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ABSTRACT

(172 WORDS)

Background: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of forced expiratory volume in 1 second (FEV₁) to assess airways reversibility. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend FEV₁ and/or forced vital capacity (FVC). This study assessed whether FVC detects reversibility in more chronic obstructive pulmonary disease (COPD) patients than FEV₁ after acute short-acting bronchodilator inhalation.

Methods: Plethysmographic data of 168 consecutive stable male COPD patients who underwent reversibility testing were analyzed.

Results: Seventy-seven patients showed a clinically significant increase in FVC, whereas only 49 patients showed a clinically significant increase in FEV₁. Thus, FVC detected reversibility in 57% more patients than FEV₁. Of the 90 patients showing clinically significant reversibility, FEV₁ did not detect 41 patients that FVC detected, indicating a 45% difference.

Conclusion: FEV₁ underestimates acute bronchodilation effects. FVC should thus be a primary clinical outcome measure of bronchodilator reversibility in COPD, as it detects reversibility in more patients. This message, forgotten by GOLD, should be promoted in future consensus statements.

KEYWORDS

1
2
3 COPD; Spirometry; Reversibility Test; Bronchodilator; Guidelines; GOLD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now defined as “the presence of airflow limitation that is not fully reversible” [1]. The effectiveness of inhaled bronchodilator (BD) in individual patients is assessed by comparing measurements from pulmonary function tests made before and after administration [2]. Generally, 1-s forced expiratory volume (FEV₁) is the marker used [2], in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1, 3]. According to the original guidelines [1] and the 2006 update [3], “an increase in FEV₁ that is both greater than 0.2 L and 12% above the pre-bronchodilator (preBD) FEV₁ value is considered significant”.

In 1983, however, Girard and Light stated that: “assessment of FVC should be utilized in addition to the FEV₁ in evaluating BD response” [4], based on their own and others’ findings [5, 6]. More recently, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) established a common interpretative strategy for lung function testing with “a 12% increase in either FEV₁ or FVC, calculated from the preBD value; and a 0.2 L increase in FEV₁ or FVC” as the reversibility criteria [7]. The ATS [8, 9] and ERS [10] first proposed FVC as a reversibility criterion in guidelines from the 1990s. It is thus surprising that, despite these recommendations and three decades of evidence, only the GOLD criterion of FEV₁ is used to interpret airways response to short-acting bronchodilators in the current literature [11-20] and most daily practices.

One explanation for the contradiction between the evidence and the GOLD recommendation is that the studies assessing response to short-acting bronchodilators had methodological limitations or recruited selected COPD patients. Most studies with large populations used retrospective analysis without precise diagnoses, *e.g.*, “non-asthmatic obstructed patients” [6, 21], retrospective database analysis of selected COPD patients with pulmonary hyperinflation [2], or reanalysis of data from patients with poorly reversible COPD (< 10% of their predicted FEV₁) [22] or “irreversible” emphysema [23]. Others investigated limited numbers of selected patients with vaguely described airways disease and relatively high improvement in FEV₁ (> 15% increase) [5]. Still others retrospectively investigated poorly reversible COPD patients [4] or prospectively analyzed only a few COPD patients [24-26]. Nevertheless, some showed that FVC, a simple parameter measured during the same spirometric maneuver as FEV₁, increased remarkably in response to BD, whereas FEV₁ remained unchanged [2, 22-24, 27]. This was shown in patients with severe COPD [24, 27], “irreversible” emphysema [23], severe hyperinflation [2], and poorly reversible COPD [4, 22], suggesting that FVC detects reversibility that is underestimated by FEV₁.

In a large group of consecutive COPD patients showing a wide range of disease severity, this study assessed whether FVC would detect clinically significant reversibility in more patients

1 than FEV₁ after acute short-acting BD inhalation. We assumed that if it did, this would constitute a
2 strong argument for FVC to become a primary clinical outcome measure of reversibility in COPD
3 in daily practice and to be taken into account in future GOLD recommendations.

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MATERIALS AND METHODS

Patients

We enrolled 168 consecutive male COPD patients over 40 years of age, all with clinically diagnosed COPD as defined by the ATS and ERS [28]. All had been referred to our laboratory between March 2006 and June 2007 for spirometry and reversibility testing to monitor and classify disease severity. The patients had smoking histories of more than 10 pack-years and post-bronchodilator (postBD) $FEV_1/FVC < 0.70$ [1, 3, 28]. All were individually evaluated by the same experienced physician who also performed the spirometric tests. To avoid confounding effects, patients with unstable respiratory state (*i.e.*, respiratory tract infection or COPD exacerbation) or oral corticosteroid treatment within 4 weeks prior to spirometry were excluded, as were those with histories of asthma, allergic rhinitis, atopy, myocardial infarction, heart failure, cardiac arrhythmia requiring drug therapy, diabetes, or oxygen therapy. Patients who had taken short- or long-acting bronchodilators within 12 hours of pulmonary function testing were also excluded. The protocol was approved by our ethics committee, and written informed consent was obtained from each patient prior to the study.

