

# Risk Factors of Readmission in Acute Exacerbation of Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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**OBJECTIVES:** More effective management of chronic obstructive pulmonary disease (COPD) and improved survival of COPD patients requires a better understanding of the risk factors for exacerbation. The aim of this study was to identify factors related to readmission in patients with moderate-to-severe COPD.

**PATIENTS AND METHODS:** Ninety patients with moderate-to-severe COPD hospitalized consecutively for acute exacerbation were studied prospectively. At discharge, the following potential predictors were assessed: clinical and spirometric variables, arterial blood gases, and respiratory muscle strength determined noninvasively. The patients were followed for a period of 3 months. Readmission for exacerbation and time intervals free of hospitalization were recorded.

**RESULTS:** Univariate analysis showed that the presence of cor pulmonale ( $P < .05$ ), long-term oxygen therapy ( $P < .05$ ), hypercapnia ( $P < .05$ ), and high inspiratory load—mean inspiratory airway pressure measured at the mouth exceeding 0.40 cm H<sub>2</sub>O and a pressure-time index greater than 0.25 ( $P < .05$  for both variables)—increased the risk of hospitalization for exacerbation. Multivariate analysis showed that only cor pulmonale ( $P < .05$ ) and a high pressure-time index ( $> 0.25$ ,  $P < .05$ ) were independently related to risk of readmission.

**CONCLUSIONS:** Cor pulmonale and a high pressure-time index are independent risk factors for hospitalization for exacerbation of moderate-to-severe COPD.

**Key words:** Chronic obstructive pulmonary disease (COPD). Exacerbation. Readmission. Inspiratory load. Pressure-time index.

Factores predictivos de reingreso hospitalario en la agudización de la EPOC moderada-grave

**OBJETIVOS:** Conocer los factores asociados a la exacerbación de la enfermedad pulmonar obstructiva (EPOC) es importante para mejorar la supervivencia de los pacientes y conseguir mayor efectividad en su tratamiento. El objetivo de este estudio es identificar las variables asociadas con el reingreso hospitalario en la agudización de la EPOC moderada-grave.

**PACIENTES Y MÉTODOS:** Se estudió de forma prospectiva a 90 pacientes con EPOC moderada-grave ingresados de manera consecutiva en nuestro Servicio de Neumología por exacerbación de su enfermedad. En el momento del alta se evaluaron las variables clínicas, espirométricas y gasométricas, así como el estado muscular, mediante medidas no invasivas. Se realizó un seguimiento de los pacientes durante 3 meses tras el alta. Recogimos las agudizaciones que requirieron ingreso hospitalario y el tiempo libre de enfermedad.

**RESULTADOS:** El análisis univariado mostró que la coexistencia de *cor pulmonale* ( $p < 0,05$ ), el uso de oxigenoterapia domiciliaria ( $p < 0,05$ ), la hipercapnia ( $p < 0,05$ ) y una elevada carga inspiratoria—presión media de la vía respiratoria medida en boca  $> 0,40$  cmH<sub>2</sub>O e índice presión-tiempo  $> 0,25$  ( $p < 0,05$  para ambas)—aumentan el riesgo de ingreso hospitalario tras una agudización. El análisis multivariado mostró como factores predictivos independientes el *cor pulmonale* ( $p < 0,05$ ) y un elevado índice presión-tiempo (mayor de 0,25;  $p < 0,05$ ).

**CONCLUSIONES:** La coexistencia de *cor pulmonale* y un elevado índice presión-tiempo son factores predictivos independientes de ingreso hospitalario por agudización en los pacientes con EPOC moderada-grave.

**Palabras clave:** EPOC. Agudización. Reingreso. Carga inspiratoria. Índice presión-tiempo.

## Introduction

Exacerbation is an event of considerable importance in the course of chronic obstructive pulmonary disease (COPD), as it plays a significant role in increased

mortality, the deterioration of patients' quality of life, and the high economic cost of the disease. An understanding of the factors associated with exacerbation, especially the risk factors for acute exacerbation, is of the utmost importance in improving survival and providing effective treatment.

