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Research Article

Twenty-four Months Longitudinal Study of Acute Exacerbations in a Cohort of Chronic Obstructive Pulmonary Disease Patients

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Abstract: Background: This study aims to follow a cohort of COPD patients so as to measure the frequency of acute exacerbation and annually correlate it with the BODE index and with the cellularity of induced sputum (IS) at admission. Methods: The longitudinal study followed 44 COPD patients for 30 months. COPD severity was determined according to the GOLD criteria and the cellularity of induced sputum was quantified. For two years, COPD patients were assessed for acute exacerbation, characterized by an intensification of COPD symptoms that required additional antibiotics or/and systemic corticosteroids. All patients were smokers and returned for regular clinical visits. IS was collected from all patients when admitted to the study and cellularity was quantified. BODE index was measured in the 1st and 2nd years. Results: Data showed that the GOLD criteria did not correlate with acute exacerbation, but the BODE index did (r = 0.587). Neutrophils and macrophages from induced sputum had good correlation with FEV_1 and there is a phenotypic profile for which acute exacerbation is more recurrent, which is chronic bronchitis ($p<0.038$). Conclusions: The frequency of acute exacerbation is similar to that of world medical literature, approximately 2 episodes per annum. The results suggest that BODE index could be used to identification of subgroup of COPD patients which has more acute exacerbation.

Keywords: BODE index, COPD, induced sputum

INTRODUCTION

The World Health Organization reports that 65 million people in the world have moderate to severe COPD; more than 3 million COPD patients died in the year 2005; in 2002, COPD was the 5th cause of mortality in the world and will be the 3rd in 2030 (WHO, 2011; GOLD, 2011). Further, COPD is one of the main causes of world morbidity. Active smoking is the principal cause of COPD and its elimination would dramatically reduce the number of cases. For many years, it was thought that only 15% of smokers would develop COPD (Balkissoon *et al*., 2005; Sullivan *et al*., 2000) but it has been recently demonstrated that smoking obstructs the airflow in up to 50% of individuals with more than 70 years of age.

COPD is a preventable and treatable respiratory disease distinguished by the persistent, but partially reversible, obstruction of airflow (WHO, 2011; GOLD, 2011). Airflow obstruction is generally progressive and associated with an abnormal inflammatory response of the lungs to the inhalation of toxic particles or gases, with significant systemic consequences. The chronic inflammatory process may cause alterations in the bronchi (chronic bronchitis), bronchioles (obstructive bronchiolitis) and pulmonary parenchyma (pulmonary emphysema). Predominance of these alterations varies between individuals and is related to symptoms (GOLD, 2011).

The first PUBMED publication on COPD exacerbation dates from 1970. In 1983, Winter *et al*. (1983) defined COPD exacerbation as a medical condition that requires hospital treatment. Since then, the concept of exacerbation has been intensely reviewed (Anzueto, 2010; Burge and Wedzicha, 2003).

Exacerbation, which is always considered acute, shows more specific symptoms and signs such as increased dyspnea, cough frequency and volume of expectoration and a change in its hue; and unspecific symptoms such as fever, indisposition, chills, insomnia and depressive symptoms (Burge and Wedzicha, 2003; Rodriguez-Roisin, 2000).

Exacerbation is currently defined as an event in the natural course of the disease characterized by the alteration of the patient's basal dyspnea; cough with or without expectoration and enough daily variations for the prior therapeutic conduct to be altered. Systemic corticosteroids and/or antibiotics are the medication used (GOLD, 2011; Burge and Wedzicha, 2003; Rodriguez-Roisin, 2000).

Some very relevant facts, such as a discreet increase in the quantity of exacerbations according to

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COPD (Cote *et al*., 2007) severity and greater reduction in pulmonary function after recovery from exacerbation (Hoogendoorn *et al*., 2010), suggest an inverse relationship between exacerbation and pulmonary function in COPD. In other words, exacerbation is independent from COPD in relation to FEV_1 decline (Donaldson *et al*., 2002).

The BODE index, whose name is an English acronym that represents the analysis of 4 domains {body-mass index (B), airflow obstruction (O) functional Dyspnea (D) and exercise capacity (E)} was published as a scientific follow-up tool on COPD patients that better represents the disease's complexity (Celli *et al*., 2004) Its design preserves the importance of spirometry but associates other variables to staging such as the body mass index (BMI), dyspnea graded according to the MMRC (Modified Medical Research Council) (Kovelis *et al*., 2008) dyspnea scale and exercise capacity according to a 6-Minute Walking Test (6MWT) (ATS, 2002).

