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Skeletal muscle weakness and exercise intolerance in patients with chronic obstructive pulmonary disease

Fraqueza muscular esquelética e intolerância ao exercício em pacientes com doença pulmonar obstrutiva crônica

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Abstract

The aim of this study was to evaluate the functional capacity and the performance of respiratory and quadriceps muscles in patients with chronic obstructive pulmonary disease (COPD) and relate them to nutritional status and forced expiratory volume in the first second (FEV_1). **Methods:** Twelve patients with moderate COPD (70±7 years, FEV_1 52±17% predicted, body mass index (BMI) 23±4kg/m^2) and seven healthy volunteers (69±8 years, FEV_1 127±12% predicted, BMI 27±3kg/m^2) were evaluated. All of them underwent body composition analysis, measurement of respiratory muscle strength (maximum inspiratory pressure, MIP, and maximum expiratory pressure, MEP), cardiorespiratory exercise test (CET) and evaluation of palm grip strength, peak torque and total work or endurance of the quadriceps femoris. **Results:** The patients with COPD had lower values for the free-fat mass (LBM) index (18±1 *versus* 21±1kg/m^2, p≤0.05), maximum load attained in the CET (60±20 *versus* 102±18 watts, p≤0.01), MIP (58±19 *versus* 87±21cmH_2O, p≤0.05), palm grip strength (38±6 *versus* 47±5kg, p≤0.05), peak torque (103±21 *versus* 138±18Nm, p≤0.05) and total work of the quadriceps femoris (1570±395 *versus* 2333±568J, p≤0.05) when compared with the control group (independent Student's *t* test). There was no correlation between FEV_1 and the variables studied, while the LBM correlated with the total work of the quadriceps (Pearson, r=0.6290, p≤0.05). **Conclusions:** These results indicate that patients with COPD show weakness of the inspiratory and quadriceps muscles and lower functional capacity, when compared with a healthy group. Moreover, they suggest that the degree of airflow obstruction is not a good predictor for quantifying the nutritional and muscle impairments in patients with COPD.

Key words: exercise intolerance; muscle performance; functional capacity; COPD.

Resumo

O objetivo deste estudo foi avaliar a capacidade funcional e o desempenho da musculatura respiratória e periférica e relacioná-los com o estado nutricional e volume expiratório forçado no primeiro segundo (VEF_1). **Materiais e métodos:** Foram avaliados 12 pacientes com doença pulmonar obstrutiva crônica (DPOC) moderada a grave (70±7 anos, VEF_1 de 52±17% previsto, índice de massa corpórea (IMC) de 23±4kg/m^2) e sete indivíduos saudáveis (69±8 anos, VEF_1 de 127±12% previsto, IMC de 27±3kg/m^2). Todos realizaram análise da composição corporal, medida da força muscular respiratória (pressão inspiratória máxima, PImax, e pressão expiratória máxima, PEmax), teste de exercício cardiorrespiratório (CRET), avaliação da força de preensão palmar, pico de torque e trabalho total ou endurance do quadríceps femoral. **Resultados:** Os pacientes com DPOC tiveram valores reduzidos do índice de massa magra corpórea (LBMI) (18±1 *versus* 21±1kg/m^2, p≤0,05), da carga máxima atingida no CRET (60±20 *versus* 102±18watts, p≤0,01), da PImax (58±19 *versus* 87±21cmH_2O, p≤0,05), da força de preensão palmar (38±6 *versus* 47±5kg, p≤0,05), do pico de torque (103±21 *versus* 138±18Nm, p≤0,05) e do trabalho total do quadríceps femoral (1570±395 *versus* 2333±568J, p≤0,05) quando comparado com o grupo controle (teste *t* de *Student* não pareado). Não houve correlação entre VEF_1 e as variáveis estudadas; o LBMI correlacionou-se com o trabalho total do quadríceps (Pearson, r=0,6290, p≤0,05). **Conclusões:** Estes resultados indicam que os pacientes com DPOC apresentam fraqueza muscular inspiratória e periférica e menor capacidade funcional, quando comparados com o grupo saudável. Além disso, sugere que o grau de obstrução ao fluxo aéreo não é um bom preditor para quantificar as debilidades nutricionais e musculares dos pacientes com DPOC.

