

Lower limb musculoskeletal biomechanics in patients with chronic obstructive pulmonary disease

Biomecânica musculoesquelética de membros inferiores em pacientes com doença pulmonar obstrutiva crônica

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Abstract

Introduction: The lower limb peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease (COPD) has been considered one of the main limiting factors of physical exercise. Several biomechanical techniques have been used to identify intrinsic and extrinsic muscular tissue characteristics in response to different types of acute and/or chronic physical stress. This study aimed at identifying the most discussed issues in the specific literature related to peripheral muscle dysfunction in COPD. **Methodology:** A digital search was conducted in the following databases: Periódicos CAPES, PubMed and Medline. **Results:** Three main themes were identified: 1) morphological metabolic muscle changes in COPD; 2) skeletal muscle mechanical properties in COPD; 3) the effect of acute and chronic exercise in patients with COPD. A total of thirty-two medical journals in the areas of pneumology, biomechanics, surgery and sports medicine were reviewed. **Discussion:** Changes resulting from muscle dysfunction reduced both force production capacity and resistance to fatigue, leading COPD patients to lower tolerance to exercise. The abnormal inflammatory response contributed to the occurrence of oxidative stress and to decreased formation of antioxidant agents. These factors limit muscle metabolism and decrease both the tissue's structure and function. **Conclusion:**

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Higher levels of hypoxemia and inflammation determined lower force capacity and muscle resistance in patients with COPD, which is not observed in subjects with preserved muscle mass.

Keywords: COPD; Muscle Skeletal; Biomechanics; Muscle fatigue; Lower extremity.

Resumo

Introdução: A disfunção muscular periférica de membros inferiores em pacientes com doença pulmonar obstrutiva crônica (DPOC) tem sido considerada um dos principais fatores limitantes do exercício físico. Diversas técnicas biomecânicas são utilizadas para identificar, em diferentes faixas etárias, sexos e níveis de doenças características extrínsecas e intrínsecas do tecido muscular em resposta ao estresse físico agudo e/ou crônico. Desta forma, este trabalho tem o objetivo de identificar os temas mais abordados pela literatura, em relação à disfunção muscular periférica na DPOC. **Metodologia:** Para a realização deste estudo, foi realizada pesquisa digital no Portal de Periódicos Capes, Pub Med e Medline. **Resultados:** Três principais temas foram identificados: 1) alterações morfológicas musculares na DPOC; 2) propriedades mecânicas musculares na DPOC; 3) Efeito do exercício agudo e crônico na disfunção muscular periférica de membros inferiores em pacientes com DPOC. Um total de 32 revistas voltadas a áreas médicas como pneumologia, biomecânica, cirurgia e medicina do esporte foram consultadas. **Discussão:** Alterações decorrentes da disfunção muscular reduzem a capacidade de produção de força e resistência à fadiga, o que leva indivíduos com DPOC a apresentarem menor tolerância ao exercício. Ainda é possível observar uma resposta inflamatória anormal, o que pode aumentar o estresse oxidativo e prejudicar a formação de agentes antioxidantes. Todas estas situações limitam o metabolismo muscular e alteram a estrutura e a função deste tecido. **Conclusão:** Foi possível observar que altos níveis de hipoxemia e inflamação reduzem a capacidade de força e resistência muscular. Este fato não é observado em indivíduos com a massa muscular preservada.

Palavras-chave: DPOC; Músculo esquelético; Biomecânica; Fadiga muscular; Membro inferior.

Introduction

The chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible and is accompanied by changes in peripheral skeletal muscles (1-3). Nowadays, is considered as the third leading cause of death worldwide and by the year 2020 will be among the five most common causes of functional impairment (4, 5). Smoking is the major etiologic factor of COPD, because the prolonged exposure to toxic substances contained in a cigarette causes a harmful effect on central and peripheral airways as well as on pulmonary parenchyma and vessels. The bronchial wall inflammatory process leads to further mucus production and destruction of the alveolar walls (3-6).

Dyspnea is the major symptom of the disease, and is usually accompanied by worsening of ventilation, especially during exercise. Three main factors contribute to the increase of dyspnea during exercise, and they are: 1) impairment in gas exchange due to reduced lung surface area, 2) pulmonary hyperinflation generated by destruction of alveolar elastic matrix and 3) muscle dysfunction (6-8).

Although the destruction of the lung area and the hyperinflation are important factors in the development and progression of the disease, muscular weakness has been considered by many studies as the main co-morbidity of COPD, being a potent predictor of mortality independent of lung function (1, 9, 10).

