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Microvascular oxygen extraction during maximal isometric contraction in patients with chronic obstructive pulmonary disease

Extração microvascular de oxigênio durante contração isométrica máxima em pacientes com DPOC não hipoxêmicos

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Abstract

Introduction: COPD presents decrease in oxidative metabolism with possible losses of cardiovascular adjustments, suggesting slow kinetics microvascular oxygen during intense exercise. **Objective**: To test the hypothesis that chronic obstructive pulmonary disease (COPD) patients have lower muscle performance in physical exercise not dependent on central factors, but also greater muscle oxygen extraction, regardless of muscle mass. **Methods**: Cross-sectional study with 11 COPD patients and nine healthy subjects, male, paired for age. Spirometry and body composition by DEXA were evaluated. Muscular performance was assessed by maximal voluntary isometric contraction (MVIC) in isokinetic dynamometer and muscle oxygen extraction by the NIRS technique. Student t-test and Pearson correlation were applied. A significance level of $p<0.05$ was adopted. **Results**: Patients had moderate to severe COPD (FEV1 = 44.5 ± 9.6% predicted; SpO2 = 94.6 ± 1.6%). Lean leg mass was 8.3 ± 0.9 vs. 8.9 ± 1.0 kg ($p =0.033$), when comparing COPD and control patients, respectively. The decreased muscle oxygen saturation corrected by muscle mass was 53.2% higher

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(p=0.044) in the COPD group in MVIC-1 and 149.6% higher (p=0.006) in the MVIC-2. Microvascular extraction rate of oxygen corrected by muscle mass and total work was found to be 114.5% higher (p=0.043) in the COPD group in MVIC-1 and 210.5% higher (p=0.015) in the MVIC-2. **Conclusion**: COPD patients have low muscle performance and high oxygen extraction per muscle mass unit and per unit of work. The high oxygen extraction suggests that quantitative and qualitative mechanisms can be determinants of muscle performance in patients with COPD.

Keywords: Chronic Obstructive Pulmonary Disease. Isometric Contraction. Muscle Strength. Oxygen Consumption. Metabolism.

Resumo

Introdução: *DPOC (doença pulmonar obstrutiva crônica) apresenta diminuição no metabolismo oxidativo com prejuízos dos ajustes cardiovasculares, sugerindo cinética de oxigênio microvascular lenta durante exercício intenso.* ***Objetivo****: Testar hipótese que pacientes com DPOC apresentam não só menor performance muscular em exercício físico não dependente dos fatores centrais, mas também maior extração muscular de O2 independentemente da massa muscular.* ***Métodos****: Estudo transversal, 11 pacientes DPOC e 9 indivíduos saudáveis, gênero masculino, pareados pela idade. Avaliado espirometria, composição corporal, performance muscular por contração isométrica voluntária máxima (CIVM) em dinamometria isocinética e extração muscular de oxigênio pela técnica de NIRS. Teste t-Student e correlação de Pearson foram aplicados. Adotado p<0,05 como nível de significância.* ***Resultados****: Pacientes com DPOC moderado para grave (VEF1 = 44,5 ± 9,6 % predito; SpO2 = 94,6 ± 1,6 %). Massa magra do membro inferior foi de 8,3 ± 0,9 vs. 8,9 ± 1,0 Kg (p= ,033), comparando DPOC e controle respectivamente. A redução saturação muscular de O2 corrigido pela massa muscular foi 53,2 % maior (p=0,044) no grupo DPOC na CIVM-1 e 149,6% maior (p=0,006) na CIVM-2. A taxa de extração microvascular de O2 corrigida pela massa muscular e trabalho total apresentou-se 114,5% maior (p=0,043) no grupo DPOC na CIVM-1 e 210,5% maior (p= 0,015) na CIVM-2.* ***Conclusão****: Pacientes com DPOC apresentam baixa performance muscular e alta extração de O2 por unidade de massa muscular e por unidade de trabalho. A elevada extração de O2 sugere que mecanismos quantitativos e qualitativos podem ser determinantes da performance muscular em pacientes com DPOC.*