Palavras-chave: intolerância ao exercício; desempenho muscular; capacidade funcional; DPOC.

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Introduction

The chronic obtrusive pulmonary disease (COPD) is a respiratory disorder characterized by the chronic blocking to the air flow which is not totally reversible and is associated with an inflammatory response of the lungs to harmful particles or gases, caused mainly by smoking[1]. Besides the chronic inflammation of the airways, the presence of active inflammatory cells and the increase of the plasmatic levels of pro-inflammatory cytokines in the systemic circulation were detected, which along with oxidative stress contribute to nutritional changes and skeletal muscular disorders in these patients[2], both contributing to the low endurance for physical exercise, especially among those individuals with a moderate to serious degree of obstruction in air flow[3].

Among the mechanisms involved in the development of the peripheral muscular disorder of COPD patients, the following stand out: deconditioning by disuse; pro-inflammatory cytokines (TNF-α, interleucines-6 and 8, for example), reduced anabolic hormones (testosterone), hypoxemia and/or hypercapnia, malnutrition, and long-term use of corticoids[1,4,5].

Studies have demonstrated that COPD patients often show significant mass loss[6], respiratory muscle weakness[7], upper-limb strength reduction, and obvious diminishments in strength[8,9] and endurance[10] of the quadriceps muscles when compared to healthy control subjects. All of these factors account for increases in the mortality rates among these patients, not to mention their low quality of life[4].

The aim of the present study was to point out that a more comprehensive evaluation, one that might detect the various impairments to which the bearer of such a disease may be susceptible, will contribute to better planning of elaborate pulmonary rehabilitation in a customized fashion Besides this, there are to date very few studies that make use of the isokinetic dynamometer to evaluate the endurance of the femoral quadriceps in the COPD.

Thus, this investigation intends to test the patients capacity to exercise, as well as the strength of their respiratory muscles and the performance of the palm pressure, strength and endurance of the femoral quadriceps, and to correlate these variables with their nutritional condition's and degree of airway obtrusion. It also aimed at comparisons of these results with those of sedentary individuals who did not suffer from respiratory disorders.

Materials and methods

This study was carried out between February and October of 2006, and focused on patients with a COPD diagnosis sent for treatment at the Functional Respiratory Reeducation Program. It was approved by the Committee for Ethics in Research with Human Beings of the Universidade Federal de São Carlos (UFSCar), under protocol n° 235/2006 and all of the participants (COPD group and control group) signed a term of free agreement for participation form.

Criteria for inclusion and exclusion

Male patients with a clinical diagnosis for COPD, ranging from moderate to serious, according to GOLD's[1] classification were included, as well as ex-smokers, with a long smoking history (48±17 packets/year for 44±16 years), who were clinically stable and without orthopedic, neurological, or cardiovascular impairments, and/or cognitive changes that might compromise their participation in the suggested protocol. The hypoxemic patients (peripheral oxygen saturation (SpO_2) <88% at rest) and/or those who used oxygen at home were excluded.

COPD group

Ten individuals with a moderate degree of the disease, and eight serious degree patients started the evaluations. Two seriously impaired individuals were sent to the hospital during the data collection. Out of the subjects with a moderate degree, one did not adapt to the cycloergometer cyclage, one gave up claiming to having personal problems, and two were excluded for being absent more than three times on the scheduled days. Twelve subjects with COPD concluded the tests (six moderate and six serious). Three patients (25%) had used inhalatory corticoids for at least six months prior to the study.

