Impact of Bronchodilator Use on the Prevalence of COPD in Population-Based Samples

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ABSTRACT

The aim of this study was to describe the impact of using bronchodilators on the prevalence of Chronic Obstructive Pulmonary Disease in a population-based survey (Platino study). A cluster sampling of subjects 40 years of age or older, representative of the metropolitan areas of 5 Latin American cities (Sao Paulo, Mexico, Montevideo, Santiago and Caracas) was chosen. Spirometry according to ATS standards was done before and after inhalation of 200 micrograms of salbutamol in 5183 subjects. Prevalences of airflow obstruction were estimated using different criteria, in tests done before and after bronchodilator use, and with reference values for pre- or post-bronchodilator use.

Bronchodilator testing reduced the overall prevalence of FEV1/FVC% < 0.70 from 21.7% to 14% (35%). In the group with FEV1/FVC < 0.70 after bronchodilator use, 21% were asymptomatic from the respiratory point of view, and lacked significant adverse exposures. Subjects below the 5th percentile for FEV1/FVC and FEV1/FEV6 were fewer than those with FEV1/FVC < 0.70, especially among the elderly. More subjects are below the 5th percentile of FEV1/FVC and FEV1/FEV6 using reference values for tests after bronchodilator use than using the reference values determined without bronchodilator testing. Testing after bronchodilator use reduces the prevalence of airflow obstruction from 32 to 39% depending on the definition used. In addition, the subjects who were still obstructed after bronchodilator use were the ones who showed more respiratory symptoms and exposure to tobacco and other smokes and dusts, than subjects with reversible obstruction, suggesting an increased specificity for COPD.

Keywords: COPD definition, Diagnosis of COPD, Bronchodilator response, Airflow obstruction.

The PLATINO group for this project was also formed by Luis Torre-Bouscoulet,1 Alexander Corcho-Berdugo,1 Francisco Franco-Marina,1 Cesar Victoria,2 and Carmen Lisboa.2 Spirometry supervisors were: Fernanda W. Rosa, Águiles Camelier, Oliver Nascimento, Elisa Sánchez-Gallén, Abigail Guzmán, Marcela Araya and Dolores Moreno.

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INTRODUCTION

According to the GOLD guidelines the diagnosis of Chronic Obstructive Pulmonary Disease (COPD) is a FEV1/FVC below 0.70 after bronchodilator use (postBD) (1, 2). Testing after bronchodilator use aims to exclude from COPD as many asthmatics and other subjects with reversible airflow obstruction as possible. Although guidelines to interpret bronchodilator testing have been issued (3), the magnitude of the bronchodilator response (BR) shows considerable intra-subject variation (4), and methods to assess it are heterogeneous (5, 6). In addition, BR overlaps considerably in COPD and asthma (7–9) and because it is a continuous variable, any cutoff point established to define “a significant” response is arbitrary (7, 10).

BR has been considered proportional to bronchial hyper-responsiveness, but this is not a consistent finding (11). For example, in patients with mild COPD in the Lung Health Study, BR differed in several ways from bronchial hyper-responsiveness. Variability of BR was high, increased with time, and was not predictive of a more rapid decline of FEV1 whereas bronchial hyper-responsiveness was more stable through time and predicted a rapid decline of function (12, 13).

Errors or inconsistencies in diagnoses of COPD, either false positives or false negatives, may have important consequences, although in recent studies the importance of undiagnosed COPD is usually emphasized. Subjects who have the disease but have not been diagnosed may not implement preventive measures such as smoking cessation; whereas false diagnoses may have a labeling effect and lead to unnecessary use of medication and other health services. As the main criteria for diagnosis of COPD is the post-bronchodilator FEV1/FVC, the objective of our study was to describe the impact of bronchodilator testing on the prevalence of airflow obstruction in five population-based samples from Latin American cities. In a previous study (14) bronchodilator use (0.3 mg of salbutamol) caused an overall 27% reduction in the prevalence of FEV1/FVC <0.70 in a sample of 2235 subjects from 26–82 years of age.