This study intends to study exacerbation, to learn its frequency and its relation to the BODE (Celli *et al*., 2004) index and to the cellularity of induced sputum.

MATERIALS AND METHODS

Study design: In the period from 2008 to 2009, patients from the COPD out-clinic of the State University of Rio de Janeiro agreed to take part in the stable patient cohort study. Eighty-eight patients signed a voluntary and informed consent form, but only 44 patients concluded the follow-up in January 2011. The study was observational. COPD cases, whose severity was assessed using the GOLD criteria, were followed for at least 2 years, beginning with the signature of the consent form, adding to 30 months. Thirteen patients had chronic bronchitic phenotype that means presence of a productive cough that lasts at least 3 months out of the year for 2 consecutive years of follow up. All patients remain under medical treatment at COPD out-clinic. Medical treatment followed GOLD document (GOLD, 2011).

Inclusion criteria: Inclusion criteria were: to be a smoker, to regularly attend scheduled medical appointments (every 3 to 6 months), to undergo the 6-minute walking test (6MWT) (ATS, 2002), spirometries and Induced Sputum (IS) collection at the study's 1st appointment, to use medication in compliance with GOLD and to be able to answer the MMRC dyspnea scale questionnaire (Kovelis *et al*., 2008).

Exclusion criteria: Exclusion criteria were: etiology unrelated to smoking, low adherence to pharmacological treatment, positive bronchodilator spirometry response (ATS, 1987, 1991), history of atopy (cutaneous, intestinal and respiratory) and impossibility to regularly attend medical appointments and to undergo the 6MWT, IS (Pin *et al*., 1992) or spirometries.

Exacerbation: COPD exacerbation was defined by a sudden symptom worsening requiring the temporary addition of systemic corticosteroids (oral or intravenous) and/or antibiotics (oral or intravenous). This therapeutic change was recommended by UERJ's own Pulmonology service conform GOLD recommendations (GOLD, 2011).

BODE index: BODE scores were calculated in the 1st and 2nd follow-up years. A delay of up to 3 weeks after the first and second-year time periods had elapsed was tolerated to perform BODE calculations.

Six-Minute Walking Test (6MWT): Tests were made in a 40 m corridor in the Pedro Ernesto University Hospital, marked every 1 m, under verbal encouragement, logged by examiners after every walking minute, in the morning. The previously trained examiners were always the same. All patients underwent the 6MWT twice, with a period of at least 30 min between each test so as to minimize the learning effect (ATS, 2002).

MMRC dyspnea scale: Four research internship students applied this scale in the years 2009 to 2011, after the 1st and 2nd follow-up years. These students were previously trained and one of the goals of their internship was precisely the calculation of the BODE index, which includes the MMRC scale (Kovelis *et al*., 2008).

Spirometry: Patients underwent spirometric exams in their admission day and after the 1st and 2nd follow-up years. All exams were made with the same equipment-Vita trace Spirometer (Pró-Médico Ltda), coupled with the *Spiromatic* (Engelógica Engenharia de Sistemas, Ltda) application and following the ATS standard (ATS, 1987, 1991).

Induced sputum: Induced sputum was collected from COPD patients in the beginning of the study in accordance with the Pin *et al*. (1992) method.

Statistical analysis: Outcome variables were analyzed by the Graphpad Prism 6.0 application and considered significant when tests t and Pearson correlation equations were <0.05.

Ethics: The study was approved by the Research Ethics Committee (of the Pedro Ernesto University Hospital under number 1889/2007.

RESULTS AND DISCUSSION

Of 88 eligible patients, 44 were excluded in consequence of death (two with BODE 1 and BODE 3

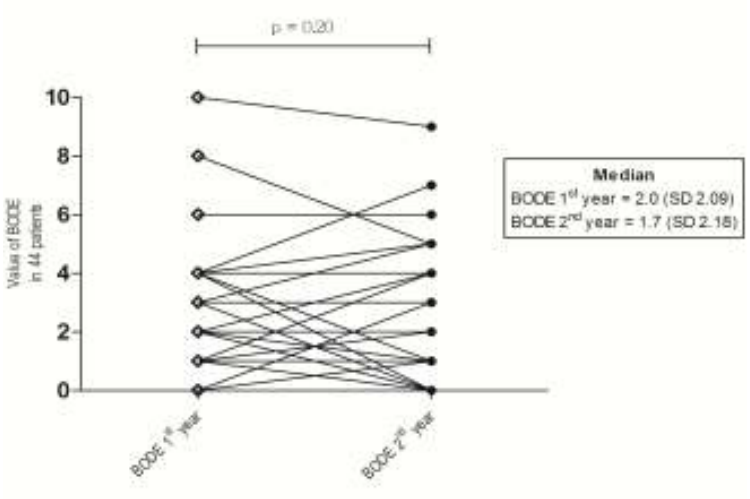

Fig. 1: BODE index in the two years; Legend 1: The dots and connecting line represent the same patient

