Original Study

Correlation between frequency of hospitalization of patients with severe COPD and severity indices

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SUMMARY.
BACKGROUND: Several parameters have been proposed as risk factors for hospitalization of patients with chronic obstructive pulmonary disease (COPD). **OBJECTIVES:** The aim of this study was to investigate the association between changes in parameters expressing various different aspects of disease severity and the frequency of hospitalization of patients with severe COPD without co-morbidities. **POPULATION AND METHODS:** Of 117 patients with severe COPD recruited for prospective study, 74 completed 2-year monitoring and were classified into 2 groups according to their frequency of hospitalization: Group A (n=39) ≤2 hospitalizations/year, Group B >2 hospitalizations/year (n=35). Parameters measured at baseline and 2 years included: FEV_1 % pred, FEV_1/FVC ratio, ratio of inspiratory capacity (IC) to total lung capacity (TLC)(IC/TLC), body mass index (BMI), fat free mass index (FFMI), 6 minute walk distance (6MWD), the Borg dyspnoea scale before and after 6MWD, dyspnoea according to the Medical Research Council (MRC) scale, pH and 8-isoprostane in exhaled breath condensate (EBC), serum levels of C-reactive protein (CRP) and fibrinogen, arterial blood gases, the BMI, airflow obstruction, dyspnoea, and exercise capacity (BODE) index and quality of life. **RESULTS:** The patients with more frequent hospitalizations showed greater change in the baseline study variables after 2 years. The specific differences were loss of muscle mass, deterioration of airway obstruction, decrease in exercise capacity, increase in airways and systemic inflammation and impairment in quality of life. The most significant changes found to be associated with hospitalization frequency using a regression model were in CRP, 6MWD, fibrinogen, 8-isoprostane and BODE. **CONCLUSIONS:** In this selected cohort of patients with severe COPD, increased hospitalization frequency was associated with changes in parameters expressing deterioration in exercise capacity and in systemic and airways inflammation. ***Pneumon 2011, 24(2):164-170.***

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by a range of pathophysiological changes resulting in wide variability in clinical presentation and heterogeneity. During recent years many parameters associated with mortality and prognosis have been evaluated for use as indices of the severity of the disease[1-4].

Exacerbations of COPD are of major global importance. They are now recognized as important events in the natural course of the disease, as emphasized in major international guidelines[5]. In general, exacerbations become more frequent and more severe as the severity of the underlying COPD increases[6], but there are great differences in yearly exacerbation incidence rates between patients with COPD of similar degrees of severity[7]. Exacerbations of COPD have a negative impact on patients' symptoms, survival, airways and systemic inflammation, the body mass index, airflow obstruction, dyspnoea, and exercise capacity (BODE) index and progression of the underlying severity of the disease, and on their quality of life[8-11]. Hospitalization for COPD exacerbation accounts for a large part of the high healthcare expenditure for COPD, with a significant proportion of patients being readmitted at least once soon after their discharge[12].

Several potential modifiable and non-modifiable factors have been reported to be risk factors for hospitalization, but data on correlation between increased hospitalizations and changes in these factors are limited[13-16]. COPD is also associated with comorbidities which can affect the disease burden due to exacerbations or the duration of hospitalization and the outcome[12-18].

The present prospective study was designed to investigate changes in possible modifiable and non-modifiable parameters of COPD severity in relation to hospitalization frequency over a 2-year period. A cohort was selected of patients with severe-to-very severe COPD, without comorbidities and under optimal medical treatment, who were monitored for 2 years, in order to identify whether the frequency of hospitalizations was associated with parameters expressing various different aspects of disease severity. As severity indices parameters were chosen expressing airways obstruction, hyperinflation, respiratory failure, dyspnoea, systemic inflammation, airways inflammation, exercise capacity, nutrition indices, quality of life and, finally, the multidimensional BODE index.

