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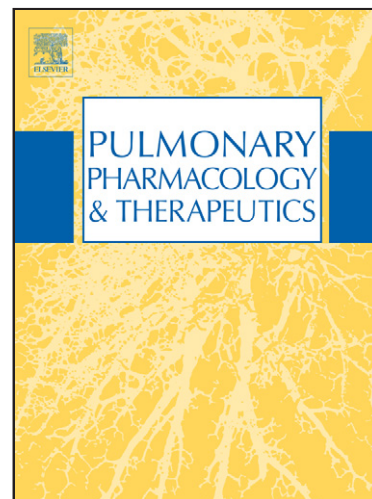
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1 ABSTRACT

2 (172 WORDS)

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

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

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

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

1

KEYWORDS

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

1 parameters were measured or calculated before BD inhalation and compared with predicted values
2 [31, 32]: FEV₁, FVC, FEV₁/FVC, FRC, residual volume (RV), and total lung capacity (TLC). The
3 exhalation time of FVC (ExT) was also measured.

4 5 *Reversibility testing and expression of bronchodilator response*

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

13 14 *Response to bronchodilator was expressed as follows:*

15 - Absolute change in FEV₁ and FVC (liter): postBD value minus preBD value [Δ FEV₁ (L) =
16 FEV₁ postBD - FEV₁ preBD; Δ FVC (L) = FVC postBD - FVC preBD].

17 - Absolute change as a percentage increase over preBD value of FEV₁ and FVC: Δ FEV_{1%}preBD
18 [Δ FEV₁ (L)/ FEV₁preBD (L)]; Δ FVC%preBD [Δ FVC (L)/ FVC preBD (L)].

19 - Similar calculations were made to assess FRC, RV, TLC and SVC responses to BD.

20 21 *“Clinically significant” reversibility according to the two international guidelines was calculated* 22 *as follows:*

23 - ATS/ERS guidelines [7]: a 12% increase calculated from the preBD value and a 0.2 L increase
24 in either FEV₁ or FVC.

25 - GOLD guidelines [1, 3]: an increase in FEV₁ both greater than 0.2 L and 12% above the
26 preBD value.

27 28 *Statistical analysis*

29 Values are presented as mean ± SD unless otherwise specified. Plethysmographic variables
30 were compared using a paired *t* test or an unpaired *t* test when needed. A Chi² test compared the
31 percentage of responders according to the two guidelines. Correlations between variables were
32 calculated using Spearman correlation coefficients. Significance was set at 0.05. Data were
33 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

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

6

7 *Changes in static lung volumes in response to bronchodilator*

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

12

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

- 14 1) The mean SVC was significantly higher than the mean FVC before BD (2.79 ± 0.85 L vs.
15 2.62 ± 0.84 L, $p < 0.05$) and after BD (3.01 ± 0.83 L vs. 2.89 ± 0.81 L, $p < 0.05$).
- 16 2) In the subgroup of 45 COPD patients who initially showed trapping phenomena, the mean SVC
17 vs. FVC difference significantly decreased after BD (0.46 ± 0.19 L to 0.26 ± 0.27 L, $p < 0.05$). In
18 21 of these patients (47%), the postBD difference was less than 0.2 L, indicating a resolution of
19 trapping.
- 20 3) Sixty-two of the 90 reversible patients showed a clinically significant increase in SVC (*i.e.*,
21 increase $\geq 12\%$ and ≥ 0.2 L of preBD), which was a significantly lower proportion than the 77
22 patients reversible for FVC ($p=0.01$).

DISCUSSION

1
2
3 A large, well-defined population of male COPD patients was prospectively and
4 consecutively assessed for BD reversibility. After acute inhalation of short-acting BD, FVC showed
5 clinically significant reversibility in more patients than did FEV₁. This appeared to be more
6 pronounced in the more severe patients. FVC thus seems to be a better variable than FEV₁ to assess
7 reversibility in these patients.

