Clinical and Functional Lung Parameters Associated With Frequent Exacerbator Phenotype in Subjects With Severe COPD

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BACKGROUND: COPD is currently recognized as a syndrome associated with a high prevalence of comorbidities and various phenotypes. Exacerbations are very important events in the clinical history of COPD because they drive the decline in lung function. In the present study, we aim to identify whether there are any clinical and functional specific features of frequent exacerbators in a population of patients with severe COPD. METHODS: We conducted a cross-sectional, case control study. All subjects had Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 COPD ($FEV_1 < 50\%$ predicted). Frequent exacerbators ($n = 183$) reported ≥ 2 exacerbations or ≥ 1 determining hospitalization during the previous 12 months, and infrequent exacerbators ($n = 162$) reported <2 exacerbations over the last 12 months without hospitalization. Multivariate logistic regression was performed to determine the clinical and functional factors significantly associated with frequent exacerbator status. RESULTS: Frequent exacerbators had a significantly lower inspiratory capacity percentage predicted. The Motley index (residual volume/total lung capacity percentage) was significantly increased in frequent exacerbators. Infrequent exacerbators had lower Modified Medical Research Council dyspnea scale and BODE index than frequent exacerbators. In the multivariate model, a reduced inspiratory capacity percentage predicted and an increase of residual volume/total lung capacity percentage, BODE index and Modified Medical Research Council dyspnea scale were associated with the frequent exacerbation phenotype. CONCLUSIONS: Static hyperinflation and respiratory disability, measured by Motley index and Modified Medical Research Council dyspnea scale, respectively, in the same way as the multidimensional BODE index staging system, were independently associated with frequent exacerbation status in subjects with severe COPD. *Key words: COPD exacerbations; COPD phenotypes; respiratory disease; body plethysmography; spirometry.* [Respir Care 2017;62(5):572–578. © 2017 Daedalus Enterprises]

Introduction

COPD is a heterogeneous disorder that is projected to become the fourth leading cause of death globally by 2030.[1]

COPD is currently recognized as a syndrome associated with a high prevalence of comorbidities and various phenotypes.[2] The pathophysiologic hallmark of COPD is exercise intolerance and exertional dyspnea, which are probably due to complex interactions among impaired ventilatory, cardiovascular, and peripheral muscle responses. The leading cause of respiratory muscle dysfunction in patients with COPD is the mechanical handicap caused by lung hyperinflation.[3] Exacerbations are very important events in the clinical history of COPD because they drive the decline in lung function,[4] reduce quality of life,[5] contribute to hospitalization and mortality, and therefore increase costs to the health system.[6] Nevertheless, we know relatively little about their incidence and their determinants.
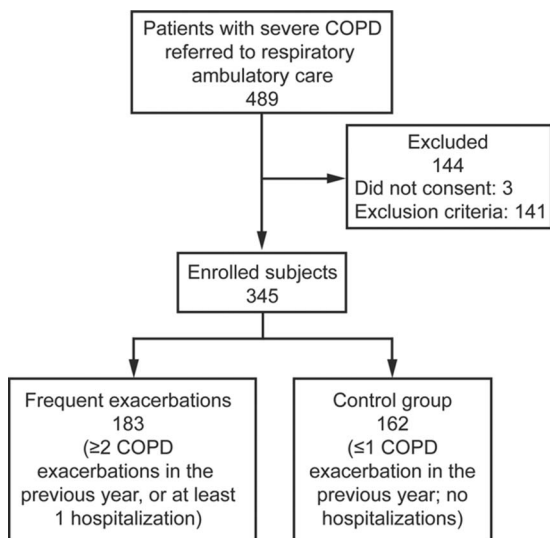
Fig. 1. Flow chart.

QUICK LOOK

Current knowledge

The annual rate of COPD exacerbations has been estimated to be between 0.5 and 3.5/patient. Exacerbations are more frequent with increasing severity of COPD.

