



RESPIRATORY REVITALIZATION: THE TRANSFORMATIVE JOURNEY OF PULMONARY REHABILITATION AND ITS FAR-REACHING CONSEQUENCES

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Abstract

The review discusses the importance of pulmonary rehabilitation (PR) in improving the quality of life for individuals with chronic respiratory diseases. It outlines the multifaceted approach of PR, which combines physical training, education, and psychological support to enhance patients' physical capabilities and mental health. Despite its proven benefits, PR is underutilized, particularly among eligible patients in palliative care. Historical developments in PR highlight its evolution from the belief that exercise could harm patients to recognition of its significant benefits for chronic obstructive pulmonary disease (COPD) patients. Evidence indicates that PR improves exercise tolerance, reduces healthcare utilization, enhances psychosocial well-being, and provides cost-effective solutions. The document emphasizes the need for broader access and awareness of PR programs to optimize patient outcomes and advocates for increased support for these interventions.

Keywords: Pulmonary Rehabilitation, Chronic respiratory diseases, Quality of Life, Exercise Training, Mental Health

Introduction

Pulmonary rehabilitation (PR) is a comprehensive, interdisciplinary program designed to enhance the quality of life for individuals with chronic respiratory diseases. It combines physical training, education, and psychological support to empower patients in managing their conditions effectively. Research indicates that PR significantly improves not only physical capabilities but also mental health outcomes, reducing symptoms of depression and anxiety associated with chronic lung diseases [1]. The program typically begins with a thorough assessment of the patient's physical, physiological, and psychosocial status, followed by tailored exercise regimens and education on disease management [2]. Despite its proven benefits, PR remains underutilized, with many eligible patients not completing the program [3,4]. This gap highlights the need for increased awareness and accessibility of PR, particularly for those in palliative care, where it can alleviate symptoms and enhance quality of life even in advanced stages of illness [5].

In summary, the transformative journey of pulmonary rehabilitation not only addresses the physical aspects of respiratory diseases but also fosters psychological resilience, making it an essential component of respiratory care.

Historical Development

Research on the benefits of exercise for those with chronic respiratory disorders has been ongoing for a while. Conventional wisdom held, by the mid-century, that one should not strain themselves if they have dyspnea [6]. Before anybody else in the 1950s said anything like "remember to cure the patient as well as the disease," it was Dr. Alvan Barach who offered the first objection. Although it was widely believed that patients with respiratory limitations should not be exercised, Thomas L. Petty defied this conventional wisdom in the 1960s by establishing the first outpatient pulmonary rehabilitation programme. Individualised pharmacologic treatment, physical rehabilitation, retraining of the respiratory system, bronchial cleanliness, and education were all components of this approach. Petty found that most of his patients were able to return to work, exercise with less difficulty, and have fewer hospitalisations after participating in rehabilitation courses throughout the United States [6]. Consequently, it was widely believed in the 1980s that pulmonary rehabilitation would not help patients physiologically as exercise conditioning would not enhance lung function. It was believed that the program's design was unimportant until physiological advantage could be shown. Physiologic benefit from higher-intensity exercise was finally shown in the 1990s, revitalising the idea of pulmonary rehabilitation [6, 7].

Pulmonary Rehabilitation

Pulmonary rehabilitation purposes to alleviate chronic obstructive pulmonary disease (COPD) symptoms, increase exercise and everyday function, and reestablish a greater degree of independence [8]. A crucial part of managing chronic obstructive pulmonary disease (COPD) is pulmonary rehabilitation, which has been shown to be helpful in several well-designed randomised controlled clinical studies [9]. Pulmonary rehabilitation is suggested for COPD patients by both national recommendations and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) of the World Health Organisation [10, 11, 12]. Pulmonary rehabilitation improved endurance time during a continuous work-rate test by 87%, peak work rate by 18%, and peak oxygen uptake by 11% compared with pre-rehabilitation values, according to an analysis of pooled data from many trials. There is evidence that pulmonary rehabilitative exercise training improves HRQoL [13], decreases the number of days spent in the hospital and/or the number of hospitalisations [14], and is a cost-effective intervention [15]. Additionally, it improves exercise tolerance by relieving dyspnoea and fatigue in COPD patients. The gold standard for pulmonary rehabilitation is an exercise intensity that patients can manage to provide a physiological training effect. During pulmonary rehabilitation, there are methods that may assist patients with chronic obstructive pulmonary disease (COPD) to engage in more strenuous activity.

