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SEVERITY GRADING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE CONFOUNDING EFFECT OF PHENOTYPE AND THORACIC GAS COMPRESSION

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ABSTRACT

Current guidelines recommend severity of chronic obstructive pulmonary disease be graded using forced expiratory volume in 1 s (FEV_1). But this measurements is biased by thoracic gas compression depending on lung volume and airflow resistance. The aim of this study was to test the hypothesis that the effect of thoracic gas compression on FEV_1 is greater in emphysema than chronic bronchitis due to larger lung volumes and this influences severity classification and prognosis. FEV_1 was simultaneously measured by spirometry and body plethysmography ($FEV_{1\text{-}pl}$) in 47 subjects with dominant emphysema and 51 with dominant chronic bronchitis. Subjects with dominant emphysema had larger lung volumes, lower diffusion capacity and lower FEV_1 than those with dominant chronic bronchitis. However, $FEV_{1\text{-}pl}$, patient-centered variables (dyspnea, quality of life, exercise tolerance, exacerbation frequency), arterial blood gases, and respiratory impedance were not significantly different between groups. Using $FEV_{1\text{-}pl}$ instead of FEV_1 shifted severity distribution towards less severe classes in dominant emphysema more than chronic bronchitis. The Body mass, Obstruction, Dyspnea, and Exercise (BODE) index was significantly higher in dominant emphysema than chronic bronchitis but this difference significantly decreased when $FEV_{1\text{-}pl}$ was substituted for FEV_1. In conclusion, the FEV_1 is biased by thoracic gas compression more in subjects with dominant emphysema than in those with chronic bronchitis. This variably and significantly affects the severity grading systems currently recommended.

INTRODUCTION

Ever since the pioneering work of Tiffeneau (34), the forced expiratory volume in 1 s (FEV_1) has been used as the key measurement of lung function for both diagnosis and severity assessment of obstructive lung disorders. The underlying rationale is grounded on the concept that maximal expiratory flow and thus the FEV_1 decreases in disease and this is the result of a variable combinations of decrease in lung elastic recoil, decrease in airway size at choke point, increase in resistance upstream from the flow limiting segment, and increased airway collapsibility downstream from this segment (17). However, this analysis does not consider that during forced expiration thoracic gas is compressed because the expiratory pressure is well in excess to that necessary to generate maximal flow (17). As a result of the large effort, lung volume and thus recoil will decrease. This will cause a decrease of driving pressure and transmural pressure at choke point, which can explain why the FEV_1 is systematically less than that measured in body plethysmograph ($FEV_{1\text{-}pl}$) by the amount of thoracic gas compression volume (TGCV) (21). Confirmatory evidence for this has been brought by Krowka et al. by showing that with decreasing expiratory effort TGCV to a minimal value the FEV_1 becomes similar to $FEV_{1\text{-}pl}$ (21). In addition to the expiratory effort, airflow resistance and absolute lung volume crucially contribute to increase TGCV (17, 18), and thus the difference between $FEV_{1\text{-}pl}$ and FEV_1 (32, 33).

Current international guidelines and strategy documents (9, 10, 26, 29, 31, 35) recommend severity of chronic obstructive pulmonary disease (COPD) be graded by the FEV_1 reduction below predicted values, irrespective of the underlying mechanisms. This is justified by the fact that expiratory flow limitation in COPD may be equally due to intrinsic airway narrowing, the characteristic feature of chronic bronchitis, or reduced lung elastic recoil, the characteristic feature of emphysema (6). However, emphysema is also characterized by an increase in absolute lung volume, thus exposing a larger amount of thoracic gas to compression during a forced expiratory maneuver. Therefore, it can be hypothesized that, for a given airway

resistance, the FEV_1 overestimates the magnitude of airflow limitation in subjects with dominant emphysema compared with those with dominant bronchitis and this may confound severity classification and prognosis (9, 10, 26, 29, 31, 35).

This study was designed to test this hypothesis by comparing FEV_1 and compression-free FEV_1 measured in a body plethysmograph ($FEV_{1\text{-}pl}$) with absolute lung volumes, respiratory impedance, diffusion capacity, arterial gas tensions, dyspnea, quality of life, exercise performance, and exacerbations rate in two groups of COPD subjects with either dominant emphysema or chronic bronchitis. The impact of thoracic gas compression on different severity classification systems was estimated by substituting $FEV_{1\text{-}pl}$ for FEV_1.

METHODS

Subjects

The study included 98 subjects with a clinical diagnosis of COPD (31) and not completely reversible airflow obstruction documented by a post-bronchodilator FEV_1 to vital capacity (VC) ratio (FEV_1/VC) below the lower limit of normality and total lung capacity within or above the limits of normality (27). Severity of disease was graded using the criteria proposed by the Global Initiative for Obstructive Lung Disease (GOLD) in 2007 (31) and 2013 (35), and the Body mass index, Obstruction, Dyspnea, and Exercise capacity (BODE) index (8).

All subjects were required to be in stable clinical conditions and not to have suffered from respiratory exacerbations in the previous four weeks. Subjects with a history suggestive of bronchial asthma were excluded. Prior to each study session, long-acting β_2-agonists (salmeterol or formoterol) were suspended for at least 12 h and tiotropium for 24 h. No subject was taking indacaterol or muscarinic antagonists other than tiotropium. The study protocol was approved by the S. Luigi Hospital Ethics Committee (Orbassano, Torino) (number 103, 23-06-2006) and written informed consent was obtained from each subject prior to the study.

Study design

On a pre-study day, subjects underwent clinical examination, evaluation for inclusion and exclusion criteria, and assessment of clinical stability.