Control group

Ten male volunteers composed the control group, all aged 58 or older, sedentary or with a low level of physical activity (a two hour weekly walk, at most), non-smokers, without any osteomuscular, neurological, cardiovascular or pulmonary pathologies that might have prevented them from undergoing the tests. Three volunteers were excluded, one of them for interrupting the cardiorespiratory test (CRT) too soon due to joint pain in the left knee, one for showing hypertension before the CRT, and another one for having undergone prostate micro-surgery during the evaluations. Thus, the final sample was made up of seven individuals.

Procedures

All the healthy patients and volunteers were submitted to a pulmonary function test using the Vitalograph Spirotrac IV®

syprometer, duly calibrated, following the guidelines of the Brazilian Society of Pneumology and Tisiology[11]. The forced vital capacity (FVC) and the forced expiratory volume in the first second (FEV_1) measurements were taken, and Tiffenau's index (VEF_1/CVF) was calculated.

The complete evaluation occurred over the course of four different days, in no longer than two weeks, consisting of:

- anthropometric evaluations and body mass index (BMI): the measurements were taken on a Filizola® anthropometric scale, with the subject bare foot and semi-nude. These were the total body mass (BM) in kg, and the height in m, and then the BMI (BMI=mass/height^2) was calculated, according to the following classification: BMI<20kg/m^2 as low mass, BMI between 20 and 24.9kg/m^2 as normal mass, BMI from 25 to 29.9kg/m^2 as overmass and BMI≥30 kg/m^2, obese[12];
- evaluation of the body composition: the evaluation of the body composition was carried out by means of the bioelectric impendence analysis (BIA) at 50kHz on digital scales (Tanita®, model UltimateScale) following the recommendations of the manufacturer. All of the subjects underwent the analysis after fasting for at least ten hours to standardize liquid uptake. Stemming from the fat obtained, the Lean Body Mass (LBM) was calculated with the formula

$$\mathbf{LBM = BM - \left(\frac{BM \times Fat\ \%}{100}\right)}^{13}.$$

Next, the lean body mass index (LBMI) was determined, which is the relation between the LBM and the height squared (kg/m^2)[14,15]. The classification of malnutrition for men through the LBMI varied from LBMI≤16kg/m^2 [16] to 17.4kg/m^2 [15];

- functional capacity evaluation: the incremental test was performed on a cyclo-ergometer fitted with an electronic brake system (Ergo-FIT®, model Ergo 167 Cycle). The protocol was as follows: initial phase (two minutes) seated, without activity, on the bike's saddle; loading incremental phase (10watts at every two minutes), starting at 15watts until the individual got exhausted; period of active recovery (15watt load for two minutes); recovery phase (six minutes) without activity on the bike's saddle. During the last 30 seconds of each phase described above and before each stage of the incremental loading phase, some measures were taken, namely blood pressure (BP), heart rate (HR), SpO2, and the score of Borg's CR10 Scale[17], which was obtained upon questioning the subjects about fatigue or dyspnea and pain or fatigue in the lower limbs. Criteria for interrupting the test: reaching the maximum HR given by the formula: 220-age, systolic above 220mmHg or its non-increase with a greater workload and/or variation of the diastolic BP greater than 15mmHg, SpO2 reduction under 80% or at the individual's request due to pain or thoracic burn, dizziness, cephalea, intense dyspnea, pain in the lower limbs and/or fatigue;
- muscular performance evaluation (at least 72 hours after CRET):
  - the evaluation of the respiratory muscular strength was obtained through maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using a manovacuometer (Ger-Ar®) scaled between 300 and +300cmH_2O, equipped with an adapter for the mouthpiece and containing a escape valve through an orifice of approximately 2mm in diameter, to dissipate the pressures generated by the muscles of the face and of the oropharynx[18]. Both the MIP and the MEP were performed at least three times for each individual, in the orthostatic position, and with the use of a nose clip. The MIP was obtained by means of the residual volume, whereas the MEP was from the total pulmonary capacity. The patient received due verbal encouragement and in case there was a difference of more than 10% between the measurements, a new maneuver was performed. In the interest of statistical analyses, the greatest value was maintained.
  - the evaluation of the isometric force developed by the muscles of the forearm and of the hand was made through palm pressure with a hand-grip style dynamometer (Takei Physical Fitness Test®, model TKK 5401 Grip-D). The protocol that was used was with the subject in an orthostatic position, with the upper limb (UL) stretched out down the body. Five maximal voluntary contractions (MVC) were required for each limb with a 30-second rest between each repetition[19]. For the statistical analyses, the greatest value obtained in the hand-grip was considered regardless of the UL where it originated.
  - strength and endurance measurements of the dominant quadriceps were taken through the evaluation of the peripheral muscles performance (femoral quadriceps) of the dominant lower limb (LL) was carried out using an isokinetic dynamometer (Biodex®, model Biodex Multi-Joint System 2, Biodex Medical System Inc.) by means of concentric MVCs following a reciprocal protocol extension and flexion in two distinct situations (strength and endurance). For the evaluation of muscle strength, the subject performed five MVCs in a row at an angular speed of 60°/s, using the greatest torque peak of the extensor muscle for strength analysis. After a five-minute rest, the endurance measurement began by means of three accumulated series of 15 MVCs each at 150°/s[19], with a four-minute rest between them, and the total work developed by the quadriceps muscle was calculated. The individuals

