



REVIEW

Adaptations in limb muscle function following pulmonary rehabilitation in patients with COPD – a review



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Abstract Even though chronic obstructive pulmonary disease (COPD) is primarily a disease of the respiratory system, limb muscle dysfunction characterized by muscle weakness, reduced muscle endurance and higher muscle fatigability, is a common secondary consequence and a major systemic manifestation of the disease. Muscle dysfunction is especially relevant in COPD because it is related to important clinical outcomes such as mortality, quality of life and exercise intolerance, independently of lung function impairment. Thus, improving muscle function is considered an important therapeutic goal in COPD management. Pulmonary rehabilitation (PR) is a multidisciplinary, evidence-based and comprehensive approach used to promote better self-management of the disease, minimize symptom burden, optimize functional status, and increase participation in activities of daily life. Exercise training, including cardiovascular and muscle exercises, is the cornerstone of PR and is considered the best available strategy to improve exercise tolerance and muscle function among patients with COPD. This paper addresses the various components of exercise training within PR used to improve limb muscle function in COPD, providing clinicians and health-care professionals with an overview and description of these various exercise modalities and of their effects on limb muscle function. Guidance and recommendations to help design optimal limb muscle training regimens for these patients are also presented.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. The international prevalence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 and higher COPD is estimated to be 10%, a figure that is steadily increasing.^{1,2} COPD is estimated by the World Health Organization to be the third leading cause of death in 2030.³ Although COPD is characterized by chronic airflow limitation, limb muscle dysfunction is a common consequence and a major systemic manifestation in COPD.^{4–6} Limb muscle dysfunction is associated with important clinical outcomes such as increased mortality,^{7,8} reduced quality of life,⁹ greater healthcare utilization,¹⁰ and exercise intolerance,^{11–13} independently of lung function impairment. Exercise intolerance is considered one of the key disabling factors in COPD with dyspnea and leg fatigue being the most frequently reported exercise limiting symptoms.^{4,14} Clinical manifestations of limb muscle dysfunction in COPD include muscle atrophy, weakness, reduced endurance, and/or greater muscle fatigability.⁴ Assessment of limb muscle mass and limb muscle function in COPD is therefore highly encouraged and improving this common feature of COPD is an important therapeutic goal.^{6,15}

This article provides clinicians and health-care professionals with an overview and description of the various exercise modalities used within pulmonary rehabilitation (PR) to improve limb muscle function, especially highlighting effective modalities at the muscle level. Our objective is to provide guidance and recommendations to help clinicians' design optimal limb muscle training during PR for patients with COPD.

Limb muscle function in patients with COPD

Limb muscle dysfunction encompasses muscle weakness, reduced endurance or greater muscle fatigability.¹⁵ Prevalence rates of muscle weakness ranges from 20 to 40% depending on disease severity,¹⁶ while reduced limb muscle endurance and muscle fatigue occur in 30–80% of patients with COPD.^{6,17,18} The impairment in limb muscles function in COPD is heterogeneous with strength and endurance of upper limbs seemingly more preserved than those of lower limbs.^{6,19–21} Decreased limb muscle strength and endurance, especially when involving lower limbs, are associated with reduced walking capacity²² and physical activity,^{13,20,23} exercise intolerance,^{11,24} morbidity, mortality as well as increased health care service use, dyspnea and poor quality of life.^{8,10,9,25} Lower limb muscles of patients with COPD also exhibit a greater susceptibility to fatigue than that of age-matched healthy individuals.^{13,26} Limb muscle dysfunction is the end result of several muscle structural, molecular and cellular alterations which are summarized in Fig. 1 and include weakness, atrophy, fiber-type distribution shifts, reduced oxidative capacity, mitochondrial dysfunction, and reduced capillarisation that are mediated by numerous etiological factors.^{6,27,28} These include sedentarity, poor nutritional status, repeated COPD exacerbations and systemic use of corticosteroids.⁵ Other relevant etiological factors include cigarette smoke, hypoxia, hypercapnia and acidosis, metabolic alterations of several types

including vitamin D and testosterone deficiencies, systemic inflammation and co-morbidities.^{5,6,29}

In patients with COPD, limb muscle strength is a determinant of the level of physical activity³⁰ and of functional capacity⁴. Moreover, muscle strength is related to dyspnea as well as to quality of life.^{10,8} Quadriceps muscle strength significantly predicts mortality in COPD⁸, while weakness is associated with impaired balance and an increase risk of falls.³¹ Despite its clinical relevance, muscle strength mostly reflects the action of fast-twitch fibers³² and represents only one aspect of limb muscle function.¹³ Limb muscle endurance, defined as the muscle's ability to sustain or repeat a specific task over time,³³ and muscle fatigability, the reversible reduction in force generated by the muscle during a given task, reflect other aspects of muscle function such as muscle oxidative capacity and oxygen supply³⁴ that are relevant to the endurance tasks that are part of daily life physical activities of patients with COPD.^{35,36} Limb muscle endurance is also related to walking capacity and upper limb muscle function in COPD.²² An important concept is that strength and endurance cannot be predicted from each other as they reflect different muscle properties.³⁷ Understanding that strength and endurance are both clinically important and that they reflect different muscle properties is important in the design of rehabilitative interventions aimed at improving limb muscle function in COPD.

