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Association between respiratory variables and exercise capacity in COPD patients

Associação entre variáveis respiratórias e capacidade de exercício em portadores de DPOC

Asociación entre variables respiratorias y capacidad de ejercicio en portadores de EPOC

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RESUMO

Justificativa e Objetivos: A DPOC é caracterizada pela limitação progressiva do fluxo aéreo associada a uma resposta inflamatória. O objetivo do estudo foi avaliar a influência e a associação das variáveis respiratórias sobre a capacidade de exercício em portadores de DPOC. **Métodos:** Estudo transversal avaliou 39 portadores de DPOC para obtenção do volume expiratório forçado no primeiro segundo (VEF_1) e a capacidade vital forçada (CVF). A força muscular respiratória (FMR) avaliada em seus componentes de pressão inspiratória máxima (PImax) e pressão expiratória máxima (PEmax). Capacidade de exercício avaliada pelo Teste de Caminhada de Seis Minutos (TC6m) e *Incremental Shuttle Walking Test* (ISWT). **Resultados:** O VEF_1 (% 39,8±15,3) e CVF (% 60,2±17,1) se encontram reduzidos em relação ao predito classificando-os em estadiamento grau II (21%), III (51%) e IV (28%). A PImax (92,7±14,6 % predito) e PEmax (97,6±19,0 % predito) se encontram dentro dos valores previsto para os sujeitos. Evidenciada correlação moderada entre a distância percorrida no ISWT *vs* VEF_1 (r=0,35; p=0,02) e ISWT *vs* CVF (r=0,42; p<0,001), TC6m *vs* VEF_1 (r=0,38; p=0,01) e TC6m *vs* CVF (r=0,52; p<0,001). A FMR se correlacionou diretamente com a distância percorrida no ISWT [PImax (r=0,44; p=0,005); PEmax (r=0,57; p<0,001)] e com TC6m [PImax (r=0,43; p=0,006); PEmax (r=0,59; p<0,001)]. A PEmax e o VEF^1 influenciaram 37% do desempenho no TC6m e a PEmax influenciou isoladamente 58% da distância percorrida no ISWT. **Conclusão:** A força muscular respiratória e os volumes pulmonares reduzidos se associaram e influenciaram diretamente na capacidade de exercício máximo e submáximo de portadores de DPOC.

Descritores: *Doença Pulmonar Obstrutiva Crônica. Teste de esforço. Força muscular.*

ABSTRACT

Background and Objectives: Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow limitation associated with an inflammatory response. The aim of the study was to evaluate the influence and the association of respiratory variables on exercise capacity in COPD patients. **Methods:** A cross-sectional study evaluated 39 COPD patients to obtain forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). Respiratory muscle strength (RMS) was evaluated at its maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) components. Exercise capacity was assessed by Six-Minute Walk Test (6MWT) and Incremental Shuttle

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Walking Test (ISWT). **Results:** FEV_1 (39.8±15.3%predicted) and FVC (60.2±17.1% predicted) were reduced, which classified them in stages II (21%), III (51%) and IV (28%). MIP (92.7±14.6% predicted) and MEP (97.6±19.0% predicted) were within the expected values. A moderate correlation was observed between the ISWT *vs* FEV_1 (r=0.35;p=0.02) and ISWT *vs* FVC (r=0.42;p<0.001), 6MWT *vs* FEV_1 (r=0.38;p=0.01) and 6MWT *vs* FVC (r=0.52;p<0.001). RMS showed a moderate correlation with the ISWT [MIP (r=0.44;p=0.005); MEP (r=0.57;p<0.001)] and 6MWT [MIP (r=0.43;p=0.006); MEP (r=0.59;p<0.001)]. MEP and FEV_1 influenced 37% of performance at the 6MWT and MEP alone influenced 58% of distance walked at the ISWT. **Conclusion:** Reducing both respiratory muscle strength and lung volumes were associated with changes in exercise and they adversely affected the maximum and submaximal exercise capacity in COPD patients.
Keywords: *Pulmonary Disease, Chronic Obstructive. Exercise Test. Airway obstruction. Muscle strength.*

