Original Article

Inspiratory capacity, exercise limitation, markers of severity, and prognostic factors in chronic obstructive pulmonary disease*

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Abstract

Objective: To correlate the postbronchodilator (post-BD) inspiratory capacity (IC), % of predicted, with other markers of severity and prognostic factors in chronic obstructive pulmonary disease (COPD). **Methods:** Eighty stable patients with COPD performed forced vital capacity and slow vital capacity maneuvers, as well as the 6-min walk test, prior to and after receiving albuterol spray (400 μg). Patients were divided into four groups, based on post-BD forced expiratory volume in one second. Several variables were tested to establish correlations with the post-BD distance walked, using univariate and multivariate analysis. Post-BD IC was found to correlated with Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging and with the Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index. **Results:** Multivariate regression analysis revealed that the distance walked, % predicted, correlated significantly with the IC post-BD, % predicted ($p = 0.001$), long-term oxygen use ($p = 0.014$), and number of medications used in the treatment ($p = 0.044$). IC ≤ 70% was observed in 56% patients in GOLD stages 3 or 4 *vs.* 20% in GOLD 1 or 2 ($p < 0.001$). IC ≤ 70% was observed in (60%) patients with BODE score 3 or 4 *vs.* (33%) BODE score 1 or 2 ($p = 0.02$). **Conclusion:** Post-BD IC% predicted is the best functional predictor of distance walked and is significantly associated with GOLD staging and BODE index. Therefore, we propose that the inspiratory capacity should be added to the routine evaluation of the COPD patients.

Keywords: Pulmonary disease, chronic obstructive; Walking; Respiratory function tests; Inspiratory capacity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, usually progressive and debilitating, disease that is characterized by airflow limitation. This disease is not fully reversible and is associated with a pulmonary inflammatory response to noxious particles or gases.[1]

The staging of COPD is important in order to establish the prognosis and categorize the treatment. An ideal staging system should strongly correlate with mortality, morbidity, and health status. Traditionally, the severity of COPD is defined by the degree of obstruction, evaluated by the forced expiratory volume in one second after bronchodilator use (post-BD FEV_1). The cut-off points suggested for the measurement of FEV_1 for staging vary, and there are significant differences among the guidelines issued by the various prestigious pulmonology societies.[2-4] However, FEV_1 does not correlate well with dyspnea, which is the most important symptom in patients with COPD.[5] The FEV_1 value is not a good marker of survival, incidence of hospitalization, and functional capacity, especially in more severe patients. In addition, the patient with COPD presents systemic manifestations which are not represented by FEV_1.

Recent studies suggest that parameters other than FEV_1 are important independent predictive prognostic factors in COPD, and that some are, in fact, better markers than FEV_1.[6-9] Such parameters include the following: body mass index (BMI); degree of dyspnea; distance covered on the 6-minute walk test (6MWT); health-related quality of life; oxygen uptake (VO_2); the inspiratory capacity/total lung capacity (IC/TLC) ratio; the Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index; and the long-term use of oxygen.

Various factors account for exercise intolerance in patients with COPD, although airflow limitation and peripheral muscle dysfunction play important roles.[10,11] In COPD, the loss of lung elastic recoil and progressive expiratory airflow limitation promote air trapping, with increased functional residual capacity and decreased IC. Static hyperinflation and its increase during exercise (dynamic hyperinflation) have been associated with exercise intolerance in individuals with COPD.[11,12] Reduction of hyperinflation, expressed as an increase in post-BD IC, correlates with better exercise tolerance and reduction of dyspnea.[13] There is also a correlation between a lower IC/TLC ratio and higher mortality.[14]

In addition to dynamic hyperinflation and skeletal muscle weakness, other factors, such as gas exchange abnormalities and pulmonary hypertension, contribute to exercise intolerance. Furthermore, patients with COPD frequently present smoking-related diseases, such as hypertension and heart disease, which also contribute to limiting exercise capacity. The 6MWT reflects all these factors, including the systemic effects associated with the disease and with airflow limitation.[15]

Among the various respiratory function parameters, it would be interesting to select the one which correlates the most closely with exercise capacity, for inclusion in staging systems, since the contribution of the ventilatory part can vary, regardless of the degree of peripheral limitation.

