Universitat Autònoma de Barcelona

Departament de Medicina
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TESI DOCTORAL

DETERMINANTS AND EFFECTS OF EXERCISE CAPACITY DECLINE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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METHODS– COMPLETE VERSION

Study design and participants

Subjects were recruited during their first hospitalization due to a COPD exacerbation in 9 teaching hospitals in Spain between January 2004 and March 2006. The diagnosis of COPD (post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV_1/FVC) <0.70) was confirmed in stable clinical conditions at least 3 months after discharge, during a first evaluation visit.[1] Following the original protocol, 18 to 24 months (2006-2008) after this first visit, patients were invited to participate in a second evaluation for follow-up assessment. Of the 342 patients originally recruited into the PAC-COPD study[2] 226 (66%) had measures of exercise capacity in the two evaluation visits. Subjects lost to follow-up were older, had more co-morbidities and lower FEV_1, as described elsewhere.[3] The Clinical Research Ethical Committee of all participating hospitals approved the study and written informed consent was obtained from all participants.

Measurements

Assessments were performed on clinical stability and at least 3 months after discharge. Exercise capacity was assessed by the 6-minute walk test (6MWT).[4] In the first visit, patients completed two tests with at least a 30-min rest between them, and the longest of both 6-minute walk distances (6MWD) was used for analysis. Only one test was conducted in the second evaluation. The annual rate of change in exercise capacity was defined as the difference between the distance walked at the second evaluation minus that at baseline divided by follow-up time in each subject. Heart rate, oxygen saturation, dyspnoea and fatigue score (Borg scale)[5] were collected before and at the end of each exercise test.

At baseline and in clinical stability, patients underwent complete lung function tests, including forced spirometry (before and after bronchodilator), static lung volumes by whole-body plethysmography, diffusing capacity for carbon monoxide (DLco), arterial blood gases and maximum inspiratory and expiratory pressures (MIP and MEP, respectively).[6,7] Hyperinflation, according with the classical definition, was considered

as any value of total lung capacity (TLC) above 120% of predicted.[8] IC/TLC was taken as an index of inspiratory constraint derived from static hyperinflation of the lung. For analysis, disease severity was classified according to the American Thoracic Society and European Respiratory Society (ATS/ERS) criteria.[9]

Patients also answered a computerized epidemiological questionnaire that included socio-demographic data, life-style information, the modified Medical Research Council (mMRC) scale for the assessment of dyspnoea,[10] and self-reported co-morbid conditions. The Charlson index of comorbidity[11] was calculated accordingly. Physical activity was assessed using the Yale Physical Activity Survey (YPAS)[12] in its Spanish version validated for COPD patients.[13] The validated Spanish-language version[14] of the St George's Respiratory Questionnaire (SGRQ)[15] was used to measure health status. Anxiety and depression were assessed using the validated Spanish-language version[16] of the Hospital Anxiety and Depression Scale (HAD).[17] Information on concomitant medications use, continuous long-term oxygen therapy, participation in pulmonary rehabilitation programs and exacerbations in the previous year (defined as a worsening of the patient's respiratory symptoms that required a change in medication)[18] were also collected at baseline.

Weight and height were measured and the body mass index (BMI) was calculated and the fat free mass index (FFMI) was obtained by bioimpedance. Data on airway inflammatory markers (interleukin [IL] -1ß, IL-6, IL-8 concentration) and bronchial colonisation were collected and assessed as previously reported.[19] Serum levels of C-reactive protein and tumour necrosis factor-α were also determined, as reported elsewhere.[1,19] C-reactive protein levels greater than 5 mg/L were considered as elevated [20]. Cardiac function was assessed by Doppler echocardiography following standardized methodology and emphysema quantification was assessed by High-Resolution Computed Tomography (HRCT).[21,22] Emphysema was defined as sharply delineated low-density areas subdivided into acinar, panlobular or subpleural in both lungs. Emphysema was expressed as a dichotomous variable (presence or absence) Detection of emphysema in any lobe was considered as the presence of emphysema.[23] A hand dynamometer was used to measure peripheral muscle function. Detailed information

about the methods, questionnaires, standardization of the tests, and fieldwork supervision has been previously reported.[1]

Statistical analysis

Sample size of 342 was fixed by the primary scientific objectives of the PAC-COPD Study. [22] Prior to any analysis we calculated, using the program GRANMO 5.2,[24] that statistical power was 96% using data from the literature on 6MWD,[25,26] assuming a difference of 40 m in 6MWD between two equally sized groups, and accepting an alpha risk of 0.05 in a two-sided contrast.

To account for selective attrition and missing values, we used multiple imputation (20 times) through chained equations, replacing missing values by imputations drawn from the predicted distribution of each variable.[27] By performing these analyses all data from 342 PAC-COPD patients were included. Characteristics of study participants at baseline using complete cases and imputed datasets have been previously reported.[3] Data are presented as frequencies and percentages for qualitative variables and mean±SD for quantitative variables, if not otherwise stated. IC/TLC, as a continuous variable or categorized in tertiles, was selected a priori as the main exposure variable. The bivariate association between static hyperinflation, as well as other potential determinants of exercise capacity decline, and change in 6MWD (dependent variable) were analysed using Students' t test or ANOVA, as appropriate depending on the number of categories of the independent variable. Those of them that were significantly related to the outcome were then introduced in a multiple linear regression model to determine the predictors of exercise capacity decline, after adjusting for baseline 6MWD. Variables were kept in the model if they were significantly associated with the outcome and/or they modified (at least 10%) the coefficient for other variables in the model. Goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Because previous research has identified different determinants of exercise capacity in obese and normal weighted COPD patients,[28] we stratified the models according to BMI. Additional analyses using reserve volume/total lung capacity (RV/TLC) as a marker of air trapping were also

implemented. Finally, sensitivity analyses were conducted (i) using complete case analyses, (ii) measuring changes in the 6MWD as percentage with respect to baseline level, (iii) excluding patients enrolled in pulmonary rehabilitation programs, and (iv) forcing into the model variables previously related to 6MWD decline.[29–31] Analysis was conducted using Stata 12.1 (StataCorp, College Station, TX, USA). A $p<0.05$ was considered significant.

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Table S1. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed up for 1.7 years (linear regression model), using RV/TLC as a marker of air trapping.

	Using RV/TLC as a market of air trapping (n=342)		**Using IC/TLC as a market of lung hyperinflation (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.1 (-21.7;-6.6)	0.001	-14.3 (-21.8; -6.7)	<0.001
Baseline RV/TLC (%)	-0.7 (-1.2; -0.1)	0.016	--	--
Baseline IC/TLC (%)	--	--	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.1; -3.2)	0.012	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.2)	0.503	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.11 (-2.6; 2.3)	0.928	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-1.2 (-8.2; 5.6)	0.742	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.134*		*0.137*	

Definition of abbreviation: 95% CI = 95% confidence interval; mMRC = Modified Medical Research Council dyspnoea scale; RV/TLC= residual volume/total lung capacity; IC/TLC= inspiratory capacity/total lung capacity; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance; 6MWT= 6-minute walk test.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean RV/TLC ratio (or mean IC/TLC), SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table S2. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), according to baseline BMI.

	BMI<30 kg.m^{-2} (n=221)		**BMI≥30 kg.m^{-2} (n=121)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-11.7 (-22.5; -1.0)	0.035	-11.8 (-31.2; 7.4)	0.223
Baseline IC/TLC (%)	0.9 (0.3; 1.6)	0.006	0.6 (-0.3; 1.6)	0.196
Significant dyspnoea (mMRC ≥2) at baseline	-15.7 (-29.2;-2.2)	0.028	-15.0 (-35.8; 5.7)	0.154
SGRQ at baseline	-0.2 (-0.6; 0.26)	0.430	0.1 (-0.68; 0.77)	0.910
C-reactive protein at baseline (mg/l)	-0.2 (-4.0; 3.7)	0.938	0.4 (-3.2; 3.9)	0.855
Borg dyspnoea at the end of 6MWT	0.2 (-2.3; 2.7)	0.882	-1.7 (-5.6; 2.2)	0.385
Baseline 6MWD (meters)	-0.2 (-0.2; -0.1)	0.002	-0.2 (-0.3; -0.1)	0.008
Adjusted R^2	*0.165*		*0.120*	

Definition of abbreviation: 95% CI = 95% confidence intervals; IC/TLC= inspiratory capacity/total lung capacity; mMRC = Modified Medical Research Council dyspnoea scale; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline six-minute walk distance. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table S3. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), using complete cases and imputed datasets.