METHODS

Patients

From January to December 2005, 225 patients attending the Veterans' Hospital with clinically stable severe to very severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[5], were recruited and initially evaluated, regardless of their previous history of hospitalizations. The inclusion criteria were: medication according to GOLD guidelines, no self-reported asthma or reversibility >12% of airway obstruction after administration of a β_2-agonist and no history of participation in a rehabilitation programme in the past year or during the study. Patients were excluded if they had had a respiratory infection in the last four weeks, history of chronic liver or renal failure, malignancy, diabetes mellitus, use of systemic corticosteroids, significant cardiovascular comorbidities (i.e., clinically apparent heart failure, unstable coronary disease, life threatening arrhythmias), or a history of cancer, tuberculosis, collagen or vascular diseases. In addition, those were excluded who developed any of the above comorbidities during the period of monitoring. All the study patients were receiving optimal treatment, according to the GOLD guidelines.

Variables studied

Pulmonary Function Tests

Forced expiratory volume in one second (FEV_1), Forced vital capacity (FVC) and the FEV_1/FVC ratio were measured with a dry spirometer (Vica-test, Model VEP2; Mijnhardt; Rotterdam, Holland). Lung hyperinflation was assessed by the ratio of inspiratory capacity (IC) to total lung capacity (TLC)(IC/TLC) as described elsewhere[19]. IC was determined as previously described[20] and measurement of TLC was performed by body plethysmography (Vmax22, SensorMedics, Yorba Linda, CA). Arterial blood gases were obtained in room air and analyzed with a standard blood gas analyzer (Ecosys II, Eschweiler compact BGA, Kiel, Germany).

Nutrition Assessment

Body mass index (BMI) was calculated as weight/height^2 (Kg/m^2). Fat free mass (FFM) was measured as previously described by bioelectrical impedance analysis using a BIA 101 system analyzer (Akern, Florence, Italy) with an operating frequency of 50 KHz at 800μA[21]. FFM was standardized for height and expressed as FFM/height^2 (fat-free mass index, FFMI).

Dyspnoea and Exercise Capacity

Chronic dyspnoea was assessed using the Medical Research Council (MRC) scale[22]. Exercise capacity was as-

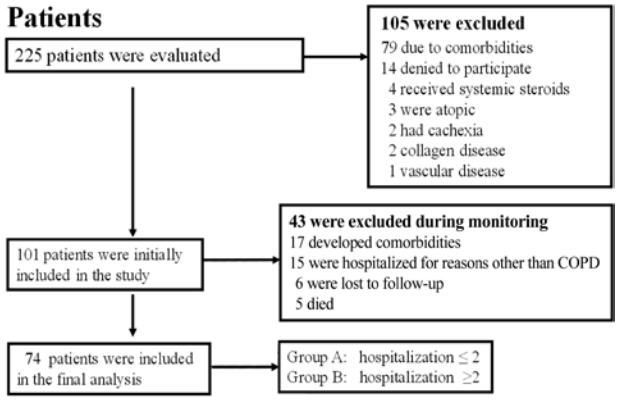

FIGURE 1. Flow chart of recruitment and monitoring of patients with severe chronic obstructive pulmonary disease (COPD).

sessed with the 6 minutes walking distance test (6MWD)[23]. The difference in breathlessness on the Borg scale (ΔBorg) before and at the end of 6MWD was also assessed[24].

Quality of Life

The emotional part of the Chronic Respiratory Questionnaire (CRQ), validated for the Greek population was assessed in all patients[25].

Assessment of systemic inflammation

The level of C-reactive protein (CRP) in the serum was measured using highly sensitive nephelometry (Da de Herring 035041, Marburg, Germany) and of fibrinogen as described by Clauss[26].

BODE index

The BODE index was calculated as previously described[1].

Airways inflammation

Exhaled breath condensate (EBC) pH measurement was conducted as previously described[27-29]. 8-isoprostane concentration was determined by a specific enzyme immunoassay kit (Cayman Chemicals, Ann Arbor, MI, USA), as described elsewhere[28-30]. The detection limit of the assay was 5pg/ml.