Lung function

Spirometric measurements were performed with a body plethysmograph (ZAN 500 Body II, Meßgreräte GmbH, Germany), carefully following ATS/ERS recommendations [29, 30]. The plethysmographic technique followed these steps: 1) the procedure was explained to patients in detail, 2) the plethysmograph door was closed and time was allotted for thermal transients to stabilize and patients to relax, and 3) patients were then instructed to attach the mouthpiece and breathe quietly until they achieved stable end-expiration. 4) When patients were at or near functional residual capacity (FRC), the shutter was closed at end-expiration for 2-3 s, and they were instructed to perform a series of gentle pants (± 1 kPa) at a frequency of 0.5-1.0 Hz. 5) After a series of 3-5 technically satisfactory panting maneuvers was recorded, 6) the shutter opened and patients performed an expiratory reserve volume maneuver followed by a slow inspiratory vital capacity (SVC) maneuver. 7) With regards to repeatability, at least three plethysmographic FRC values that agreed within 5% were obtained and the mean value reported. The FVC maneuver had three distinct phases: maximal inspiration, a blast of exhalation, and continued complete exhalation to the end of testing. Patients were verbally encouraged to continue exhaling air at the end of the maneuver to obtain optimal effort. The criterion for end of testing was a volume-time curve showing no change in volume (0.025 L) for 1 s, despite the patient's effort to exhale for at least 6 s. Repeatability was acceptable when the difference between the largest and the next largest FVC was ≤ 0.1 L and 5%, and the difference between the largest and next largest FEV_1 was ≤ 0.1 L and 5%. The following

parameters were measured or calculated before BD inhalation and compared with predicted values [31, 32]: FEV₁, FVC, FEV₁/FVC, FRC, residual volume (RV), and total lung capacity (TLC). The exhalation time of FVC (ExT) was also measured.

Reversibility testing and expression of bronchodilator response

The reversibility test comprised the following steps [3, 7]: 1) patients first completed three acceptable FVC maneuvers and 2) after gentle and incomplete expiration, a dose of 100 µg of short-acting β₂-agonists (salbutamol) was then inhaled in one breath to TLC with a valve spacer device. The breath was held for 5-10 s before the subjects could exhale. Four separate doses (total dose 400 µg) were delivered at 30-s intervals. 3) Complete plethysmographic measurements (*i.e.*, FRC, SVC, RV and TLC, and then FEV₁ and FVC) were recorded ≥ 10 min and up to 15 min later, using the same procedures, number of maneuvers, and repeatability and end of testing criteria as for preBD.

Response to bronchodilator was expressed as follows:

- Absolute change in FEV₁ and FVC (liter): postBD value minus preBD value [$\Delta\text{FEV}_1 \text{ (L)} = \text{FEV}_1 \text{ postBD} - \text{FEV}_1 \text{ preBD}$; $\Delta\text{FVC (L)} = \text{FVC postBD} - \text{FVC preBD}$].
- Absolute change as a percentage increase over preBD value of FEV₁ and FVC: $\Delta\text{FEV}_{1\% \text{preBD}}$ [$\Delta\text{FEV}_1 \text{ (L)} / \text{FEV}_{1\text{preBD}} \text{ (L)}$]; $\Delta\text{FVC}_{\% \text{preBD}}$ [$\Delta\text{FVC (L)} / \text{FVC preBD (L)}$].
- Similar calculations were made to assess FRC, RV, TLC and SVC responses to BD.

“Clinically significant” reversibility according to the two international guidelines was calculated as follows:

- ATS/ERS guidelines [7]: a 12% increase calculated from the preBD value and a 0.2 L increase in either FEV₁ or FVC.
- GOLD guidelines [1, 3]: an increase in FEV₁ both greater than 0.2 L and 12% above the preBD value.

Statistical analysis

Values are presented as mean ± SD unless otherwise specified. Plethysmographic variables were compared using a paired *t* test or an unpaired *t* test when needed. A Chi2 test compared the percentage of responders according to the two guidelines. Correlations between variables were calculated using Spearman correlation coefficients. Significance was set at 0.05. Data were analyzed using Statistica (Statistica Kernel version 6, StatSoft, France).

