Can the six-minute walk distance predict the occurrence of acute exacerbations of COPD in patients in Brazil?

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INTRODUCTION

According to the Global Initiative for Obstructive Lung Disease (GOLD), an exacerbation of COPD is defined as an acute event characterized by worsening from baseline in respiratory symptoms—including increased lung hyperinflation, reduced airflow, dyspnea, and hypoxemia—requiring a change in regular medication. Although exacerbations of COPD are common during the course of the disease, they should be prevented in order to avoid worsening of the pulmonary and systemic involvement characteristic of COPD.

Acute exacerbations of COPD commonly result in reduced lung function, reduced peripheral muscle strength, reduced respiratory muscle strength, reduced physical activity in daily life, reduced exercise capacity, increased mortality, increased health care costs, and reduced health-related quality of life. Therefore, it is important to prevent exacerbations of COPD. Predictors of COPD exacerbations include lung function, a history of exacerbations, exercise capacity, and health status, all of which can contribute to improving the clinical management of patients with COPD.

Given that the six-minute walk test (6MWT) is simple, is easy to perform, is inexpensive, and has good responsiveness, it is widely used in order to assess functional exercise capacity and predict exacerbations of COPD. A six-minute walk distance (6MWD) of < 350 m has been employed as a predictor of COPD exacerbation. Given that the 6MWD is longer in individuals in Brazil than in those in other countries, the aforementioned 6MWD might not be applicable to COPD patients in Brazil, a different cut-off point therefore being required.

Although a cut-off point for the 6MWD has yet to be established in Brazil, previous studies have used a cut-off point of 80% of the predicted value. A cut-off point expressed as a percentage of the predicted value might be more appropriate for two reasons: 1) it takes into account individual patient characteristics; and 2) it prevents the introduction of an absolute value bias when it is applied to different populations, the 6MWD being longer in Brazil than in other countries.

Individuals in whom the 6MWD is > 80% of predicted are considered to have preserved exercise capacity. To the best of our knowledge, there have been no studies examining the...
6MWD as a predictor of COPD exacerbations in patients in Brazil not participating in a rehabilitation program and not recently hospitalized, currently participating in a rehabilitation program and having recently been hospitalized being factors that influence the prediction of exacerbations. Therefore, the objective of the present study was to evaluate whether the 6MWD can predict acute exacerbations of COPD over a 2-year period in COPD patients in Brazil. Our hypothesis was that the risk of acute exacerbation of COPD over a 2-year period would be higher in patients in whom the 6MWD was ≤ 80% of the predicted value than in those in whom the 6MWD was > 80% of the predicted value.

**METHODS**

This was a retrospective observational study involving a convenience sample and including data collected in the 2010-2013 period regarding COPD patients who had been invited to participate in a rehabilitation program but for various reasons (including difficulties with transportation and lack of time) underwent the initial evaluation only; that is, they did not undergo physical training. The criteria for inclusion in the present study were as follows: having been diagnosed with COPD in accordance with the GOLD criteria; being clinically stable, i.e., having had no exacerbations in the last 3 months; having no comorbidities that could affect the tests performed; and having participated in no exercise training programs in the year prior to the study. The exclusion criteria were as follows: unavailable medical records; inability to contact patients or close relatives by telephone; and a 6MWD and pulmonary function test results characterizing outliers (i.e., values within ± 2 SDs of the mean).

The present study was conducted in the Respiratory Therapy Research Laboratory of the State University at Londrina and at the Health Sciences Research Center of the University of Northern Paraná, both of which are located in the city of Londrina, Brazil, and was approved by the Human Research Ethics Committee of the State University at Londrina (Protocol no. 123/09). All patients gave written informed consent.

**Pulmonary function testing (spirometry)**

 Spirometry was performed with a Pony® spirometer (Cosmed, Rome, Italy). All tests were performed in accordance with the American Thoracic Society and European Respiratory Society guidelines and post-bronchodilator values were used. The reference values for the Brazilian population were those established by Pereira et al.

**6MWT**

The 6MWT was performed in accordance with international guidelines by trained raters. Patients were instructed to walk in a 30-m corridor for 6 min, receiving standard encouragement during the test. Two tests were performed, at least 30 min apart, the longer 6MWD being used for analysis. Blood pressure, HR, and SpO₂, as well as dyspnea and fatigue (as assessed by the modified Borg scale), were assessed before and after each test.

For all analyses, patients were divided into two groups: that of those in whom the 6MWD was > 80% of the distance predicted by applying a formula proposed by Britto et al. (equation 1); and that of those in whom the 6MWD was ≤ 80% of the predicted distance.

**Evaluation of exacerbations**

The occurrence of exacerbations of COPD within 2 years of the evaluation of exercise capacity by the 6MWT was determined by analyzing medical records and contacting patients by telephone. We investigated the occurrence of acute exacerbations of COPD independently of the number of events occurring during the study period. An exacerbation of COPD was defined as a worsening of respiratory symptoms that is beyond normal day-to-day variations and that requires a change in regular medication, although it does not require hospitalization.