However, the maintenance of muscular tension depends on its intrinsic and extrinsic capacities,

and these are influenced by many COPD risk factors (9, 11, 12). The literature classifies pathological factors in COPD in local and systemic (2-4,10). Among the local factors, we found reduced muscle contractility during daily life activities, local inflammation and alterations in the muscle redox system. The systemic factors are malnutrition, treatment with systemic steroids, hypoxemia, hypercapnia and pulmonary inflammation (11, 13, 14).

One of the main evidence related to muscular dysfunction is the slow-twitch fibers metabolic decrease, which leads to muscle atrophy. This selective atrophy determines an increased percentage of fast-twitch fibers compared to healthy subjects. However, this selective atrophy seems to occur in smaller magnitude in the upper limb muscles compared to the lower limb muscles. This seems to be related to a preservation of daily life activities with the use of the upper limbs (11, 13, 15-17).

The large lower limb muscle impairment causes difficulties for COPD patients when there is a need for higher degrees of physical demand, leading to an early termination or interruption of exercise due to dyspnea symptoms. Thus, the muscle tissue is significantly changed and its biomechanical properties are compromised (13, 16, 18).

The characterization of the muscle structure and function is important to identify the responsiveness of this tissue to overload induced by exercise during the periodization of a physical training. Therefore, this article aims to review the current literature on the biomechanics of the lower limb muscles of patients with COPD and to present the main clinical aspects to be considered during and after exercise which can help organize physical training programs.

Methods

In this study, a digital research was conducted on existent journals in CAPES database, Pub Med, Scopus and Medical Literature Analysis and Retrieval System Online (Medline). The inclusion criteria and the localization of the relevant subjects, as well as the delimitation of the topic were done in articles published preferable between the years 2005 and 2011, and by key words such as: COPD, skeletal muscle, biomechanics, muscle fatigue and lower limb.

Results

After the search on all databases, a total of 119 manuscripts were selected. From this total, 73 manuscripts were excluded because they were related to surgical and pharmacological interventions, and also because they did not consider the peripheral muscle dysfunction. Therefore, the 46 remaining manuscripts were used in this review.

The research material identified three main themes directly associated with musculoskeletal biomechanics of the lower limbs in patients with COPD. They are: 1) morphological and metabolic alterations in COPD muscle, 2) muscle mechanical properties in COPD, 3) acute and chronic exercise effects on peripheral muscle dysfunction of the lower limbs in patients with COPD. The manuscripts were distributed in 32 peer-review journals in the areas of pneumology, biomechanics, surgery and sports medicine.

Lower limb muscles morphological and metabolic changes in COPD

The loss of muscle mass is a common finding in chronic conditions such as cancer, human immunodeficiency virus (HIV), infection and COPD, and all these conditions are related to

limitations in performing physical exercise, reduction in quality of life and increased mortality (11, 24). A large proportion of the population with COPD is above 50 years, which also leads to a reduced contractility of the muscle associated with aging, so that it becomes difficult to differentiate the effects deriving from the disease of those from the natural aging process.

A study evaluated, by magnetic resonance imaging (MRI), the anatomical cross-sectional area (CSA) and the muscle volume (Vol) of the thigh muscles (quadriceps, hamstrings and adductors), and correlated those variables with measures of circumference of the lower limb in 20 healthy elderly subjects, compared with 20 elderly patients with COPD. The authors observed a reduction in CSA of the thigh muscles in three different regions: a) proximal portion 30% of the thigh (adductor reduction), b) middle portion 50% of the thigh (quadriceps reduction) c) distal portion 80% of the thigh (quadriceps and hamstrings reduction). They also identified a reduction in muscle volume of the quadriceps, hamstrings and adductors (20).

The literature also compares the capacity of knee extensor strength normalized by lean mass of the lower limbs of patients with COPD to the healthy group. They evaluated the lean mass using dual X-ray absorption (DEXA). In addition, they assessed the isokinetic and isometric force and total work (Wt). The authors observed a reduced ability to produce power in all situations in patients with COPD compared with controls (21).

All of these previously described evidences show the existence of changes in the type and size of muscle fibers. Studies evaluating the cellular structure using biopsy showed that muscles of patients with COPD are not changed in the amount of muscle fibers, but there is a significant selective atrophy. It is further identified a larger atrophy of type I slow fibers as well as type IIa fast intermediate fibers, and consequently there is an increase in the percentage of type IIb fast fibers. Those studies suggest that muscle inactivity and prolonged hypoxia are the main causes of the increased percentage of type IIb fast fibers, which may reduce the capacity of maintaining force during any physical activity (20, 22).

