INSPIRATORY CAPACITY-TO-TOTAL LUNG CAPACITY RATIO AND DYSPNOEA PREDICT EXERCISE CAPACITY DECLINE IN COPD

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SUMMARY AT A GLANCE

In clinically stable COPD patients, IC/TLC and dyspnoea, but not forced spirometric parameters, predict exercise capacity decline. This may help to screen candidates for early therapeutic interventions, including pulmonary rehabilitation.

ABSTRACT

Background and objective: Exercise capacity decline is a predictor of mortality in patients with chronic obstructive pulmonary disease (COPD). Static pulmonary hyperinflation is a key determinant of exercise performance, but its effect on the longitudinal decline in exercise capacity remains unknown. We aimed to study the relationship between the inspiratory capacity-to-total lung capacity (IC/TLC) ratio and exercise capacity decline in COPD.

Methods: We measured IC/TLC and other relevant clinical and functional variables in 342 clinically stable COPD patients. The 6-minute walk distance (6MWD) was determined at recruitment and after a mean$\pm$SD of 1.7$\pm$0.3 years. The annual rate of change in 6MWD was calculated. Multiple imputation to account for losses during follow-up was implemented and multivariate regression was used to analyse predictive factors of 6MWD decline.

Results: Mean decline rate in the 6MWD was 21.9$\pm$34.1m/y. In the bivariate analysis, patients with lower levels of IC/TLC had greater 6MWD decline (-27.4$\pm$42.5, -24.9$\pm$36.5 and -13.4$\pm$39.9 m/year in the 1st, 2nd and 3rd tertile of IC/TLC, respectively; p-for-trend=0.018). From other potential risk factors considered, dyspnoea, health status, serum C-reactive protein and Borg dyspnoea score at the end of the exercise test were related to exercise capacity decline. In the multivariate regression model, only IC/TLC (β= 0.7m/y per each percentage unit of IC/TLC; p=0.007) and dyspnoea (mMRC$\geq$2) (β=-14.6m/y; p=0.013) were associated with the annual rate of 6MWD change.

Conclusions: IC/TLC and dyspnoea in clinically stable COPD patients predict their exercise capacity decline and may help to guide early therapeutic interventions.

SHORT TITLE: IC/TLC and dyspnoea predict 6MWD decline.

LIST OF ABBREVIATIONS

BMI: body mass index

COPD: chronic obstructive pulmonary disease

DL_{CO}: diffusing capacity for carbon monoxide

FEV_1: forced expiratory volume in 1s

GOLD: Global Initiative for Chronic Obstructive Lung Disease

IC: inspiratory capacity

MEP: maximum expiratory pressures

MIP: maximum inspiratory pressures

mMRC: Modified Medical Research Council dyspnoea scale

PaO_2: arterial oxygen tension

RV: residual volume

SGRQ: Saint George's respiratory questionnaire

TLC: total lung capacity

6MWT: 6-minute walk test

6MWD: 6-minute walk distance

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) frequently suffer a limitation of their exercise capacity,[1] which is multifactorial and results from complex interactions between physical, both pulmonary and non-pulmonary, and psychological factors.[2–4] Exercise capacity limitation worsens health status and reduces survival.[5,6] Furthermore, exercise capacity often declines over time.[7–10] This decline appears to be independent of longitudinal changes in airflow limitation[9,10] and it is a strong predictor of mortality.[8–10] Finally, exercise capacity decline can be prevented with therapeutic strategies including pulmonary rehabilitation.[11] Therefore, it is important to identify what factors are associated with exercise capacity decline in COPD.