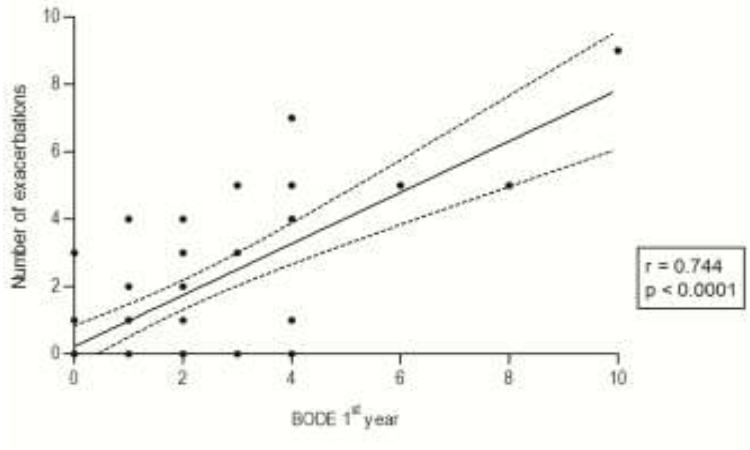

Fig. 2: Linear correlation between BODE index and acute exacerbations in the 1st year; Legend 2: The BODE index and the number of acute exacerbations has a good and positive correlation

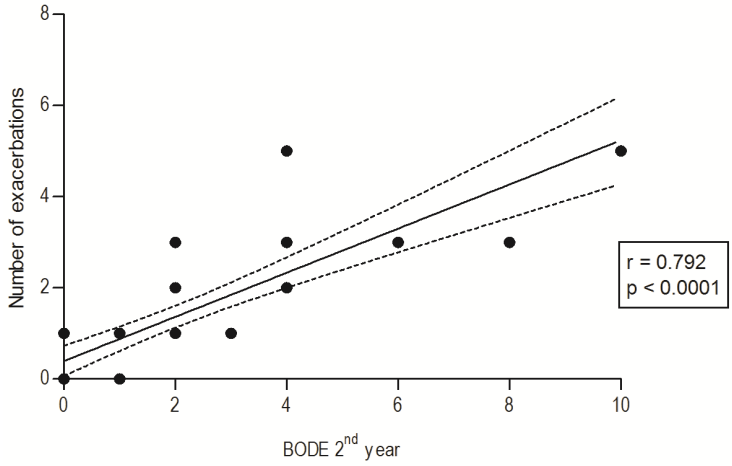

Fig. 3: Linear correlation between BODE index and acute exacerbations in the 2nd year; Legend 3: The BODE index and the number of acute exacerbations has a similar correlation in the second year of the study

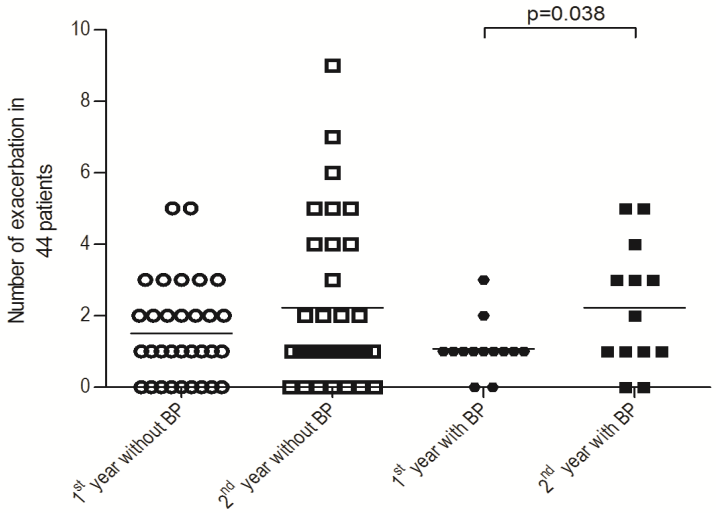

Fig. 4: Acute exacerbations in bronchitic and non-bronchitic phenotypes; Legend 4: The bronchitic phenotype has more exacerbations at 2nd year