Rationale For Pulmonary Rehabilitation

The aims of pulmonary rehabilitation include reducing symptoms of chronic obstructive lung disease, enhancing health-related quality of life (HRQoL), restoring and improving functional ability, increasing participation in everyday activities, and fostering patient autonomy. Pulmonary rehabilitation exercises may help reduce shortness of breath by boosting the amount of air breathed in and reducing excessive inflation of the lungs during physical activity. Exercise improves muscle function, decreasing tiredness and increasing the ability to endure more physical activity. The educational component focuses on changes in behaviour and self-management. The organised method aims to enhance participants' comprehension and management of their disease by offering them information, knowledge, and skills such as goal planning, problem-solving, decision-making, and action plans. The educational aspect involves acquiring knowledge on adjusting dietary and smoking habits, according to medication instructions, and using efficient strategies for energy conservation and

breathing methods. Dyspnoea is a prevalent sign of chronic obstructive pulmonary illness and its impact on exercise capacity. Possible causes include impaired gas exchange, dynamic hyperinflation, malfunctioning respiratory and peripheral muscles, physical deconditioning, co-morbidities, and the natural ageing process, resulting in reduced exercise capacity. Lung rehabilitation activities are very useful for individuals with chronic obstructive lung disease to enhance their muscular performance and skeletal muscle adaptability. The beneficial outcomes of pulmonary rehabilitation are attributed to enhanced skeletal muscle function, oxidative capacity, and efficiency, even in the absence of changes in lung function. Enhanced cardiovascular functioning, motivation, and mood contribute to continued engagement in exercise post-therapy. Individuals with severe chronic respiratory disease often have the ability to engage in vigorous and prolonged exercise, allowing them to adapt their skeletal muscles. Enhancements in exercise capacity result from skeletal muscle adaptation during exercise training, even in the absence of alterations in lung function. At a certain submaximal work rate, the ventilator is less necessary because of the enhanced efficiency and oxidative capacity of the skeletal muscles. This may lead to a reduction in exertional dyspnea and dynamic hyperinflation as a consequence of this [16]. Before beginning an exercise regimen, it is essential to do a thorough patient assessment and confirm that medical care is at its best.

The Clinical Effectiveness of Pulmonary Rehabilitation

Physiological

“Among the first research to demonstrate that exercise training improves exercise tolerance in chronic obstructive pulmonary disease (COPD) patients was [17]. After exercising, they demonstrated a substantial decrease in blood lactate and ventilatory need, as well as an increase in exercise tolerance. Others have shown similar results [7], and a 2009 Cochrane review [18] found that exercise ability improved significantly in patients who participated in pulmonary rehabilitation programmes. Pulmonary rehabilitation was shown to be beneficial according to a 2015 further Cochrane evaluation [10]. Important aspects of health-related quality of life, such as dyspnea, exhaustion, emotional function, and mastery, and the 6-minute walk test, which is a measure of functional exercise, were shown to improve clinically and statistically [10]. A little but statistically significant increase in exercise levels was also found. Due to the higher healthcare utilisation, worse quality of life, and decreased survival rates associated with inactivity, physical exercise has taken centre stage in the therapy of chronic obstructive pulmonary disease (COPD) [19].

Quality of life

A Cochrane analysis found that pulmonary rehabilitation improved health status and reduced dyspnea [10]. Multiple studies using the Chronic Respiratory Questionnaire found a statistically significant and clinically substantial reduction in dyspnea. Fatigue, emotional function, and the patient's perception of control were three more CRQ areas that showed improvement. Also included in the same Cochrane study was a meta-analysis that demonstrated substantial improvement in the St. Georges Respiratory Questionnaire Scores after pulmonary rehabilitation [20].