To date, only a few studies have investigated risk factors associated with exercise capacity decline in COPD, mainly using the 6-minute walk test (6MWT) as an index of exercise capacity.[7,12,13] These studies identified that older age,[4] lower body mass index (BMI),[4] more severe airflow limitation (FEV_1)[4,7,12] and a lower level of regular physical activity[12] were related to exercise capacity deterioration. However, these previous studies[7,12,13] suffered from varying proportions of losses during follow-up, which conditions their results to a certain degree of bias due to selective attrition.[14] Nowadays statistical methods are available to account for missing values during follow-up, thus increasing the accuracy of estimated statistical associations.[15]

Moreover, the relationship between lung hyperinflation, a variable contributing to dyspnoea, morbidity and mortality in COPD,[16–18] and exercise capacity decline has not

been reported in any of the of the abovementioned studies.[7,12,13] Inspiratory capacity-to-total lung capacity (IC/TLC) ratio, a static hyperinflation-derived variable reflecting the mechanical inspiratory constraint, has been shown to be an important predictor of exercise performance in cross-sectional studies[16,19–21]. Therefore, IC/TLC might be a determinant of exercise capacity deterioration in COPD.

We hypothesised that IC/TLC can be a predictor of the decline in exercise capacity in COPD patients and tested this contention in 342 COPD patients prospectively followed-up in the "Phenotype and Course of COPD (PAC-COPD)" Study.[22]

METHODS

Study design and participants

Subjects were recruited during their first hospitalisation 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.[23] 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[24] 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 reported elsewhere.[25] The Clinical Research Ethical Committee of each centre approved the study and written informed consent was obtained from all participants.

Measurements

Exercise capacity was assessed by the 6MWT.[26] 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)[27] were collected before and at the end of each exercise test.

At baseline, while on stable conditions, patients also underwent complete lung function tests (forced spirometry, plethysmographic lung volumes, diffusing capacity for carbon monoxide (DLco) and arterial blood gases). Static lung hyperinflation was considered as any value of TLC above 120% of predicted.[28] IC/TLC was taken as an index of inspiratory constraint derived from static hyperinflation of the lung.[17] For analysis, disease severity was classified according to the American Thoracic Society and European Respiratory Society (ATS/ERS) criteria.[29]

Patients also answered a questionnaire that included socio-demographic data, smoking, physical activity, dyspnoea (modified Medical Research Council), comorbidities, health status (St George's Respiratory Questionnaire), anxiety and depression. Information on concomitant medications use, continuous long-term oxygen therapy, participation in pulmonary rehabilitation programmes and exacerbations in the previous year (defined as a worsening of the patient's respiratory symptoms that required a change in medication)[30] was obtained from medical records. Data on body mass index (BMI), fat free mass index, airway inflammatory markers, serum levels of C-reactive protein and tumour necrosis factor-α, cardiac function by Doppler echocardiography, emphysema quantification by High-Resolution Computed Tomography (HRCT), maximum inspiratory and expiratory pressures (MIP and MEP, respectively) and handgrip muscle force were collected at baseline following standardised methodology. Detailed information about the methods, questionnaires, standardisation of the tests, and fieldwork supervision has been previously reported.[23]

Statistical analysis

Sample size power estimation is detailed in the Online Supplement.

To account for selective attrition and missing values, we used multiple imputation (20 times) through chained equations.[15] By performing these analyses all data from 342 PAC-COPD patients were included. Characteristics of study participants using complete cases and imputed datasets have been previously reported.[25]

IC/TLC, as a continuous variable or categorized in tertiles, was selected a priori as the main exposure variable. The bivariate association between IC/TLC, 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 by 10%) the coefficient of 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[31], we stratified the models according to BMI. Additional analyses using residual 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 reported to be associated with 6MWD decline.[7,12,13] Analysis was conducted using Stata 12.1 (StataCorp, College Station, TX, USA).

RESULTS

Table 1 shows the main clinical and functional characteristics of the 342 study participants at baseline. Patients were mostly male (92%) with a mean±SD age of 67.9±8.6 years. Airflow limitation was moderate to severe in the majority of patients (mean post-bronchodilator FEV_1 was 54±17% of predicted) but there was significant variability. Static hyperinflation was present in 67 (20%) patients. Thirteen (5%) patients were enrolled in pulmonary rehabilitation programs, 8 (2%) were on continuous long-term oxygen therapy, and 120 (35%) on chronic inhaled steroids.