The objective of the study was to evaluate how post-BD IC (% of predicted) correlates with other parameters of airflow limitation, such as forced vital capacity (FVC), post-BD FEV_1 (% of predicted), FEV_1/FVC, post-6MWT dyspnea, number of exacerbations, use of oxygen, and number of drugs used in the treatment, as well as with variables indicating the prognosis and severity of COPD, such as the post-BD distance covered on the 6MWT (% of predicted), the BODE index, and the staging system proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Patients and methods

This was a cross-sectional, descriptive study, comprising 80 stable patients with COPD. Inclusion criteria were as follows: being over 35 years of age; having a smoking history of more than 20 pack-years; and presenting a post-BD FEV_1/FVC (% of predicted) lower than 70% in the functional evaluation. Patients were selected from two Pulmonology Units in Brasília and were monitored for at least two months, presenting good compliance with treatment, which was instituted according to symptoms and severity, as per the GOLD guidelines.[1] The following exclusion criteria were applied: presenting unstable disease; using high doses of oral corticosteroids ($\geq$ 40 mg of prednisone); having used antibiotics within the four weeks preceding the study outset; and presenting uncontrolled comorbidities, such as myopathies, peripheral vascular

disease, and rheumatic/orthopedic diseases that impair locomotion, as well as coronary ischemia and arrhythmia.

The patients were divided into four groups by degree of obstruction, as proposed by the GOLD consensus,[1] according to post-BD FEV_1: mild, moderate, severe, and very severe. In parallel, they were also divided into four groups according to the BODE index, which defines death risk.[2] They were submitted to traditional spirometry, including measurement of slow vital capacity and IC. After spirometry, the 6MWT was performed, according to the norms proposed by the American Thoracic Society, adding measurement of peripheral oxygen saturation (SpO_2) before, during, and after the test.[16] All of the tests were repeated 15 minutes after inhalation of albuterol spray (400 μg). After the 6MWT, dyspnea was evaluated using the Borg scale. The rhythm of the walk was determined by the patients, who were accompanied and given oral encouragement standardized by the pulmonologist. The patients who used oxygen at home walked using oxygen.

The predicted values for the FVC maneuver and IC were based on the values suggested for the Brazilian population.[17,18] The values predicted for the distance walked were those already established in the literature.[19]

Several variables were tested, through univariate analysis, using Spearman's and Pearson's tests, and through multivariate analysis, with post-BD distance walked expressed as the percentage of predicted. Normality in the distribution of variable data was tested using the Kolmogorov-Smirnov test. A parametric test was used for those presenting normal distribution of data. When the distribution was not normal, a nonparametric test was applied. The level of statistical significance for the tests was set at $p \leq 0.05$. Calculations were made using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA).

All participating patients gave written informed consent, and the study design was approved by the Ethics Committee of the University of Brasília School of Health Sciences.

Results

The general data of the 80 patients with COPD are shown in Table 1.

The study sample comprised 57 men and 23 women. According to the GOLD classification, among those 80 patients, the obstruction was mild in 5 (6%), moderate in 29 (36%), severe in 34 (43%), and very severe in 12 (15%). Regarding the BODE index, 32 patients (40%) were classified in quartile 1, 25 (31%) in quartile 2, 17 (21%) in quartile 3, and 6 (8%) in quartile 4. A total of 15 patients (19%) presented BMI $\leq$ 21 kg/m^2. The BMI correlated negatively with the GOLD score, in a significant,

Table 1 - General data in 80 patients with chronic obstructive pulmonary disease.

