Title: Respiratory and peripheral muscle strength influence recovery of exercise capacity after severe exacerbation of COPD? An observational prospective cohort study

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Abstract

Background: Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) have decreased exercise tolerance, which may persist for months. In this context, little is known about the associations between muscle strength and recovery of exercise capacity.

Objective: To assess whether respiratory and peripheral muscle strength influence recovery of exercise capacity in patients hospitalized due to AECOPD.

Methods: Twenty-seven AECOPD patients (aged 69 ± 7 years, 56% male) were included. The following assessments were performed within 24 to 72 hours of hospital admission: (i) respiratory muscle strength, measured by maximal inspiratory and expiratory pressures (MIP and MEP); (ii) peripheral muscle strength, assessed by handgrip and quadriceps muscle strength; and (iii) exercise capacity, measured by 6-min walking distance (6MWD). The 6MWD was reassessed 30 days later to determine the recovery of exercise capacity.

Results: After 30 days, while 63% of the patients showed clinically important improvement in the 6MWD (recovery ≥ 30 m), 37% showed no change (recovery < 30 m). During hospital stay, the non-recovered group had lower quadriceps muscle strength compared to the recovered group (15 ± 5 vs. 22 ± 6 kgf; $P = 0.006$), with no significant difference for MIP, MEP and handgrip strength. Only quadriceps muscle strength was associated with recovery of exercise capacity ($r = 0.56$; $P = 0.003$).

Conclusion: AECOPD patients with quadriceps muscle weakness during hospitalization have poor recovery of exercise capacity after 30 days. This finding suggests the importance of early rehabilitation to improve quadriceps strength and accelerate functional recovery after AECOPD.

Keywords: COPD; Hospitalization; Muscle strength; Exercise capacity.

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is characterized as an acute worsening of respiratory symptoms, which is usually triggered by respiratory infections caused by viruses or bacteria.[1] Increased airway inflammation, increased mucus production and marked gas trapping are pathophysiological hallmarks of AECOPD that contribute to increased dyspnea and other symptoms such as sputum volume, cough and wheeze.[1,2] Consequences of these clinical features lead AECOPD patients to experience a profound negative impact on health status, which often contributes to disease progression and increased rates of hospitalization, morbidity and mortality.[2]

Exercise intolerance is a major debilitating consequence of AECOPD.[3] Clinical evidence suggests that reduction in exercise capacity commonly lasts for months after AECOPD, especially in severe cases that require hospitalization.[4] In this context, predicting exercise capacity recovery may have a valuable prognostic value, given the influence of functional impairment on hospital readmissions and mortality following AECOPD.[5] However, although few studies have investigated the impact of AECOPD on exercise capacity[6,7], none of them has been concerned with identifying factors that are associated with functional recovery.

Muscle dysfunction often occurs in AECOPD and may involve both respiratory and peripheral muscles.[8] Although muscle strength is considered a determinant of exercise capacity in stable patients[9], little is known about whether it plays a role in recovery after AECOPD. Previous evidence suggests that muscle strength is a good predictor for changes in functional status of hospitalized patients.[10] However, this has been little investigated in AECOPD patients. Understanding the factors that lead to exercise intolerance in the post-exacerbation period is clinically important, as it can contribute to the development of therapeutic strategies that improve the patient's functional status such as post-exacerbation pulmonary rehabilitation. Thus, our study aimed to assess whether respiratory and peripheral muscle strength influence the recovery of exercise capacity in patients hospitalized due to AECOPD. We hypothesized that overall muscle weakness limits short-term recovery of exercise capacity after severe AECOPD.

Methods

Study design and participants. This was an observational prospective cohort study including patients of both sexes and hospitalized with a clinical diagnosis of AECOPD at the University Hospital of UFSCar (São Paulo, Brazil) and the Santa Casa of São Carlos (São Paulo, Brazil) between October 2016 and November 2019. All patients were assessed in a hospital ward setting within 24 to 72 hours of admission and 30 days later. Exclusion criteria were age >80 years, lung or other types of cancer, acute heart disease, need for transfer to intensive care unit, contraindication or without clinical conditions for walking, and refusal to participate. All study procedures were approved by the Research Ethics Committee at the Federal University of São Carlos (CAAE: 46431415.0.0000.5504).