Subjects were followed-up for a mean±SD of 1.7±0.34 years. The mean±SD 6MWD was 433±93 m at baseline and 396±99 m at the second evaluation. Mean change in 6MWD was -21.9±34.1 m/year.

In the bivariate analysis, patients with higher levels of static hyperinflation (i.e., low IC/TLC) had greater 6MWD decline (-27.4±42.5, -24.9±36.5 and -13.4±39.9 m/year in the 1st, 2nd and 3rd tertile of IC/TLC, respectively; p-for-trend=0.018). From other potential risk factors considered, dyspnoea, health status, serum C-reactive protein and Borg dyspnoea score at the end of the exercise test were related to exercise capacity decline in the bivariate analyses (Figure 1). Other potential determinants did not relate to 6MWD decline (Figures S1, S2 and S3 in the Online Supplementary Information). FEV_1 was not associated with exercise capacity decline neither as a continuous nor as a categorical variable.

In the multivariate regression model (Table 2), only IC/TLC ratio and dyspnoea remained statistically significantly associated with the 6MWD decline, after adjusting for baseline 6MWD. The adjusted predicted change in 6MWD (and 95% confidence interval) was plotted against IC/TLC ratio (Figure 2), and shows that the lower the baseline IC/TLC ratio, the greater the longitudinal decline in exercise capacity in a linear dose-response shape.

Additional analyses using RV/TLC as a marker of air trapping (Table S1 in Online Supplement), stratification according to BMI (Table S2 in Online Supplement), as well as sensitivity analyses (Table S3, S4, S5 and S6 in Online Supplement) yielded very similar results. Linear regression goodness of fit tests did not reveal any abnormality.

DISCUSSION

Our study shows that IC/TLC and dyspnoea are associated with 6MWD decline in moderate-to-severe clinically stable COPD patients. However, other variables traditionally considered of clinical relevance in this setting, such as age, BMI or severity of airflow limitation (FEV_1), did not influence 6MWD decline in this population once adjusted for selective attrition.

Previous studies

Three previous studies have investigated factors related to 6MWD decline in COPD.[7,12,13] Spruit et al.[13] reported in the ECLIPSE cohort that age, BMI and GOLD grades of airflow limitation were significantly related (after adjustment) with exercise capacity deterioration. In the Bergen COPD cohort, Frisk et al.[12] found that airflow limitation severity and self-reported physical activity predicted changes in 6MWD in a multivariate regression model. Finally, Casanova et al.,[7] using data from the BODE cohort, found that 6MWD declined significantly in patients with FEV_1 lower than 50% of predicted, although the association was not adjusted for potentially relevant confounders. None of these studies tested the role of pulmonary function tests other than forced spirometry (i.e., lung volumes or CO diffusing capacity), systemic inflammation, cardiac function, skeletal muscle force and/or concomitant treatments, among others.

A novel finding of our study is that IC/TLC predicts exercise capacity decline. Lung hyperinflation is frequently observed in patients with COPD. It has potentially negative

pulmonary and cardiovascular consequences[32] and is a powerful predictor of mortality in these patients[17]. We add to this knowledge by showing that COPD patients with lower IC/TLC experience a higher longitudinal decline in 6MWD. This is in agreement with previous experimental research that demonstrated that a low IC/TLC predisposes to critical mechanical constraints on tidal volume expansion as ventilatory requirements increase, which in turn results in reduced exercise capacity.[16,33]

Secondly, we found that exertional dyspnoea, a cardinal symptom of patients with COPD,[30] was also related to the decline in exercise capacity, independently of static hyperinflation. A strong association between dyspnoea and exercise capacity has been reported in previous cross-sectional studies.[34] Also some interventions, such as pulmonary rehabilitation, result in an improvement of both parameters.[1] Then, it is plausible that those COPD patients with worse baseline dyspnoea in our study showed a greater decline in exercise capacity.