Pulmonary rehabilitation (PR)

PR is an individualized, comprehensive and multidisciplinary approach that involves exercise training, education, psychosocial support, and nutritional interventions, in order to promote better self-management of the disease, minimize symptom burden, optimize functional status, and increase participation in activities of daily life.^{38–41} Body composition abnormalities (such as weight loss and muscle wasting) are prevalent in COPD.^{6,42} Sarcopenia has been reported in about 15% of patients with COPD and impairs function and health status of the individual patient. Patients with COPD and sarcopenia have reduced exercise capacity, functional performance, level of physical activity and health status compared with patients with COPD without sarcopenia.⁴³ Nutritional interventions, dietary counseling, food fortification, and supplementation^{44,45} are recommended and may be efficient for increasing weight, fat-free mass, exercise tolerance as well as survival in compliant patients. Educational sessions should address smoking cessation, basic information about COPD and pathophysiology of the disease, general approach to therapy and specific aspects of medical treatment, strategies to help minimize dyspnea, advice about when to seek help, self-management and decision making during exacerbations, and advance directives and end-of-life issues.^{3,46} PR is perhaps the best example of evidence-based medicine in pulmonology as it improves, among other things, exercise capacity, health-related quality of life, as well as relieving dyspnea and fatigue.⁴⁷ Risks of hospitalization, mortality,^{38,47} and healthcare utilization costs⁴⁸ are also reduced with PR. Although there is currently no consensus regarding the optimal duration of a PR program, the current recommendations suggest 8–12 weeks, while keeping in mind that extending this length

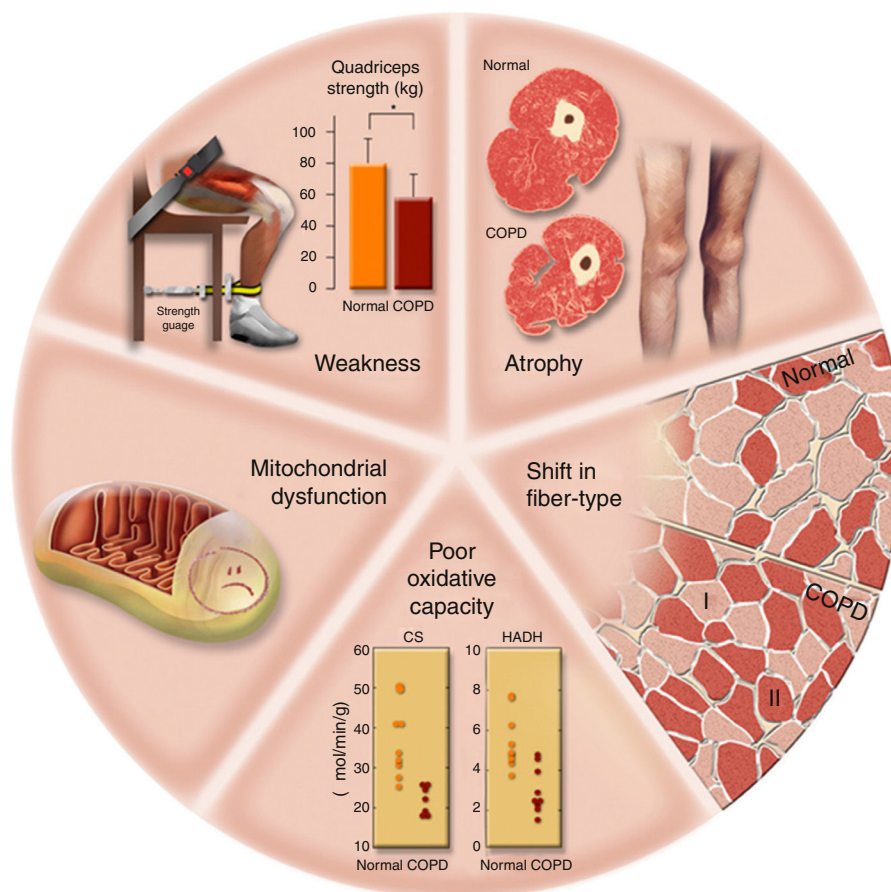


Figure 1 Morphological and structural alterations reported in limb muscles in patients with chronic obstructive pulmonary disease (COPD). CS, citrate synthase; HADH, 3-hydroxyacyl CoA dehydrogenase. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society.

