informa
healthcare

ORIGINAL RESEARCH

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

Rogelio Pérez-Padilla[1] (perezpad@servidor.unam.mx), **Pedro Curi Hallal**[2] (prchallal@terra.com.br),
Juan Carlos Vázquez-García[1] (jcvaz@prodigy.net.mx), **Adriana Muiño**[3] (amuinio@adinet.com.uy),
María Máquez[3] (mariamp@adinet.com.uy), **María Victorina López**[3] (mlopez@chasque.net),
María Montes de Oca[4] (mmdeoca@cantv.net), **Carlos Tálamo**[4] (carlostalamo@hotmail.com),
Gonzalo Valdivia[5] (valdivia@med.puc.cl), **Julio Pertuzé**[5] (jpertuze@med.puc.cl), **Jose Jardim**[6] (joserjardim@yahoo.com.br),
and **Ana Maria B. Menezes**[2] (anamene@terra.com.br), **on behalf of the PLATINO group**

[1]*National Institute of Respiratory Diseases, Mexico City, Mexico*
[2]*Federal University of Pelotas – Brazil*
[3]*University of the Republic, Faculty of Medicine, Montevideo, Uruguay*
[4]*Pulmonary Division, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela*
[5]*Pontificia Universidad Católica de Chile, Santiago, Chile*
[6]*Federal University of Sao Paulo –Brazil*

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 $FEV_1/FVC\% < 0.70$ from 21.7% to 14% (35%). In the group with $FEV_1/FVC < 0.70$ after bronchodilator use, 21% were asymptomatic from the respiratory point of view, and lacked significant adverse exposures. Subjects below the 5th percentile for FEV_1/FVC and FEV_1/FEV_6 were fewer than those with $FEV_1/FVC < 0.70$, especially among the elderly. More subjects are below the 5th percentile of FEV_1/FVC and FEV_1/FEV_6 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.

INTRODUCTION

According to the GOLD guidelines the diagnosis of Chronic Obstructive Pulmonary Disease (COPD) is a FEV_1/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 FEV_1 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 FEV_1/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 $FEV_1/FVC < 0.70$ 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 (*EasyOne* 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), but 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 FEV_1 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 (deltaFEV_1 in mL, deltaFVC in mL, deltaFEV_6 in mL, delta $FEV1/FEV_6$ in % and deltaFEV_1/FVC in %), but also as the percentage change of the preBD value (postBD–preBD)*100/preBD, (deltaFEV_1%, deltaFVC%, deltaFEV_6%, deltaFEV_1/FEV_6%, delta deltaFEV_1/FVC%), and finally as postBD-preBD, both expressed as a percentage of predicted values (deltaFEV_1%p, deltaFVC%p, deltaFEV_6%p, deltaFEV_1/FEV_6%p, and deltaFEV_1/FVC%p).

We recognized tests that complied with the current criteria for significant bronchodilator response: an increase in 200 mL and 12% of either FEV_1 or FVC after bronchodilator use (23).

We identified subjects with airflow obstruction before and after inhaling the bronchodilator using several definitions: (a) $FEV_1/FVC < 0.70$, the criteria used in the GOLD guidelines (1), (b) FEV_1/FVC (3) or (c) FEV_1/FEV_6 (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 FEV_1 and FVC repeatable to within 150 mL, thus complying with the 2005 ATS-ERS standards (19), whereas 95.3% had FEV_1 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)