METHODS

Ethical approval was obtained from the Ethics Committees of the institutions involved in the study. Written, informed consent was provided by all subjects. The sampling and testing methods of the PLATINO study have been described previously (15), as have the prevalence results (16) and reference values for spirometric testing (17). Briefly, multi-stage cluster sampling was used, with a similar design in the five areas; selecting 68 census tracts from each city, representative of the metropolitan area including suburbs, and aiming for a minimum sample of 800 subjects per city.

A portable, ultrasound transit-time based spirometer (Easy-One from NDD, Switzerland) was used. Calibration was verified daily using a 3-liter syringe (Hans Rudolph). All technicians participating in the study were trained in spirometry testing and in the use of the equipment by the same team. An additional, experienced technician or physician at each site acted as a spirometry supervisor.

We followed standard procedures for spirometry (18), and subjects (seated and wearing a nose clip) were allowed to perform up to 15 forced expiratory maneuvers (the maximum accepted by the spirometer) in order to obtain three acceptable maneuvers according to the criteria proposed by the American Thoracic Society (ATS). The goal was to obtain an FVC and FEV1 reproducible to 150 mL (19). A bronchodilator (salbutamol 200 µg) was then administered by inhalation through a 500-mL spacer, and the test was repeated 15 minutes later.

Several ways of expressing bronchodilator response have been described (6, 7, 10, 12, 20–22). We expressed BR as the spirometric measurement after bronchodilator use (postBD) minus the measurement before bronchodilator use (preBD) expressed in original units (deltaFEV1 in mL, deltaFVC in mL, deltaFEV6 in mL, delta FEV1/FEV6 in % and deltaFEV1/FVC in %), but also as the percentage change of the preBD value (postBD-preBD)*100/preBD, (deltaFEV1%, deltaFVC%, deltaFEV6%, deltaFEV1/FEV6%, delta deltaFEV1/FVC%), and finally as postBD-preBD, both expressed as a percentage of predicted values (deltaFEV1%p, deltaFVC%p, deltaFEV6%p, deltaFEV1/FEV6%p, and deltaFEV1/FVC%p).

We recognized tests that complied with the current criteria for significant bronchodilator response: an increase in 200 mL and 12% of either FEV1 or FVC after bronchodilator use (23).

We identified subjects with airflow obstruction before and after inhaling the bronchodilator using several definitions: (a) FEV1/FVC <0.70, the criteria used in the GOLD guidelines (1), (b) FEV1/FVC (3) or (c) FEV1/FEV6 (24) below the 5th percentile for age and gender according to internally-derived reference values obtained from subjects with no evidence of respiratory disease (17), both before and after inhaling a bronchodilator as well as from the NHANES III reference values for Mexican-Americans (25) obtained from spirometric tests done without bronchodilator use.

Statistical analysis was done with Stata software (26). For all analyses, we considered the complex sampling and clustering of data using the “survey” commands of the software.