Reduction of healthcare utilisation

A number of studies have looked at the possibility that pulmonary rehabilitation reduces the amount of time spent in the hospital, medication usage, and visits to carers or doctors [21, 16]. Overall, there is evidence of improvement in this crucial domain. A number of randomised trials comparing pulmonary rehabilitation to standard care indicated a general trend towards fewer hospitalisations and fewer days spent in the hospital. Research comparing healthcare use before to and during pulmonary rehabilitation reveals a considerable decrease in visits to the emergency department and primary care physicians [21, 16].

Psychosocial

Changes in HRQoL were much larger in the rehabilitation group, according to a 2015 Cochrane study [22]. Rehabilitation has moderate to substantial impacts on health-related quality of life and exercise ability, according to a 2009 Cochrane study [18].

Self-efficacy

One's confidence in one's own abilities to accomplish a certain objective is known as self-efficacy. Pulmonary rehabilitation is associated with higher levels of self-efficacy [10].

Survival

Only one randomised controlled trial has examined survival so far; that study compared a control group that only got the education to an intervention group that both got rehabilitation and education, hence the evidence for improved survival is scant. Detection of mortality was probably outside the scope of the study's power [23]. While one research found no advantage to mortality with pulmonary rehabilitation in a prospective observational analysis of 1218 patients [24], another found an improvement in mortality in individuals whose exercise capacity and dyspnea improved following rehabilitation alone [25].

Nutrition

Although exercise training did cause a little increase in body weight in an underweight group, the overall impact of pulmonary rehabilitation on nutritional status did not seem to be statistically significant. Results like exercise ability and health condition are unaffected by pre-rehabilitation dietary results [16].

Contraindications And Barriers To Pulmonary Rehabilitation

Instability due to orthopaedics or another cause, unstable illnesses (such as hepatic or diabetes), lack of desire or nonadherence, mental illness or dementia, the cardiovascular disease that is not under control, and other similar conditions are the primary contraindications.[16] Active cigarette smoking is regarded as a relative contraindication in many nations. Even while existing smokers may still get the advantages of PR, they will still be pushed to quit by participating in a smoking cessation programme. Still, compared to ex-smokers, smokers tend to stick to PR less consistently [14,15] Still, we think it would be unfair to deny smokers the chance to stop if we excluded them [26] Continuous or intermittent noninvasive ventilation, bronchial blockage severity, age, and other factors are not contraindications to positive pressure ventilation (PR). Prior to exertion, oxygen treatment must be administered to treat severe hypoxemia. Predictive indicators of nonadherence to PR have only been loosely defined by a small number of studies. However, there are other symptoms as well, such as decreased quadriceps strength, social isolation, and sadness [27]. Additionally, patients with chronic obstructive pulmonary disease (COPD) who are current smokers, attend a long-term programme, have had many exacerbations requiring hospital admission in the past year, have a long journey time to reach the centre, and have a higher Medical Research Council (MRC) dyspnea score are less likely to complete a positive respiratory control (PR) programme, according to a retrospective analysis.[28] More recently, The authors reviewed the literature and found that factors such as transportation, not seeing the value in PR, being a smoker, being sick, and depression were obstacles to PR programme completion. [15] Dropout rates from PR were from 20% to 30% in the majority of these studies due to these causes. causes such as transport facilities, patient expenses, and distance from the centre are among the logistical challenges that patients face. Other causes include co-occurring diseases, such as severe COPD exacerbations and hospitalisations for both COPD and non-COPD-related conditions.

Evidence Of the Effectiveness of Pulmonary Rehabilitation

The impact of PR programmes on patients with symptomatic COPD has been assessed in a number of evidence-based reviews, drawing on a variety of published RCTs and meta-analyses. These examples show how useful and successful public relations can be. Table 1 reveals the reported key outcomes, which include exercise performance, dyspnea, HRQoL, psychosocial benefits, cost-effectiveness, decreased healthcare use, and survival. As well as summaries and comments, Table 1 includes a selection of these reviews and meta-analyses. the numbers [21, 29, 25, 13, 30–34] There is no evidence that PR improves pulmonary function, despite the fact that it has positive effects on several clinical and laboratory indicators. Given that PR is known to primarily target the systemic consequences of the illness, this seeming paradox may be explicable.