What this paper contributes to our knowledge

In a population of subjects with severe COPD, high Motley index (residual volume/total lung capacity percentage) and Modified Medical Research Council dyspnea scale were independently associated with frequent exacerbator status. COPD staging by body plethysmography, in severe forms, can differentiate patients at highest risk of exacerbations.

In a few studies, increasing GOLD stage,[7] chronic cough and sputum production,[8,9] lower FEV_1 percent of predicted,[7,9-11] low forced expiratory flow during the middle half of the FVC maneuver,[12] enphysematous phenotype,[13] advanced age,[9,11,14] BODE category, and clinical depression were associated with the development of exacerbations.[11,14-16]

Clinical experience shows patients living with frequent exacerbations, as opposed to patients in whom this problem is infrequent or absent. Several studies have shown that the number of exacerbations from year to year in a single subject is highly reproducible and that a history of exacerbations predicts future exacerbations,[4,17,18] potentially indicating a definable phenotype of exacerbation susceptibility. The characterization of these 2 phenotypes within a cohort of subjects with severe COPD could offer further information about why some patients have frequent exacerbation, whereas others remain partly protected. In the present study, we aim to identify whether there are any clinical and functional specific features of frequent exacerbators in a population of patients with severe COPD.

Methods

Study Design and Subject Population

The design of the study was cross-sectional, case control (Fig. 1). We studied all consecutive patients with COPD referred to our respiratory ambulatory care between April 2013 and May 2016 who satisfied the selection criteria and provided informed consent according to the Declaration of Helsinki guidelines. Inclusion criteria were: smokers or ex-smokers with a smoking history ≥10 pack-years, age 40–75 y, with a diagnosis of severe COPD for ≥12 months,

which was defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4: a post-bronchodilator $FEV_1/FVC < 0.70$ and a post-bronchodilator $FEV_1 < 50\%$ predicted.[19] Exclusion criteria included: current or recent lower respiratory tract infection (<6 weeks ago); history of asthma; home noninvasive ventilation use; inability to perform the walking test; previous diagnosis of lung cancer, tuberculosis, asbestosis, chronic use of systemic corticosteroids, organ transplantation, lung volume reduction surgery, or previous lung resection; myocardial infarction within the previous 12 months; and known moderate-to-severe renal impairment.

At the enrollment visit, exacerbations or hospitalizations associated with COPD in the previous 12 months were assessed retrospectively by subjects' medical history and subsequently established by review of their medical follow-up records. Exacerbations were defined as "events in the natural course of the disease, characterized by a change in the patients' baseline dyspnea, cough and/or sputum, which is beyond normal day-to-day variations, acute in onset and leading to a change in medication."[20] Subjects with ≥2 reported exacerbations or ≥1 with hospitalization were identified as case subjects (frequent exacerbator group). Subjects with no exacerbations or one exacerbation without hospitalizations were identified as control subjects (infrequent exacerbator group). To calculate pack-years of smoking, the average of number of cigarettes smoked per day was divided by 20 to give packs/day and multiplied by the total number of years of smoking. Ex-smokers were former smokers who had not smoked for ≥6 months.

Pulmonary Function Testing

Subsequently, pulmonary function measurements were always performed in the same order: first body plethys-

mography, followed by spirometry. Inspiratory capacity, total lung capacity (TLC), residual volume (RV), and their ratio (RV/TLC percentage) were recorded by body plethysmography (Masterscope, Erich Jaeger, Essen, Germany). FEV_1 and FVC were measured using a spirometry system (Masterscreen-PFT, Erich Jaeger), and FEV_1/FVC was calculated. A full explanation and training in the performance of each lung function test was given to each subject before the study. All lung function measurements were made according to European Respiratory Society/American Thoracic Society standardizations both before and approximately 20 min following the administration of inhaled short-acting bronchodilator (400 μg of salbutamol through a metered-dose inhaler using an Aerochamber spacer).[21]

