Severity grading of chronic obstructive pulmonary disease: the confounding effect of phenotype and thoracic gas compression

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Pellegrino R, Crimi E, Gobbi A, Torchio R, Antonelli A, Gulotta C, Baroffio M, Sferrazza Papa GF, Dellacà R, Brusasco V. Severity grading of chronic obstructive pulmonary disease: the confounding effect of phenotype and thoracic gas compression. J Appl Physiol 118: 796–802, 2015. First published November 20, 2014; doi:10.1152/japplphysiol.00801.2014.—Current guidelines recommend severity of chronic obstructive pulmonary disease be graded by using forced expiratory volume in 1 s (FEV1). But this measurement 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 FEV1 is greater in emphysema than chronic bronchitis because of larger lung volumes, and this influences severity classification and prognosis. FEV1 was simultaneously measured by spirometry and body plethysmography (FEV1-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 FEV1 than those with dominant chronic bronchitis. However, FEV1-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 FEV1-pl instead of FEV1 shifted severity distribution toward 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 FEV1-pl was substituted for FEV1. In conclusion, the FEV1 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.

forced expiratory volume in 1 s; plethysmography; emphysema; chronic bronchitis.

EVER SINCE the pioneering work of Tiffeneau (34), the forced expiratory volume in 1 s (FEV1) has been used as the key measurement of lung function for both diagnosis and severity assessment of obstructive lung disorders.1 The underlying rationale is grounded on the concept that maximal expiratory flow, and thus the FEV1, decreases in disease, and this is the result of 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 FEV1 is systematically less than that measured in body plethysmograph (FEV1-pl) by the amount of thoracic gas compression volume (TGV) (21). Confirmatory evidence for this has been brought by Krowka et al. (21) by showing that with decreasing expiratory effort TGV to a minimal value the FEV1 becomes similar to FEV1-pl. In addition to the expiratory effort, airflow resistance and absolute lung volume crucially contribute to increase TGV (17, 18), and thus the difference between FEV1-pl and FEV1 (32, 33).

Current international guidelines and strategy documents (9, 25a, 26, 29, 31, 35) recommend severity of chronic obstructive pulmonary disease (COPD) be graded by the FEV1 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 FEV1 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, 25a, 26, 29, 31, 35).

This study was designed to test this hypothesis by comparing FEV1 and compression-free FEV1 measured in a body plethysmograph (FEV1-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 FEV1-pl for FEV1.

1 This article is the topic of an Invited Editorial by Ole F. Pedersen (26a).

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Subjects. The study included 98 subjects with a clinical diagnosis of COPD (31) and not completely reversible airflow obstruction documented by a post-bronchodilator FEV₁ to vital capacity (VC) ratio (FEV₁/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 4 wk. Subjects with a history suggestive of bronchial asthma were excluded. Prior to each study session, long-acting β₂-agonists (salmeterol or formoterol) were suspended for at least 12 h, and tiotropium. The study protocol was approved by the S. Luigi Hospital Ethics Committee (Orbassano, Torino) (No. 103, 23-06-2006), and written informed consent was obtained from each subject prior to the study.

Study design. On a prestudy 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 PaO₂ and PaCO₂ measurements (ABL 520, Radiometer, Copenhagen, Denmark). Then the Medical Research Council (MRC) questionnaire for dyspnea and the 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 mo. 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, CA). 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 and/or 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, VC, and FEV₁. Compression-free FEV₁ was simultaneously obtained by plotting mouth flow against change in plethysmographic volume to measure FEV₁–pl (Fig. 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 cmH₂O 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 cmH₂O·l⁻¹·s⁻¹) on the other side. Airway opening pressure and flow were measured by piezoresistive transducers (DCXL10DS and DCXL10DS Sensortechs, Germany, respectively) and sampled at 200 Hz. A 15-l-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 (R₅ and X₅, respectively) and 19 Hz (R₁₉ and X₁₉, respectively). Artifacts due to glottis closure or expiratory airflow limitation were avoided by discarding breaths showing any of the following: 1) tidal volume <0.1 liters or >2.0 liters, 2) difference between measured flow oscillation and ideal sine wave with the same Fourier coefficients >0.2 (23), and 3) 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 R₅,R₅–1₉, and X₅ were retained for analysis. Of the main function parameters of the FOT, R₅ was taken as an index of overall airflow resistance of the respiratory system, R₁₉ as an index of central airways resistance, R₅–1₉ as an index of serial or peripheral heterogeneous ventilation, and X₅ as an index of capacitative component of the respiratory system. Tidal volume (V₄₅), breathing frequency (BF), and minute ventilation (Vₑ) were averaged over the same tidal breaths used for FOT data collection. Single-breath D₂CO was measured following the recommendation of the American Thoracic Society and European Respiratory Society (22) and 6-min walking distance (6MWD) according to ATS guidelines (3).