Clinical assessment. A clinical history and physical exam were performed to obtain demographic characteristics, smoking habit, comorbidities, body weight and height, use of oxygen therapy, and vital signs at rest. Body mass index (BMI) was calculated as weight divided by height in meters squared (BMI = kg/meters^2). Respiratory symptoms were assessed with the COPD Assessment Test.[2] Frequent exacerbation was defined by two or more exacerbations in the previous year.[2] Laboratory data were obtained on the day of assessment and included inflammatory blood markers, such as C-reactive protein, leukocytes, and differential eosinophils. Medications were obtained from the electronic patient record.

Respiratory muscle strength. Respiratory muscle strength was assessed using a previously calibrated analog manovacuometry device (Ger-Ar®, São Paulo, SP, Brazil), with a measurement capacity between -300 to +300 cmH_2O. All measurements were performed with the patient in the sitting position, using a nose clip and flanged mouthpiece. Maximal inspiratory pressure (MIP) was obtained through a maximal inspiratory effort maneuver after maximum expiration, close to the residual volume. Maximal expiratory pressure (MEP) was obtained through a maximal expiratory effort, after a maximal inspiration, close to total lung capacity. The maneuvers were performed at least three times and, at most, five times, if there was a variation greater than 10% between the values obtained. The rest time between the maneuvers was at least 30 seconds or according to the patient's tolerance. The highest MIP and MEP values were considered for analysis, and predicted values were calculated according to reference equations for the Brazilian population.[11]

Handgrip strength. Handgrip strength was evaluated using a hydraulic hand dynamometer (Jamar, Sammons Preston, Bolingbrook, Illinois, USA). The measurement was performed with the patient seated, with the elbow flexed at 90 degrees and the wrist in neutral. At least three measures were performed for dominant hand, and the highest value was considered for analysis. Predicted values were calculated as previously described.[12]

Quadriceps strength. Quadriceps strength was assessed with a handheld dynamometer (MicroFet 2, Salt Lake City, Utah, USA), using a standardized procedure with excellent reliability.[13] The measurement was performed with the patient seated in an ergonomic adjustable chair, with the legs suspended over the edge of the chair, with the hips and knees flexed at 90 degrees. The dynamometer was attached to the anterior distal portion of the tibia and at 2 cm above the malleolus, under an inextensible nylon band fastened to the posterior region of the ergonomic chair. During the test, the dynamometer was stabilized by the evaluator to avoid possible displacements under the band. Patients were instructed to perform a maximum voluntary contraction, based on a standardized verbal command: “Inhale. Exhale and force, force, force!”. The maximum voluntary contraction on expiration aimed to avoid a Valsalva maneuver. Three maximal isometric contractions were performed on both legs, and the duration of each muscular contraction was at least 4 s followed by 30 s of rest. The higher peak isometric force was obtained for each leg, and the greater of these two values was considered as the final quadriceps strength (expressed in kilogram-force).

Exercise capacity. Exercise capacity was assessed using the 6-minute walk test (6MWT).[14] The test was carried out in a 30-meter hallway, and all patients were instructed to walk as far as possible for six minutes. During the test, vital signs were monitored and, if necessary, supplemental oxygen was used to maintain the oxygen saturation (SpO_2) ≥ 85%. The primary outcome was 6-minute walking distance (6MWD) in meters. Predicted values were calculated according to reference for the Brazilian population: $6MWD_{pred} = 890.46 - (6.11 \times age) + (0.0345 \times age^2) + (48.87 \times gender) - (4.87 \times BMI)$.[15] The 6MWT was repeated 30 days after the hospital assessment, and recovery of exercise capacity was determined by Δ 6MWD (6MWD after 30 days – 6MWD at the hospital). According to the minimal important difference of 30 m[14], patients were also divided into two subgroups: recovered (Δ 6MWD ≥ 30 m) and non-recovered (Δ 6MWD < 30 m).

