Efficacy of the FEV_1/FEV_6 ratio compared to the FEV_1/FVC ratio for the diagnosis of airway obstruction in subjects aged 40 years or over

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Abstract

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The present cross-sectional, population-based study was designed to evaluate the performance of the FEV_1/FEV_6 ratio for the detection of airway-obstructed subjects compared to the FEV_1/FVC <0.70 fixed ratio test, as well as the lower limit of normality (LLN) for 1000 subjects ≥40 years of age in the metropolitan area of São Paulo, SP, Brazil. After the exclusion of 37 (3.7%) spirometries, a total of 963 pre-bronchodilator (BD) and 918 post-BD curves were constructed. The majority of the post-BD curves (93.1%) were of very good quality and achieved grade A (762 curves) or B (93 curves). The FEV_1/FEV_6 and FEV_1/FVC ratios were highly correlated ($r^2 = 0.92$, $P < 0.000$). Two receiver operator characteristic curves were constructed in order to express the imbalance between the sensitivity and specificity of the FEV_1/FEV_6 ratio compared to two FEV_1/FVC cut-off points for airway obstruction: equal to 70 (area under the curve = 0.98, $P < 0.0001$) and the LLN (area under the curve = 0.97, $P < 0.0001$), in the post-BD curves. According to an FEV_1/FVC <0.70, the cut-off point for the FEV_1/FEV_6 ratio with the highest sum for sensitivity and specificity was 0.75. The FEV_1/FEV_6 ratio can be considered to be a good alternative to the FEV_1/FVC ratio for the diagnosis of airway obstruction, both using a fixed cut-off point or below the LLN as reference. The FEV_1/FEV_6 ratio has the additional advantage of being an easier maneuver for the subjects and for the lung function technicians, providing a higher reproducibility than traditional spirometry maneuvers.

Introduction

The definition of airflow limitation by spirometry classically considers either a FEV_1/FVC ratio <0.70 or a value below the lower limit of normality (LLN) derived from reference equations (1-3). Some studies have recently suggested that reducing the forced expiratory maneuver to a 6-s duration (also called FEV_6) could replace the forced vital capacity (FVC) maneuver as a surrogate of the FEV_1/FVC ratio for the diagnosis of airway obstruction (4-8). The advantages of FEV_6 described in the literature are: easy execution (for patients and technicians) (9,10), elimination of very low flow sensor accuracy limitations at the end of FVC maneuvers, reduction in the total duration of the spirometry test, and possibly a reduction in spirometry complications (such as syncope) (11-13).

Analysis of published studies shows that the criteria adopted to define obstruction from the FEV_1/FEV_6 ratio are quite variable: some studies used the sensitivity and specificity values associated with receiver operator characteristic (ROC) curve analysis to find the best cut-off point (3,6), some used an empiric fixed FEV_1/FEV_6 ratio of 0.70 (4), and finally others used the LLN, derived from reference equations, as the best option (5,7,11,12,14). Important limitations of such studies are: the reference equations used were developed in a setting different from that of the subjects in whom the FEV_1/FEV_6 ratio was measured and there was a wide variation in the population concerning age, height, weight, and ethnicity, possibly leading to a limitation of the external validation (8). Finally, there was the possibility of a selection bias since some studies were conducted on patients referred to pulmonary function test laboratories, a fact that might influence the accuracy of the FEV_1/FEV_6 ratio (4,5,9,11,14).

The PLATINO study was conducted in order to determine the prevalence of chronic obstructive pulmonary disease (COPD) in the population of five large cities in Latin America (15). Spirometric reference equations derived from the PLATINO study (including FEV_6 and FEV_1/FEV_6) have been published (3). Specific data regarding the Brazilian subsample are available (16).

The present study was designed to evaluate the performance of the FEV_1/FEV_6 ratio in detecting airflow limitation using the FEV_1/FVC <0.70 fixed ratio and LLN in the Brazilian subsample of the PLATINO study.

Material and Methods

Participants

Between December 2002 and March 2003, subjects aged 40 years and over (COPD target population) were recruited according to a multi-stage cluster sampling strategy, in order to obtain representative samples of adults living in the metropolitan area of São Paulo, the largest city in South America (690 m above sea level and 23º latitude South), which has a population of 17.3 million people. Within the 1113 households sampled there were 1150 individuals eligible for the study; of these, 1000 answered the questionnaires, and 963 performed spirometry (with 918 completing the post-bronchodilator (BD) phase). The overall non-response rate was 15.3%, taking into account both household and individual contact failures and refusals (including refusals only for spirometry). Therefore, spirometry analyses were carried out using the post-BD curves.