Associated with reduced muscle mass, it is also observed a lower capillarization of muscle tissue. Simard et al. (23) showed, using electron microscopy, that the number of capillaries per area of the vastus lateralis muscle in COPD patients was 53% lower than in healthy subjects. However, the authors found that there was no difference in the number of mitochondria per unit of area between the groups. The authors also found a reduction of 59% in the ratio between the number of capillaries and the amount of mitochondria, which may explain an impaired distribution of nutrients within the muscle cell. It is known that low capillarity can reduce the levels of myoglobin by 25%, which contributes to the deficit of oxygen in the muscle (24). These changes alter the levels of oxidative enzymes such as citrate synthase, succinate dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase, and these alterations do not occur in the glycolytic enzymes such as lactate dehydrogenase and hexokinase (20, 25, 26).

Thus, the mentioned changes cooperate in some way to muscle metabolism loss. Studies using magnetic resonance spectroscopy provide non-invasive measurements of bioenergetics in skeletal muscle at rest, during exercise and recovery. One of the main findings of this technique is the determination of the amount of high energy phosphate and phosphocreatine (PCr), as well as inorganic phosphate (Pi), the spectrum of adenosine triphosphate (ATP) and intracellular pH. The recovery rate of PCr following from submaximal exercise is a measurement used to assess mitochondrial capacity tissue. Therefore, the relationship $PCr/(PCr+Pi)$ and ATP concentrations are often used to evaluate changes in metabolism. When this ratio is high, there is a high consumption of energy by the tissue. Changes in the

ratios PCr/Pi or PCr/(PCr+Pi) are dependent on the aerobic metabolic rate, which a decrease indicates a low utilization of aerobic metabolism²⁰. In patients with COPD, the ratio PCr/Pi is decreased and this is one reason for the low recovery after exercise (27, 28).

Hypoxia may also be associated with some type of muscular dysfunction, such as the inability to maintain the force in response to a specific load (fatigue) (29, 30). It may also increase the secretion of leptin, which is a hormone responsible for the inhibition of appetite causing a state of cachexia due to the reduction in the quantity of nutrients to the muscle tissue (10, 30-32). Furthermore, activation of inflammatory cytokines due to low oxygen concentration in muscle and a strong correlation between inflammatory mediators and muscle weakness in those patients have been described (10, 30, 32).

Muscle mechanical properties in COPD

The mechanical property of a muscle is its ability to generate tension in response to a stimulus. Therefore, the changes observed in patients with COPD mentioned in the previous session should necessarily produce changes in muscle mechanical properties.

A preserved strength of the adductor pollicis and the diaphragm is observed in patients with COPD when compared to normal subjects; however, the force of the quadriceps muscle is reduced in those patients. The authors reported that the atrophy of the lower limbs was associated with smaller walking distance tests such as the six-minute walk and with a reduction in the maximum oxygen consumption during cycloergometer tests (33). Thus, it appears that reduced muscle mass directly affects the lower limb muscle properties in COPD patients.

Some techniques are able to identify the contractile behavior and muscle strength and endurance (27, 33, 35). One of the most widely used techniques for biomechanical evaluation is the ratio of muscle strength and frequency of artificial electrical stimulation. When this test is performed by patients with COPD, a shift to the right in the ratio is observed when compared to subjects with normal muscles that have a higher percentage of slow twitch fibers. It is known that, in submaximal frequencies during this test, slow twitch fibers produce more power than fast twitch fibers due to the summation process during tetanic contraction that occurs at lower frequencies. Physiologically speaking, this difference is determined by the release of Ca²⁺ of the sarcoplasmic reticulum in a given frequency of activation. However, due to the hypoxia in the muscle tissue caused by the COPD, changes in muscle cell pH of patients with COPD alters the kinetics of Ca²⁺, which impairs the process of excitation-contraction coupling and the return of this ion to the sarcoplasmic reticulum (4, 30). This causes a shift of the force-frequency curve toward higher frequencies of stimulation. In other words, the summation process of maximum power during tetany only occurs at higher frequencies of stimulation. This suggests that differences should exist in the capacity of maximum voluntary force between patients with COPD and healthy subjects.

