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ORIGINAL ARTICLE

Influence of pulmonary rehabilitation in patients with COPD exacerbator phenotype

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ABSTRACT

Objective: To verify if there are differences in Chronic Obstructive Pulmonary Disease (COPD) patient exacerbator and non-exacerbator phenotypes undergoing a Pulmonary Rehabilitation Program (PRP). **Methods:** A real life retrospective study included outpatients with COPD from public primary care who completed a 12-weeks PRP, three times a week. All were assessed before and after PRP using the six-minute walk test (6MWT), the modified Medical Research Council (mMRC) dyspnea index, quality of life and Body-mass Index, airflow Obstruction, Dyspnea and Exercise (BODE index). **Results:** A total of 151 patients were analyzed and mean age was 65.0 ± 8.1 years and mean Forced Expiratory Volume (FEV) 1% of predicted was 39.8 ± 15.9. The predominant gender was male (66.9%). Of these patients 31 (20.5%) were exacerbator phenotype There was a significant improvement in the mean distance in the 6MWT in both groups, with the largest change observed in the exacerbator group [mΔ (95% CI): 84.9 (57.1-112.6) vs. 48.6 (37-60.2) p= 0.018]. Significant reduction in dyspnea on the mMRC scale occurred in both groups, with the highest intensity in the exacerbator group [mΔ (95% CI): - 0.8 (-1.11 to 0.51) vs. -1.6 (-2.20 to -1.13) p = 0.006]. Improvement in the BODE index occurred in both groups, but the mean variation was also significantly greater in the exacerbator group [mΔ (95% CI): -1.44 (-2.17 to -0.70) p= 0.045]. **Conclusion:** Patients with COPD exacerbator phenotype had a greater magnitude of response to PRP (36 meters) when compared to non-exacerbator phenotype regardless the severity of airflow obstruction, also showing improvement in prognosis measured by the BODE index.

Keywords: Chronic obstructive pulmonary disease; Phenotype; Rehabilitation.

INTRODUCTION

The natural history of Chronic Obstructive Pulmonary Disease (COPD) is punctuated by exacerbations, especially in patients with moderate to severe airflow obstruction. These exacerbation events are characterized by a change in the intensity of respiratory symptoms, which may require switches of regularly used medication. An exacerbator is defined as a patient diagnosed with COPD who has presented two or more exacerbations in the past year or at least one exacerbation requiring hospitalization.[1] These exacerbations must be separated by at least four weeks from the end of the treatment of the last exacerbation or six weeks from the beginning of the event.[2] A recent study[3] tracking more than two thousand COPD patients showed that the best predictor of an exacerbation was the history of exacerbations in the previous year.

Pulmonary Rehabilitation (PR) is a comprehensive intervention based on thorough patient assessment, followed by specific therapies that include, but are not limited to, physical training, education and changing of attitudes, which are designed to improve patients' physical and psychological condition with Chronic Respiratory Diseases (CRDs), in addition to promoting long-term adherence to health-improving behaviors.[4] Since exacerbations have a negative and significant impact on quality of life, disease progression, mortality and health treatment costs, pulmonary rehabilitation has been recommended as a more comprehensive strategy, in addition to pharmacological treatment.[1]

Currently, pharmacological management of patients with COPD is based on phenotypes, and the exacerbator phenotype poses a bigger therapeutic challenge as it presents greater morbidity and higher mortality.[5] Among all therapeutic strategies to reduce exacerbations and hospitalizations, there is still a gap in the understanding of the role of PR.[6-8] Since the studies that address PRP do not have an approach based on phenotypes, as all COPD patients have an indication for this type of treatment, the aim of the present study was to verify whether COPD patients with exacerbator and non-exacerbator phenotypes respond differently when treated in a Pulmonary Rehabilitation Program (PRP).

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METHODS

A real-life retrospective study was undertaken with COPD patients from the public outpatient primary care network from March 2005 to December 2018, whose clinical data were collected at the time of evaluation by physicians and other professional members of the PRP. Patients were followed for a period of twelve weeks, when they finished the Program and were reassessed by all professionals. The PRP is an extension project serving patients in the pulmonology and in primary care outpatient clinics of the municipality of Novo Hamburgo, in the state of Rio Grande do Sul (RS) since 2002. The study protocol was approved by the Ethics Committee of the University where the study was developed and all participants signed a Free and Informed Consent Form (ICF).

The COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards, using patients' clinical history, physical examination and confirmation of airflow obstruction measured by means of the ratio of Forced Expiratory Volume in one second (FEV1) with respect to Forced Vital Capacity (FVC) under 70 after the use of a bronchodilator.[1] A patient with a COPD diagnosis was considered an exacerbator if they had two or more exacerbations in the previous year or one exacerbation requiring hospitalization.[1] In order to minimize systematic bias, no patient was included for treatment during exacerbation, and those patients who did not complete PRP were also excluded from the analysis even if they presented all the clinical information necessary for diagnosis and baseline data.

Patients were asked about their degree of dyspnea according to the certified version of the modified Medical Research Council (mMRC) dyspnea scale for COPD patients, whose score comprises five levels ranging from zero to four in accordance with the different activities that lead to shortness of breath: 0: no dyspnea, except after strenuous exercise; 1: shortness of breath when walking quickly on level ground or climbing a gentle slope; 2: walks more slowly than a person of the same age on level ground due to shortness of breath, or needs to stop to catch their breath; 3: stops to catch their breath after walking one block (90 to 120 m) or after a few minutes on level ground; 4: too dyspneic to leave the house or dyspneic when dressing up.[9]

The following variables were considered for calculation of the Body-mass Index, airflow Obstruction, Dyspnea and Exercise (BODE index): Body Mass Index (BMI); forced expiratory volume in one second, as a percentage of predicted values (FEV1% predicted); mMRC score and the distance covered in the Six-Minute Walk Test (6MWT). The score was considered according to the results obtained for the four variables (0-3 for FEV1; 0-3 for mMRC; 0-3 for DPTC6 and 0-1 for BMI),[3] with the total score ranging from 0 to 10 (higher scores indicate greater severity).[10]

To assess quality of life, the Saint George Hospital Quality of Life Questionnaire (SGRQ) was used. This questionnaire comprises three domains: symptoms, activities, and impact, plus total. The questionnaires, containing objective questions, were handed to patients, who were asked to read, interpret and mark the answers. Values above 10% reflected an altered quality of life in a given domain. Reductions equal to or greater than 4% after an intervention, in any domain or in the total sum of points, indicated a clinically significant improvement in the patients' quality of life.[11]

The 6MWT was performed according to the American Thoracic Society (ATS) criteria,[12] and the following variables were monitored during the test: Heart Rate (HR) and peripheral oxygen saturation (SpO2), using a Morrya® model 1001 oximeter (Ipiranga - São Paulo State, Brazil). The Borg CR-10 Scale was used to measure the sensation of dyspnea at the beginning and end of the 6MWT. The test was carried out on a level corridor, with previously demarcated distances of 10 m. The entire corridor measured 50 m, and the distance traveled by the patient was measured at the end. The patient's height was checked using a Cardiomed wall stadiometer and weight was measured using a Welmy scale (Santa Bárbara do Oeste, São Paulo State, Brazil). With these data, the BMI was calculated using the weight divided by height squared. Application of SGRQ and 6MWT before and after PRP was performed on different days. A reference equation developed for the Brazilian population was used to calculate the predicted value of the distance covered during the 6MWT.[13]

The PRP consisted of a multidisciplinary program, lasting three months, during which patients received medical, psychological, nutritional and physical training applied by a physiotherapist and physical educator. Patients performed warm-ups, aerobic exercises, exercises to gain muscle strength and stretches. Warm-up: functional diagonals were performed for upper limbs and lower limbs. Aerobic exercises were performed on a Moviment brand treadmill (Pompeia, São Paulo State, Brazil), with progressive training time varying between 5 and 30 minutes of walking, and speed variation according to the patient's subjective perception of effort and HR. Strength training for upper and lower limbs, on the other hand, was performed on weight training equipment (high pulley, extensor, supine position and dorsal chair) of the Tech Press brand (São Paulo, Brazil) at intensities varying between 50 and 80% of the maximum load, obtained in the Maximum Load Test performed by the physical educator and, at the end of the exercises, patients stretched the main muscle groups involved in the training.