Predicted values for the spirometry and lung volumes were from Quanjer et al. (30). To estimate predicted FEV₁–pl, the predicted FEV₁ was increased by 4.5%. This was the difference between FEV₁–pl and FEV₁ observed in a group of 81 healthy subjects [31 women and 50 men, aged 46 ± 12 yr, with a body mass index (BMI) of 24 ± 3 kg·m⁻²].

Table 1. Subjects’ main anthropometric and lung function data

<table>
<thead>
<tr>
<th>Sex</th>
<th>M/F</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Pack years</th>
<th>BMI, kg·m⁻²</th>
<th>FEV₁, % of predicted</th>
<th>FEV₁/VC, %</th>
<th>FRC, % of predicted</th>
<th>RV, % of predicted</th>
<th>TLC, % of predicted</th>
<th>D₂CO, % of predicted</th>
<th>D₂CO/V₄₅, % predicted</th>
<th>CRS, units</th>
<th>PaO₂, mmHg</th>
<th>PaCO₂, mmHg</th>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>39/8</td>
<td>66 ± 9</td>
<td>170 ± 8</td>
<td>46/1</td>
<td>45 ± 18</td>
<td>23 ± 4</td>
<td>48 ± 17</td>
<td>148 ± 29</td>
<td>179 ± 45</td>
<td>115 ± 14</td>
<td>60 ± 20</td>
<td>74 ± 24</td>
<td>0.71 ± 0.06</td>
<td>70 ± 8</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>Female</td>
<td>42/9</td>
<td>67 ± 8</td>
<td>168 ± 8</td>
<td>51/0</td>
<td>37 ± 15</td>
<td>26 ± 4</td>
<td>60 ± 17</td>
<td>131 ± 29</td>
<td>155 ± 40</td>
<td>108 ± 12</td>
<td>84 ± 22</td>
<td>98 ± 26</td>
<td>&lt;0.0001</td>
<td>0.42 ± 0.06</td>
<td>39 ± 5</td>
</tr>
</tbody>
</table>
| BMI, body mass index; FEV₁, forced expiratory volume in 1 s; VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; D₂CO, single-breath lung diffusion capacity; Vₑ, alveolar volume; CRS, clinical and radiological score. Data are means ± SD. P, significance levels by Student’s unpaired t-test or χ² test with Yates’ correction where appropriate.
Table 2. Lung function data before and after bronchodilator

<table>
<thead>
<tr>
<th></th>
<th>Dominant Emphysema</th>
<th></th>
<th>Dominant Chronic Bronchitis</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreBD</td>
<td>PostBD</td>
<td></td>
<td></td>
<td>Groups</td>
</tr>
<tr>
<td>FEV₁, liters</td>
<td>1.36 ± 0.57</td>
<td>1.50 ± 0.60</td>
<td>1.64 ± 0.65</td>
<td>1.79 ± 0.67</td>
<td>0.0210</td>
</tr>
<tr>
<td>FEV₁-pl, liters</td>
<td>1.90 ± 0.58</td>
<td>1.99 ± 0.60</td>
<td>2.02 ± 0.66</td>
<td>2.16 ± 0.68</td>
<td>0.2391</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>2.90 ± 0.90</td>
<td>3.16 ± 0.94</td>
<td>2.93 ± 0.96</td>
<td>3.14 ± 0.97</td>
<td>0.9703</td>
</tr>
<tr>
<td>Rₑ, cmH₂O·l⁻¹·s⁻¹</td>
<td>3.78 ± 1.15</td>
<td>3.22 ± 1.03</td>
<td>4.08 ± 1.81</td>
<td>3.28 ± 1.45</td>
<td>0.5998</td>
</tr>
<tr>
<td>Rₑ, cmH₂O·l⁻¹·s⁻¹</td>
<td>2.91 ± 0.67</td>
<td>2.60 ± 0.61</td>
<td>3.13 ± 0.92</td>
<td>2.76 ± 0.75</td>
<td>0.2014</td>
</tr>
<tr>
<td>Xₜ, cmH₂O·l⁻¹·s⁻¹</td>
<td>0.87 ± 0.84</td>
<td>0.62 ± 0.71</td>
<td>0.96 ± 1.16</td>
<td>0.52 ± 0.92</td>
<td>0.8176</td>
</tr>
<tr>
<td></td>
<td>−1.61 ± 0.95</td>
<td>−1.36 ± 0.90</td>
<td>−1.76 ± 1.41</td>
<td>−1.30 ± 1.07</td>
<td>0.9722</td>
</tr>
</tbody>
</table>