On the other hand, the contractile properties and morphology of the knee extensors of 16 subjects with COPD assessed by dynamometry, magnetic resonance imaging and biopsy were compared to 9 healthy sedentary subjects. The authors found no differences between groups in parameters such as maximum voluntary isometric contraction (MVIC) normalized by the CSA of thigh extensors and CSA fibers evaluated by biopsy. However, there was a lower percentage of slow fibers in patients with COPD (26 ± 12%) when compared with the healthy subjects (39 ± 11%) with a concomitant increase in the percentage of type IIb fibers (COPD 20 ± 16%; CONTROL 8 ± 4%). There was no difference between groups in percentage of type II fibers. Furthermore, the authors explained a slight tendency

for a shift in the “in vitro” force-frequency of artificial electrical stimulation relationship to the right, although no significant differences were found for these parameters (34).

Couillard et al. (36) reported that the muscle dysfunction in COPD favors the production of reactive oxygen species. The authors compared patients with COPD to normal subjects. The subjects performed a 30% of maximum voluntary isometric contraction (MVIC) knee extension fatigue protocol at a frequency of 6 contractions per minute. Twitch tests were performed at rest, 10 minutes before and after the fatigue protocol, whereas evaluation of CSA's thigh, MVIC and biopsy of the quadriceps were performed 48 hours after exercise. Biopsy was used to observe muscle fiber type, oxidative stress markers and antioxidants. Regarding evaluation of oxidative stress, a greater amount of lipid peroxidation and oxidative proteins was observed as well as a smaller amount of glutathione peroxidase in patients with COPD. However, the authors also found an inverse correlation between muscle fatigue and levels of oxidative stress markers. No significant difference between groups was found in the twitch at rest normalized by quadriceps CSA. The authors also demonstrated a reduction in thigh CSA in COPD patients compared to healthy subjects. A similar reduction was found in the MVIC. There were no differences in the percentage of fast fibers among the groups; however, there was a lower percentage of type I fibers in COPD patients compared to the control group. According to the authors, these changes have influenced the difference in the ability to support the exercise.

One study assessed the ability to produce maximum voluntary and involuntary isometric contractions, as well as the quadriceps and hamstrings capacity to sustain strength in COPD patients with the same level of lean mass as that of a group of healthy subjects. The authors demonstrated that there was no difference in force, relationship between muscle strength and frequency of artificial electrical stimulation and in the lower limb fatigue resistance between healthy subjects and COPD patients without cachexia (37).

Degees et al. (38) demonstrated that acute hypoxia is not primarily responsible for changes in muscle mechanical properties, but rather interferes with the resistance of the muscle tissue. The authors studied muscle function in healthy women in different situations: a) normoxia and b) hypoxia. Three different tests were used: 1) MVIC, 2) artificial electrical stimulation to obtain the force-frequency relationship, 3) concentric fatigue tests at 30% and 70% of MVIC. There was no difference between groups in the MVIC test, force-frequency relationship and fatigue test at 70% of MVIC. However, the time of sustained strength in the 30% of MVIC fatigue test was lower in the hypoxia group. The authors concluded that acute hypoxemia did not affect the maximum muscle force production in vivo; however, it had a negative effect on muscle strength during contractions of low intensity, possibly causing changes in muscle tissue metabolism.