RESULTS

A total of 5183 spirometries were performed before and after bronchodilator use. Of the postBD tests, 90.9% had at least 3 acceptable maneuvers, with FEV1 and FVC repeatable to within 150 mL, thus complying with the 2005 ATS-ERS standards (19), whereas 95.3% had FEV1 and FVC repeatable within 200 mL, which complies with the 1994 ATS standards (18). Of the total number of spirometry tests, 97.9% had three or more acceptable maneuvers according to 1994 ATS standards, 1.4% had two, 0.3% had one and only 19 tests (0.4%) had none. Of the total, 92% of the tests complied with the 1994 ATS standards simultaneously before and after bronchodilator use and 83% fulfilled the 2005 ATS-ERS standards. On average, each subject performed 5–6 maneuvers pre-bronchodilator (preBD) and 4–5 postBD. Table 1 describes the studied population, including...
Table 1. Characteristics of the reported population (Means and SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>High risk for COPD subjects</th>
<th>Low risk for COPD subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women 1810</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>56.8</td>
<td>11.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>68.5</td>
<td>14.7</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>28.9</td>
<td>5.9</td>
</tr>
<tr>
<td>FEV₁ preBD (L)</td>
<td>2.14</td>
<td>0.5</td>
</tr>
<tr>
<td>FVC preBD (L)</td>
<td>2.85</td>
<td>0.7</td>
</tr>
<tr>
<td>FEV₁ preBD (L)</td>
<td>2.72</td>
<td>0.6</td>
</tr>
<tr>
<td>FEV₁/FVC preBD</td>
<td>74.8</td>
<td>8.6</td>
</tr>
<tr>
<td>FEV₁/FEV₆ preBD</td>
<td>78.3</td>
<td>6.7</td>
</tr>
<tr>
<td>FEV₁ %P</td>
<td>93.7</td>
<td>16.4</td>
</tr>
<tr>
<td>FVC %P</td>
<td>98.4</td>
<td>16.6</td>
</tr>
<tr>
<td>FEV₆ %P</td>
<td>95.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Delta FEV₁ mL</td>
<td>85.5</td>
<td>133.1</td>
</tr>
<tr>
<td>Delta FEV₁ %</td>
<td>4.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Delta FEV₁ %P</td>
<td>3.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Delta FEV₆ mL</td>
<td>38.9</td>
<td>169.5</td>
</tr>
<tr>
<td>Delta FEV₆ %</td>
<td>2.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Delta FEV₆ %P</td>
<td>1.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Delta FVC mL</td>
<td>−4.0</td>
<td>232.1</td>
</tr>
<tr>
<td>Delta FVC %</td>
<td>−0.21</td>
<td>8.8</td>
</tr>
<tr>
<td>DeltaFVC %P</td>
<td>−0.02</td>
<td>8.2</td>
</tr>
<tr>
<td>Delta FEV₁/FVC</td>
<td>3.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Delta FEV₁/FVC %</td>
<td>4.5</td>
<td>7.2</td>
</tr>
<tr>
<td>Delta FEV₁/FVC %P</td>
<td>4.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Delta FEV₁/FEV₆</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Delta FEV₁/FEV₆ %</td>
<td>2.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Delta FEV₁/FEV₆ %P</td>
<td>2.5</td>
<td>4.1</td>
</tr>
</tbody>
</table>

All subjects performed post-bronchodilator testing. PreBD is the test before bronchodilator use. Delta refers to the difference between the postBD measurement and the preBD measurement.

%P is the spirometric value expressed as a percentage of internal predicted values. BMI is body mass index. SD is standard deviation.

*“Low risk” women and men, lacked significant exposures, cough, dyspnea, wheezing and did not refer a medical diagnosis of asthma or COPD. The remaining subjects were considered of high risk for COPD.

mean responses to bronchodilator use separated by gender and by respiratory health status.

The distribution of the bronchodilator responses to FEV₁, FEV₆, FVC, FEV₁/FEV₆ and FEV₁/FVC were uni-modal and approximately Gaussian, whether expressed in absolute terms, relative to preBD values, or as percentages of predicted values; and also whether analyzed for the entire population or only among respiratory healthy subjects. We observed average increases in all variables studied, including FEV₆ (except in healthy men) and in the FEV₁/FEV₆ and FEV₁/FVC ratios, but mean changes in FVC after bronchodilator use were not statistically different from zero.

The overall 95th percentile for the change in FEV₁ was 290 mL (11.4% of preBD and 11.7% of predicted); for FVC it was 337 mL (10.9% of preBD and also of predicted), for FEV₆ it was 277 mL (10.4% of preBD and 9.4% of predicted) for FEV₁/FVC was 9% (13% of preBD and 11.4% of predicted) and for FEV₁/FEV₆ it was 6.6% (8.7% of preBD and 8.0% of predicted). The three forms of expressing the bronchodilator response for the studied variables showed a high correlation among themselves and a negative correlation with the baseline lung function.

