Spirometry Reference Values After Inhalation of 200 µg of Salbutamol

Rogelio Pérez-Padilla,[a] Luis Torre Bouscoulet,[a] Juan Carlos Vázquez-García,[a] Adriana Muiño,[b] María Márquez,[b] María Victorina López,[b] María Montes de Oca,[c] Carlos Tálamo,[c] Gonzalo Valdivia,[d] Julio Pertuze,[d] José Jardim,[e] and Ana María B. Menezes[f] on behalf of the PLATINO group*

[a]Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico
[b]Facultad de Medicina, Universidad de la República, Montevideo, Uruguay
[c]División Pulmonar, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela
[d]Pontificia Universidad Católica de Chile, Santiago, Chile
[e]Universidad Federal de São Paulo, São Paulo, Brazil
[f]Universidad Federal de Pelotas, Pelotas, Brazil

OBJECTIVE: The criteria for disease severity established by the Global Initiative for Chronic Obstructive Lung Disease are based on forced expiratory volume in 1 second (FEV_1) expressed as a percentage of the predicted value after application of a bronchodilator. This study aims to determine postbronchodilator spirometry reference values.

SUBJECTS AND METHODS: A cluster sample of subjects aged 40 years or over was chosen to be representative of the metropolitan areas of 5 Latin American cities (São Paulo, Mexico City, Montevideo, Santiago, and Caracas). Spirometry was performed on 5183 subjects following the recommendations of the American Thoracic Society before and after inhalation of 200 µg of salbutamol. Multiple linear regression equations were fitted for the postbronchodilator spirometric values–FEV_1, forced expiratory volume in 6 seconds (FEV_6), peak expiratory flow rate, forced vital capacity (FVC), FEV_1/FEV_6, FEV_1/FVC and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}). These were adjusted for sex, age, and height in 887 asymptomatic subjects with no history of lung disease.

RESULTS: The postbronchodilator reference values for FEV_1, FEV_1/FVC, and FEV_1/FEV_6 were on average 3% higher than those obtained before bronchodilation. This apparently small difference caused an upward shift in the 5th percentile (lower limit of normal) of the predicted values. When prebronchodilation instead of postbronchodilation reference values were used, 3.2% of the results for airflow obstruction in our population of over-40-year-olds were false negatives.

CONCLUSIONS: The reported reference values are more appropriate for postbronchodilator spirometry and make it possible to reduce the number of misclassifications.

Key words: *Chronic obstructive pulmonary disease (COPD). Bronchodilator response. Reference values. Spirometry. Cross-sectional study. Latin America. PLATINO.*

*The remaining members of the PLATINO group are listed at the end of the article.

This study was financed by a Boehringer-Ingelheim research grant. The company played no role in the data analysis or preparation of the manuscript.

Correspondence: Dr. R. Pérez-Padilla.
Instituto Nacional de Enfermedades Respiratorias.
Tlalpan, 4502. 14080 Mexico City, Mexico.
E-mail: perezpad@servidor.unam.mx

Manuscript received September 3, 2006. Accepted for publication September 19, 2006.

Valores de referencia para la espirometría después de la inhalación de 200 mg de salbutamol

OBJETIVO: La clasificación de la gravedad de la enfermedad pulmonar obstructiva crónica (EPOC) se basa, de acuerdo con la iniciativa GOLD, en el volumen espiratorio forzado en el primer segundo (FEV_1) después de usar broncodilatador, expresado como porcentaje del esperado. El propósito de este trabajo ha sido determinar los valores de referencia para la espirometría después de la administración de broncodilatador.

SUJETOS Y MÉTODOS: Se realizó un muestreo por conglomerados de sujetos de 40 años o más, representativos de las zonas metropolitanas de São Paulo, Ciudad de México, Montevideo, Santiago y Caracas. Se realizó una espirometría a 5.183 sujetos de acuerdo con las recomendaciones de la American Thoracic Society, antes y después de la inhalación de 200 µg de salbutamol. Se efectuaron regresiones lineales múltiples para los valores espirométricos –FEV_1, volumen espiratorio forzado en 6 s (FEV_6), índice de flujo espiratorio máximo, capacidad vital forzada (FVC), FEV_1/FEV_6, FEV_1/FVC y flujo mesoespiratorio forzado–después del uso del broncodilatador, ajustando por sexo, edad y altura, en 887 sujetos sin evidencia de enfermedad pulmonar previa.

