, in most cases, patients are no longer diagnosed in this way, the only tool used being the imaging performed by HRCT that shows typical lesions (4);(5).

Complex treatment

Prolonging survival rates in those affected by IPF implies that a complex treatment is used by a multidisciplinary team. The treatment itself is supportive and symptomatic, as there is no medical cure for this disease to date. A common strategy used is lung transplantation that has on average a survival rate of 5 years after the procedure, being among the lowest among organ transplantations (Kotloff & Thabud, 2011).

As we stated before, so far there is no medical treatment that can cure IPF, only drugs that can slow down the evolution of fibrosis in the lung. The main drugs that are currently used in IPF are: N-acetylcysteine, pirfenidone and nintedanib. The main advantage of N-acetylcysteine is that it has an antioxidant effect and research has shown that it can also slow down the progression of pulmonary fibrosis, although more studies are needed to pinpoint the exact therapeutic dose and to prove its effects as it is not currently included in the treatment guidelines (Demedts at al., 2005; Raghu et al., 2017). On the other hand, pirfenidone has proven itself in many studies and it has been shown to slow down pulmonary fibrosis and also has an antiinflammatory effect (Noble et al., 2011; Azuma et al., 2005). Similarly, nintedanib has a favorable effect on disease progression and slows down the reduction of FVC, which is why it is widely used in the treatment of IPF (Richeldi et al., 2014).

In addition to general measures and medical or surgical treatments, the importance of pulmonary rehabilitation should also be taken into consideration as it is becoming widely used in this category of patients due to the fact that medical treatment is often ineffective. Therefore, based on the proven effectiveness of respiratory rehabilitation in patients suffering from COPD, we can hope to achieve the same results in patients affected by idiopathic pulmonary fibrosis.

The aims of pulmonary rehabilitation in patients suffering from IPF

Amongst patients suffering from IPF, dyspnea is the main factor that leads to a decreasing functional capacity and quality of life. The main goal of pulmonary rehabilitation is to alleviate dyspnea and to delay the onset of lung failure. Generally, affected patients become less physically active and will eventually end up being bed-ridden as the symptoms worsen due the escalation of pulmonary fibrosis. Consequently, respiratory rehabilitation programs aim to increase tidal volume and peripheral oxygen saturation, increase fat-free body mass, increase the stamina of the quadriceps muscle and improve the overall efficiency of skeletal muscle strength at a cellular and molecular level. These effects are seen as a clinically and statistically significant improvement of physical capacity, quality of life and reduction of the severity of dyspnea (Swigris et al., 2005a).

Furthermore, before and after lung transplantation, all patients are required to follow a complex respiratory rehabilitation program. It has been proven that some aspects such as improved quality of well-being, functional exercise capacity and lumbar bone mineral density are better for those patients that have followed a complex respiratory rehabilitation program (Mitchell et al., 2003; Manzetti et al., 1994; Stiebellehner et al., 1998).

Evaluation before and after rehabilitation

Initial assessment of a patient is done on 3 levels: symptomatic, functional, and overall physical capacity.

- *Symptomatic*: done using questionnaires, including those that focus on depression.
- *Functional*: done by using spirometry and TLCO
- *Physical* capacity is assessed by doing a 6 minute walking test (6MWT) and by using cardiopulmonary exercise testing.

There are many methods used in order to evaluate a patient with respiratory pathologies before and after a rehabilitation program is initiated to ascertain the positive effects that the rehabilitation can have. The most commonly used evaluation methods are: the 6 minute walking test (6MWT), the modified Borg dyspnea scale and the Medical Research Council (MRC) dyspnea scale (Matcovschi et al., 2011).

While the Borg and the MRC scales are based on the evaluation of dyspnea using a subjective severity scale, the 6 minute walking test on a flat surface or on a treadmill is a more objective way to quantify a patient's functional capacity, the best parameter to monitor being the distance walked that is compared to a predicted, reference value. The predicted value is calculated using anthropomorphic parameters such as age, height, weight and sex to estimate the normal walking distance of a healthy person. Nevertheless, the situations where a 6 MWT is contraindicated should also be taken into account: unstable angina or recent myocardial infarction (<30 days), heart rate over 120 bpm after 10 minutes of rest, systolic blood pressure over 200 mmHg, a diastolic value of over 120 mmHg, peripheral oxygen saturation less than 85% or a major physical disability (5).

Additionally, we should also consider the effect on mental health that is exerted by using pulmonary rehabilitation programs; therefore, we should quantify a patient's mental health before and after the program. It is well known that the prevalence of depression among those suffering from chronic illnesses is higher than in healthy individuals and a recent study conducted by Akhtar et al. shows that 49.2% of patients suffering from IPF have depression, a significantly higher proportion compared to the general population (Moussavi et al., 2007; Akhtar et al., 2013; ***, 2010).

In conclusion, before and after a pulmonary rehabilitation program is initiated, a questionnaire that is called Tool to Assess Quality of Life in Idiopathic Fibrosis (ATAQ-IPF) can be used, which contains 74 questions related to symptoms, sleep, emotions, relations, therapy and finances for patients suffering from idiopathic pulmonary fibrosis (Swigris et al., 2005b).