At variance with previous studies, we did not observe an association between baseline FEV_1 and exercise capacity decline. Some explanations can be conceived to interpret this discrepancy including: 1) Differences in patients' characteristics among studies. Our COPD patients walked somewhat more at baseline than those from the ECLIPSE and the BODE cohort (mean 369m and 388m respectively) and had lower airflow limitation than participants in the BODE cohort (mean FEV_1=39% predicted). This fact could have lead to the detection of different determinants of exercise capacity decline. 2) Failure to consider patients lost to follow up in the analysis of previous studies. Between 16% and 45% of patients were lost to follow up in these previous studies and

they were not included in the analysis. Because patients lost to follow up in longitudinal studies usually have poorer health status and lower FEV_1 values (as also observed in our PAC-COPD cohort), not including them in the analysis may lead to biased results (usually called survival bias).[14] Among the several statistical techniques to deal with survival bias, we used multiple imputation.[15] For didactic purposes, we repeated our analysis with a complete case approach (Figure S4), which resulted in an *spurious* association between FEV_1 and 6MWD decline. Therefore, consideration of patients lost to follow up in longitudinal analyses using appropriate statistical techniques not only prevents missing relevant information, but, most importantly, reduces bias which increases the validity of the estimates.[35]

Also, at difference with Spruit *et al.,*[13] BMI did not play a role in the 6MWD annual decline in our study patients. This may be partly due to the lack of variability in BMI in our COPD study group, preventing us to detect possible association or interactions with exercise capacity decline. Also, the lack of association between 6MWD decline and participation in pulmonary rehabilitation is likely explained by the reduced number of patients enrolled in such programmes in our study sample (n=13).

Clinical implications

Timed walking tests, and specially the 6MWD, have been extensively used in the clinical evaluation of patients with COPD, mainly because of their simplicity, reliability and safety. At present, it is recognized that this test adds useful information for the clinical staging of patients (e.g., the BODE index[36]). Moreover, longitudinal changes in the 6MWD are strong predictors of mortality.[8–10] It is therefore important to identify

factors associated with this decline in exercise capacity in order to better tailor potential therapeutic interventions, such as pulmonary rehabilitation, that can modify this course. The 2013 ATS/ERS Task Force statement on pulmonary rehabilitation highlights that any individual with chronic respiratory disease could be referred to a pulmonary rehabilitation programme.[1] However, in real life such programmes are not accessible to many COPD patients from around the world due to the cost-constraint situation in many healthcare systems. Our group previously reported that hospital admissions, frequently observed in COPD patients during the course of their disease, may accelerate the decline of exercise capacity in these patients,[25] suggesting that patients admitted to a hospital are potential candidates to benefit the most from pulmonary rehabilitation. Our current analysis extends these previous observations and shows that the assessment of clinically stable COPD patients might help clinicians to predict future changes in exercise capacity. We propose that severe dyspnoea and IC/TLC, because of their association with exercise capacity decline, could be used as indicators to prioritise candidates for pulmonary rehabilitation.

Finally, our results might also help to identify those COPD patients who could benefit most from treatments that enable to increase tidal volume during activities, including some drugs and lung volume reduction strategies, thus reducing exertional dyspnoea and interrupting the vicious cycle of worsening exercise capacity.[37]

Strengths and limitations

The consideration of static volumes and other relevant clinical and functional variables not covered in previous research is a clear strength of our study. Likewise, the large

cohort of COPD patients (all recruited at the same disease evolution stage) with wide spectrum of disease severity is another strength. Finally, we used multiple imputations to account for selective attrition and missing values, as missing data could have introduced bias in our estimates.[14] Some limitations of our study, however, should also be noted and discussed. First, even though the PAC-COPD study had no exclusion criteria in relation to sex, few women were included, so we cannot generalise the results to both sexes. Also, since patients were recruited at their first hospitalisation they may not represent the COPD population at large. Finally, only two evaluations were performed during the study period and the time span between them was relatively short (1.7 y).