	Complete cases (n=226)		**Multiple imputation (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.8 (-22.1; -7.4)	<0.001	-14.3 (-21.8; -6.7)	<0.001
Baseline RV/TLC (%)	0.8 (0.3; 1.4)	0.003	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-9.4 (-21.9; 3.1)	0.140	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.2)	0.639	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.1 (-2.6; 2.5)	0.928	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-1.7 (-3.9; 0.5)	0.101	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (meters)	-0.1 (-0.2; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.101*		*0.137*	

Definition of abbreviation: 95% CI = 95% confidence interval; IC/TLC= inspiratory capacity/total lung capacity; mMRC = Modified Medical Research Council dyspnoea scale; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2 and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table S4. Adjusted predictive factors of exercise capacity decline expressed in absolute values and as percentage with respect to baseline level in 342 COPD patients followed during 1.7 years (linear regression model).

	6MWD decline, meters (n=342)		**6MWD decline, % from baseline (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-2.15 (-4.98; 0.68)	0.133
Baseline IC/TLC (%)	0.7 (0.2; 1.2)	0.007	0.14 (0.11; 0.18)	0.045
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-5.00 (-9.48; -0.71)	0.023
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	0.02 (-0.13; 0.16)	0.825
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	0.14 (-0.92; 1.19)	0.792
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-0.02 (-0.76; 0.73)	0.966
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.04 (-0.04; -0.03)	<0.001
Adjusted R^2	*0.137*		*0.080*	

Definition of abbreviation: 95% CI = 95% confidence interval; IC/TLC= inspiratory capacity/total lung capacity; mMRC = Modified Medical Research Council dyspnoea scale; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Table S5. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), excluding patients enrolled in pulmonary rehabilitation programs.

	All patients (n=342)		**Patient not enrolled in pulmonary rehabilitation (n=329)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-11.3 (-20.6; -1.9)	0.018
Baseline RV/TLC (%)	0.7 (0.2; 1.2)	0.007	0.9 (0.4; 1.4)	0.001
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-11.8 (-24.0; 0.4)	0.052
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	-0.1 (-0.5; 0.3)	0.522
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	0.1 (-2.6;2.8)	0.934
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-1.0 (-3.2; 1.1)	0.352
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.1 (-0.2; -0.1)	<0.001
Adjusted R^2	*0.137*		*0.156*	

Definition of abbreviation: 95% CI = 95% confidence interval; IC/TLC= inspiratory capacity /total lung capacity; mMRC = Modified Medical Research Council dyspnoea scale; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT and mean baseline 6-minute walk distance. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

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Table S6. Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), forcing variables previously related to 6MWD decline.

	Original model (n=342)		**Model after forcing variables previously related to 6MWD decline (n=342)**	
	Coefficient† (95%CI)	p	Coefficient† (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001	-14.4 (-22.3; -6.5)	<0.001
Baseline RV/TLC (%)	0.7 (0.2; 1.2)	0.007	0.9 (0.3; 1.6)	0.007
Significant dyspnoea (mMRC ≥2) at baseline	-14.6 (-26.2; -3.1)	0.013	-13.8 (-25.3; -2.3)	0.019
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	-0.2 (-0.6; 0.2)	0.361
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	-0.3 (-2.8; 2.2)	0.826
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-0.7 (-2.9; 1.6)	0.560
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Age at baseline	--	--	-0.7 (-1.4; -0.1)	0.037
Body Mass Index (Kg/m^2)	--	--	-0.3 (-1.5; 0.9)	0.657
FEV_1 (% pred)	--	--	0.1 (-0.6; 0.5)	0.515
YPAS physical activity index	--	--	-0.1 (-0.3; 0.1)	0.303
Adjusted R²	*0.137*		*0.164*	

Definition of abbreviation: 95% CI = 95% confidence interval; IC/TLC= inspiratory capacity /total lung capacity; mMRC = Modified Medical Research Council dyspnoea scale; SGRQ= Saint George's respiratory questionnaire 6MWD= 6-minute walk distance; FEV_1= forced expiratory volume in 1 second; YPAS=Yale physical activity survey.

*Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with mMRC<2, and mean IC/TLC ratio, SGRQ, C-reactive protein, Borg dyspnoea at the end of 6MWT, 6-minute walk distance, age, Body Mass Index, FEV_1 and mean baseline YPAS physical activity index. Negative values represent decline.

†Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

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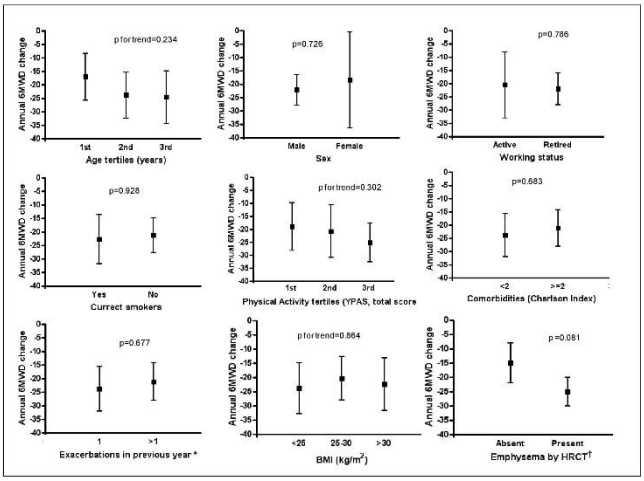
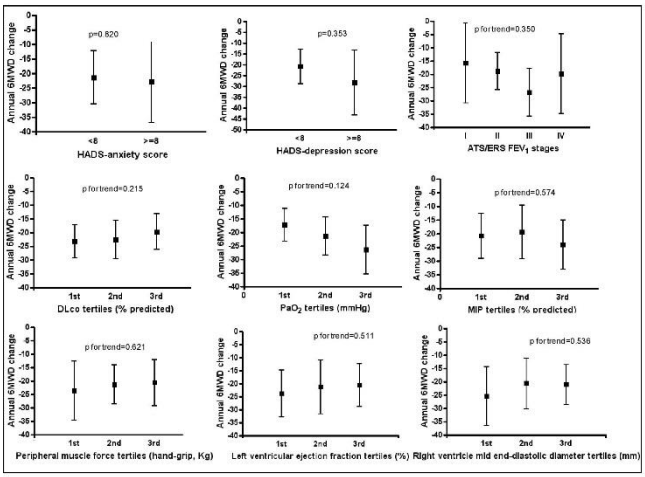
Figure S1. Relationship between relevant socio-demographic, life-style and clinical data and the annual change in 6-minute walk distance (6MWD) in 342 COPD patients.



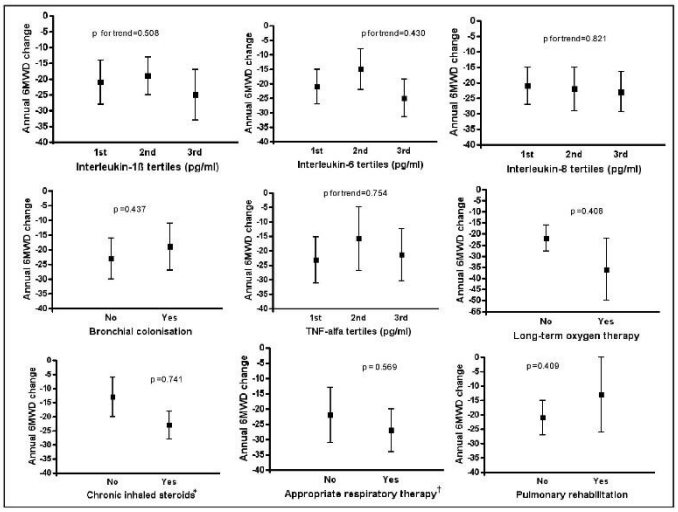
Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD: 6-minute walk distance; YPAS: Yale physical Activity Survey; BMI: Body Mass Index; HRCT: High-Resolution Computed Tomography. *All patients had at least one exacerbation in the previous year, as they were recruited during their first COPD admission. †Emphysema was defined as sharply delineated low-density areas subdivided into acinar, panlobular or subpleural in both lungs.

Figure S2. Relationship between anxiety and depressive symptoms, lung function parameters, blood gases, muscle force, cardiac function and the annual change in 6-minute walk distance (6MWD) in 342 COPD patients.



Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD= 6-minute walk distance; HADS=Hospital Anxiety and Depression Scale; FEV_1= forced expiratory volume in 1 second; DLco= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension; MIP=maximum inspiratory pressure.