had their HR, SpO_2 and BP monitored before and soon after each one of the aforementioned tests.

The tests with the isokinetic dynamometer were carried out by a single trained examiner. The equipment was duly calibrated, following the manufacturer's instructions. The individual was seated, and the suitable adjustments for the ideal alignment of the knee joint to the center of the dynamometer were maintained and the attachments to the member tested and to the trunk. Gravity-correction procedures were taken prior to the tests, as well as warming-up (three submaximal contractions before each speed applied), as well as verbal encouragement during the tests.

Statistical analyses

The variables studied are shown as their mean values±standard deviation (sd). Considering the normal behavior of the variables, given by Kolmogorov and Smirnov's test, the non-paired t-Student test was used for comparisons between the groups, and paired for intra-group comparisons. For the study of the correlations between the variables, the Pearson's correlation coefficient was used with the level of significance set at $p \leq 0.05$. For the sample composition of the study, $\alpha=0.05$ and power greater than or equal to 80% were used to detect significant differences in the variables under scrutiny by means of the StatMate 2 Program (GraphPad Software, Inc., v. 2.0).

Table 1. Subject characteristics and studied variables.

	COPD (n=12)	Control (n=7)
Age (years)	70±7	69±8
Mass (kg)	64±13	73±8
Length (m)	1.66±0.06	1.66±0.03
BMI (kg/m²)	23±4	27±3
LBMI (kg/m²)	18±1*	21±1
LBM (kg)	51±4*	57±4
FEV_1 (% pred)	52±17#	127±12
FVC (% pred)	78±15#	126±15
FEV_1/FVC (%)	51±9#	86±13
MIP (cmH_2O)	58±19*	87±21
MEP (cmH_2O)	79±19	87±16
Maximal work rate (W)	60±20#	102±18
Muscle function		
Hand-grip (kg)	38±6*	47±5
Peak torque LL (Nm)	103±21*	138±18
Total work LL (J)	1570±395*	2333±568
Handgrip/LBM (kg/kg)	0.75±0.1	0.84±0.1
Peak torque/LBM (Nm/kg)	2±0.4*	2.5±0.4
Total work /LBM (J/kg)	30±7*	42±12

Data are presented as mean±sd, *p≤0.05, #p≤0.01. BMI=body mass index; LBMI=free-fat mass index; LBM=free-fat mass; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; FEV_1/FVC=Tiffeneau index; MIP=maximal inspiratory pressure; MEP=maximal expiratory pressure; LL=lower limbs.