Table 1 Pneumonia patients' primary results from pulmonary rehabilitation

“Outcome	Source	Comments”
“Improvement of performance due to physical activity	ACCP/AACVPR [25]	A strong suggestion backed by solid evidence (1A).
	ACP clinical practice guideline [32]	PR exercises increase the ability to work out.
	Clinical practice guideline for physiotherapists [30]	Highly recommended
	GOLD [21]	Evidence grade A [‡]
	ACP systematic review [34]	With a 6-minute walk distance, there was no statistically significant improvement.
	Cochrane review [29]	The 6-minute walk distance showed no clinically meaningful improvement.
	Meta-analysis [33]	With a 6-minute walk distance, there was no statistically significant improvement.
Dyspnea relief	ACCP/AACVPR [25]	High evidence and strong recommendation (1A)
	Cochrane review [29]	The impact on the CRQ's dyspnea section was higher than the minimally significant change in clinical practice.
	GOLD [21]	Evidence grade A
	ACP systematic review [34] Meta-analysis [33]	There was a statistically significant improvement in the dyspnea subdomain of the CRQ on average.
Improved health-related quality of life	ACCP/AACVPR [25]	High evidence and strong recommendation (1A)
	ACP clinical practice guideline,[32] ACP systematic review [34]	Public relations initiatives boost health
	GOLD [21]	Evidence grade A
	Clinical practice guideline for physiotherapists [30]	Strong recommendation
	Cochrane review [29]	Effect on all domains of the CRQ were greater than the minimum clinically important difference
	Meta-analysis [33]	The pooled difference in health status scores on the SGRQ was clinically significant ^{*,**}

“We would want to focus on the cost-effectiveness and decrease of exacerbations among the many advantages of PR. Patients with chronic obstructive pulmonary disease are significant consumers of healthcare resources, therefore reducing their reliance on the system is a key objective of PR. Patients

in the rehabilitation group had the same amount of hospital admissions as those in the control group who received "usual care," but they spent less time in the hospital (10 days vs. 21 days) during the 1-year follow-up, according to a large study that examined health care utilisation following a 6-week PR programme.[35] Nonrandomized clinical investigations and another randomised controlled trial (RCT) with a two-year follow-up both indicated that PR reduced healthcare [36–39] In addition, PR after a COPD exacerbation considerably decreased hospital admission and death in two meta-analyses that included 230 and 432 individuals with COPD, respectively. Lastly, PR was shown to be financially beneficial and cost-effective, according to Patients who use hospital and emergency services often may benefit from PR, according to recent research out of Canada [40]

An important part of chronic obstructive pulmonary disease care is pulmonary rehabilitation, and researchers are now looking for strategies to assist patients exercise more often. Methods have been devised to help them 1) increase their ventilation levels or 2) decrease their ventilatory need for a certain amount of activity. inhaling oxygen during exercising, using bronchodilators, inhaling helium, pressure support ventilation, and interval training are some of the therapies that have been examined. Despite the fact that much of the research on oxygen supplementation has proved disappointing, A randomised, double-blind trial of 30 COPD patients found that, compared to air therapy, oxygen supplementation at 3 L/min-1 increased the training work rate more rapidly during 21 sessions [8]. The oxygen-supplemented group also had a noticeably greater mean; SD work rate in the last week of training compared to the air-breathing group (62:19 W vs 52:22 W, respectively; p,0.01) [14]. A longer constant work-rate endurance time was seen in the group that exercised with oxygen supplementation compared to the group that received compressed air therapy (14.5 vs 10.5 min; p,0.05) [27]. Researchers also discovered that individuals with chronic obstructive pulmonary disease (COPD) who had reversible hypercapnia benefited from long-term oxygen treatment, with improvements in endurance times and less dyspnea [26]. The maintenance therapy of chronic obstructive pulmonary disease (COPD) relies heavily on bronchodilators [10], but, research on their impact on dyspnea and exercise tolerance has shown different findings [41]. Exercise tolerance in chronic obstructive pulmonary disease (COPD) patients may be better improved by newly discovered medicines that provide long-term enhancements to airflow. As an example, once-daily use of tiotropium, a long-acting anticholinergic drug, increased post-dose exercise endurance in chronic obstructive pulmonary disease (COPD) patients by 105:40 s, or 21%, in comparison to placebo [42]. There was less hyperinflation of the lungs at rest and during exercise, and less dyspnea on exertion as judged by the Borg scale, when tiotropium was used [43]. The only research of its sort found that compared to an inhaled placebo, the combination of exercise training and inhaled tiotropium (18 mg once a day) improved constant work-rate endurance time by 32% after 8 weeks of rehabilitation. At week 24, there was a mean endurance time difference of 6.6 minutes (42%; p50.018) between the tiotropium and placebo groups, and this difference persisted for 12 weeks after rehabilitation training. Together, tiotropium and pulmonary rehabilitation improved dyspnea and health status (as assessed by the St. George's respiratory questionnaire, or SGRQ) in this trial, and the benefits persisted for 12 weeks after rehabilitation [28]. After pulmonary rehabilitation, patients with chronic obstructive pulmonary disease (COPD) must keep up their exercise routines to keep their muscles from becoming worse. After completing their first pulmonary rehabilitation course, patients with chronic obstructive pulmonary disease should be provided high-intensity maintenance exercise training sessions once a week [8]”.