Lung function. Spirometry was performed 30 days after the hospital assessment, on the same day as the 6MWT, and at least one hour before the test. Lung function was assessed pre- and post-bronchodilator, using a validated spirometer device (BreezeSuite, MedGraphics, Saint Paul, Minnesota, USA). Absolute values of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were obtained. Predicted values were calculated according to a Brazilian population.[16] Based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, a post-bronchodilator $FEV_1/FVC < 0.7$ was used to confirm COPD diagnosis, and FEV_1 (% of predicted) was considered to determine disease severity (GOLD I, II, III or IV).[2]

Statistical analysis. Quantitative data are presented as mean and standard deviation, whereas categorical variables are shown as absolute frequency (percentage). The normality of continuous variables was verified using the Shapiro-Wilk test. Comparison of subgroup characteristics (recovered vs. non-recovered) was performed using the chi-square test, unpaired t test, or Mann-Whitney U test. Intragroup exercise performance (6MWD) during hospitalization and after 30 days were compared using the paired t test. Pearson's correlation coefficients were calculated to verify the association between recovery of exercise capacity (Δ 6MWD) and muscle strength parameters (MIP, MEP, handgrip strength and quadriceps strength). Linear regression was used to estimate recovery of exercise capacity using potential muscle strength predictors. A value of $P < 0.05$ was considered significant. All statistical tests were performed in GraphPad Prism 5.0 software (San Diego, California, USA).

Results

From 110 patients assessed for eligibility, 48 were assessed at hospital admission, and 27 were included in the final analysis (Figure 1). According to 6MWD at hospitalization and after 30 days, 17 patients (63%) recovered exercise capacity (Δ 6MWD ≥ 30 m) and 10 patients (37%) did not (Δ 6MWD < 30 m) (Table 1). Analysis of characteristics during hospitalization showed that the non-recovered subgroup was treated with less short-acting beta-agonist (SABA) and short-acting muscarinic antagonist (SAMA) when compared to the recovered subgroup (*P* < 0.05). Muscle strength results showed that, when compared to the recovered subgroup, the non-recovered subgroup had lower quadriceps muscle strength during hospitalization (*P* = 0.006), with no significant difference for MIP, MEP and handgrip strength (*P* > 0.05).

Figure 1 and Table 1

Recovered and non-recovered subgroups showed similar lung function (*P* > 0.05), with a predominance of GOLD III severity (Table 2). After 30 days of recovery, the total group (n = 27) had a 27% significant increase of absolute 6MWD (241 ± 93 m to 306 ± 98 m; *P* < 0.001) and % of $6MWD_{pred}$ (45 ± 17 % to 58 ± 18 %; *P* < 0.001) (Figure 2). In the subgroup analysis, while recovered patients had an expected improvement in absolute 6MWD (226 ± 93 m to 341 ± 94 m; *P* < 0.001) and % of $6MWD_{pred}$ (43 ± 17 % to 64 ± 17 %; *P* < 0.001), the non-recovered subgroup showed a non-significant decrease of absolute 6MWD (267 ± 92 m to 250 ± 79 m; *P* = 0.105) and % of $6MWD_{pred}$ (50 ± 19 % to 47 ± 15 %; *P* = 0.097). Comparing recovered and non-recovered subgroups, respectively, there were no statistical differences regarding the use of oxygen in the 6MWT during hospitalization (82% vs. 60%; *P* = 0.201) and 30 days later (6% vs. 0%; *P* = 0.434). None of the patients in the non-recovered subgroup reported any major clinical events during the follow-up that could justify the worsening in exercise capacity.

Table 2 and Figure 2

Correlation analyses (Figure 3) showed that patients with worse recovery of exercise capacity (∆ 6MWD) had lower quadriceps muscle strength during hospitalization (r = 0.56; *P* = 0.003), without the influence of other muscle strength measures (MIP, MEP and handgrip strength). A simple linear regression was used to test if quadriceps strength (kgf) at hospitalization could predict recovery of exercise capacity after 30 days. The fitted regression model was: Δ 6MWD = -77.107 + (7.498 × Quadriceps strength). The overall regression was statistically significant (r^2 = 0.32, F = 11.157, P = 0.003). It was found that quadriceps strength significantly predicted recovery of exercise capacity (β = 7.498, 95% confidence interval of 2.862 to 12.134, with P = 0.003).

Figure 3

Discussion

The present study investigated whether respiratory and peripheral muscle strength influence the recovery of exercise capacity after severe AECOPD. As the main finding, we found that lower quadriceps muscle strength, assessed during hospitalization, was associated with poor recovery of exercise capacity, as measured by the change in 6MWD after 30 days. We did not observe a significant influence of respiratory muscle strength or handgrip strength on recovery of exercise capacity.