RESUMEN

Justificación y objetivos: La EPOC se caracteriza por la limitación progresiva del flujo aéreo asociada a una respuesta inflamatoria. El objetivo del estudio fue evaluar la influencia y la asociación de las variables respiratorias sobre la capacidad de ejercicio portadores de EPOC. **Métodos:** Estudio transversal evaluó 39 portadores de EPOC para obtener el volumen espiratorio forzado en el primer segundo (VEF_1) y la capacidad vital forzada (CVF). La fuerza muscular respiratoria (FMR) evaluada en sus componentes de presión inspiratoria máxima (PImax) y presión espiratoria máxima (PEmax). Capacidad de ejercicio evaluada por la Prueba de Caminata de seis minutos (TC6m) e *Incremental Shuttle Walking Test* (ISWT). **Resultados:** El VEF_1 (% 39,8 ± 15,3) y CVF (% 60,2 ± 17,1) se encuentran reducidos en relación al predicado clasificándolos en estadificación grado II (21%), III (51%) y IV (28%). La PImax (92,7 ± 14,6% predito) y PEmax (97,6 ± 19,0% predito) se encuentran dentro de los valores previstos para los sujetos. Se observó una correlación moderada entre la distancia recorrida en el ISWT *vs* VEF_1 (r = 0,35; p = 0,02) e ISWT *vs* CVF (r = 0,42; p <0,001), TC6m *vs* VEF_1 (r = 0,38; p = 0,01) y TC6m *vs* CVF (r = 0,52; p <0,001). La FMR se correlacionó directamente con la distancia recorrida en el ISWT [PImax (r = 0,44; p = 0,005); (P = 0,001) y con TC6m [PImax (r = 0,43; p = 0,006); PEmax (r = 0,59; p <0,001)]. La PEmax y el VEF_1 influenciaron el 37% del rendimiento en el TC6m y la PEmax influenció aisladamente el 58% de la distancia recorrida en el ISWT. **Conclusión:** La fuerza muscular respiratoria y los volúmenes pulmonares reducidos se asociaron e influenciaron directamente en la capacidad de ejercicio máximo y submáximo de portadores de EPOC.
Palabras Clave: *Enfermedad Pulmonar Obstructiva Crónica. Prueba de Esfuerzo. Obstrucción de las Vías Aéreas. Fuerza Muscular.*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by progressive airflow limitation associated with an inflammatory response to harmful particles and gases, mainly caused by smoking.[1] Inflammatory cells are active and there are increased plasma levels of proinflammatory cytokines in the systemic circulation that causes oxidative stress, which, in turn, will result in musculoskeletal disorders and reduced exercise capacity.[2] Therefore, pulmonary dysfunction, systemic manifestations and increased dyspnea lead to progressive worsening in physical fitness and inactivity.[3,4] It is noteworthy that physical inactivity in COPD patients predisposes them to heart disease, increased risk of hospitalizations and higher mortality rate.[4,5]

Exercise capacity is commonly assessed by maximal and submaximal tests, which reflect different pathophysiological alterations in COPD regarding aerobic, muscular strength, cardiovascular and respiratory fitness systems.[6-8] The submaximal exercise capacity can be assessed by the Six-Minute Walk Test (6MWT) and the maximal capacity through the Incremental Shuttle Walking Test (ISWT) and both allow assessing the impact of COPD on the quality of life and activities of daily living (ADLs).[6,7]

The causes and mechanisms of exercise intolerance in these patients are still complex and involve respiratory function, gas exchange limitations and reduced peripheral skeletal muscle mass.[9,10] Thus, it is extremely important to identify and understand what changes in pulmonary volumes and reduction of respiratory muscle strength may impact the submaximal and maximal exercise capacity in patients with moderate - very severe COPD. Our aim was to evaluate the influence and association of respiratory variables (pulmonary function and respiratory muscle strength) on maximal and submaximal exercise capacity of patients with COPD. We hypothesized that respiratory changes such as reduced lung volumes and respiratory muscle strength may directly influence exercise capacity in COPD patients.