Palavras-chave*: Doença Pulmonar Obstrutiva Crônica. Contração Isométrica. Força Muscular. Consumo de Oxigênio. Metabolismo. Dinamômetro de Força Muscular. Eletromiografia.*

Introduction

Changes in pulmonary function and imbalanced gas exchange during physical effort are characteristic of chronic obstructive pulmonary disease (COPD) (1, 2). Consequently, the interaction of aerobic exercise-COPD has been extensively studied. However, other factors reflect the complexity of COPD. Musculoskeletal dysfunction has been shown to be the major determinant of physical performance in this population. Anaerobic performance, instead of aerobic, is a better predictor of the ability to perform lower limb physical activity among patients with COPD (3). Several studies have demonstrated that maximum strength is associated with the level of daily physical activity (4), it is a better predictor of mortality (compared to age, body mass index (BMI) and FEV1 - forced expiratory volume in the first second) (5) and correlates with peak oxygen consumption (peak VO2) and the oxygen uptake efficiency slope (OUES) (6) in COPD. Specifically, maximum isometric strength is better associated with numerous types of functional testing rather than the VO_{2peak} and $Watts_{peak}$ obtained from cardiopulmonary testing (7).

The maximum force obtained by maximum voluntary isometric contraction (MVIC) on a dynamometer is a method of high reliability and reproducibility (8). Although the MVIC is present in hundreds of studies, its use has been summarized merely for strength evaluation, torque in Newtonmeter (Nm), and less frequently for the work in Joules (J), while the determining physiological mechanisms of muscle performance, on this type of assessment, have received little attention, especially in COPD.

Muscle oxygenation, the recruitment of muscle fibers, and the efficiency of the ATP pathway resynthesis are determining the force applied during sustained muscle contraction. These determinants of muscle efficiency are importantly altered in COPD (9, 10). In particular, muscle oxygenation is dependent on the: capillary density of muscle fibers, muscular oxidative function, myoglobin concentration, and blood flow to the muscles. In addition, the supply of oxygen to the working muscles also has a close relationship with the types of muscular activity performed (11). According to this scenario, COPD patients cannot only have decreased muscle performance (↓Nm,↓Joules) during physical exercise (MVIC) not dependent on central factors (cardiorespiratory), but also greater muscle O_2 extraction (↓ muscle O_2 saturation (SmO_2%) and ↑ of microvascular O_2 extraction rate ($E_{\mu vasc}O_2$,%) regardless of muscle mass.

Methods

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (CEP 1196/11). All participants were informed about the procedures and risks present and signed the Terms of Free and Informed Consent form.

The sample of this study consisted of 11 patients with COPD, male, referred by the pulmonology clinic of the Federal University of São Paulo (UNIFESP), aged over 60 years, and BMI less than 30 kg/cm^2, compared to nine healthy volunteers, paired by age and gender. The COPD group was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and classified as stage II-III; showing forced expiratory volume (FEV_1) less than 80% of predicted value and FEV_1/forced vital capacity (FVC) less than 0.70.

All patients were stable in the previous four weeks. None of the participants were involved in a rehabilitation program, used corticosteroids, or oxygen therapy. Cardiac, renal, hematological, endocrine, hepatic, neurological, vascular or orthopedic disorders that prevented the study were considered as exclusion criteria.

Spirometry

The COPD group underwent spirometry analysis by the Clinical Pulmonary Function Spirometry-CPF-S™ system (Medical Graphics Corporation, St. Paul, MN, USA). The airflow was measured using a Pitot tube (Prevent Pneumotach™); a flow and volume calibration was performed with all tests, considering the temperature, humidity and local barometric pressure. Fifteen minutes after administration of 400µg of Salbutamol, a repeated measurement was obtained, and the patients completed at least three forced expiratory maneuvers, which is acceptable and reproducible in accordance with the Guidelines for Lung Function of the Brazilian Society of Pneumonology and Thoracics (Sociedade Brasileira de Pneumologia e Tisiologia - SBPT).