Variables	Mean ± SD or %	Minimum/maximum values
Age (years)	70 ± 8	52/86
Males (%)	71	
BMI (kg/m^2)	25 ± 4	15/40
Use of oxygen (%)	9	
Number of exacerbations/year	2	1/5
Smoking (pack-years)	51 ± 24	20/145
Post-BD FVC (% of predicted)	80 ± 16	43/136
Post-BD FEV_1 (% of predicted)	49 ± 18	15/101
FEV_1/FVC% (found)	49 ± 11	28/69
Post-BD IC (% of predicted)	78 ± 22	37/157
Post-BD distance covered on the 6MWT (% of predicted)	88 ± 21	22-137
Post-BD distance covered on the 6MWT (m)	397 ± 99	88/606
Post-6MWT post-BD SpO2 (%)	88 ± 5	74/95

SD = standard deviation; BMI: body mass index; post-BD FEV_1: forced expiratory volume in one second after bronchodilator use; post-BD FVC: forced vital capacity after bronchodilator use; post-BD FEV_1/FVC%: Forced expiratory volume in one second/forced vital capacity after bronchodilator use, percentage found; Post-BD IC: Inspiratory capacity after bronchodilator use; 6MWT: 6-minute walk test; and Post-6MWT post-BD SpO_2: peripheral oxygen saturation after the 6MWT and after bronchodilator use.

albeit weak, manner (r = –0.26 p = 0.017), as well as with the BODE index, also weakly (r = –0.27, p = 0.015).

The distance covered on the 6MWT (% of predicted) did not differ by gender and did not correlate significantly with age, height, or BMI. In the patients with a BMI < 21 kg/m^2, the distance covered on the 6MWT (% of predicted) was 81 ± 16%, compared to 89 ± 22% in the other patients (t = 1.32, p = 0.19).

Comorbidities such as systemic arterial hypertension, coronary disease, arrhythmia, diabetes, and hypothyroidism were present in 42 patients. The distance covered on the 6MWT (% of predicted) in the group of patients with comorbidities was 84 ± 20%, compared to 91 ± 22% in the group of patients without comorbidities (p = 0.11). The seven patients who used oxygen in the home, long-term, covered the shortest distance on the 6MWT, expressed in % of predicted, when compared to the patients who did not use oxygen (47 ± 20% *vs.* 92 ± 17%, t = 6.0, p = 0.0001). The distance covered on the 6MWT (% of predicted) correlated inversely with the annual number of exacerbations (r_s = –0.29, p = 0.009), as did the distance covered on the 6MWT (% of predicted) with the number of drugs used in the treatment (r_s = –0.46, p = 0.0001).

Among the functional variables obtained after the administration of bronchodilator, we found that the distance covered on the 6MWT (% of predicted) correlated with the following: % of predicted FVC (r = 0.42, p < 0.00); % of predicted FEV_1 (r = 0.44, p < 0.001); % of predicted FEV_1/FVC (r = 0.47, p < 0.001); number of drugs used in the treatment (r = −0.49, p < 0.001); GOLD (r = −0.52, p < 0.001); BODE index (−0.60, p < 0.001); % of predicted IC (r = 0.61, p < 0.001); post-6MWT Borg scale score (r = −0.41, p < 0.001); and post-6MWT SpO_2 (r = 0.31, p = 0.005). Using multivariate regression analysis, three variables were significantly associated with the distance covered on the 6MWT (% of predicted): % of predicted post-BD IC (p < 0.001); long-term use of oxygen (p = 0.001); and number of drugs used in the treatment (p = 0.034). Using anterograde multivariate regression analysis, these three variables accounted for 59% of the variation in the distance covered on the 6MWT, IC alone accounting for 38%, and the use of oxygen and IC together accounting for 55%. Excluding the seven patients who used oxygen and repeating the anterograde multivariate analysis, IC (% of predicted), post-6MWT Borg scale dyspnea score, and the number of drugs used in the treatment remained significant. Once again, % of predicted IC accounted for 38% of this variation, followed by dyspnea, the addition of which raised the r^2 to 51%. The correlation between IC and the distance covered on the 6MWT (% of predicted) is shown in Figure 1.

