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RESPIRATORY MUSCLE STRENGTH DURING AND AFTER HOSPITALIZATION FOR COPD EXACERBATION.

Running head

RESPIRATORY MUSCLE STRENGTH DURING COPD EXACERBATION.

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Institution of development

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The authors report no conflicts of interest.

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Previous presentations

Mr Mesquita presented preliminary results of this paper at the Annual Congress of the European Respiratory Society, held September 24-28, 2011, in Amsterdam, the Netherlands.

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Abstract

BACKGROUND: A more profound investigation of the respiratory muscle strength during Chronic Obstructive Pulmonary Disease (COPD) exacerbations needs to be done. We aimed to investigate the strength of the respiratory muscles and its related factors in patients with COPD during and after hospitalization for exacerbation. METHODS: Nineteen patients (12 males, mean age 67 ± 11 years, median forced expiratory volume in the first second [FEV_1] 26 [19-32]% predicted) had their lung function, respiratory and quadriceps muscle strength assessed at admission (day 1), discharge and one month after discharge (1mD) for a hospitalization due to disease exacerbation. RESULTS: At admission, 68% of the patients presented inspiratory muscle dysfunction (IMD, Maximal Inspiratory Pressure [PImax]<70% predicted). The inspiratory muscle strength increased from day 1 to 1mD (56 [45-64] *vs* 65 [51-74] cmH_2O, respectively; *P*<.05), as well as the expiratory muscle strength from day 1 to both discharge and 1mD (99 [65-117] *vs* 109 [77-136] and 114 [90-139] cmH_2O, respectively; *P*<.05). The inspiratory capacity (IC) increased from discharge to 1mD (1.59 ± 0.44 *vs* 1.99 ± 0.54 liters, respectively; *P*<.05). No significant change was observed in other lung function variables or in quadriceps strength (*P*>.05 for all). Moreover, at admission the IMD and the reduction in IC (<80% predicted) correlated linearly (rφ=0.62, *P*=.03), while the expiratory muscle strength correlated inversely to the FEV_1 (Spearman's rho=-0.61, *P*=.005) and the IC (Spearman's rho=-0.54, *P*=.02). CONCLUSIONS: There was a high prevalence of inspiratory muscle dysfunction during hospitalization due to COPD exacerbation. Inspiratory and expiratory muscle strength, however, increased markedly during and after hospitalization. The degree of airflow obstruction and hyperinflation were related to both these variables.

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Key Words: Chronic Obstructive Pulmonary Disease; Exacerbation; Hospitalization; Respiratory Muscles; Respiratory Muscle Strength; Observational Study.

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Introduction

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are well known as harmful, although common, events in the natural course of the disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD exacerbation as an acute event characterized by a worsening in the respiratory symptoms of the patients, that is beyond normal day-to-day variations and requires a change in medication[1].

Among the main consequences of COPD exacerbation presented in the literature, the following ones can be highlighted due to their direct impact on patient's health: increase in mortality[2], impairment in health-related quality of life[3], faster decline in lung function[4], marked reduction in physical activity levels[5], and worsening of peripheral muscle weakness[6].

Despite the key importance of the respiratory muscles in COPD, only a few studies have focused on the understanding of the relationship between these muscles and the exacerbation process. Two recent cross-sectional studies have observed that respiratory muscle dysfunction is associated with an increased risk for hospital admission due to exacerbation[7;8]. Two other studies with prospective designs have identified inspiratory muscle overload as a risk factor for hospitalization due to exacerbation[9;10]. Surprisingly, the function of the respiratory muscles during and after an exacerbation of COPD seems to have been poorly investigated. We identified only three studies that assessed the respiratory muscle strength prospectively during and after hospitalizations for COPD exacerbations[5;11;12]. In brief, González et al.[12] and Martínez-Llorens et al.[11] found an increase in inspiratory muscle strength from admission to discharge, while Pitta et al.[5] found no statistically

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significant difference during or after hospitalization regarding this variable. The expiratory muscle strength, in turn, decreased during the hospitalization in the study of Martínez-Llorens et al.[11], but also remained unaltered in the study of Pitta et al.[5]. Decreased respiratory muscle strength is an important sign to be considered, since it has been associated with more dyspnea and exercise intolerance[13], outcomes which have been previously associated with disease severity.