Instruments and examinations

The PLATINO core questionnaire is a composite including sections of the following questionnaires: ATS/DLD (17), European Community Respiratory Health Survey II (18) and Lung Health Study (19). It contains questions about respiratory symptoms, COPD risk factors, previous medi-

cal diagnosis and diagnostic tests, and medications. The exclusion criteria for the study were mental disease and institutionalization.

Anthropometric measurements

Height and weight were measured with a portable Seca® stadiometer (Hamburg, Germany) with 0.1-cm precision and an electronic Tanita® scale (Tokyo, Japan) with 200-g precision, respectively. Body mass index was calculated by dividing weight by squared height (kg/m^2).

Spirometry

Spirometry was carried out by personnel who had received training in a quality control course for spirometry testing approved by the National Institute for Occupational Safety and Health. Two spirometric readings were taken, one at baseline, and the other 15 min after the application of 200 μg salbutamol through a spacer, and their reproducibility was graded according to quality control grades A to F. Subjects were seated and used nose clips. An ultrasound spirometer (Easy One, NDD Technopark, Zurich, Switzerland), which met all ATS quality control criteria was used (20). Calibration was verified daily with a 3-L syringe. All spirometry results were sent to the investigators in the Quality Control center, located in Mexico City, Mexico, and a weekly feedback report to the center in São Paulo, Brazil, was provided (21). The spirometry reference equations used in the present study were developed from the data for five Latin American cities in the PLATINO study, including São Paulo (3). FEV_6 was obtained from the same FVC curve. Exclusion criteria for spirometry were: thoracic or abdominal surgery, myocardial infarction, eye surgery (or detached retina), and hospitalization for any cardiac problem in the previous three months, as well as current treatment for tuberculosis or pregnancy.

Statistical analysis

Data are reported as means ± SD. The Student t-test and ANOVA were used to compare means. The performance of the separate sets of variables was analyzed using two-by-two tables. Sensitivity, specificity, positive predictive value, negative predictive value, and ROC curves were calculated and compared using a fixed cut-off point of $FEV_1/FVC <0.70$ or based on the identification of the LLN (derived from the PLATINO spirometry reference equations) as reference for airway obstruction (3). The level of significance was set at $P < 0.05$. Analyses were carried out using the STATA and SPSS (v13) programs.

Ethics

The Ethics Committee of the Federal University of São Paulo approved the study and written informed consent was obtained from each subject. For additional data, we suggest consultation of PLATINO methods (22).

Results

Sample baseline characteristics

One thousand subjects aged 40 years or more were interviewed in the great metropolitan area of São Paulo, Brazil. Thirty-seven (3.7%) subjects did not meet the inclusion criteria for spirometry, 963 subjects performed pre-BD spirometry and 918 completed the post-BD phase. The baseline characteristics of the sample studied are shown in Table 1.

Twenty-four percent of the subjects (240) were current smokers and 9.1% (91 patients) were former smokers.

Spirometry quality control

Quality control of the flow-volume curves

Table 1. Characteristics of the study group.

Variables	Mean ± SD
Age (years)	55.2 ± 11.3
Weight (kg)	70 ± 15.7
Height (cm)	160.1 ± 9.5
BMI (kg/m^2)	27.3 ± 5.6
Tobacco exposure (pack-years)	18.3 ± 22.7
FVC (L) pre-BD	3.4 ± 1
FEV_1 (L) pre-BD	2.6 ± 0.8
FEV_1/FVC (%) pre-BD	75.6 ± 9.4
FEV_6 (L) pre-BD	3.3 ± 1
FEV_1/FEV_6 (%) pre-BD	78.7 ± 7.6
FVC (L) post-BD	3.4 ± 0.95
FEV_1 (L) post-BD	2.7 ± 0.8
FEV_1/FVC (%) post-BD	77 ± 9.2
FEV_6 (L) post-BD	3.3 ± 0.9
FEV_1/FEV_6 (%) post-BD	80.7 ± 7.3
Intratest coefficient of variability of post-BD FEV_6	2.23 ± 7.3
Intratest coefficient of variability of post-BD FVC	1.86 ± 2.25
Intratest coefficient of variability of post-BD FEV_1/FEV_6	0.74 ± 0.92
Intratest coefficient of variability of post-BD FEV_1/FVC	1.23 ± 1.51

Data are reported as means ± SD for 1000 subjects (434 males and 566 females). BMI = body mass index; FVC = forced vital capacity; FEV = forced expiratory volume; BD = bronchodilator.