On a first study day, a 3-mL arterial blood sample was drawn for PaO_2 and $PaCO_2$ measurements (ABL 520, Radiometer, Copenhagen, Denmark). Then, Medical Research Council (MRC) questionnaire for dyspnea and Saint George's Respiratory Questionnaire (SGRQ) were administered. A chest X-ray with posterior-anterior and right-left projections was taken if not available over the previous 6 months. Exacerbations were defined according to Vestbo et al. (35) and their number recorded over the last two years.

On a second study day, the patients underwent full lung function examination. Spirometry and absolute lung volumes were obtained with the subjects sitting in a body plethysmograph (Autobox, SensorMedics Inc., CA, USA). After at least four regular breaths, thoracic gas volume was measured with the subject panting against a closed shutter at a frequency slightly <1 Hz with his/her cheeks supported by hands. Then, the shutter was opened and the subject took a full deep breath to total lung capacity (TLC) before forcefully expiring to residual volume (RV) for at least 6 s. This maneuver allowed calculating functional residual capacity (FRC) from thoracic gas volume corrected for any difference between the volume at which the shutter was closed and the average end-expiratory tidal volume of the four preceding regular breaths, TLC, RV, vital capacity (VC), and FEV_1. Compression-free FEV_1 was simultaneously obtained by plotting mouth flow against change in plethysmographic volume to measure $FEV_{1\text{-pl}}$ (Figure 1). Three sets of technically acceptable maneuvers were obtained and appropriately selected values (24, 36) were retained for analysis. Respiratory impedance was measured by a forced-oscillation technique (FOT) previously described (12, 15). Sinusoidal pressure oscillations (5-Hz, ~ 2-cmH_2O peak-to-peak) were generated by a loudspeaker with a diameter of 16-cm (model CW161N, Ciare, Italy) and applied at the mouth. The loudspeaker was mounted in a rigid plastic box and connected in parallel to a mesh pneumotachograph and mouthpiece on one side and to a low-resistance high-inertance tube (overall

load at tidal breathing frequency, 0.98 cm $H_2O \cdot L \cdot s^{-1}$) on the other side. Airway opening pressure and flow were measured by piezoresistive transducers (DCXL10DS and DCXL01DS Sensortechnics, Germany, respectively) and sampled at 200 Hz. A 15-$L \cdot min^{-1}$ bias flow of air generated by an air pump (CMP08, 3A Health Care, Italy) was used to reduce dead space to about 35 mL. Respiratory resistance and reactance were computed by a least squares algorithm (19, 20) at 5 Hz (R_5 and X_5, respectively) and 19 Hz (R_{19} and X_{19}, respectively). Artifacts due to glottis closure or expiratory airflow limitation were avoided by discarding breaths showing any of the following: i) tidal volume <0.1 L or >2.0 L, ii) difference between measured flow oscillation and ideal sine wave with the same Fourier coefficients >0.2 (23), and iii) ratio of minimum to average X>3.5 (14). Measurements were taken during two sets of maneuvers, each consisting of 2-min tidal breathing on which mean R_5, R_{19}, $R_{5\text{-}19}$, and X_5 were retained for analysis. Of the main function parameters of the FOT, R_5 was taken as an index of overall airflow resistance of the respiratory system, R_{19} as an index of central airways resistance, $R_{5\text{-}19}$ as an index of serial or peripheral heterogeneous ventilation and X_5 as an index of capacitative component of the respiratory system. Tidal volume (V_T), breathing frequency (BF), and minute ventilation ($\dot{V}_E$) were averaged over the same tidal breaths used for FOT data collection. Single-breath D_LCO was measured following the recommendation of the American Thoracic Society and European Respiratory Society (22) and 6MWD according to ATS guidelines (3).

Predicted values for the spirometry and lung volumes were from Quanjer et al. (30). To estimate predicted $FEV_{1\text{-}pl}$, the predicted FEV_1 was increased by 4.5%. This was the difference between $FEV_{1\text{-}pl}$ and FEV_1 observed in a group of 81 healthy subjects (31 females and 50 males, aged 46±12 yr., with a BMI of 24±3 $kg \cdot m^{-2}$), independent of anthropometric data. Predicted values for D_LCO were from Cotes et al. (11) and those of 6MWD from the ATS guidelines (3).

Data analysis

At the end of studies, subjects were grouped depending on dominant phenotype, i.e., chronic bronchitis or emphysema (Table 1), based on the clinical and radiological score (CRS) proposed by Pistolesi et al. (28) This score was obtained by a multivariate model with the following independent variables: sputum purulence, adventitious chest sounds, chest hyperresonance, FEV_1/VC, and radiographic signs of increased vascular markings, bronchial wall thickening, reduced lung density, increased lung volume. A score >0.56 was taken as suggestive of dominant emphysema and ≤0.56 of dominant chronic bronchitis (28).

Differences in baseline characteristics between groups were assessed for statistical significance by unpaired t-test. Between-within group data were tested by a mixed repeated-measure ANOVA. Categorical data were compared by Fischer exact test with Freeman-Halton's extension for 2x4 contingency tables when appropriate. Values of $p<0.05$ were considered statistically significant. Data are presented as mean ± standard deviation. Statistical analyses were done by StatSoft Statistica and VassarStats website packages.