Figure S3. Relationship between relevant inflammatory markers, bronchial colonisation and respiratory treatments at baseline and the annual change in 6-minute walk distance (6MWD) in 342 COPD patients.



Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Definition of abbreviation: 6MWD: 6-minute walk distance; TNF: Tumour necrosis factor. *Alone or in combination with other drug treatments; †Defined as some kind of long-acting beta adrenergic, corticosteroids, or a combination of both.

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HOSPITAL ADMISSIONS AND EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

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ORIGINAL ARTICLE
COPD

Hospital admissions and exercise capacity decline in patients with COPD

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ABSTRACT Exercise capacity declines with time and is an important determinant of health status and prognosis in patients with chronic obstructive pulmonary disease (COPD). We hypothesised that hospital admissions are associated with exercise capacity decline in these patients.

Clinical and functional variables were collected for 342 clinically stable COPD patients. The 6-min walk distance (6MWD) was determined at baseline and after a mean±SD of 1.7±0.3 years. Information on hospitalisations during follow-up was obtained from centralised administrative databases. Linear regression was used to model changes in exercise capacity.

Patients were mostly male (92%), with mean±SD age 67.9±8.6 years, post-bronchodilator forced expiratory volume in 1 s 54±17% predicted and baseline 6MWD 433±93 m. During follow-up, 6MWD decreased by 21.9±51.0 m·year^{-1} and 153 (45%) patients were hospitalised at least once. Among patients admitted only for COPD-related causes (50% of those ever admitted), the proportion presenting a clinically significant loss of 6MWD was higher than in patients admitted for only nonrespiratory conditions (53% *versus* 29%, p=0.040). After adjusting for confounders, annual 6MWD decline was greater (26 m·year^{-1}, 95% CI 13–38 m·year^{-1}; p<0.001) in patients with more than one all-cause hospitalisation per year, as compared with those with no hospitalisations.

Hospitalisations are related to a greater decline in exercise capacity in COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by poorly reversible airflow limitation [1] and reduced exercise capacity [2]. This often decreases the ability to participate in activities of daily living and the quality of life of COPD patients [3]. Furthermore, exercise limitation in COPD relates to higher healthcare resource utilisation and is a predictor of mortality [4, 5]. Accordingly, the assessment of exercise capacity is currently considered an important outcome to determine prognosis and response to therapeutic interventions in COPD [6, 7].

Previous studies have clearly shown that exercise capacity declines over time in patients with COPD [8, 9]. This decline appears higher than that observed in other functional variables such as forced expiratory volume in 1 s (FEV_1) [9], suggesting that repeated measures of exercise capacity might be a more sensitive marker of changes in clinical status in these patients than measurements of pulmonary function. However, there is a limited understanding of the factors that affect exercise capacity decline over time in COPD. Identifying such factors will be helpful to design and/or implement interventions that reduce exercise capacity deterioration and, consequently, its deleterious impact.

Patients with COPD often require hospitalisation during the course of their disease. It is well established that these episodes of hospitalisation negatively affect their functional status and health outcomes [10, 11]. In particular, hospitalisations are known to be associated with a significant decrease in peripheral muscle force [12], probably in relation to prolonged bed rest and physical inactivity [13, 14]. In fact, early introduction of a rehabilitation programme following a hospitalisation is highly effective in improving exercise capacity and reducing future hospital admissions in these patients [15]. Conceivably, hospitalisations during the course of the disease can therefore be a major factor of the decline in exercise capacity that occurs in COPD. Accordingly, we hypothesised that, in patients with COPD: 1) hospitalisations (irrespective of their cause) are associated with a faster decline in exercise capacity over time, and that a higher rate of hospitalisation and/or a longer cumulative hospital stay are associated with a greater loss of exercise capacity; and 2) the relationship between hospitalisations due to COPD exacerbation and exercise decline is greater than that observed in other causes of hospitalisations. Thus, the present study was designed to investigate the association between hospitalisations and exercise capacity decline in patients with COPD.

Methods

Detailed information about the methods has been previously reported [16, 17] and is summarised in the online supplementary material.

Study design and participants

The present longitudinal study is based on the population of the Phenotype and Course of COPD (PAC-COPD) study described elsewhere [17]. Briefly, COPD patients were recruited during their first hospitalisation due to COPD exacerbation, in nine teaching hospitals in Spain [16]. Patients were evaluated 3 months after discharge, when clinically stable (baseline). The diagnosis of COPD was established according to the American Thoracic Society/European Respiratory Society guidelines [18]. Patients were invited to participate in a second visit for follow-up assessment 18–24 months later. Of the 342 patients enrolled in PAC-COPD, 226 (66%) had exercise capacity measures in the two visits (online supplementary fig. E1, and tables E1 and E2). The study was approved by the ethics committees of participating hospitals and all patients gave their informed consent.

Measurements

As reported elsewhere [16], sociodemographic data, smoking history, dietary habits, dyspnoea, health-related quality of life, anxiety and depression, comorbidities, physical activity, FEV_1/forced vital capacity ratio before and after bronchodilation, residual volume (RV), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (D_{LCO}), arterial oxygen tension (P_{aO_2}), body mass index (BMI), fat-free mass index, handgrip strength, maximum inspiratory (MIP) and expiratory pressures (MEP), and serum levels of tumour necrosis factor-α were determined at baseline following standardised methodology. Participation in pulmonary rehabilitation programmes during follow-up was also recorded.

Exercise capacity was assessed using the 6-min walk distance (6MWD) following published recommendations [6]. The annual rate of change in exercise capacity was calculated as the difference between the follow-up and baseline 6MWD divided by follow-up time in each patient, and patients were classified into two groups according to the updated minimal clinically important difference (MCID) of $\geqslant 35$ or <35 m·year^{-1} [19, 20].

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Information on dates and causes of hospitalisations during follow-up was obtained from a national administrative database. Hospitalisation rate was defined as the number of hospitalisations (all causes) during follow-up divided by follow-up time in each subject. Causes of admission were classified according to the International Classification of Diseases, 9th revision (see the online supplementary material for more details). To study the specific role of COPD admissions, patients were classified in two main groups: 1) patients with "only COPD" hospitalisations, due exclusively to a COPD exacerbation; and 2) patients with "nonrespiratory" hospitalisations, due to causes unrelated to respiratory conditions. A third group of patients combining respiratory and nonrespiratory admissions was labelled as "mixed cause" hospitalisations, and used only for descriptive purposes. In patients requiring hospitalisation during follow-up, we computed the cumulative hospital stay during follow-up, and the time elapsed between the last hospital discharge and the second visit.

Statistical analysis

Statistical analysis and sample size power estimation are detailed in the online supplementary material. To account for selective attrition and missing values, we used multiple imputation (20 times) through chained equations, replacing missing values by imputations drawn from the predictive distribution of each variable [21]. Table E3 shows the descriptive characteristics of both the real population and the imputed population. Multivariate linear regression models were used to assess the association between hospitalisations and exercise capacity decline, after adjusting for baseline 6MWD. Potential confounders were tested and included in the final models if 1) they related to both the exposure and the outcome, 2) they modified (>10% change in regression coefficient) the estimates of the remaining variables, or 3) there was consistent evidence in the literature of their association with exercise capacity. Further stratification analyses according to sex, age, BMI, daily physical activity, FEV_1 and muscle force (handgrip, MIP and MEP) were conducted in order to study possible interactions. Sensitivity analysis was conducted 1) using the cut-off point of 26 m·year^{-1} as the clinically significant threshold of exercise capacity decline [22], 2) excluding subjects who participated in any pulmonary rehabilitation programme during follow-up and 3) using a complete case analysis. Analysis was conducted using Stata 9.1 (StataCorp, College Station, TX, USA).

Results

Table 1 presents the main clinical and functional characteristics of the 342 patients studied at baseline. Most participants (92%) were males. Mean±SD age was 67.9±8.6 years. About a third of patients were current smokers. Comorbidities were frequent and about half of patients reported significant dyspnoea. On average, airflow limitation was moderate, ranging from mild to very severe. Most patients had gas trapping and impaired D_{LCO} with mild arterial hypoxaemia.