RESULTS

Population baseline characteristics and respiratory data

Table 1 shows the baseline characteristics and respiratory data of our patients and the stages of COPD severity [3, 28]. Eighty-eight patients (52%) had static lung hyperinflation defined as FRC higher than the upper normal limit of the predicted value [33]. Forty-five patients (27%) showed gas trapping, defined as a difference between SVC and FVC greater than 0.2 L [10]. Table 1 also shows patient subgroups according to the BD response: non-reversible, clinically significant increase in FEV₁, and clinically significant increase in FVC. As can be deduced from these data, 46% of the patients (n=77) showed a clinically significant increase in FVC, whereas 29% (n=49) showed a clinically significant increase in FEV₁, a difference that reached statistical significance (p=0.03).

Changes in forced expiratory volumes and in response to bronchodilator

Table 2 shows in details the reversibility test values for FEV₁ and FVC, for above subgroups. Figure 1 shows the step by step distribution of the total COPD patient group with respect to clinically significant changes in FEV₁ (Figure 1A) and FVC (Figure 1B) in response to BD, based on the above-described expressions. Depending on the FEV₁ and FVC patterns of response, each subgroup was distinguished in different cells (A₁-A₂; B₁ to B₄).

The analysis of Figure 1 revealed the following:

- 1) Seventy-seven patients showed a clinically significant increase in FVC (B₂+B₃), whereas only 49 patients showed a clinically significant increase in FEV₁ (A₁). Thus, FVC detected 57% more patients than FEV₁.
- 2) Among the 90 patients showing clinically significant reversibility (A₁+B₃), FEV₁ did not detect 41 patients (B₃) that FVC detected, indicating a 45% difference.
- 3) Ninety patients (A₁+B₃) were reversible according to the ATS/ERS guidelines [7], whereas only 49 patients (A₁) were reversible according to GOLD [3]. The corresponding proportion was 53% vs. 29%, a statistically significant difference (p=0.003).

The ExT in response to BD was also assessed in several ways. In the entire group, the mean ExT significantly increased after BD (from 8.2±2.1 s to 8.7±2.0 s, p<0.05). Post-bronchodilator increase in ExT was 0.6±0.7 s for the 77 patients reversible for FVC, and 0.5±0.7 s for the 49 reversible for FEV₁, a non-significant difference (p=0.31).

Table 3 shows the FEV₁ vs. FVC responses to BD in two subpopulations based on COPD severity: stages I and II [3], *i.e.*, mild to moderate severity [28], vs. stages III and IV [3], *i.e.*, severe

to very severe COPD [28]. As can be seen, the FVC response was clinically significant in a higher proportion of patients in the more severe subpopulation than in the less severe subpopulation. In addition, in the more severe patient subpopulation, FEV₁ did not detect 60% of the reversible patients. The results were similar for patients separated according to absence or presence of pulmonary hyperinflation.

Changes in static lung volumes in response to bronchodilator

Table 4 shows the details of the changes in static lung volumes in response to BD for the above-mentioned subgroups. PostBD FRC and RV were significantly decreased in all subgroups, but to a greater degree in the reversible patients. PostBD SVC significantly increased in the reversible patients, whereas minimal changes were found for TLC.

The comparison of SVC and FVC responses to BD revealed the following:

- 1) The mean SVC was significantly higher than the mean FVC before BD (2.79 ± 0.85 L vs. 2.62 ± 0.84 L, $p < 0.05$) and after BD (3.01 ± 0.83 L vs. 2.89 ± 0.81 L, $p < 0.05$).
- 2) In the subgroup of 45 COPD patients who initially showed trapping phenomena, the mean SVC vs. FVC difference significantly decreased after BD (0.46 ± 0.19 L to 0.26 ± 0.27 L, $p < 0.05$). In 21 of these patients (47%), the postBD difference was less than 0.2 L, indicating a resolution of trapping.
- 3) Sixty-two of the 90 reversible patients showed a clinically significant increase in SVC (i.e., increase $\geq 12\%$ and ≥ 0.2 L of preBD), which was a significantly lower proportion than the 77 patients reversible for FVC ($p=0.01$).

DISCUSSION

A large, well-defined population of male COPD patients was prospectively and consecutively assessed for BD reversibility. After acute inhalation of short-acting BD, FVC showed clinically significant reversibility in more patients than did FEV₁. This appeared to be more pronounced in the more severe patients. FVC thus seems to be a better variable than FEV₁ to assess reversibility in these patients.