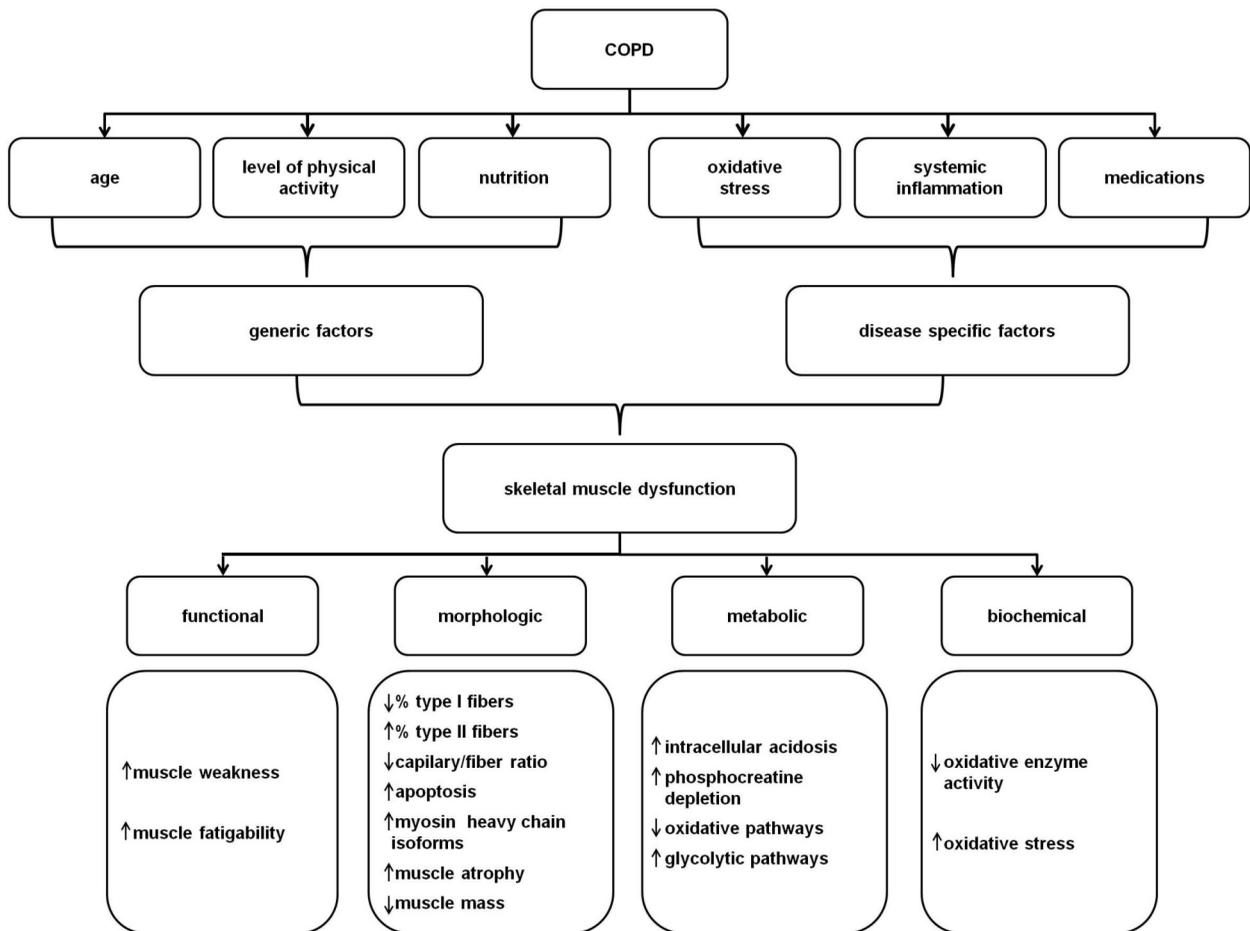
The chronic manifestation of muscle hypoxia without the presence of COPD was also observed. Wüst et al. (8) analyzed the mechanical properties and resistance to muscle fatigue in smokers compared to nonsmokers. There was no difference in the ability to produce power between groups. However, smokers had a lower ability to sustain strength in the fatigue test when compared to nonsmokers. The authors speculated that the low fatigue resistance occurred due to the lower oxygen supply and not due to muscle carbon monoxide in myoglobin, this process being reversed for situations approaching the physical exercise as method of intervention.

The knee extensors mechanical properties between female smokers and nonsmokers were also evaluated (35). The authors found no between-groups difference in quadriceps CSA (measured at 50% of thigh length), isometric torque, CSA/torque ratio and in the knee extensor strength-frequency

of artificial electrical stimulation relationship. However, after using artificial electrical stimulation (30Hz for 2 minutes - on1_s / off1_s) a 17% reduction in torque was observed for smokers compared to nonsmokers.

In general, these results suggest that muscle dysfunction in COPD patients seems to be due to a chronic degree of inactivity, which is secondarily generated after a state of inability to support force due to increased levels of dyspnea. Then, long-term muscle atrophy is established causing an inability to recruit muscle fibers, characterizing a state of inhibition in this tissue. In order to present the muscular changes resulting from COPD, a theoretical organization chart is shown in Figure 1.

Figure 1 | Organogram representing the theoretical mechanism of muscle dysfunction in COPD.



All these changes lead to physical limitations during exercise in COPD patients. Thus, besides characterizing the musculoskeletal system, it also becomes necessary to evaluate the response to different types of physical exercises and / or methods of physical training in those patients.

Effect of acute and chronic exercise in COPD

Exercise intolerance leads to decreased quality of life in COPD patients (36, 39). Physical training is one way to reverse the deleterious effects of muscle dysfunction. By characterizing the musculoskeletal system, volumes and intensities of exercise may be established for different stages in a physical training program.