The time course evolution of the respiratory muscle strength during exacerbations still needs to be better understood. Therefore, the aim of the present study was to investigate in depth the strength of the respiratory muscles (inspiratory and expiratory), and its related factors, in patients with COPD during and after the course of a hospitalization for exacerbation of the disease.

Methods

Study design

This observational study was carried out from January 2010 to February 2012 involving patients with COPD hospitalized due to an exacerbation of the disease in an university hospital (State University of Londrina, Brazil). Respiratory and quadriceps muscle strength, and lung function were assessed in the first 24h of hospitalization (day 1) and reassessed at discharge and 1 month after discharge (1mD). In the last assessment (1mD), patients returned to the hospital to be reassessed. Arterial blood gases, symptoms, and the combined COPD assessment were investigated at day 1 only. This study was approved by the ethics committee of the State University of Londrina and all patients gave written informed consent.

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Patients

Patients were included in the study if they presented: COPD diagnosis based on GOLD criteria[1] (post-bronchodilator forced expiratory volume in the first second [FEV_1]/forced vital capacity [FVC] < 0.70); hospital admission due to an exacerbation of the disease (i.e., severe exacerbation according to the definition of Rodriguez-Roisin[14]); spontaneous breathing on hospital admission (i.e., not being on mechanical ventilation); absence of pathological conditions (e.g., neuromuscular, cerebrovascular, or severe cardiac diseases) that could impair the performance on the proposed tests; no recent hospitalization due to COPD exacerbation; and no participation in any exercise training in the previous six months. The decision to admit patients to the hospital was made by the attending physician, who was not involved in the present study. Patients were excluded in case of death, withdrawing consent, or missing values in more than 1 day of assessment (i.e., discharge and 1mD).

Assessments

Gender, age, anthropometric variables (weight, height, and body mass index [BMI]), and clinical variables (number of exacerbations in the previous year and previous corticosteroids use) were collected at the moment of inclusion in the study. Data concerning corticosteroids use and physiotherapy treatment during the hospitalization were retrieved retrospectively from the patients' medical file after discharge.

Respiratory muscle strength, the primary outcome, was measured by the assessment of maximal inspiratory and expiratory pressures (PImax and PEmax, respectively) using a digital manovacuometer (MVD 300, GlobalMed, Porto Alegre, Brazil) and a plastic tube mouthpiece with a small leak to prevent glotic closure and

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to reduce the use of buccal muscles[15]. The Black and Hyatt[16] protocol was used, in which patients were assessed in the seated position, wore a noseclip, and had the PImax measured near residual volume and the PEmax near total lung capacity. PImax and PEmax were maintained for at least two seconds and the peak value was recorded. Although negative, the values of PImax were presented as positive values to avoid misinterpretation of its changes. The best of three acceptable and reproducible consecutive maneuvers was considered for analysis. The criteria for acceptability were adequate effort and duration, no postural compensation, and no cough or perioral air leak during the maneuvers, while the criterion for reproducibility was a difference ≤ 10% of the highest value between the two highest values. Reference values were also used to express the results[17].

Quadriceps muscle strength was measured by the assessment of quadriceps peak torque (QPT) from an isometric contraction of the quadriceps at the dominant side and at 60º of knee flexion[18]. A hand-held electrical dynamometer (microFET2, Hoggan Health, USA) anchored in a fixed multigym equipment was used to register the QPT; this adaptation was previously validated[19]. The best of three acceptable and reproducible maneuvers was considered for analysis. QPT was expressed in Newton meters (N·m), Newton per kilogram ($N \cdot kg^{-1}$), and as percentage of the predicted values[20]. Lung function was measured with spirometry (Spirobank G, MIR, Italy) by the assessment of slow and forced vital capacities after bronchodilation, according to international reccomendations[21] and considering national reference values[22;23]. All the tests were performed by a trained physiotherapist.