Clinical Parameters and Medications

Additional variables assessed during the study were recorded at baseline as follows. Chronic bronchitis was considered present if a person had cough and phlegm production on most days for $\geq$3 months of the year for $\geq$2 y. Respiratory disability was assessed using the Modified Medical Research Council dyspnea scale (mMRC).[22] Body mass index was calculated as kg/m^2. The 6-min walk test was performed according to the American Thoracic Society guidelines.[23] BODE index was calculated using the model described by Celli et al.[24] All subjects underwent arterial blood gas analysis at rest for at least 15 min on room air, and then P_{aO_2} and P_{aCO_2} were collected.

A list of current medications was obtained during the study visit and recorded in the following categories as being present or absent: long-acting β_2 agonists, long-acting muscarinic antagonists, inhaled corticosteroids, chronic home oxygen use, mucolytics, methylxanthine, hydroxymethylglutaryl-CoA reductase inhibitors (statins), aspirin, diuretics, any anti-hypertensive and anti-arrhythmic medications, $\beta1$-selective blockers, oral antidiabetic drugs, and proton-pump inhibitors. Finally, the Charlson comorbidity index was calculated according to the specifications described by Charlson et al.[25] The study was approved by the Bari University General Hospital institutional review committee.

Statistical Analysis

Univariate comparisons between groups were performed by the Student t test for independent samples and the Mann-Whitney U test for normally and non-normally distributed variables, respectively. Comparisons between binary and ordinal variables were performed using the Fisher exact test and the chi-square test for trend, respectively. Variables significant at $P \leq .20$ were further combined and analyzed by multivariate logistic regression analysis, including adjustment for FEV_1 percent of predicted. The

Table 1. Exacerbation Incidence in the Previous 12 Months in 345 Subjects With COPD

Categories	n (%)
No exacerbations	78 (23)
1 exacerbation without hospitalization	84 (24)
$\geq$2 exacerbations without hospitalization	109 (32)
$\geq$1 exacerbations with hospitalization	74 (21)

relationships between the number of exacerbation episodes during the previous 12 months and the RV/TLC percentage value and mMRC value were also assessed using Spearman's rank correlation coefficient. Medication use variables were excluded in the multivariate model due to risk of confounding by indication. A P value of $<.05$ was considered to be significant.

Results

We enrolled a total of 345 eligible subjects with severe COPD. Incidence of exacerbations is shown in Table 1. The annual rate of COPD exacerbations/subject was 1.51. Characteristics of the study population and univariate comparison between infrequent exacerbators and frequent exacerbators are shown in Table 2. No significant differences were found in age, sex, body mass index, current smoker percentage, pack-years smoked, and presence of chronic cough between frequent exacerbators and infrequent exacerbators. Mean FEV_1/FVC and TLC percentage predicted values did not change significantly in the 2 populations. Frequent exacerbators had significantly lower inspiratory capacity percentage predicted. Furthermore, RV/TLC percentage was significantly increased in frequent exacerbators. Infrequent exacerbators had lower mMRC and BODE index than frequent exacerbators. No significant differences were reported for 6-min walk distance, P_{aO_2}, P_{aCO_2}, and Charlson comorbidity index between the 2 groups.

The percentage of drug use (Table 3) shows significant high rates of long-acting muscarinic antagonists and inhaled corticosteroid use in subjects with frequent exacerbations. On the contrary, there were no significant differences in the percentage of long-acting β_2 agonists, non-pulmonary medication, and home oxygen use.

In the multivariate model, a reduced inspiratory capacity percentage predicted and an increase of RV/TLC percentage, mMRC score, and BODE index were associated with frequent exacerbator status (Table 4). A positive correlation was found both between mMRC score and frequent exacerbations (Spearman's rho = 0.18, $P < .001$; Fig. 2) and between RV/TLC percentage and frequent exacerbations (Spearman's rho = 0.20, $P < .001$; Fig. 3).