The increased capacity of muscle strength and endurance contributes to higher exercise intensities without showing higher levels of dyspnea. Thus, lower limb musculoskeletal physical training becomes important for pulmonary rehabilitation programs (18, 41, 46). Table 1 describes the studies that examined the effects of acute and chronic exercise in lower limb musculoskeletal dysfunction of patients with COPD, smokers without COPD or induced hypoxia.

Table 1 | Studies analyzing the mechanical properties of muscle in smokers and COPD patients.

Authors	Sample	Methodology	Conclusion
Wust et al ⁸	Smokers: 19 M; 21W Control: 22 M; 23W	Acute: knee extensors fatigue. Assessments: MVIC; strength x Hz (30Hz 2min – on 1 _s /off 1 _s)	Smokers: + fatigue; = MVIC; = Genders
Malaguti et al ²¹	39 COPD 17 Control	Acute: knee extensors dynamometry. Assessments: isokynetics; isometric; W total; Ratios: maximal isokinetic torque /Muscle Mass; Wtotal/MM	COPD: ↓dynamometry parameters; ↓ratios
Debigare et al ³⁴	16 COPD	Acute: Dynamometry; vastus lateralis biopsy. Assessments: Strength x Hz “in vitro”	COPD: ↑% of type IIb fibers; ↓type I fibers; tendency → Strength x frequency
Morse et al ³⁵	Smokers 9 W with COPD 10 M with COPD	Acute: knee extensors dynamometry. Assessments: MVIC; Strength x Hz	↓17% in the ratio Strength x Hz
Degens et al ³⁷	9 W with COPD 9 Control	Acute: knee extensors dynamometry. MVIC: quadriceps and hamstrings. Strength x Hz quadriceps	= Muscle strength = Strength x Hz
Degens et al ³⁸	N=10 1 ^a Hipoxia 2 ^a Normoxia	Acute: knee extensors dynamometry. Assessments: MVIC; Strength x Hz Strength x time 70% MVIC Strength x time 30% MVIC	Hipoxia group: + fatigue in 30% (MVIC)
Couillard et al ³⁶	12 COPD 10 Control	Acute: quadriceps fatigue (6 contractions / min.- 30% MVIC) Assessments: vastus lateralis biopsy, maximal magnetic stimulation (10 minutes before and after exercise); MVIC	COPD: ↓% of type I fibers; ↑lipoperoxidation; ↑ oxidized proteins; ↓glutathione peroxidase; ↑ resistance and fatigue ↓oxidative stress
Mador et al ⁴⁰	9 COPD 9 Control	Acute: cycloergometer. COPD:60% Wmax to exhaustion. Control: 60%Wmax of COPD to exhaustion Assessment: quadriceps fatigue	COPD: + quadriceps fatigue

Table 1 | Studies analyzing the mechanical properties of muscle in smokers and COPD patients. Conclusion

Authors	Sample	Methodology	Conclusion
Hoff et al ⁴¹	6 COPD 6 Control	Chronic: training (85-90% of 1MR). Knee extensors dynamometry. Assessments: force production rate; mechanical efficiency (VO ₂ max. – VO ₂ rest./ W on cycloergometer)	↑rate of force development 105±22.8%. ↑Mechanical efficiency 32±7%
Mador et al ⁴²	21 COPD	Chronic: treadmill and cycloergometer. Assessments: MVIC pre e post training. Quadriceps fatigue	↑fatigue resistance in patients with COPD. Aerobic training: ↑MVIC by 15±5% ↓peripheral muscular
Vogiatzis et al ⁴³	10 COPD constant load 10 COPD interval load	Chronic: interval training x constant load training in cycloergometer. Assessments: vastus lateralis biopsy; dyspnea and knee extensors discomfort	Both groups: ↑all morphological and biochemical variables of vastus lateralis. Interval group: ↓discomfort lower limbs; ↓dyspnea
Mador et al ⁴⁴	11 COPD combined training 13 COPD aerobic training	Chronic: combined training x aerobic training. Assessments: 1RM, exercises: knee extension, knee flexion, pec deck flyes, pulldown Fatigue pre and post cycloergometer.	Combined training ↑ strength of quadriceps and latissimus dorsi when compared to aerobic training
Ortega et al ⁴⁵	17 COPD resistance training 16 COPD aerobic training 14 DPOC Combined training	Chronic: 12 weeks of training and 12 weeks of detraining. Comparisons: strength training, aerobic and combined training. Assessments: strength pre and post training and detraining: rowing; pec deck flyes; development; knee extension and flexion. Aerobic evaluation on cycloergometer.	Post-training: improves de specificity of each training. Detraining: ↓in the strength training on pec deck flyes, rowing, knee flexion. Aerobic training: = dyspnea levels and quality of life