Arterial blood gases levels (i.e., partial pressure of oxygen and carbon dioxide) were assessed at admission by the hospital staff. Also at admission,

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the combined COPD assessment[1] was performed to get a multidimensional estimate of disease severity. This assessment involves airflow limitation, exacerbation frequency, and symptoms - which were assessed by the Medical Research Council (MRC) scale[24] -, and classifies patients in one of the four groups: A (low risk, less symptoms), B (low risk, more symptoms), C (high risk, less symptoms), or D (high risk, more symptoms).

Statistical Analyses

The study by González et al.[12] was used for sample size calculation. Considering the difference in means pooled ± standard deviation of 15 ± 21 cmH_2O between hospital admission and discharge concerning the maximal inspiratory pressure, an alpha value of .05, and a power of 80%, the present study needed a sample size of 17 participants (using the paired t test). Adding a drop out rate of 25%, verified in a previous study with similar design[5], the required sample size increased to 21 subjects.

Categorical variables were described as absolute and/or relative frequencies, while continuous variables were tested for normality by the Shapiro-Wilk test and presented as mean ± standard deviation, when normally distributed, or median (interquartile range 25%-75%), when non-normally distributed. Multiple imputation method was used to impute the missing values, which were considered missing completely at random (MCAR) according to Little's MCAR test. Only the results with imputed data were presented, unless a difference between these and the results from complete-case analysis was verified.

Chi-square test was used for the comparison of categorical data. Repeated measures ANOVA or Friedman test was used for the comparisons among

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the three days of assessment, with Tukey's or Dunn's test as post hoc test, respectively. The changes (delta) in respiratory pressures were compared by the paired t test or Wilcoxon test, and the comparison of these deltas between PImax and PEmax was performed by the unpaired t test or Mann-Whitney test. Spearman or Phi coefficient was used to analyze correlations. The level of statistical significance was considered as $P<.05$ and all the analyses were performed using the Statistical Package of Social Science (SPSS) 17.0 (SPSS Inc., Chicago, IL, USA) or the GraphPad Prism 5 (GraphPad Software Inc., La Jolla, California, USA).

Results

Twenty-one exacerbated patients with COPD were included. During the course of the study, two patients died from respiratory complications of COPD (one during hospitalization and the other nearly before the 1mD assessment) and two did not attend the last assessment. The two patients who died were excluded and the two who did not attend the follow-up were handled with the multiple imputation method. Only one patient was hospitalized again after discharge, but before the 1mD assessment. However, a sensitivity analysis revealed that this patient did not bias the results. Patients who dropped out and the remainder patients had similar age, anthropometric measures and lung function. On the contrary, patients who died were older, had lower BMI and presented more exacerbations in the last year.

Clinical information before and during hospitalization

Table 1 describes the clinical characteristics of the nineteen patients included in the study on the first day of assessment (day 1). It can be noticed that the

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majority of patients were classified as GOLD IV and belonged to group D in the combined COPD assessment. During hospitalization, sixteen patients (84%) received systemic corticosteroids (hydrocortisone, prednisone, prednisolone or methyl-prednisolone) and three (16%) did not receive them. Still regarding the hospitalization period, eighteen patients (95%) received bronchodilators (combination of fenoterol and ipratropium, terbutaline, or tiotropium), while nine patients (47%) received respiratory physiotherapy. The physiotherapy techniques were mainly calisthenics-and-breathing exercises or bronchopulmonary hygiene techniques, with no endurance, strength or respiratory muscle training. The hospitalization lasted a median period of 4 (3-5) days.

Respiratory muscle strength during and after hospitalization

The behavior of PImax during and after hospitalization is presented in Figure 1A. In comparison to day 1 (56 [45-64] cmH_2O), PImax did not change significantly at discharge (62 [45-69] cmH_2O, $P \geq .05$), but did increase at 1mD (65 [51-74] cmH_2O, $P < .05$). PEmax showed a similar pattern (Figure 1B); however, the post hoc test revealed that, in comparison to day 1 (99 [65-117] cmH_2O), PEmax increased already at discharge (109 [77-136] cmH_2O, $P < .05$) and also at 1mD (114 [90-139] cmH_2O, $P < .05$).