RESULTADOS: Los valores de referencia tras broncodilatador para FEV_1, FEV_1/FVC y FEV_1/FEV_6 fueron en promedio un 3% mayores que los obtenidos con la espirometría realizada antes de la inhalación del broncodilatador. Esta diferencia, que parece pequeña, causa un desplazamiento hacia arriba en el percentil 5 (límite inferior de la normalidad) de los valores esperados. Si se utiliza el valor de referencia prebroncodilatador, en lugar del posbroncodilatador, se genera un 3,2% de falsos negativos para obstrucción al flujo aéreo en el total de la población de 40 o más años de edad.

CONCLUSIONES: Los valores de referencia indicados son más apropiados para espirometrías realizadas después de la inhalación del broncodilatador y permiten minimizar los errores de clasificación.

Palabras clave: *EPOC. Respuesta al broncodilatador. Valores de referencia. Espirometría. Estudio transversal. Latinoamérica. PLATINO.*

Introduction

The current diagnostic criterion for chronic obstructive pulmonary disease (COPD), as established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1,2] is a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) less than 0.7 after application of a bronchodilator (post-BD). This criterion renders forced spirometry reference values unnecessary. However, according to the GOLD initiative, severity of disease is classified according to the post-BD FEV_1 expressed as a percentage of the predicted value. In most cases, this is based on reference values from spirometry tests performed without a bronchodilator. In these circumstances, post-BD spirometry volumes, which tend to be greater, are compared with reference values obtained before application of the bronchodilator (pre-BD). This could lead to misclassification, as the fifth percentile tends to shift upward when compared with the pre-BD spirometry tests. The definition of COPD drawn up by the GOLD initiative contrasts with recommendations for the interpretation of spirometry test results,[3] which consider that airflow is obstructed when the FEV_1/FVC ratio is below the lower limit of normal (LLN), ie, below the fifth percentile. If the LLN is accepted as the criterion for defining airflow obstruction, based on its statistical validity, then classification errors could be generated, not only in terms of severity but also with respect to the diagnosis of COPD. Little information is available on post-BD reference values, although Johannessen et al[4] recently established such values and compared them with pre-BD values in 515 European subjects. The objective of the present study was to describe the reference values for post-BD forced spirometry and their role in the diagnosis of COPD using the healthy subjects enrolled in the Latin American population-based PLATINO study.[5]

Subjects and Methods

The study was approved by the ethics committees of the participating institutions and all the subjects gave their written informed consent. The sample and PLATINO study design have been described elsewhere,[5] as have the prevalence of COPD according to the GOLD criteria[6] and the pre-BD spirometry reference values.[7] Briefly, similarly designed multistage cluster sampling was used to obtain population samples for the metropolitan areas of the 5 participating cities (Caracas, Mexico City, Santiago, São Paulo, and Montevideo). Sixty-eight electoral zones representative of each of the metropolitan areas were chosen in order to include a minimum sample of 800 subjects per city.