Table 2. Clinical Characteristics of Study Subjects

Variables	Infrequent Exacerbators (n = 162)	Frequent Exacerbators (n = 183)	P
Age, mean ± SD y	67.6 ± 7.4	68.5 ± 6.9	.21
Male sex, %	61.1	67.2	.26
Current smokers, %	24.0	18.5	.24
Chronic bronchitis, %	37.6	43.3	.32
Pack-years, mean ± SD	52.8 ± 24.1	53.7 ± 23.8	.29
BMI, mean ± SD kg/m^2	26.5 ± 5.0	25.8 ± 4.5	.67
P_{aO_2}, mean ± SD mm Hg	67.3 ± 8.4	66.4 ± 9.3	.54
P_{aCO_2}, mean ± SD mm Hg	42.7 ± 4.4	43.5 ± 4.6	.58
FEV$_1$, mean ± SD % predicted	38.4 ± 9.1	37.3 ± 8.3	.41
FVC, mean ± SD % predicted	65.0 ± 11.0	63.9 ± 10.0	.36
FEV$_1$/FVC, mean ± SD	0.47 ± 0.14	0.48 ± 0.12	.41
IC, mean ± SD % predicted	56.1 ± 10.1	53.2 ± 9.4	.02
TLC, mean ± SD % predicted	127.2 ± 28.2	130.5 ± 30.6	.10
RV/TLC, mean ± SD %	57.9 ± 11.1	62.2 ± 10.3	<.001
6MWD, mean ± SD m	332.0 ± 70.1	319.1 ± 65.6	.08
BODE index	4.1 ± 1.4	4.5 ± 1.3	.01
mMRC	2.4 ± 0.8	2.7 ± 0.7	<.001
Charlson comorbidity index	2.1 ± 1.1	2.3 ± 1.2	.28

Lung function variables reported are post-bronchodilator values.
BMI = body mass index
IC = inspiratory capacity
TLC = total lung capacity
RV = residual volume
6MWD = 6-min walk distance
mMRC = Modified Medical Research Council dyspnea scale (0–4, 4 representing severe shortness of breath)

Table 3. Medication Use

Variables	Infrequent Exacerbators (n = 162)	Frequent Exacerbators (n = 183)	P
Long-acting muscarinic antagonists	62.3	75.4	.01
Long-acting β agonists	89.5	91.8	.57
Inhaled corticosteroids	67.9	80.9	.006
Methylxanthine	1.2	2.7	.45
Aspirin	24.7	26.8	.71
HMG-CoA reductase inhibitor (statin)	22.2	24.6	.61
Diuretics	34.6	38.5	.50
Anti-hypertensive medications	47.5	51.9	.45
β_1-selective blockers	21.0	23.5	.61
Anti-arrhythmic medications	13.5	10.9	.51
Oral antidiabetic drugs	18.3	25.1	.15
Proton-pump inhibitors	38.3	45.4	.19
Home oxygen use (current)	6.2	10.4	.12

Data are presented as percentages.
HMG-CoA reductase = hydroxymethylglutaryl-CoA reductase

Discussion

Exacerbations of COPD cause morbidity, hospital admissions, and mortality, and strongly influence health-related quality of life. A better understanding of the predictors of exacerbations becomes essential for effective

Table 4. Multivariate Model for Frequent Exacerbator Status

Variables	OR (95% CI)	P
IC, % predicted	0.74 (0.43–0.97)	.008
TLC, % predicted	0.92 (0.61–1.38)	.22
RV/TLC, %	1.66 (1.36–2.07)	<.001
6MWD, m	0.72 (0.31–1.24)	.10
BODE index	1.47 (1.16–1.77)	.02
mMRC score	1.45 (1.12–1.91)	<.001
FEV$_1$, % predicted	0.81 (0.59–1.08)	.31