8
9 The pattern of spirometric response to BD varied greatly in this large group of COPD
10 patients with different stages of disease severity, despite careful spirometric procedures following
11 ATS/ERS recommendations [29, 30]. Some patients showed clinically significant increases in both
12 FEV₁ and FVC, others showed changes in either FEV₁ or FVC alone, and a minority showed
13 clinically significant changes in neither, as previously reported [34, 35]. The term “clinically
14 significant” is presently used to describe an increase in FVC or FEV₁ of sufficient clinical
15 importance ($\geq 12\%$ and ≥ 0.2 L of preBD), as recently defined by a joint ATS and ERS expert
16 committee [7], although the best method for the interpretation of BD tests is still under debate [36].
17 Using this criterion in a patient population that reflects the range of COPD seen in a pulmonary
18 function test laboratory, we found that FVC detected more reversible patients than FEV₁. Moreover,
19 approximately one out of every two patients showing clinically significant response to BD would
20 have been declared non-reversible if assessment of FVC, a simple spirometric parameter, had been
21 omitted. One conclusion to be drawn from these results is that if only one parameter has to be
22 chosen to assess reversibility in COPD, FVC is better than FEV₁. Although this contradicts the
23 conventional thinking in clinical practice and the recent GOLD recommendations, we believe that
24 our study presents new and convincing data that confirm and strengthen many of the findings of the
25 last three decades [2, 4-6, 21-26]. For practical routine assessments, FEV₁ now seems to be an
26 oversimplification because it underestimates the true BD effects. The addition of FVC to their
27 evaluations will help physicians to better interpret airways reversibility tests, particularly in more
28 severe patients, without adding spirometric maneuvers or measurements. Although these
29 observations have to be verified in a wider range of COPD patients, including women, we believe
30 that this parameter is important and should be included in the daily practice of pulmonary medicine
31 and promoted by GOLD.

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

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

11
12 We found significant changes in FRC, RV, SVC, and the SVC vs. FVC difference after BD
13 inhalation. Our results are in line with previous studies in COPD patients [2, 22, 23, 38-42], and
14 reflect a decrease in static pulmonary hyperinflation and gas trapping. In addition, we found the
15 changes in FVC to be greater in severe and/or hyperinflated patients, similar to findings in patients
16 with severe emphysema [23, 24]. To fully appreciate BD efficacy in COPD patients, the assessment
17 of lung volumes and capacities was proposed as a means to obtain additional information regarding
18 hyperinflation [43]. However, most centers report FEV₁ and FVC before and after BD
19 administration but not other lung function parameters like lung volumes [2], probably because of the
20 impracticality of repeating complete plethysmographic measurements in patients. Therefore, the
21 main practical advantage of FVC analysis, which is often neglected in interpretation, is that it is
22 measured during the same spirometric maneuver as FEV₁. Moreover, an improvement in FVC
23 provides useful information about the function of small airways, the most important sites of
24 inflammatory and remodeling processes [44] that are difficult to measure [45].

25
26 Our results showed a predominant “volume effect” of acute BD inhalation, as the “flow
27 effect” is more limited in COPD patients [2]. Still under debate in the literature [2, 23, 24, 27, 38-
28 41], the differential volume vs. flow effect is not fully understood in these patients. As previously
29 argued, a postBD change in FVC without a concomitant change in FEV₁ suggests that the airways
30 smooth muscle tone, which is the point of impact of all inhaled bronchodilators, is a major
31 determinant of airways caliber at low but not high lung volumes [24, 27, 36, 40]. Bronchodilation
32 likely relieves gas trapping, especially in particularly overdilated areas of the lungs [2, 45]. The
33 poor correlation between flow and volume responses in our study and others has been attributed to
34 functional fast and slow spaces [2, 45]. The slow space, with its very long time constants, has flow
35 rates too low for detection by short maximal flow parameters like FEV₁. Improved flows in the

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

6
7 We found that ExT increased after BD in our COPD patients, in line with previous
8 observations [4]. It has been suggested that FVC increases only because patients learn to blow
9 longer with repeated testing and that it is therefore a type of artifact [4]. In our study, several points
10 run counter to this hypothesis. First, we carefully followed the spirometry standardization steps,
11 which require several maneuvers to obtain at least three acceptable and reproducible measurements
12 [29]. The maneuvers therefore must be learned before the stringent criteria for acceptable preBD
13 FVC can be met. Second, we found no statistical difference in ExT between patients with and
14 without significant clinical increase in FEV₁. The learning effect from the preBD to postBD
15 maneuver, if real, was thus likely to be equally distributed throughout the whole population, and not
16 only among the reversible patients. Third, patients with only an “isolated volume response”
17 (increase in FVC alone) did not show significantly longer ExT than patients with a flow effect
18 (concomitant increases in FEV₁ and FVC). In fact, an increase in ExT is likely to represent a real
19 BD effect that may also explain changes in static volumes.

20
21 In conclusion, reversibility of airflow limitation is difficult to assess in individual COPD
22 patients since it is both parameter- and guidelines-dependent. Using a non-restrictive approach,
23 probably one out of two patients would present reversibility. Therefore, in daily practice,
24 reversibility should be identified in all COPD patients using the changes in FVC as a primary
25 outcome, as it appears to detect a high proportion of patients that are not detected by FEV₁ and
26 other spirometric measures. Sufficient evidence is now available to justify promoting this message,
27 particularly through the consensus statements of highly influential organizations like GOLD. It is
28 time for professional societies to standardize the spirometric criteria of airways reversibility in
29 COPD.