COPD patients have an average of 2 exacerbations per year.<sup>1</sup> Moderate or severe exacerbations are the most frequent cause of hospital admissions and account for 41% of the health care costs generated directly by the disease. Treatment failure and hospital admissions

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account for the largest share of the cost of exacerbations.<sup>2</sup> An understanding of risk factors of readmission can help to avoid the recurrence of such episodes. The following factors have been associated with an increased risk of hospitalization: hypercapnia, pulmonary hypertension,<sup>3</sup> number of previous exacerbations, low forced expiratory volume in 1 second (FEV<sub>1</sub>), and physical activity.<sup>4</sup> Recently, inhaled corticosteroids have been shown to reduce the number of hospitalizations per exacerbation<sup>5</sup> and even to reduce severity,<sup>6</sup> but in a multicenter randomized, double-blind placebo-controlled clinical trial published this year<sup>7</sup> no differences were found in the number of hospital admissions between the group receiving inhaled corticosteroids and the placebo group. Respiratory muscle weakness in COPD patients has been associated with high utilization of health care resources.<sup>8</sup> It is well known that COPD patients are at greater risk than healthy subjects for developing respiratory muscle fatigue, since the force developed with each inhalation is high compared with their maximal inspiratory muscle force.<sup>9</sup> The role of the inspiratory load that patients breathe against during an acute exacerbation has not been analyzed in previous studies. In the present study, we attempted to identify the risk factors associated with hospital readmission in COPD, including the role of inspiratory load, by studying prospectively a cohort of patients with moderate-to-severe COPD admitted to the respiratory medicine ward of a tertiary hospital for exacerbation of their disease.

## Patients and Methods

Ninety patients with moderate-to-severe COPD admitted to a tertiary hospital for exacerbation between January and December 1997 were studied prospectively. Clinical diagnosis of COPD was confirmed by history and spirometry for all patients. Percent of predicted FEV<sub>1</sub> was used to define severity of disease according to criteria established by the American Thoracic Society.<sup>10</sup> Exacerbation was defined as an increase in dyspnea, in sputum production, or in sputum prurulence.<sup>11</sup> Those patients with exacerbations that did not respond to outpatient treatment (increased daily doses of bronchodilators, antibiotics, and a short course of oral corticosteroids) were hospitalized. We excluded from the study hospitalizations due to programmed surgery or diagnostic procedures, admissions due to insufficient home care resources, patients with chest x-rays showing bronchiectasis or pneumonia, and patients receiving noninvasive home ventilation.

Patient characteristics studied included: age, body mass index (BMI), smoking history, number of exacerbations requiring hospitalization in the previous year, and comorbidity (diabetes mellitus, arterial hypertension, cor pulmonale), and use of long-term oxygen therapy.

During hospitalization, all patients received conventional drug therapy with systemic corticosteroids, inhaled bronchodilators, antibiotics, and oxygen therapy according to results of arterial blood gas analysis. In each case, the decision to admit or discharge the patient was taken in accordance with

the criteria of the American Thoracic Society<sup>10</sup> by the attending physician, who was unaware of the objective of the study.

Cor pulmonale was diagnosed by Doppler echocardiography, a method used to estimate pulmonary artery pressure indirectly by calculating tricuspid regurgitation flow velocity using the modified Bernoulli formula.<sup>12</sup> Pulmonary hypertension was considered to be present when mean pulmonary artery pressure exceeded 20 mm Hg.

Upon discharge, a flow-volume curve was obtained using a Lilly-type pneumotachograph (Micro S-2000, C. Schatzman, Madrid, Spain). A minimum of 3 curves were plotted and the highest FEV<sub>1</sub>, forced vital capacity (FVC), and FEV<sub>1</sub>/FVC values were selected for the calculations.

Inspiratory muscle strength was assessed by obtaining the maximal inspiratory pressure (MIP) and the pressure-time index (PTI),<sup>13</sup> using an electromanometer (Siebelmed 163, Siebel, Barcelona, Spain) connected to a recorder (x-y Servogor 731, Goertz Metrawatt, Nuremberg, Germany). MIP was obtained at close to residual volume. The highest value obtained from 3 reproducible maneuvers with less than 10% variability was used. The reference values were those established by Black and Hyatt.<sup>14</sup>

PTI was derived from the following equation<sup>13</sup>:

$$PTI=(P_{awo}/MIP)\times(T_i/T_{tot})\times 100,^{13}$$

where P<sub>awo</sub> represents mean airway pressure measured at the mouth during spontaneous breathing, T<sub>i</sub>, inspiratory time, and T<sub>tot</sub>, total breathing cycle time. The pressure signal curve was recorded over a period of 15 minutes at a paper speed of 6 cm/min. Mean airway pressure was calculated by adding all the pressure values obtained during each interval and dividing the sum by the number of intervals.