Our findings confirm that hospitalized AECOPD patients have a markedly reduced exercise capacity during hospitalization. Even though baseline exercise capacity was not known, we observed that the total group walked less than 50% of the $6MWD_{pred}$ during exacerbation. Similar findings showing decreased exercise capacity have also been reported in other studies. Alahmari et al. found that patients with moderate AECOPD (managed in the community) showed a decline in 6MWD from a median of 422 m when stable to 373 m on day 3 post-exacerbation (P = 0.001).[6] Cote et al. reported that even patients who only experienced one severe AECOPD showed a mean decline of 72 m (~20%) in 6MWD during exacerbation.[4] Turan et al. cross-sectionally studied COPD groups matched by age, sex, and FEV_1, and found that exacerbated patients had significantly lower exercise capacity compared with stable patients (6MWD of 232 ± 149 m vs. 336 ± 120 m, $P = 0.003$).[17]

Many factors may be related to reduced exercise capacity in COPD patients, such as age, airflow severity, dyspnea, respiratory muscle strength and peripheral muscle strength.[18] During severe AECOPD, patients may develop further skeletal muscle dysfunction due to a combination of several factors, including disuse, systemic inflammation, hypoxia and hypercapnia, electrolyte derangements, corticosteroid treatment, and nutrition/energy balance.[19] Additionally, these patients tend to drastically decrease the level of physical activity during hospitalization, leading to a cycle of deconditioning, exercise intolerance, increased symptoms, immobility and muscle weakness.[3] In our study, although we did not directly assess the physical activity during hospitalization, it was found that patients had a decrease in overall muscle strength, since the mean values of MIP, MEP and handgrip strength were below 70% of predicted. Even though there is no data on the patients' previous muscle condition, this finding corroborates other evidence that suggests skeletal muscle weakness is a clinical feature associated with AECOPD.[8]

After AECOPD, patients can have variable recovery and little is known about recovery of exercise capacity.[5] Pitta et al. showed that hospitalized AECOPD patients increased the 6MWD by a median of 64 m (268 m to 332 m; $P = 0.01$) after 1 month of discharge when compared to the end of the hospitalization period (day 8 after exacerbation).[7] However, the authors did not analyze whether all patients improved in that recovery time. In our study, we found a similar 6MWD recovery in the total group, with an average increase of 65 m (241 m to 306 m; $P < 0.001$) 30 days after the initial assessment. Of this total group, however, 10 patients (37%) showed worsening or did not recover their exercise capacity (267 to 250 m). In theory, this result indicates that this subgroup of non-recovered patients was more susceptible to negative clinical outcomes, considering that a lower 6MWD is associated with a higher risk of death[20], with a cutoff threshold < 317 m for prediction of mortality.[21] Even though these patients did not experience major adverse events, our follow-up was limited to 30 days, and outcomes after this period were not recorded.

The factors that influence delayed or incomplete exercise recovery following AECOPD have been poorly studied. Pitta et al. monitored 17 hospitalized AECOPD patients with accelerometers and found that the reduction in quadriceps force during hospitalization was significantly correlated with less improvement in walking activity time after 1 month ($r = 0.58$; $P = 0.03$).[7] Interestingly, this degree of correlation is close to that found in our study, when we evaluated the relationship between quadriceps strength and 6MWD recovery ($r = 0.56$; $P = 0.003$). The most likely explanation for this similarity can be attributed to the strong correlation between 6MWD and physical activity in COPD patients ($r = 0.76$, $P < 0.0001$).[22] Therefore, even though our study did not directly assess physical activity, we believe that patients with poorer exercise capacity recovery likely also had a low level of physical activity as underlying condition.