Sample size was calculated using G*Power for Windows, version 3.1.9.2 software (Franz Faul, Universitat Kiel, Germany). A minimum of 29 individuals in each group was needed to make up the study sample in order to detect a minimum difference of 30 meters in the 6MWT (effect size equal to 0.75) between groups after PRP, adopting $\alpha = 5\%$ and test power $(1-\beta)$ equal to 80%.

Data processing and analysis were performed using the Statistical Package for the Social Sciences (SPSS)

software version 21.0. Descriptive analysis consisted of means, standard deviations, medians, percentiles and proportions. The Shapiro-Wilk and Levene tests, respectively, were used to verify compliance with the assumptions of data normality and homogeneity of variances between groups. Fisher's exact test was used in order to verify the association between categorical variables. Continuous variables were compared by Student's *t* test for independent samples. Continuous variables of repeated measurements were analyzed using Generalized Estimation Equations (GEE). Statistical significance was set at $p < 0.05$.

RESULTS

Out of a total of 367 patients enrolled in the PRP, 151 patients diagnosed with COPD who completed the Program were included retrospectively in the study and had their pre- and post-rehabilitation data analyzed (Figure 1). Of the 151 patients who completed the three months of PRP, the majority (79.5%) were considered as belonging to a non-exacerbator phenotype. The mean age of the patients was 65 ± 8.1 years and, of these, the majority were men (66.9%). The average BMI was 25.4 ± 4.8 kg / m-$_2$. As shown in Table 1, the groups showed similar results with regard to lung function. However, in FEV1% of predicted, the group of patients considered as exacerbating had a significantly lower average (41.1 ± 16.3 vs. 34.3 ± 13.1; $p < 0.05$). The 6MWT variables, level of dyspnea and BODE index, as well as smoking burden, were not different between groups. Exacerbation average was 0.8 ± 1.4, with the non-exacerbator group having an average of 0.2 ± 0.4 and the exacerbator group an average of 3.2 ± 1.8. The drug treatment used is described in both groups.

The results regarding distance walked, dyspnea index, prognosis and quality of life had a statistically significant