The pattern of spirometric response to BD varied greatly in this large group of COPD patients with different stages of disease severity, despite careful spirometric procedures following ATS/ERS recommendations [29, 30]. Some patients showed clinically significant increases in both FEV₁ and FVC, others showed changes in either FEV₁ or FVC alone, and a minority showed clinically significant changes in neither, as previously reported [34, 35]. The term “clinically significant” is presently used to describe an increase in FVC or FEV₁ of sufficient clinical importance ($\geq 12\%$ and ≥ 0.2 L of preBD), as recently defined by a joint ATS and ERS expert committee [7], although the best method for the interpretation of BD tests is still under debate [36]. Using this criterion in a patient population that reflects the range of COPD seen in a pulmonary function test laboratory, we found that FVC detected more reversible patients than FEV₁. Moreover, approximately one out of every two patients showing clinically significant response to BD would have been declared non-reversible if assessment of FVC, a simple spirometric parameter, had been omitted. One conclusion to be drawn from these results is that if only one parameter has to be chosen to assess reversibility in COPD, FVC is better than FEV₁. Although this contradicts the conventional thinking in clinical practice and the recent GOLD recommendations, we believe that our study presents new and convincing data that confirm and strengthen many of the findings of the last three decades [2, 4-6, 21-26]. For practical routine assessments, FEV₁ now seems to be an oversimplification because it underestimates the true BD effects. The addition of FVC to their evaluations will help physicians to better interpret airways reversibility tests, particularly in more severe patients, without adding spirometric maneuvers or measurements. Although these observations have to be verified in a wider range of COPD patients, including women, we believe that this parameter is important and should be included in the daily practice of pulmonary medicine and promoted by GOLD.

The clinical usefulness of short-acting BD testing in COPD is still under debate in the literature. Some authors recently argued that this test may have diagnostic, therapeutic and prognostic implications [36]. Calverley et al., however, reported test limitations in poorly reversible COPD patients and observed that the BD response was a continuous variable [22]. On the other

hand, in stable COPD patients, Omata et al. [37] showed a cross-sectional relationship between BD reversibility and the respective items of health-related quality of life (HRQoL) and activities of daily living. Interestingly, the acute FVC response to BD was significantly correlated with numerous HRQoL items, which was not the case for the FEV₁ response. In addition, the trapping index [defined as: (SVC-FVC)×100/SVC] was also correlated with HRQoL items. The authors thus argued that the assessment of reversibility using FVC measurement may become a useful clinical marker in terms of HRQoL and that this measurement might provide different clinical information than that provided by FEV₁. Therefore, this study provided support for the clinical usefulness of reversibility testing and reinforced our present observations that FVC should be a primary clinical outcome measure of BD reversibility in COPD.

We found significant changes in FRC, RV, SVC, and the SVC vs. FVC difference after BD inhalation. Our results are in line with previous studies in COPD patients [2, 22, 23, 38-42], and reflect a decrease in static pulmonary hyperinflation and gas trapping. In addition, we found the changes in FVC to be greater in severe and/or hyperinflated patients, similar to findings in patients with severe emphysema [23, 24]. To fully appreciate BD efficacy in COPD patients, the assessment of lung volumes and capacities was proposed as a means to obtain additional information regarding hyperinflation [43]. However, most centers report FEV₁ and FVC before and after BD administration but not other lung function parameters like lung volumes [2], probably because of the impracticality of repeating complete plethysmographic measurements in patients. Therefore, the main practical advantage of FVC analysis, which is often neglected in interpretation, is that it is measured during the same spirometric maneuver as FEV₁. Moreover, an improvement in FVC provides useful information about the function of small airways, the most important sites of inflammatory and remodeling processes [44] that are difficult to measure [45].

Our results showed a predominant “volume effect” of acute BD inhalation, as the “flow effect” is more limited in COPD patients [2]. Still under debate in the literature [2, 23, 24, 27, 38-41], the differential volume vs. flow effect is not fully understood in these patients. As previously argued, a postBD change in FVC without a concomitant change in FEV₁ suggests that the airways smooth muscle tone, which is the point of impact of all inhaled bronchodilators, is a major determinant of airways caliber at low but not high lung volumes [24, 27, 36, 40]. Bronchodilation likely relieves gas trapping, especially in particularly overdistended areas of the lungs [2, 45]. The poor correlation between flow and volume responses in our study and others has been attributed to functional fast and slow spaces [2, 45]. The slow space, with its very long time constants, has flow rates too low for detection by short maximal flow parameters like FEV₁. Improved flows in the

slow spaces would permit further emptying during prolonged and more complete exhalation, resulting in an increase in FVC and a reduction of gas trapping [2, 23]. This might ultimately lead to a final, complex rearrangement of the lung volume components of the TLC, and not only a “direct transfer” from vital capacity to RV, as was expected to be the case. Unfortunately, to our knowledge this “regional BD effect” has never been directly confirmed in COPD patients.