**Statistical analysis**

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Normality of the data was tested by the Shapiro-Wilk test, and the results were described as means and standard deviations. The two groups of patients were compared by unpaired t-test. The log-rank test and the Kaplan-Meier method were used in order to compare the groups in terms of the occurrence of exacerbations. Cox regression adjusted for confounding variables (gender, body mass index—BMI—and lung function) was used in order to determine whether a 6MWD = 80% of predicted was able to predict exacerbations over a 2-year follow-up period. The level of significance was set at p < 0.05.

**RESULTS**

Our convenience sample consisted of 67 patients. However, 9 were excluded because we were unable to gain access to all relevant information and 8 were excluded because they were considered to be outliers regarding pulmonary function test results, the 6MWD, or a combination of the two. Of the 50 patients who remained in the study (Table 1), 5 died (4 from pneumonia and 1 from acute myocardial infarction) and 25 experienced exacerbations during the 2-year follow-up period. With regard to functional exercise capacity, the mean 6MWD was 469 ± 60 m (86 ± 10% of predicted).

There were no significant differences between the patients in whom the 6MWD was > 80% of predicted (n = 33) and those in whom the 6MWD was ≤ 80% of predicted (n = 17) regarding age, gender, height, weight, BMI, or lung function.

The Kaplan-Meier curves (Figure 1) showed a significant difference (p = 0.01) between the two groups of patients regarding the occurrence of exacerbations.
exacerbations, which were more common in those in whom the 6MWD was ≤ 80% of predicted than in those in whom the 6MWD was > 80% of predicted. This difference was more pronounced from the tenth month of follow-up onward.

The Cox regression model showed that, even after adjustment for confounding variables, patients in whom the 6MWD is ≤ 80% of predicted are 2.6 times more likely to experience exacerbations over the course of 2 years than are those in whom the 6MWD is > 80% of predicted (95% CI: 1.1-5.8; p = 0.02).

DISCUSSION

The results of the present study show that, in Brazil, COPD patients in whom the 6MWD is < 80% of the predicted value are more than twice as likely to experience exacerbations within 2 years after the 6MWT as are those whose exercise capacity is preserved.

In addition to normal day-to-day variations in the natural course of the disease, patients with COPD experience exacerbations requiring at least 90 days for a return to baseline health status; in some cases, recovery is incomplete even after 90 days. In addition to normal day-to-day variations in the natural course of the disease, patients with COPD experience exacerbations requiring at least 90 days for a return to baseline health status; in some cases, recovery is incomplete even after 90 days. (22) Given that morbidity and mortality are high in patients with COPD, it is extremely important to prevent and predict acute exacerbations in order to avoid loss of lung function and the high costs of treatment.

Previous studies (14,15) have shown that the 6MWD can predict exacerbations in patients with COPD. Andrianopoulos et al. (15) recommended that a 6MWD of 375 m be used as a cut-off point to predict a higher risk of COPD exacerbation over a 3-year follow-up period. However, that cut-off point might not be appropriate for the Brazilian population, given that the 6MWD is greater in Brazil than in other countries.

In a study conducted in Brazil, (23) multidimensional indices were used in order to predict COPD exacerbations, including the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE) index, (24) which is more comprehensive than the 6MWD alone. Given that the BODE index assesses different outcomes (BMI, FEV₁, dyspnea—as assessed by the modified Medical Research Council scale—and the 6MWD), it is more difficult to perform and it takes longer to be calculated, therefore being more difficult to use in clinical practice. The present study showed that, in COPD patients in Brazil, the 6MWD alone can predict acute exacerbations of the disease. Casanova et al. (16) showed that the 6MWD is longer in healthy individuals in Brazil than in those in other countries, whereas Pitta et al. (25) showed that daily physical activity levels are higher in COPD patients in Brazil than in those in Europe. The fact that daily physical activity levels in the Brazilian population correlate, albeit moderately, with functional exercise capacity (26) reinforces the need to adopt specific indices for different populations.

In the present study, the Kaplan-Meier curves showed a significant difference between the patients in whom the 6MWD was > 80% of the predicted value and those in whom the 6MWD was ≤ 80% of the predicted value regarding the exacerbation rate. This finding is consistent with the literature, (15) and this difference apparently becomes more pronounced after the tenth month of follow-up.

To the best of our knowledge, this is the first study to evaluate the role of the 6MWD in predicting exacerbations of COPD in patients in Brazil not participating in a rehabilitation program. Marino et al. (27) demonstrated that the 6MWD and dependent covariates (BMI and lean body mass) are associated with risk of exacerbation; however, the fact that the aforementioned study involved patients in Brazil participating in a physical therapy program constitutes a limitation, given that physical activity prevents exacerbations. (1)
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