RESULTS

The two groups were well matched for anthropometric characteristics except than for body mass index (BMI), which was slightly lower in dominant-emphysema group (Table 1). Subjects with dominant emphysema had significantly lower D_LCO, D_LCO/V_A, and FEV_1 and significantly larger TLC, FRC and RV than subjects with dominant chronic bronchitis (Table 1). However, neither $FEV_{1\text{-pl}}$ nor FVC, nor impedance components, i.e., respiratory resistance and reactance, were significantly different between groups either before or after albuterol administration (Table 2). Analysis of the main quality control indexes such as back-extrapolation volume, time to peak flow, and tidal breathing pattern, viz., breathing frequency and minute ventilation ($\dot{V}_E$) did not reveal significant differences between groups (Table 3). Moreover, there were no significant differences between groups concerning arterial blood gases, degree of dyspnea (MRC score), quality of life (SGRQ), physical performance (6MWD), and number of

exacerbations per year (Table 4). Post- bronchodilator $FEV_{1\text{-}pl}$ was significantly larger than FEV_1 ($p<0.0001$) in both groups, but this difference was significantly larger in dominant emphysema than chronic bronchitis group ($p=0.0026$). Consistent with these data, post-bronchodilator $FEV_{1\text{-}pl}$ was not significantly different between dominant emphysema and chronic bronchitis groups (Table 2 and Figure 2).

Grading the severity of disease using old GOLD score by FEV_1 led to a significant ($p=0.0115$) excess of III-IV classes in dominant emphysema compared with chronic bronchitis group (Figure 3). By using $FEV_{1\text{-}pl}$ the class distribution was not significantly different between groups ($p=0.3162$) and the proportion of subjects shifting from III-IV to I-II classes was significantly ($p=0.0348$) larger in dominant emphysema (16 out of 47) than chronic bronchitis (8 out of 51) group. With the new GOLD grading system, the distribution of A-B and C-D stages was insignificantly different between groups using either FEV_1 or $FEV_{1\text{-}pl}$.

The BODE score was significantly higher in subjects with dominant emphysema than those with chronic bronchitis using either spirometric FEV_1 or $FEV_{1\text{-}pl}$ ($p=0.0079$) (Figure 4), but the difference between groups became significantly less (interaction $p=0.0168$) when $FEV_{1\text{-}pl}$ was substituted for FEV_1. There was a prevalence of more severe BODE stages in dominant emphysema than chronic bronchitis group using either FEV_1 ($p=0.0111$) or $FEV_{1\text{-}pl}$ ($p=0.0324$). But the proportion of subjects shifting from III-IV to I-II stages using $FEV_{1\text{-}pl}$ instead of $FEV_1$was significantly ($p=0.0180$) larger in dominant emphysema (9 out of 47) than chronic bronchitis (2 out of 51) group (Figure 5).

DISCUSSION

The main results of the present study are the following: 1) FEV_1 was significantly less in subjects with dominant emphysema than those with chronic bronchitis, 2) $FEV_{1\text{-}pl}$, respiratory impedance parameters, arterial blood gases, and patient-centered variables, namely, dyspnea, quality of life, physical performance, and number of exacerbations/yr were similar between

groups, 3) using $FEV_{1\text{-}pl}$ instead of FEV_1 resulted in a significant shift towards lower severity classes more in dominant emphysema than chronic bronchitis group, and 4) BODE index was significantly higher in dominant emphysema than chronic bronchitis group using FEV_1 but this difference was significantly attenuated by using $FEV_{1\text{-}pl}$.

Interpretation of results

The use of FEV_1 as an index of severity of pulmonary disorders stems from the paper by Fletcher and Peto (13) suggesting that this parameter may decline with age at the faster rate in smokers than in healthy subjects. Further longitudinal studies in COPD showed indeed that FEV_1 is a predictor of either respiratory or all-cause mortality (4, 35). Therefore, current guidelines and strategy documents have recommended the use of FEV_1 to stratify COPD subjects by severity (9, 10, 26, 29, 31, 35). However, the observation that FEV_1 is weakly correlated with patient-centered variables, such as dyspnea (37), exercise tolerance (5), and health-related quality of life (16), has prompted the introduction of composite classification criteria (8, 35). Furthermore, it has been recently proposed that a classification based not only on severity but also on phenotype may represent a step forward for personalized treatment of COPD patients (25).

In whatever stratification system, the severity of lung function abnormality has been graded based on the FEV_1 (1, 2, 9, 25, 26, 27, 29, 31, 35). In theory, this is justified by the fact that the FEV_1 reflects expiratory flow limitation, which is a marker of the disease. Yet, forced expiratory flow and thus FEV_1 are determined by different yet indistinguishable mechanisms, such as lung elastic recoil, resistance upstream from the flow limiting segment, and airway size and stiffness (17). In addition, during a forced expiratory maneuver, part of intrathoracic gas is compressed as a result of an excess in alveolar pressure with respect to critical pressure necessary to generate maximal flow (17, 18, 21), thus causing the FEV_1 measured at the mouth to be lower than the simultaneous change in chest wall volume measurable by a body

plethysmograph. This difference is small in healthy subjects but it may become large in disease as a result of the increase in airflow resistance, or lung volume, or both (21, 32, 33).

The present study is the first one in which the impact of thoracic gas compression on the severity classification of COPD has been examined in relation to dominant phenotypes. The findings show that FEV_1 measured at the mouth was consistently lower in subjects with dominant emphysema with respect to those with dominant chronic bronchitis despite similar patient-centered variables, blood gas data, and indexes of respiratory mechanics measured during tidal breathing by FOT. The fact that the two phenotypes did not differ for R_5, R_{19}, R_{5-19} and X_5, which are very sensitive indexes of airway mechanics and FEV_{1-pl} strongly suggests that the more severe reduction of FEV_1 observed in emphysema than chronic bronchitis phenotype is not a reflection of greater degree of airflow obstruction but rather a greater amount of thoracic gas compression volume. Although such a difference of FEV_1 could be due to different expiratory efforts, this possibility is presumably ruled out by the similarities of time to peak flow and back extrapolation volume between groups. More likely, the differences in FEV_1 between phenotypes were due to larger lung volume in emphysema, as predicted on the ground of the wave-speed theory of expiratory flow limitation. During a forced expiration, alveolar pressure increases and gas is compressed within the lung, thus causing lung volume and lung elastic recoil to decrease. A reduction of elastic recoil pressure will result in a reduction of driving pressure and transmural pressure at choke point, which can explain why FEV_1 was systematically less than FEV_{1-pl}. Being the amount of thoracic gas compression larger in larger than smaller lungs, for a given pressure and airflow resistance, this would explain why the difference between FEV_{1-pl} and FEV_1 was greater in dominant emphysema than chronic bronchitis group.