STUDY PROTOCOL

The study patients were monitored regularly, every two months, at which time detailed medical assessment was performed. All the patients, because of their specific origin (veterans), were evaluated, treated and, when necessary, hospitalized in the same hospital during the monitoring period. When hospitalization occurred, a medical consultation by one of the investigators (E.G. or S.L.) was performed within 48 hours, in order to evaluate whether the study exclusion criteria applied. Hospitalizations considered related to COPD were those for respiratory infection, pulmonary embolism, cardiac failure due to respiratory failure and pneumonia accompanied with exacerbated disease. Exacerbation was defined according to previously published criteria[31]. During the study period exacerbations related to COPD which did not require hospitalization were also recorded.

The study variables were assessed at enrolment and repeated 2 years after the initial enrolment in the study. After final evaluation, patients were divided into two groups according to the mean number of hospitalizations per year. Group A mean number ≤2, group B >2. The study was approved by the scientific committee of the Veterans' Hospital and all participants gave their written informed consent.

Statistical analysis

Data are presented as mean±SD. Statistical comparisons within groups and between the two groups were estimated by paired t-test with the exception of MRC values which were compared using the Mann-Whitney test. Linear regression analysis was performed using Δvalues of the severity indices (difference between first and second measurements) as the dependent variable and total number of hospitalizations as the independent variable, after adjustment for age, gender, BMI and smoking habits. p values <0.05 were considered significant. Statistical analysis was performed using SPSS 15.0 (Chicago IL, USA).

RESULTS

Patient characteristics

After application of the inclusion and exclusion criteria of the study, 117 patients (98 males), aged 65±7.65 years, 65 smokers, 52 ex-smokers, all non atopic, were included in the study. Figure 1 summarizes the reasons for exclusion of patients, in a flow chart.

The baseline characteristics of the patients included in the study and the mean number of hospitalizations/year and mean duration of hospitalization are summarized in Table 1. The mean number of exacerbations/year

not requiring hospitalization did not differ significantly between the groups (group A had 1.1±0.3/year, group B had 1.4±0.4/year, p=0.7).

In group A, 68 hospitalizations were recorded (57 due to respiratory infection, 4 due to pulmonary embolism and 7 due to cardiac failure) and in group B, 226 hospitalizations were recorded (209 due to respiratory infection, 3 due to pulmonary embolism and 14 due to cardiac failure).

Changes in study variables

The Δvalues of the parameters studied, expressed either as absolute values or as % difference from baseline in each group are summarized in Table 2. Briefly, no significant differences were observed in Δ values in group A, except for serum CRP and fibrinogen where a weak but statistically significant decrease was observed. Patients in group B showed statistically significant differences in relation to baseline for FEV_1, FEV_1/FVC, FFMI, 6MWD, CRP, 8-isoprostane, MRC and BODE index (Table 2). When Δ values were compared between the two groups, statistically significant higher values were observed in group B for FEV_1 % predicted, FEV_1/FVC ratio, FFMI, 6MWD, ΔBorg, CRQ, CRP, fibrinogen, 8-isoprostane, MRC and the BODE index (Table 2).

Association of hospitalization frequency and Δvalues of severity indices (Table 3)

After adjustment for age, gender, BMI and smoking habits, hospitalization frequency showed a significant positive association with ΔCRP, (p=0.001), Δ6MWD (p=0.04) Δfibrinogen (0.05), Δ8-isoprostane (p=0.003) and ΔBODE (p=0.001).

DISCUSSION

In this selected cohort of patients with severe COPD increased hospitalization frequency was found to be associated with changes in variables expressing various different aspects of disease severity, including systemic inflammation (CRP), airway obstruction (FEV_1/FVC), exercise capacity (6MWD), quality of life and loss of muscle mass (FFMI) and the BODE index. The most significant associations were observed for exercise capacity, airway and systemic inflammation and the BODE index.