Table 2 shows the prevalence of airflow obstruction and the impact of testing after bronchodilator use in 1895 subjects considered to be of low risk for COPD, due to the absence of respiratory symptoms (i.e., reports of cough, phlegm, wheezing and dyspnea), and low exposure levels (<10 pack years smoking, <200 hour-years of exposure to biomass smoke, <5 years exposure to occupational dust) and with no report of previous medical diagnosis of asthma or COPD. The remaining 3288 subjects were considered of high risk for COPD. Using the current COPD definition by the GOLD criteria (FEV₁/FVC <0.70) leads to a prevalence from 7 to 9 times higher among the older age group compared to the youngest group. On the other hand, using the definitions based on the lower limit of normal (below the 5th percentile), the prevalence of airflow obstruction in the elderly with low risk for COPD increases less than 3 times compared to the youngest subjects.

The overall impact of bronchodilator testing was a reduction in the prevalence of airflow obstruction of a magnitude that varied from 32% to 39%, depending on the definition used. Conversely, in spirometric testing before using the bronchodilator we obtained prevalences of airflow obstruction ranging from 50 to 65% higher than after bronchodilator use. For
**Table 2.** Impact of age in the prevalence (%) of airflow obstruction (standard error) in subjects considered to be of high and low risk for COPD

<table>
<thead>
<tr>
<th>Age group</th>
<th>PreBD tests</th>
<th>PostBD tests</th>
<th>PreBD tests</th>
<th>Post BD tests</th>
<th>PreBD tests</th>
<th>PostBD tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–45</td>
<td>12.7 (1.4)</td>
<td>6.5 (1.0)</td>
<td>9.7 (1.3)</td>
<td>9.0 (1.1)</td>
<td>10.3 (1.2)</td>
<td>8.6 (1.2)</td>
</tr>
<tr>
<td>45–50</td>
<td>17.2 (1.2)</td>
<td>10.4 (0.9)</td>
<td>12.4 (1.0)</td>
<td>11.0 (0.9)</td>
<td>11.0 (0.9)</td>
<td>11.1 (1.0)</td>
</tr>
<tr>
<td>50–60</td>
<td>28.1 (1.6)</td>
<td>18.7 (1.5)</td>
<td>14.8 (1.3)</td>
<td>14.5 (1.3)</td>
<td>13.6 (1.2)</td>
<td>13.1 (1.4)</td>
</tr>
<tr>
<td>60–70</td>
<td>43.4 (2.3)</td>
<td>30.3 (2.2)</td>
<td>20.4 (1.9)</td>
<td>20.2 (1.8)</td>
<td>19.8 (1.8)</td>
<td>18.0 (1.7)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>50.3 (2.9)</td>
<td>38.7 (2.6)</td>
<td>21.3 (2.4)</td>
<td>20.7 (2.2)</td>
<td>19.3 (2.3)</td>
<td>21.7 (2.2)</td>
</tr>
<tr>
<td>All age groups</td>
<td>26.2 (0.8)</td>
<td>17.4 (0.7)</td>
<td>14.5 (0.7)</td>
<td>13.8 (0.6)</td>
<td>13.6 (0.6)</td>
<td>13.2 (0.6)</td>
</tr>
</tbody>
</table>

**Definition of airflow obstruction**

1. $\text{FEV}_1/\text{FVC} < 0.70$
2. FEV$_1$ below 5th percentile
3. FEV$_1$/FEV$_6$ below 5th percentile

Subjects with high risk for COPD were asymptomatic, with low exposure (<10 pack years, <200 hour-years of biomass smoke, <5 years exposed to dust) and did not refer a medical diagnosis of asthma or COPD. The remaining subjects were considered as high-risk. See text for details; 5th percentiles according to internal reference values for preBD or postBD tests (17).

A FEV$_1$/FVC $<0.70$, the definition currently used in the GOLD guidelines, prevalences without using bronchodilator were 55% higher than after bronchodilator use.

Table 3 shows the prevalence of subjects with FEV$_1$/FVC and FEV$_1$/FEV$_6$ below the 5th percentile, using reference values for tests done before and after bronchodilator. Again, use of a bronchodilator reduces the prevalence of airflow obstruction under any definition applied, if comparison is done with the same reference values, as shown in Table 3 (moving horizontally from left to right in the table). However, subjects below the 5th percentile in tests after BD are more numerous using reference equations for postBD tests, than for preBD tests: 10.8% of subjects had a FEV$_1$/FVC $<$ LLN using reference values postBD, vs. 7.6% using reference values preBD, see Table 3.