The present results are in keeping with previous studies. Krowka et al (21) found that decreasing expiratory effort was associated with a tendency of FEV_1 to increase above the threshold of natural variability and suggested that this negative effort-dependence of forced expiratory flow may confound the interpretation of spirometry and bronchomotor tests if

maneuvers are performed with different efforts. Sharafkhaneh et al. (32) measured simultaneously FEV_1 and $FEV_{1\text{-pl}}$ in COPD subjects undergoing lung volume reduction surgery and found that about 40% of the increase in FEV_1 after surgery was explained by the reduction in the amount of thoracic gas compression.

Limitations of the study

The present study has limitations. First, no quantitative assessment of emphysema was made by high-resolution computed-tomography (HRCT). However, the clinical and radiological score model was validated against HRCT (28) and, although a zone of overlap may be present, the two groups of this study exhibited values quite far from the cutoff value. Moreover, there were significant differences between groups in TLC and D_LCO, which are strong correlates of anatomical emphysema (7) that were not included in the model. Thus, it seems justified to assume that the method used for grouping subjects with dominant emphysema or chronic bronchitis was adequate for the purposes of this study. Second, predicting equations for $FEV_{1\text{-pl}}$ are not available and therefore predicted values were obtained by increasing predicted FEV_1 by a fixed amount determined in a group of healthy subjects. This might have determined systematic over- or under-estimation of severity in both groups, but this would unlikely explain differences between groups. Third, because of its cross-sectional nature, the study cannot provide direct information on the prognostic role of different pulmonary function tests. Nevertheless, the present data show that thoracic gas compression could potentially affect BODE index, which has been proposed as a sensitive predictor of mortality.

Clinical and therapeutic implications

The results of the present study have practical implications owing to the use of severity grading for choice of treatment (9, 10, 26, 29, 31, 35) and prognosis (8). Indeed, using $FEV_{1\text{-pl}}$ instead of FEV_1 caused a shift from GOLD III-IV to GOLD I-II classes in a larger number of

subjects with dominant emphysema than dominant chronic bronchitis. Were this classification used as a treatment guidance, more subjects with dominant emphysema would have received combined treatment with inhaled steroids than subjects with dominant chronic bronchitis even if clinical variables and airway mechanical conditions were not dissimilar. With the 2013 GOLD classification based on the FEV_1, dyspnea, and exacerbation number, using $FEV_{1\text{-}pl}$ instead of FEV_1 did not lead to significant differences between subjects with dominant chronic bronchitis or emphysema. We speculate that this is because of a relatively minor role for lung function with respect to dyspnea and exacerbations in this multidimensional grading system. The BODE index albeit multidimensional was affected by gas compression more in dominant emphysema than chronic bronchitis group. Using $FEV_{1\text{-}pl}$ instead FEV_1 the difference between dominant emphysema and chronic bronchitis group was significantly reduced but still significant, presumably because of the lower BMI in dominant emphysema group. Indeed, when a score including $FEV_{1\text{-}pl}$, MRC and 6MWD but not BMI was calculated there was no difference between dominant emphysema and chronic bronchitis group ($p=0.3249$).

Conclusions

The present study challenges the use of FEV_1 as the sole lung function parameter for severity grading in COPD, because of its dependence on dominant phenotype.

Assuming that lung function measurements are still needed to confirm objectively the clinical diagnosis COPD, the practical question is which tests are more adequate than spirometric FEV_1 to reflect COPD severity. An answer to this question will require longitudinal studies comparing the predicting value of different lung function tests on clinical outcomes in relation to the major phenotypes of this complex disease. These should include not only the classical measurements of lung volumes and D_LCO, but also tests that are independent of thoracic gas compression and sensitive to airway caliber and ventilation heterogeneity.