Quadriceps fatigue levels in COPD patients were evaluated by an interpolated twitch test during MVIC before and after maximal exercise on a cycle ergometer (10, 30 and 60min) before and after a protocol of cardiopulmonary rehabilitation. The patients performed exercises on a cycle ergometers or a treadmill three times a week for eight weeks. After training there was an increase in quadriceps fatigue resistance and in MVIC performed after rehabilitation. The authors reported that a training program on a treadmill and on a cycle ergometer had a positive effect on capillarization of the muscle fibers, on the number of mitochondria and oxidative enzymes. These changes increased the fatigue resistance and the quadriceps strength (42).

Some years later, the same authors (40) compared the quadriceps fatigability after cyclic exercises in COPD patients with that of healthy subjects using the interpolated twitch technique during a MVIC pre- and post- a fatigue test on a cycle ergometer. Patients exercised at 60% of the maximum load until exhaustion, while the workload of the healthy group was chosen so that the oxygen consumption (VO_2) was similar to that of COPD patients. The major finding of this study was that for the same VO_2 and exercise duration, there was a higher fatigue on the contractility of the quadriceps in COPD patients compared to healthy elderly. One of the factors attributed by the authors for muscle weakness was the atrophy of this tissue, which determined a reduction of 32% of MVIC in COPD patients. Furthermore, the authors add that the ventilatory muscles compete with lower-limb muscles for oxygen consumption, which restricts the blood flow to the legs. This reduction of the peripheral blood flow also reduces the amount of nutrients to the lower limbs, causing fatigue and a greater need for ventilatory response. Therefore, patients with COPD tend to reach the anaerobic threshold early and aerobic training has been recommended to increase the amount of oxidative enzymes and exercise tolerance.

In order to observe the changes in the enzymatic characteristics of muscle fibers, a comparison between interval training and training with constant load on a cycle ergometer was performed. In each group there were 10 patients with COPD. The training with constant load was held constantly for 30 minutes per day on an average intensity of $75 \pm 5\%$ of maximum workload on a cycle ergometer. The interval training was performed during 45 minutes a day. Each session was organized in successive sets of 30 seconds of cycling on a cycle ergometer at high intensity with 30 seconds intervals on a lower work rate (W). From week 1 to week 3 the intervals of high intensities training were 100% W, increasing to 120% from week 4 to week 6 and 140% W for the remaining 4 weeks. Both groups trained three times a week for 10 weeks. Vastus lateralis biopsy was used to evaluate the fiber type, fibers CSA, the number of capillaries and oxidative enzymes. It was observed that when performed biopsy of the vastus lateralis before and after training both groups showed an increase in AST fibers type I and II, as well as fiber capillarization. In addition, we observed an increase in citrate synthase activity and increase of $19 \pm 5\%$ at the peak of the maximal work rate during exercise in both groups. Nevertheless, the authors found no differences in the variables between the two types of training. However, levels of dyspnea and discomfort in the lower limbs of the group that performed interval training were lower. According to the authors, this would be associated with interval training methodology for optimizing system utilization of energy during exercise when compared to the continuous group, thereby determining a more stable ventilation with less dyspnea. (43).

Another way to change the workload using exercise is combined training, which consists of periods of cardiorespiratory endurance and periods of muscle strength in the same session. This methodology has been used in elderly populations as an attempt to improve oxygen consumption and muscle mass, concomitantly.

For a period of 8 weeks, Mador et al. (44) compared the effects of combined training to an aerobic training in COPD patients. The patients underwent training three times a week. The aerobic group started with a loading of 50% of the maximum working rate, and when patients were submitted to 20 minutes of exercise without producing high levels of dyspnea (controlled by Borg scale), the work rate was increased by 10%. In addition, patients also underwent training on a treadmill with an initial load of 1.1-2.0 miles/hour for 15 minutes with a speed increase in the absence of dyspnea. The combined training group performed the same exercises described above coupled with the strength