Conclusions

IC/TLC and dyspnoea in clinically stable COPD patients predict their exercise capacity decline and may help to guide early therapeutic interventions.

ACKNOWLEDGEMENTS

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Table 1. Characteristics of study participants.

|	All patients* n=342
Anthropometric and clinical data	
Males	314 (92)
Age (years)	67.9 ± 8.6
Current smokers	120 (35)
Active workers	61 (18)
YPAS physical activity index (score 0 to 137)	34 (20-53)
SGRQ total score (0 to100)	33 (23-48)
Charlson index $\geq$2, n (%)	194 (57)
Body mass index (kg/m^2)	28.2 ± 4.7
Fat free mass index (kg/m^2)	19.7 ± 3.1
mMRC dyspnoea score (0 to 4)	2 (2-3)
Exacerbation in previous year >1[†]	141 (41)
Inflammatory markers	
Interleukin-6 (pg/ml)	128 (43-259)
C-reactive protein (mg/l)	3.8 (1.7-7.1)
Tumour necrosis factor-α (pg/l)	2.1 (0.5-10.2)
Pulmonary function and blood gases	
Postbronchodilator FEV_1 (% pred)	54.4 ± 17.2
Airflow limitation severity[‡]	
Mild ($FEV_1 \geq$80%)	19 (6)
Moderate ($FEV_1 \geq$50%, <80%)	164 (48)
Severe ($FEV_1 \geq$30%, <50%)	132 (38)
Very severe (FEV_1 <30%)	27 (8)
IC (% pred)	67.3 ± 20.2
IC/TLC (%)	30.9 ± 9.8
TLC (% pred)	100.4 ± 18.4
RV/TLC (%)	$55.9 + 10.5$
DLco (% pred)	64.4 ± 22.7
PaO_2 (mmHg)	74.4 ± 10.9
Cardiac function	
Left Ventricle Ejection Fraction (%)	59.0 ± 8.9
Transtricuspid regurgitant velocity (m/sec)	2.4 ± 0.9
Right ventricle-Mid end-diastolic diameter (mm)	31.6 ± 4.5
Muscle force and Exercise capacity	
Respiratory muscle force (MIP, %)	68 ± 27
Peripheral muscle force (hand-grip, Kg)	30.5 ± 8.5
6MWD at baseline (meters)	433 ± 93
6MWD at follow-up visit (meters)	396 ± 99
Annual change in 6MWD (meters/year)	-21.9 ± 34.1

Data are presented as n (%), mean$\pm$SD or median (P_{25}-P_{75}). 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; IC: inspiratory capacity; IC/TLC: inspiratory capacity/total lung capacity; TLC: total lung capacity; RV/TLC: residual volume/total lung capacity; DLco: diffusing capacity for carbon monoxide; PaO_2: arterial oxygen tension; MIP: maximum inspiratory pressure; 6MWD: 6-minute walk distance. *: Descriptive analyses conducted using imputed datasets where existing missing data. Characteristics of study participants at baseline using complete cases and imputed datasets have been previously reported[25]. †: All patients had at least one exacerbation in the previous year, as they were recruited during their first COPD admission. ‡: According to the criteria of the ATS/ERS. [29]

Table 2. Adjusted predictive factors of exercise capacity decline in 342 COPD patients

followed up for 1.7 years.

	All patients (n=342)	
	Coefficient[†] (95%CI)	p
Constant*	-14.3 (-21.8; -6.7)	<0.001
Baseline IC/TLC (%)	0.7 (0.2; 1.2)	0.007
Significant dyspnoea (mMRC≥2) at baseline	-14.6 (-26.2; -3.1)	0.013
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001
Adjusted R²	*0.137*	

95% CI: 95% confidence interval; mMRC: Modified Medical Research Council dyspnoea scale; 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 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.