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FIGURE LEGENDS

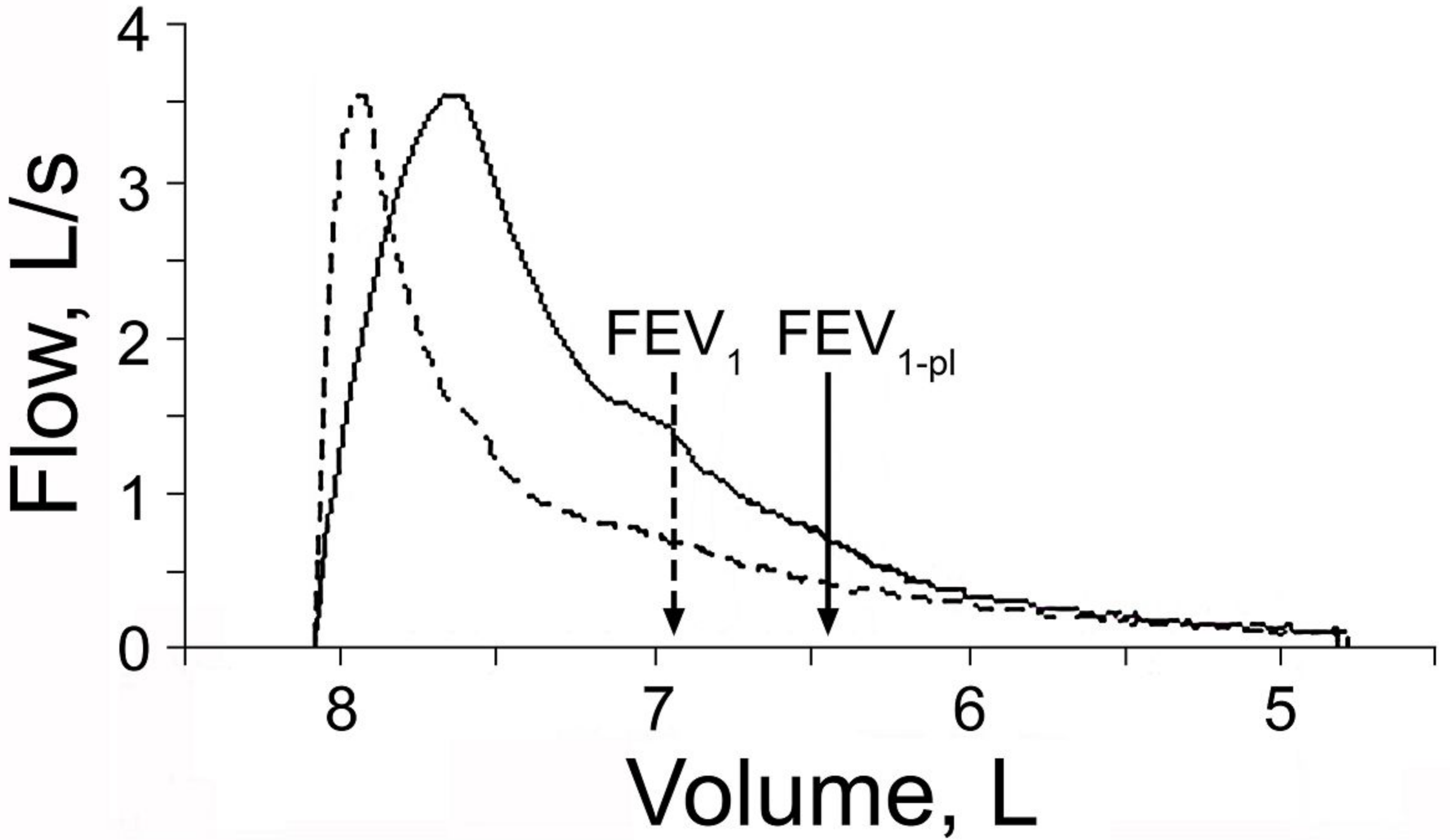
Figure 1. Representative flow-volume curves of a COPD subject with dominant emphysema. Flow is plotted against expired volume (dashed line) or plethysmographic volume (continuous line). Forced expiratory volume in 1 s measured at mouth (FEV_1) was 1.26 L and by plethysmography ($FEV_{1\text{-}pl}$) 1.75 L.

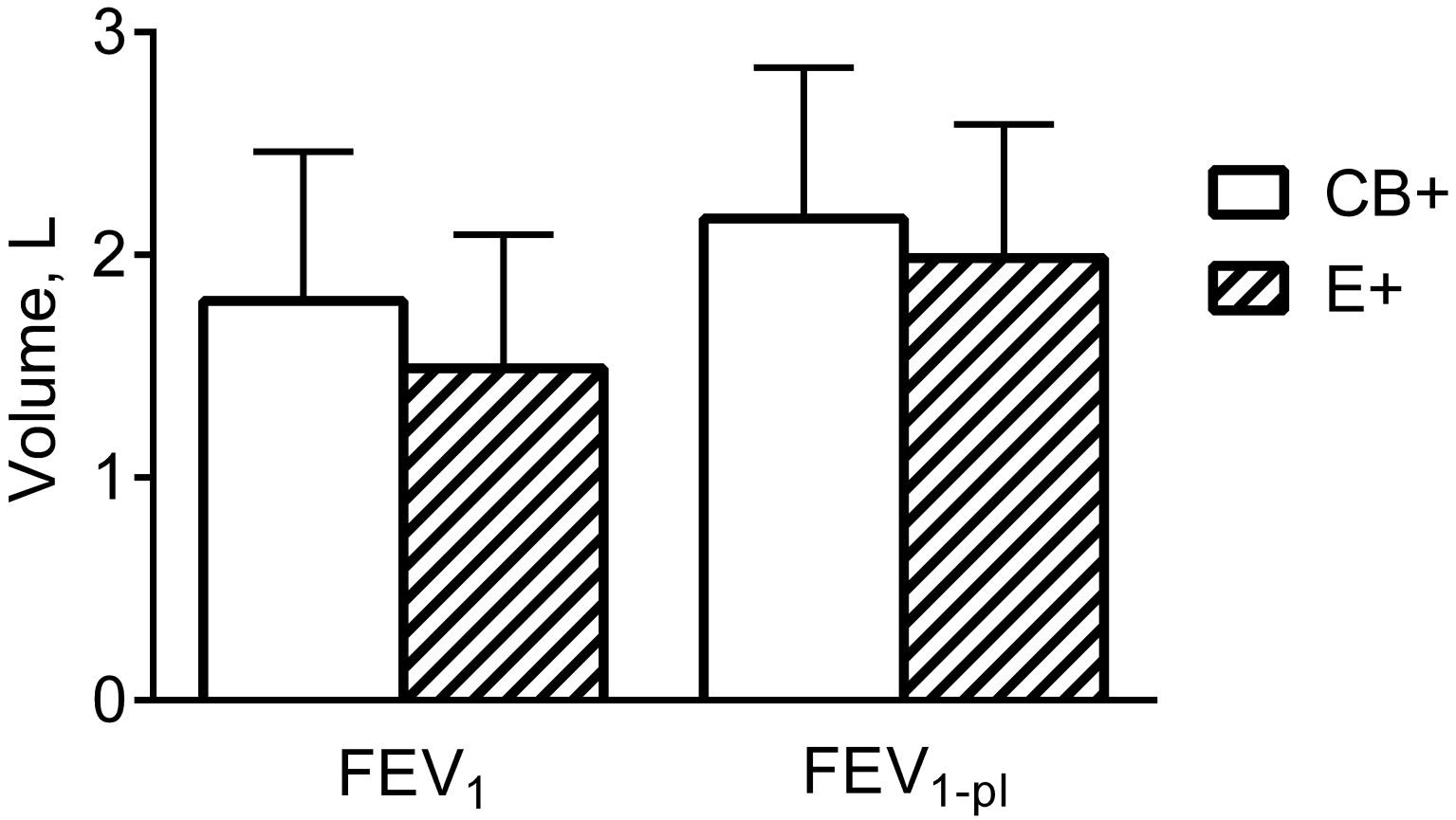
Figure 2. Post-bronchodilator $FEV_{1\text{-}pl}$ in subjects with dominant emphysema (E+, n=47) or chronic bronchitis (CB+, n=51). E+ vs. CB+, p= 0.1081; FEV_1 vs. $FEV_{1\text{-}pl}$, p< 0.0000; interaction, p=0.0026. This would indicate that gas compression significantly affected forced expiratory volume in both groups, but significantly more in E+ than CB+. Values are mean and standard deviation.