No statistical difference was found when the delta (i.e., the relative change normalized to the values obtained at day 1) between day 1 and discharge was compared to the delta between day 1 and 1mD, for both PImax and PEmax ($P > .05$ for all, Figure 2), and it was noticed that the improvement in PImax and PEmax from day 1 to discharge accounted for 68% and 61%, respectively, of the improvement from day 1 to 1mD. PEmax was higher than PImax in the comparison of

both the delta from day 1 to discharge (14 ± 22 *vs* 13 ± 20 %, respectively; *P*=.001, Figure 2) and from day 1 to 1mD (23 ± 31 *vs* 19 ± 22 %, respectively; *P*=.003, Figure 2).

At day 1, the PImax correlated significantly with the PEmax (Spearman's rho=0.49, *P*=.04) and with the QPT (Spearman's rho=0.57, *P*=.01), while the PEmax, in addition to the correlation with the PImax, correlated inversely to the FEV_1 (Spearman's rho=-0.61, *P*=.005) and the inspiratory capacity (IC) (Spearman's rho=-0.54, *P*=.02), both in % predicted. It was also observed that, still at day 1, the proportion of patients with reduced IC (< 80% of predicted[25]) was exactly the same as with inspiratory muscle dysfunction (IMD, suggested by Vilaró et al.[7] as PImax < 70% of predicted), which is 13 patients (68%). Indeed, the IC of patients with IMD was observed to be lower than the IC of patients without IMD (62 [53-72] *vs* 93 [71-139] % predicted, respectively; *P*=.02) and the classifications of reduced IC and IMD were associated (rφ=0.62, *P*=.03). The delta of PImax between day 1 and 1mD linearly correlated with the same delta of PEmax (Spearman's rho=0.58, *P*=.01), both in cmH_2O, while the latter inversely correlated with the PEmax assessed at day 1 (Spearman's rho=-0.52, *P*=.02).

Lung function and peripheral muscle strength during and after hospitalization

The behavior of lung function and peripheral muscle strength during and after hospitalization is shown in Table 2. It can be observed that no statistical difference was found in the comparison of FEV_1 and FVC among the three assessment days. The IC in liters significantly increased from discharge to 1mD (*P*<.05).

There was no statistical difference in the comparison of QPT among

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the three assessment days. During all assessments, no adverse effects were observed.

Discussion

This study clearly showed that the inspiratory muscle strength is reduced at the onset of a hospitalization for COPD exacerbation, but increases markedly by one month after discharge. The expiratory muscle strength presents a similar pattern, but already increases from admission to discharge and also to one month after discharge. Lung function at hospital admission was found to be related to both inspiratory and expiratory muscle strength.

Two out of the three studies that prospectively evaluated the inspiratory muscle strength during and/or after hospitalization found that this variable increased from admission to discharge[11;12], while the other study found a trend of improvement from discharge to one month after[5]. At first glance it may seem that our results do not corroborate any of these studies, as we found significant difference only between day 1 and one month after discharge, however these results actually do agree with the two formers. Although the comparison between PImax from admission to discharge in our study was not statistically different, higher values were observed at discharge (which represent an 11% increase in PImax in comparison to day 1). This represented 68% of the whole improvement observed in PImax. One possible explanation to the lack of statistical significance may rely on the post hoc analysis, which might have been underpowered.

At hospital admission, the inspiratory muscle dysfucntion was found to be related to the reduction in inspiratory capacity. Indeed, this supports previous

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explanations for the reduction in inspiratory muscle strength during exacerbation. Martínez-Llorens et al.[11] and González et al.[12] justify this reduction by the mechanical disadvantage caused by hyperinflation, a mechanism better explained in previous studies by O'Donnell and colleagues[26;27]. Another factor that supports this hypothesis is the rapid improvement observed in the absence of any specific treatment for the inspiratory muscles. Nevertheless, other factors such as malnutrition, inflammatory markers and corticosteroids use should be investigated in details, since they might contribute to respiratory muscle dysfunction.