The subjects underwent spirometry testing with a portable spirometer measuring ultrasonic transit time (Easy-One, NDD, Zurich, Switzerland). The device was calibrated daily using a 3-L syringe (Hans Rudolph, Kansas City, Missouri, USA).[8] Standard recommendations for spirometry testing[9] were followed, although the subjects (seated and wearing nose clips) were allowed to perform up to 15 forced expiratory maneuvers (the maximum number accepted by the spirometer) in order to obtain 3 acceptable maneuvers according to American Thoracic Society (ATS) criteria,[10] with FVC and FEV_1 values reproducible to within 150 mL. These are the current quality criteria accepted by American and European pulmonology societes.[9] The subjects then received 200 µg of a bronchodilator (salbutamol) using a reservoir or spacer and the spirometry test was repeated 15 minutes later. An increase of 200 mL and 12% in either the post-BD FEV_1 or FVC was considered a positive response.[3] Patients with the following conditions were excluded from the spirometry test: a history of acute myocardial infarction, current pregnancy, a heart rate greater than 120 beats/min, surgery in the previous 3 months, and current antituberculosis therapy. In order to generate the reference values, we selected subjects with a healthy respiratory function according to the previously described criteria[7] for pre-BD reference values; that is, they had no respiratory symptoms (cough, phlegm, wheezing, or dyspnea) and no previous or current diagnosis of asthma, COPD, chronic bronchitis, emphysema, tuberculosis, or lung cancer. Subjects who had undergone lung resection were excluded. Active smokers (cigarettes, cigars, or pipe), ex-smokers, and subjects who had smoked more than 400 cigarettes in their lifetime were excluded, as were 23 subjects who performed fewer than 2 acceptable spirometric maneuvers and 8 subjects aged over 90 years. The latter were excluded as there were few subjects of this age and not all the participating cities were able to recruit individuals in this age group. These criteria agreed with those of the ATS. Furthermore, data from subjects with a body mass index greater than 30 kg/m^2 were not analyzed because obesity was found to have an adverse effect on lung function in this study population. Of the remaining 906 subjects, a post-BD test was obtained from 887, and these make up the group studied in the present research. The selection criteria were very similar to those used by Hankinson et al,[11] except that we did not eliminate data from the 61 patients aged over 80 years, nor did we include data from obese subjects. The spirometric values FEV_1, FVC, peak expiratory flow rate, FEV_1/FVC, forced expiratory volume in 6 seconds (FEV_6), FEV_1/FEV_6, and forced expiratory flow, midexpiratory phase were included in multiple regression models and analyzed by sex, with age and height in centimeters as predictors. Linear models were preferred to curvilinear ones unless there was a significant improvement in the coefficient of determination (R^2) with the latter and a reduction in the residual SD. The LLN (fifth percentile) was calculated by subtracting 1.645 times the residual SD from the average value or by using quantile regression to calculate the fifth percentile directly for men and women based on age and height. The statistical analysis was carried out using the Stata package.[12] For all the analyses, sampling was by clusters; therefore, the survey command of the statistical package was used. Values of P below .05 were considered statistically significant.

Results

Of all the spirometry tests performed post-BD, 90.9% had at least 3 acceptable maneuvers and an FEV_1 and FVC that were reproducible to within 150 mL, ie, they met current ATS and European Respiratory Society (ERS) standards,[9] and 95.3% had FEV_1 and FVC that were reproducible to within 200 mL, ie, they met with the 1994 ATS standards.[13] Of all the spirometry tests performed, 97.9% had 3 or more acceptable maneuvers according to the 1994 ATS standards, 1.4% had 2 acceptable maneuvers, 0.3% had 1 acceptable maneuver, and only 19 tests (0.4%) had no acceptable maneuvers. The post-BD spirometry values were higher than the mean (SE) pre-BD values in 3.2% (0.3%) for FEV_1, 0.6% (0.2%) for FEV_6, 3.5% (0.2%) for FEV_1/FVC, 2.4% (1.6%) for FEV_1/FEV_6, 3.4% (0.4%) for the peak expiratory flow rate, and 13.9% (0.8%) for the forced expiratory flow, midexpiratory phase (figure). The average change in post-BD FVC was not significantly different from 0.