Patients were followed for a mean of 1.7±0.3 years. The mean 6MWD was 433±93 m at baseline and 396±99 m at the second evaluation. Mean change in 6MWD was -21.9±51.0 m·year^{-1} (table 1 and fig. E2) and ~20% of patients experienced an increase in exercise capacity during follow-up. A 6MWD decline ⩾35 m·year^{-1} (MCID) occurred in 113 (33%) subjects. According to spirometric severity, there was a trend in the association between baseline 6MWD and COPD severity grades (466±122, 443±94, 431±96 and 358±116 m in patients with mild, moderate, severe and very severe COPD, respectively; $p<0.001$ for trend). However, there were no differences in 6MWD changes across these COPD groups (-16±70, -19±51, -27±55 and -19±75 m·year^{-1}, respectively; $p=0.350$ for trend). During follow-up, 153 (45%) patients were hospitalised (all causes). The most frequent cause of admission was a COPD exacerbation (52%). Tables 2 and 3 present detailed information on the characteristics of hospitalisations during follow-up. A very small proportion (5%) of patients was enrolled in pulmonary rehabilitation programmes during follow-up.

Hospitalisations during follow-up, as well as the frequency of all-cause hospitalisations, were associated with a significantly greater decline in 6MWD in unadjusted analyses (table 4 and fig. 1). The rate of 6MWD decline was greater in patients with only-COPD admissions than in patients admitted for nonrespiratory causes, but this difference was not statistically significant (table 4 and fig. 2). A higher proportion of patients with only-COPD admissions experienced a clinically significant loss in 6MWD compared with patients with nonrespiratory admission (53% *versus* 29%, $p=0.040$). There was no association between 6MWD decline and cumulative hospital length of stay or time elapsed from last hospital discharge to the second evaluation (table 4).

Table 5 shows that, after adjusting for age, sex, dyspnoea, BMI, RV/TLC, P_{aO_2} and baseline 6MWD, suffering one or more than one (all-cause) hospitalisation per year was associated with an increase in the mean annual decline of 6MWD by 7.4 and 26.1 m, respectively, as compared with patients who were not hospitalised during follow-up ($p=0.211$ and $p<0.001$, respectively). This decline was similar across causes of admissions.

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TABLE 1 Characteristics of study participants

	All patients[#]
Patients n	342
Anthropometric and clinical data	
Males	314 (92)
Age years	67.9±8.6
Current smokers	120 (35)
YPAS physical activity index[¶]	34 (20–53)
SGRQ total score[+]	33 (23–48)
Charlson index ⩾2	194 (57)
Body mass index kg·m^{-2}	28.2±4.7
Fat-free mass index kg·m^{-2}	19.7±3.1
Significant dyspnoea[§]	158 (46)
Lung function	
Post-bronchodilator FEV1 % pred	54±17
COPD severity	
Stage I[f]	19 (6)
Stage II[##]	164 (48)
Stage III[¶¶]	132 (38)
Stage IV[++]	27 (8)
RV/TLC %	55.9±10.5
*D*LCO % pred	64.4±22.7
Pa_{O_2} mmHg	74.4±10.9
Exercise capacity and muscle force	
6MWD at baseline m	433±93
6MWD at follow-up visit m	396±99
Change in 6MWD m·year^{-1}	-21.9±51.0
Patients with clinically significant change in 6MWD[§§]	113 (33)
Handgrip muscle force kg	30.5±8.5
MIP % pred	68±27
Pulmonary rehabilitation during follow-up[ff]	13 (5)
Follow-up time years	1.70±0.34

Data are presented as n (%), mean±SD or median (interquartile range), unless otherwise stated. YPAS: Yale Physical Activity Survey; SGRQ: St George's Respiratory Questionnaire; FEV1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; RV: residual volume; TLC: total lung capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; Pa_{O_2}: arterial oxygen tension; 6MWD: 6-min walk distance; MIP: maximum inspiratory pressure. [#]: descriptive analyses were conducted using imputed datasets where there were missing data; online supplementary table E3 shows the descriptive characteristics of both complete cases and imputed samples. [¶]: scored from 0 to 137. [+]: scored from 0 to 100. [§]: modified Medical Research Council score ⩾2. [f]: mild (FEV1 ⩾80% pred). [##]: moderate (FEV1 ⩾50% or <80% pred). [¶¶]: severe (FEV1 ⩾30% or <50% pred). [++]: very severe (FEV1 <30% pred). [§§]: ⩾35 m·year^{-1}. [ff]: n=251.

TABLE 2 Hospital admissions during 1.7-year follow-up of 342 chronic obstructive pulmonary disease patients

Any[#] admission during follow-up	153 (45)
Number of admissions[#] per year during follow-up	
0	189 (55)
>0 and ⩽1	73 (21)
>1	80 (24)
Distribution of patients according to admissions and their causes[¶]	
No admission	189 (55)
Only COPD	77 (23)
Nonrespiratory	43 (13)
Mixed causes	33 (10)
Cumulative hospital stay[+] days	13 (5–28)
Time from last discharge to second evaluation[+] days	206 (103–363)

Data are presented as n (%) or median (interquartile range). [#]: all causes; [¶]: see main text for definitions; [+]: n=153.

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TABLE 3 Causes of 376 hospital admissions during 1.7-year follow-up of 153 chronic obstructive pulmonary disease (COPD) patients

	ICD9 code	All admissions	
		Cause of admission#	Length of hospital stay days
All-cause admissions		376 (100)	6 (3–10)
COPD	490–496	196 (52)	6 (3–9)
Other respiratory non-COPD	460–519 except 490–496	46 (12)	7 (4–10)
Cardiovascular	390–459	38 (10)	7 (3–14)
Cancer	140–239	28 (7)	6 (3–10)
Digestive	520–579	21 (6)	4 (3–8)
Genitourinary	580–629	17 (5)	6 (5–9)
Aftercare	V50–V69	7 (2)	4 (2–8)
Musculoskeletal	710–739	7 (2)	8 (7–8)
Infectious and parasitic diseases	001–139	4 (1)	36 (7.5–80)
Injury and poisoning	800–999	3 (0.8)	8 (6–17)
Nervous system and sense organs	320–389	3 (0.8)	17 (2–25)
Diseases of the skin	680–709	3 (0.8)	5 (2–13)
Diseases of the blood	280–289	1 (0.3)	12¶
Endocrine disorders	240–279	1 (0.3)	15¶
Mental disorders	290–319	1 (0.3)	2¶

Data are presented as n (%) or median (interquartile range). There were no admission causes other than those included here. ICD9: International Classification of Diseases, 9th revision. #: ordered by frequency; ¶: n=1.

TABLE 4 Unadjusted relationship between hospital admissions and annual change in 6-min walk distance# (6MWD) during 1.7-year follow-up of 342 chronic obstructive pulmonary disease (COPD) patients

	Change in 6MWD m·year^{-1}	p-value	Clinically significant loss¶		
			No+	Yes§	p-value
Any^{f} admission during follow-up					
No	-13.8±35.9	0.003	142 (75)	47 (25)	0.002
Yes	-32.5±51.7		87 (57)	66 (43)	
Number of admissions^{f} per year during follow-up					
0	-13.8±32.9	0.002¶	142 (75)	47 (25)	0.001¶
>0 and ⩽1	-26.1±51.9		46 (63)	27 (37)	
>1	-38.4±70.9		41 (52)	39 (48)	
Cause of admission##					
Only COPD	-36.2±56.2	0.236++	36 (47)	41 (53)	0.040++
Nonrespiratory	-24.2±48.9		31 (71)	12 (29)	
Mixed causes	-28.2±48.7		20 (61)	13 (39)	
Quartiles of cumulative hospital stay## days					
1 to ⩽5	-29.8±37.6	0.610¶	25 (61)	16 (39)	0.682¶
>5 to ⩽13	-33.1±48.7		20 (51)	18 (49)	
>13 to ⩽28	-29.1±49.8		23 (64)	13 (36)	
>28	-38.1±51.5		19 (50)	19 (50)	
Quartiles of time from last discharge to second evaluation## days					
0 to ⩽103	-36.3±42.1	0.445¶	21 (52)	18 (48)	0.735¶
>103 to ⩽206	-33.8±48.9		23 (60)	15 (40)	
>206 to ⩽363	-36.1±49.4		20 (53)	18 (47)	
>363	-25.8±46.4		23 (60)	15 (40)	

Data are presented as mean±SD or n (%), unless otherwise stated. #: presented both as a continuous variable and according to clinically significant change, for a better understanding of the effect of hospitalisations; each combination of hospitalisation variables and change in the 6MWD is a single unadjusted model. ¶: ⩾35 m·year^{-1}. +: n=229. §: n=113. f: all causes. ##: n=153. ¶¶: p-value for trend. ++: "only COPD" *versus* "nonrespiratory"; "mixed causes" is only presented for descriptive purposes.