METHODS

Study design

This cross-sectional study was designed following recommendations of the STROBE statement. The patients were screened from Pulmonary Rehabilitation (PR) program of Hospital Santa Cruz, in Santa Cruz do Sul, state of Rio Grande do Sul, Brazil and performed the evaluations in the PR. The study was approved by the Research Ethics Committee of University of Santa Cruz do Sul (Protocol N. 1.514.705) and all subjects involved in the study agreed to participate and signed the Informed Consent Form.

Subjects

The initial sample consisted of 41 COPD patients. Two subjects were excluded for not meeting the study inclusion criteria, which determined a clinical diagnosis of COPD attained by spirometry test, with a sedentary life style and clinically stable. Individuals with musculoskeletal disorders and/or neurological sequelae that affected the musculoskeletal system, those with cognitive impairment, skin lesions in the lower extremities, non-controlled ischemic heart disease or those with disease exacerbations within 30 days prior to the study were excluded.

Measurements

The evaluations were carried out in 3 days: (1) the sample was evaluated regarding its demographic, clinical and epidemiological profile, including date of birth, sex, smoking history and body mass index (BMI), pulmonary function and respiratory muscle strength (RMS); (2) Submaximal exercise capacity; (3) Maximal exercise capacity.

Pulmonary function

Pulmonary function was assessed using a digital spirometer (EasyOne®, Model 2001, Zurich, Switzerland) and the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and the association between these variables (FEV_1/FVC) were obtained. The test was performed according to guidelines of the American Thoracic Society and the results analyzed according to the values predicted by Pereira, Sato and Rodrigues (2007).[11,12] Disease staging was assessed according to GOLD (2018), as mild (GOLD I), moderate (GOLD II), severe (GOLD III) and very severe (GOLD IV).[1]

Respiratory muscle strength

RMS was evaluated at its maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) components using a digital manometer (MDI® model MVD300, Porto Alegre, Brazil). The highest value obtained from the three measurements was considered for the assessment and these values were compared with those described in literature and expressed as percentage of predicted values. [13]

Maximal exercise capacity

The Incremental Shuttle Walking Test (ISWT) was performed according to Holland et al., (2014) in a 10-meter corridor, signaled at each end by a cone with a 0.5-meter setback.[14] The subject was instructed regarding the incremental nature of the test, which is indicated by sound media that emits short and long signals. The short signals demarcate the meters during the level and the long signal indicates change in level and the increase in step cadence. The test was terminated when the subject showed intolerance or when he/she reached the end of the corridor up to the sound signal for two consecutive times.[15] The percentage of the predicted walked distance (dISWT) was calculated considering sex, age, height and weight of each patient.[14]

Submaximal exercise capacity

The 6MWT was carried out according to the guidelines of the ATS (2006), in order to measure the distance walked during the 6-minute test on a flat 30-meter corridor.[16] The subjects were instructed to walk as far as possible, at a constant speed. The 6MWT was developed based on the study by Holland et al. (2014).[15] The test was terminated when the subject showed intolerance. The percentage of the predicted distance walked was calculated considering sex, age, height and weight of each patient based on the equation of Enright et al. (2003).[17]

Statistical analysis

The data were analyzed using the SPSS software (version 20.0). The results were evaluated for normality using the Shapiro-Wilks test and showed descriptively as mean and standard deviation, frequency (%) or median (minimum and maximum values). The association between variables was assessed by Spearman's correlation. Simple and multiple linear regression models were used to evaluate the effect of independent variables on the distance traveled during the exercise testing. The significance of the final model was evaluated by the ANOVA F-test and quality adjustment by the adjusted determination coefficient (adjusted R^2). Residues were evaluated according to the assumptions of normality, constant variance and independence. Significance level was set at $p < 0.05$.

RESULTS

The sample consisted of 39 patients with COPD and their clinical characteristics are showed in Table 1. Where we observed predominance of male, obese, staging of severe disease and low distance of predicted in the ISWT.