Results

The subjects' characteristics are shown in Table 1. There were no significant differences in the anthropometric and demographic data, such as age, mass, height, and BMI. Nevertheless, the LBMI was quite lower in the COPD group than in the control group. Those patients demonstrated considerably lower spyrometric values than those obtained by the control group. The FEV_1 did not demonstrate any significant correlations between the selected variables ($p>0.05$). Of the 12 patients evaluated, three (25%) showed energetic-protein malnutrition for having BMI<20kg/m² and LBMI<17.4kg/m².

Functional capacity

The maximal load achieved by the COPD group was substantially lower than the one reached by the control group (Table 1), and there was a positive correlation (Pearson, $r=0.8038$, $p \leq 0.01$) between the maximal load attained and the torque peak of the dominant lower limb (Figure 1). Of the 12 patients evaluated, four (33.3%) interrupted the CRET due to pain in their lower limbs, one (8.3%) because of pain in his lower limbs and dyspnea, four (33.3%) due to dyspnea, two (17%) because of general fatigue, and one (8.3%) for reaching the maximal HR for his age group.

Muscular performance

For the MIP (58±19 *versus* 87±21cmH_2O), the palm pressure was (38±6 *versus* 47±5kg), torque peak (103±21 *versus* 138±18Nm), and the femoral quadriceps endurance (1570±395 *versus* 2333±568J) were significantly smaller in COPD patients when compared to the control group (Table 1). The femoral quadriceps endurance showed a positive correlation (Pearson, $r=0.6290$, $p \leq 0.05$), with the LBMI (Figure 1).

Expressed as a percentage of the mean value of the healthy subjects[9], the COPD group showed palm pressure strength of 82±12%, torque peak 75±15%, and quadriceps endurance of 67±17%. Upon comparing the percentages of the palm pressure strength developed in relation to the torque peak and to the quadriceps endurance, in the COPD group, there was a noteworthy difference between the limbs (paired t-Student test, $p \leq 0.05$), which revealed less strength of the lower limb (in relation to the upper limb). In the control group, these differences were not observed. Additionally, the muscular function of the dominant quadriceps, both strength and endurance, expressed by the LBM (Table 1) were significantly lower in the COPD group if compared to the control group. However, the strength developed by the upper limbs using the hand-grip as shown by the LBM, did not show significant differences between the groups (Table 1).

Discussion

This study showed that the nutritional condition evaluated by the LBMI, as well as the functional capacity and the muscular performance in absolute terms were reduced in patients with COPD when compared to healthy individuals having similar anthropometric characteristics. No correlations were observed between the nutritional condition, functional capacity and muscular performance and the FEV_1.

The causes of intolerance to exercise in the COPD patients are traditionally focused on the limitations of the ventilatory system and gas exchange[20]. Nonetheless, some studies[3,21] have demonstrated that these are not the only reasons for low capacity for exercise. A relevant factor causing physical limitations is peripheral muscle dysfunction, marked by structural abnormalities, by lowering of the muscular mass and mitocondria relations, changes in the type and size of the muscle fibers and reduction of the oxidative enzymes, reduction of functional strength and resistance, or related to the muscular bioenergetics, such as reductions of oxygen uptake and pH, and increases in the levels of lactates[4]. Peripheral muscle disorders compromise COPD patients' capacities to exercise[5] since the reduction of peripheral muscle strength is related to physical capacity and to the intensity of symptoms during the incremental exercise test, regardless of the pulmonary function[21,22].

In the course of this investigation, we found a strength reduction of the femoral quadriceps muscle in the COPD group, when compared to the control group, a finding that is corroborated by other reports[8,23]. We also detected positive correlations between femoral quadriceps strength evaluated by peak torque, and the maximum load achieved in the CRET, which suggests that the less strength this muscle develops, the less it is capable of performing dynamic exercises for this muscle group. Aside from the peripheral muscle weaknesses, there were also a significant correlations between the ventilatory parameters (minute ventilation, current volume, and respiratory frequency) and the tolerance to exercise, although with a low correlation with the disease's seriousness as evaluated by the FEV_1[24]. No significant correlations were found between the maximal exercise load or the muscular performance and the FEV_1. It was evident that the airway obtrusion was not a good predictor to estimate the physical and muscular capacity of individuals with COPD.