Another important finding was the predictive value of quadriceps muscle strength in the recovery of exercise capacity. In our regression model, we found a β coefficient of 7,498 in the association between quadriceps strength and recovery of exercise capacity (Δ 6MWD). This means that for every 1 kgf of quadriceps muscle strength lost during hospitalization, a ~7.5 m decrease in 6MWD is expected 30 days after exacerbation presentation. Therefore, a 4 kgf reduction in quadriceps muscle strength would represent an almost 30 m decrease in 6MWD after 30 days, which is interpreted as a clinically significant change, indicating a higher risk of death.[23] Thus, in this population of severe AECOPD patients, we believe that early physical rehabilitation such as with post-exacerbation pulmonary rehabilitation should prioritize the increase in lower limb muscle strength, since this could provide a more satisfactory short-term functional recovery. On this topic, a recent randomized clinical trial showed that early exercise training promoted an increase in both exercise capacity and quadriceps muscle strength in hospitalized patients due to AECOPD.[24] However, these beneficial effects have only been demonstrated during hospitalization, and further studies would be welcome to assess whether these gains positively influence short and medium-term outcomes during recovery of AECOPD.

Limitations

Our study has some limitations. First, the sample size was small, which limits the power of the study. Second, the 6MWT was performed only once during hospitalization. According to the European Respiratory Society/American Thoracic Society[14], two tests should be performed, as there is strong evidence of a learning effect that can influence 6MWD. Indeed, this effect was previously observed in hospitalized AECOPD patients, but when the 6MWT was performed on the day of hospital discharge.[25] In our study, the 6MWT was performed from 24 to 72 hours of hospitalization, and we have no evidence of a learning effect in this period. In addition, we believe that performing an additional submaximal exercise test could provide unnecessary physiological stress, with the potential to negatively influence the health status of the patient who was still undergoing clinical treatment for AECOPD. Another limitation was the lack of control for potentially influencing factors in the recovery of exercise capacity after hospital discharge. Although both groups were discharged from hospital with similar lengths of stay, this does not exclude the possibility that the patients had some degree of persistent symptoms, which may have limited physical activity during recovery. Finally, the measurement of quadriceps muscle strength using handheld dynamometry may be a limitation for application in clinical practice, since it would be necessary to acquire the dynamometer device. Therefore, a feasible option would be the measurement through manual muscle strength tests (e.g., Medical Research Council scale for muscle strength). However, the agreement of these assessment instruments, as well as the relationship with the main outcome (recovery of exercise capacity), should be evaluated in future studies.

Conclusion

AECOPD patients with quadriceps muscle weakness during hospitalization have poor recovery of exercise capacity after 30 days. These results suggest the potential of quadriceps strength not only as a predictor of functional decline after an exacerbation but also as a useful clinical marker to identify patients with higher priority for an early pulmonary rehabilitation program. Future studies should assess whether an early exercise-based intervention focused on increasing lower limb muscle strength could add benefit to short- and medium-term functional recovery.

Declaration of competing interest. None.