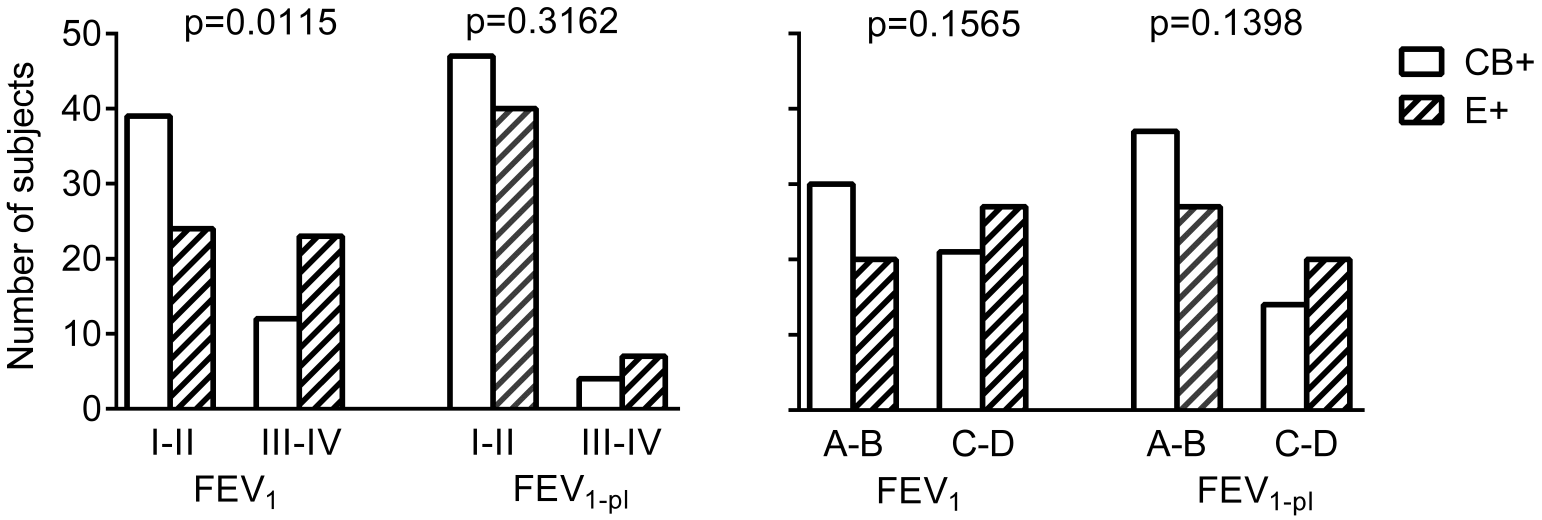
Figure 3. Effect of thoracic gas compression on severity classifications of subjects with dominant emphysema (E+, n=47) or chronic bronchitis (BC+, n=51) according to the 2007 GOLD criteria (left panel) and 2013 GOLD criteria (right panel). P values indicate significance of differences in categorical distributions between groups by using FEV_1 or $FEV_{1\text{-}pl}$.