In the present study, the inspiratory capacity increased from the hospitalization period in comparison to one month after discharge. This means that a more hyperinflated pattern was observed during hospitalization, corroborating our results in which reduced values of respiratory muscle strength were observed during hospitalization. IC at discharge was slightly and not significatly lower than the IC at admission, and we hypothesized that patients in our study stayed hospitalized for a relatively short period of time (i.e., 4 [3-5] days) when compared to previous studies (around 10 days)[5;6;11]. Additionally, no clinical pathway was used to treat patients, meaning that different treatment regimes were adopted. These facts may have led patients to be discharged without having their lung function completely recovered.

From the best of our knowledge only two studies prospectively assessed the strength of the expiratory muscles during the course of a hospitalization for COPD exacerbation, and their results were divergent. Martínez-Llorens et al.[11] verified a significant decrease in the expiratory muscle strength from hospital admission to discharge. On the other hand, Pitta et al.[5] did not find significant differences among three assessment days (two during hospitalization and one after discharge), but did find an increasing pattern from hospital admission to after

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discharge. We observed the same pattern in our study, and even reached statistical significance. Martínez-Llorens et al.[11] stated that the expiratory muscles are not affected by dynamic hyperinflation. We agree that they may not be directly affected as much as the inspiratory muscles, but based on previous findings[28] and on our own results, it is reasonable to postulate that these variables might be at least related. We observed a negative correlation between expiratory muscle strength and the degree of airflow limitation and hyperinflation. It is well known in the literature that during hyperinflation the activity of the expiratory muscles is increased[28;29]. Hence, we believe that the hyperinflation elicited by the exacerbation may have over-recruited the expiratory muscles, which might explain the observed negative correlations between PEmax and IC. In fact, it has been shown that patients with history of multiple hospital admissions due to exacerbations present higher values of expiratory muscle strength in comparison to more stable patients[7;8].

Regarding QPT, we observed no difference in this variable among the three assessment moments, similarly to Troosters et al.[18]. Two other studies[5;6], however, verified a decrease of 5% predicted in the QPT during the hospitalization period. Besides the study of Troosters et al.[18], which found no decrease in this variable, in the study of Spruit et al.[6] 48% of patients presented no change or even an increase in this variable, allowing to hypothesize that maybe there is a phenotype of patients more prone to show peripheral muscle dysfunction during exacerbations. Furthermore, also for QPT, differences in sample characteristics, pharmacological treatment adopted and physiotherapy regimen performed during the hospitalization period may account, at least in part, for these conflicting results.

This study was useful to clarify previous findings in the literature, and its main message is possibly that the hyperinflation observed during the onset of an

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exacerbation has an impact on the respiratory muscles, further reducing their strength. Despite our useful findings, this study has some limitations that should be acknowledged. Probably the main one relies on the fact that we were not aware of the respiratory muscle strength before hospitalization. However, the inclusion of this assessment moment would probably logistically complicate the study. Another point of concern could be the use of a volitional test (maximal static pressures measured at the mouth) for the assessment of respiratory muscle strength. The test used, however, has shown to be valid, simple to perform, and better tolerated by patients than non-volitional tests[15], considered by some researchers as the gold-standard method. More specific assessments of respiratory muscle strength, however, could provide new results, although probably not different ones. We did not prospectively assess outcomes such as dyspnea sensation, quality of life or blood gases, which could provide further understanding of the respiratory muscles behavior. These outcomes, however, can also be influenced by others such as hyperinflation or exercise capacity, complicating the analysis of their relationship with the respiratory muscles. In our study, the moments of assessment were not standardized among patients, what can also be considered a limitation. However, the hospital where patients were assessed did not use any standardized protocol for exacerbated COPD patients, compromising a standardized assessment. Another point of criticism could be the use of the t test, rather than the ANOVA test, for sample size calculation. However, the direct application of ANOVA test seemed not feasible, once different disease severities and time frames can be found in the deltas of the present study. Finally, the use of peak respiratory pressures instead of one-second plateau pressures or the mean pressure over one second, most frequently used, might be another point of concern. A very well designed study[17], however, concluded that peak

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and plateau pressures were comparable in terms of predicted variables, between-subject variability and reproducibility.