We found that ExT increased after BD in our COPD patients, in line with previous observations [4]. It has been suggested that FVC increases only because patients learn to blow longer with repeated testing and that it is therefore a type of artifact [4]. In our study, several points run counter to this hypothesis. First, we carefully followed the spirometry standardization steps, which require several maneuvers to obtain at least three acceptable and reproducible measurements [29]. The maneuvers therefore must be learned before the stringent criteria for acceptable preBD FVC can be met. Second, we found no statistical difference in ExT between patients with and without significant clinical increase in FEV₁. The learning effect from the preBD to postBD maneuver, if real, was thus likely to be equally distributed throughout the whole population, and not only among the reversible patients. Third, patients with only an “isolated volume response” (increase in FVC alone) did not show significantly longer ExT than patients with a flow effect (concomitant increases in FEV₁ and FVC). In fact, an increase in ExT is likely to represent a real BD effect that may also explain changes in static volumes.

In conclusion, reversibility of airflow limitation is difficult to assess in individual COPD patients since it is both parameter- and guidelines-dependent. Using a non-restrictive approach, probably one out of two patients would present reversibility. Therefore, in daily practice, reversibility should be identified in all COPD patients using the changes in FVC as a primary outcome, as it appears to detect a high proportion of patients that are not detected by FEV₁ and other spirometric measures. Sufficient evidence is now available to justify promoting this message, particularly through the consensus statements of highly influential organizations like GOLD. It is time for professional societies to standardize the spirometric criteria of airways reversibility in COPD.

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APPENDIX: ABBREVIATION LIST

- 1
- 2
- 3 ATS: American Thoracic Society
- 4 BD: Bronchodilator
- 5 COPD: Chronic obstructive pulmonary disease
- 6 Δ : Change
- 7 ERS: European Respiratory Society
- 8 ExT: Exhalation time for forced vital capacity
- 9 FEV₁: Forced expiratory volume in 1 second
- 10 FRC: Functional residual capacity
- 11 FVC: Forced vital capacity
- 12 GOLD: Global Initiative for Chronic Obstructive Lung Disease
- 13 HRQoL: Health-related quality of life
- 14 postBD: Post-bronchodilator
- 15 preBD: Pre-bronchodilator
- 16 RV: Residual volume
- 17 SVC: Slow vital capacity
- 18 TLC: Total lung capacity

REFERENCE

- [1] Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256-1276.
- [2] 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;121:1042-1050.
- [3] GOLD. Global strategy for the diagnosis, management, and prevention of chronic pulmonary disease. Update 2006. Available at <http://www.goldcopd.com>. December 2006.
- [4] Girard WM, Light RW. Should the FVC be considered in evaluating response to bronchodilator? *Chest* 1983; 84: 87-89.
- [5] Light RW, Conrad SA, George RB. The one best test for evaluating the effects of bronchodilator therapy. *Chest* 1977; 72:512-516.
- [6] Ramsdell JW, Tisi GM. Determination of bronchodilation in the clinical pulmonary function laboratory. Role of changes in static lung volumes. *Chest* 1979; 76:622-628.
- [7] Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26:948-968.
- [8] American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144:1202-1218.
- [9] American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med* 1995; 152:1107-1136.
- [10] European Thoracic Society. Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16:1-100.
- [11] Beier J, Chanez P, Martinot JB, Schreurs AJ, Tkacova R, Bao W, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 2007; 20:740-749.
- [12] Broseghini C, Testi R, Polese G, Tosatto R, Rossi A. A comparison between inhaled salmeterol and theophylline in the short-term treatment of stable chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2005; 18:103-108.
- [13] Casaburi R, Briggs DD, Jr., Donohue JF, Serby CW, Menjoge SS, Witek TJ, Jr. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. *Chest* 2000; 118:1294-1302.
- [14] Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159:1267-1271.