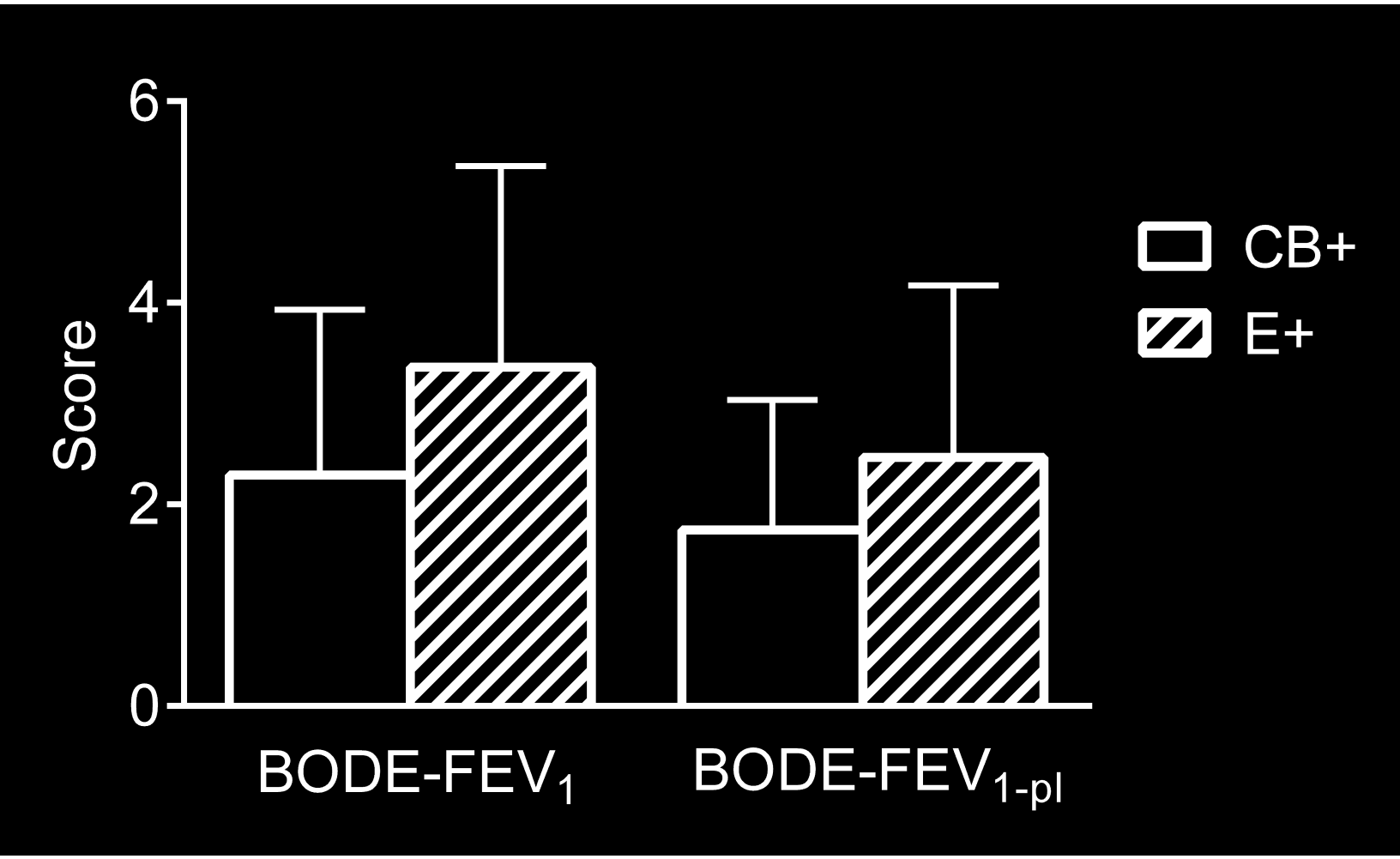
Figure 4. Effect of thoracic gas compression on BODE score in subjects with dominant emphysema (E+, n=47) or chronic bronchitis (CB+, n=51). E+ vs. CB+, p= 0.0079; FEV_1 vs. $FEV_{1\text{-}pl}$, p< 0.0000; interaction, p=0.0168. This would indicate that gas compression significantly affected forced expiratory volume in both groups, but significantly more in E+ than CB+. Values are presented as mean and standard deviation.

Figure 5. Effect of thoracic gas compression on distribution of BODE stages. P values indicate significance of differences in categorical distributions between groups.


Flow, L/s
4
3
2
1
0
FEV1
FEV1-pl
8
7
6
5
Volume, L


3
2
1
0
Volume, L
FEV1
FEV1-pl
CB+
E+


p=0.0115
p=0.3162
p=0.1565
p=0.1398
Number of subjects
50
40
30
20
10
0
I-II
III-IV
I-II
III-IV
A-B
C-D
A-B
C-D
FEV1
FEV1-pl
FEV1
FEV1-pl
CB+
E+