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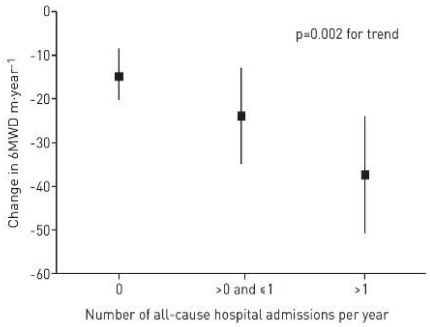

FIGURE 1 Annual change in 6-min walk distance (6MWD) according to annual rate of hospital admission during 1.7-year follow-up in 342 chronic obstructive pulmonary disease patients. Data are presented as means with 95% confidence intervals.

Stratification according to potential effect modifiers did not show any difference. All sensitivity analyses yielded very similar results (table E4 compares the main results using both complete case and imputed datasets).

Discussion

There are three main novel findings in this study. First, 6MWD decline was greater in those COPD patients who were hospitalised (all causes) during follow-up; second, this association is significantly greater in patients with frequent hospitalisations (all causes); and third, the decline does not seem to be related to the cause of admission.

Previous studies

It is well established that hospital admissions contribute to poor health outcomes in COPD patients [1, 10, 11]. So far, however, the relationship between exacerbations and hospitalisations and the decline in exercise capacity has been rarely studied. A previous smaller study (56 patients) investigated the association between the frequency and duration of COPD exacerbations and changes in the BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) index, which includes the 6MWD, and reported that their duration had a greater impact on 6MWD than their frequency [23]. Unfortunately, these results cannot be compared with ours because that study did not distinguish between exacerbations requiring hospital care and those managed in the community; besides, no information was collected about admissions due to comorbidities.

Interpretation of findings

The results of this study identify a clear and statistically significant association of all-cause hospitalisation with exercise capacity decline in COPD. Several potential mechanisms can be conceived to explain this relationship. For instance, it is well known that bed rest and physical inactivity impair skeletal muscle mass and function [13, 14]. Likewise, all-cause hospitalisations can be markers of poor general health and, hence,

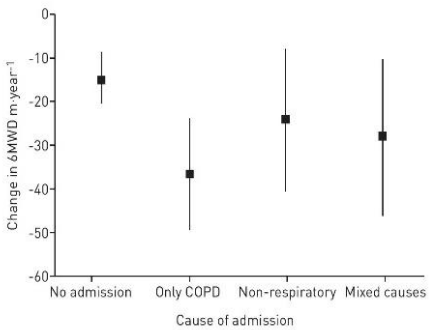

FIGURE 2 Annual change in 6-min walk distance (6MWD) according to cause of hospital admission during 1.7-year follow-up in 342 chronic obstructive pulmonary disease (COPD) patients. Data are presented as means with 95% confidence intervals.

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TABLE 5 Adjusted association between hospitalisation rate and annual change in 6-min walk distance (6MWD) during 1.7-year follow-up in 342 chronic obstructive pulmonary disease (COPD) patients[#] in all patients and according to cause of admission

	All patients		Patients with only-COPD admissions[¶] *versus* no admissions[+]		Patients with nonrespiratory admissions[§] *versus* no admissions[+]	
	Coefficient[f] (95% CI)	p-value	Coefficient[f] (95% CI)	p-value	Coefficient[f] (95% CI)	p-value
Constant[##]	-7.3 (-15.8–1.2)	0.088	-7.7 (-15.8–0.6)	0.068	-8.5 (-16.7– -0.3)	0.043
Number of hospital admissions per year during follow-up						
0	Reference		Reference		Reference	
>0 and ⩽1	-7.4 (-19.1–4.3)	0.211	-13.8 (-28.2–2.1)	0.092	-1.5 (-18.7–15.7)	0.865
>1	-26.1 (-38.6– -13.1)	<0.001	-28.0 (-45.1– -10.7)	0.002	-27.3 (-48.9– -5.6)	0.014
Significant dyspnoea[¶¶] at baseline	-17.2 (-27.8– -6.6)	0.002	-16.9 (-28.3– -5.4)	0.004	-15.3 (-26.4– -4.1)	0.008
Age at baseline years	-0.6 (-1.3–0.01)	0.057	-0.6 (-1.2–0.1)	0.089	-0.6 (-1.3–0.1)	0.098
Female sex	-11.1 (-30.2–7.9)	0.249	-8.6 (-29.1–11.9)	0.407	-4.3 (-24.9–16.3)	0.679
Baseline body mass index kg·m^{-2}	-0.3 (-1.5–0.9)	0.664	-0.2 (-1.4–1.1)	0.782	-0.6 (-1.8–0.7)	0.389
Baseline RV/TLC %	-0.5 (-1.0–0.04)	0.069	-0.5 (-1.2–0.1)	0.087	-0.4 (-0.9–0.2)	0.223
Baseline $P_{a}O_2$ mmHg	0.1 (-0.2–0.4)	0.692	0.1 (-0.3–0.4)	0.726	0.1 (-0.2–0.5)	0.398
Baseline 6MWD m	-0.2 (-0.3– -0.1)	<0.001	-0.2 (-0.3– -0.1)	<0.001	-0.2 (-0.3– -0.1)	<0.001
Adjusted R^2	0.223		0.229		0.193	

RV: residual volume; TLC: total lung capacity; $P_{a}O_2$: arterial oxygen tension. [#]: linear regression model. [¶]: n=77. [+]: n=189. [§]: n=43. [f]: expressed as change in metres of 6MWD per: 1) unit of the continuous covariate, or 2) a change with respect to the reference category in categorical covariates. [##]: adjusted mean value based on the linear regression equation corresponding to the mean change in 6MWD in a subject with no COPD hospitalisations per year and modified Medical Research Council score <2, who was male and of mean age, body mass index, RV/TLC, $P_{a}O_2$ and baseline 6MWD; negative values represent decline. [¶¶]: modified Medical Research Council score ⩾2.

poor prognosis. Other more specific factors may also operate in particular causes of admissions including: 1) a burst of systemic inflammation, known to occur during exacerbations of COPD [24] or acute cardiovascular diseases [25], that can reduce quadriceps strength and exercise capacity [12]; or 2) the use of systemic corticosteroid therapy [1, 18], commonly used in case of COPD admissions, that can cause skeletal muscle dysfunction [26]. The fact that, in this study, neither the total duration of hospital stay nor the time from hospital discharge to the second evaluation were related to the annual 6MWD decline suggest that other specific mechanisms may play a more active and important pathogenic role than simply the passive physical inactivity associated with any hospitalisation event. Certainly, further clinical and experimental research is needed to identify these mechanisms, since this is usually beyond the scope of epidemiological studies.

Two other findings of this study deserve specific discussion. Firstly, the results indicate that dyspnoea is an independent predictor of the decline in exercise capacity in COPD patients. The association of dyspnoea with exercise capacity is well established in COPD [27]. In addition, an enhanced perception of dyspnoea can reduce the practice of physical activity, which subsequently would decrease exercise capacity. Furthermore, previous studies have shown that dyspnoea is a predictor of survival in these patients [28] and that it gets better after improving exercise capacity through pulmonary rehabilitation programmes [29]. To our knowledge, however, no previous study has reported a relationship between dyspnoea and an accelerated annual decline in exercise capacity in COPD. Secondly, and surprisingly, baseline FEV_1 and RV/TLC were not related to 6MWD decline in our study. Yet this is in keeping with the results of a previous study of 198 patients with severe COPD followed for 2 years, which showed that the annual decline of 6MWD was independent of FEV_1 changes [8].

An estimated 20% of patients evaluated in our study experienced an increase in exercise capacity during follow-up. This fact has been previously reported for FEV_1 [30]. Potential explanations include 1) regression to the mean, 2) a learning effect in patients who underwent repeated exercise capacity tests with their doctors during follow-up, or 3) an improvement of clinical and functional status if the first hospitalisation triggered a more aggressive treatment by doctors or higher awareness in relation to disease in patients and their carers.

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Clinical implications

The results of this study have clinical implications given that poor exercise performance has been related to a greater risk of hospitalisation and mortality in COPD patients [4, 8]. Pulmonary rehabilitation programmes starting within a few days of hospital admission or immediately after discharge has been shown to produce clinically meaningful improvements in exercise capacity and quadriceps strength in COPD patients [29]. In addition, a recently published meta-analysis of randomised controlled trials concluded that post-exacerbation rehabilitation can reduce hospital re-admissions and mortality in COPD patients [15]. Thus, these data complement and extend the previous observations, and support the need for pulmonary rehabilitation in COPD patients during or immediately after hospitalisation. The high proportion (56%) of patients with a clinically relevant loss of exercise capacity among those admitted only for COPD-related causes as compared with other conditions makes COPD admission a highly specific target for such interventions. Unfortunately, only a small proportion (5%) of our hospitalised COPD patients were enrolled in pulmonary rehabilitation programmes, so we were not able to explore the potential effectiveness of such programmes in our study population.