Airflow was measured by a Lilly type pneumotachograph connected to a Mingograph (Siemens-Elema, Germany). To measure T<sub>i</sub> and T<sub>tot</sub>, the inspiratory line was separated from the expiratory line by resetting the volume signal to zero. The T<sub>i</sub>/T<sub>tot</sub> ratio was calculated as the average of 20 cycles at a rate of 30 cm/min and was expressed as a percentage.

Arterial blood gas analysis was performed using an ABL-520 (Radiometer, Copenhagen, Denmark).

After discharge, patients were followed for 3 months. During this period readmission for acute exacerbation and intervals free of hospitalization were recorded. Emergency room and outpatient visits for exacerbations that resolved with increased doses or changes in medication were not considered in the study. Long-term medication during follow-up included long- and short-acting bronchodilators, oral methylxanthines, and short courses of antibiotics or oral corticosteroids.

We performed a descriptive analysis of the data, in which continuous variables were expressed as means (SD) and dichotomous variables as percentages of the total. We also performed a univariate analysis for the variables associated with readmission using the  $\chi^2$  test for the dichotomous variables and the Student *t* test for the continuous variables. A *P* value less than .05 was considered significant. We used receiver operating characteristic curves to define subgroups for continuous variables, choosing the value with the best sensitivity-specificity ratio as the cut point. The Cox proportional hazards regression model was used to obtain variables independently related to readmission. The Kaplan-Meier method was used to determine intervals free of hospitalization.

TABLE 1  
Patient Characteristics (n=90)\*

Age, years	69.3(7.5)
Pack-years	75.3(40.0)
Severity of disease	
FEV <sub>1</sub> =35%-49%	59.8% (n=53)
FEV <sub>1</sub> <35%	34.4%% (n=31)
BMI, kg/m <sup>2</sup>	26.8(4.3)
Long-term oxygen therapy	30% (n=27)
Previous admissions	1.38(0.83)
Comorbidity	
Arterial hypertension	25.7% (n=19)
Diabetes mellitus	8.2% (n=6)
Cor pulmonale	32.6% (n=29)
Mean length of hospital stay, days	12.2(9.1)

\*Data are presented as percentages or means (SD). FEV<sub>1</sub> indicates forced expiratory volume in 1 second; BMI, body mass index.

TABLE 2  
Arterial Blood Gas Levels, Lung Function, and Respiratory Muscle Strength (n=90)\*

FEV <sub>1</sub> , %	43.03(8.1)
pH	7.42(0.03)
PaO <sub>2</sub> , mm Hg	62.7(9.3)
PaCO <sub>2</sub> , mm Hg	48.3(8.9)
RF, breaths/min	18(4.7)
T <sub>i</sub> , s	1.31(0.43)
T <sub>i</sub> /T <sub>tot</sub>	0.38(0.05)
VT/T <sub>i</sub> , mL/s	0.60(0.18)
Pawo, cm H <sub>2</sub> O	0.34(0.10)
MIP, cm H <sub>2</sub> O	73.3(23.2)
PTI	0.19(0.10)

\*Data are presented as mean (SD). FEV<sub>1</sub> indicates forced respiratory volume in 1 second; RF, respiratory frequency; T<sub>i</sub>, inspiratory time; T<sub>tot</sub>, total breathing cycle time; VT, tidal volume; Pawo, mean inspiratory airway pressure measured at the mouth; MIP, maximal inspiratory pressure; PTI, pressure-time index.

## Results

Table 1 shows the characteristics of the patients included in the study at baseline. All patients were men, with a mean age of 69.3(7.5) years. Of these patients, 93.3% were smokers: 48 patients (57%) were active smokers and 36 (42%) ex-smokers. FEV<sub>1</sub> was less than 35% of predicted in 34% of the patients. All patients had hypoxemia (mean PaO<sub>2</sub>: 62.7[9.1] mm Hg) and moderate hypercapnia (mean PaCO<sub>2</sub>: 48.3[8.9]) mm Hg). Of the 90 patients selected, 27 (30%) had a PaO<sub>2</sub> less than 60 mm Hg and were treated with long-term oxygen therapy for an average of 34 months; 45 patients (50%) had a PaCO<sub>2</sub> more than 45 mm Hg (Table 3).