Table 2. Sensitivity and specificity of the FEV_1/FEV_6 ratio compared to FEV_1/FVC = 70, pre-BD curves.

	Pre-BD FEV_1/FVC = 70				
	Sensitivity	Specificity	PPV	NPV	Prevalence
FEV_1/FEV_6 = 70	47.9% (41.2-54.8)	100% (99.4-100)	100% (95.6-100)	86.7% (84.3-88.9)	10.9% (9.0-13.1)
FEV_1/FEV_6 = 71	56.6% (49.8-63.2)	99.7% (98.9-100)	98.4% (93.8-99.7)	88.6% (86.2-90.7)	13.1% (11.0-15.3)
FEV_1/FEV_6 = 72	63.9% (57.1-70.2)	99.4% (98.5-99.8)	97.2% (92.6-99.1)	90.4% (88.1-92.2)	15.0% (12.8-17.4)
FEV_1/FEV_6 = 73	73.0% (66.6-78.7)	99.1% (97.9-99.5)	95.8% (91.2-98.1)	92.9% (90.8-94.5)	17.3% (15.0-19.9)
FEV_1/FEV_6 = 74	83.1% (77.3-87.7)	98.1% (96.8-98.9)	92.9% (88.1-95.9)	95.2% (93.3-96.5)	20.4% (17.9-23.1)
FEV_1/FEV_6 = 75	89.0% (84.0-92.7)	95.4% (93.6-96.8)	85.2% (79.7-89.4)	96.7% (95.1-97.8)	23.8% (21.2-26.6)
FEV_1/FEV_6 = 76	94.06% (89.8-96.7)	91.0% (88.6-92.9)	75.5% (69.8-80.3)	98.1% (96.7-98.9)	28.3% (25.5-31.3)
FEV_1/FEV_6 = 77	95.89% (92.1-98.0)	85.7% (83.0-88.1)	66.5% (60.9-71.6)	98.6% (97.3-99.3)	32.8% (29.9-35.9)
FEV_1/FEV_6 = 78	97.7% (94.4-99.2)	80.0% (76.9-82.8)	59.0% (53.7-64.0)	98.8% (97.5-99.5)	37.7% (34.6-40.8)
FEV_1/FEV_6 = 79	98.6% (95.7-99.6)	72.3% (69.3-75.9)	51.7% (46.8-56.5)	99.4% (98.2-99.8)	43.5% (40.4-46.7)

Data are reported as percent with 95% confidence intervals in parentheses. PPV = positive predictive value; NPV = negative predictive value. For other abbreviations, see legend to Table 1.

Table 3. Sensitivity and specificity of the FEV_1/FEV_6 ratio compared to FEV_1/FVC = 0.70, post-BD curves.