- 1 [15] Lehmann S, Bakke PS, Eide GE, Gulsvik A. Bronchodilator response to adrenergic beta(2)-
2 agonists: Relationship to symptoms in an adult community. *Respir Med* 2007; 101:1183-
3 1190.
- 4 [16] Lehmann S, Bakke PS, Eide GE, Humerfelt S, Gulsvik A. Bronchodilator reversibility
5 testing in an adult general population; the importance of smoking and anthropometrical
6 variables on the response to a beta2-agonist. *Pulm Pharmacol Ther* 2006; 19:272-280.
- 7 [17] Meslier N, Racineux JL, Six P, Lockhart A. Diagnostic value of reversibility of chronic
8 airway obstruction to separate asthma from chronic bronchitis: a statistical approach. *Eur*
9 *Respir J* 1989; 2:497-505.
- 10 [18] Quadrelli SA, Roncoroni AJ, Montiel GC. Evaluation of bronchodilator response in patients
11 with airway obstruction. *Respir Med* 1999; 93:630-636.
- 12 [19] Ramirez-Venegas A, Ward J, Lentine T, Mahler DA. Salmeterol reduces dyspnea and
13 improves lung function in patients with COPD. *Chest* 1997; 112:336-340.
- 14 [20] Cazzola M, Vinciguerra A, Di Perna F, Matera MG. Early reversibility to salbutamol does
15 not always predict bronchodilation after salmeterol in stable chronic obstructive pulmonary
16 disease. *Respir Med* 1998; 92:1012-1016.
- 17 [21] Berger R, Smith D. Acute postbronchodilator changes in pulmonary function parameters in
18 patients with chronic airways obstruction. *Chest* 1988; 93:541-546.
- 19 [22] Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility
20 testing in chronic obstructive pulmonary disease. *Thorax* 2003; 58:659-664.
- 21 [23] O'Donnell DE, Forkert L, Webb KA. Evaluation of bronchodilator responses in patients with
22 "irreversible" emphysema. *Eur Respir J* 2001; 18:914-920.
- 23 [24] Cerveri I, Pellegrino R, Dore R, Corsico A, Fulgoni P, van de Woestijne KP, et al.
24 Mechanisms for isolated volume response to a bronchodilator in patients with COPD. *J Appl*
25 *Physiol* 2000; 88:1989-1995.
- 26 [25] Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction.
27 *Chest* 1998; 114:1607-1612.
- 28 [26] Aliverti A, Rodger K, Dellaca RL, Stevenson N, Lo Mauro A, Pedotti A, et al. Effect of
29 salbutamol on lung function and chest wall volumes at rest and during exercise in COPD.
30 *Thorax* 2005; 60:916-924.
- 31 [27] Schermer T, Heijdra Y, Zadel S, van den Bemt L, Boonman-de Winter L, Dekhuijzen R, et
32 al. Flow and volume responses after routine salbutamol reversibility testing in mild to very
33 severe COPD. *Respir Med* 2007; 101:1355-1362.
- 34 [28] Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a
35 summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23:932-946.

- [29] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005; 26:319-338.
- [30] Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26:511-522.
- [31] Garcia-Rio F, Pino JM, Dorgham A, Alonso A, Villamor J. Spirometric reference equations for European females and males aged 65-85 yrs. *Eur Respir J* 2004; 24:397-405.
- [32] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16:5-40.
- [33] Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. *Eur Respir J* 1995; 8:492-506.
- [34] Anthonisen NR, Wright EC. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133:814-819.
- [35] O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160:542-549.
- [36] Rodriguez-Carballeira M, Heredia JL, Rue M, Quintana S, Almagro P. The bronchodilator test in chronic obstructive pulmonary disease: interpretation methods. *Respir Med* 2007; 101:34-42.
- [37] Omata M, Wakabayashi R, Kudoh S, Kida K. Correlation between bronchodilator responsiveness and quality of life in chronic obstructive pulmonary disease. *Allergol Int* 2007; 56:15-22.
- [38] Tantucci C, Duguet A, Similowski T, Zelter M, Derenne JP, Milic-Emili J. Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J* 1998; 12:799-804.
- [39] Hadcroft J, Calverley PM. Alternative methods for assessing bronchodilator reversibility in chronic obstructive pulmonary disease. *Thorax* 2001; 56:713-720.
- [40] Pecchiari M, Pelucchi A, D'Angelo E, Foresi A, Milic-Emili J. Effect of heliox breathing on dynamic hyperinflation in COPD patients. *Chest* 2004; 125:2075-2082.
- [41] Di Marco F, Milic-Emili J, Boveri B, Carlucci P, Santus P, Casanova F, et al. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. *Eur Respir J* 2003; 21:86-94.

- 1 [42] Boni E, Corda L, Franchini D, Chiroli P, Damiani GP, Pini L, et al Volume effect and
2 exertional dyspnoea after bronchodilator in patients with COPD with and without expiratory
3 flow limitation at rest. *Thorax* 2002; 57:528-532.
- 4 [43] Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and
5 hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest*
6 2003; 124:1743-1748.
- 7 [44] Persson C. Small airway relaxation-A forgotten medical need. *Pulm Pharmacol Ther* 2008;
8 21:1-3.
- 9 [45] O'Donnell DE. Is sustained pharmacologic lung volume reduction now possible in COPD?
10 *Chest* 2006; 129:501-503.