1

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2

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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

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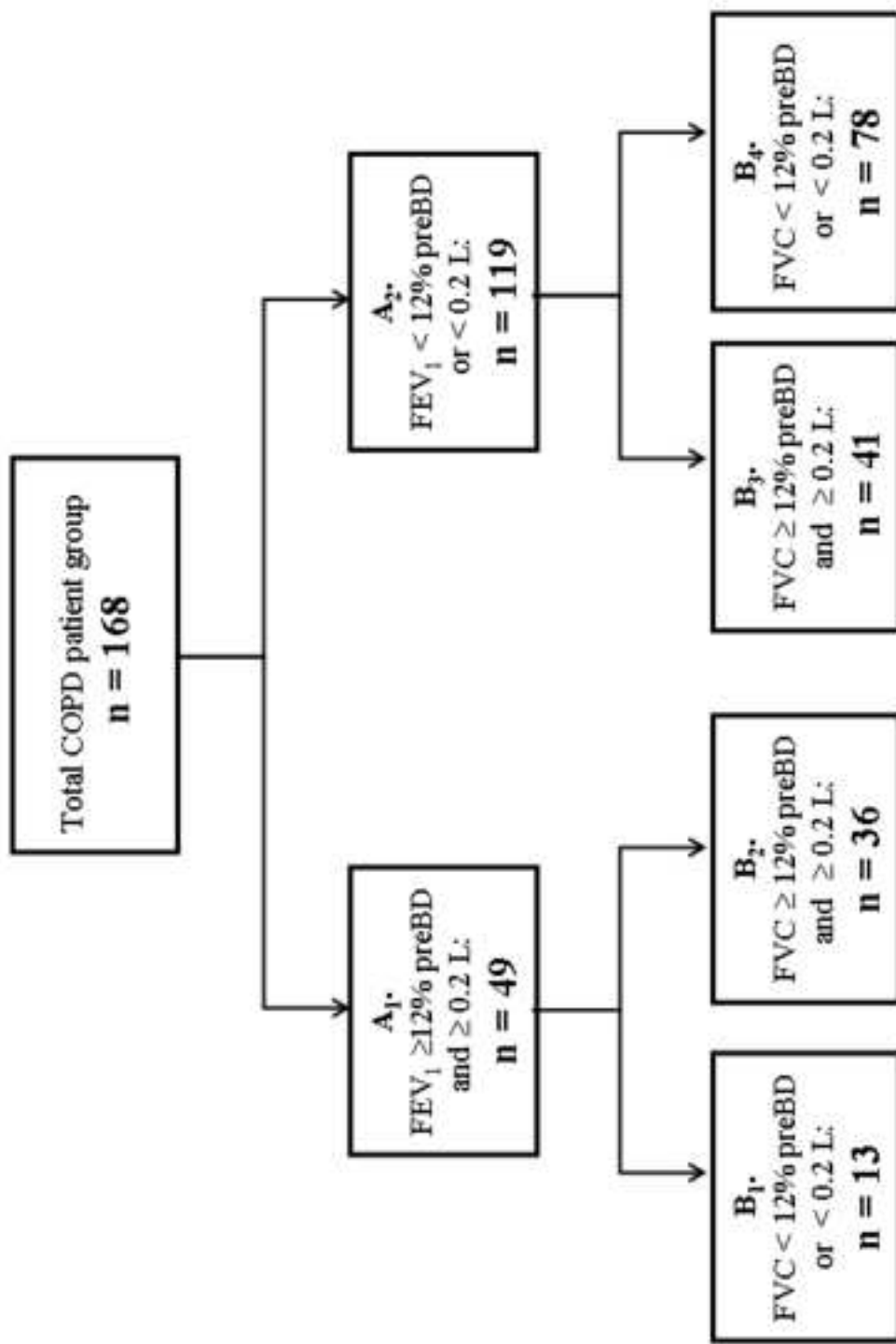


Figure 1

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)	FEV₁-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)
Δ FEV ₁ , L	0.16±0.16	0.11±0.12
Δ FEV _{1%} preBD, %	9±10	13±13
Δ FVC, L	0.22±0.28	0.33±0.21 ⁺
Δ FVC _{%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). $\Delta_{\%preBD}$: Absolute change as the percentage increase over the preBD value.

Patients with reversible FEV₁: Δ (L) \geq 0.2 L and $\Delta_{\%preBD} \geq$ 12%.

Patients with reversible FVC: Δ (L) \geq 0.2 L and $\Delta_{\%preBD} \geq$ 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 \geq 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				
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.