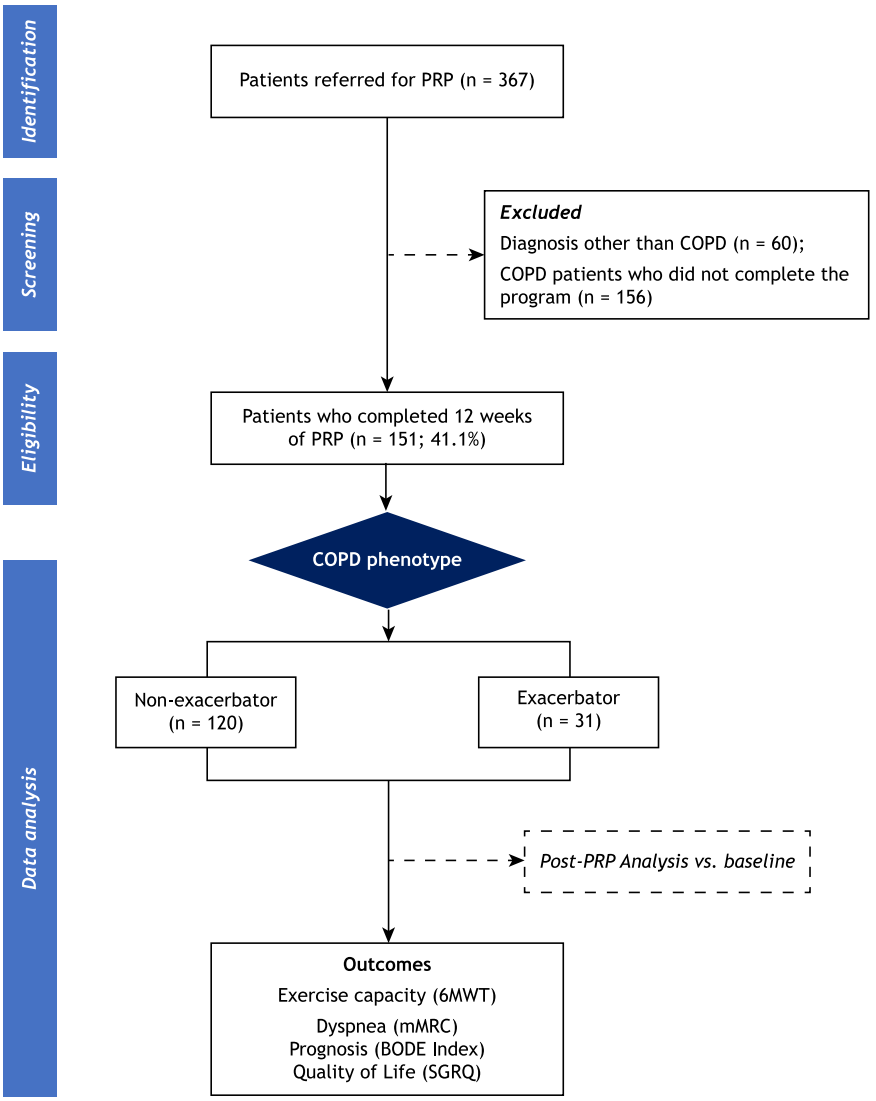

Figure 1. Flowchart of inclusion of patients in the study. 6MWT: Six-Minute Walk Test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. COPD (Chronic Obstructive Pulmonary Disease), PRP (Pulmonary Rehabilitation Program).

Table 1. Baseline characteristics of 151 patients diagnosed with COPD undergoing a pulmonary rehabilitation program.

Variable	All (n = 151)	Non exacerbator (n = 120)	Exacerbator (n = 31)
Age, years	65.0 ± 8.1	65.1 ± 8.4	64.9 ± 6.8
BMI, kg/m^{-2}	25.4 ± 4.8	25.3 ± 4.6	25.7 ± 5.5
Gender			
Male	101 (66.9)	79 (65.8)	22 (71)
Female	50 (33.1)	41 (34.2)	9 (29)
Lung Function			
FVC, L	2.29 ± 0.88	2.29 ± 0.91	2.26 ± 0.81
FVC, % of predicted	64.7 ± 19.5	64.9 ± 20.1	63.6 ± 17.4
FEV_1, L	1.12 ± 0.55	1.15 ± 0.57	1.0 ± 0.47
FEV_1, % of predicted	39.8 ± 15.9	41.1 ± 16.3	34.3 ± 13.1*
FEV_1/ FVC	49.1 ± 13.8	50.0 ± 13.4	45.3 ± 14.9
Six-Minute Walk Test (6MWT)			
6MWD baseline (m)	392.4 ± 96.7	396.4 ± 94.9	376.1 ± 103.9
Distance predicted (m)[a]	543.5 ± 33	543.1 ± 33.4	545.4 ± 31
mMRC (0-4)	2.13 ± 1.32	2.11 ± 1.31	2.19 ± 1.36
BODE Index (0-10)	3.5 ± 1.8	3.3 ± 1.8	4.3 ± 1.5
Packs/year, mean (25-75)	35 (16-75)	35 (18-74)	42.5 (1-83)
Number of exacerbations in last year	0.8 ± 1.4	0.2 ± 0.4	3.2 ± 1.8**
Spirometric classification, GOLD			
Mild	1 (0.7)	1(0.8)	0 (0)
Moderate	39 (25.8)	33 (27.5)	6 (15.4)
Severe	61 (40.4)	50 (41.7)	11 (35.5)
Very severe	50 (33.1)	36 (30)	14 (45.2)
Medication treatment			
LABA	20 (13.2)	14 (11.7)	6 (19.4)
LAMA	31 (20.5)	25 (20.8)	6 (19.4)
LABA + ICS	46 (30.5)	38 (31.7)	8 (25.8)
LABA + ICS + LAMA	23 (15.2)	18 (15)	5 (16.1)