Some of the early consequences of the increased hospitalization rate were the worsening of dyspnoea, the loss of muscle mass, as assessed by the FFMI and the diminished exercise capacity as assessed by 6MWD. Similar

TABLE 1. Baseline characteristics of patients with chronic obstructive pulmonary disease (n= 74) according to hospitalization frequency: Group A ≤2 hospitalizations/year, group B >2 hospitalizations/year

Group	A (n=39)	B (n=35)	p value
Age (years)	65±6	63±6	0.7
Gender	34M/5F	28M/7F	
Smoking history (Pack years)	47±12	51±12	0.35
Hospitalization frequency/year	0.8±0.5	3.2 ±1.1	**<0.001**
Mean time spent in the hospital (days)	8± 6	7.8±5	0.4
BMI Kg/m^2	24.5±5	26.2±5.6	0.3
FFMI Kg/m^2	19 ±2	19.5±2.5	0.47
FEV_1 % predicted	36±8	37±7	0.36
FEV_1/FVC %	59±5	59±6	0.65
IC/TLC %	0.32±0.08	0.32±0.05	0.43
6MWD (m)	183±30	184±24	0.32
ΔBorg	3±2	3.5±3	0.28
PaO_2 (mmHg)	67±4	63±4	0.53
$PaCO_2$ (mmHg)	43±5	44±5	0.6
MRC	2.8±0.7	2.9±0.6	0.7
CRQ	61±9	58±7.5	0.4
BODE index	6.6±1.1	6.3±0.8	0.6
8-isoprostane in EBC pg/ml	31± 6	28±7	0.5
pH in EBC	7.21± 0.12	7.22±0.13	0.8
CRP mg/dl	0.38±0.1	0.57±0.4	0.1
Fibrinogen mg/dl	285±48	289±38	0.43
Treatment regimens			
ICS			
LABA			
Tiotropium			
SABA			

Data presented as mean±SD. Bold letters indicate statistical significance and refer to statistically higher values in group B. BMI=Body mass index, CRP=C reactive protein, EBC=Exhaled breath condensate, FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity, FFMI=Fat free mass index, PaO_2=Arterial oxygen tension, $PaCO_2$=Arterial carbon dioxide tension, 6MWD=6 minute walk distance, IC=Inspiratory capacity, TLC=Total lung capacity, MRC=Medical Research Council dyspnoea index, CRQ=Chronic Respiratory Questionnaire, BODE index=body mass index, airflow obstruction, dyspnoea, and exercise capacity, ΔBorg=difference in breathlessness on the Borg dyspnoea scale before and at the end of 6MWD

TABLE 2. Δvalues –absolute and % difference- in study variables between baseline measurements and final evaluation after 2 years of patients with chronic obstructive pulmonary disease (n=74) according to hospitalization frequency: Group A ≤2 hospitalizations/ year, group B >2 hospitalizations/year

Group	A (n=39)	B (n=35)	p value
Smoking history (pack-years)	1.4±0.1	1.9±0.3	** 0.17
BMI Kg/m^2	0.01±0.5 (0.04%)	-0.3±1 (-1.1 %)	*A=0.42, B=0.21 ** 0.12
FFMI Kg/m^2	-0.14±0.5 (-0.7%)	**-0.8±0.9 (-4 %)**	*A=0.3, **B=0.007** ** <0.001
FEV_1 % predicted	-1.7±3 (-4.7%)	**-5±5 (-13.5%)**	*A=0.07, **B=0.01** ** **0.002**
FEV_1/FVC %	-0.5±2.3 (-0.9)	**-5±4 (-8.4%)**	*A=0.3, **B=0.03** ** **0.0007**
IC/TLC	-0.01±0.02 (-3%)	-0.01±0.03 (-3%)	*A=0.06, B=0.09 ** 0.12
6MWD (m)	-4±18 (-2.1%)	**-24±18 (-13%)**	*A=0.3, **B=0.001** ** **0.002**
ΔBorg	0.1±1 (3%)	0.4±2 (11%)	*A=0.6, B=0.4 ** **<0.001**
PaO_2 (mmHg)	-1.9±4 (-2.9%)	-3±6 (-4.8%)	*A=0.7, B=0.5 ** 0.2
$PaCO_2$ (mmHg)	1.2 ±3.5 (2.8%)	2±5 (4.5%)	*A=0.5, B=0.4 ** 0.3
MRC dyspnoea	0.02±0.5 (0.7%)	**0.65±0.6 (22%)**	*A=0.7, **B=0.003** ** **0.006**
CRQ	-2±4 (-3.2%)	-6±8 (-10%)	*A=0.2, B=0.05 ** **<0.001**
BODE index	-0.17±0.8 (2.5%)	**1.3±1 (20%)**	*A=0.9, **B=0.002** ** **<0.0001**
pH in EBC	-0.01±0.1 (-0.3%)	-0.05± 0.09 (-0.3%)	*A=0.5, B=0.8 ** 0.08
8-isoprostane pg/ml	2± 0.9 (6.4%)	**7± 0.9 (25%)**	*A=0.4, **B=0.002** ** **0.008**
CRP mg/dl	-0.09±0.1 (-23%)	**0.21±0.7 (37 %)**	***A=0.01**, **B= <0.0001** ** **<0.0001**
Fibrinogen mg/dl	-20±30 (-7%)	17±19 (6 %)	***A=0.04**, B=0.07 ** **0.001**