Among the participants of the COPD group, the interruptions in the CRET were caused, most of the times, either by dyspnea or by pain in the lower limbs implying that, for some patients, the limiting symptom of the effort is caused by deficiencies of the peripheral muscles, as suggested by some authors[5,25], and not only to ventilatory changes. The weaknesses

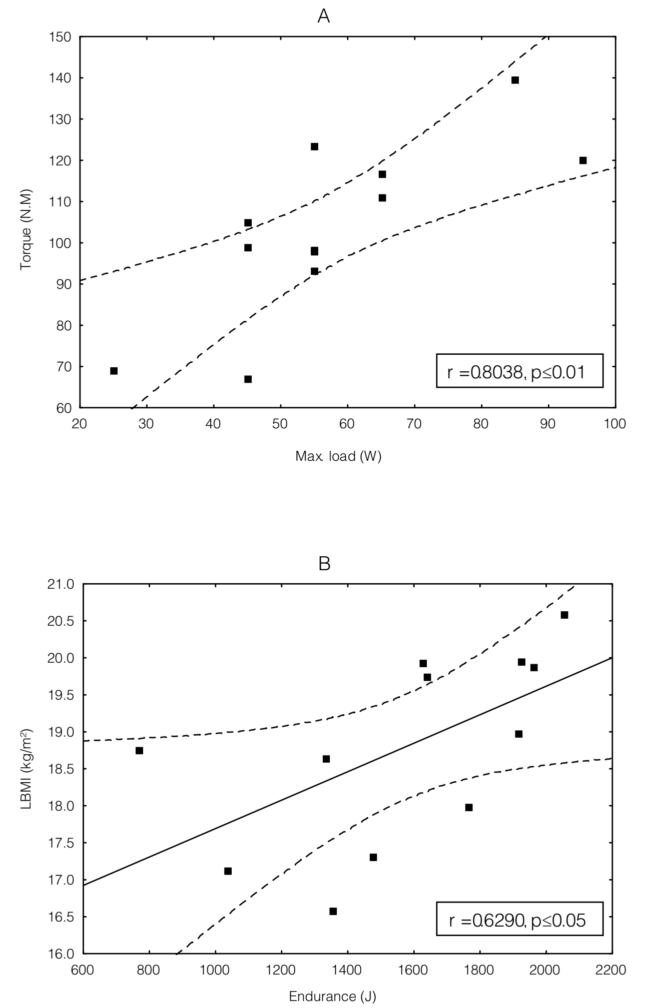

Figure 1. Correlations COPD group (A) Correlation between the peak torque (Nm) quadríceps and maximal work rate in CRET (W). (B): Correlations between LBMI (kg/m^2) and quadriceps endurance (J).

of the peripheral muscles of the lower limb in patients with COPD have often been attributed to atrophy by disuse or to physical deconditioning[10,23], with an obvious reduction of the transverse section of the thigh area evaluated by a computed tomography[8,9] as well as increases in the proportion and atrophy of type IIA and IIX fibers[26].

In the COPD group, the palm pressure strength corresponded to 82% of the value scored by the control group, and the strength and endurance of the quadriceps corresponded respectively to 75 and 67% of the values obtained by the control group. These results suggested that the muscular debility in the COPD particularly affected the lower limb muscles when compared to the upper limbs, a finding confirmed by other researchers[5,8]. One possible explanation for that would be the reduction of activities which involved walking, in attempt to avoid the sensations of dyspnea, the predominance of daily life activities with the use of the upper limb, and the use of the scapular girdle muscles during accessory breathing. This reduced the impairment of the upper limbs through disuse.