Body composition

The assessment of body composition was performed by dual-energy X-ray absorptiometry (DEXA), using the DPX-IQ device (Lunar Radiation, Madison, WI). The source and detector were passed through the body, allowing for image reconstruction of tissues and quantification of total lean body mass in different segments. The presence of depletion was determined by the depletion index (12) (FFMI) = ((Fat Mass – Free Mass)/height^2), being positive when ≤ 16Kg/m^2.

Muscular oxygenation

Muscle oxygenation was assessed by the near-infrared spectroscopy technique (NIRS), using the Oxiplex TS ™ Model 99200 (Champaign, IL, USA) with a modulated frequency of 110MHz. This technique allows fora non-invasive measurement of total hemoglobin and muscle saturation, among other variables, from the application of the Photon migration theory (13, 14). Both absorption and dispersion coefficients are determined from the changes in amplitude modulation, by the mean light intensity, and in the change phase. Thus, it measures the absolute level of absorption and scattering of light in tissues. Consequently, the variables mentioned can be obtained.

The muscular oxygenation profile was assessed in the medial vastus lateralis muscle portion; the probe was positioned around 10 to 12 cm above the patella and covered with a black band, to avoid loss of light and possible interference from external luminosity. The probe used had a 3.0 - 4.4 cm distance between the four light emitters and the detector. The penetration of the emitted light is = 2 cm from the surface of the skin (i.e., half the distance between the emitter and detector) (13), which proved to

be sufficient for achieving a light signal reflected from the target muscle (15). The light absorption was measured in different spectra (690 nm to 830 nm). At a wavelength of 830 nm, both oxyhemoglobin as well as deoxyhemoglobin exhibited similar absorption coefficients. The light absorption at this wavelength is proportional to the total hemoglobin on the evaluated muscle. The NIRS technique does not allow a separate evaluation between hemoglobin and myoglobin, due to their similar characteristics. However, due to the relationship between the hemoglobin and myoglobin concentrations in human muscle, the signal obtained is considered as if it is derived only from hemoglobin (14). The absolute concentrations of total hemoglobin (HBT(μM/L) and muscular oxygen saturation (SmO_2(%)) was obtained (16). The microvascular O_2 extraction ($E_{\mu vasc}O_2$) was obtained using the following equation (17).

$$E\mu vascO_2 = \left[\frac{SpO_2 - SmO_2}{SpO_2}\right] * 100$$

SpO_2 is the saturation of oxygenated hemoglobin in arterial blood, measured by pulse oximetry in the right hand (POX 010-340; Mediaid, Torrance, CA). SmO_2 is the oxygen saturation of hemoglobin in venous blood within the muscle, measured in the belly of the vastus lateralis muscle of the exercised limb.

For each of these variables, the mean of the three last seconds before the beginning of the MVIC and the mean of the final three seconds of the MVIC was calculated. Consequently, the amplitude variation derived from the difference between these means was obtained.

Maximal voluntary isometric contraction

Isokinetic dynamometry (Con-Trex™, CH 8046 Zurich, Switzerland) was used for MVIC evaluation of the knee extensor muscle of the dominant limb (18). In a sitting position, with 100 ° of knee flexion and the point of support at the distal portion of the leg, the subjects were tested twice on isometric force for 20 seconds with an interval of five minutes between tests. The maximum torque, high torque and total work were obtained.

Statistical analysis

Data normality was verified by the Shapiro-Wilk normality test. For the between-groups analysis, the independent Student t-test was used. The correlations were verified using the Pearson correlation test. The Statistical Process for the Social Sciences software, version 20.0 (SPSS™, Chicago, IL, USA), was used for statistical analysis. The type I error probability was established at 0.05 for all tests.