Conclusions

In summary, the present study showed that there is inspiratory muscle dysfunction at hospital admission and that the inspiratory muscle strength increases markedly by one month after discharge. The expiratory muscle strength, in turn, already increases from admission to discharge and also to one month after discharge. The degree of airflow obstruction and hyperinflation at hospital admission were found to be related to both inspiratory and expiratory muscle strength. The understanding of the possible causes of the changes observed in respiratory muscle strength during an exacerbation are important to be investigated in future studies, as well as the possible consequences of these changes.

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FIGURE LEGENDS

Figure 1. Maximal respiratory pressures (in cmH_2O; A: maximal inspiratory pressure; B: maximal expiratory pressure) during and after hospitalization. Data expressed as median (interquartile range). *P* value from Friedman test: A) *P*=.03; B) *P*=.005.

Figure 2. Changes in maximal respiratory pressures (in percentage of the values obtained at day 1; solid circles: maximal inspiratory pressure; open circles: maximal expiratory pressure) through the days of assessment. The dotted line corresponds to the zero value. Data presented as mean ± standard deviation.

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Table 1. Clinical characteristics of the patients in the first 24h of hospitalization.

Characteristics	Values
Gender (n, M / F)	12 / 7
Age (years)	67 ± 11
BMI ($kg \cdot m^{-2}$)	23 (19-27)
FEV_1 (% pred)	26 (19-32)
FEV_1/FVC (%)	38 ± 12
GOLD grades (n, I / II / III / IV)	0 / 1 / 6 / 12
Previous exacerbations (n / %)	
0-1	15 / 79
≥ 2	4 / 21
Symptoms (MRC scale)*	3 ± 1
Combined COPD assessment* (%, A / B / C / D)	0 / 0 / 25 / 75
Previous corticosteroid use (n / %)	
Inhaled corticosteroids†	9 / 47
Oral corticosteroids‡	3 / 16
Pa_{O_2} (mm Hg)	61 ± 14
Pa_{CO_2} (mm Hg)	39 (31-43)

Data expressed as absolute frequency, relative frequency, mean ± standard deviation or median (interquartile range). *Data available for eight patients only, who did not differ from the remainder patients of the sample in terms of age, anthropometric variables, and lung function. †For a mean period of 24 months. ‡20 $mg \cdot day^{-1}$ of prednisone or prednisolone for a mean period of 26 months. BMI: body mass index; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council; Pa_{O_2}: arterial partial pressure of oxygen; Pa_{CO_2}: arterial partial pressure of carbon dioxide.

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Table 2. Lung function and peripheral muscle strength during and after hospitalization.

	LUNG FUNCTION			
Characteristics	**Day 1**	**Discharge**	**One month after discharge**	***P* value**
FEV_1				
L	0.74 (0.61-0.86)	0.75 (0.61-0.86)	0.69 (0.59-0.90)	.21
% predicted	26 (19-32)	25 (19-32)	26 (21-35)	.75
FVC				
L	2.07 ± 0.80	2.04 ± 0.68	2.10 ± 0.84	.91
% predicted	50 (43-68)	51 (41-73)	62 (41-76)	.78
IC				
L	1.93 ± 0.60	1.59 ± 0.44	1.99 ± 0.54*	.02
% predicted	71 (58-85)	54 (43-85)	70 (58-91)	.12
	PERIPHERAL MUSCLE STRENGTH			
Characteristic	**Day 1**	**Discharge**	**One month after discharge**	***P* value**
QPT				
N·m	79 ± 34	78 ± 35	85 ± 38	.10
% predicted	66 (45-77)	65 (51-77)	72 (44-81)	.37
$N \cdot kg^{-1}$	4.00 ± 1.49	3.87 ± 1.39	4.20 ± 1.36	.34

Data expressed as mean ± standard deviation or median (interquartile range). *P<.05 *vs* discharge. FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; IC: inspiratory capacity; QPT: quadriceps peak torque.