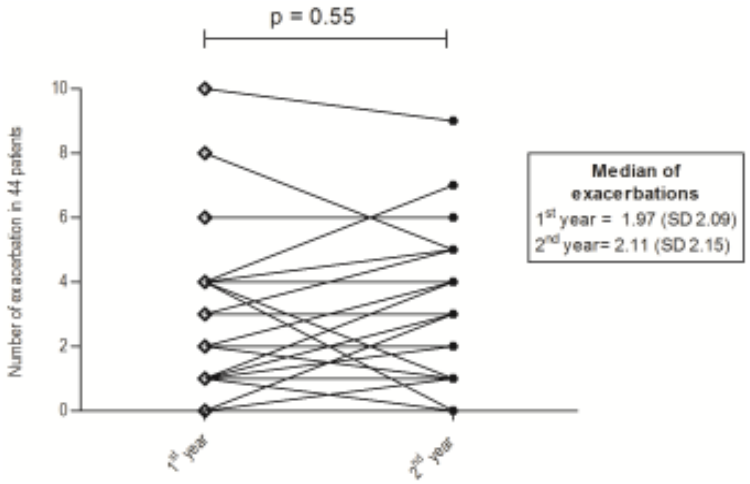

Fig. 5: Acute exacerbations in the two years; Legend 5: The median of exacerbations was similar

scores), induced sputum inadequate for analysis (13) and non-attendance to medical appointments (29). Of the 44 patients that completed the study, 25 were male. Average Tobacco Load (TL) was 47 pack years. Male and female TL was similar, respectively at 46.44 and 47.13. Median age was 67.3 years, ranging from 51 to 88. Male median age (67.83 years) was slightly higher than female (67.27 years). Nineteen patients continued smoking in spite of guidance given during medical appointments.

According to GOLD (2011), groups were characterized as mild (9), moderate (20), severe (13) and very severe (2). There was no statistically significant variation in BODE during the two years of analysis (Fig. 1). BODE correlated positively with the number of exacerbations both in the 1st and 2nd years ($p<0.0001$) (Fig. 2 and 3). There was a statistically significant difference from BODE for bronchitic phenotype patients (BP) (Fig. 4). No statistically significant correlation was found between eosinophils, neutrophils and macrophages, exacerbation frequency and the BODE index between the 1st to the 2nd year (Fig. 5). There were a real balance between neutrophils and macrophages in IS in COPD patients (Fig. 6). Demographic data are shown in table.

BODE is a multidimensional COPD severity index that incorporates four parameters (Celli *et al*., 2004). Although it is labor intensive, it is referred as more relevant to COPD prospective analyses that the FEV_1 percent value, which is still used and accepted by the medical community, including for therapeutic purposes, as published by GOLD (2011) and Celli *et al*. (2004). The study by Celli *et al*. (2004) has shown that this index is highly reliable for the clinical prognosis assessment of COPD patients, considering the death of the 627 selected patients as the work's main outcome event.

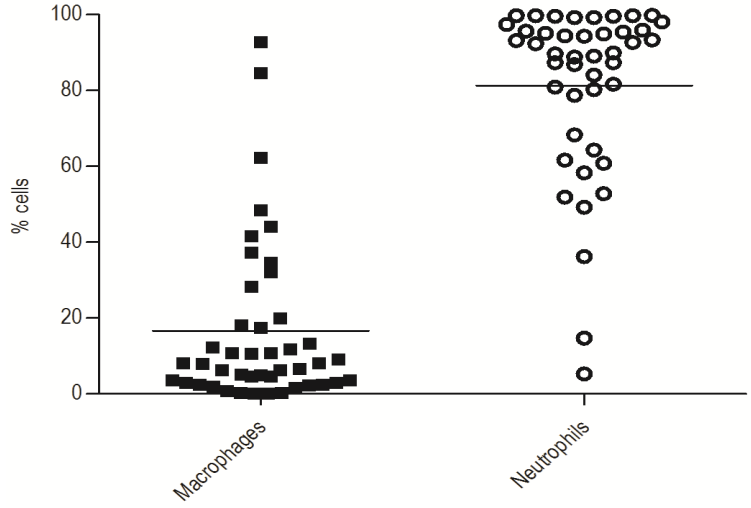

Fig. 6: Main cells in induced sputum of stable COPD patients; Legend 6: There was a balance between macrophages and neutrophils in the IS from COPD patients