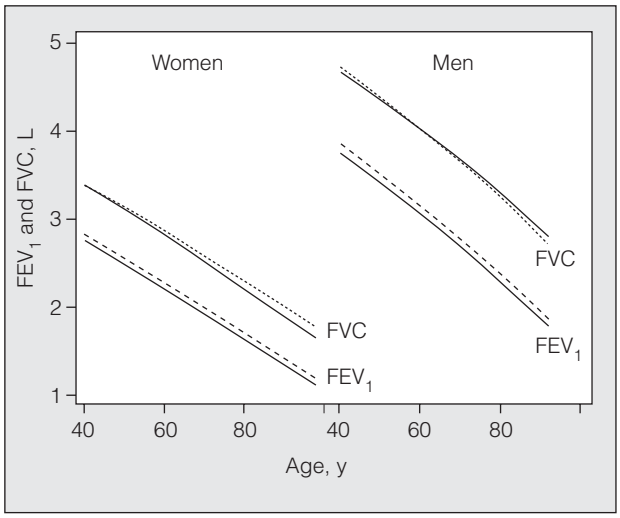

Figure. Estimated forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) for women (left) and men (right) in the study population: prebronchodilator values (solid lines) and postbronchodilator values (broken lines) according to age. The data are from the PLATINO study and those presented are the smoothed data of all the participants following the LOWESS (local weighted scatterplot smoothing) method. FEV_1 increases uniformly with application of the bronchodilator, unlike FVC; therefore, the FEV_1/FVC ratio also increases after application of the bronchodilator. Not using suitable reference values according to whether the test was carried out before or after application of the bronchodilator can lead to misclassification.

TABLE 1
Characteristics of the Study Population*
(=887, 268 Men and 619 Women)

Characteristic	Women		Men	
	Mean	(SD)	Mean	(SD)
Age, y	57.3	(12.1)	55.6	(12.2)
Height, cm	153.6	(6.9)	167.1	(7.2)
Weight, kg	60.5	(8.2)	71.8	(9.7)
Body mass index, kg/m^2	25.6	(2.9)	25.6	(2.8)
FEV_1, L	2.33	(0.58)	3.31	(0.71)
FVC, L	2.90	(0.65)	4.18	(0.86)
FEV_6, L	2.83	(0.63)	4.04	(0.83)
FEV_1/FVC, %	80.0	(7.2)	79.3	(6.8)
FEV_1/FEV_6, %	81.9	(5.9)	81.8	(5.2)
	%		%	
Tests meeting the 1994 ATS quality criteria†	93.5		97.0	
Tests meeting the 2005 ATS-ERS quality criteria‡	90.1		91.0	

*All data are given as mean (SD). FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; ATS, American Thoracic Society; ERS, European Respiratory Society.
†Three acceptable maneuvers and FEV_1 and FVC reproducible to within 200 mL.
‡Three acceptable maneuvers and FEV_1 and FVC reproducible to within 150 mL.

Table 1 shows descriptive data for the study population and the quality of the spirometry tests in the group with a healthy respiratory function. Table 2 shows the reference values for men and women with an estimation of the average values. Estimation of the median value using quantile regression gave almost identical results (not shown). Table 2 also shows the residual SD—the fifth percentile can be calculated by subtracting 1.645 times the residual SD from the average value. Table 3 shows the direct estimations of the fifth percentile or LLN using a quantile regression. These equations predict slightly lower values in elderly patients compared with those obtained by subtracting 1.645 times the residual SD from the average value obtained in Table 2, given that the data tended to disperse more with age. All the participating cities contributed subjects of all ages and heights.[7]

Table 4 uses the pre-BD and post-BD reference values to compare the percentage of subjects below the fifth percentile considered "normal." As in most tests, the post-BD reference values are higher; therefore, the number of subjects below the fifth percentile also increases if it is compared with the pre-BD reference values. The percentage of subjects below the LLN if the whole study population is taken into account is shown at the top of Table 4. Except for FVC, the comparison with the post-BD reference values resulted in a greater number of subjects considered as having a "normal" pulmonary function.

TABLE 2
Reference Equations for Tests Carried Out After Application of the Bronchodilator From a Sample of 887 Subjects With Healthy Respiratory Function*