	High risk for COPD subjects				Low risk for COPD subjects*			
Variable	Women 1810	SD	Men 1478	SD	Women 1309	SD	Men 586	SD
Age	56.8	11.7	56.9	11.6	55.6	11.7	53.7	10.9
Height (cm)	154.0	6.6	167.6	7.5	153.7	6.7	167.1	7.1
Weight (Kg)	68.5	14.7	77.3	14.9	66.6	13.5	75.0	12.4
BMI (Kg/m^2)	28.9	5.9	27.4	4.4	28.2	5.5	26.8	4.0
FEV_1 preBD (L)	2.14	0.5	2.98	0.8	2.27	0.5	3.23	0.7
FVC preBD (L)	2.85	0.7	4.09	0.9	2.93	0.6	4.22	0.8
FEV_6 preBD (L)	2.72	0.6	3.85	0.9	2.82	0.6	4.05	0.8
FEV_1/FVC preBD	74.8	8.6	72.8	9.9	77.6	7.1	76.7	7.0
FEV_1/FEV_6 preBD	78.3	6.7	76.9	7.9	80.5	5.4	79.8	5.5
FEV_1 %P	93.7	18.4	93.4	18.6	98.9	16.9	99.3	15.6
FVC %P	98.4	16.6	97.3	16.5	100.7	16.7	99.4	15.1
FEV_6 %P	95.8	16.0	95.8	16.2	98.9	15.7	99.3	14.6
Delta FEV_1 mL	85.5	133.1	102.0	197.2	71.9	205.2	89.8	169.5
Delta FEV_1 %	4.0	8.4	3.4	7.2	2.8	9.2	2.7	5.4
Delta FEV_1 %P	3.9	6.1	3.2	6.1	3.2	8.6	2.8	5.5
Delta FEV_6 mL	38.9	169.5	43.4	244.5	23.5	243.4	3.6	210.5
Delta FEV_6 %	2.0	7.7	1.7	8.7	1.9	21.8	0.4	5.9
Delta FEV_6 %P	1.5	6.2	1.1	6.1	0.9	8.5	0.2	5.4
Delta FVC mL	−4.0	232.1	−2.8	299.9	−13.4	299.9	−31.7	266.0
Delta FVC %	−0.21	8.8	−0.15	7.8	−0.8	9.6	−0.8	6.8
DeltaFVC %P	−0.02	8.2	−0.05	7.2	−0.4	10.4	−0.7	6.5
Delta FEV_1/FVC	3.1	4.8	2.6	4.0	2.7	5.3	2.7	4.3
Delta FEV_1/FVC %	4.5	7.2	3.9	6.1	3.8	7.7	3.7	6.1
Delta FEV_1/FVC %P	4.0	6.2	3.5	5.3	3.5	6.8	3.5	5.7
Delta FEV_1/FEV_6	2.0	3.3	1.9	2.9	1.8	3.8	2.1	3.2
Delta FEV_1/FEV_6 %	2.7	4.4	2.5	4.1	2.4	5.5	2.8	4.2
Delta FEV_1/FEV_6 %P	2.5	4.1	2.3	3.7	2.2	4.7	2.7	4.0

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 (17). 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 FEV_1, FEV_6, FVC, FEV_1/FEV_6 and FEV_1/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 FEV_6 (except in healthy men) and in the FEV_1/FEV_6 and FEV_1/FVC ratios, but mean changes in FVC after bronchodilator use were not statistically different from zero.

The overall 95th percentile for the change in FEV_1 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 FEV_6 it was 277 mL (10.4% of preBD and 9.4% of predicted) for FEV_1/FVC was 9% (13% of preBD and 11.4% of predicted) and for FEV_1/FEV_6 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 ($FEV_1/FVC<0.70$) 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

| | Definition of airflow obstruction | | | | | |
| | $FEV_1/FVC<0.70$ | | $<$5th percentile FEV_1/FVC | | $<$ 5th percentile FEV_1/FEV_6 | |
Age group	PreBD tests	PostBD tests	PreBD tests	Post BD tests	PreBD tests	PostBD tests
Subjects with high risk for COPD						
40–45	12.7 (1.4)	6.5 (1.0)	9.7 (1.3)	9.0 (1.1)	10.3 (1.2)	8.6 (1.2)
45–50	17.2 (1.2)	10.4 (0.9)	12.4 (1.0)	11.0 (0.9)	11.0(0.9)	11.1 (1.0)
50–60	28.1 (1.6)	18.7 (1.5)	14.8 (1.3)	14.5 (1.3)	13.6 (1.2)	13.1 (1.4)
60–70	43.4 (2.3)	30.3 (2.2)	20.4 (1.9)	20.2 (1.8)	19.8 (1.8)	18.0 (1.7)
>70	50.3 (2.9)	38.7 (2.6)	21.3 (2.4)	20.7 (2.2)	19.3 (2.3)	21.7 (2.2)
All age groups	26.2 (0.8)	17.4 (0.7)	14.5 (0.7)	13.8 (0.6)	13.6 (0.6)	13.2 (0.6)
Subjects with low risk for COPD						
40–45	5.4 (1.2)	2.9 (0.8)	5.2 (1.1)	3.5 (0.9)	4.0 (0.9)	3.8 (0.9)
45–50	7.7 (1.0)	4.4 (0.8)	5.0 (0.9)	5.0 (0.8)	4.7 (0.8)	4.6 (0.8)
50–60	14.5 (1.7)	7.6 (1.2)	5.7 (1.2)	5.2 (1.1)	5.2 (1.1)	5.4 (1.1)
60–70	29.8 (2.9)	17.9 (2.2)	9.2 (1.8)	9.5 (1.9)	6.9 (1.5)	6.9 (1.6)
>70	38.0 (4.1)	27.1 (3.4)	10.9 (2.7)	8.5 (2.3)	10.1 (2.7)	8.5 (1.4)
All age groups	13.8 (0.8)	8.2 (0.6)	6.2 (0.6)	5.6 (0.5)	5.3 (0.5)	5.2 (0.5)