BD, bronchodilator; FEV₁-pl, forced expiratory volume in 1 s measured in the body plethysmograph; Rₑ and Rₑ, inspiratory resistance at 5 and 19 Hz, respectively; Xₜ, inspiratory reactance at 5 Hz; Data are means ± SD. P, significance levels by two-factor repeated measure ANOVA.

kg/m², independent of anthropometric data. Predicted values for DLCO 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, FEV₁/VC; radiographic signs of increased vascular markings, bronchial wall thickening, reduced lung density, and 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’s exact test with Freeman-Halton’s extension for 2 × 4 contingency tables when appropriate. Values of P < 0.05 were considered statistically significant. Data are presented as means ± standard deviation. Statistical analyses were done by StatSoft Statistica and VassarStats website packages.

RESULTS

The two groups were well matched for anthropometric characteristics except for BMI, which was slightly lower in the dominant emphysema group (Table 1). Subjects with dominant emphysema had significantly lower D₁CO, D₁CO/Vₐ, and FEV₁ and significantly larger TLC, FRC, and RV than subjects with dominant chronic bronchitis (Table 1). However, neither FEV₁-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., BF and minute ventilation (Ve) 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). Postbronchodilator FEV₁-pl was significantly larger than FEV₁ (P < 0.0001) in both groups, but this difference was significantly larger in the dominant emphysema group than in chronic bronchitis group (P = 0.0026). Consistent with these data, postbronchodilator FEV₁-pl was not significantly different between the dominant emphysema and the chronic bronchitis groups (Table 2 and Fig. 2).

Grading the severity of disease using the old GOLD score by FEV₁ led to a significant (P = 0.0115) excess of III to IV classes in the dominant emphysema group compared with the chronic bronchitis group (Fig. 3). By using FEV₁-pl, the class distribution was not significantly different between groups (P = 0.3162), and the proportion of subjects shifting from the III to IV to the I to II classes was significantly (P = 0.0348) larger in the dominant emphysema group (16 out of 47) than in the chronic bronchitis group (8 out of 51). With the new GOLD grading system, the distribution of A to B and C to D stages was insignificantly different between groups using either FEV₁ or FEV₁-pl.

By using either spirometric FEV₁ or FEV₁-pl the BODE score was significantly higher in subjects with dominant emphysema than those with chronic bronchitis (P = 0.0079) (Fig. 4), but the difference between groups became significantly less (interaction P = 0.0168) when FEV₁-pl was substituted for FEV₁. By using either FEV₁ (P = 0.0111) or FEV₁-pl (P = 0.0324) there was a prevalence of more severe BODE stages in the dominant emphysema group than in the chronic bronchitis group. But the proportion of subjects shifting from the III-IV to the I-II stages by using FEV₁-pl instead of FEV₁ was significantly (P = 0.0180) larger in the dominant emphysema group (9 out of 47) than in the chronic bronchitis (2 out of 51) group (Fig. 5).

Table 3. Spirometry quality control additional data and breathing pattern

<table>
<thead>
<tr>
<th></th>
<th>Dominant Emphysema</th>
<th></th>
<th>Dominant Chronic Bronchitis</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreBD</td>
<td>PostBD</td>
<td></td>
<td></td>
<td>Groups</td>
</tr>
<tr>
<td>PEFT, ms</td>
<td>0.06 ± 0.02</td>
<td>0.06 ± 0.02</td>
<td>0.06 ± 0.02</td>
<td>0.06 ± 0.02</td>
<td>0.9291</td>
</tr>
<tr>
<td>BEV, l</td>
<td>0.05 ± 0.02</td>
<td>0.06 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>0.07 ± 0.03</td>
<td>0.3081</td>
</tr>
<tr>
<td>BF, min⁻¹</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
<td>16 ± 4</td>
<td>15 ± 4</td>
<td>0.6014</td>
</tr>
<tr>
<td>Ve, l-min⁻¹</td>
<td>15 ± 5</td>
<td>15 ± 5</td>
<td>13 ± 4</td>
<td>14 ± 4</td>
<td>0.1063</td>
</tr>
</tbody>
</table>

PEFT, time to peak flow; BEV, back-extrapolation volume; BF, breathing frequency; Ve, minute ventilation. Data are means ± SD.
DISCUSSION

The main results of the present study are the following: 1) \( \text{FEV}_1 \) was significantly less in subjects with dominant emphysema than those with chronic bronchitis; 2) \( \text{FEV}_{1\text{-pl}} \), respiratory impedance parameters, arterial blood gases, and patient-centered variables, namely, dyspnea, quality of life, physical performance, and number of exacerbations per year were similar between groups; 3) the use of \( \text{FEV}_{1\text{-pl}} \) instead of \( \text{FEV}_1 \) resulted in a significant shift toward lower severity classes more in the dominant emphysema group than in the chronic bronchitis group; and 4) by using \( \text{FEV}_1 \), the BODE index was significantly higher in the dominant emphysema group than in the chronic bronchitis group, but this difference was significantly attenuated by using \( \text{FEV}_{1\text{-pl}} \).