Variable	FEV_1, L	FVC, L	FEV_6, L	PEFR, L/s	$FEF_{25\%-75\%}$, L/s	FEV_1/FVC	FEV_1/FEV_6
Men (n=268)							
Intercept	–2.0591763	–4.5463804	–3.8589553	1.7250924	4.2815745	112.16916	105.57033
Age, y	–0.02934785	–0.02330921	–0.02709438	–0.0623005	–0.0611128	–0.26957917	–0.19315095
Height, cm	0.04188969	0.05997246	0.05629552	0.06645916	0.01557965	–0.10702505	–0.07780354
R^2	51.8	42.9	47.5	28.7	31.2	21.9	19.4
RSD	0.49594	0.65183	0.6042	1.5439	1.1545	6.075	4.70
Women (n=619)							
Intercept	–0.90375706	–1.8118119	–1.5648769	0.25734207	1.6343256	101.42294	97.628742
Age, y	–0.02350681	–0.02165998	–0.02303585	–0.04989254	–0.03987396	–0.22344908	–0.17709288
Height, cm	0.02980617	0.03877828	0.03721715	0.05900097	0.02111287	–0.0561345	–0.03648568
R^2	46.1	42.3	46.1	32.5	27.9	13.2	12.5
RSD	0.42926	0.49774	0.46583	1.1828	0.87235	6.68	5.49

* FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; PEFR, peak expiratory flow rate; $FEF_{25\%-75\%}$, forced expiratory flow, midexpiratory phase; RSD, residual SD.

TABLE 3
Fifth Percentile for the Main Spirometric Values After Application of the Bronchodilator (n=887 Subjects With Healthy Respiratory Function)*

Variable	FEV_1, L	FVC, L	FEV_6, L	FEV_1/FVC	FEV_1/FEV_6	PEFR, L/s	$FEF_{25\%-75\%}$, L/s
Women (n=619)							
Height, cm	0.01643303	0.02498616	0.02379931	0.14965179	0.03442017	0.07650396	0.01214155
Age, y	–0.02446298	–0.02079104	–0.02194339	–0.35195551	–0.29891433	–0.0581962	–0.02931671
Intercept	0.60258664	–0.46081121	–0.23967477	65.736842	84.498383	–3.8439474	1.0791805
Men (n=268)							
Height, cm	0.03312168	0.03357509	0.0360836	–0.12752433	–0.13428533	0.05448363	0.013936
Age, y	–0.03149245	–0.03028723	–0.03533026	–0.46476388	–0.28229844	–0.05893268	–0.03558766
Intercept	–1.2960897	–0.78985789	–1.0076617	115.70231	111.74811	1.0450524	1.4201256

*FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; $FEF_{25\%-75\%}$, forced expiratory flow, midexpiratory phase; PEFR, peak expiratory flow rate.

Discussion

In the present study, the application of a bronchodilator (200 µg of salbutamol inhaled through a high-flow spacer device) was associated with an increase of 3% in FEV_1, FEV_1/FVC, and FEV_1/FEV_6, with a minimum increase in FEV_6 and a nonsignificant increase in FVC. The post-BD reference values increase by the same proportion if they are compared with pre-BD reference values. To date, most reference values, including those generated during the NHANES-III study,[11] have been obtained without applying a bronchodilator. The LLN is often based on an arbitrary cutoff separating 5% of normal subjects with lower values—the fifth percentile—which is therefore affected by the application of the bronchodilator. Therefore, the results of spirometry tests performed pre-BD must be compared with reference values obtained without administration of a bronchodilator. However, the post-BD spirometry test results should be compared with the post-BD reference values in order to maintain an LLN that would be equivalent to the fifth percentile so as to minimize misclassification.

Even when a relatively small increase (3%) in post-BD spirometry values is observed, the magnitude of the misclassification arising from the use of inappropriate reference values could have serious consequences in the general population. For example, if the post-BD spirometry results were compared with the pre-BD reference values, 3.2% of the total population would be classified as false negatives. On the other hand, if we define obstruction as a test result below the LLN for the post-BD ratio FEV_1/FVC (ie, adjusted for age) but perform spirometry testing on the subject or population without applying a bronchodilator and compare the results with our pre-BD reference values, 3.7% of the cases would be false positives and 3.1% would be false negatives in terms of airflow obstruction. If the current GOLD criteria for airflow obstruction (FEV_1/FVC <70%) are applied, the classification of the severity of the obstruction is only affected by the variations in the reference values.