The patients using oral corticosteroids covered a shorter distance on the 6MWT (% of predicted), compared to those who did not use corticosteroids (62 ± 24% *vs.* 92 ± 18%, t = 4.73, p = 0.000), as well as presenting lower % of predicted post-BD FEV_1 (32 ± 16% *vs.* 51 ± 17%, t = 3.44, p = 0.001). In the multivariate analysis, the use of oral corticosteroids remained significant in relation to the distance covered on the 6MWT when FEV_1, the use of oxygen, and other relevant factors were included (p = 0.016).

Thirty-three patients presented a post-BD IC ≤ 70% of predicted. An IC ≤ 70% was observed in 26/46 patients (56%) in GOLD stages 3 or 4, compared to 7/34 patients (20%) in GOLD stages 1 or 2 (χ^2 = 10.41, p = 0.001; Figure 2). An IC ≤ 70% was observed in 14/23 patients (60%) with a BODE score of 3 or 4, compared to 19/57 patients with a BODE score of 1 or 2 (33%) (χ^2 = 5.127, p = 0.02; Figure 3).

Discussion

The results presented suggest that post-BD IC (% of predicted) is a good marker of severity and

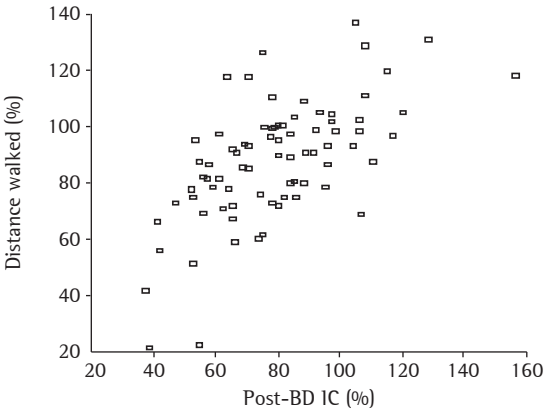

Figure 1 - Correlation between the distance covered on the 6-minute walk test and inspiratory capacity after bronchodilator use (post-BD IC), both expressed as the % of predicted.

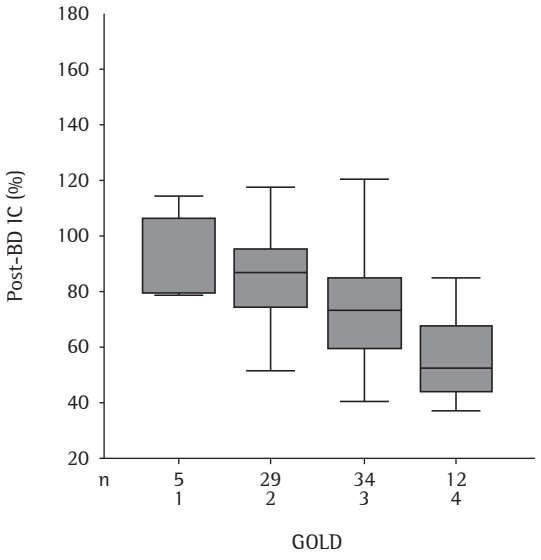

Figure 2 - Relationship between inspiratory capacity after bronchodilator use (post-BD IC), expressed as the % of predicted, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging of severity.

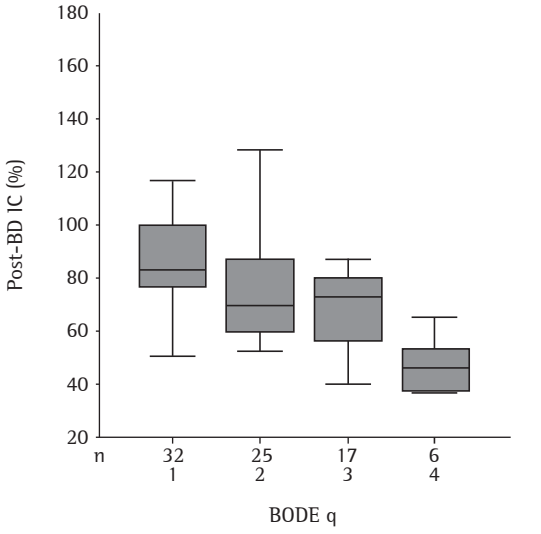

Figure 3 - Relationship between inspiratory capacity after bronchodilator use (post-BD IC), expressed as the % of predicted, and Body mass index, airway Obstruction, Dyspnea, and Exercise capacity (BODE) index, separated by quartiles.