FIGURE CAPTIONS

FIGURE 1. Distribution of COPD patients with respect to clinically significant changes in FEV₁ (Figure 1A) and FVC (Figure 1B) in response to bronchodilator.

n: number of patients. **COPD:** Chronic obstructive pulmonary disease. **FEV₁:** Forced expiratory volume in 1 s. **FVC:** Forced vital capacity. **preBD:** Pre-bronchodilator value.

Figure 1

A: FEV₁ response
to BD total n=168

B: FVC response
to BD total n=168

Table 1. Baseline characteristics and respiratory data

	Total sample (n=168)	Non-reversible group (n=78)	FEV ₁ -reversible group (n=49)	FVC-reversible group (n=77)
Age, year	63±9	61±10	61±9	65±8
Height, m	1.69±0.07	1.71±0.07	1.68±0.07	1.67±0.07
Weight, kg	71±13	71±13	72±14	71±15
BMI, kg.m ⁻²	25±4	24±4	26±5	25±5
FEV ₁ , % predicted	49±17	57±16	46±17	39±13
FVC, % predicted	70±18	78±15	69±18	59±13
FEV ₁ /FVC, %	55±11	58±10	51±10	52±12
SVC, % predicted	71±17	79±15	70±17	62±13
FRC, % predicted	134±35	126±35	141±36	145±33
TLC, % predicted	105±19	103±20	107±19	107±19
RV, % predicted	166±54	153±53	178±59	183±53
Classification of COPD severity*, number (%)				
Stage I	17 (10%)	10 (%)	7 (%)	2 (%)
Stage II	75 (45%)	47 (%)	20 (%)	24 (%)
Stage III	65 (39%)	19 (%)	22 (%)	42 (%)
Stage IV	11 (6%)	2 (%)	0 (%)	9 (%)

Data are presented as mean±SD unless otherwise indicated.

BMI: Body mass index; **FEV₁:** Forced expiratory volume in 1 s. **FVC:** Forced vital capacity. **SVC:** Slow vital capacity. **FRC:** Functional residual capacity. **TLC:** Total lung capacity. **RV:** Residual volume. **PreBD:** Pre-bronchodilator. **PostBD:** Post-bronchodilator.

The responses to bronchodilator (BD) were expressed as follows: Δ (L): Absolute change (liter). $\Delta_{\%preBD}$: Absolute change as the percentage increase over the preBD value.

Non-reversible group : Δ (L) < 0.2 L and/or $\Delta_{\%preBD}$ < 12% (for FVC and/or FEV₁).

FEV₁-reversible group : Δ (L) ≥ 0.2 L and $\Delta_{\%preBD}$ ≥ 12%.

FVC-reversible group : Δ (L) ≥ 0.2 L and $\Delta_{\%preBD}$ ≥ 12%.

*Defined according to the 2006 GOLD classification [3]: **Stage I** (mild): FEV₁ postBD ≥ 80% predicted; **Stage II** (moderate): 50% ≤ FEV₁ postBD < 80% predicted; **Stage III** (severe): 30% ≤ FEV₁ postBD < 50% predicted; **Stage IV** (very severe): FEV₁ postBD < 30% predicted.

Table 2. Forced expiratory volume responses to the bronchodilator test

	Total sample (n=168)		Non-reversible group (n=78)		FEV ₁ -reversible group (n=49)		FVC-reversible group (n=77)	
	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC	FEV ₁	FVC
PreBD, L	1.46±0.62	2.62±0.84	1.77±0.59	3.05±0.78	1.35±0.55	2.59±0.73	1.09±0.40	2.13±0.55
PostBD, L	1.59±0.65 ⁺	2.89±0.81 ⁺	1.83±0.62	3.12±0.80	1.65±0.63 ⁺	3.00±0.77 ⁺	1.28±0.48 ⁺	2.61±0.64 ⁺
Δ (L), L	0.14±0.15	0.27±0.25	0.06±0.11	0.08±0.15	0.30±0.10	0.42±0.21	0.19±0.14	0.48±0.18
Δ _{%preBD} , %	11±12	12±13	3±7	3±5	23±7	17±9	18±12	24±9

Data are presented as mean±SD.

FEV₁: Forced expiratory volume in 1 s. **FVC**: Forced vital capacity. **PreBD**: Pre-bronchodilator value. **PostBD**: Post-bronchodilator value.

The responses to bronchodilator (BD) were expressed as follows: Δ (L): Absolute change (liter). Δ_{%preBD}: Absolute change as the percentage increase over the preBD value.

Non-reversible group : Δ (L) < 0.2 L and/or Δ_{%preBD} < 12% (for FVC and/or FEV₁).

FEV₁-reversible group: Δ (L) ≥ 0.2 L and Δ_{%preBD} ≥ 12%.