Of the 5183 subjects with post-bronchodilator testing, 21.7% had a FEV$_1$/FVC $<$ 0.70 before bronchodilator and 14.0% after bronchodilator. Characteristics associated with irreversible obstruction compared to the group with reversible obstruction (airflow obstruction before but not after bronchodilator use) were: older age, male gender, current or past smoking, a medical diagnosis of COPD, and reports of wheezing. Frequency of medical diagnoses of asthma and individuals with a lower body mass index were similar in subjects with reversible or irreversible airflow obstruction.

**Table 3.** Prevalence of FEV$_1$/FVC and FEV$_1$/FEV$_6$ below the 5th percentile (lower limit of normal, LLN) before and after bronchodilator use, according to three reference values

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Prevalence (%)</th>
<th>SE</th>
<th>Prevalence (%)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$/FVC $&lt;0.70$</td>
<td>21.7</td>
<td>0.6</td>
<td>14.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Reference equations obtained from pre BD tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$/FVC $&lt;$ LLN NHANES III</td>
<td>19.3</td>
<td>0.6</td>
<td>11.7</td>
<td>0.5</td>
</tr>
<tr>
<td>FEV$_1$/FEV$_6$ $&lt;$ LLN NHANES III</td>
<td>14.1</td>
<td>0.5</td>
<td>9.5</td>
<td>0.4</td>
</tr>
<tr>
<td>FEV$_1$/FVC $&lt;$ LLN PLATINO</td>
<td>11.5</td>
<td>0.5</td>
<td>7.6</td>
<td>0.4</td>
</tr>
<tr>
<td>FEV$_1$/FEV$_6$ $&lt;$ LLN PLATINO</td>
<td>10.6</td>
<td>0.4</td>
<td>7.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Reference equations obtained from postBD tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$/FVC $&lt;$ LLN PLATINO</td>
<td>17.4</td>
<td>0.6</td>
<td>10.8</td>
<td>0.4</td>
</tr>
<tr>
<td>FEV$_1$/FEV$_6$ $&lt;$ LLN PLATINO</td>
<td>15.3</td>
<td>0.5</td>
<td>10.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

NHANES III refers to the reference values from Hankinson et al. (25), obtained from the third NHANES study, from spirometries done without the use of a bronchodilator. Internal reference values were obtained from the healthy subjects of the PLATINO study, either from tests done before using the bronchodilator (17), or from tests done after use of bronchodilator, respectively.
Previous medical diagnoses of asthma and COPD were strong predictors of a positive BR as defined by ATS, present in 22% of those subjects with both diagnoses, 10% of those with either asthma or COPD and only 5% of those with none of these diagnoses.

DISCUSSION

As previously described, the distribution of bronchodilator response was uni-modal and continuous in the studied population. BD responses in respiratory healthy subjects, though lower in the remaining subjects, did not differ considerably. We assessed the response to bronchodilator use in terms of FEV$_1$ and FVC as recommended by current guidelines (3), but also in terms of subjects’ FEV$_1$/FVC (27) ratio, the spirometric variable most commonly used to identify airflow obstruction. Expiratory time may change after using a bronchodilator and the comparison of FEV$_1$/FVC before and after BD can be questioned, but not changes in FEV$_1$/FEV$_6$ induced by bronchodilator use, as this index is estimated at fixed times. We found that use of the bronchodilator increases FEV$_1$/FVC and FEV$_1$/FEV$_6$ significantly, because the increase in FEV$_1$ is higher than in FVC or FEV$_6$. In fact, the mean increase in FVC was not different from zero in the studied population. None of the criteria for bronchodilator response now in use are ideal. All three that we tested: change in original units, and as percentage of preBD value, or percentage of predicted, correlate negatively with baseline lung function (21). In this situation, subjects with lower lung function were more likely to have responses above the 95th percentile, regardless of the way it is expressed. We also should acquire more experience with BD response in terms of FEV$_1$/FVC and FEV$_1$/FEV$_6$; that is, on units currently used to define airflow obstruction and COPD. Additional information is needed on the reproducibility of deltaFEV$_1$ or deltaFVC, but this requires repeated bronchodilator testing on different days.