prognosis in COPD, since there was strong significant correlation between IC (% of predicted) and the distance covered on the 6MWT (% of predicted), as well as since IC was found to correlate significantly with the GOLD stages of severity and the BODE index prognostic score.

The GOLD severity stages take into account the degree of obstruction based on post-BD FEV_1 (% of predicted).[1] The GOLD stages 3 and 4, or < 50% FEV_1 (% of predicted), correlated with <70% IC (% of predicted).

The BODE index contains a component that quantifies ventilatory disorder by FEV_1, another that detects the perception of dyspnea, in addition to other independent components, which are the distance covered on the 6MWT and the BMI, which reflect the systemic consequences of COPD.[6] The score in points, based on these variables, is a better predictor of the prognosis of the disease, compared to FEV_1 in isolation.[6] Decreased BMI is a good marker of COPD systemic involvement and has been associated with greater mortality.[6] However, we did not find a strong correlation between BMI and the distance covered on the 6MWT (% of predicted). The small number of patients presenting a BMI < 21 kg/m^2 (n = 15) might have influenced this result.

The 6MWT has been increasingly used to complement the functional evaluation of patients with COPD, since it reflects the systemic manifestations of the disease and airflow limitation. The variation in the distance covered on the 6MWT correlates with changes in spirometry and with the survival of the patients with COPD. A recent longitudinal study,[20] for the first time, described the prognostic value of the distance covered on the 6MWT in patients with severe COPD. Regardless of accompanying comorbidities, the distance covered on the 6MWT was a better predictor of mortality than was FEV_1 or BMI. In the advanced stage of the disease, the drop in the distance covered on the 6MWT is independent of the drop in FEV_1.[14,20] A limitation of the present study was not correlating IC (% of predicted) and the distance covered on the 6MWT (% of predicted) with mortality, which would have underscored the value of IC as a marker of COPD disease severity. There were 5 patients (8%) who died during the data collection period.

In the univariate analysis, we found the distance covered on the 6MWT (% of predicted) to present significant inverse correlations with the number of exacerbations per year, long-term use of oxygen, number of drugs, especially systemic corticosteroids, and Borg scale dyspnea score measured at the end of the test, as well as direct correlations with

post-BD FVC (% of predicted), post-BD FEV_1 (% of predicted), post-BD FEV_1/FVC (% of predicted), post-BD IC (% of predicted), and post-6MWT, post-BD SpO_2.

The distance covered on the 6MWT can be influenced by height, weight, age, gender, motivation, previous performance of the test, drugs used before the test, comorbidities, peripheral muscle strength, and use of supplemental oxygen.[16] Due to the influence of anthropometric variables on the distance covered on the 6MWT, we adopted the predicted values suggested in the literature for the North-American population.[19] Reference values for the 6MWT are not available for the Brazilian population. Some studies evaluated the influence that a number of variables have on the distance covered on the 6MWT in COPD patients. However, depending on the study, some variables were measured, and others were ignored. A multivariate analysis of the factors that could influence the distance covered on the 6MWT, in a study involving 83 patients with COPD,[21] revealed that four factors accounted for 78% of the total variance of the data: the heart rate pattern, *exercise* capacity, oxygen transport capacity, and dyspnea. The IC was not included in the data analysis. Muscle strength, including respiratory muscle strength and upper-body strength, as well as the diffusing capacity of the lung for carbon monoxide, significantly influence the performance on the walk test in COPD patients.[22-24] However, these were not measured in the present study.