Strengths and limitations

The large sample size, careful phenotypic characterisation of participants [17], relatively long period of follow-up and novelty of the hypothesis investigated are clear strengths of this study. In addition, missing data could have introduced selection bias in the estimates of our analyses. Therefore, we used multiple imputation to compensate for the underrepresentation of subjects lost to follow-up, which is known to be more accurate than complete case analyses in estimating statistical associations [21]. Among potential limitations, we acknowledge that the PAC-COPD study reflects a population with sex and severity distributions that may not be representative of COPD patients from countries with different social or sanitary organisations. However, such differences are unlikely to affect the results of the association between hospital admissions and exercise capacity decline. Our study was restricted to patients who were hospitalised for COPD and, thus, our findings may be considered to apply only to relatively severe COPD. However, the selection of patients at their first hospital admission due to COPD should be seen as a strength that allows for a more valid study of the factors that affect the prognosis of COPD [31].

PAC-COPD lacks a control arm, but in the current analysis we compared COPD patients who required hospitalisations with those who did not, which makes a control group unnecessary. Likewise, we do not have information on quadriceps strength, which is a strong correlate of exercise capacity in COPD. Instead, we tested hand-grip strength and respiratory muscle force *versus* exercise capacity changes and no association was observed. Thus, considering that both upper and lower muscle function can be impaired in COPD patients [32], we believe that any residual confounding effect should be very small, if any. In PAC-COPD, a practice 6-min walk was not conducted at the follow-up visit. As there was a relatively long time interval between the baseline and second evaluation, the learning effect could have been missed at follow-up. However, the absence of a practice test was present equally in patients who suffered a hospitalisation and those who did not, so we doubt that this could constrain our conclusions. Finally, our study has only two time-points, which prevents us from analysing trajectories of decline in exercise capacity.

Conclusion

This study shows that hospitalisations, particularly if frequent, are significantly related to a greater annual decline in exercise capacity in COPD patients.

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SUPPLEMENTARY MATERIAL

HOSPITAL ADMISSIONS AND EXERCISE CAPACITY DECLINE IN PATIENTS WITH COPD

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METHODS – COMPLETE VERSION

Study Design and Ethics

The "Phenotype and Course of COPD (PAC-COPD)" Study is a prospective cohort study described elsewhere [E1]. Briefly, COPD patients were recruited during their first hospitalization due to a COPD exacerbation, in nine teaching hospitals in Spain between January 2004, and March 2006, as published before [E2, E3]. Patients were evaluated three months after discharge, when clinically stable, at what constituted the baseline assessment. Eighteen to 24 months afterwards, patients were invited to participate in a second visit for follow-up assessment. The study was approved by the Clinical Research Ethical Committee of all participating hospitals and written informed consent was obtained from all participants.

Patients

The diagnosis of COPD was confirmed by spirometry (post-bronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV1/FVC) $\leq$0.70) [E4]. The current analysis includes only those patients recruited into the PAC-COPD study who had exercise capacity measures in the two evaluation visits. Of the 342 patients originally recruited into the PAC-COPD study [E2], 19 died before the second visit, 32 refused to continue, 13 could not be contacted, 27 were excluded because of appearance of severe co-morbidities, and for 25 the exercise capacity test could not be conducted at follow-up, providing a total of 226 (66%) patients with repeated measures of exercise capacity (Figure E1). Subjects who died or were lost to follow-up during the study period were older, had more co-morbidities and lower FEV_1 than those who completed the study (Tables E1 and E2).

Measurements

Exercise capacity

Exercise capacity was assessed using the six-minute walk test (6MWT) according to published recommendations [E5, E6], and the six-minute walk distance (6MWD) was determined for each patient. In the baseline assessment, patients completed two 6MWT with at least a 30-min rest between, and the longer of the two distances was used for analysis. Only one test was conducted in the second evaluation. The annual rate of change

in exercise capacity was defined as the difference between the 6MWD at the second evaluation minus the baseline 6MWD, divided by follow-up time for each subject. Patients were classified according to what is considered a Minimal Clinically Important Difference (MCID) for exercise capacity decline [E7], as having a clinically significant loss (≥35 m/year), or a less than clinically significant decline (<35 m/yr).

Hospital admissions

Information on hospital admissions, including dates and causes, from first to second assessment was obtained from the Minimum Basic Dataset (CMBD), a national administrative database. Hospitalization rate was defined as the number of hospitalizations (all-causes) during follow-up divided by follow-up time in each subject. Causes of admission were classified according to the International Classification of Diseases, 9th revision. Because some patients suffered more than one hospital admission during follow-up, the association between admissions and exercise capacity change according to causes could not be performed at a "single causes" level, but at the patients' level. Thus, to study the specific role of COPD admissions, patients were classified in two main groups: (i) patients with "only COPD" hospitalizations, due exclusively to a COPD exacerbation (primary cause of admission at discharge ICD-9 codes 490-496, or primary cause ICD-9 466 or 518.81 if second cause was ICD-9 491.21), and (ii) patients with "non-Respiratory" hospitalizations, due to causes unrelated to respiratory conditions (primary cause different than ICD-9 460-519). A third group of patients combining respiratory and non-respiratory admissions was labelled as "mixed cause" hospitalizations, and used only for descriptive purposes. In patients who required hospitalization at least once during follow-up, we computed the cumulative hospital stay as defined by the total number of days of admission (all-cause admissions) during follow-up, and the time from the last discharge to the second evaluation.

Additional measurements

Detailed information about the methods, questionnaires, standardization of the tests, and fieldwork supervision has been previously reported [E1]. Briefly, during the baseline assessment all participants answered an epidemiological questionnaire that included socio-demographic data, life-style information, a previously validated 122-item food frequency questionnaire (FFQ) [E8] to asses dietary habits, the modified Medical Research Council

(mMRC) scale for the assessment of dyspnoea [E9], the validated Spanish-language version [E10] of the St George's Respiratory Questionnaire (SGRQ) [E11] to measure health-related quality of life, and the validated Spanish-language version [E12] of the Hospital Anxiety and Depression Scale (HAD) [E13]. The Charlson index of comorbidity [E14] was calculated from doctor diagnosis of co-morbid conditions. Physical activity was assessed using the validated Spanish version of the Yale Physical Activity Questionnaire (YPAS) [E15] validated for COPD patients [E16]. In addition to forced spirometry (before and after bronchodilator), static lung volumes by whole-body plethysmography (residual volume (RV), total lung capacity (TLC)), diffusing capacity for carbon monoxide (DLco) and arterial blood gases (arterial oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$)) were determined. Likewise, weight and height were measured and the body mass index (BMI) was calculated and the fat free mass index (FFMI) was measured by bioimpedance. A hand dynamometer was used to measure peripheral muscle function. Respiratory muscle strength was tested using the maximum inspiratory (MIP) and expiratory pressures (MEP) and reference values were used [E17]. Serum inflammatory biomarkers (Tumour Necrosis Factor alpha) were also assessed at baseline. Finally, participation in pulmonary rehabilitation programs during follow-up was recorded.

Statistical analysis

Given that the 34% of patients without repeated measures of exercise capacity exhibited some differences in age, FEV_1 and comorbidities compared with the remaning patients (Tables E1 and E2 in the Online supplementary material), and that selective attrition is known to introduce bias into analysis if using a complete case strategy [E18], we used multiple imputation to compensate for the underrepresentation of the older, more severe population. Moreover, other variables had a small proportion (<15%) of missing values that, assuming ignorability holds, were considered either completely at random or at random [E19]. Thus, multiple imputation through chained equations was used, replacing missing values by imputations drawn from the predictive distribution of each variable [E20], which was obtained from a regression model (logistic, lineal, or politomous depending on the type of variable), where variables that were associated with the quantities of main interest and variables that were associated with the probability of missingness were used as covariates (age, sex, Charlson index of comorbidity, mMRC dyspnoea score, SGRQ total score, YPAS physical activity index, BMI, FFMI, FEV_1, RV/TLC, DL_{CO},

PaO_2, MIP, handgrip muscle force, baseline 6MWD and hospitalization rate). To account for the additional uncertainty produced by the fact that missing values are substituted by estimates [E21], we imputed missing values 20 times. Table E3 in the Online supplementary material shows the descriptive characteristics of both the real population and the imputed population.