Figure 1. Factors associated to the annual change in 6-minute walk distance (6MWD) in 342 COPD patients.
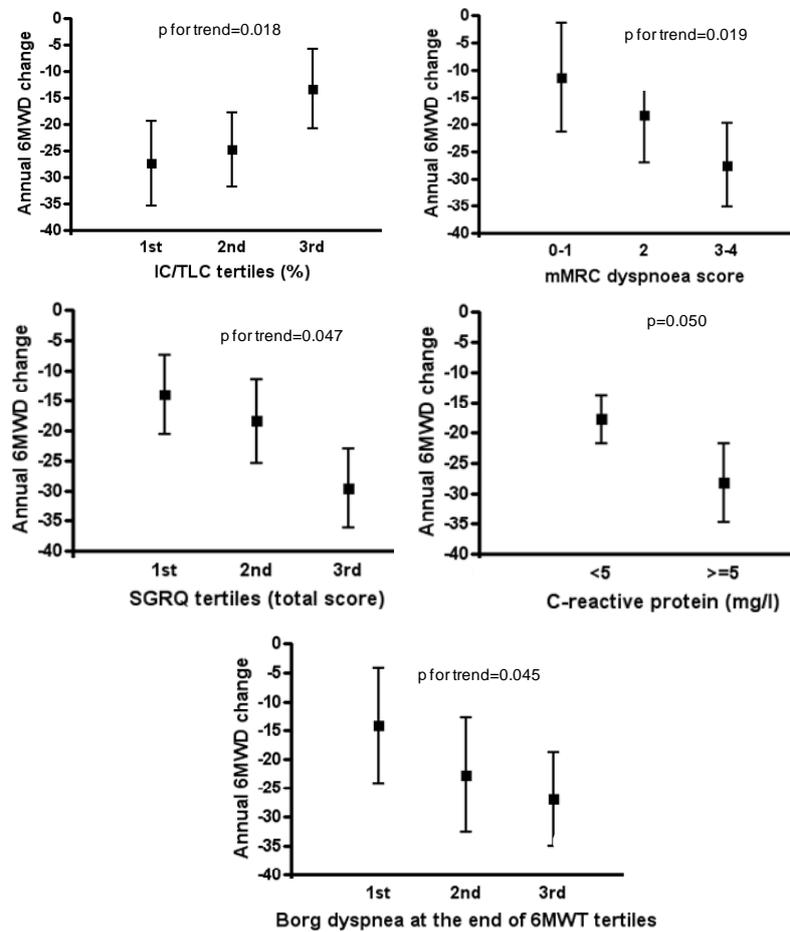
 Data are presented as mean and 95% confidence intervals. Change in 6-minute walk distance is shown in meters/year. Negative values represent decline. 6MWD: 6-minute walk distance; IC/TLC: inspiratory capacity/total lung capacity; mMRC: Modified Medical Research Council dyspnoea scale; SGRQ: Saint George's respiratory questionnaire; 6MWT: 6-minute walk test.