FEV$_1$% post-bronchodilator was forced included into the model.
OR = odds ratio
IC = inspiratory capacity
TLC = total lung capacity
RV = residual volume
6MWD = 6-min walk distance
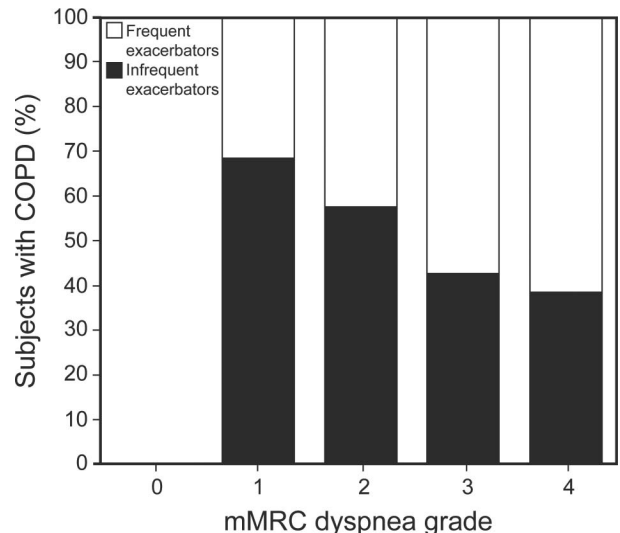mMRC = Modified Medical Research Council dyspnea scale

Fig. 2. Modified Medical Research Council dyspnea scale (mMRC) grade entry in relation to the frequency of COPD exacerbations.

implementation of preventive interventions. This study demonstrated that higher RV/TLC, low inspiratory capacity percentage predicted, and high mMRC score were independently associated with frequent exacerbations of COPD, whereas FEV$_1$ was not. The characterization of frequent exacerbators and relatively resistant non-exacerbators in a large observational study has generated some doubts about the association between traditional risk factors and exacerbations.[18] The results of our study support the evidence in the literature that has led to the definition of these 2 phenotypes of COPD exacerbations and introduce possible risk factors. We observed several findings of note. First, the Motley index (RV/TLC percentage), and not air-flow limitation, was independently associated with frequent exacerbations of COPD, suggesting that the severity of air trapping was more closely linked to frequent
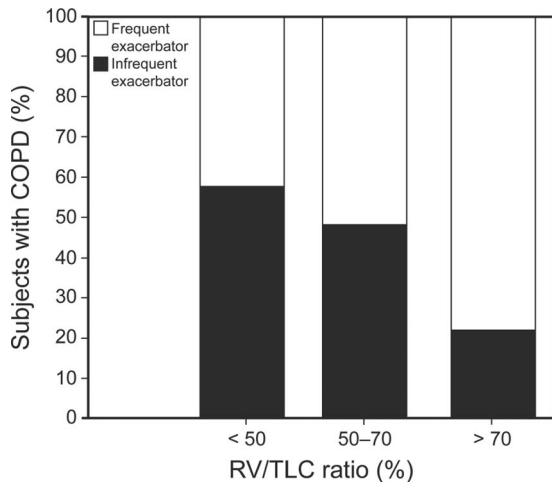
Fig. 3. Residual volume/total lung capacity (RV/TLC) percentage entry in relation to the frequency of COPD exacerbation.