Low-risk subjects (a total of 1895) 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, a lower FVC before bronchodilator use 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

| | PreBD tests | | PostBD tests | |
Proportion	Prevalence (%)	SE	Prevalence (%)	SE
$FEV_1/FVC<0.70$	21.7	0.6	14.0	0.5
Reference equations obtained from pre BD tests				
$FEV_1/FVC<LLN$ NHANES III	19.3	0.6	11.7	0.5
$FEV_1/FEV_6 <$ LLN NHANES III	14.1	0.5	9.5	0.4
$FEV_1/FVC<LLN$ PLATINO	11.5	0.5	7.6	0.4
$FEV_1/FEV_6 <$ LLN PLATINO	10.6	0.4	7.2	0.4
Reference equations obtained from postBD tests				
$FEV_1/FVC<LLN$ PLATINO	17.4	0.6	10.8	0.4
$FEV_1/FEV_6 <$ LLN PLATINO	15.3	0.5	10.2	0.4

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 than 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 if. 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 im-

pact 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 $FEV_1/FEV_6<$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 FEV_1/FVC and FEV_1/FEV_6 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.
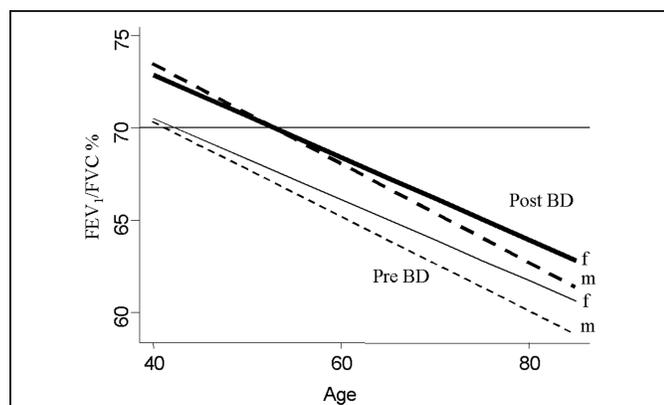
Figure 1. Estimated lower limit of normality (5th percentile) of FEV_1/FVC for normal men (broken lines) and women (continuous lines) for spirometry done before (thin lines), and after bronchodilator use (thick lines) as a function of age. Data from the PLATINO study for subjects of average height (167 cm for men and 154 cm for women). FEV_1/FVC increases after bronchodilator use, and decreases with age slightly more in men than in women. The horizontal line is at a FEV_1/FVC of 70%, a common criterion for diagnoses of COPD that does not take into account aging or gender.
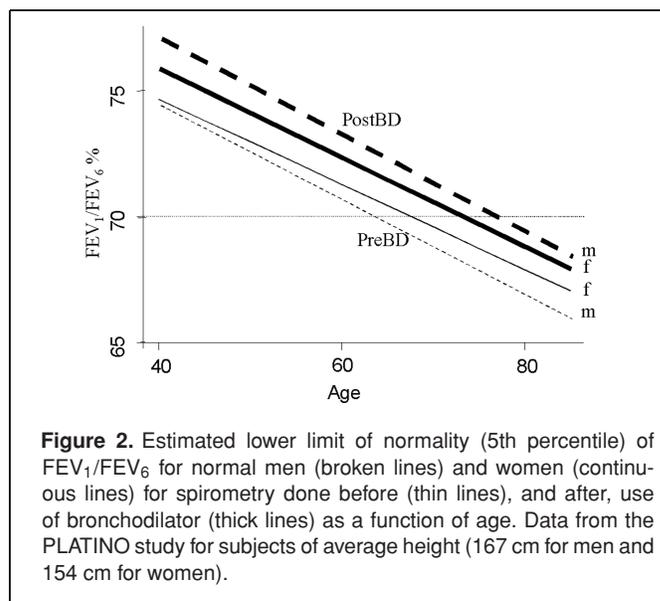
Figure 2. Estimated lower limit of normality (5th percentile) of FEV_1/FEV_6 for normal men (broken lines) and women (continuous lines) for spirometry done before (thin lines), and after, use of bronchodilator (thick lines) as a function of age. Data from the PLATINO study for subjects of average height (167 cm for men and 154 cm for women).