The new proposals of the ATS-ERS for lung function tests recommend applying 400 µg of salbutamol to carry out reversibility testing,[3] although it is made clear that no consensus has been reached on the dose, drug, or route of administration. In the present study and in others,[14,15] lower doses of inhaled salbutamol were administered (200 µg). In some subjects, 200 µg of salbutamol could cause a less marked effect than 400 µg; however, when this study was being designed, the ethics committees voiced their concern over the safety of administering a β-agonist in an open-population study, with the result that it was decided to administer 200 µg. This decision was accepted by all the ethics committees of the participating centers.

To conclude, the correct definition of the LLN (fifth percentile) requires separate reference values for spirometry

TABLE 4
Percentage of the Open Population Aged 40 or Over That Is Under the Fifth Percentile for Several Spirometric Measurements According to Whether the Test Was Performed With or Without a Bronchodilator and Whether Reference Values Are Compared With or Without the Bronchodilator*

	FEV_1	FVC	FEV_1/FVC	FEV_1/FEV_6
Normal subjects				
Pre-BD tests				
Pre-BD reference values†	4.6	4.3	5.5	5.1
Post-BD reference values‡	5.4	4.7	10.0	8.2
Post-BD tests				
Pre-BD reference values†	3.5	3.6	3.4	3.0
Post-BD reference values‡	4.1	3.5	5.9	5.4
All subjects from the PLATINO study				
Pre-BD tests				
Pre-BD reference values†	9.1	5.8	11.5	10.6
Post-BD reference values‡	10.6	5.9	17.4	15.3
Post-BD tests				
Pre-BD reference values†	6.4	4.6	7.5	7.2
Post-BD reference values‡	7.6	4.5	10.8	10.3

*The percentages are estimations for the total number of subjects aged 40 or over from the metropolitan areas of the cities studied: Mexico City, Santiago, São Paulo, Montevideo, and Caracas. FEV_1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; FEV_6, forced expiratory volume in 6 seconds; BD bronchodilator.
†Reference values also from the PLATINO study.
‡Reference values from the present study.

tests carried out with or without a bronchodilator in order to obtain the most accurate classification of patients. This study makes it possible to predict classification errors if the results of post-BD spirometry testing are compared with pre-BD reference values.

Other members of the PLATINO group who participated in the study:

Pedro Curi Hallal (Universidad Federal de Pelotas, Pelotas, Brazil), Alexander Corcho-Berdugo and Francisco Franco-Marina (Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico), Dolores Moreno (Facultad de Medicina, Universidad de la República, Montevideo, Uruguay), and Carmen Lisboa (Pontificia Universidad Católica de Chile, Santiago, Chile).

Spirometry testing was supervised by Fernanda W. Rosa, Aquiles Camelier, Oliver Nascimento, Elisa Sánchez-Gallén, Abigail Guzmán, Marcela Araya, and Dolores Moreno.

REFERENCES

1. 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;23:932-46.
2. GOLD. Workshop report, global strategy for diagnosis, management and prevention of COPD. Available from: http://www.gold-copd.com/
3. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68.
4. Johannessen A, Lehmann S, Omenaas ER, et al. Post-bronchodilator spirometry reference values in adults and implications for disease management. Am J Respir Crit Care Med. 2006;173:1316-25.
5. Menezes AM, Victora CG, Pérez-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;4:15.
6. Menezes AM, Pérez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366:1875-81.
7. Pérez Padilla J, Valdivia G, Muiño A, et al. Valores de referencia espirométrica en 5 grandes ciudades de Latinoamérica para sujetos de 40 o más años de edad. Arch Bronconeumol. 2006;42:317-25.
8. Pérez-Padilla R, Vázquez-García J, Márquez M, et al. The long-term stability of portable spirometers used in a multinational study of COPD prevalence. Respir Care. 2006;51:1167-71.
9. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.
10. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis. 1991;144:1202-18.
11. 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;159:179-87.
12. StataCorp. Stata Statistical Software: release 9.0. College Station, TX: Stata Corporation; 2005.
13. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107-36.
14. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. Chest. 1998;114:1607-12.
15. Tweeddale PM, Alexander F, McHardy GJ. Short term variability in FEV1 and bronchodilator responsiveness in patients with obstructive ventilatory defects. Thorax. 1987;42:487-90.