	Post-BD FEV_1/FVC = 70				
	Sensitivity	Specificity	PPV	NPV	Prevalence
FEV_1/FEV_6 = 70	44.4% (36.2-52.9)	100% (99.4-100)	100% (92.9-100)	90.6% (88.4-92.5)	7.0% (5.4-8.9)
FEV_1/FEV_6 = 71	54.9% (46.4-63.1)	100% (99.4-100)	100% (94.2-100)	92.3% (90.1-94.0)	8.6% (6.9-10.6)
FEV_1/FEV_6 = 72	60.4% (51.9-68.4)	99.6% (98.8-99.9)	96.7% (89.9-99.1)	93.11% (91.1-94.7)	9.8% (8.0-12.0)
FEV_1/FEV_6 = 73	72.2% (64.0-79.2)	99.5% (98.6-99.8)	96.3% (90.2-98.8)	95.1% (93.3-96.4)	11.8% (9.8-14.1)
FEV_1/FEV_6 = 74	79.2% (71.4-85.3)	99.0% (97.9-99.5)	93.44% (87.1-96.9)	96.2% (94.6-97.4)	13.3% (11.2-15.7)
FEV_1/FEV_6 = 75	88.2% (81.5-92.8)	97.4% (96.0-98.4)	86.4% (79.5-91.3)	97.8% (96.4-98.7)	16.0% (13.7-18.6)
FEV_1/FEV_6 = 76	90.3% (83.9-94.4)	93.7% (91.2-94.9)	73.44% (66.2-79.7)	98.1% (96.8-98.9)	19.3% (16.8-22.0)
FEV_1/FEV_6 = 77	93.1% (87.3-96.4)	90.6% (88.2-92.5)	64.7% (57.8-71.1)	98.6% (97.3-99.3)	22.54% (19.9-25.4)
FEV_1/FEV_6 = 78	94.4% (89.0-97.4)	86.2% (83.3-88.5)	56.0% (49.5-62.3)	98.8% (97.6-99.4)	26.4% (23.6-29.4)
FEV_1/FEV_6 = 79	97.2% (92.1-99.1)	80.87% (86.2-90.8)	48.6% (42.7-54.5)	98.4% (98.3-99.8)	31.4% (28.4-34.5)

Data are reported as percent with 95% confidence intervals in parentheses. PPV = positive predictive value; NPV = negative predictive value. For other abbreviations, see legend to Table 1.

was evaluated by analyzing the reproducibility of the three best curves for each subject, in both phases of spirometry (pre- and post-BD). The majority of the post-BD curves (93.1%) was of very good quality, achieving grade A (762 curves) or B (93 curves). Twenty-eight curves achieved grade C (3.05%) and 35 (3.8%) achieved D, E, or F grades.

Analysis of the sensitivity and specificity of the FEV$_1$/FEV$_6$ ratio

Before the analysis of accuracy, a scatterplot graph between post-BD FEV$_1$/FEV$_6$ and FEV$_1$/FVC ratios was constructed, and $r^2 = 0.92$ (P < 0.000) was found.

A FEV$_1$/FVC ratio of 0.70 was taken as the reference value for the diagnosis of airway obstruction. The sensitivity and specificity of the FEV$_1$/FEV$_6$ ratio were analyzed for both the pre-BD and post-BD curves (Tables 2 and 3, respectively). The highest sum of sensitivity and specificity was detected with an FEV$_1$/FEV$_6$ ratio threshold of 0.75 post-BD. Two ROC curves were constructed in order to express the balance between the sensitivity and specificity of the FEV$_1$/FEV$_6$ ratio compared to two FEV$_1$/FVC cut-off points for airway obstruction: one considered values equal to 0.70 and the other values below the LLN. The results are shown in Figure 1.

COPD diagnosis and misclassification according to the post-BD FEV$_1$/FEV$_6$ ratio

The diagnosis of air flow limitation according to a fixed post-BD FEV$_1$/FVC ratio <0.70 (as stated by the ATS/ERS and Brazilian guidelines) was compared to the diagnosis of air flow based on a post-BD FEV$_1$/FEV$_6$ ratio <0.75, using a 2 x 2 table (Table 4). Based on an FEV$_1$/FVC ratio <0.70, 15.7% of the sample was considered to have airway obstruction, while this number slightly increased to 16.03% taking into consideration an FEV$_1$/FEV$_6$ ratio <75%.

The positive and negative predictive values were 85.8 and 97.8%, respectively. Discordant diagnosis was found in 4.14% of cases (Table 4).

A cut-off point using the LLN derived from PLATINO reference equations was also analyzed (Table 5). A discordant diagnosis
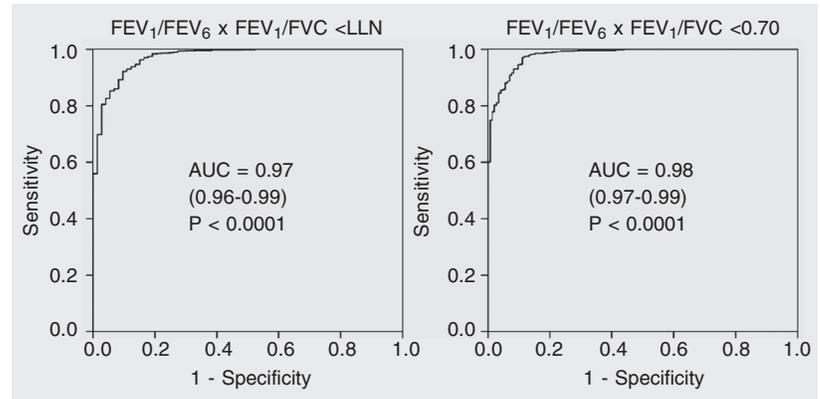