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 FEV_1/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 smokes. 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 FEV_1/FVC or FEV_1/FEV_6 (instead of $FEV_1/FVC<0.70$) 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

1. **GOLD.** Workshop report, global strategy for diagnosis, management and prevention of COPD http://www.goldcopd.com/ 2005.

2. **Celli BR, MacNee W.** Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004; 23(6):932–946.

3. **Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J.** Interpretative strategies for lung function tests. Eur Respir J 2005; 26(5):948–968.

4. **Kerstjens HA, Brand PL, Quanjer PH, van der Bruggen-Bogaarts BA, Koeter GH, Postma DS.** Variability of bronchodilator response and effects of inhaled corticosteroid treatment in obstructive airways disease. Dutch CNSLD Study Group. Thorax 1993; 48(7):722–729.

5. **Jenkins C, Young I.** Assessing bronchodilator reversibility: agreed standards are urgently needed. Med J Aust 2004; 180(12):605–606.

6. **Dompeling E, van Schayck CP, Molema J, Akkermans R, Folgering H, van Grunsven PM, van Weel C.** A comparison of six different ways of expressing the bronchodilating response in asthma and COPD; reproducibility and dependence of prebronchodilator FEV_1. Eur Respir J 1992; 5(8):975–981.

7. **Brand PL, Quanjer PH, Postma DS, Kerstjens HA, Koeter GH, Dekhuijzen PN, Sluiter HJ.** Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. Thorax 1992; 47(6):429–436.

8. **Chhabra SK.** Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. J Asthma 2005; 42(5):367–372.

9. **Kesten S, Rebuck AS.** Is the short-term response to inhaled beta-adrenergic agonist sensitive or specific for distinguishing between asthma and COPD? Chest 1994; 105(4):1042–1045.

10. **Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW.** Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003; 58(8):659–664.

11. **Douma WR, de Gooijer A, Rijcken B, Schouten JP, Koeter GH, Weiss ST, Postma DS.** Lack of correlation between bronchoconstrictor response and bronchodilator response in a population-based study. Eur Respir J 1997; 10(12):2772–2777.

12. **Anthonisen NR, Lindgren PG, Tashkin DP, Kanner RE, Scanlon PD, Connett JE.** Bronchodilator response in the lung health study over 11 yrs. Eur Respir J 2005; 26(1):45–51.

13. **Hansen EF, Vestbo J.** Bronchodilator reversibility in COPD: the roguish but harmless little brother of airway hyperresponsiveness? Eur Respir J 2005; 26(1):6–7.

14. **Johannessen A, Omenaas ER, Bakke PS, Gulsvik A.** Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. Thorax 2005; 60(10):842–847.

15. **Menezes AM, Victora CG, Perez-Padilla R.** The Platino project: methodology of a multicenter prevalence survey of chronic obstructive pulmonary disease in major Latin American cities. BMC Med Res Methodol 2004; 4(1):15.

16. **Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, Montes de Oca M, Talamo C, Hallal PC, Victora CG.** Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 2005; 366(9500):1875–1881.

17. **Perez-Padilla R, Valdivia G, Muino A, Lopez MV, Marquez MN, Montes de Oca M, Talamo C, Lisboa C, Pertuze J, B. J. JR, B. M. AM**. Spirometric reference values in 5 large Latin American cities for subjects aged 40 years or over. Arch Bronconeumol 2006; 42(7):317–325.

18. **American Thoracic Society.** Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med 1995; 152(3):1107–1136.

19. **Miller MR., Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J.** Standardisation of spirometry. Eur Respir J 2005; 26(2):319–338.

20. **Borrill ZL, Houghton CM, Woodcock AA, Vestbo J, Singh D.** Measuring bronchodilation in COPD clinical trials. Br J Clin Pharmacol 2005; 59(4):379–384.