Table 1. Clinical characteristics of the COPD patients and performance in the exercise tests.

Variables	COPD (n=39)
Age (years)	63.5±7.3
Sex, male n (%)	22 (56.4)
Ethnicity	
Caucasian n (%)	34 (87,2)
Non-caucasian n (%)	5 (12,9)
BMI (Kg/m²)	27.5±6.4
BMI Classification	
Underweight n (%)	6 (15.4)
Normal weight n (%)	13 (33.3)
Obesity n (%)	20 (51.3)
Smoking Status	
Former n (%)	31 (79.5)
Current n (%)	8 (20.5)
RMS	
MIP (cmH2O)	- 63.5±24.2
MIP (%predicted)	92.7 ± 14.6
MEP (cmH_2O)	108.1±38.5
MEP (%predicted)	97.6±19.0
Pulmonary function	
FEV1 (L/s)	1.0±0.4
FEV1 (L/s) (% predicted)	39.8±15.3
FVC (L/s)	2.0±0.7
FVC (% predicted)	60.2±17.1
FEV1/FVC	0.6 (0.2-82.0)
FEV1/FVC (% predicted)	65.9 (33.0-104.0)
Staging (GOLD)	
Stage II n (%)	8 (21)
Stage III n (%)	20 (51)
Stage IV n (%)	11 (28)

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ISWT	
Distance (meters)	257.4±109.2
Distance % predicted	38.1±16.2
6MWT	
Distance 6MWT (meters)	390.9±133.8
Distance % predicted	86.6±38.2

Data are presented as mean ± SD and median (minimum and maximum); n (%): number sample (frequency);); COPD: Chronic Obstructive Pulmonary Disease; BMI: Body Mass Index; RMS: Respiratory Muscle Strength; MIP: Maximum Inspiratory Pressure; MEP: Maximum Expiratory Pressure; FVC: Forced Vital Capacity; FEV1, Forced Expiratory Volume in the 1 second; FEV_1/FVC= Forced Expiratory Volume in the 1 second / Forced Vital Capacity; GOLD: Global Initiative for Chronic Lung Disease; ISWT: Incremental Shuttle Walking Test; 6MWT: 6-Minute Walk Test.

A moderate and significant correlation was demonstrated between the distance walked in the ISWT and FEV_1 (r=0.35; p=0.028) and FVC (r=0.42; p=0.007) and between the distance walked in the 6MWT and FEV_1 (r =0.38; p=0.019) and FVC (r=0.52; p=0.001) (Figure 1). Demonstrating the direct association between pulmonary volumes with maximal and submaximal exercise capacity.

RMS was moderately correlated with the distance at the ISWT [MIP (r =0.44; p=0.005); MEP (r=0.57; p <0.001)] and at the 6MWT [MIP (r=0.43; p=0.006), MEP (r= 0.59; p<0.001)] (Figure 2). Demonstrating the direct association between RMS with maximal and submaximal exercise capacity.

A multiple linear regression test showed that MEP and FEV_1 influenced the performance at the 6MWT by 37% (Table 2). Simple linear regression showed that MEP alone influenced the distance walked at the Incremental Shuttle Walk Test by 58% (Table 2).