Subjects with a FEV$_1$/FVC <0.70 after bronchodilator use (sometimes referred to as having irreversible obstruction) were older, more often men, had more smoking and wheezing, a lower body mass index and more common diagnoses of COPD than those with “reversible obstruction”: FEV$_1$/FVC <0.70 before bronchodilator but not after it. On the other hand, we found no difference in the number of subjects with reported medical diagnoses of asthma between the reversible and irreversible groups. This suggests that bronchodilator testing succeeds in identifying more COPD but fails to exclude asthmatics. Several reasons may explain this, but only some of them could be explored in this study. We observed a consistent increase in FEV$_1$ but no consistent increase in FVC in the reversible group or in the entire population. On the other hand, the group with “irreversible” obstruction did in fact show a significant increase in FVC (19% of the subjects had >200 mL and 12% increase vs. 2% of those with “reversible” obstruction), which explains to a great extent why this group maintains a low FEV$_1$/FVC after bronchodilator use.

In reality, they have more often significant responses to bronchodilator than the reversible group, but with a predominant impact on FVC so they maintain a low FEV$_1$/FVC. Isolated volume response to bronchodilators is described in patients with airflow obstruction (28, 29) and correlates with clinical improvement (29). Emphysema is associated with a predominant FVC response in COPD (29, 30), but it can also occur among asthmatics (31). As expected, subjects with isolated or predominant volume response to BD show a drop in FEV$_1$/FVC after bronchodilator use, just like our subjects with irreversible obstruction. It is contradictory that bronchodilator use reduces the FEV$_1$/FVC ratio in these subjects, the most common criteria of airflow obstruction. It has been reported that some subjects may have beneficial volume reduction after bronchodilator use that is not detected by spirometry because it involves a parallel drop in total lung capacity and in residual volume with no change in vital capacity (29). In addition, asthma and COPD have known links and in fact these two conditions may occur together. For example, subjects with BHR, are at risk for a more rapid decline of lung function in smokers and COPD (1).

Although an extensive under-diagnosis of COPD has been emphasized (32–35), over-diagnosis and incorrect labeling are also important concerns (36, 37). The definition used has a huge impact on the prevalence of COPD (38–41). Under the current definition of COPD a considerable proportion of the adult population is included, especially elderly males, because it is based on a lax definition of airflow obstruction that does not take into account the drop in FEV$_1$/FVC with aging, nor differences in the ratio due to gender, nor the presence of symptoms and exposures (39, 40).

If we define airflow obstruction by a FEV$_1$/FVC <lower limit of normal (<5th percentile) for age and gender post-BD, then the prevalence of airflow obstruction in our sample is reduced from 14% (GOLD criteria) to 10.8% (see Table 3) and by a little more in subjects with low risk of COPD (Tables 2 and 3). Furthermore, the prevalence of airflow obstruction in low risk subjects does not increase as much with age as with the current GOLD criteria and is not very different from the expected 5%, especially with the FEV$_1$/FEV$_6$ variable (Table 2). The proportion of “low risk for COPD” subjects in the group with irreversible obstruction was higher using the FEV$_1$/FVC <0.70 criteria (21.3%), than the FEV$_1$/FVC <5th percentile criteria (18.8%), and than the FEV$_1$/FEV$_6$ <5th percentile criteria (16.2%). This suggests a slightly greater specificity of the <5th percentile criteria especially for FEV$_1$/FEV$_6$. The current criteria for airflow obstruction recommended by the ATS and the ERS is a FEV$_1$/VC<LLN (3), which is based on a similar statistical principle as that used in our study, but requires slow and forced vital capacity maneuvers.