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FIGURES

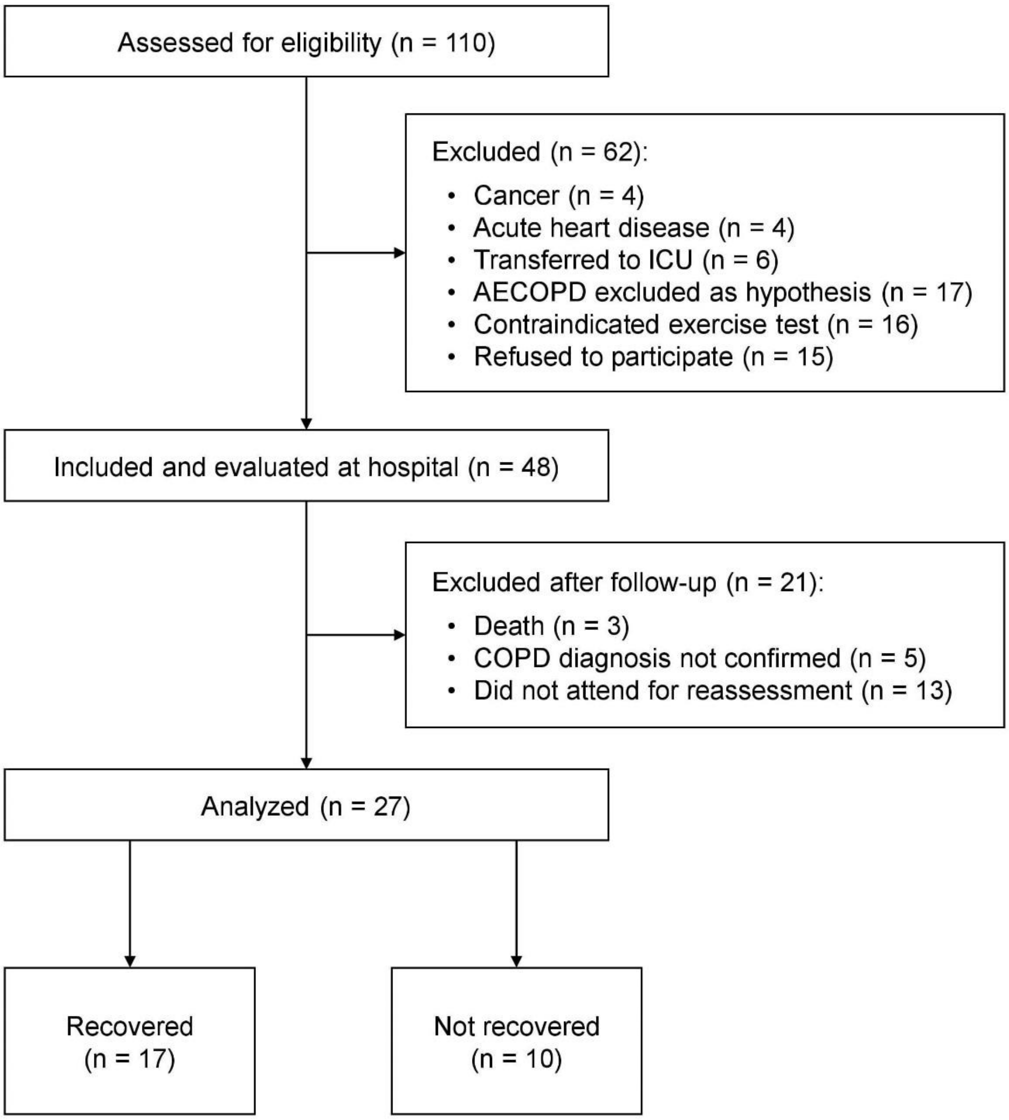

Figure 1. Flow diagram of patients included in the study. AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease.

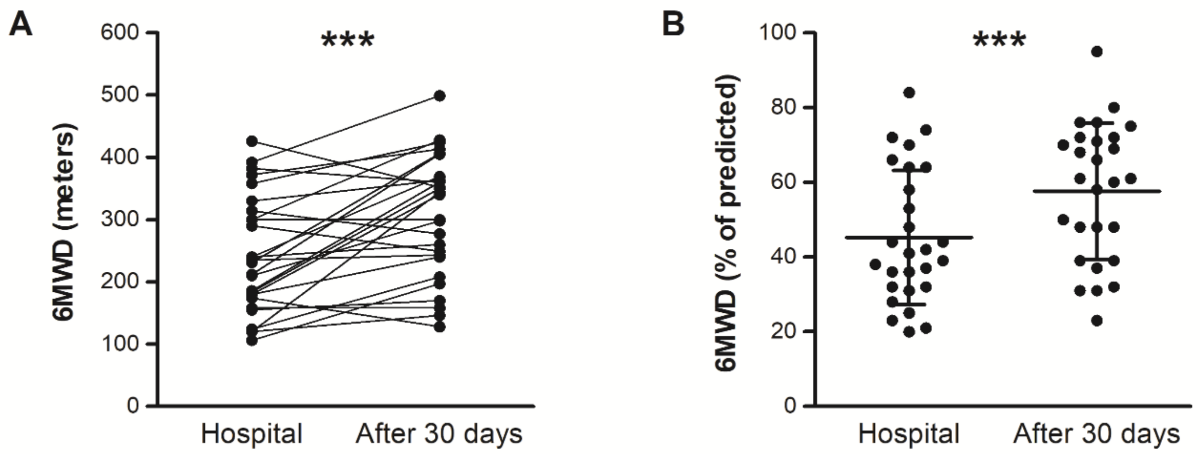

Figure 2. Comparisons of the 6-minute walk distance (6MWD) at hospitalization and after 30-days recovery: (A) absolute 6MWD (mean of 241 ± 93 m vs. 306 ± 98 m); and (B) % of predicted 6MWD (mean of 45 ± 17 % vs. 58 ± 18 %). Triple asterisk (***) denotes a *P* < 0.001.