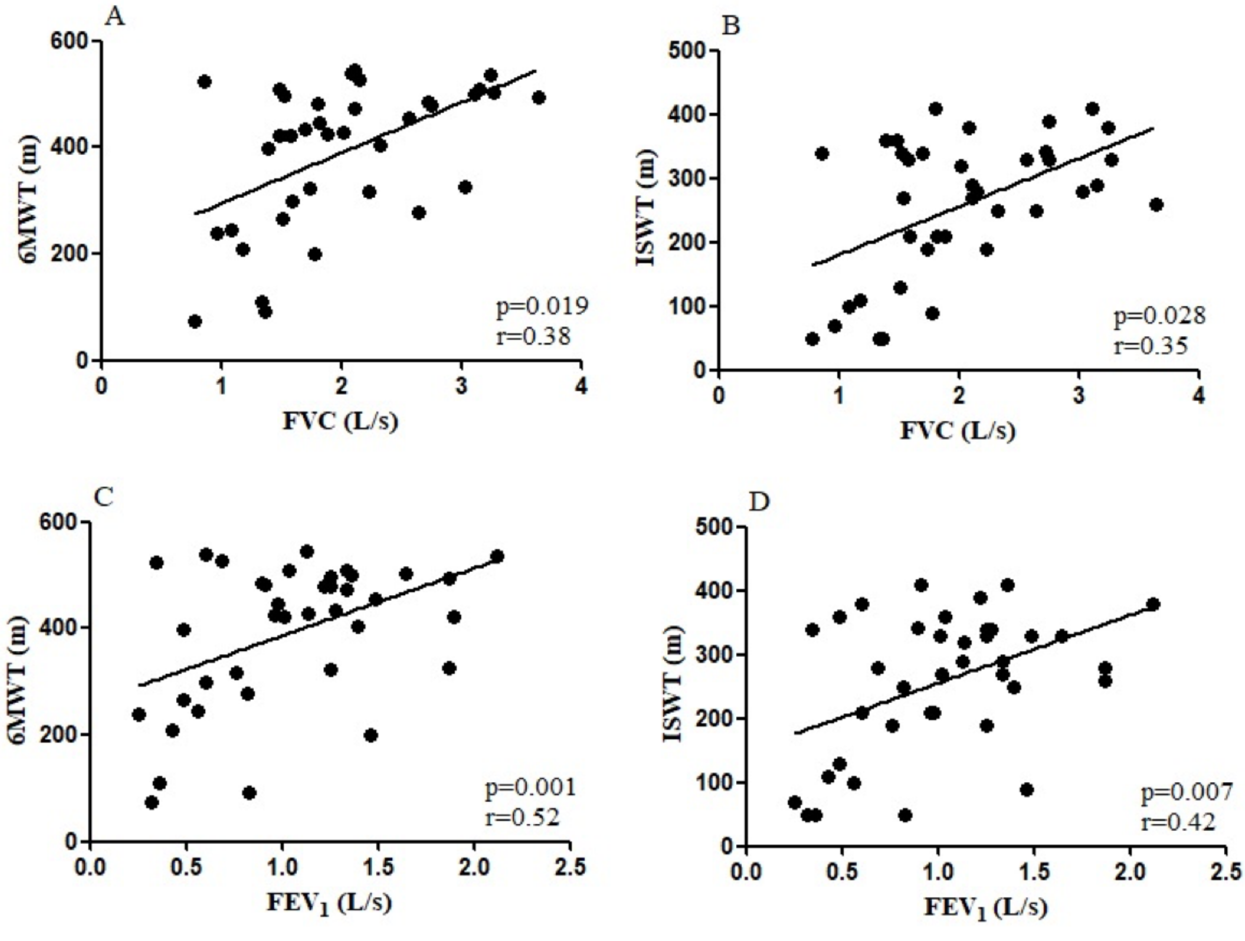

Figure 1. Correlations were also observed between respiratory muscle strength with exercise capacity in COPD

A. Correlations between maximum inspiratory pressure (MIP) and distance Incremental shuttle walking test (ISWT);
B. Correlations between maximum inspiratory pressure (MIP) and distance 6-minute walk test (6MWT);
C. Correlations between maximum expiratory pressure (MEP) and distance Incremental shuttle walking test (ISWT);
D. Correlations between maximum expiratory pressure (MEP) and distance 6-minute walk test (6MWT). The association between the variables was analyzed by using Spearman´s correlation test (p<0,05).