During follow-up 13 patients (14.4%) were readmitted, 8 of them (61.5%) during the first month following discharge. The total number of readmissions in the 3-month period was 16. The results of the univariate analysis are shown in Table 2. The following factors increased the risk of hospitalization: the use of home oxygen therapy and a duration of use of more than 8 months, the presence of cor pulmonale, the presence of hypercapnia (PaCO<sub>2</sub>>48 mm Hg), and the persistence of an excessive inspiratory muscle load (Pawo>0.4 cm H<sub>2</sub>O; PTI>0.25). The results of the multivariate analysis (Table 4) showed that only the presence of cor pulmonale (odds ratio [OR]=2.2; 95% confidence interval [CI], 1.2-4.2) and a high PTI (>0.25; OR=2.7; 95% CI, 1.4-5.3). The results of the Kaplan-Meier log-rank test were significant for the 2 variables (Figures 1 and 2).

## Discussion

The main result of our study was that high PTI and cor pulmonale are independent risk factors for hospitalization for exacerbation of moderate-to-severe COPD.

No other factors—including PaO<sub>2</sub> or PaCO<sub>2</sub> values, the number of admissions in the previous year, or

TABLE 3  
Univariate Analysis of Variables Possibly Associated With Readmission\*

Variable	Hospitalized (%)	OR	95% CI	P
Age>70 years	43.5 compared to 43.8	0.99	0.6-1.5	NS
Smoker	44.3 compared to 25	1.03	0.9-1.1	NS
Pack-years>77	47.6 compared to 39.5	1.17	0.7-1.8	NS
BMI<26 kg/m <sup>2</sup>	47.6 compared to 45.2	1.04	0.7-1.6	NS
Previous admissions	55.3 compared to 37	1.5	0.9-2.5	NS
Hypertension	57.9 compared to 41.8	1.6	0.7-3.5	NS
Diabetes mellitus	50 compared to 44.8	1.2	0.2-5.6	NS
Cor pulmonale	62.1 compared to 35.4	2.1	1.1-3.9	<.05
LTOT	66.7 compared to 34.3	2.5	1.2-5.1	<.05
LTOT>8 months	68.2 compared to 36.1	2.77	1.2-6.1	<.05
Mean stay> 10 days	51 compared to 36.6	1.3	0.9-1.8	NS
FEV <sub>1</sub> <40% of predicted	58.5 compared to 37.2	1.5	0.9-2.4	.05
pH<7.43	51.1 compared to 46.2	1.1	0.7-1.6	NS
PaO <sub>2</sub> <63 mm Hg	47.7 compared to 50	0.95	0.6-1.4	NS
PaCO <sub>2</sub> >48 mm Hg	63.2 compared to 35.6	1.8	1.1-3.0	<.05
RF>17 breaths/min	50 compared to 45.5	1.1	0.7-1.6	NS
T <sub>i</sub> /T <sub>tot</sub> <0.38	56.4 compared to 40.4	1.4	0.8-2.2	NS
VT/T <sub>i</sub> <0.57 mL/s	56.8 compared to 38.1	1.4	0.9-2.1	NS
Pawo>0.31 cm H <sub>2</sub> O	60.5 compared to 34.9	1.67	1.0-2.6	<.05
MIP <70 cm H <sub>2</sub> O	65.6 compared to 32.1	1.9	1.1-3.2	<.05
PTI>0.25	72 compared to 38.3	2.8	1.3-6.0	<.05

\*Percentage of patients with the studied variable admitted (eg, patients older than 70 years admitted compared to patients under 70 years). OR indicates odds ratio; CI, confidence interval; BMI, body mass index; LTOT, long-term oxygen therapy; FEV<sub>1</sub>, forced expiratory volume in 1 second; RF, respiratory frequency; T<sub>i</sub>, inspiratory time; T<sub>tot</sub>, total respiratory cycle time; VT, tidal volume; Pawo, mean inspiratory airway pressure measured at the mouth; MIP, maximal inspiratory pressure; PTI, pressure-time index; NS, not significant.

TABLE 4  
Results of Cox Proportional Hazards Regression Model\*

Predictive Variable	Relative Risk	95% CI	P
Cor pulmonale	2.2	1.2-4.2	<.05
PTI>25 compared to <25	2.7	1.4-5.3	<.05

\*PTI indicates pressure-time index; CI, confidence interval.