Interpretation of results. The use of \( \text{FEV}_1 \) 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 a faster rate in smokers than in healthy subjects. Further longitudinal studies in COPD showed, indeed, that \( \text{FEV}_1 \) is a predictor of either respiratory or all-cause mortality (4, 35). Therefore, current guidelines and strategy documents have recommended the use of \( \text{FEV}_1 \) to stratify COPD subjects by severity (9, 25a, 26, 29, 31, 35). However, the observation that \( \text{FEV}_1 \) 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 \( \text{FEV}_1 \) (1, 2, 9, 25, 26, 27, 29, 31, 35). In theory, this is justified by the fact that the \( \text{FEV}_1 \) reflects expiratory flow limitation, which is a marker of the disease. Yet, forced expiratory flow and thus \( \text{FEV}_1 \) 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 the critical pressure necessary to generate maximal flow (17, 18, 21), thus causing the \( \text{FEV}_1 \) 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 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 \( \text{FEV}_1 \) 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 \( R_5, R_{19}, R_5, R_{19}, \) and \( X_5 \), which are very sensitive indexes of airway mechanics, and \( \text{FEV}_{1\text{-pl}} \) strongly suggests that the more severe reduction of \( \text{FEV}_1 \) observed in emphysema than chronic bronchitis phenotype is not a reflection of greater degree of airflow obstruction but rather a greater amount of TGCV. Although such a difference of \( \text{FEV}_1 \) 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 \( \text{FEV}_1 \) 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 \( \text{FEV}_1 \) was systematically less than \( \text{FEV}_{1\text{-pl}} \). The amount of thoracic gas compression being larger in larger lungs than smaller lungs, for a given pressure and airflow resistance, this would explain why the difference between \( \text{FEV}_{1\text{-pl}} \) and \( \text{FEV}_1 \) was greater in the dominant emphysema group than in the 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 \( \text{FEV}_1 \) to increase above the threshold of natural variability and suggested that this negative

Table 4. Patient-centered variables.

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

MRC, Medical Research Council dyspnea score; SGRQ, Saint George’s Respiratory Questionnaire; 6MWD, 6-min walking distance. Data are means ± SD. \( P \), significance levels by Student’s unpaired \( t \)-test.
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 FEV1 and FEV1_pl in COPD subjects undergoing lung volume reduction surgery and found that about 40% of the increase in FEV1 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 CRS 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 Dl,CO, 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 FEV1_pl are not available, and, therefore, predicted values were obtained by increasing predicted FEV1 by a fixed amount determined in a group of healthy subjects. This might have determined systematic over- or underestimation 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 the 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, 25a, 26, 29, 31, 35) and prognosis (8). Indeed, using FEV1_pl instead of FEV1 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 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 FEV1 to reflect COPD severity. An answer to this question will require longitudinal studies comparing the predicting value of FEV1 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 the dominant emphysema group than in the chronic bronchitis group. By using FEV1_pl instead of FEV1 the difference between the dominant emphysema group and the chronic bronchitis group was significantly reduced but still significant, presumably because of the lower BMI in the dominant emphysema group. Indeed, when a score including FEV1_pl, MRC, and 6MWD, but not BMI, was calculated, there was no difference between the dominant emphysema group and the chronic bronchitis group (P = 0.3249).

Conclusions. The present study challenges the use of FEV1 as the sole lung function parameter for severity grading in COPD because of its dependence on dominant phenotype.
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 $D_lP\text{CO}_2$, but also tests that are independent of thoracic gas compression and sensitive to airway caliber and ventilation heterogeneity.

DISCLOSURES

R. Pellegrino, E. Crimi, R. Torchio, A. Antonelli, C. Gulotta, M. Baroffio, G. F. Sferrazza Papa, and V. Brusasco declare that no potential conflicts of interest exist with any companies and/or organizations whose products or services may be discussed in this article. A. Gobbi, R. Dellaca, and Politecnico di Milano University (institution of A. Gobbi and R. Dellaca) own stocks of a spin-off company involved in the development of forced oscillation devices.

AUTHOR CONTRIBUTIONS


REFERENCES


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