In the present study, we found a significant inverse correlation between the number of exacerbations and the distance covered on the 6MWT (% of predicted). In COPD, there is a significant reduction in skeletal muscle strength in patients hospitalized during exacerbation, compared to those hospitalized during the stable state. Over a three-month period of hospitalization, the former present only partial recovery, which can be attributed to various factors.[25] The number of exacerbations is a risk factor of mortality, as is the long-term use of corticosteroids.[26] We found a significantly lower value of the distance covered on the 6MWT (% of predicted) in the group of patients using systemic corticosteroids. Similarly, we found a significantly lower value of the distance covered on the 6MWT (% of predicted) in the group of patients with long-term use of oxygen, compared to those who did not use oxygen. This difference was underestimated, since these patients did the test using oxygen, which is known to increase the distance covered on the 6MWT.

Some authors[14] reported that hyperinflation, estimated by the IC/TLC ratio, designated the inspiratory index, is a predictor of long-term survival in COPD, regardless of FEV_1. This finding was confirmed in the long-term cohort study conducted by the National Emphysema Treatment Trial Research Group,[7] which determined the risk factors of greater mortality in patients with severe emphysema. The following factors were identified as markers of worse prognosis and predictors of greater mortality: old age; reduced BMI; use of oxygen; decreased exercise capacity, defined by maximum load achieved on a cycle ergometer; emphysema predominant in the lower lobes; a lower IC/TLC ratio; and an altered BODE index. The determination of the IC/TLC ratio presupposes the measurement of TLC by plethysmography, available in few centers. The IC (% of predicted) is a noninvasive test and can be easily measured by the slow vital capacity maneuver. However, rigorous reproducibility criteria should be observed.[27] The unavailability of predicted values for IC is seen as a limitation in various countries, although this does not occur in Brazil.[18] Most studies estimate IC by analyzing pulmonary volumes rather than by simple spirometry.[7,14]

In recent years, the role of hyperinflation in dyspnea and exercise intolerance in COPD has been clearly established.[28] The measurement of IC reflects the degree of hyperinflation in COPD, although it is also influenced by inspiratory muscle strength, as well as by the extent of the mechanical load imposed upon the muscles. The IC also provides information on the position of the tidal volume in the pressure-volume curve of the respiratory system. A lower IC brings the TLC closer to the tidal volume, a region in which the pressure-volume ratio becomes alinear, increasing lung elastic recoil. In patients with COPD, an increased respiratory rate during exercise results in increased air trapping, as well as increasing the tidal volume, thereby creating greater elastic demand for inspiration. Hyperinflation upon exertion in COPD was demonstrated with the walk test. Therefore, in the present study, IC was found to be the greatest determinant of the distance covered on the 6MWT, which is not surprising.

In one study of patients with COPD,[5] dyspnea was a better predictor of five-year survival than was the degree of airflow obstruction. Therefore,

dyspnea should be included as a variable for the evaluation of mortality in these patients. Various previous studies have demonstrated that dyspnea plays an important role in determining the distance covered on the 6MWT by patients with COPD.[24,29]

Other authors[12] measured IC at rest and at the end of the 6MWT in patients with COPD and demonstrated, similar to what has been previously shown on cycle ergometer tests, that the drop in IC during exercise, which reflects hyperinflation, correlates with dyspnea, as measured using the Borg scale. The data were obtained before the use of bronchodilator, and the correlation between IC and the distance covered on the 6MWT was significant, albeit lower than that observed in the present study ($r = 0.41$ *vs.* $r = 0.61$). We always considered all functional variables after the use of bronchodilator, since severity scores suggest that the patient should be classified after the relief of bronchospasm. This can also result in better learning for the performance of the 6MWT, and in better correlation with IC.