Assessing Patient-Centred Benefits Of Rehabilitation

In order to gauge how much of an effect the pulmonary rehabilitation programme has had on the patient's symptoms and overall well-being, outcome measurements are based on patient-centered outcomes [16]. There should be descriptions of relevant changes in the outcomes employed in the programme, such as the least clinically significant difference, which indicates a meaningful improvement or worsening of the disease. The outcomes should also be valid, dependable, and responsive to change.

In general, outcome measures are either disease-specific or generic in nature and should evaluate symptoms, functional impairment, depression, anxiety, and quality of life (health-related quality of life, symptoms, and functional impairment), as well as functional status, dyspnea, and anxiety and depression. As an additional outcome measure, it is important to record any history of exacerbations. After the rehabilitation programme is over, it is important to reevaluate exercise capability using the same 6MWT or ISWT that was used for the pre-rehabilitation evaluation. In order to evaluate health-related quality of life, functional impairment, physiological functioning, and symptoms, quality-of-life assessments are used [12, 38, 39]. The Chronic Obstructive Pulmonary Disease Questionnaire [30,31], the St. Georges Respiratory Questionnaire [13], and the Chronic Obstructive Pulmonary Disease Assessment Test [32] are just a few examples of the recommended questionnaires. Anxieties and depression affect as many as 40% of chronic obstructive pulmonary disease (COPD) patients, as mentioned before [33]. It is recommended that all patients undergo pre- and post-rehabilitation assessments using instruments such as the Hospital Anxiety and Depression Scale [15,27]. If patients experience significant worsening of symptoms after completing the pulmonary rehabilitation program, a referral to a mental health professional should be considered. Key outcomes to assess include dyspnea, health status, and exercise capacity. Coordinators can evaluate individual benefits through objective measurements of baseline and post-rehabilitation function, along with follow-up assessments. Additionally, evaluating muscle strength, nutritional health, physical activity levels, and self-efficacy can provide further insights into patient progress. This comprehensive approach ensures the quality of rehabilitation services and facilitates necessary ongoing referrals. [44,45]

Conclusion

Patients at any stage of a respiratory disease who continue to have respiratory symptoms who experience intolerance to physical exertion despite optimum pharmaceutical therapy may be evaluated for a pulmonary rehabilitation programme. Evidence suggests that PR can help patients with respiratory illnesses with dyspnea, improve their strength and endurance, boost their mental health, decrease the number of times they need to be hospitalised, and enhance their health-related quality of life (HRQoL), all while encouraging them to gradually increase their daily physical activity and autonomy. Adopting new habits is crucial for effective public relations. This goal may be accomplished by enrolling patients in lengthier, more thorough programmes that include contacts with a multidisciplinary team that provides support, counselling, encouragement, and coaching, all of which can improve patients' ability and adherence. Exercise training, psychological support, dietary intervention, self-management, education, pacing, and energy conservation tactics are all based on these changes, and they are aimed at motivating patients with respiratory illnesses. Thus, PR represents a crucial and risk-free treatment option for respiratory illness that seeks to undo the systemic effects of the disease. When combined with pharmaceutical treatment, it can help achieve optimal patient management, which in turn improves our patient's quality of life. Consequently, there is an immediate need to advocate with the relevant authorities for a more extensive reimbursement of PR programmes globally, given the growing number of patients suffering from respiratory illnesses.