21. **Lehmann S, Bakke PS, Eide GE, Humerfelt S, Gulsvik A.** Bronchodilator reversibility testing in an adult general population; the importance of smoking and anthropometrical variables on the response to a beta(2)-agonist. Pulm Pharmacol Ther 2006; 19(4):272–280.

22. **Johannessen A, Lehmann S, Omenaas ER, Eide GE, Bakke PS, Gulsvik A.** Post-bronchodilator spirometry reference values in adults and implications for disease management. Am J Respir Crit Care Med 2006, Jun 15; 173(12):1316–1325.

23. **American Thoracic Society.** Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis 1991; 144(5):1202–1218.

24. **Ferguson GT, Enright PL, Buist AS, Higgins MW.** Office spirometry for lung health assessment in adults: a consensus statement from the National Lung Health Education Program. Chest 2000; 117(4):1146–1161.

25. **Hankinson JL, Odencrantz JR, Fedan KB.** Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159(1):179–187.

26. **StataCorp.** Stata Statistical Software: release 9.0 Stata Corporation, College Station, TX, USA 2005.

27. **Cerveri I, Dore R, Corsico A, Zoia MC, Pellegrino R, Brusasco V, Pozzi E.** Assessment of emphysema in COPD: a functional and radiologic study. Chest 2004; 125(5):1714–1718.

28. **Newton MF, O'Donnell DE, Forkert L.** Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 2002; 121(4):1042–1050.

29. **O'Donnell DE, Forkert L, Webb KA.** Evaluation of bronchodilator responses in patients with "irreversible" emphysema. Eur Respir J 2001; 18(6):914–920.

30. **Cerveri I, Pellegrino R, Dore R, Corsico A, Fulgoni P, van de Woestijne KP, Brusasco V.** Mechanisms for isolated volume response to a bronchodilator in patients with COPD. J Appl Physiol 2000; 88(6):1989-1995.

31. **Barros MJ, Rees PJ.** Bronchodilator responses to salbutamol followed by ipratropium bromide in partially reversible airflow obstruction. Respir Med 1990; 84(5):371–375.

32. **McIvor RA, Tashkin DP.** Underdiagnosis of chronic obstructive pulmonary disease: a rationale for spirometry as a screening tool. Can Respir J 2001; 8(3):153–158.

33. **Takahashi T, Ichinose M, Inoue H, Shirato K, Hattori T, Takishima T.** Underdiagnosis and undertreatment of COPD in primary care settings. Respirology 2003; 8(4):504–508.

34. **Dal Negro R, Rossi A, Cerveri I.** The burden of COPD in Italy: results from the Confronting COPD survey. Respir Med 2003; 97 Suppl C:S43–50.

35. **Johannessen A, Omenaas E, Bakke P, Gulsvik A.** Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. Int J Tuberc Lung Dis 2005; 9(8):926–932.

36. **Wilt T, Niewoehner DE, Kim C, Kane RL, Linabery A, Tacklind J, MacDonald R, Rutks I.** Use of spirometry for case finding, diagnosis, and management of Chronic Obstructive Pulmonary Disease. Summary. Agency for Healthcare Research and Quality, Rockville, MD, 2005.

37. **Boushey H, Enright P, Samet J.** Spirometry for chronic obstructive pulmonary disease case finding in primary care? Am J Respir Crit Care Med 2005; 172(12):1481–1482.

38. **Celli BR, Halbert RJ, Isonaka S, Schau B.** Population impact of different definitions of airway obstruction. Eur Respir J 2003; 22(2):268–273.

39. **Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O.** Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J 2002; 20(5):1117–1122.

40. **Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist SA.** Case definitions for Chronic Obstructive Pulmonary Disease. COPD: Journal of Chronic Obstructive Pulmonary Disease 2006; 3:95–100.

41. **Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci S, Carrozzi L, Giuntini C.** Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. Chest 2000; 117(5 Suppl 2):339S-45S.

42. **Celli BR, Halbert RJ, Nordyke RJ, Schau B.** Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. Am J Med 2005; 118(12):1364–1372.