A recent review article questioned the routine evaluation of dynamic hyperinflation by measurement of IC during exercise through ergospirometry.[30] The author emphasizes the value of cardiopulmonary exercise testing in COPD and, principally, the evaluation of post-exercise dyspnea reported by the patient, which would result from dynamic hyperinflation, more simply determined. In our study, dyspnea correlated significantly with the distance covered on the 6MWT (% of predicted), as well as with IC (% of predicted), which demonstrates the multifactorial origin of dyspnea in COPD. However, hyperinflation during exercise, despite being the most important mechanism, does not completely explain the post-6MWT dyspnea.

In conclusion, post-BD IC (% of predicted) is a good predictor of the distance covered on the 6MWT, and is strongly associated with other markers of severity and prognosis in COPD, such as the GOLD staging and BODE index. We suggest that post-BD IC (% of predicted) be included in the routine functional evaluation of patients with COPD. A 70% cut-off point can be used to classify the patients.

References

1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256.
2. Celli BR. The importance of spirometry in COPD and asthma: Effect on approach to management. Chest. 2000;117(2 Suppl):S15-S9.
3. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med. 1995;152 (5 Pt 2):S77-S121
4. BTS guidelines for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS. Thorax. 1997;52(suppl 5):S1-S28.
5. Nishimura K, Izuni T, Tsukino M, Oga T. Dyspnea is a better predictor of survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434-40
6. 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.
7. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med. 2006;173(12):1326-34.
8. Dolan S, Varkey B. Prognostic factors in chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2005;11(2):149-52
9. Jones PW, Agusti AG. Outcomes and markers in assessment of chronic obstructive pulmonary disease. Eur Respir J. 2006;27(4):822-32
10. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med. 1999;159(4 Pt2):S1-S40.
11. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):770-7.
12. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6 minute walk test in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(6):1395-9.
13. Rodrigues JR, Pereira CAC. Resposta a broncodilatador na espirometria.: que parâmetros e valores são clinicamente relevantes em doenças obstrutivas? J Pneumol. 2001;27(1):35-47.
14. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory to total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171(6):591-7.
15. Johnson JE. Which exercise test should be used for patients with symptomatic COPD? Chest. 2004;126(3):668-70.
16. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Repir Crit Care Med. 2002;166(1):111-7.
17. Pereira CAC, Sato T, Rodrigues S. Novos valores de referência para espirometria forçada em brasileiros adultos de raça branca. J Bras Pneumol. In press 2007.
18. Neder JA, Andreoni S, Castelo-Filho A, Nery LE. Reference values for lung function tests. Static volumes. Braz J Med Biol Res. 1999;32(6):703-17.

19. Enright PL, Sherril DL. Reference equations for the six minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1384-7.
20. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J. 2004;23(1):28-33.
21. van Stel HF, Bogaard JM, Rijssenbeek-Nouwens LH, Colland VT. Multivariable assessment of the 6-min walking test in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(7):1567-71.
22. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med. 1996;153(3):976-80
23. Wijkstra PJ, TenVergert EM, van der Mark TW, Postma DS, Van Altena R, Kraan J, et al. Relation of lung function, maximal inspiratory pressure, dyspnea, and quality of life with exercise capacity in patients with chronic obstructive pulmonary disease. Thorax. 1994;49(5):468-72.
24. Dourado VZ, Antunes LC, Tanni SE, de Paiva SA, Padovani CR, Godoy I. Relationship of upper-limb and thoracic muscle strength to 6-min walk distance in COPD patients. Chest. 2006;129(3):551-7.
25. Pitta F, Troosters T, Probst *VS*, Spruit MA, Decramer M, Gosselink R. Physical activity and hospitalization for exacerbation of COPD. Chest. 2006;129(3):536-44.
26. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003;124(2):459-67.
27. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para Testes de Função Pulmonar. J Pneumol. 2002;28:1-221.
28. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3(2):180-4.
29. Grazzini M, Stendardi L, Gigliotti F, Scano G. Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). Respir Med. 2005;99(11):1403-12.
30. Calverley PM. Dynamic hyperinflation: is it worth measuring? Proc Am Thorac Soc. 2006;3(3):239-44.