Data presented as mean±SD, with % difference from baseline in parenthesis. Bold letters indicate statistical significance. *p value for statistical difference within group, **p value for statistical difference for comparisons between the two groups. The significant difference for Δ values between the two groups refers to greater values in group B for all the statistically significant results.
BMI=Body mass index, FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity, CRP=C reactive protein, IC=Inspiratory capacity, TLC=Total lung capacity, FFMI=Fat free mass index, 6MWD=6 minute walk distance, MRC=Medical Research Council, PaO_2=Arterial oxygen tension, $PaCO_2$=Arterial carbon dioxide tension. CRQ=Chronic Respiratory Questionnaire, BODE index=body mass index, airflow obstruction, dyspnoea, and exercise capacity, ΔBorg=difference in breathlessness on the Borg dyspnoea scale before and at the end of 6MWD.

changes were also observed in a previous study where FFMI was not included in the study variables[8]. Considering that FFMI better reflects the state of skeletal muscle mass, an important issue is to explain the association between worsening dyspnoea, diminished exercise capacity, loss of muscle mass and frequency of hospitalization. One

TABLE 3. Association between hospitalization frequency and Δvalues of study variables in patients with severe chronic obstructive pulmonary disease (n=74)

Variable	B	95% CI for B	p value
ΔFEV_1	-0.025	-0.142 to 0. 093	0.67
$\Delta FEV_1/FVC$	-0.114	-0.0247 to 0.019	0.09
Δ6MWD	-0.023	-0.050 to 0.004	0.04
ΔMRC	0.558	-0.637 to 1.75	0.35
ΔFFMI	-0.279	-0.865 to 0.307	0.34
ΔBorg	0.03	-0.54 to 1.13	0.21
Δfibrinogen	0.131	0.042 to 0.22	0.05
ΔpH in EBC	-0.034	-0.755 to 0.3	0.3
ΔCRP	2.99	0.542 to 5.443	0.001
ΔCRQ	0.12	-0.616 to 0.862	0.7
ΔIC/TLC	-6.442	-18.97 to 6.086	0.3
Δ8-isoprostane in EBC	0.023	0.008 to 0.039	0.003
BODE	0.21	0.13 to 0.29	0.001

Associations are presented after adjustment for age, gender, BMI and smoking habit.

Δ indicates difference between baseline and 2-year measurements. B represents the unstandardized coefficient. Bold figures represent statistically significant linear relations. CI: confidence intervals.

FEV_1=Forced expiratory volume in one second, FVC=Forced vital capacity, CRP=C reactive protein, IC=Inspiratory capacity, TLC=Total lung capacity, FFMI=Fat free mass index, 6MWD=6 minute walk distance, MRC=Medical Research Council dyspnoea index, CRQ=Chronic Respiratory Questionnaire, BODE index=body mass index, airflow obstruction, dyspnoea, and exercise capacity, Borg=degree of breathlessness on the Borg dyspnoea scale

explanation, previously reported, might be deconditioning among patients exhibiting peripheral muscle weakness. This deconditioning could be related to the high energy expenditure at rest, due to the increased work of breathing and inadequate dietary intake[32], and to the presence of hypoxia and the more frequent use of systemic corticosteroids during hospitalizations[12]. It appears obvious and reasonable that such deconditioning will result in deterioration in both exercise capacity and dyspnoea. A controversial issue remains as to whether muscle wasting represents the defect which leads to diminished exercise capacity and dyspnoea, or whether it is the result of a multifactorial process, whereby the low exercise capacity in relation to severe obstruction, airflow limitation and progressive dyspnoea leads to loss of skeletal mass.