One clear consequence of defining COPD by the post-bronchodilator test is a reduction in the overall prevalence of COPD and probably the obtaining of a more specific definition. In our study, the prevalence of FEV$_1$/FVC <0.70 before bronchodilator use was 21.7%, while after use it was 14.0%, a very significant 35% reduction, similar to the 27% found previously in a sample of 2235 subjects from 26–82 years of age after inhaling 0.3 mg of salbutamol (14). In addition, prevalence of subjects without significant exposure (smoking for >10 pack
years, exposure to biomass smoke for >200 hour-years and exposure to occupational dust for >5 years), as well as lacking respiratory symptoms (dyspnea, cough, phlegm and wheezing) was reduced from 40.1% in non-obstructed subjects, to 30.1% in those with “reversible obstruction”, and to 21.2% in those with irreversible obstruction.

This can be interpreted as a substantial increase in specificity for COPD due to BD testing. However, although this 21% of subjects with postBD “COPD” asymptomatic and lacking significant exposures may include ill subjects with uncommon or unknown exposures (42), it is likely that many of them are false positives (39, 40). For many purposes a 21% rate of (presumably) false positives is too high. If diagnosis implies treatment or follow-up, it would be best to “confirm” clinically the suspected diagnosis and consider spirometry testing as a screening test, especially if used with an open population. Subjects with “low risk” for COPD are reduced to 16.1% in those with a FEV1/FEV6<5th percentile, with no important increase in prevalence with age suggesting more specificity.

However, the rate of abnormal subjects using this criterion depends strongly on the reference equations used and whether or not they were calculated using prebronchodilator tests or postbronchodilator tests. Usual reference equations are based on tests done without the use of bronchodilators, while we apply them to tests done after bronchodilator use. Lower limits of normal (5th percentiles) based on tests done after bronchodilator (Table 3), results in an increase in the prevalence of abnormal tests, because use of the bronchodilator results in an overall increase in FEV1/FVC and FEV1/FEV6 and, therefore, the 5th percentile is displaced upwards (Figures 1 and 2). To reduce misclassifications, reference values obtained from tests done after bronchodilator use are ideal as would improved data on the reproducibility of bronchodilator testing.

Several difficulties should be acknowledged. The type and dose of bronchodilator used could change the results unless a maximal bronchodilation is assured by selecting dose and possibly a combination of beta agonists and anticholinergic bronchodilators. However a “maximal bronchodilation” is unlikely to be accepted for a population based survey.

It is questionable whether or not COPD, currently defined by the GOLD committee (1), the ATS and the ERS (2) as a complex, multi-systemic disease, can be identified correctly by only a low FEV1/FVC, especially after proposing a multidimensional evaluation (43).

Current definitions specify that COPD is related mainly to exposure to tobacco or other similar fumes or inhaled toxins. Thus, less confusion would be generated if COPD were defined as airflow obstruction in smokers or in those exposed (heavily) to dusts or smoke. We wait impatiently for studies on the longitudinal consequences of experiencing airflow obstruction according to different definitions, in order to choose the one that most closely resembles a disease. In the meantime, to properly assess reported COPD prevalences, we must take into account the definition of airflow obstruction, the use of a bronchodilator and the reported prevalences of “COPD” in low-risk subjects (low pre-test probability of COPD) such as asymptomatic non-smokers who also lack exposure to other dusts and fumes and previous diagnoses of COPD or asthma.

Our study shows little justification to screen for COPD subjects with low pre-test probability of airway disease. On the other hand our study supports testing after bronchodilator use and defining airflow obstruction by the fifth percentile of the FEV1/FVC or FEV1/FEV6 (instead of FEV1/FVC<0.70) using appropriate reference values. The 5th percentile in tests done after bronchodilator use can be defined precisely only with reference equations obtained from post-BD tests, although this requires additional reference values, which are not widely available at present.
REFERENCES


EDITORIAL

Don’t Diagnose Mild COPD Without Confirming Airway Obstruction after an Inhaled Bronchodilator

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Spirometry results from the excellent PLATINO study of COPD prevalence in Latin American countries, as reported in this issue (1), provide 3 important lessons for both clinicians and pulmonary epidemiologists:

1. People with a low pre-test probability for COPD should not be screened for COPD;
2. Values below the 5th percentile of FEV1/FVC from healthy subjects should be used to detect airway obstruction (not the fixed ratio 0.70 recommended by GOLD); and
3. Post-bronchodilator (post-BD) spirometry must be done for smokers with mild pre-BD airway obstruction, since up to one-third do not have COPD.