Figure 1. Area under the receiver operator characteristic curves (AUC) and 95% confidence intervals for the FEV$_1$/FEV$_6$ ratio compared to an FEV$_1$/FVC ratio equal to the lower limit of normality (LLN) and to 0.70. FEV = forced expiratory volume; FVC = forced vital capacity.

Table 4. Analysis of discordant cases when using the FEV$_1$/FEV$_6$ <75 and FEV$_1$/FVC <70 ratios for airway obstruction with post-BD curves.

FEV$_1$/FEV$_6$	FEV$_1$/FVC		Total
	<70%	≥70%	
<75%	127	21	148
≥75%	17	753	770
Total	144	773	918

For abbreviations, see legend to Table 1.

Table 5. Analysis of the discordant cases when using the FEV$_1$/FEV$_6$ and FEV$_1$/FVC ratio <LLN for airway obstruction with post-BD curves.

FEV$_1$/FEV$_6$	FEV$_1$/FVC post-BD		Total
	<LLN	≥LLN	
<LLN	117	17	134
≥LLN	23	806	829
Total	140	823	963

LLN = lower limit of normality. For other abbreviations, see legend to Table 1.

was present in 40 (4.35%) of the subjects studied.

Discussion

The present study showed that the FEV_1/FEV_6 ratio is a good substitute for the detection of airway-obstructed subjects using either an FEV_1/FVC ratio <0.70 (fixed ratio) or a threshold below the LLN as reference. The main strengths of the present study are the fact that the study group consisted of a randomized population-based sample (15,16) and the use of a set of spirometry reference equations derived from the same sample (3). The best cut-off point of the FEV_1/FEV_6 ratio was 0.75. These aspects were considered to be points to be addressed in future studies (9). Two other studies showed a similar cut-off point (0.73) of the FEV_1/FEV_6 ratio for the detection of airway obstruction, both using the fixed FEV_1/FVC <0.70 ratio for comparison. Vandevoorde et al. (9) used a spirometry database of referenced patients from a medical facility, whereas Melbye et al. (10) recruited subjects from a highly homogeneous population-based sample in a northern city of Norway. Despite the different population background between these two studies and the present one, a similar cut-off point for the FEV_1/FEV_6 ratio was found. The advantage of using a fixed cut-off value for the FEV_1/FEV_6 ratio instead of choosing the LLN from a reference equation to diagnose airway obstruction is emphasized by the main COPD guidelines (1,13). The specific use of the FEV_1/FEV_6 ratio for the diagnosis of airflow obstruction has the advantage of being less time consuming and easier for the patient and technician. This should be an interesting point to consider when establishing diagnostic units for respiratory diseases in large primary care centers.

Analysis of the ROC curves for the FEV_1/FVC ratio using the value below 0.70 and lower values than the LLN as cut-off points to predict the best accuracy showed similar results in identifying a cut-off for the FEV_1/FEV_6 ratio according to the analysis of the 95%CI (Tables 2, 3, 4, and 5, Figure 1). Besides the fact that the two parameters had an excellent correlation, the best cut-off point to be chosen in clinical practice should take into account the proportion of wrong diagnoses (discordant cases), which in the present study could be considered small, i.e., about 4% (Tables 4 and 5).

The authors believe that this new information will set a new basis for the clinical judgment of which parameter and cut-off point should be chosen as a reference for clinical use.

Study limitations

The present study was originally designed to estimate COPD prevalence in a population-based survey. The reference values used in this study were based on those obtained for the residents of five Latin American cities of the PLATINO study (15) as a whole. Considered separately, no city subsample had enough power to develop local equations.

We may conclude that the FEV_1/FEV_6 ratio can be considered a good alternative to the FEV_1/FVC ratio in the diagnosis of airway obstruction, either considering a fixed cut-off point or a value below the LLN.

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