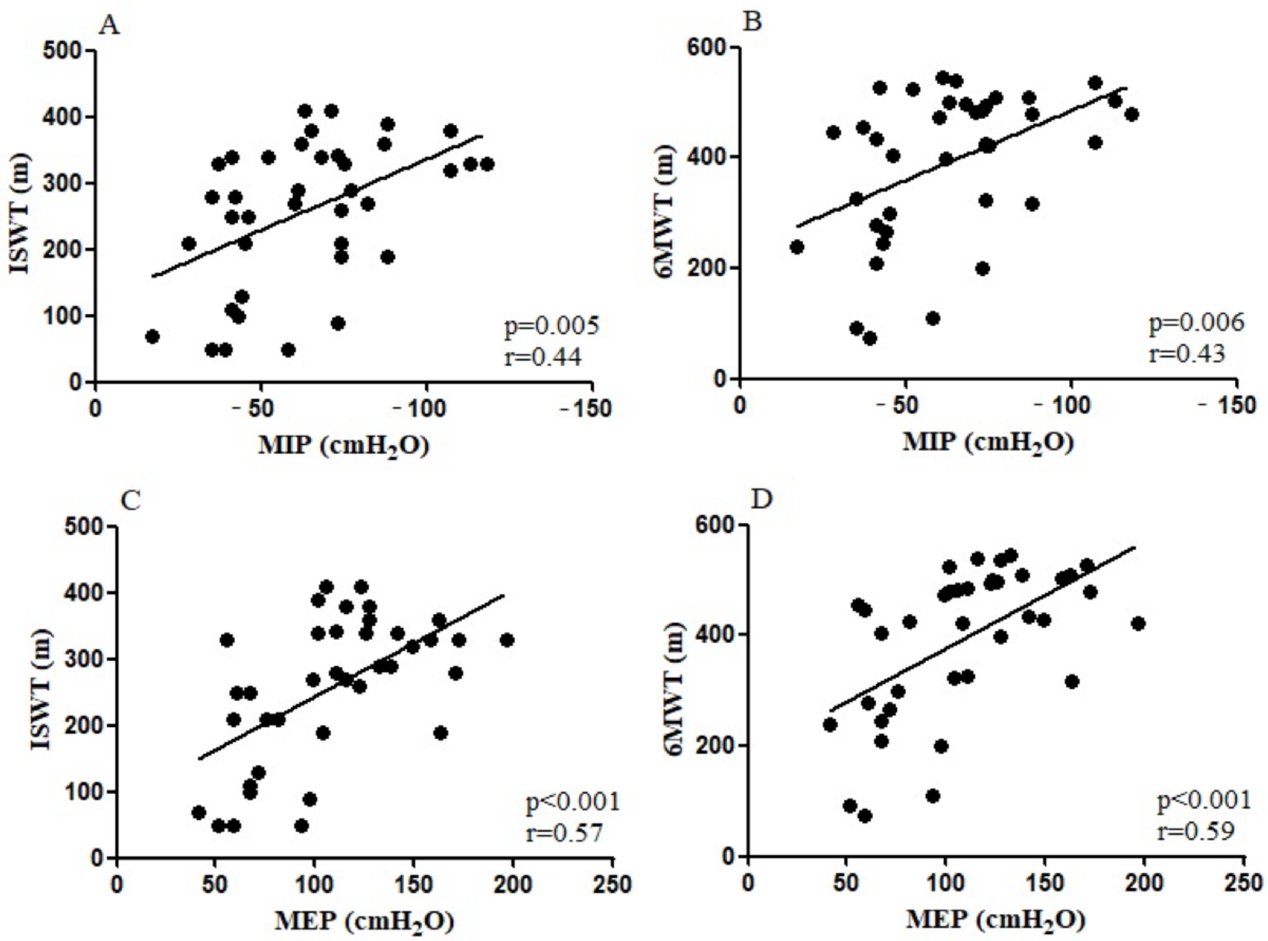

Figure 2. Correlations were also observed between pulmonary function with exercise capacity in COPD patients.

A. Correlations between forced vital capacity (FVC) and distance 6-minute walk test (6MWT);
B. Correlations between forced vital capacity (FVC) and distance Incremental shuttle walking test (d ISWT);
C. Correlations between forced expiratory volume in the 1 second (FEV1) and distance 6-minute walk test;
D. Correlations between forced expiratory volume in the 1 second (FEV1) and distance Incremental shuttle walking test.
The association between the variables was analyzed by using Spearman´s correlation test (p<0,05).