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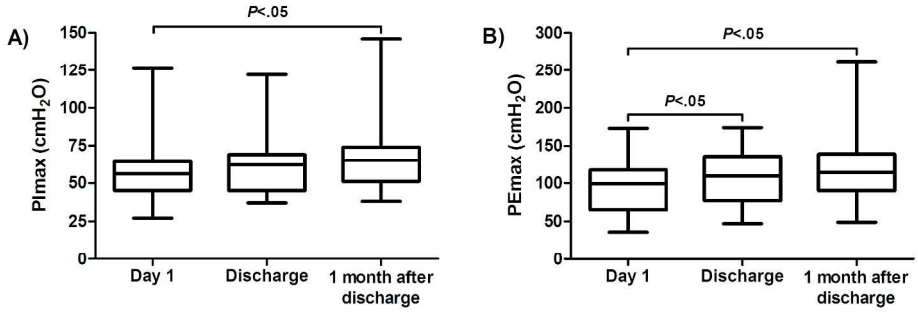

Maximal respiratory pressures (in cmH_2O; A: maximal inspiratory pressure; B: maximal expiratory pressure) during and after hospitalization. Data expressed as median (interquartile range). *P* value from Friedman test: A) *P*=.03; B) *P*=.005.
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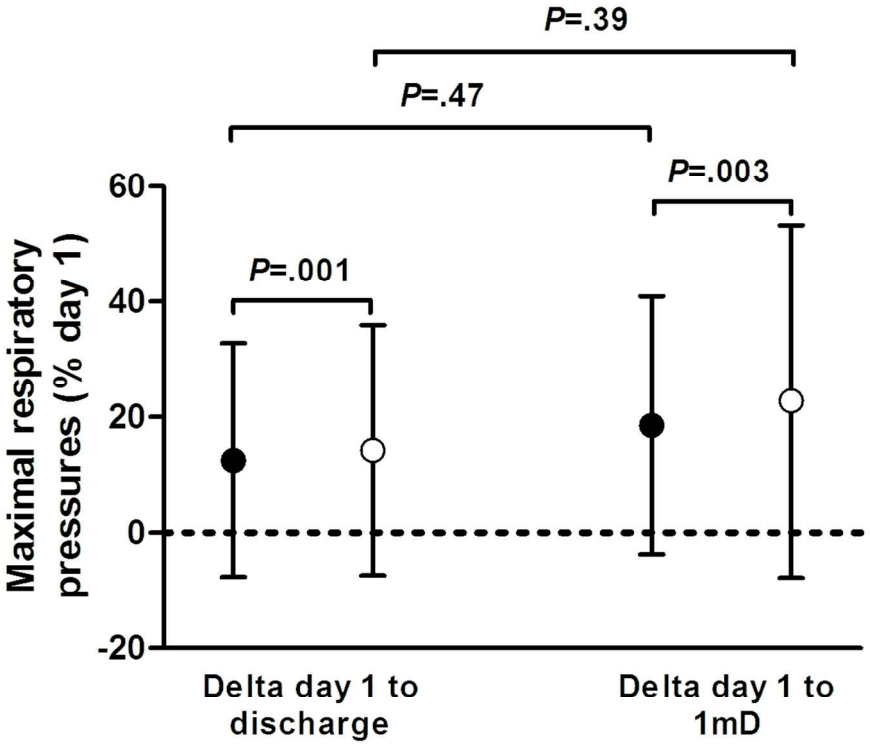

Changes in maximal respiratory pressures (in percentage of the values obtained at day 1; solid circles: maximal inspiratory pressure; open circles: maximal expiratory pressure) through the days of assessment. The dotted line corresponds to the zero value. Data presented as mean ± standard deviation.
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