Values are expressed as means, standard deviations (except for smoking load, expressed as average and 25 and 75 percentiles) and proportions; BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; L: Liters 6MWT: Six-Minute Walk Test; 6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council*; LABA: *Long-Acting Beta$_2$ Agonists*; LAMA: *Long-Acting Muscarinic Antagonists*; ICS: *Inhaled Corticosteroids*. GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Predicted distance m= 622. 461 − (1.846 × Age in years) + (61.503 × Gender $_{men = 1;\ women = 0}$); GEE: Generalized Estimating Equations; Bonferroni correction; Fisher's exact test for categorical variables and Independent Student's *t* test for continuous variables; *p<0.05; **p<0.001 between exacerbators and non-exacerbators.

improvement in both groups when comparing numbers before and after, as shown in Table 2. Regarding the exercise capacity assessed through the 6MWT before and after the PRP, the non-exacerbator and exacerbator groups significantly increased the distance covered, which also occurred with dyspnea assessed by means of the mMRC. Both groups improved their prognosis of the disease as assessed by means of the BODE index. The results of the Quality of Life assessment also showed significant benefits after PRP in both the non-exacerbator and exacerbator groups (p <0.0001).

Table 3 shows the variation in exercise capacity, dyspnea, quality of life and prognosis measured by the BODE index between the two groups. Figure 2 shows the comparison of the distance covered in the 6MWT before and after PRP, according to the disease exacerbation phenotype and adjusted for baseline lung function (FEV1%).

The average variation in the reduction of the BODE index and dyspnea was significantly greater in the exacerbating group when compared to the non-exacerbating group. Variation in the various sectors of the quality of life questionnaire did not differ significantly between groups, despite being measured intra-group.

DISCUSSION

Our study showed that PRP improved exercise capacity, dyspnea, quality of life and prognosis for this group of patients diagnosed with COPD. More importantly, it demonstrated that the improvement in exercise capacity, assessed through the absolute distance covered and that predicted in the 6MWT, was significantly greater in exacerbators than in non-exacerbators, even after adjustment for FEV1%, as shown in Figure 2. It is also worth noting that both groups reached distances much longer than those considered clinically

Table 2. Exercise capacity (submaximal), dyspnea, prognostic index and quality of life in 151 patients diagnosed with COPD undergoing a pulmonary rehabilitation program.

Variable	Non-exacerbator		Exacerbator	
	Baseline	Post-PRP	Baseline	Post-PRP
6MWD (m)	396.4±94.9	445.0±99.0*	376.1±103.9	461±94.2*
% of predicted[a]	73.0±17.0	82.0±17.0*	69.0±18.0	84.0±16.0*
mMRC (0-4)	1.9±1.3	1.1±1.1*	2.9±1.1	1.3±1.4*
BODE Index (0-10)	3.3±1.8	2.7±1.9**	4.3±1.5	2.9±1.5**
SGRQ Symptoms	46.8±20.3	32.6±18*	52.9±20.9	34.9±21.1*
SGRQ Activities	65.8±23.1	52.1±23.1*	76.9±21.7	57.5±21.8*
SGRQ Impact	32.9±18.9	20±15.4*	40.7±18.7	24.5±18.5*
SGRQ Total	46.3±16.9	32.7±16.3*	54.0±16.0	36.3±18.1*

6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. [a]Predicted distance m= 622. 461 – (1.846 × Age in years) + (61.503 × Gender $_{males = 1}$; $_{females = 0}$); Generalized Estimating Equations (GEE); Bonferroni adjustment; *p<0.0001 of baseline; **p<0.01 of baseline.

Table 3. Variation in exercise capacity, dyspnea, prognostic index and quality of life in 151 COPD patients undergoing a pulmonary rehabilitation program.