Table 2. Linear regression analysis to identify influence of clinical variables on exercise capacity.

To predict distance in 6MWT from MEP and FEV_1 [$R^2_{adjusted}$= 0.374; F= 12.37 (*p*= 0.001)].		
Variables	**B coefficient**	***p*-value**
Constant	129.23	0.026
MEP (cmH_2O)	1.61	0.001
FEV_1 (L/s)	85.79	0.027
To predict distance in ISWT from MEP [R^2adjusted= 0,577; F= 17,94 (*p*= <0,001)].		
Variables	**B coefficient**	***p*-value**
Constant	82,89	0,050
MEP (cmH_2O)	1,61	<0,001

MEP: Maximum Expiratory Pressure; FEV_1: Forced Expiratory Volume in the 1 Second;

DISCUSSION

Our results showed reduced respiratory capacity and moderate associations between pulmonary function and respiratory muscle strength with performance at the 6MWT and ISWT, with a reduced performance being shown in submaximal and maximal exercise capacity as demonstrated by the regression models used. In COPD patients, some factors directly contribute to the reduction in exercise capacity, among which nutritional depletion, skeletal muscle dysfunction and respiratory muscle weakness are emphasized.[18]

Studies that show the influence of FEV_1 and FVC reduction on exercise capacity used the 6MWT so that the use of ISWT and its association with respiratory muscle strength leads to original results in our study.[19,20] The response required by the 6MWT reflects the efforts made in ADL and the short distance walked in the test reproduces such limitations in daily life, which may also be used as a predictor of exercise capacity and COPD severity.[19,21] That is because exercise intolerance is multifactorial in patients with COPD, involving more effort and oxygen consumption by respiratory muscles, which are at a mechanical disadvantage due to dynamic pulmonary hyperinflation, and lower-limb skeletal muscle dysfunction.[22] Notwithstanding the evidence in the literature, in our study FEV_1 and MEP influenced 37% of the 6MWT; however, this finding did not reflect on the test performance, which reached on average 86% of the predicted.

Because ISWT induces a progressive effort and requires physiological responses from the cardiorespiratory system that reflect the aerobic capacity, it has been used to evaluate the effectiveness of rehabilitation programs (cardiac and pulmonary), being considered less stressful to the cardiovascular system when compared to the treadmill stress testing with progressive load, but more stressful than the 6MWT.[23,24] We found that the MEP explains 58% of the performance at the ISWT and this is a relevant finding, as COPD patients in this study reached an average of 38% of the predicted value for this test.

It is known that the pathophysiological mechanism of COPD can cause respiratory muscle weakness and peripheral muscle dysfunction and it should be emphasized that these aspects can be explained by changes in muscle fiber composition and subsequent atrophy.[25,26] Respiratory muscle weakness may be associated with increased mortality in patients with COPD and there is evidence that expiratory muscle weakness is a risk factor for the occurrence of exacerbations by triggering hyperinflation, increased sensation of dyspnea and, in individuals with severe COPD, it may reflect CO_2 retention during exercise, thus hindering daily activities or exercise.[25,27] As cardiorespiratory responses require more effort in ISWT due to the influence of changes in expiratory muscle strength, they were also more significant in these patients with COPD.

As a limitation, it should be emphasized that only patients with GOLD II to IV were selected for this study and early-stage disease could have a lower impact on respiratory changes. In clinical practice, using spirometry and manometry, one cannot predict exercise intolerance. Therefore, it is necessary to use and associate functional criteria, such as submaximal and maximal exercise capacity, to better quantify, diagnose and determine treatment for patients with moderate to very severe COPD. Moreover, due to the associations found by this study, we suggest that by using ISWT, it is possible to monitor disease progression, as well as disease response to PR programs.

In conclusion, we emphasize that changes in respiratory muscle strength and assessed pulmonary volumes were directly associated with the reduction in maximal and submaximal exercise capacity in patients with COPD.

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