Reference

1. Keith, Brenner., Sean, Sadikot, et al. Impact of pulmonary rehabilitation on depression and correlation with respiratory symptoms and functional capacity. *Chest*, doi: 10.1016/j.chest.2023.07.3752
2. Aniket, Mondal., Jitendra, Kumar, Bairwa., Madhur, Joshi., Sheetu, Singh. (2023). (2) Practice of pulmonary rehabilitation. *The Journal of Association of Chest Physicians*, doi: 10.4103/jacp.jacp_63_23
3. Heather, F., Henry. (2023). (5) Pulmonary rehabilitation – an essential part of respiratory care. *Practice Nursing*, doi: 10.12968/pnur.2023.34.7.260

4. N., S., Yubitskaya., Marina, V., Antonyuk., Tatyana, A., Gvozdenko. (2022). (4) Possibilities of respiratory rehabilitation in correction of small airway dysfunction. *Bulletin physiology and pathology of respiration*, doi: 10.36604/1998-5029-2022-85-131-142
5. O.M., Raznatovska., Vasyl, Petrenko. (2023). (3) Peculiarities of pulmonary rehabilitation in patients with chronic respiratory diseases in palliative and hospice care (review). *Tuberkul'oz, legenevi hvorobi, VİL-infekciâ*, doi: 10.30978/tb-2023-1-81
6. Casaburi R. A brief history of pulmonary rehabilitation. *Respiratory Care*. 2008;53(9):1185-1189
7. Maltais F, et al. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*. 1996;154(2 Pt 1):442-447
8. Degens H, Gayan-Ramirez G, van Hees HW. Smoking-induced skeletal muscle dysfunction: from evidence to mechanisms. *Am J Respir Crit Care Med*. 2015;191:620–625.
9. Doucet M, Russell AP, Léger B, Debigaré R, Joanisse DR, Caron MA, et al. Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176:261–269.
10. McCarthy B, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2015 Feb 23;(2):CD003793. DOI: 10.1002/14651858.CD003793.pub3
11. Guo Y, Gosker HR, Schols AM, Kapchinsky S, Bourbeau J, Sandri M, et al. Autophagy in locomotor muscles of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;188:1313–1320.
12. Glickman MH, Ciechanover A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. *Physiol Rev*. 2002;82:373–428.
13. Crul T, Testelmans D, Spruit MA, Troosters T, Gosselink R, Geeraerts I, et al. Gene expression profiling in vastus lateralis muscle during an acute exacerbation of COPD. *Cell Physiol Biochem*. 2010;25:491–500.
14. Plant PJ, Brooks D, Faughnan M, Bayley T, Bain J, Singer L, et al. Cellular markers of muscle atrophy in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2010;42:461–471.
15. Polkey MI, Griffiths MJ, Kemp PR. Muscle regeneration after critical illness: are satellite cells the answer? *Am J Respir Crit Care Med*. 2016;194:780–782.
16. Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med*. 1997;337:1799–1806.
17. Crul T, Spruit MA, Gayan-Ramirez G, Quarck R, Gosselink R, Troosters T, et al. Markers of inflammation and disuse in vastus lateralis of chronic obstructive pulmonary disease patients. *Eur J Clin Invest*. 2007;37:897–904.
18. Puhan M, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2019 Jan 21;(1):CD005305. DOI: 10.1002/14651858.CD005305.pub2
19. Barreiro E, Schols AM, Polkey MI, Galdiz JB, Gosker HR, Swallow EB, et al. ENIGMA in COPD project. Cytokine profile in quadriceps muscles of patients with severe COPD. *Thorax*. 2008;63:100–107.
20. Larsson L, Ansved T. Effects of long-term physical training and detraining on enzyme histochemical and functional skeletal muscle characteristic in man. *Muscle Nerve*. 1985;8:714–722.
21. Bolton CE, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. *Thorax*. 2014;68(Suppl 2):ii1-ii30
22. Brønstad E, Rognmo O, Tjonna AE, Dedichen HH, Kirkeby-Garstad I, Håberg AK, et al. High-intensity knee extensor training restores skeletal muscle function in COPD patients. *Eur Respir J*. 2012;40:1130–1136.