Results

Demographic data. No significant differences were identified between groups related to age and anthropometric data. Although differences in BMI were not observed, the muscle mass of the right lower limb of the COPD group was 9.8% (p = 0.033) lower than the control group. The COPD group showed, as expected, low percentages of FEV_1 and FEV_1/FVC ratio compared to the predicted. A significantly lower O_2 saturation pulse was identified in the COPD group than in the control group. The hemodynamic variables did not differ between groups, however, a trend was observed (p = 0.084) for increased resting heart rate in the COPD group (Table 1).

Table 1 - General characteristics of the COPD group and control group

Variables	COPD group (n = 11)	Control group (n = 9)	P
Age (Years)	63.7 ± 5.5	65.7 ± 3.8	0.363
Height (cm)	166.3 ± 5.5	170.7 ± 7.8	0.158
Weight (Kg)	70.51 ± 10.7	76.7 ±11.6	0.231
BMI (Kg/m2)	25.4 ± 3.10	26.2 ± 3.33	0,554
LMRLL (kg)	8.3 ± 0.9	9.2 ± 0.5	0.033
FEV1 (% predicted)	44.5 ± 9.6	-	-
FEV1/ FVC (% predicted)	53.0 ± 11.7	-	-
SpO2rest (%)	94.6 ± 1.6	96.6 ± 1.3	0.008
HRrest (bpm)	82 ± 12	73 ± 7	0.084
SBPrest (mmHg)	122.7 ± 9.0	126.6 ± 11.1	0.395
DBPrest (mmHg)	78.1 ± 6.0	77.7 ± 6.6	0.888

Note: Data presented as mean ± standard deviation. BMI (kg/m_2), Body mass index in kilograms per square meter; FEV_1, forced expiratory volume in first second; LM_{RLL}, lean mass in right lower limb ; SpO_2, pulse oxygen saturation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; rest, values obtained at rest. FVC, forced vital capacity.

Muscle performance. In all investigated muscular performance indices ($work_{total}$ (J), $torque_{peak}$ (Nm) and

$torque_{medium}$ (Nm), the COPD group showed significantly lower values, both in the first as well as in the second maximal voluntary isometric contraction (Table 2).

Table 2 - Maximum voluntary isometric contraction evaluation

Variables	COPD group (n = 11)	Control group (n = 9)	p
1ª MVIC			
Work total (J)	1863.4 ± 589.5	2293.2 ± 544.4	0.049
Torquepeak (Nm)	116.1 ± 31.3	148.9 ± 18.6	0.013
Torquemedium (Nm)	88.7 ± 24.0	114.6 ± 27.2	0.037
2ª MVIC			
Work total (J)	1777.1 ± 403.5	2193.9 ± 555.8	0.048
Torquepeak (Nm)	119.0 ± 30.6	145.2 ± 25.1	0.034
Torquemedium (Nm)	88.8 ± 20.2	109.7 ± 27.8	0.037

Note: Data presented as mean ± standard deviation. Maximal voluntary isometric contraction (MVIC); Newton-meters (Nm); Joules (J).

No significant differences were observed in muscle O_2 saturation (SmO_2%) and in microvascular O_2 extraction rate ($E_{\mu vasc}O_2$, %) at rest, when the groups were compared. However, significant differences were observed in the deltas of these variables. The reduction delta of the muscular O_2 saturation, when corrected by the muscle mass of the lower limb, was 53.2% higher (p = 0.044) in the COPD group in MVIC-1 and 149.6% higher (p = 0.006) in MVIC-2 when compared to the control group (Figure 1). When the microvascular O_2 extraction rate was corrected by the amount of muscle mass of the lower limb and also corrected by the total work done (%/kg/J), it was 114.5% higher (p = 0.043) in the COPD group with the MVIC-1 and 210.5% higher (p = 0.015) with the MVIC-2, when compared to the control group (Figure 2).

Significant correlations were observed between the muscle mass of the lower limb with the maximum torque in both groups. But this correlation was stronger in the COPD group (Figure 3).