FVC-reversible group : Δ (L) ≥ 0.2 L and Δ_{%preBD} ≥ 12%.

⁺: PostBD vs. preBD: p < 0.05.

1

Table 3. FEV₁ vs. FVC responses to the bronchodilator test according to COPD severity*

	Stages I and II (n=92)	Stages III and IV (n=76)
ΔFEV₁, L	0.16±0.16	0.11±0.12
ΔFEV₁%_{preBD}, %	9±10	13±13
ΔFVC, L	0.22±0.28	0.33±0.21 ⁺
ΔFVC%_{preBD}, %	8±11	18±13 ⁺
% of patients with reversible FEV₁	16	13
% of patients with reversible FVC	15	30 ⁺

Data are presented as mean±SEM unless otherwise indicated.

COPD: Chronic obstructive pulmonary disease. **FEV₁:** Forced expiratory volume in 1 s. **FVC:** Forced vital capacity. **PreBD:** Pre-bronchodilator value. **PostBD:** Post-bronchodilator value.

The responses to bronchodilator (BD) were expressed as follows: Δ (L): Absolute change (liter). Δ%_{preBD}: Absolute change as the percentage increase over the preBD value.

Patients with reversible FEV₁: Δ (L) ≥ 0.2 L and Δ%_{preBD} ≥ 12%.

Patients with reversible FVC: Δ (L) ≥ 0.2 L and Δ%_{preBD} ≥ 12%.

*Severity defined according to the GOLD classification [3] and the ATS/ERS spirometric severity classification [28]: **Stages I and II** (mild and moderate): FEV₁ postBD ≥ 50% predicted; **Stages III and IV** (severe and very severe): FEV₁ postBD < 50% predicted.

⁺: (Stages I and II) vs. (Stages III and IV): p < 0.001.

2

Table 4. Volume responses to the bronchodilator test

	Total sample (n=168)				Non-reversible group (n=78)				FEV ₁ -reversible group (n=49)				FVC-reversible group (n=77)			
	FRC	TLC	RV	SVC	FRC	TLC	RV	SVC	FRC	TLC	RV	SVC	FRC	TLC	RV	SVC
PreBD, L	4.60 ±1.22	6.68 ±1.26	3.92 ±1.31	2.79 ±0.85	4.35 ±1.21	6.70 ±1.24	3.60 ±1.34	3.21 ±0.77	4.79 ±1.25	6.78 ±1.35	4.09 ±1.30	2.72 ±0.75	4.95 ±1.19	6.70 ±1.28	4.35 ±1.22	2.30 ±0.61
PostBD, L	4.33 ±1.13 ⁺	6.57 ±1.27	3.57 ±1.24 ⁺	3.01 ±0.83 ⁺	4.14 ±1.10 ⁺	6.54 ±1.28	3.30 ±1.28 ⁺	3.23 ±0.81	4.44 ±1.06 ⁺	6.81 ±1.21	3.70 ±1.13 ⁺	3.15 ±0.77 ⁺	4.57 ±1.14 ⁺	6.55 ±1.34	3.88 ±1.18 ⁺	2.72 ±0.70 ⁺
Δ (L), L	-0.26 ±0.65	-0.11 ±0.81	-0.35 ±0.67	0.22 ±0.31	-0.20 ±0.60	-0.16 ±0.83	-0.29 ±0.60	0.03 ±0.24	-0.35 ±0.75	0.03 ±0.78	-0.39 ±0.73	0.43 ±0.19	-0.38 ±0.65	-0.15 ±0.76	-0.47 ±0.70	0.42 ±0.25
Δ% _{preBD} , %	-5 ±14	-1 ±12	-8 ±17	10 ±13	-4 ±13	-2 ±11	-7 ±17	1 ±8	-6 ±15	2 ±14	-8 ±19	17 ±9	-7 ±13	-2 ±11	-10 ±15	19 ±12

Data are presented as mean±SD.

FRC: Functional residual capacity. **TLC**: Total lung capacity. **RV**: Residual volume. **SVC**: Slow vital capacity. **PreBD**: Pre-bronchodilator.

PostBD: Post-bronchodilator.

The responses to bronchodilator (BD) were expressed as follows: Δ (L): Absolute change (liter). Δ%_{preBD}: Absolute change as the percentage increase over the preBD value.

Non-reversible group : Δ (L) < 0.2 L and/or Δ%_{preBD} < 12% (for FVC and/or FEV₁).

FEV₁-reversible group: Δ (L) ≥ 0.2 L and Δ%_{preBD} ≥ 12%.

FVC-reversible group : Δ (L) ≥ 0.2 L and Δ%_{preBD} ≥ 12%.

⁺: PostBD vs. PreBD: p < 0.05.