43. **Celli BR, Calverley PM, Rennard SI, Wouters EF, Agusti A, Anthonisen N, Macnee W, Jones P, Pride N, Rodriguez-Roisin R, Rossi A, Wanner A.** Proposal for a multidimensional staging system for chronic obstructive pulmonary disease. Respir Med 2005; 99(12):1546–1554.

informa
healthcare

EDITORIAL

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

Paul Enright[1] (lungguy@aol.com) and **Philip Quanjer**[2] (pquanjer@xs4all.nl)

[1] *College of Public Health, University of Arizona, Tucson, Arizona*
[2] *University of Leiden, The Netherlands*

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 FEV_1/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 FEV_1/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

Correspondence to:
Paul Enright
College of Public Health
University of Arizona
4460 East Ina Road
Tucson, AZ 85718
email: lungguy@aol.com

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 post-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).

REFERENCES

1. **Perez-Padilla R, Hallal PC, Vazquez-Garcia JC, et al, on behalf of the PLATINO group.** Impact of bronchodilator use on the prevalence of COPD in population-based samples. COPD 2007; in press.
2. **Perez-Padilla R, Vazquez-Garcia JC, Marquez MN, Jardim JR, Pertuze J, Lisboa C, Muino A, Lopez MV, Talamo C, de Oca MM, Valdivia G, Menezes AM; Latin American COPD Prevalence Study (PLATINO) Team.** The long-term stability of portable spirometers used in a multinational study of the prevalence of chronic obstructive pulmonary disease. Respir Care 2006; 51(10):1167–1171.
3. **Buist AS, Vollmer WM, Sullivan SD, Weiss KB, Lee TA, Menezes AM, Crapo RO, Jensen RL, Burney PG.** The Burden of Obstructive Lung Disease Initiative (BOLD): rationale and design. COPD 2005 Jun; 2(2):277–283.
4. **US Wellness.** Are you a respiratory therapist with spirometry experience? Consider joining the US Wellness network of health care professionals. <www.nrtc-usa.org/CareerOpportunities.html> and <www.uswellness.com> Accessed March 6, 2007.
5. **Ferguson GT, Enright PL, Buist AS, Higgins MW.** Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 2000; 117:1146–1161.
6. **Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS; GOLD Scientific Committee.** Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease Workshop summary. Am J Respir Crit Care Med 2001; 163:1256–1276.
7. **Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS.** Case definitions for chronic obstructive pulmonary disease. COPD 2006 Jun; 3(2):95–100.
8. **Quanjer P.** For the Falling Ratio Working Group. FEV1% predicted versus Lower Limit of Normal for FEV1. <www.spirxpert.com/controversies/controversy1.html>, accessed March 10, 2007.
9. **Global Initiative for Chronic Obstructive Lung Disease.** Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2006 Update. <www.goldcopd.com> (Accessed March 10, 2006).
10. **AHRQ Minnesota Evidence-based Practice Center of the Agency for Healthcare Research and Quality.** Use of Spirometry for Case Finding, Diagnosis, and Management of COPD. Publication No. 05-E017-2, August 2005. <http://www.ahrq.gov/clinic/tp/spirotp.htm> Accessed March 7, 2007.
11. **Albers M, Schermer T, van den Boom G, et al.** Efficacy of inhaled corticosteroids in undiagnosed subjects at high risk for COPD. Chest 2004; 126:1815–1824.
12. **Enright P.** Does screening for COPD by primary care physicians have the potential to cause more harm than good? Chest 2006 Apr; 129(4):833–835.
13. **Naberan K, delaRoza C, Lamban M, Bobartt E, Martin A, Miravitlles M.** Use of spirometry in the diagnosis and treatment of COPD in primary care. Arch Bronconeumol 2006; 42:638–644.
14. **Lusuardi M, de Benedetto F, Paggiaro P, et al.** A randomized controlled trial on office spirometry in asthma and COPD in tandard office practice. Chest 2006; 129:844–852.
15. **Lee TA, Bartle B, Weiss KB.** Spirometry use in clinical practice following diagnosis of COPD. Chest 2006; 129(6):1509–1515.
16. **Brand PL, Quanjer PH, Postma DS, et al.** Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. Thorax 1992; 47:429–436.
17. **Dompeling E, Van Schayck CP, Molema J, et al.** A comparison of six different ways of expressing the bronchodilating response in asthma and COPD: reproducibility and dependence of prebronchodilator FEV_1. Eur Respir J 1992; 5:975–981.
18. **Calverley PMA, Burge PS, Spencer S, Anderson JA, Jones PW, for the ISOLDE Study Investigators.** Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 2003; 58:659–664.