Figure 2. Mean (and 95% confidence intervals) annual decline in 6MWD according to IC/TLC. From a linear regression model with IC/TLC as a continuous variable, and adjusted for dyspnoea, quality of life, C-reactive protein, and baseline 6MWD.
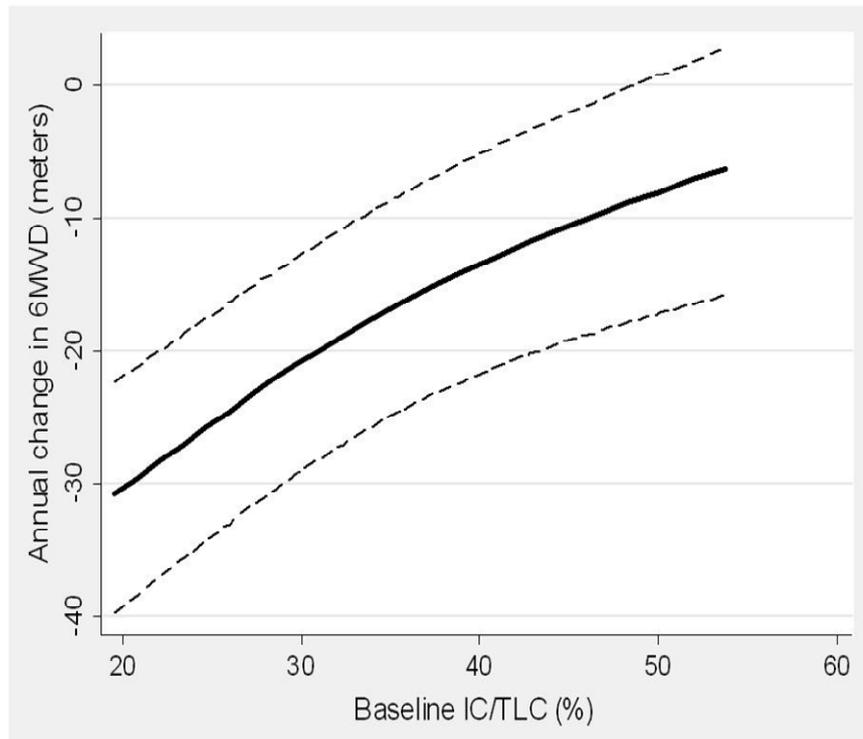
INSPIRATORY CAPACITY-TO-TOTAL LUNG CAPACITY RATIO AND DYSPNOEA PREDICT EXERCISE CAPACITY DECLINE IN COPD

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- **Methods – Complete version**
- **Table S1.** Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed up for 1.7 years (linear regression model), <u>using RV/TLC as a marker of air trapping.</u>
- **Table S2.** Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), <u>according to baseline BMI.</u>
- **Table S3.** Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), <u>using complete cases and imputed datasets.</u>
- **Table S4.** Adjusted predictive factors of <u>exercise capacity decline expressed in absolute values and as percentage with respect to baseline</u> level in 342 COPD patients followed during 1.7 years (linear regression model).
- **Table S5.** Adjusted predictive factors of exercise capacity decline in 342 COPD patients followed during 1.7 years (linear regression model), <u>excluding patients enrolled in pulmonary rehabilitation programs.</u>

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.

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

	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 $\geq$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), <u>according to baseline BMI</u>.

	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), <u>using complete cases and imputed datasets.</u>

	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 R²	*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 <u>exercise capacity decline expressed in absolute values and as percentage with respect to baseline</u> 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 R²	*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), <u>excluding patients enrolled in pulmonary rehabilitation programs</u>.

	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 R²	*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.

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

	Original model		Model after forcing variables previously related to 6MWD decline	
	(n=342)		(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 $\geq$2) at baseline	-14.6 (-26.2; -3.1)	0.013	-13.8 (-25.3; -2.3)	0.019
SGRQ at baseline	-0.1 (-0.5; 0.3)	0.691	-0.2 (-0.6; 0.2)	0.361
C-reactive protein at baseline (mg/l)	-0.4 (-2.8; 2.1)	0.777	-0.3 (-2.8; 2.2)	0.826
Borg dyspnoea at the end of 6MWT	-0.8 (-2.9; 1.3)	0.457	-0.7 (-2.9; 1.6)	0.560
Baseline 6MWD (meters)	-0.2 (-0.3; -0.1)	<0.001	-0.2 (-0.3; -0.1)	<0.001
Age at baseline	--	--	-0.7 (-1.4; -0.1)	0.037
Body Mass Index (Kg/m^2)	--	--	-0.3 (-1.5; 0.9)	0.657
FEV$_1$ (% pred)	--	--	0.1 (-0.6; 0.5)	0.515
YPAS physical activity index	--	--	-0.1 (-0.3; 0.1)	0.303
Adjusted R^2	*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.

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.

Figure S4. Relationship between airflow limitation (FEV$_1$) and the annual change in 6-minute walk distance (6MWD) in 342 COPD patients, using complete case and multiple imputations strategies.

Data are presented as mean and 95% coefficient intervals.
Definition of abbreviations: FEV$_1$= forced espiratory volume in 1 second; 6MWD= 6-minute walk distance.

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