might benefit patients who need more time to achieve clinical improvements.^{38,49} Even though the content of PR may vary depending on factors such as healthcare systems, resources, personnel or settings, individually tailored exercise training is considered the cornerstone of PR.⁴⁷ Whole body aerobic training involving upper and lower extremities and strengthening exercises are recommended components of exercise training in patients with COPD.⁴⁰ Exercise training within the context of PR is also considered one of the best available means to improve limb muscle function in COPD, demonstrating increase limb muscle strength, limb muscle endurance as well as reduced fatigability.⁴⁰

It is recommended that an exercise assessment be carried out before commencing PR and exercise training in order to tailor the exercise prescription to the individual's specific requirements and goals.^{40,50} Such an assessment should include evaluation of exercise capacity and of muscle function. Design of exercise programs should always be based on the foremost principles of exercise training, including but not limited to, the principles of specificity, progressive overload and variation⁵¹ (Table 1). Firstly, the principle of specificity states that all training adaptations are specific to the stimulus applied.⁵² Second, the above discussion about muscle strength,⁵³ endurance and fatigability implies that specific interventions are required to address these

different aspects of muscle function. Lastly, specific aims of the training should be kept in mind in designing the program.

Increasing limb muscle strength

In the latest official American Thoracic Society/European Respiratory Society (ATS/ERS) statement on key concepts and advances in PR, increasing muscle strength was highlighted as an important goal of rehabilitation in COPD.⁴⁰ Aerobic exercises such as walking and cycling have been found to increase muscle strength in patients with COPD.^{37,54,55} Aerobic exercise, either of interval or constant-load modalities also increases muscle cross-sectional area (CSA)^{56–58} and reduces the proportion of type IIx fibers in the quadriceps.^{57,58} Metabolic adaptations, such as, but not limited to, increased oxidative capacity of the quadriceps muscle and reduction in exercise induced lactic acid production are also seen after aerobic training protocols in patients with COPD.^{6,57,58} Even though the optimal intensity is still debatable, higher intensities (>60% of maximal work rate) seems to be preferable over lower aerobic training intensities to induce a physiological adaptation to training.⁵⁹

Nevertheless, if the goal is to improve muscle strength, resistance training has a greater potential than aerobic

Table 1 Principles of exercise training.

Principles	Description	Considerations when designing exercise training
Specificity	All training adaptations are “specific” to the stimulus applied	Physiological adaptations are determined by various factors including: (i) muscle actions involved, (ii) speed of movement, (iii) range of motion, (iv) muscle groups trained, (v) energy systems involved and (vi) intensity and volume of the exercise performed.
Progressive overload	For continuous adaptations to occur a gradual increase of stress placed upon the body during exercise is necessary	Alternating one or more of the following: (i) exercise intensity (i.e., loading), (ii) duration, (iii) repetition speed, (iv) rest periods, (v) training volume and (vi) training frequency could be done for progressive overload.
Periodization (variation)	As the human body adapts to a specific training stimulus a systemic variation/alteration of one or more program variable(s) are necessary for long-term progression	Several modes of variation are available including (i) classic periodization (high initial training volume at a low intensity where volume decreases and intensity increases as training progresses), (ii) reverse periodization (low initial training volume at a high intensity where volume increases and intensity decreases as training progresses and (iii) nonlinear periodization (rotation of exercise protocols to allow variations in intensity and volume).

training protocols.⁴⁰ Greater effects on muscle strength are obtained with resistance training in comparison to aerobic training or when resistance training is added to an aerobic training protocol.^{40,55,60–62} The tolerability of resistance training is also considered to be superior to that of aerobic training since it results in less exercise induced dyspnea,⁶³ allowing more patients to reach targeted exercise intensities, thus optimizing the effect of the exercise performed. As all training adaptations are specific to the stimulus applied (principle of specificity),⁵² greater effects on muscle strength are expected with resistance training protocols as these regimens are specifically designed for increasing muscle strength, particularly when they use fairly large weights and a low number of repetitions (often 8–15 repetitions).^{62,64} In contrast, aerobic based protocols (involving submaximal contractions over a long time, normally 20–60 minutes or more)⁴⁰ use a different exercise setup that might not be optimal to increase limb muscle strength.⁵²