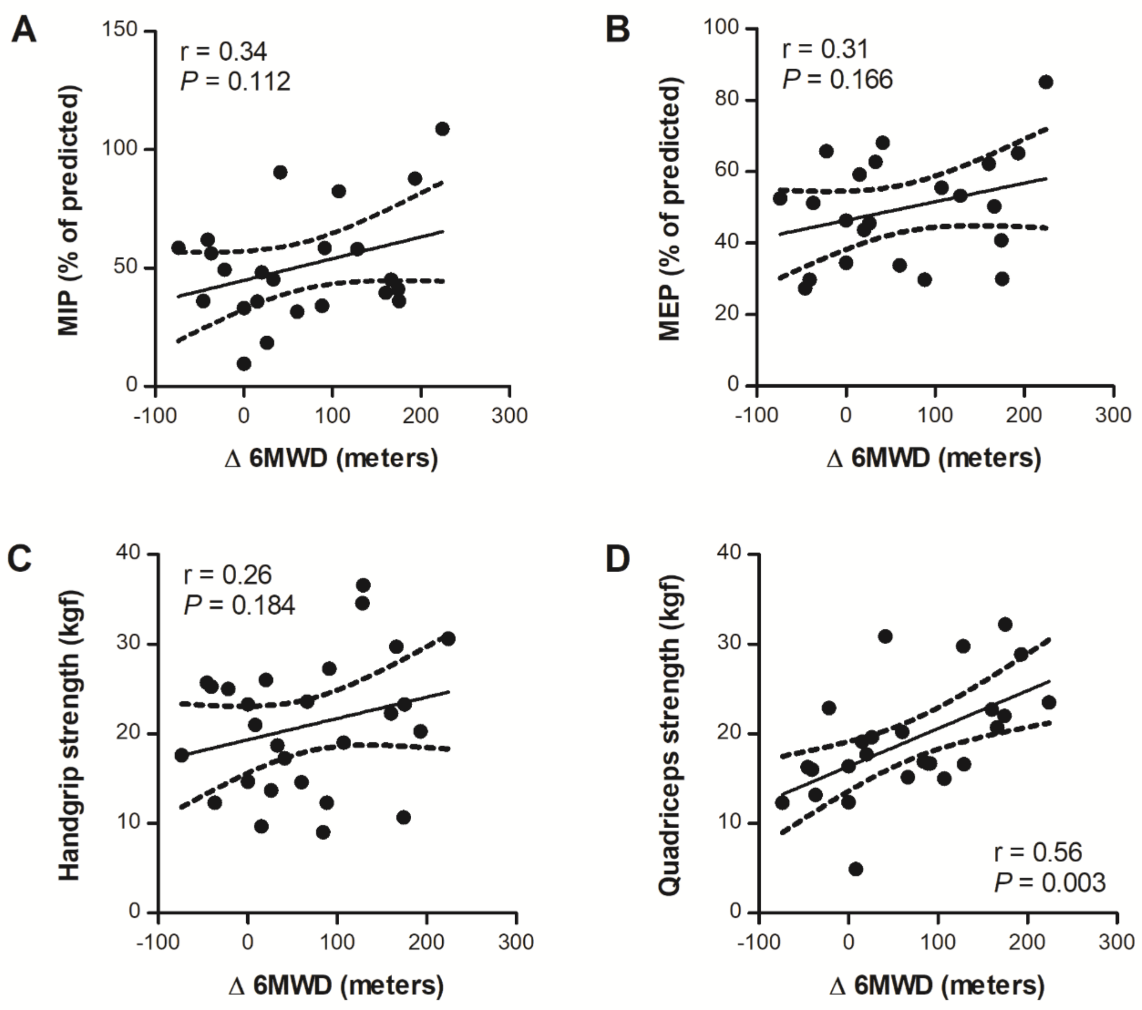

Figure 3. Correlations of respiratory (A and B) and peripheral (C and D) muscle strength, obtained during hospitalization, with the recovery of exercise capacity, evidenced by the Δ of 6-minute walk distance (Δ 6MWD = 6MWD after 30 days – 6MWD at the hospital). MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. Dashed lines represent 95% confidence interval.