Exacerbation: COPD severity is an important criterion for therapeutic management (GOLD, 2011). More severe patients, according to FEV_1, must use more medication and receive more attention from multidisciplinary workgroups (GOLD, 2011; Donaldson *et al*., 2002). However, a single criterion, the FEV_1 percent value, may not be enough for an efficient therapeutic management (Lusuardi *et al*., 2008; Anthonisen *et al*., 1987). Some patients, especially very severe ones, already use several medications, take adequate prophylactic and physiotherapy measures but, in spite of everything, suffer more exacerbations (Donaldson *et al*., 2002; Anthonisen *et al*., 1987). The authors showed a correlation between the number of exacerbations in the 1st and 2nd year and the severity of BODE index, but not with the GOLD criteria. One of the great difficulties in exacerbation analysis lies in its definition. Clinical criteria are too subjective and mostly mimic the Winnipeg criteria (Anthonisen *et al*., 1987), which consider expectoration aspect and volume and dyspnea symptom intensification as indications for the use of antibiotics. Another factor is the non-blind character of the study, with rigorous inclusion and exclusion criteria. Patients had regular medical appointments and their medication was occasionally adjusted. This is a relevant fact because, in the general population, much information on disease severity and evolution arise from the patient's partial adherence to therapeutic guidelines, which several researchers refer to as the real world. Moreover, there are significant variations between American and Brazilian societies (Gigante *et al*., 2009; Faganello *et al*., 2010). Their BMI and 6MWT are different and it may not be adequate to use the same index for phenotypically diverse populations all over the world with no regard to cultural regionalims.

Disease severity groups according to GOLD were heterogeneous, with only two very severe patients. Further, population studied comes from other health units, giving the same bias to these two data, patient selection or pre-selected sample.

The average was two exacerbations per annum during the two follow-up years, regardless of GOLD stage and BODE index. However, there was a discreet and significant increase in the second year for the chronic bronchitis phenotype. Some studies have correlated exacerbations with lower FEV_1 percentages or higher BODE scores (Lacy *et al*., 2005; Rodriguez-Roisin, 2000). Another important find is the larger number of exacerbations in bronchitis phenotype patients that expectorate when coughing (Burrows *et al*., 1987). One is tempted to suppose that exacerbation may be triggered in bronchitic patients by higher bacterial counts and increased bacterial load or that the constant and increased inflammatory fluid in these patient's tracheobronchial tree facilitates peripheral ventilation imbalances that increase respiratory effort and cause the feeling of dyspnea.

Induced sputum: According to this study, IS cellularity does not suggest that the cellular profile indicates a higher or lower number of COPD clinic exacerbations. Some published works suggest that the IS neutrophil cellular profile could be related to COPD exacerbation (Lacy *et al*., 2005). Neutrophil and macrophage percentages did not correlate with the number of exacerbations nor with the BODE index. However, regardless of the fact that FEV_1 percentage is one of the variables that compose the BODE index, there was no correlation between this index and IS neutrophil and macrophage count. IS research with COPD patients, however, has well shown that FEV_1 percentage correlates very well, inversely, to neutrophil count and positively, to macrophage count. Only a

small number (6) of patients had low neutrophil counts (<15.0%) in IS. This begs the question: if the BODE index is a prognosis marker, why does it not correlate with cell count? Perhaps this cellular sample was too repetitive in the follow-up years, so that, beginning with the neutrophilic transformation of IS, it will always be neutrophilic and this would be BODE's advantage: to offer a dynamic and, sometimes, reversible analysis, as seen in a few cases. It was shown that clinic exacerbation is a common alteration in COPD patients, regardless of stage, occurring at least twice a year.

BODE index: In the present study, patients with higher BODE scores had suffered frequent exacerbations. The literature shows that higher BODE scores indicate more frequent exacerbations, which is confirmed by the current data (Anzueto, 2010; Lacy *et al*., 2005). The correlation was significant, in spite of the very small number of very severe patients, only 2, according to GOLD criteria. Casanova *et al*. (2011) mention that the BODE index alters negatively after exacerbations. The index may change with each exacerbation. This may be explained by the study published by Donaldson *et al*. (2002), which shows greater reduction in FEV_1 percentage in relation to non-exacerbated COPD. In our study, several patients, even severe ones, had no exacerbation for 1 or even 2 years. Perhaps, in these cases, GOLD's therapeutic scheme is sufficient. One difference between our study and others is that our sample included only active smokers at admission.

Two out of the 88 original patients died. However, it was curious that these two were initially working and had very low BODE scores (1 and 3). Similarly some very severe patients according to BODE could maintain or even reduce their scores. This allows us to infer that the index is an important dynamic follow-up tool. A similar fact was found in a recent publication that considered that both GOLD and the BODE index have a similar capacity to forecast the risk of death (Faganello *et al*., 2010).

We concluded that the number of exacerbations in the two follow-up years was similar and that there was no significant change to the BODE index during that period. The higher Bode indexes are correlated with frequency of acute exacerbation. The IS cellularity did not help in identification of subgroup of COPD patients who had more acute exacerbation.

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