The multi-center PLATINO study used a spirometer with excellent quality checks and demonstrated long-term accuracy (2). A strict spirometry quality assurance program, with the same standardized protocol used by the Burden of Obstructive Lung Disease (BOLD) Initiative (3), successfully produced 95% of pre- and post-BD test sessions exceeding American Thoracic Society 1994 goals. Multiple methods of interpreting airflow limitation and describing BD reversibility were analyzed and compared. In short, the study design, population-based sampling and spirometry methods, results, and analyses were superb.

1. The investigators wisely separated the adults into two groups: low pre-test probability for COPD and high pre-test probability (risk) for COPD. The very low prevalence of airway obstruction (about 6% overall) in those with low pre-test probability for COPD argues strongly that screening spirometry should not be done for people without respiratory symptoms, less than 10 years of smoking, no history of asthma, and low workplace exposures to respiratory hazards. Unfortunately, screening spirometry programs at sporting events in the United States have targeted tens of thousands of such individuals during the past 5 years (4). In our opinion, the “selling of sickness” in relatively low risk populations will detract from legitimate COPD case-finding among high risk patients in primary care settings (5).

2. The PLATINO investigators also confirmed previous studies demonstrating that the overly simplistic 2001 GOLD definition of airway obstruction (6) using a fixed ratio (0.70) causes a very large false positive rate in older people (7). Since almost all studies show that in healthy subjects the FEV1/FVC falls with normal aging (8) to well below 0.7, and that all office spirometers have a microprocessor which computes the appropriate lower limit of the normal range (the 5th percentile) for spirometry variables, we are not impressed with rationalizations for continued support of an arbitrary fixed ratio to define airway obstruction. The GOLD group acknowledged this in their 2006 update of recommendations (9): “However, because the process of aging does affect lung volumes, the use of this fixed ratio may result in over diagnosis of COPD in the elderly, especially of mild disease. Using the lower limit of normal (LLN) values for FEV1/FVC, that are based on the normal distribution and classify the bottom 5% of the healthy population as abnormal, is one way to minimize the potential misclassification.” Considering the paucity of evidence for a benefit from any intervention for mild COPD other than smoking cessation (10, 11), falsely affixing a COPD label is likely to cause more harm than good (12).

3. The results of PLATINO spirometry also conclusively demonstrate that post-BD testing (as recommended by most guidelines) is necessary before affixing the COPD label on any subject with respiratory symptoms and mild (pre-BD) airway obstruction. About one-third of those...
with pre-BD airway obstruction did not have airway obstruction post-BD (firmly ruling out COPD). While spirometry testing is generally under-utilized for patients with respiratory symptoms and for confirming a diagnosis of COPD, those who do provide spirometry in their office almost never take the extra time for post-BD spirometry (13–15). Since asthma is nearly as common as COPD in adults with respiratory symptoms, the lack of pre-BD spirometry means that asthma is often misdiagnosed as COPD. Such faulty medical decision-making hurts patients since the treatment and prognosis of asthma differs substantially from that of COPD.

It’s easy to confuse the concepts of BD-responsiveness and post-BD airway obstruction when attempting to differentiate asthma from COPD in adults. In patients with an increased pre-test probability of asthma, baseline airway obstruction with a “significant” BD response increases the (post-test) probability of asthma. On the other hand, the lack of BD-responsiveness does not rule out asthma in such patients, and thus provides no clinically important information.

In patients with a high pre-test probability of COPD, moderate to severe post-BD airway obstruction confirms COPD, and normal post-BD spirometry rules out COPD. However, BD responsiveness in adult smokers (with or without baseline airway obstruction) rarely provides clinically useful information. It varies widely from visit-to-visit (16, 17), does not increase the probability of COPD, and does not substantially increase the likelihood of response to bronchodilator or corticosteroid therapy (18).

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