Variable	Alteration of baseline (Δ)			
	Non-exacerbator	Exacerbator	Wald	p
6MWD (m)	48.6 (37.0 to 60.2)	84.9 (57.1 to 112.6)	5.57	*0.018**
% of predicted[a]	8.9 (6.7 to 11.0)	15.4 (10.1 to 20.7)	5.51	*0.019**
% of change	14.8 (10.7 to 18.9)	29.5 (13.3 to 45.6)	2.98	*0.084*
mMRC (0-4)	- 0.8 (-1.11 to - 0.51)	-1.6 (-2.20 to -1.13)	7.49	*0.006**
BODE Index (0-10)	- 0.61(-0.94 to - 0.28)	-1.44 (-2.17 to -0.70)	4.03	*0.045**
SGRQ Symptoms	-14.2 (-18.2 to -10.2)	-18.0 (-27.0 to -9.0)	0.57	*0.450*
SGRQ Activities	-13.7 (-18.2 to -9.2)	-19.3 (-28.5 to -10.2)	1.17	*0.279*
SGRQ Impact	-13.0 (-16.0 to -9.9)	-16.1 (-23.1 to -9.1)	0.65	*0.419*
SGRQ Total	-13.6 (-10.8 to -16.5)	-17.7 (-10.9 to -24.5)to	1.14	*0.285*

Values expressed as means and 95% Wald Confidence Intervals. Six-Minute Walk Test; 6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. [a]Predicted distance m= 622. 461 – (1.846 × Age in years) + (61.503 × Gender $_{males = 1}$; $_{females = 0}$); Generalized Estimating Equations (GEE); Bonferroni adjustment: *p<0.05 between groups.

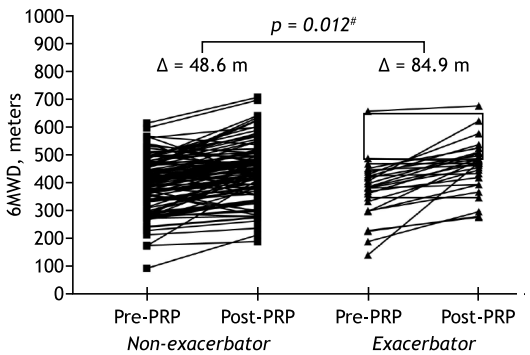

Figure 2. Comparison of submaximal exercise capacity (6MWD), before and after pulmonary rehabilitation program (PRP), according to the phenotype for disease exacerbation, adjusted for baseline lung function (FEV1,%).

significant, which are of 25 to 35 meters,[4] with the group of non-exacerbator patients walking on average 48.6 meters after rehabilitation and the exacerbator ones, an average of 84.9 meters, i.e. 36.3 meters more than non-exacerbators.

In patients with COPD, the severity of the disease and the prognosis are not determined solely by changes in lung function. In individuals with mild or moderate disease, exercise capacity and daily life activities are often altered, which impacts negatively on quality of life. Thus, in addition to the drug treatment used to improve dyspnea, lung function and reduce the number of exacerbations,[14] PRP has been advocated as a non-pharmacological strategy to be used,[15] and in this group of exacerbator patients it has shown to be much more beneficial when compared with the benefit for patients with a non-exacerbator phenotype.

When analyzing the behavior of the dyspnea index measured by the mMRC, a significant improvement was observed in both groups, along with a greater magnitude in the group of patients of the exacerbator phenotype (-0.8 vs. -1.6; p <0.006). Dyspnea is certainly the main symptom and the most limiting factor in this disease, especially for patients' day-to-day activities or during physical exercise. This symptom usually improves significantly with aerobic physical training, but the mechanism is still not well understood. Lower pulmonary ventilation in identical work rates and also in oxygen consumption, signaling a lower hyperinflation, would not fully explain the improvement obtained.[15]

Quality of life as assessed by the Saint George questionnaire improved in both groups in levels well

above the 4 percentage points recognized as the clinically significant minimum difference. Most studies highlight the improvement in quality of life as the major benefit of pulmonary rehabilitation,[4,15,16] which was also observed in our study in both groups. However, when comparing the quality of life between patients with COPD of the exacerbator and non-exacerbator phenotypes, no statistically significant difference was observed.