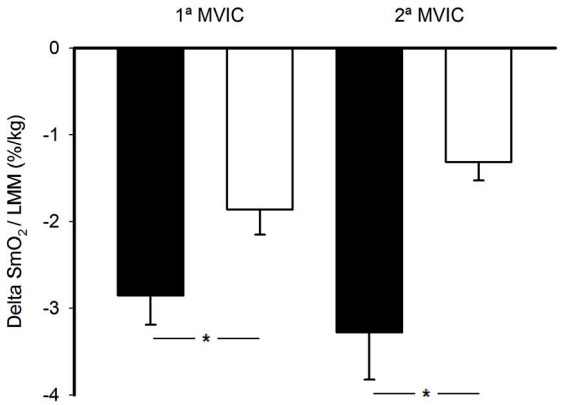

Figure 1 - Mean and Standard Deviation. O2 muscle saturation delta adjusted by the leg muscle mass. Note the worst adaptation to stress in the COPD group by reducing muscle saturation. * P < 0.05 on the analysis between groups.

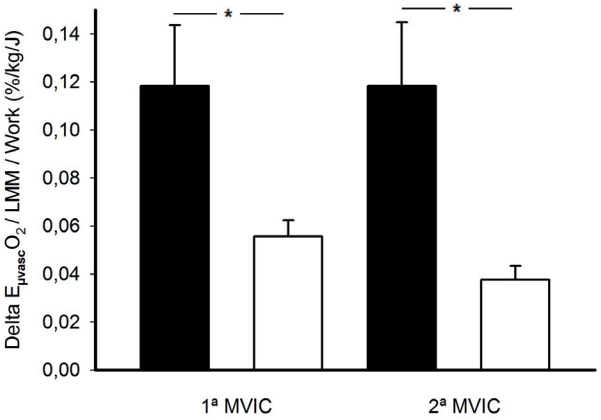

Figure 2 - Mean and standard deviation. Microvascular O2 extraction delta corrected by the leg muscle mass (LMM) and the total work in the MVIC. Note the high energy cost according to the work performed by COPD group by mean of high O2 extraction. * P <0.05 on the analysis between groups.

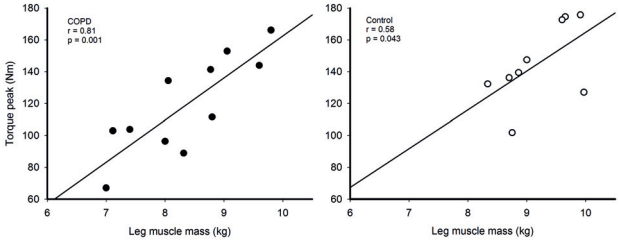

Figure 3 - Pearson's correlation. Nm - Newton meter. Note the significant influence of muscle mass in muscle strength, especially in the COPD group.

Discussion

The main findings of this study were the high O_2 extraction and reduced ability to generate work in the knee extensor muscles in patients with COPD. Consequently, a high O_2 extraction per unit of work was observed.

Low muscular capacity

Several aspects of local and systemic character can justify the low muscle performance observed in different types of physical exercise performed by patients with COPD. However, the maximal voluntary isometric contraction was used in this study, and therefore, systemic factors had less importance in muscle performance. Studies have shown that blood flow is importantly reduced during MVIC (19) and thus, muscle performance is further dependent on the intracellular muscle status. We are aware that during the isometric contractions, blood flow can be significantly reduced by over 25% to 35% of MVIC intensities (19). The reduced oxidative capacity associated with reduced blood flow (↑intramuscular pressure on isometrics) (19) imply a greater resynthesis of ATP by anaerobic pathways with increased lactate, H^+ and potassium imprisonment, with a consequent decline in contractile efficiency (20). This cascade of events, present in healthy individuals, is even more pronounced in COPD. The reduction in muscle oxidative enzymes (19), mitochondrial dysfunction (9), changes in the percentage distribution of type I and II fibers (10) and negative changes in energy metabolism, observed by spectroscopy of phosphorus[31] by magnetic resonance (21), can justify this minor contractile efficiency observed in COPD (Table 2).