Provided sample size was fixed by the primary scientific objectives of the PAC-COPD Study [E3], prior to any analysis we calculated whether the available number of patients would allow for identification of significant differences in 6MWD decline between groups (admitted *vs.* non-admitted during follow-up). Calculations using the program GRANMO 5.2 [E22] showed that, assuming a standard deviation of 100 meters in the 6MWD [E23, E24], a 1:2 ratio of hospitalized: not hospitalized [E3], a correlation between first and second measurements of 0.84 [E25], and accepting an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided contrast, a sample size of 342 patients allows for a 20 meter or more difference in the 6MWD decline between groups to be identified as statistically significant. This difference is lower than the test's minimal important difference [E7], suggesting the sample has sufficient power to provide clinically meaningful results.

The bivariate association between hospitalization and the annual rate of change in the 6MWD was analyzed using either unpaired t-test, analysis of variance, Chi-square, or Fischer's exact tests, as appropriate. As the annual rate of 6MWD change was normally distributed (Figure E2), multivariate linear regression models were used to assess the effect of hospitalizations as the exposure and adjusting for baseline 6MWD. Age, sex, smoking history, working status, daily physical activity, daily consumption of processed meats, vegetables and fruits, Charlson index of comorbidity, BMI, mMRC dyspnoea scale, SGRQ scores, HAD depression scale, severity of airflow limitation (FEV_1), gas trapping (RV/TLC), pulmonary diffusion impairment (DL_{CO}), arterial oxygenation (PaO_2), muscle force (handgrip, MIP and MEP), serum TNFα, inhaled corticosteroids use, and participation in pulmonary rehabilitation programs, were tested as potential confounders and included in the final model if (i) related to both the exposure and the outcome, (ii) modified (>10% change in regression coefficient) the estimates of the remaining variables, or (iii) there is consistent evidence in the literature on their association with exercise capacity. To assess whether exercise capacity exhibits different decline depending on the

causes of hospitalization, linear regression models were stratified according the main cause of the hospitalization. Further stratification analyses according to sex, age, BMI, daily physical activity, FEV_1 and muscle force (handgrip, MIP and MEP) were conducted in order to study possible interactions, using the median as cut off point for continuous variables. Goodness of fit was assessed by means of normality of residuals, heteroscedasticity, linearity, collinearity and identification of influential data. Sensitivity analysis was conducted (i) using the cutoff point of 26 meters/yr as the clinically significant threshold of exercise capacity decline [E26], (ii) excluding subjects who participated in any pulmonary rehabilitation program during follow-up, and (iii) using a complete case analysis.

Data analysis was conducted using Stata 9.1 (StataCorp, College Station, TX, USA).

Table E1. Comparison between participants with repeated measures of exercise capacity and patients lost to follow-up.

	Participants (n=226)	Lost to follow up (n=91)	p
Sex: Males, n (%)	209 (9)	85 (93)	0.773
Age (years), mean ± SD	67.4 ± 8.3	67.9 ± 9.4	0.658
Smoking: current smoker, n (%)	78 (35)	35 (38)	0.507
YPAS index (score 0 to 137), median (P25-P75)	36 (23-53)	31 (18-49)	0.139
Co-morbidities: Charslon index ≥2, n (%)	115(51)	61 (67)	0.009
Charlson Co-morbidities, n (%)			
Myocardial infarction	19 (8)	12 (14)	0.163
Congestive heart failure	11 (5)	7 (8)	0.290
Peripheral vascular disease	20 (9)	14 (16)	0.071
Cerebrovascular disease	8 (4)	4 (5)	0.745
Connective tissue disease	3 (1)	3 (3)	0.355
Ulcer disease	23 (10)	14 (16)	0.137
Mild liver disease	13 (6)	6 (7)	0.722
Moderate or severe liver disease	1 (0.4)	2 (2)	
Diabetes	38 (17)	21 (24)	0.151
Hemiplegia	0	2 (2)	0.078
Moderate or severe renal disease	11(5)	8 (9)	0.159
Diabetes with end organ damage	3 (1)	3 (3)	0.355
Any malignancy	25 (11)	10 (11)	0.939
Cancer	0	0	
AIDS	0	0	
Self- reported comorbidities, n (%)			
Arthrosis or rheumatism	79 (35)	28 (31)	0.466
Paralysis	5 (2)	2 (2)	0.994
Chronic Back-Ache	49 (22)	15 (16)	0.289
Varices	56 (25)	23 (25)	0.943
Cataracts	61 (27)	24 (26)	0.911
Blindness	4 (2)	3 (3)	0.403
BMI kg/m^2, mean (SD)	28.2 ± 4.6	27.7 ± 4.8	0.307
FFMI kg/m^2, mean (SD)	19.8 ± 3.2	19.0 ± 2.7	0.063
Significant dyspnoea (mMRC ≥2), n (%)	95 (42)	48 (53)	0.083
PostBD FEV_1 (% pred), m ± SD	54 ± 17	49 ± 16	0.019
PostBD FEV_1/FVC (%), m ± SD	54 ± 12	52 ± 12	0.099
COPD severity, n (%)[#]			
I: Mild (FEV_1 ≥80%)	15 (7)	4 (4)	0.289
II: Moderate (FEV_1 ≥50%, <80%)	111 (49)	37 (41)	
III: Severe (FEV_1 ≥30%, <50%)	85 (37)	40 (44)	
IV: Very severe (FEV_1 <30%)	15 (7)	10 (11)	
RV (% pred) , mean ± SD	155.3 ± 46.6	157.6 ± 54.7	0.723
TLC (% pred) , mean ± SD	101.3 ± 17.8	100.3 ±20.0	0.674
RV/TLC (%), mean ± SD	55.1 ± 10.1	56.5 ± 10.1	0.298
DLco (% pred) , mean ± SD	66.5 ± 20.7	62.8 ± 19.9	0.189
PaO_2 (mmHg) , mean ± SD	74.9 ± 11.2	72.6 ± 9.4	0.094
Handgrip muscle force (Kg) , mean ± SD	31.3 ± 8.3	29.1 ± 8.1	0.043
Baseline 6MWD (meters)[¶], mean ± SD	444 ± 83	411 ± 107	0.066

Definition of abbreviations: mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced espiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= Residual Volume/Total Lung Capacity; DLCo= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension.

[#]According to the American Thoracic Society/European Respiratory Society criteria [E4]

[¶]The best of two six-minute walk distance tests separated by ≥30 min.

Table E2. Comparison between participants with repeated measures of six minute walk distance (6MWD) and subjects without repeated measures.

	Participants with repeated measures of 6MWD (n=226)	Subjects without repeated measures of 6MWD (n=25)	p
Sex: Males, n(%)	209 (92)	24 (96)	0.999
Age (years), mean ± SD	67.4 ± 8.3	72.5 ± 7.0	0.003
Smoking: current smoker, n (%)	78 (35)	7(28)	0.657
YPAS index (score 0 to 137), median (P25-P75)	36 (23-53)	29 (19–46)	0.260
Charslon index ≥2, n (%)	115(50.88)	18 (72)	0.045
Charslon Co-morbidities, n (%)			
Myocardial infarction	19 (8)	5 (29)	0.074
Congestive heart failure	11 (5)	3 (12)	0.152
Peripheral vascular disease	20 (9)	3 (12)	0.711
Cerebrovascular disease	8 (4)	0	1.000
Connective tissue disease	3 (1)	1 (4)	0.344
Ulcer disease	23 (10)	3 (12)	0.731
Mild liver disease	13 (6)	1 (4)	1.000
Moderate or severe liver disease	1 (0.4)	0	1.000
Diabetes	38 (17)	6 (24)	0.405
Hemiplegia	0	0	1.000
Moderate or severe renal disease	11(5)	2 (8)	0.625
Diabetes with end organ damage	3 (1)	1 (4)	0.344
Any malignancy	25 (11)	5 (20)	0.196
Cancer	0	0	
AIDS	0	0	
Self- reported comorbidities, n (%)			
Arthrosis or rheumatism	79 (35)	15 (60)	0.016
Paralysis	5 (2)	0	1.000
Chronic Back-Ache	49 (22)	9 (36)	0.133
Varices	56 (25)	5 (20)	0.806
Cataracts	61 (27)	11 (44)	0.074
Blindness	4 (2)	0	1.000
BMI (kg/m^2), mean ± SD	28.2 ± 4.6	29.5 ± 4.6	0.194
FFMI kg/m^2, mean ± SD	19.78 ± 3.2	20.6 ± 2.5	0.226
Significant dyspnoea (mMRC ≥2), n (%)	95 (42)	15 (60)	0.094
PostBD FEV_1 (% pred), m ± SD	54 ± 17	52 ± 12	0.648
PostBD FEV_1/FVC (%), m ± SD	54 ± 12	55 ± 11	0.798
COPD severity, n (%)[#]			
I: Mild (FEV_1 ≥80%)	15 (7)	0	0.379
II: Moderate (FEV_1 ≥50%, <80%)	111 (49)	16 (64)	
III: Severe (FEV_1 ≥30%, <50%)	85 (37)	7 (28)	
IV: Very severe (FEV_1 <30%)	15 (7)	2 (8)	
RV (% pred), m ± SD	155.3 ± 46.6	137.8 ± 38.6	0.083
TLC (% pred), m ± SD	101.3 ± 17.8	92.7 ± 17.0	0.027
RV/TLC (%), m ± SD	55.1 ± 10.1	55.7 ± 9.5	0.798
DLco (% pred),m ± SD	66.5 ± 20.7	61.2 ± 22.9	0.259
PaO_2 (mmHg), m ± SD	74.9 ± 11.2	74.6 ± 9.0	0.903
Handgrip muscle force (Kg), m ± SD	31.3 ± 8.3	28 ± 8.3	0.068
Baseline 6MWD (meters)[¶], mean ± SD	444 ± 83)	415 ± 98	0.251