Studies connecting pulmonary rehabilitation with exacerbations have focused on the ability of this intervention to reduce the number of occurrences, emergency-room visits and hospitalizations. While a study with two hundred patients showed that pulmonary rehabilitation reduced hospitalizations related to breathing difficulties over one year, with a 50% drop in hospitalization time,[17] another study with sixty patients showed more exacerbations in the control group, but saw no difference in number of hospitalizations per patient.[18]

A meta-analysis showed that, although randomized controlled trials suggested that PRPs reduced subsequent admissions, the results of cohort studies did not corroborate this benefit. The authors argued that the heterogeneous nature of the patients included in the various observational studies and the diversity of protocols used by the different PRPs could justify these findings.[19] In view of this response from different studies regarding use of PRP to reduce exacerbations, which is still controversial, advantages obtained in other parameters, such as exercise capacity and improvement in quality of life, support its prescription.

To date, few studies have been concerned with analyzing the response to pulmonary rehabilitation in the different COPD phenotypes. Studying 73 patients with COPD from mild to very severe, Jenkins et al.[20] showed that fewer exacerbator patients completed the PRP when compared to non-exacerbators (45% vs. 69%), and that the effects between groups were similar. A prospective and multicenter study[21] that aimed at studying the response to PRP in different COPD phenotypes included 364 patients in six centers, divided between patients with obstruction of airways and patients with destruction of the parenchyma. It found that both benefited from the treatment, with no difference between the groups. Our study differs from the previous ones in that it included only patients who had completed the PRP, and also in that they were classified as exacerbator and non-exacerbator and not as airway disease and lung parenchyma destruction patients. It is known that exacerbations are independent predictors of mortality in patients with COPD, increasing the chance of death by almost five times,[22] and this phenotypic dichotomization could provide more relevant information, as demonstrated in our study.

Besides its value as a predictor of hospitalization and mortality in COPD patients participating in a PRP,[23] in our study the BODE index was significantly lowered after treatment in the group of exacerbator patients when compared to non-exacerbator patients. In spite of the absence of follow-up data on the number of exacerbations and even hospitalizations after completion of rehabilitation, this index clearly shows a better prognosis when compared to the situation before rehabilitation.

Our study, however, has some limitations. The first is its retrospective design, although the data analyzed were collected in a prospective and standardized manner, as they are used in the final report to be sent to the attending physician. Another limitation was the fact that the transitional dyspnea index was not used, although it could better assess dyspnea after interventions than mMRC. However, this is a real-life study that corroborates the benefit of PRP for all COPD patients, and particularly for those with an exacerbator phenotype.

In conclusion, patients with a diagnosis of COPD and an exacerbator phenotype benefited the most from PRP, walking an average of 36 meters more in the 6MWT when compared to the non-exacerbator one. This benefit is also corroborated by the greater reduction of dyspnea and the improvement in prognosis as measured by the BODE index. Prospective cohort studies will be needed to further confirm these findings.

AUTHOR CONTRIBUTIONS

Ivo Bohn Júnior. Participated in the preparation of the study, data collection, data analysis and wrote the article. Cassia Cinara da Costa participated in the study design, data collection and revised the article. Rafael Machado de Souza participated in the study design, data collection and revised the article. Álvaro Huber dos Santos participated in the data analysis and revised the article. Paulo José Zimermann Teixeira participated in the preparation of the study, data collection, data analysis and revised the article.

REFERENCES

1. GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease. Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Fontana: GOLD; 2020.
2. Soler-Cataluña JJ, Rodriguez-Roisin R. Frequent chronic obstructive pulmonary disease exacerbators: how much real, how much fictitious? COPD. 2010;7(4):276-84. http://dx.doi.org/10.3109/15412555.2010.496817. PMid:20673037.
3. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Evaluation of COPD Longitudinally to Identify Predctive Surrogate Endpoints (ECLIPSE) investigator susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128-38. http://dx.doi.org/10.1056/NEJMoa0909883. PMid:20843247.
4. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An Official American Thoracic Society/European Respiratory Society Statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):1011-27. http://dx.doi.org/10.1164/rccm.201309-1634ST. PMid:24127811.