Patients with COPD exhibit loss of muscle mass from 18 to 36%, and this loss is associated with increased morbidity and mortality (22 - 24). The reduced contractile efficiency could be justified by this lower lean mass, especially given the strong correlation observed in this study, (Fig 3) and the findings obtained in other studies conducted by this laboratory, in which strong correlations were observed between muscle mass of the lower limb with peak torque, isometric force and total work in patients with COPD (25, 26). However, this scenario was characterized by less muscle mass (agent) and lower torque or generated work (product), which does not explain the increased O_2 extraction observed in this study (constant of proportionality: ↓extraction O_2 ∝ ↓agent ‹=› ↓product).

The high O_2 extraction in COPD

Changes in diffusion and convective transport of O_2 may explain the higher values of O_2 extraction, as well as a greater fatigue in COPD, as demonstrated in detail by Katayama et al (27). However, patients were not hypoxic and did not show clinical signs of hypoxemia during the protocol, in this study. When comparing patients with COPD and healthy people, Chiappa et al., showed that at high intensities of exercise, the O_2 consumption was significantly higher in COPD patients, suggesting a slower kinetics of O_2 delivery during intense exercise microvascular (28). Although in the present study, a higher O_2 extraction was observed, the same mechanistic behavior could not be anticipated by the characteristics of maximum voluntary contraction (↑intramuscular pressure=↓of blood flow).

Many mechanisms interact synergistically to maintain physical effort (29), however MVIC requires a high ATP demand and therefore a significant activation of the anaerobic resynthesis process (phosphocreatine and glycolysis), leading to accumulation of metabolites (e.g., lactate, inorganic phosphate ions, hydrogen) and reduced contractile efficiency (30). However, concomitant activation of type I and type II muscle fibers in a MVIC results in a significant participation of oxidative phosphorylation in this exercise modality (31), and may contribute more significantly (Δ 16%) with the maintenance of contractile efficiency, than the phosphocreatine (% Δ 9) and anaerobic glycolysis (Δ 10%) in the resynthesis of ATP (32). Specifically in COPD, the reduction in the ratio of type I/type II muscle fibers (33) can significantly change the O_2 extraction.

Several studies have shown that the energy cost per unit of work generated is higher in type II fibers (34). A greater extraction of O_2 has been observed in the gastrocnemius muscle (type II fibers) compared to the soleus muscle (type I fibers) during muscle contractions induced by electrical stimulation (35). This behavior is mainly due to the metabolic characteristics of these fibers. The oxidative phosphorylation rate is controlled by the concentration of adenosine diphosphate (ADP), and high concentrations of ADP can be observed in patients with COPD in routine activities such as walking (36). Moreover,

mitochondrial O_2 consumption rate is closely correlated to the muscle phosphocreatine break-down (37), which is greater per unit time in type II fibers (38). It can be assumed that the vascular changes in the musculature of the COPD patients (⬆ % type II fibers) associated with the characteristics of muscle recruitment in the MVIC, would be responsible for the high consumption of O_2, leading to a reduction in muscle O_2 pressure (⬇ PO_2, mmHg), and consequently, to a greater pressure gradient of O_2 extraction in this population.

Clinical applications

The gaining of strength and muscular hypertrophy are closely linked to the intensity of exercise or the percentages of load used. Several studies have shown that working intensities below 30% of one maximal repetition are unable to promote significant adjustments (39). The improvement in muscle strength not only affects the improvement of activities of daily living, but also contributes to the reduction of mortality. Thus, understanding the mechanisms involved in muscle performance in high intensity activities is critical to the adequacy of rehabilitation programs.

Conclusion

In summary, this study confirms the hypothesis that muscle performance is decreased in COPD and, although the maximum force (torque) is dependent on muscle mass, this study provides further support to the concept that less muscular efficiency (work) in COPD is not totally dependent on the amount of muscle mass. The high microvascular O_2 extraction observed suggests that not only quantitative mechanisms, but also qualitative, may be determinants of muscle performance in patients with chronic obstructive pulmonary disease.

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