exercises such as leg extension (quadriceps), leg flexion (hamstring), pec deck flyes (pectoral) and pulldown (latissimus dorsi). Patients performed 3 sets of 10 repetitions at 60% of the maximum load established in a test of one repetition maximum (1RM). A 5 pounds increase was determined in each exercise if patients did not show any degree of dyspnea at the end of three repetitions. Quadriceps muscle strength, muscle fatigue by the interpolated twitch technique, and the six-minute walk test were evaluated in both groups before and after intervention. The intra-group comparison revealed an increase in muscle strength during all exercises: quadriceps (23.6%), hamstring (26.7%), pectoralis major (17.5%) and latissimus dorsi (20%) for the combined training group. For the aerobic training group there was a decrease in muscle strength for the quadriceps (1.1%) and latissimus dorsi (2.8%), and an increase in hamstring (12.2%) and pectoralis major (7.8%). The between-groups comparison revealed that the quadriceps and latissimus dorsi muscle strength of the combined training group was significantly higher, while for the pectoralis major muscle and hamstring there was no statistically significant difference. There was no difference between groups in the six-minute walk and in the quadriceps fatigue test pre- and post-exercise.

The resistance training emphasizing the concentric phase of muscle contraction seems to increase the mechanical efficiency of COPD patients. A study evaluated the changes due to maximal strength training in COPD patients compared to normal sedentary subjects. Subjects performed a strength training three times a week for 8 weeks with 85-90% of knee extensors 1RM on a leg-press machine. The knee extensors rate of force production and mechanical efficiency ($VO_2\text{max-}VO_2\text{rep/W}$ on the cycle ergometer) were evaluated. The authors found an increased rate of force production and increased mechanical efficiency by $105 \pm 22.8\%$ and $32 \pm 7\%$, respectively, in COPD patients, whereas no change was observed in the control group (41).

Despite the literature showing the beneficial effects of physical exercise, only one study that evaluated which training strategy has greater ability to maintain its effects during detraining was found (45). The authors compared the effects of 12 weeks of resistance training, aerobic training and combined training (aerobic and strength exercises in the same session) and 12 weeks of detraining. The aerobic training consisted of 40 minutes of pedaling on a cycle ergometer at 70% of maximum work rate previously assessed in an incremental test. Strength training consisted of the following exercises: 1) rowing (latissimus dorsi), 2) pec deck flyes (pectoralis major), 3) development (deltoid and triceps), 4) knee flexion (hamstrings) and 5) leg extension (quadriceps). These exercises were performed in 4 sets of 6-8 repetitions with 70-85% 1RM test, and this test was repeated every two weeks to adjust the training load. The combined training consisted of the same methodology of strength training added by 20 minutes of aerobic training on a cycle ergometer. In all groups, strength was evaluated in the same exercises of the strength training, and aerobic performance on a cycle ergometer, before and after the interventions. At the end of the training program, all groups increased strength in all exercises. The group that performed strength training showed a similar result in lower limbs when compared to the combined training group, and a higher result than the aerobic training group. The aerobic training group showed greater strength in the lower limbs compared to upper limbs. In relation to detraining, a greater decrease in muscle strength in the strength training group was found in comparison to the aerobic training group in the following muscles: 1) the latissimus dorsi, 2) pectoralis major and 3) hamstrings. In the aerobic training group, the parameters of dyspnea and quality of life improved, and did not change during a period of three months of detraining. This study observed that the specificity of training can influence the result. In other words, the aerobic training group showed improvement in resistance to submaximal exercise, the strength training group

showed higher values of power production, and the combined training group in both parameters. However, only the aerobic training group maintained the benefits of exercise during detraining.

Conclusion

This review showed that many factors can interfere in the increased fitness of COPD patients when the muscle response to exercise training is evaluated. Additionally, studies suggest that when the muscle mass is preserved, COPD patients can produce force equally to healthy subjects. Patients with low levels of hypoxemia show a decrease in muscle strength, but not on maximum power generation. However, patients with advanced disease show worse hypoxemia and also have high levels of inflammatory and oxidative stress, modifying muscle metabolism. While the disease progresses, morphological changes such as reduction in muscle mass, reduced capillary, selective atrophy of type I and type IIa fibers can provide higher tissue acidosis, inhibiting the use of aerobic routes. These changes modify the force manifestation in response to exercise and may contribute to exercise intolerance. Moreover, our review shows that there are few studies that characterize the musculoskeletal system in COPD patients, especially in different stages of the disease. The understanding of the pathophysiological aspects of the underlying disease, as well as the characterization of the peripheral muscles on chronic respiratory diseases, such as COPD, are important for properly determine the work intensity and volume during physical training. Different training methods are used with this population. However, several questions remain regarding the optimal exercise protocol for COPD patients. A better characterization of the biomechanical situation and the movements involving the daily-life activities could help to elucidate those questions.

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