Muscle fiber CSA, arrangement of muscle fibers according to their pennation angle, muscle length, joint angle and contraction velocity are all factors influencing muscle strength.^{6,52} Increases in mid-thigh CSA, diminished inflammation and stimulation of satellite cells (which maintain muscle mass and contribute in muscle fibers regeneration)⁶⁵ have all been shown after resistance training regimes in COPD. Other limb muscle adaptations following resistance training included upregulation of muscle insulin-like growth factor-I system as well as of myogenic regulatory factors.⁶⁶

The optimal resistance training prescription for patients with COPD has yet to be determined.⁴⁰ The American College of Sports Medicine (ACSM) guidelines for enhancing muscle strength in older adults are useful to consider for patients with COPD (Table 2). The ACSM recommends performing

resistance training, 1–3 sets of 8–12 repetitions undertaken against high load on 2–3 days each week. Initial loads equivalent to either 60–70% of the one repetition maximum (1 RM) (that is, the maximal load that can be moved only once over the full range of motion without compensatory movements) or one that evokes fatigue after 8–12 repetitions are recommended. It is further proposed that exercise dosage must increase over time (following the exercise principle of progressive overload) to facilitate improvements in muscular strength and muscle mass).^{40,52} This overload can be achieved by increasing the resistance or weight, increasing the repetitions per set, increasing the number of sets per exercise, and/or decreasing the rest period between sets or exercises.^{52,67} (Table 1). The majority of studies that have investigated the effects of resistance training on muscle strength in COPD have used exercise approaches similar to the ACSM recommendations.⁶⁴ Nevertheless, other resistance training approaches, such as 4 sets of 5 repetitions at 85–90% of 1 RM,⁶⁸ 6–8 repetitions at 70–85% of 1 RM^{66,69} and even 2 sets of 20–25 repetitions at 40–55% of 1 RM have demonstrated significant increases in muscle strength among patients with COPD.^{70,71}

In addition to aerobic and resistance training protocols, transcutaneous neuromuscular electrical stimulation (NMES) training may also increase muscle strength in COPD.⁷² The technology induces muscle contractions by depolarizing motor neurons through the application of an electrical current via electrodes placed on the skin over the targeted muscles. NMES is a feasible alternative to resistance training in severely disabled patients in whom the tolerance to traditional whole body training might be compromised.^{72,73} High-frequency NMES, is recommended over low-frequency NMES and has shown comparable muscle strengthening effects than resistance training in severely dyspneic patients

Table 2 Resistance training recommendations for improving limb muscle function.

	Limb muscle strength	Limb muscle endurance
Muscle actions	Concentric, isometric and eccentric	Concentric, isometric and eccentric
Intensity (loading)	60–70% of 1 RM or fatigue after 8–12 repetitions	15–25 repetitions or more, approximately 45–65% of 1 RM
Volume	1–3 sets	1–3 sets
Exercise selection	Unilateral and bilateral single- and multiple-joint exercises.	Unilateral and bilateral single- and multiple-joint exercises.
Exercise order	Perform large muscle group exercises before small muscle group exercises, multiple-joint exercises before single-joint exercises, higher-intensity exercises before lower-intensity exercises, or rotation of upper and lower body exercises or performing one exercise for a specific muscle group followed by an exercise for the opposing muscle group (agonist–antagonist)	Exercise order is not as important as during limb muscle strength training
Velocity of muscle action	Slow and moderate velocities (1–2 s or higher in concentric and eccentric phase of the movement)	Moderate to fast velocities for high repetitive (15–20 repetitions or more)
Rest periods	2–3 min between sets	1–2 min between sets
Frequency	2–3 days per week	2–3 days per week
Progression	Increase with up to 10% when current workload could be performed for 1–2 repetitions over targeted for two consecutive sessions	Increase with up to 10% when current workload could be performed for 1–2 repetitions over targeted for two consecutive sessions

RM, repetition maximum.

with COPD.⁷⁴ NMES could also be an alternative for home use and in this context, may increase in type II fiber CSA with a decrease in type I fiber CSA of the quadriceps muscle in patients with COPD.⁷⁵

Increasing limb muscle endurance

Limb muscle endurance is decreased among patients with COPD, often to a larger magnitude than strength.^{18,76} Limb muscle endurance is also seemingly more closely related to walking capacity as well as to upper limb muscle function than limb muscle strength in this group of patients.²² However, although the effects of PR on limb muscle strength are well documented, the effect of PR on limb muscle endurance has not been investigated to the same extent. Available data suggest that exercise training improves lower as well as upper extremity functional capacity, demonstrated by increased walking capacity, arm endurance and arm function following eight weeks of high-repetitive resistance training.⁷⁰ The decrease in limb muscle endurance reported in patients with COPD is at least partly related to intrinsic muscle abnormalities, and the need to include some forms of muscle-specific training is warranted if one goal of PR should be to increase limb muscle endurance.¹⁸ There are currently no specific recommendations on how to increase limb muscle endurance among patients with COPD. ACSM nevertheless suggests that healthy adults perform multiple sets of resistance exercises using light loads involving 15–25