Rehabilitation strategies in idiopathic pulmonary fibrosis

Pulmonary rehabilitation is beneficial for patients suffering from chronic pulmonary diseases as a large number of studies point out that such a program could alleviate symptoms, improve the functional capacity and quality of life (Nici et al., 2006). Nevertheless, it should not be forgotten that chronic illnesses have a big financial impact on a person's life. A particular study conducted in patients with COPD who attended a respiratory rehabilitation program showed that it had a positive effect in reducing the number of admissions for COPD exacerbations and thus lowering the overall cost of hospitalization because these events were responsible for 40-79% of the healthcare expenses for these patients (Farias et al., 2014).

In general, a pulmonary rehabilitation program takes between 4 and 12 weeks and it initially involves exercises that the patient can do easily and then, as the intensity of the workouts increases gradually, patients can also use supplemental oxygen during the sessions. Most such programs that involve pulmonary rehabilitation have a more intense period of 6-8 weeks, followed by a maintenance component for those patients that want to continue the program. Such programs can also be continued at home (6);(7). Furthermore, it is advisable that each week includes at least two rehabilitation sessions (Bolton et al., 2013). One study pointed out that there is no statistically significant difference between the outcomes of those attending a program for 4 weeks compared to those who had 7 weeks of pulmonary rehabilitation, although the 4-week program, because of its short length, included more patients (Sewell et al., 2006).

Respiratory rehabilitation is a very popular treatment

in patients with COPD and a lot of studies focus on this type of therapy. The respiratory rehabilitation program can be found in the treatment guidelines of COPD (8). Although IPF is not as common as COPD, the respiratory rehabilitation program has similar results for both diseases. One study conducted by Arizono et al. showed that after 10 weeks of rehabilitation, similar results were noted for patients with IPF and patients with COPD (Arizono et al., 2017).

Additionally, respiratory rehabilitation is a very popular choice in treating patients suffering from chronic pulmonary diseases. Physical inactivity has been shown to reduce lifespan, increase the need of medical services and eventually lead to a worse quality of life (Garcia-Aymerich., 2013).

Practicing exercise therapy can help patients with dyspnea, and generally the aim is to train a large group of muscles in order to increase cardiorespiratory endurance. Exercises such as walking on a flat surface or on a treadmill are preferred by therapists, while biking can be an alternative. Flexibility and endurance exercises can also improve respiratory function. Walking is indicated in 30-60 minute sessions for 3-5 times a week (Braddom et al., 2011). While for some patients doing a 30 minute continuous workout can prove to be difficult, it is recommended to add regular pauses to a session and to add up the total workout time to around 30 minutes for a session (Bolton et al., 2013).

Endurance and stamina increasing exercises can be done using weights adapted for each patient, having 10-15 repetitions and then a 48 hour pause between sessions. While in the past, the focus was on cardio exercises, nowadays endurance exercises have proven their point in the rehabilitation of patients with IPF (Phillips et al., 2006). Another type of exercises that help these patients are those that focus on flexibility and they should be added to the rehabilitation program. Some guidelines recommend that 4-5 stretching exercises for 15-30 seconds should be used such as seated single leg hamstring stretch, standing quadriceps stretch, chest stretch, overhead reach stretch and wall cat stretch (Ferguson, 2014).

A key component of a respiratory rehabilitation program that is often used in COPD patients is pursed lip breathing. This type of breathing helps recruit more muscles from the torso and abdomen in order to improve the respiratory process, increasing peripheral oxygen saturation and also reducing dyspnea (Breslin,1992; Cabral et al., 2015). However, one study showed that pursed lip breathing had no effect on dyspnea, did not improve the 6MWT or gas exchanges in patients with interstitial lung disease (Parisien-La Salle et al., 2019). Consequently, it should be interesting to assess the effect of this type of exercise in patients suffering from idiopathic pulmonary fibrosis.

Furthermore, a study conducted by Nishiyama et al. showed that following a rehabilitation program, patients with IPF had an improved 6 minute walking test and better overall quality of life, but their bodyweight (calculated with BMI) or the severity of their dyspnea (Nishiyama et al., 2008) was not influenced.

In conclusion, we cannot challenge the positive effect that rehabilitation programs can have on patients suffering from chronic pulmonary diseases, but the magnitude of the effect is not yet well known in patients that have idiopathic pulmonary fibrosis, because it is generally a less encountered pathology as opposed to asthma and COPD.

Pulmonary fibrosis in the pandemic context of COVID-19

Considering that we cannot yet fully understand the long term effects that the SARS-COV-2 infection has on patients' lungs, we can only use data from similar viral infections that occurred in the past. Other viral infections such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) have created diseases similar to COVID-19 (Weiss, 2020).

One study conducted in patients with MERS showed that on average, 43 days after discharge approximately one third of patients had pulmonary fibrosis (Das et al., 2017). Generally, pulmonary fibrosis can be encountered as a residual lesion in patients who had ARDS, as one study performed on 201 COVID-19 patients in Wuhan showed that 40% had ARDS (Wu et al., 2020).

At the present time, the long-term effects of COVID-19 can only be speculated, but these must be considered as more and more people become infected with this disease. Likewise, patients who have other pulmonary diseases and become infected with SARS-COV-2 should not be overlooked (Spagnolo et al., 2020).

Conclusions

1. Idiopathic pulmonary fibrosis is a crippling disease and although it is not so often diagnosed, the existence of a specific rehabilitation protocol for this pathology should raise the interest of more physicians and researchers worldwide.

2. Rehabilitation programs that handle chronic pulmonary diseases have been found to be effective in improving lung function, mental health and overall quality of life for those patients that suffer from lung diseases.

Conflicts of interests

There are no conflicts of interests.

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