5. Miravitlles M, Calle M, Soler-Cataluña JJ. Fenotipos clinicos de la EPOC: identificacón, definitión e implicaciones para las guías de tratamiento. Arch Bronconeumol. 2011;48(3):86-98. http://dx.doi.org/10.1016/j.arbres.2011.10.007. PMid:22196477.
6. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;12(12):CD005305. http://dx.doi.org/10.1002/14651858.CD005305.pub4. PMid:27930803.
7. Moore E, Newson R, Joshi M, Palmer T, Rothnie KJ, Singh S, et al. Effects of pulmonary rehabilitation on exacerbation number and severity in people with COPD: an historical cohort study using electronic health records. Chest. 2017;152(6):1188-202. http://dx.doi.org/10.1016/j.chest.2017.05.006. PMid:28526656.
8. Ryrsø CK, Godtfredsen NS, Kofod LM, Lavesen M, Mogensen L, Tobberup R, et al. Lower mortality after early supervised pulmonary rehabilitation following COPD- exacerbations: a systematic review and meta-analysis. BMC Pulm Med. 2018;18(1):154. http://dx.doi.org/10.1186/s12890-018-0718-1. PMid:30219047.
9. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validation of the Modified Pulmonary Functional Status and Dyspnea Questionnaire and the Medical Research Council scale for use in Brazilian patients with chronic obstructive pulmonary disease. J Bras Pneumol. 2008;34(12):1008-18. http://dx.doi.org/10.1590/S1806-37132008001200005. PMid:19180335.
10. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12. http://dx.doi.org/10.1056/NEJMoa021322. PMid:14999112.
11. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-7. http://dx.doi.org/10.1164/ajrccm/145.6.1321. PMid:1595997.
12. ATS: American Thoracic Society . ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7. http://dx.doi.org/10.1164/ajrccm.166.1.at1102. PMid:12091180.
13. Iwama AM, Andrade GN, Shima P, Tanni SE, Godoy I, Dourado VZ. The six-minute walk test and body weight-walk distance product in healthy Brazilian subjects. Braz J Med Biol Res. 2009;42(11):1080-5. http://dx.doi.org/10.1590/S0100-879X2009005000032. PMid:19802464.
14. Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst J, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;50(3):1602265. http://dx.doi.org/10.1183/13993003.02265-2016. PMid:28889106.
15. Troosters T, Demeyer H, Hornikx M, Camillo CA, Janssens W. Pulmonary rehabilitation. Clin Chest Med. 2014;35(1):241-9. http://dx.doi.org/10.1016/j.ccm.2013.10.006. PMid:24507849.
16. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler D, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest. 2007;131(5, Suppl.):4S-42S. http://dx.doi.org/10.1378/chest.06-2418. PMid:17494825.
17. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000;355(9201):362-8. http://dx.doi.org/10.1016/S0140-6736(99)07042-7. PMid:10665556.
18. Güell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, et al. Long-term effects of outpatient rehabilitation of COPD: a randomized trial. Chest. 2000;117(4):976-83. http://dx.doi.org/10.1378/chest.117.4.976. PMid:10767227.
19. Moore E, Palmer T, Newson R, Majeed A, Quint JK, Soljak MA. Pulmonary rehabilitation as a mechanism to reduce hospitalizations for acute exacerbations of COPD: a systematic review and meta-analysis. Chest. 2016;150(4):837-59. http://dx.doi.org/10.1016/j.chest.2016.05.038. PMid:27497743.
20. Jenkins A, Gibbons L, Holden N, Jones AW. Responses of exacerbation phenotypes of COPD to community pulmonary rehabilitation. Thorax. 2018;73:A155.
21. Ambrosino N, Venturelli E, de Blasio F, Paggiaro P, Pasqua F, Vitacca M, et al. A prospective multicentric study of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease and different clinical phenotypes. Respiration. 2015;89(2):141-7. http://dx.doi.org/10.1159/000371471. PMid:25634602.
22. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925-31. http://dx.doi.org/10.1136/thx.2005.040527. PMid:16055622.
23. Moberg M, Vestbo J, Martinez G, Williams JE, Ladelund S, Lange P, et al. Validation of the I-BODE index as a predictor of hospitalization and mortality in patients with COPD participating in pulmonary rehabilitation. COPD. 2014;11(4):381-7. http://dx.doi.org/10.3109/15412555.2013.836171. PMid:24111845.