repetitions or more, 2–3 days each week with moderate to fast repetition velocities and rest periods between 1 and 2 min (Table 2). There is no specific recommendation concerning the percentage of 1 RM at which exercises should be performed,⁵² but 40–65% of 1 RM has been used during resistance training among patients with COPD allowing 15–25 repetitions per set. This strategy was followed by Nyberg et al. 2015, incorporating upper and lower extremity exercises performed during 25 repetitions at 55% of 1 RM and it resulted in increases in both upper and lower limb muscle endurance as well as increases in quadriceps strength, walking distance and arm function.⁷⁰ A similar approach was used by Wurtemberger and Bastian,⁷¹ however no measurements of limb muscle endurance was performed. Another type of low intensity limb muscle training was tested by Clark et al.⁷⁷ and was composed of 10 upper and lower-body home exercises undertaken for 30 s (with 15-s progressions up to 60 s) every day during 12 weeks with only body weight used as resistance. These authors reported increased isotonic upper (shoulder flexion) and lower (knee extension and flexion) limb muscle endurance, and reduced ventilation during exertion in the trained group compared to the control group. Finally, a study by Arnardottir et al.⁷⁸ also utilized a high number of repetitions, (15–20 repetitions at 65% of 1 RM), however no assessment of limb muscle function was incorporated. Intrinsic mechanisms explaining the effects of high-repetitive resistance training on limb muscle endurance in patients with COPD still require further investigation. In healthy untrained men, an increased

percentage of type IIAX muscle fibers, myosin heavy chain isoform and muscle CSA have been demonstrated following eight weeks of high-repetitive (20–28 RM) resistance training.⁷⁹ In addition to being associated with improved limb muscle endurance, high-repetitive resistance training may also improve oxygen uptake and increased maximal mitochondrial respiration in trained muscles.⁸⁰

Quadriceps muscle endurance could also be improved using NMES in patients with COPD.⁷⁴ Even though high-frequency NMES seem to result in greater improvements of muscle endurance than low-frequency NMES, both low- and high-frequency NMES have shown effects on muscle endurance comparable of those achieved from a strength training protocol.⁷⁴ However, interpretation of the comparable results on limb muscle endurance should be treated with caution considering that the strength training protocol used included 4 sets of 8 repetitions at 70% of 1 RM, i.e., not in line with ACSM recommendations for increasing limb muscle endurance.⁵² Lastly, phototherapy with combination of super-pulsed laser and light-emitting diodes can increase quadriceps muscle endurance when compared to a placebo treatment. However, the trial was small and the effect in comparison to a resistance training protocol was not investigated.⁸¹

Studies using aerobic exercise modalities (e.g., interval or continuous cycling protocols) often lack specific assessment of the limb muscle.¹⁸ Nevertheless, quadriceps muscle endurance was evaluated by O'Donnell et al.,³⁷ who did not see any changes in quadriceps muscle endurance following 6 weeks of walking, treadmill and cycling exercises for the lower limbs. The main focus of aerobic training studies has been to demonstrate the positive impact of exercise training on muscle determinants of muscle endurance such as muscle fiber capillarization, mitochondrial density and oxidative capacity.^{57,82} More research on the specific effects of aerobic training on limb muscle endurance is warranted.

Discussion

If the goal of exercise training is to improve specific aspects of limb muscle function such as strength and endurance, resistance training should be preferred over other available exercise modalities within PR. Resistance training protocols seem superior to aerobic training protocols with regard to increasing limb muscle function, especially limb muscle strength, in patients with COPD.^{37,40,52,55,60–62} Other exercise alternatives such as high-frequency NMES are feasible, especially in more severe patients,⁷² but more studies are needed to compare their effects with those of traditional exercise training protocols.

The requirements for improving limb muscle strength or endurance are different and this has serious implications for the exercise training approach to be used for optimal benefits. The exercise programs should be built on the founding principles of exercise training (progressive, overload, specificity and variation) (Table 1) and individualized and adapted to the specific goals of treatment. It would seem advisable to follow ACSM recommendations^{40,52} for increasing limb muscle strength or limb muscle endurance (Table 2).