Another finding of this investigation was the reduction of the femoral quadriceps muscle endurance, which can be explained by the putative change of the fiber-type proportions. This might favor the reduction of the oxidative capacity, thus heightening the disposition to fatigue and diminishing the resistance of the peripheral muscles, as remarked by other researchers[28,29]. Other factors, already mentioned, that may have also contributed to muscle loss are the use of oral corticoids[8] and mass loss[6].

Concerning the use of oral systemic corticoids, none of the patients in the COPD group used this medicine and three (25%) used it for at least six months prior to the study (the association of β_2 agonist/inhalatory corticoid (formoterol/budesonida). Nevertheless, the inhalatory corticoids (budesonida, for example) have milder adverse systemic effects when compared to the systemic corticoids (prednosolona, for example)[30].

COPD patients often lose mass and/or have LBM reduction[6]. Depletion of the lean mass may occur even in patients whose mass is within normal standards, and is commonly accompanied by BMI or total body mass reduction[16,31]. The lean mass is regarded as an indirect measure of muscle mass, and its reduction affects both the peripheral muscles, respiratory functions, the capacity to exercise, and increases the risk of mortality[6,12]. Therefore, nutritional depletion exerts a considerable impact on COPD.

This paper considered the prevalence of nutritional depletion in relation to functional capacity, muscle performance, and airway obtrusion in a group of COPD patients. Twenty-five per cent of subjects suffered from energy-protein malnutrition, which was close to the expected percentages among stable out-patient clinical individuals, which is usually around 27%[16]. Although several studies relate LBM and/or LBMI reductions to a reduction of the respiratory and peripheral muscular functions, as well as tolerance to exercise[31], this research showed that the LBMI only had significant correlations with the quadriceps endurance, which demonstrated that the smaller the LBM, the less resistance the muscles will have to remain in dynamic activity.

Engelen et al.[9] showed that the absolute strength of the MS and of the femoral quadriceps were lower in COPD patients when compared to healthy subjects, but the ratio between peripheral strength with the LBM or the LBM of the extremities was not significant between the groups when tested separately. This suggests that the lowest peripheral strength developed by the patients with COPD was caused by the reduction of the muscular mass, with no associations between the muscular function and the FEV_1. The present results are in accordance with these findings, which attested that the UL and LL muscular performance of patients with COPD was reduced when compared to healthy individuals, and that there was no connection with the FEV_1. Besides, the relation between palm pressure strength and the LBM, did not significantly differ between both groups Yet, the ratio of the quadriceps strength and the LBM contrasted with the findings of Engelen et al.[9], since a difference between those groups was detected. It is suggested that the muscular weakness of the upper limbs, as measured indirectly by means of the hand-grip in COPD patients may be attributed to the reduction of lean mass. Still, the weakness of the upper limbs did not result in the same responses as the upper limb muscles. However, one of the drawbacks of this study was the lack of predicting correction formulae and/or of regression equations[15] to obtain the LBM by using the BIA. The equipment used did not provide the tissue resistance values, essential for the use of predictive formulae. Thus, a more simple model was used to verify the body composition as a reference point, by using only two components (fat and lean tissues) which could generate less reliable LBM results[32].

The physical training improved the both the muscular functions and tolerance to exercise[4] and induced an anabolic response, with an increase of the LBM in normal mass COPD patients[19]. On the other hand, with individuals who suffered from malnutrition, the training was related to the increase of the protein catabolism, causing the thin mass depletion condition to worsen[33].

It was concluded that, besides pulmonary impairment, COPD brought about systemic manifestations that triggered intolerance to exercise and muscular weakness, not to mention probable nutritional changes. Based on the findings of this study, Physical Therapy evaluations must contemplate the various aspects related to COPD, thus contributing to the elaboration of a custom-made pulmonary rehabilitation program that focuses on the evident weaknesses, and providing special attention and guidance to those patients suffering from malnutrition.

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