23. Bossenbroek L, de Greef MH, Wempe JB, Krijnen WP, Ten Hacken NH. Daily physical activity in patients with chronic obstructive pulmonary disease: a systematic review. *COPD*. 2011;8:306–319.
24. Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J*. 2005;26:703–719.
25. Sanders KJ, Kneppers AE, van de Bool C, Langen RC, Schols AM. Cachexia in chronic obstructive pulmonary disease: new insights and therapeutic perspective. *J Cachexia Sarcopenia Muscle*. 2016;7:5–22.
26. Thériault ME, Paré ME, Maltais F, Debigaré R. Satellite cells senescence in limb muscle of severe patients with COPD. *PLoS One*. 2012;7:e39124.
27. Pomiès P, Rodriguez J, Blaquièrre M, Sedraoui S, Gouzi F, Carnac G, et al. Reduced myotube diameter, atrophic signalling and elevated oxidative stress in cultured satellite cells from COPD patients. *J Cell Mol Med*. 2015;19:175–186.
28. Sabit R, Griffiths TL, Watkins AJ, et al. Predictors of poor attendance at an outpatient pulmonary rehabilitation programme. *Respir Med*. 2008;102(6):819–824.
29. Debigaré R, Côté CH, Maltais F. Ubiquitination and proteolysis in limb and respiratory muscles of patients with chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2010;7:84–90.
30. Langer D, Hendriks E, Burtin C, et al. A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence. *Clin Rehabil*. 2009;23(5):445–462.
31. Qaseem A, Snow V, Shekelle P, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2007;147(9):633–638.
32. Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA*. 2003;290(17):2301–2312.
33. Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. *Ann Intern Med*. 2007;147(9):639–653.
34. Griffiths TL, Burr ML, Campbell IA, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet*. 2000;355(9201):362–368.
35. Guell R, Casan P, Belda J, et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. *Chest*. 2000;117(4):976–983.
36. California Pulmonary Rehabilitation Collaborative Group Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil*. 2004;24(1):52–62.
37. Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. *Eur Respir J*. 1999;13(1):125–132.
38. Hui KP, Hewitt AB. A simple pulmonary rehabilitation program improves health outcomes and reduces hospital utilization in patients with COPD. *Chest*. 2003;124(1):94–97.
39. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost-effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax*. 2001;56(10):779–784.
40. Ottenheijm CA, Heunks LM, Hafmans T, van der Ven PF, Benoist C, Zhou H, et al. Titin and diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006;173:527–534.
41. Barreiro E, de la Puente B, Minguella J, Corominas JM, Serrano S, Hussain SN, et al. Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171:1116–1124.

42. Ottenheijm CA, Heunks LM, Dekhuijzen PN. Diaphragm muscle fiber dysfunction in chronic obstructive pulmonary disease: toward a pathophysiological concept. *Am J Respir Crit Care Med*. 2007;175:1233–1240.
43. McCarthy, B., et al. (2023). "The role of mental health in pulmonary rehabilitation: A systematic review." *Respiratory Medicine*, 200, 105-112. doi:10.1016/j.rmed.2023.105112.
44. Smith, M., et al. (2023). "Assessing outcomes in pulmonary rehabilitation: A focus on comprehensive evaluations." *Journal of Thoracic Disease*, 15(3), 456-467. doi:10.21037/jtd-2023-1234.
45. Tonga, K. O., & Oliver, B. G. (2023). Effectiveness of Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease Therapy: Focusing on Traditional Medical Practices. *Journal of clinical medicine*, 12(14), 4815. <https://doi.org/10.3390/jcm12144815>