The vast majority of resistance training regimens, aimed at improving limb muscle function in patients with COPD

has used weight machines as a primary choice of exercise equipment.^{62,64} However, there is a growing evidence in COPD that exercise training using minimal equipment such as body weight and/or elastic resistance bands is also effective in improving both limb muscle strength and limb muscle endurance.^{70,83,84} The use of elastic resistance bands is also considered clinically applicable both for patients as well as care providers and could be considered a practicable and less costly alternative to weight machines,⁸⁵ that could be more easily implemented outside specialized centers. The principle of progressive overload and, to some extent, the principle of specificity have been used in resistance training regimes for patients with COPD. However, variation or periodization which could be done by systemic variations of, for example, exercise volume and intensity, is rarely incorporated. Since the body adapts quickly to exercise regimens, variations in training parameters may help to ensure continual progression and optimization of the training intervention.⁵² Classic, reverse or undulation variation strategies could theoretically be used, however data on patients with COPDs are lacking.⁴⁰ In one study, nonlinear exercise training was found to be superior to traditional non-varied exercise training with regard to improving aerobic work capacity on cycle ergometry.⁸⁶ The potential use of nonlinear periodization in resistance training for improving limb muscle function among patients with COPD is interesting, but has yet to be investigated. Since improving limb muscle strength and endurance requires different exercise approaches, a periodized exercise approach including both high load, low-repetitive (muscle strength) and low load, high-repetitive (muscle endurance) components would appear to be a promising approach in this group of patients.

Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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References

- Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370:741–50.
- Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006;28:523–32.
- Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187:347–65.
- Butcher SJ, Pikaluk BJ, Chura RL, Walkner MJ, Farthing JP, Marciniuk DD. Associations between isokinetic muscle strength, high-level functional performance, and physiological parameters in patients with chronic obstructive pulmonary disease. *Int J Chronic Obstr Pulm Dis*. 2012;7:537–42.
- Barreiro E, Respiratory Gea J. Limb muscle dysfunction in COPD. *COPD*. 2015;12:413–26.
- Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2014;189:e15–62.
- Marquis K, Debigaré R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166:809–13.
- Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ, et al. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax*. 2007;62:115–20.
- Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med*. 2000;94:859–67.
- Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J*. 1997;10:417–23.
- Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med*. 1996;153:976–80.
- Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med*. 1995;152:2021–31.
- Coronell C, Orozco-Levi M, Mendez R, Ramirez-Sarmiento A, Galdiz JB, Gea J. Relevance of assessing quadriceps endurance in patients with COPD. *Eur Respir J*. 2004;24:129–36.
- Houchen L, Steiner MC, Singh SJ. How sustainable is strength training in chronic obstructive pulmonary disease. *Physiotherapy*. 2009;95:1–7.
- Nyberg A, Saey D, Maltais F. Why and how limb muscle mass and function should be measured in patients with COPD. *Ann Am Thorac Soc*. 2015;12:1269–77.
- Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WD, Jackson A, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur Respir J*. 2010;36:81–8.
- Mador MJ, Kufel TJ, Pineda LA, Steinwald A, Aggarwal A, Upadhyay AM, et al. Effect of pulmonary rehabilitation on quadriceps fatiguability during exercise. *Am J Respir Crit Care Med*. 2001;163:930–5.
- Evans RA, Kaplovitch E, Beauchamp MK, Dolmage TE, Goldstein RS, Gillies CL, et al. Is quadriceps endurance reduced in COPD? A systematic review. *Chest*. 2015;147:673–84.
- Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulmonary Rehabil*. 2000;20:353–60.
- Franssen FM, Broekhuizen R, Janssen PP, Wouters EF, Schols AM. Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. *Med Sci Sports Exerc*. 2005;37:2–9.
- Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. *Eur Respir J*. 2000;15(1):92–7.
- Nyberg A, Törnberg A, Wadell K. Correlation between limb muscle endurance, strength and functional capacity in individuals with chronic obstructive pulmonary disease. *Physiother Can*. 2016;68:46–53.
- Janaudis-Ferreira T, Wadell K, Sundelin G, Lindstrom B. Thigh muscle strength and endurance in patients with COPD compared with healthy controls. *Respir Med*. 2006;100:1451–7.
- Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med*. 1995;152:2021–31.
- Shoup R, Dalsky G, Warner S, Davies M, Connors M, Khan M, et al. Body composition and health-related quality of life in patients with obstructive airways disease. *Eur Respir J*. 1997;10:1576–80.
- Mador MJ, Bozkanat E, Kufel TJ. Quadriceps fatigue after cycle exercise in patients with COPD compared with healthy control subjects. *Chest*. 2003;123:1104–11.
- Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J*. 2005;26:703–19.
- Jobin J, Maltais F, Doyon JF, LeBlanc P, Simard PM, Simard AA, et al. Chronic obstructive pulmonary disease: capillarary and fiber-type characteristics of skeletal muscle. *J Cardiopulm Rehabil*. 1998;18:432–7.
- Gea J, Agusti A, Roca J. Pathophysiology of muscle dysfunction in COPD. *J Appl Physiol*. 2013;114:1222–34.
- Osthoff AK, Taeymans J, Kool J, Marcar V, van Gestel AJ. Association between peripheral muscle strength and daily physical activity in patients with COPD: a systematic literature review and meta-analysis. *J Cardiopulm Rehabil Prev*. 2013;33:351–9.
- Beauchamp MK, Sibley KM, Lakhani B, Romano J, Mathur S, Goldstein RS, et al. Impairments in systems underlying control of balance in COPD. *Chest*. 2012;141:1496–503.
- Ribeiro F, Lepine PA, Garceau-Bolduc C, Coats V, Allard E, Maltais F, et al. Test–retest reliability of lower limb isokinetic endurance in COPD: a comparison of angular velocities. *Int J Chronic Obstruct Pulmon Dis*. 2015;10:1163–72.
- Thompson WRG, Neil F, Pescatello Linda S. ACSM's guidelines for exercise testing and prescription. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
- Bassett DR Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32:70–84.
- Enoka RM, Duchateau J. Muscle fatigue: what, why and how it influences muscle function. *J Physiol*. 2008;586:11–23.
- Bigland-Ritchie B, Furbush F, Woods JJ. Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. *J Appl Physiol*. 1986;61:421–9.
- O'Donnell DE, McGuire M, Samis L, Webb KA. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med*. 1998;157:1489–97.