Definition of abbreviations: mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced espiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= Residual Volume/Total Lung Capacity; DLCo= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension.

[#]According to the American Thoracic Society/European Respiratory Society criteria (E4)

[¶]The best of two six-minute walk distance tests separated by ≥30 min.

Table E3. Characteristics of study participants at baseline using complete cases and imputed datasets.

	All patients n=342	
	Complete cases[#]	Multiple imputation
Anthropometric and clinical data		
Males, n (%)	314 (92)	314 (92)
Age (years)	67.9 ± 8.57	67.9 ± 8.57
Current smokers	120 (35)	120 (35)
YPAS physical activity index (score 0 to 137)	34 (20-53)	34 (20-53)
SGRQ total score (0-100)	33 (23-47)	33 (23-48)
Charlson index ≥2	194 (57)	194 (57)
Body mass index (kg/m^2)	28.2 ± 4.7	28.2 ± 4.7
Fat free mass index (kg/m^2)	19.7 ± 3.0	19.7 ± 3.1
Significant dyspnoea (mMRC ≥2)	158 (46)	158 (46)
Lung function		
Postbronchodilator FEV_1 (% pred)	54 ± 16	54 ± 17
COPD severity		
Stage I: Mild (FEV_1 ≥80%)	19 (6)	19 (6)
Stage II: Moderate (FEV_1 ≥50%, <80%)	164 (48)	164 (48)
Stage III: Severe (FEV_1 ≥30%, <50%)	132 (38)	132 (38)
Stage IV: Very severe (FEV_1 <30%)	27 (8)	27 (8)
RV/TLC(%)	55.5 ± 10.1	55.9 ± 10.5
DLco (% pred)	65.2 ± 20.7	64.4 ± 22.7
PaO_2 (mmHg)	74.3 ± 10.6	74.4 ± 10.9
Exercise capacity and muscle force		
6MWD at baseline (meters)	435 ± 90	433 ± 93
6MWD at follow-up visit (meters)	407 ± 94	396 ± 99
Annual change in 6MWD (meters/year)	-20.4 ± 39.2	-21.9 ± 51.0
Patients with clinically significant annual decline of 6MWD (≥ 35m/year)	65 (29)	113 (33)
Handgrip muscle force (Kg)	30.5 ± 8.3	30.5 ± 8.5
MIP (% pred)	68 ± 25	68 ± 27
Pulmonary Rehabilitation during follow-up, n (%)	13 (5)	13 (5)[¶]
Follow up time (years)	1.70 ± 0.34	1.70 ± 0.34

Definition of abbreviations: YPAS= Yale physical activity survey; SGRQ= Saint George's respiratory questionnaire; mMRC = modified Medical Research Council dyspnoea scale; FEV_1= forced expiratory volume in 1 second; FEV_1/FVC= forced espiratory volume in 1 second/forced vital capacity; RV/TLC= residual volume/total lung Capacity; DLco= diffusing capacity for carbon monoxide; PaO_2= arterial oxygen tension; MIP=maximum inspiratory pressure.

[#]Some variables had missing values: Fourteen in physical activity index, 4 in quality of life, 13 in fat free mass index, 27 in RV/TLC, 46 in DLco, 11 in PaO_2, 33 in baseline 6MWD, 107 in 6MWD at follow-up visit, 116 for annual change in 6MWD and for clinically significant annual decline of 6MWD, in 13 in handgrip muscle force, 43 in MIP, 91 in pulmonary rehabilitation during follow-up.

[¶]Variable not imputed.

Table E4. Adjusted association between hospitalization rate and annual change in the six-minute walk distance in 342 COPD patients followed during 1.7 years (linear regression model), using complete cases and imputed datasets.

	Complete cases (n=226)		Multiple imputation (n=342)	
	Coefficient[¶] (95%CI)	**p**	**Coefficient[¶] (95%CI)**	**p**
Constant[#]	-6.4 (-14.5; 1.6)	0.117	-7.3 (-15.8; 1.2)	0.088
Hospitalization Rate:				
0 per year	*(reference)*		*(reference)*	
>0 and ≤1 per year	-13.6 (-26.7; -0.5)	0.042	-7.4 (-19.1; 4.3)	0.211
>1 per year	-34.2 (-49.3; -19.1)	<0.001	-26.1 (-38.6; -13.1)	<0.001
Significant dyspnoea (mMRC ≥2) at baseline	-15.3 (-26.6; -4.1)	0.008	-17.2 (-27.8; -6.6)	0.002
Age at baseline (years)	-0.7 (-1.4; 0.02)	0.058	-0.6 (-1.3; 0.01)	0.057
Sex (women)	-12.8 (-33.0; 6.9)	0.198	-11.1 (-30.2; 7.9)	0.249
Baseline Body Mass Index (Kg/m^2)	-0.6 (-1.8; 0.7)	0.631	-0.3 (-1.5; 0.9)	0.664
Baseline RV/TLC (%)	-0.5 (-1.0; 0.1)	0.079	-0.5 (-1.0; 0.04)	0.069
Baseline PaO_2 (mmHg)	0.1 (-0.2; 0.4)	0.586	0.1 (-0.2; 0.4)	0.692
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Adjusted R^2	*0.203*		*0.223*	

Definition of abbreviation: 95% CI = 95% confidence interval; mMRC = Modified Medical Research Council dyspnoea scale; RV/TLC= residual volume/total lung Capacity; PaO_2= arterial oxygen tension; 6MWD= six-minute walk distance.
[#]Adjusted mean value based on the linear regression equation corresponding to the mean change in 6-minutes walking distance in a subject with 0 COPD hospitalizations/year, mMRC<2, male, and mean age, Body Mass Index, RV/TLC, PaO_2 and mean baseline six-minute walk distance. Negative values represent decline.
[¶]Coefficients are expressed as changing meters of the six-minute walk distance per (i) each unit of the continuous covariates, or (ii) a change with respect to reference category in categorical covariates.

Figure E1. Flow chart of patients enrolled in the PAC-COPD study (patients at first evaluation) participating in the current analysis.

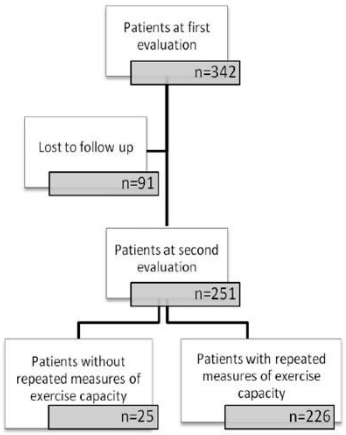
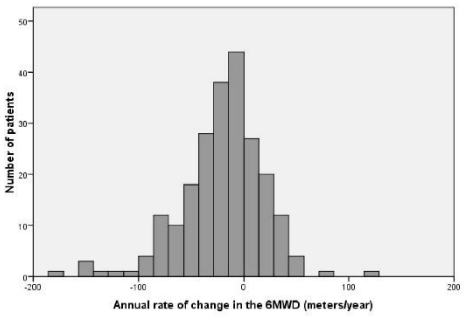


Figure E2. Distribution of annual 6MWD change in 342 COPD patients followed over 1.7 years.



Supplementary Material

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