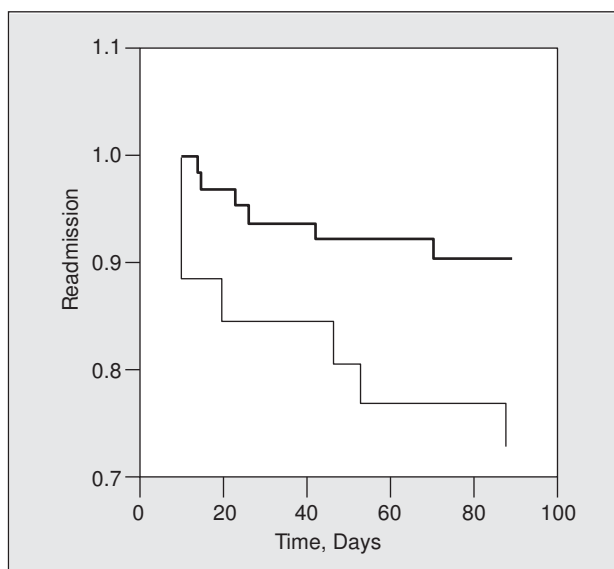


Figure 1. Intervals free of hospitalization for exacerbation in patients with and without cor pulmonale. The thick line represents the subgroup of patients without cor pulmonale and the thin line the subgroup with cor pulmonale.

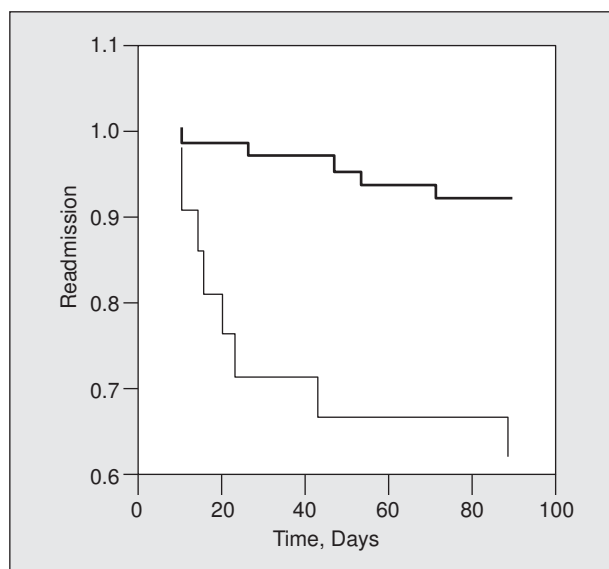


Figure 2. Intervals free of hospitalization for exacerbation in function of pressure-time index (PTI). The thick line represents the subgroup of patients with PTI less than 0.25, and the fine line the subgroup with PTI more than 0.25.

nutritional status—were independently associated with a higher or lower risk for readmission for exacerbation.

An understanding of the factors that increase the risk of hospitalization in COPD can help us to identify those patients for whom conventional therapy is inadequate or likely to fail. It can also help us to plan interventions and take measures to improve disease management during hospitalization and to provide more effective treatment.

Our study showed that cor pulmonale is an independent risk factor for exacerbation, consistent with other studies showing that heart disease is not only associated with a higher risk of hospitalization<sup>15,16</sup> but is also one of the best predictors of mortality after an exacerbation of COPD.<sup>17</sup> In our series, 29 patients (32%) had cor pulmonale, determined indirectly by Doppler echocardiography, although PaO<sub>2</sub> was less than 60 mm Hg in only 27. Pulmonary hypertension has been known to occur in patients with even moderate COPD and hypoxemia.<sup>18</sup> In a series of 64 patients with COPD, Kessler et al<sup>3</sup> showed that mean pulmonary artery pressure was the best predictor of hospitalization for acute exacerbation. Connors et al<sup>19</sup> showed that congestive heart failure and cor pulmonale were the best predictors of survival time after exacerbation.

In our series, 27 patients (30%) had a BMI less than 25 kg/cm<sup>2</sup> and it is noteworthy that only 2 of the 90 patients with moderate-to-severe COPD had a BMI less than 21 kg/cm<sup>2</sup>. BMI, which has been shown to predict a poor outcome in other series,<sup>20,21</sup> was not shown to have a significant impact on prognosis in our study. This finding is consistent with other published studies,<sup>3,17</sup> and may be attributable to the fact that BMI was relatively well maintained in our patients (mean BMI: 26 kg/cm<sup>2</sup>) and perhaps to the fact that the series was too small to determine the real relevance of this factor.