38. Saey D, Bernard S, Gagnon P, Laviolette L, Soicher J, Maltais F, et al. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Panminerva Med.* 2009;51:95–114.
39. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest.* 2007;131:4S–2S.
40. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* 2013;188:e13–64.
41. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005;172:19–38.
42. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis.* 1993;147:1151–6.
43. Jones SE, Maddocks M, Kon SS, Canavan JL, Nolan CM, Clark AL, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax.* 2015;70:213–8.
44. Weekes CE, Emery PW, Elia M. Dietary counselling and food fortification in stable COPD: a randomised trial. *Thorax.* 2009;64:326–31.
45. Sugawara K, Takahashi H, Kasai C, Kiyokawa N, Watanabe T, Fujii S, et al. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med.* 2010;104:1883–9.
46. Hill K, Holland AE. Strategies to enhance the benefits of exercise training in the respiratory patient. *Clin Chest Med.* 2014;35:323–36.
47. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015;2:CD003793.
48. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax.* 2001;56:779–84.
49. Lee AL, Holland AE. Time to adapt exercise training regimens in pulmonary rehabilitation – a review of the literature. *Int J Chronic Obstruct Pulmon Dis.* 2014;9:1275–88.
50. Andrianopoulos V, Klijn P, Franssen FM, Spruit MA. Exercise training in pulmonary rehabilitation. *Clin Chest Med.* 2014;35:313–22.
51. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. *Med Sci Sports Exerc.* 2004;36:674–88.
52. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2009;41:687–708.
53. Robles PG, Mathur S, Janaudis-Ferreira T, Dolmage TE, Goldstein RS, Brooks D. Measurement of peripheral muscle strength in individuals with chronic obstructive pulmonary disease: a systematic review. *J Cardiopulm Rehabil Prev.* 2011;31:11–24.
54. Skumlien S, Aure Skogedal E, Skrede Ryg M, Bjortuft O. Endurance or resistance training in primary care after in-patient rehabilitation for COPD? *Respir Med.* 2008;102:422–9.
55. Vonbank K, Strasser B, Mondrzyk J, Marzluf BA, Richter B, Losch S, et al. Strength training increases maximum working capacity in patients with COPD – randomized clinical trial comparing three training modalities. *Respir Med.* 2012;106:557–63.
56. Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, et al. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest.* 2011;140:744–52.
57. Vogiatzis I, Terzis G, Nanas S, Stratakos G, Simoes DC, Georgiadou O, et al. Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest.* 2005;128:3838–45.
58. Vogiatzis I, Stratakos G, Simoes DC, Terzis G, Georgiadou O, Roussos C, et al. Effects of rehabilitative exercise on peripheral muscle TNF α , IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax.* 2007;62:950–6.
59. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 1991;143:9–18.
60. Iepsen UW, Jorgensen KJ, Ringbaek T, Hansen H, Skrubbeltrang C, Lange P. A combination of resistance and endurance training increases leg muscle strength in COPD: an evidence-based recommendation based on systematic review with meta-analyses. *Chronic Respir Dis.* 2015;12:132–45.
61. Iepsen UW, Jorgensen KJ, Ringbaek T, Hansen H, Skrubbeltrang C, Lange P. A systematic review of resistance training versus endurance training in COPD. *J Cardiopulm Rehabil Prev.* 2015;35:163–72.
62. O’Shea SD, Taylor NF, Paratz J. Peripheral muscle strength training in COPD: a systematic review. *Chest.* 2004;126:903–14.
63. Probst VS, Troosters T, Pitta F, Decramer M, Gosselink R. Cardiopulmonary stress during exercise training in patients with COPD. *Eur Respir J.* 2006;27:1110–8.
64. O’Shea SD, Taylor NF, Paratz JD. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest.* 2009;136:1269–83.
65. Menon MK, Houchen L, Singh SJ, Morgan MD, Bradding P, Steiner MC. Inflammatory and satellite cells in the quadriceps of patients with COPD and response to resistance training. *Chest.* 2012;142:1134–42.
66. Kongsgaard M, Backer V, Jorgensen K, Kjaer M, Beyer N. Heavy resistance training increases muscle size, strength and physical function in elderly male COPD-patients – a pilot study. *Respir Med.* 2004;98:1000–7.
67. Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation.* 2007;116:572–84.
68. Hoff J, Tjonna AE, Steinshamn S, Hoydal M, Richardson RS, Helgerud J. Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency. *Med Sci Sports Exerc.* 2007;39:220–6.
69. Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, et al. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2002;166:669–74.
70. Nyberg A, Lindstrom B, Rickenlund A, Wadell K. Low-load/high-repetition elastic band resistance training in patients with COPD: a randomized, controlled, multicenter trial. *Clin Respir J.* 2015;9:278–88.
71. Wurtemberger G, Bastian K. [Functional effects of different training in patients with COPD]. *Pneumologie.* 2001;55:553–62.
72. Maddocks M, Nolan CM, Man WD, Polkey MI, Hart N, Gao W, et al. Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. *Lancet Respir Med.* 2016;4:27–36.
73. Sillen MJ, Speksnijder CM, Eterman RM, Janssen PP, Wagers SS, Wouters EF, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest.* 2009;136:44–61.