In this study frequently hospitalized patients experienced significant changes over 2 years in indices of inflammation of both systemic and airways (of oxidative stress origin), expressed by CRP and 8-isoprostane respectively. These two components of the inflammatory process might present another potential mechanism which could participate in muscle fatigue, since they both contribute to loss of muscle mass[33,34]. Another point relating to inflammatory process is that the frequently hospitalized patients appear to express the inflammatory phenotype for both systemic and airway inflammation while those not frequently hospitalized do not. This observation might have practical implications since they indirectly confirm the therapeutic options provided in the current guidelines. In patients with severe COPD but infrequent hospitalizations, the main symptoms are related to functional impairment and should therefore be treated mainly with bronchodilators. Conversely, patients presenting with frequent hospitalizations also express the inflammatory phenotype and therefore benefit from treatment with inhaled corticosteroids[7].

The BODE index is negatively influenced by the increased rate of exacerbations and is considered as a predictor of increased hospitalization rate[8,14]. This study confirmed that increases in the BODE index are related to the frequent hospitalization phenotype, although three of its components, BMI, MRC and FEV_1 did not appear to be associated with frequency of hospitalizations in the regression analysis model. This might be attributed to the less significant changes of BMI and FEV_1 in comparison with the two variables which appear to predominate in expressing airway obstruction (FEV_1/FVC) and nutritional depletion (FFMI), but also to the significant contribution to the index of exercise capacity as assessed by 6MWD.

Regarding the results of lung function testing observed in this study, it is concluded that low frequency of hospitalization contributes to preservation of lung function, mainly concerning toprotection from airflow limitation and obstruction rather than hyperinflation. It is difficult to explain why changes in obstruction surpassed those in hyperinflation in this series, when previous data support the concept that changes in lung volumes predominate those of obstruction[35]. In view of the relationship between frequency of hospitalization and diminished exercise capacity observed in this study, it can be speculated that the dynamic factor of hyperinflation rather than the static factor of obstruction might predominate in lung function impairment.

This study has certain limitations. The first question

arises from the excludion of patients with comorbidities. Several studies have shown that patients with COPD present more comorbidities than matched control subjects without COPD, and that these comorbidities account for a significant part of health-care utilization by patients with COPD[6,12,36]. It is still not clear whether comorbid conditions make COPD patients more susceptible to the consequences of COPD, or whether COPD increases the susceptibility of patients to the specific comorbidities. What is clear, however, is the interaction between COPD and co-morbid conditions in many aspects of disease severity, such as systemic inflammation, exercise capacity and nutritional depletetion. Despite the fact that comorbidities are part of the real world of COPD it was decided not to include co-morbid patients in order to make it possible to interpret the results of this study without any bias consequences from such interaction. Another issue is that of the small number of patients studied, which is mainly attributed to the need for homogeneity of the study population in relation to the severity of the disease. The homogeneity of the study population provided the opportunity to treat patients similarly, to ensure non-significant differences in the baseline values and to recruit patients who had already been monitored and treated according to guidelines for an adequate time period before entering the study process. Study features which partially overcame this limitation were the different aspects of disease severity studied, the close monitoring, the similar rate of exacerbations not requiring hospitalization within groups and the homogeneity of study population. There was even homogeneity in the reasons for hospitalization, since most of the patients were hospitalized for respiratory infection.

A significant issue related to both the present study and previous studies with a similar design is the inability to define whether the changes in the indices of severity represent the consequences of the increased rate of hospitalization or if they are actual determinants and should be studied as independent variables. This issue remains a topic for debate and there is no clear answer as to which of the associated factors is causative; increase in severity of COPD or increase in hospitalizations.

In conclusion, this study confirmed that increased hospitalization rate in COPD is associated with changes in severity in variables expressing the multi factorial disease profile.

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