Consistent with previously published results,<sup>7,22</sup> severity of obstruction evaluated as percent of predicted FEV<sub>1</sub> did not appear to predict hospitalization, and the spread of mean (SD) values (43.03%[8.1%]) in our patients was similar to that of other published series.<sup>3</sup> This result for severity of obstruction differs from the findings of the EFRAM study,<sup>23</sup> in which a low FEV<sub>1</sub> was a risk factor for readmission for exacerbation. FEV<sub>1</sub> may be a good indicator of the severity of disease, although not sufficiently sensitive to detect changes brought about by treatment.<sup>5,24</sup> The results of our study seem to support this possibility. The size of the sample and the use of FEV<sub>1</sub> as a dichotomous rather than a continuous variable may also have affected the importance of this factor in our study. Similarly, the degree of hypoxemia was not found to be a risk factor, consistent with reports in other published studies<sup>3</sup>. The range of values we observed was quite narrow (53.6 mm Hg-71.8 mm Hg), and all arterial blood gas measurements were taken without oxygen supplementation so that the effects of additional oxygen would not be a confounding factor in the results. Long-term oxygen therapy was shown by univariate analysis to be associated with readmission. This may be explained by the fact that patients receiving oxygen therapy have chronic respiratory insufficiency and more severe disease<sup>3</sup> (in our series, mean FEV<sub>1</sub>: 33%[7.9%]; mean PaO<sub>2</sub>: 58.37[10.1] mm Hg; mean PaCO<sub>2</sub>: 57.12[9.2] mm Hg). The under-prescribing of oxygen therapy has been shown to be a risk factor of readmission for acute exacerbations independently of other clinical and sociodemographic variables.<sup>23</sup>

Of the 90 patients enrolled in the study, 45 had PaCO<sub>2</sub> values above 45 mm Hg. Although the percentage of patients readmitted with hypercapnia (63.2%) was greater than that of patients admitted without hypercapnia

(35.6%), hypercapnia was found to be significant only in the univariate analysis. Curiously, PaCO<sub>2</sub> has been shown to be a good predictor of mortality in several studies, but only in univariate analysis, and especially in patients with severe chronic respiratory insufficiency.<sup>25,26</sup> Costello et al<sup>27</sup> found that many COPD patients admitted with associated hypercapnia reverted to normocapnia while hospitalized, but patients in whom hypercapnia persisted beyond the acute episode tended to have a poorer long-term prognosis.

Bellemare and Grassino<sup>9</sup> showed that COPD patients were more likely to develop respiratory muscle fatigue than healthy subjects, as the effort made with each inhalation is high compared to their maximal inspiratory muscle force. The results of our study showed that a high inspiratory load (Paw<sub>i</sub>>0.40 cm H<sub>2</sub>O; PTI>0.25) with a low MIP (<72 cm H<sub>2</sub>O) increased the risk of hospital readmission after an acute exacerbation. In the multivariate analysis, only PTI remained as an independent risk factor. In a recently published study, variations in PTI were shown to reflect clinical changes experienced by COPD patients during exacerbations and to provide valid information regarding inspiratory load and functional reserve of the respiratory muscles.<sup>13</sup> Similarly, Talamo et al<sup>28</sup> showed that PTI measured at the mouth correlates well with diaphragmatic electromyogram and PTI both at rest and after CO<sub>2</sub> inhalation. During COPD exacerbations, patients are at risk for developing respiratory muscle fatigue because their muscle capacity may be less than that of healthy subjects or patients with stable COPD.<sup>9</sup> Our results support the hypothesis that readmission may occur due to insufficient reduction in inspiratory muscle load at the time of discharge. The present study is the first to show that an increase in inspiratory load is an independent risk factor of readmission for exacerbation of COPD. This is of particular importance in assessing therapeutic strategies (like rehabilitation or ventilation) that aim to improve muscle condition, among other variables. A previous study carried out in our department, in which positive pressure ventilation was administered via nasal mask to 15 patients with acute chronic respiratory insufficiency, showed that improved arterial blood gas values were associated with a significant decrease in PTI compared to baseline values.<sup>29</sup> Other studies have shown that insufficient reduction in inspiratory load is a determining factor in the failure of weaning from mechanical ventilation.<sup>30</sup>

The present study has certain limitations. All the patients enrolled were men with a mean age of 69 years, a mean FEV<sub>1</sub> 43% of predicted, and a mean 1.38(0.83) exacerbations during the year prior to the study. These characteristics are typical of patients with moderate-to-severe COPD admitted to a tertiary hospital, and our results should be understood as limited to such patients.

In conclusion, the presence of cor pulmonale and a high PTI are independent risk factors of hospitalization for exacerbation in moderate-to-severe COPD. Factors

such as use of oxygen therapy, hypercapnia, or low MIP were shown to raise the risk of hospitalization according to the univariate analysis.

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