exacerbations than FEV_1. Thus, although low FEV_1 has been well established as a risk factor for exacerbations,[9,10] its usefulness may be confined to comparisons between subjects with COPD with many levels of FEV_1 impairment in all stages of disease. Additional findings that support the concept of these sub-phenotypes as independent phenomena include the absence of differences in some features such as age, sex, or rates of chronic bronchitis and current smokers between the 2 groups. The lack of association with these historical risk factors may be ascribable to the fact that our cohort was composed of subjects with advanced disease. Furthermore, the association of inspiratory capacity percentage predicted with frequent exacerbation status was not unexpected. It was a significant risk factor for morbidity in these subjects, at least in terms of the number of exacerbation-related hospitalizations.[26] The inspiratory capacity change reflects the variation of the end-expiratory lung volume that is the operative expression of the functional residual capacity. Hence, the inspiratory capacity reduction is associated with an increase in the end-expiratory lung volume, attesting to static and/or dynamic pulmonary hyperinflation. Whereas static hyperinflation is related to a decreased pulmonary elastance, conversely, elevated ventilatory demand, prolonged pulmonary time constants (due to high lung compliance and/or pulmonary and airway flow resistance), and, most of all, tidal expiratory flow limitation at rest are responsible for dynamic hyperinflation in patients with COPD.[27] Therefore, patients with COPD with resting expiratory flow limitation, who usually show decreased inspiratory capacity, have more chronic dyspnea.[28,29] These indices of hyperinflation correlate better than FEV_1 with respiratory disability and the resulting activity limitation.[30] These findings explain in part the difference in the mMRC score between the 2 groups. The significance of the mMRC in

predicting exacerbations was already reported by Hurst et al[18] and by Wan et al,[12] as well as the evidence that low mMRC grades were associated with respiratory disability and health status impairment.[31] Nevertheless, this association may be due in part to the continued reliance on the subjective report of increased shortness of breath in defining exacerbations. Regardless, the association of the mMRC with frequent exacerbator status is suggested by our data analysis.

The association between increased BODE index and frequent exacerbations was not new evidence, but it was highlighted in previous works,[14,15] showing that the integration of several parameters (clinical and functional) can lead patients to develop more frequent exacerbations. Moreover, previous works have reported that for each quartile increase in BODE index score, there is an increase in the risk for mortality, and also the index predicts mortality more accurately than FEV_1.[24,32] The BODE index has been shown to correlate well with measures of quality of life, such as the St George Respiratory Questionnaire.[33]

The 6-min walk test is a potentially useful biomarker of disease severity and survival in patients with COPD.[34] Few data have been reported in the literature concerning the evaluation of distance walked in the 6-min walk test as a predictor of exacerbation.[35] In the multivariate model, the 6-min walk test was not associated with frequent exacerbations in our subjects with severe COPD. In support of our data, we highlight the work of Polkey et al,[36] based on the ECLIPSE cohort, in which a reduction in the 6-min walk distance of ≥ 30 m was not associated with hospitalization due to exacerbation in subjects with COPD.

The efficacy of inhaled bronchodilators and corticosteroids in the treatment of severe COPD and prevention of exacerbations was extensively studied.[37-40] However, our data suggest that patients with severe COPD will continue to sustain frequent exacerbations notwithstanding aggressive maintenance inhaled therapy. In addition, the absence of significant differences in terms of the Charlson comorbidity index and non-pulmonary medication use, between the 2 groups, reduces the presence of potentially confounding comorbid conditions.

Here some limitations need to be taken into account. The modest sample size is a major limitation of our study. The retrospective and cross-sectional model of the cohort, as well as the use of patient-reported exacerbations, predisposes our study to recall bias and misclassification between case and control status. The choice to select only subjects with severe air-flow obstruction on one hand selects a uniform cohort, but it also limits the generalization of our conclusions. On the contrary, the review of medical records to verify reported exacerbations and the presence of strict exclusion criteria were an advantage of our study

design. In particular, the exclusion of patients with a history of asthma reduces the percentage of subjects with asthma-COPD overlap syndrome in our population, a relevant clinical population affected by more frequent and severe respiratory exacerbations.[41]

Conclusions

Despite some limitations, our study suggests that static hyperinflation and respiratory disability, measured by Motley index and mMRC, respectively, as the multidimensional BODE index staging system, were independently associated with frequent exacerbation status in our subjects with severe COPD. Future prospective studies should investigate the effect of static hyperinflation on the risk of frequent exacerbations.

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