6
4
2
0
Score
CB+
E+
BODE-FEV1
BODE-FEV1-pl

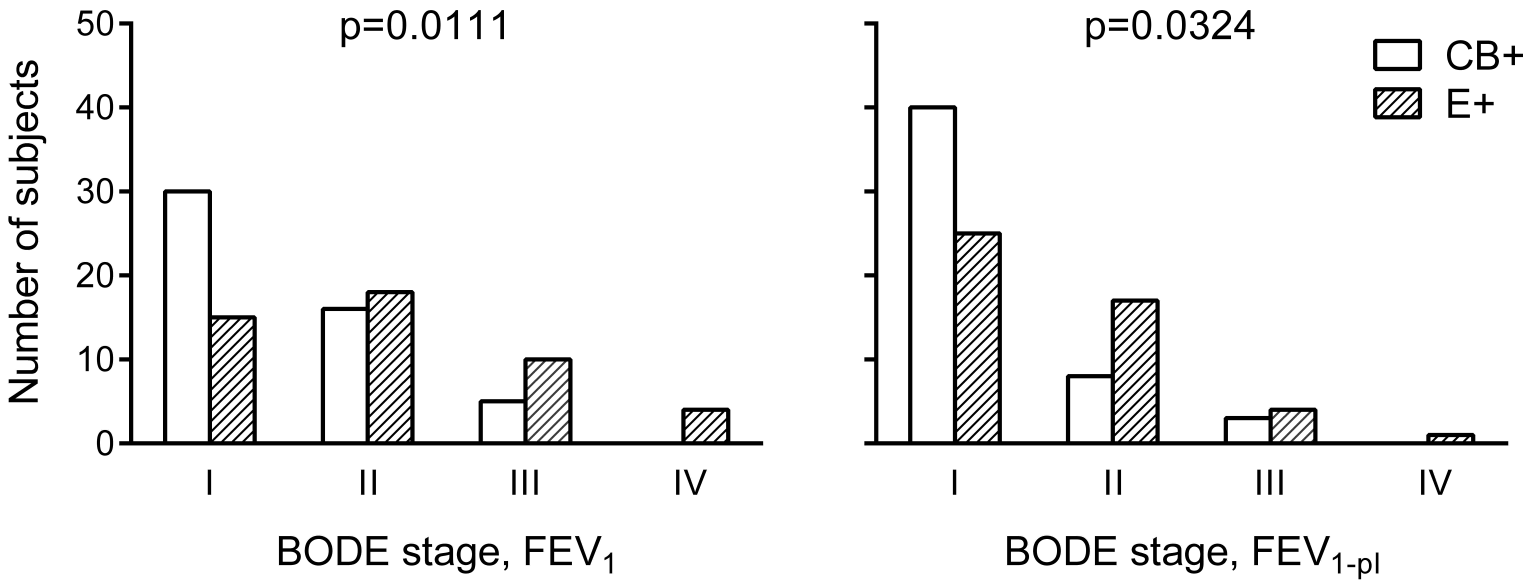

p=0.0111
p=0.0324
CB+
E+
Number of subjects
50
40
30
20
10
0
I
II
III
IV
BODE stage, FEV1
BODE stage, FEV1-pl

Table 1. Subjects' main anthropometric and lung function data.

	Dominant Emphysema	Dominant Chronic Bronchitis	P
Sex, M/F	39/8	42/9	0.9349
Age, yr	66±9	67±8	0.9080
Height, cm	170 ±8	168±8	0.1020
Smoking habit, Yes/No	46/1	51/0	0.9672
Pack-years	45±18	37±15	0.0231
BMI, $kg \cdot m^{-2}$	23±4	26±4	<0.0001
FEV_1, % of predicted	48±17	60±17	0.0016
FEV_1/VC, %	46±11	55±9	<0.0001
FRC % of predicted	148±29	131±29	0.0046
RV, % of predicted	179±45	155±40	0.0067
TLC, % of predicted	115±14	108±12	0.0145
D_LCO, % of predicted	60±20	84±22	<0.0001
D_LCO/V_A, % predicted	74±24	98±26	<0.0001
CRS, units	0.71±0.06	0.42±0.06	<0.0001
PaO_2, mmHg	70±8	72±8	0.3239
$PaCO_2$, mmHg	38±4	39±5	0.4456

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; D_LCO, single-breath lung diffusion capacity; V_A, alveolar volume; CRS, clinical and radiological score. Data are mean ± standard deviation. P, significance levels by Student's unpaired t test or Chi-square test withYates' correction where appropriated.

Table 2. Lung function data before and after bronchodilator.

	Dominant Emphysema		Dominant Chronic Bronchitis		P	
	Pre-BD	Post-BD	Pre-BD	Post-BD	Groups	Pre-Post
FEV_1, L	1.36±0.57	1.50±0.60	1.64±0.65	1.79±0.67	0.0210	<0.0001
$FEV_{1\text{-}pl}$, L	1.90±0.58	1.99±0.60	2.02±0.66	2.16±0.68	0.2391	<0.0001
FVC, L	2.90±0.90	3.16±0.94	2.93±0.96	3.14±0.97	0.9703	<0.0001
R_5, $cmH_2O \cdot s \cdot L^{-1}$	3.78±1.15	3.22±1.03	4.08±1.81	3.28±1.45	0.5998	<0.0001
R_{19}, $cmH_2O \cdot s \cdot L^{-1}$	2.91±0.67	2.60±0.61	3.13±0.92	2.76±0.75	0.2014	<0.0001
$R_{5\text{-}19}$, $cmH_2O \cdot sL^{-1}$	0.87±0.84	0.62±0.71	0.96±1.16	0.52±0.92	0.8176	<0.0001
X_5, $cmH_2O \cdot s \cdot L^{-1}$	-1.61±0.95	-1.36±0.90	-1.76±1.41	-1.30±1.07	0.9722	<0.0001

BD, bronchodilator; $FEV_{1\text{-}pl}$, forced expiratory volume in 1 s measured in the body plethysmograph; R_5 and R_{19}, inspiratory resistance at 5 and 19 Hz, respectively; X_5, inspiratory reactance at 5 Hz; Data are mean ± standard deviation. P, significance levels by two-factor repeated-measure ANOVA.

Table 3. Spirometry quality control additional data and breathing pattern.

	Dominant Emphysema		Dominant Chronic Bronchitis		P	
	Pre-BD	Post-BD	Pre-BD	Post-BD	Groups	Pre-Post
PEFT, ms	0.06±0.02	0.06±0.02	0.06±0.02	0.06±0.02	0.9291	0.8769
BEV, L	0.05±0.02	0.06±0.03	0.06±0.03	0.07±0.03	0.3081	0.5416
BF, min^{-1}	16±4	16±4	16±4	15±4	0.6014	0.5416
$\dot{V}_E$, $L \cdot min^{-1}$	15±5	15±5	13±4	14±4	0.1063	0.3492

PEFT, time to peak flow; BEV, back extrapolation volume; BF, breathing frequency; $\dot{V}_E$ minute ventilation. Data are mean ± standard deviation.

Table 4. Patient-centered variables.

	Dominant Emphysema	Dominant Chronic Bronchitis	P
MRC score, units	2.4±0.9	2.2±0.7	0.2646
SGRQ			
Symptoms	33±21	37±18	0.4140
Activity	43±21	42±19	0.9145
Impact	23±16	20±14	0.2269
Total	31±16	30±14	0.6096
6MWD			
Meters	489±101	480±110	0.6939
% predicted	92±18	96±18	0.2802
Exacerbations/yr, n	1.2±0.8	1.1±0.9	0.5071

MRC, Medical Research Council dyspnea score; SGRQ, Saint George's Respiratory Questionnaire; 6MWD, 6-minute walking distance. Data are mean ± SD. P, significance levels by Student's unpaired t test.