74. Sillen MJ, Franssen FM, Delbressine JM, Vaes AW, Wouters EF, Spruit MA. Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial. *Thorax*. 2014;69:525–31.
75. Dal Corso S, Napolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, et al. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med*. 2007;101:1236–43.
76. van't Hul A, Harlaar J, Gosselink R, Hollander P, Postmus P, Kwakkel G. Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease. *Muscle Nerve*. 2004;29:267–74.
77. Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur Respir J*. 1996;9:2590–6.
78. Arnardottir RH, Sorensen S, Ringqvist I, Larsson K. Two different training programmes for patients with COPD: a randomised study with 1-year follow-up. *Respir Med*. 2006;100:130–9.
79. Campos GE, Luecke TJ, Wendeln HK, Toma K, Hagerman FC, Murray TF, et al. Muscular adaptations in response to three different resistance-training regimens: specificity of repetition maximum training zones. *Eur J Appl Physiol*. 2002;88:50–60.
80. Brønstad E, Dedichen H, Kirkeby-Garstad I, Wisløff U, Steinshamn S. Effects of one-leg exercise training on mitochondrial function in COPD patients. *Clin Respir J*. 2011;5:9–10.
81. Miranda EF, de Oliveira LV, Antonialli FC, Vanin AA, de Carvalho Pde T, Leal-Junior EC. Phototherapy with combination of super-pulsed laser and light-emitting diodes is beneficial in improvement of muscular performance (strength and muscular endurance), dyspnea, and fatigue sensation in patients with chronic obstructive pulmonary disease. *Lasers Med Sci*. 2015;30:437–43.
82. Rochester CL. Exercise training in chronic obstructive pulmonary disease. *J Rehabil Res Dev*. 2003;40:59–80.
83. O'Shea SD, Taylor NF, Paratz JD. A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with chronic obstructive pulmonary disease: a randomised controlled trial. *Aust J Physiother*. 2007;53:229–37.
84. Alison JA, McKeough ZJ. Pulmonary rehabilitation for COPD: are programs with minimal exercise equipment effective. *J Thorac Dis*. 2014;6:1606–14.
85. Nyberg A, Lindström B, Wadell K. A cohort study to evaluate the feasibility of low load/high repetition elastic band resistance training for people with chronic obstructive pulmonary disease. *Novel Physiother*. 2014;4:190, <http://dx.doi.org/10.4172/2165-7025.1000190>.
86. Klijn P, van Keimpema A, Legemaat M, Gosselink R, van Stel H. Nonlinear exercise training in advanced chronic obstructive pulmonary disease is superior to traditional exercise training. A randomized trial. *Am J Respir Crit Care Med*. 2013;188:193–200.