TABLES

Table 1. Characteristics of patients assessed at hospitalization: total group and subgroups according to recovery of exercise capacity after 30 days of the hospital assessment

Variables	**Total** (n = 27)	**Recovered** (n = 17)	**Non-recovered** (n = 10)	***P***
Age, years	69 ± 7	68 ± 8	71 ± 6	0.258
Male gender, n (%)	15 (56)	9 (53)	6 (60)	0.722
Body mass index, kg/m^2	25 ± 5	25 ± 5	24 ± 6	0.635
Current smoker, n (%)	8 (30)	6 (35)	2 (20)	0.401
Hypertension, n (%)	15 (56)	9 (53)	6 (60)	0.722
Diabetes, n (%)	5 (19)	3 (18)	2 (20)	0.879
Heart rate, beats/min	88 ± 21	89 ± 18	86 ± 25	0.666
Systolic BP, mmHg	127 ± 21	130 ± 22	122 ± 17	0.323
Diastolic BP, mmHg	77 ± 10	78 ± 10	76 ± 10	0.597
Respiratory rate, breaths/min	22 ± 3	23 ± 4	22 ± 2	0.346
SpO_2, %	92 ± 3	92 ± 3	93 ± 3	0.638
Oxygen therapy, n (%)	20 (74)	14 (82)	6 (60)	0.201
CAT, score	24.4 ± 8.3	24.1 ± 7.8	24.8 ± 9.4	0.841
Frequent exacerbator, n (%)	10 (37)	7 (41)	3 (30)	0.561
C-reactive protein, mg/L	5.0 ± 6.0	4.1 ± 3.8	6.3 ± 8.5	0.860
Leukocytes, $10^3/mm^3$	11.2 ± 3.3	11.4 ± 3.5	10.6 ± 3.1	0.556
Eosinophils, $/mm^3$	133 ± 98	139 ± 115	122 ± 64	0.760
SABA, n (%)	17 (63)	14 (82)	3 (30)	0.007
LABA, n (%)	1 (4)	1 (6)	0 (0)	0.434
SAMA, n (%)	18 (67)	14 (82)	4 (40)	0.024
LAMA, n (%)	3 (11)	2 (12)	1 (10)	0.888
Inhaled corticosteroids, n (%)	7 (26)	5 (29)	2 (20)	0.590
Systemic corticosteroids, n (%)	20 (74)	13 (77)	7 (70)	0.711
6MWD, meters	241 ± 93	226 ± 93	267 ± 92	0.276
6MWD, % of predicted	45 ± 17	42 ± 17	49 ± 18	0.291
MIP, cmH_2O	45 ± 23	50 ± 27	37 ± 13	0.197
MIP, % of predicted	51 ± 24	56 ± 26	43 ± 16	0.230
MEP, cmH_2O	56 ± 17	60 ± 19	50 ± 13	0.160
MEP, % of predicted	50 ± 15	53 ± 16	46 ± 13	0.309
Handgrip strength, kgf	21 ± 7	21 ± 8	20 ± 6	0.660
Handgrip strength, % of predicted	63 ± 20	61 ± 20	64 ± 22	0.675
Quadriceps strength, kgf	19 ± 6	22 ± 6	15 ± 5	0.006
Hospital stay, days	7 ± 2	6 ± 2	8 ± 3	0.353

Data are expressed as mean ± SD or absolute frequency (percentage). BP: blood pressure; SpO_2: pulse oxygen saturation; CAT: COPD Assessment Test; SABA: short-acting beta-agonist; LABA: long-acting beta-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonists; 6MWD: 6-minute walk distance; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

Table 2. Lung function assessed after 30 days of hospital assessment: total group and subgroups according to recovery of exercise capacity

Variables	**Total** (n = 27)	**Recovered** (n = 17)	**Non-recovered** (n = 10)	***P***
FEV_1/FVC	0.52 ± 0.12	0.54 ± 0.12	0.48 ± 0.14	0.280
FEV_1, % of predicted	47 ± 14	48 ± 16	45 ± 11	0.635
GOLD II, n (%)	11 (41)	7 (41)	4 (40)	-
GOLD III, n (%)	13 (48)	8 (47)	5 (50)	-
GOLD IV, n (%)	3 (11)	2 (12)	1 (10)	-

Data are expressed as mean ± SD or absolute frequency (percentage). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease.