Eur Respir J 2008; 31: 742–750
DOI: 10.1183/09031936.00129607

Bronchodilator responsiveness in patients with COPD

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ABSTRACT: The degree of acute improvement in spirometric indices after bronchodilator inhalation varies among chronic obstructive pulmonary disease (COPD) patients, and depends upon the type and dose of bronchodilator and the timing of administration.

Acute bronchodilator responsiveness at baseline was examined in a large cohort of patients with moderate-to-very-severe COPD participating in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial, a 4-yr randomised double-blind trial evaluating the efficacy of 18 μg tiotropium daily in reducing the rate of decline in lung function. After wash-out of respiratory medications, patients received 80 μg ipratropium followed by 400 μg salbutamol. Spirometry was performed before and 90 min following ipratropium administration. The criteria used for forced expiratory volume in one second (FEV_1) responsiveness were: ⩾12% increase over baseline and ⩾200 mL; ⩾15% increase over baseline; and ⩾10% absolute increase in the percentage predicted value.

Of the patients, 5,756 had data meeting the criteria for analysis (age 64.5 yrs; 75% male; baseline FEV_1 1.10 L (39.3% predicted) and forced vital capacity (FVC) 2.63 L). Compared with baseline, mean improvements were 229 mL in FEV_1 and 407 mL in FVC. Of these patients, 53.9% had ⩾12% and ⩾200 mL improvement in FEV_1, 65.6% had ⩾15% improvement in FEV_1, and 38.6% had ⩾10% absolute increase in FEV_1 % pred.

The majority of patients with moderate-to-very-severe chronic obstructive pulmonary disease demonstrate meaningful increases in lung function following administration of inhaled anticholinergic plus sympathomimetic bronchodilators.

KEYWORDS: Bronchodilator, chronic obstructive pulmonary disease, reversibility, spirometry, tiotropium

Acute bronchodilator responsiveness in patients with chronic obstructive pulmonary disease (COPD) has not been characterised rigorously in large cohorts. This is because determination of the response to a bronchodilator is influenced by physiological and methodological factors, including differences in baseline degree of airflow obstruction, diurnal and day-to-day variability in bronchomotor tone, dose and class of inhaled bronchodilator therapy, method of bronchodilator administration (*e.g.* metered-dose inhaler with or without a spacer or solution nebuliser), dose of bronchodilator, timing of post-bronchodilator spirometry [1] and wash-out of maintenance respiratory medications. To add further complexity, repeated testing has shown considerable intra-individual variability in acute bronchodilator responsiveness in COPD [2, 3].

For editorial comments see page 695.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and American Thoracic Society (ATS)/European Respiratory Society COPD guidelines define COPD as a preventable and treatable disease characterised by airflow limitation that is partially reversible [4, 5]. Nevertheless, patients with COPD are still commonly thought to show diminished acute bronchodilator responsiveness compared with asthmatics, and reversibility testing is still sometimes proposed as a method of discriminating between asthma and COPD, despite evidence to the contrary [6].

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial is a large-scale 4-yr multinational clinical trial evaluating whether once daily maintenance treatment with 18 μg tiotropium is associated with a decrease in the rate of decline in forced expiratory volume in one second (FEV_1) over time in patients with COPD [7]. In this study, baseline spirometry was performed before and following administration of

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Received:
October 02 2007
Accepted after revision:
January 17 2008

STATEMENT OF INTEREST
Statements of interest for all of the authors and the study itself can be found at www.erj.ersjournals.com/misc/statements.shtml

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

the short-acting bronchodilators, ipratropium bromide and salbutamol, timed to achieve maximal or near-maximal bronchodilation [3]. The baseline post-bronchodilator FEV1 in the UPLIFT study provided a unique opportunity to: 1) examine acute bronchodilator responsiveness in a large cohort of patients with moderate-to-very-severe COPD; 2) determine the proportion of this population that would be considered responsive or nonresponsive using various reversibility criteria; and 3) explore determinants of responsiveness by examining the characteristics of patients who did and did not meet specific responsiveness criteria.

METHODS

Study design

The UPLIFT trial is a randomised double-blind, placebo-controlled, parallel-group clinical trial examining the effect of 18 μg tiotropium daily on the rate of decline in FEV1 over 4 yrs in patients with COPD [7]. The present analysis examines bronchodilator responsiveness using blinded aggregate baseline data obtained from all patients with values for both pre- and post-bronchodilator FEV1.

The protocol was approved by ethics committees and/or institutional review boards of all participating centres. Written informed consent was obtained from all patients participating in the study.

Participants

Patients were recruited from 475 investigational centres in 37 countries. They were eligible for inclusion if they had a diagnosis of COPD, were aged $\geqslant$40 yrs, had a smoking history of $\geqslant$10 pack-yrs, and had both a post-bronchodilator FEV1 of $\leqslant$70% of the predicted value and an FEV1/forced vital capacity (FVC) of $<$0.70 in response to near-maximal doses of both salbutamol and ipratropium bromide. Patients were excluded if they had experienced a respiratory infection or an exacerbation of COPD in the 4 weeks prior to screening, had a history of asthma or pulmonary resection, used supplemental oxygen for $>$12 h·day^{-1} or had a significant disease other than COPD that, in the opinion of the investigator, might influence either the results of the study or the patient's ability to participate in the study. Patients were permitted to continue using all previously prescribed respiratory medications other than inhaled anticholinergics provided that the prescriptions had not changed during the 6 weeks prior to randomisation. Details of the trial design have been published previously [6].

Procedures

At visit 1, baseline data, including demographics, smoking status, use of concomitant therapies and other relevant medical history, were obtained and initial screening spirometry was performed after administration of 200 μg salbutamol. Patients who demonstrated a post-salbutamol FEV1 of $\leqslant$70% pred and an FEV1/FVC of $<$0.70 at visit 1 were eligible to continue. These patients returned to the study centre 2 weeks later (visit 2) to undergo pre- and post-bronchodilator spirometry (baseline).

Prior to baseline pulmonary function testing at visit 2, patients were asked to adhere to medication wash-out requirements, which included withholding short- and long-acting β-agonists (for $\geqslant$8 and $\geqslant$12 h, respectively), short- and long-acting theophylline preparations (for $\geqslant$24 and $\geqslant$48 h, respectively) and antileukotrienes (for $\geqslant$48 h), prior to spirometry. Patients were discouraged from smoking during the study visit, and were not permitted to smoke within 30 min of spirometry. The subjects' self-report was relied upon regarding their adherence to these restrictions, as is routinely the case in clinical trials.

At visit 2, pre-bronchodilator spirometry was performed and then the patients received four inhalations of ipratropium (80 μg *via* metered-dose inhaler) followed 60 min later by four inhalations of salbutamol (400 μg *via* metered-dose inhaler) to ensure maximal or near-maximal bronchodilation. A spacer was not used. Post-bronchodilator spirometry was performed 30 min after inhalation of salbutamol. The spirometry was deemed acceptable if ATS criteria were met [8]. Manoeuvres were performed in triplicate and the best of three efforts, defined as the highest acceptable FEV1 and the highest acceptable FVC obtained on any of three manoeuvres (even if not from the same curve), constituted the data for the test set [8].

In order to minimise variability, all sites were provided with identical spirometry systems (KoKo Spirometer; Quantum Research, Inc., Louisville, CO, USA), including customised study-specific software, and the study staff received standardised training at the investigator meetings. All technicians were required to meet proficiency requirements in the use of the equipment and demonstrate the ability to perform technically acceptable pulmonary function tests according to ATS criteria prior to testing study patients [8]. During testing, the spirometry software provided immediate feedback to the technician regarding the acceptability and reproducibility of FVC efforts. Following test completion, spirometric measurements were electronically transmitted for centralised quality review (nSpire Health, Inc., Louisville, CO, USA) following ATS recommendations. Feedback was provided to centres on a regular basis in order to maintain quality over time [6, 8].

Statistical analysis

Data from all the randomised patients with moderate-to-very-severe COPD who performed technically acceptable pre- and post-bronchodilator pulmonary function manoeuvres at baseline were included in the analysis. Data from patients with mild COPD (n=3) and those without technically acceptable pre- and post-bronchodilator measurements (n=233; 3.9%) were excluded from the present analysis.

FEV1 responsiveness was assessed using three different published criteria: $\geqslant$12% and $\geqslant$200 mL improvement [8–10]; $\geqslant$15% increase over baseline [11, 12]; and $\geqslant$10% absolute increase in the percentage predicted value [2, 13, 14]. In order to further examine bronchodilator responsiveness and the influence of baseline severity of airflow limitation, FEV1 and FVC improvements above baseline were stratified according to GOLD stage using the criteria of $\geqslant$12% and $\geqslant$200 mL improvement, and $\geqslant$15% increase over baseline. The cohort was analysed for the proportion of patients achieving these predefined increases in FEV1 and FVC according to the following criteria: 1) FEV1 response with or without an FVC response; 2) FVC response with or without an FEV1 response; 3) FEV1 response without an FVC response; 4) FVC response without an FEV1 response; 5) either an FEV1 or an FVC response; and 6) both an FEV1 and an FVC response. The

results are displayed for descriptive purposes and were not analysed statistically due to the smaller individual groupings.

The characteristics of patients with and without bronchodilator responsiveness who did and did not meet these criteria were summarised descriptively, and p-values were computed using unpaired t-tests for independent variables. The frequency distributions of bronchodilator responses according to percentage increase and absolute increase (in millilitres) in FEV1 were generated. Multivariate logistic regression, with covariates including sex, smoking status, age, self-reported smoking history (in pack-yrs) COPD duration, baseline pre-bronchodilator FEV1 (percentage predicted) and St George's Respiratory Questionnaire (SGRQ) total score, was used to analyse the association between baseline characteristics and the presence or absence of acute bronchodilator responses according to each of the three criteria used. A stepwise model selection procedure was used to identify the significant variables.

RESULTS

Study population

A total of 8,019 patients were screened for participation in the study over 14 months. Of these, 5,993 patients met the eligibility criteria and were randomised into the UPLIFT study. Technically acceptable baseline pre- and post-bronchodilator pulmonary function data were available for 5,756 moderate-to-very-severe COPD patients. The results presented herein are from this cohort. The demographics, baseline characteristics and baseline use of respiratory medications are displayed in table 1.

TABLE 1 Demographics and baseline characteristics of analysis cohort

Subjects n	5756
Age yrs	64.5±8.5
Males	74.6
Race	
White	90.0
Asian	6.3
Black	1.6
Unavailable	2.0
Current smoker	30.6
Smoking history pack-yrs	48.7±27.9
Duration of COPD yrs	9.8±8.3
BMI kg·m^{-2}	26.0±5.1
SGRQ total score	45.9±17.1
Pre-bronchodilator FEV1 % pred	39.3±12.0
Post-bronchodilator FEV1 % pred	47.6±12.6
GOLD stage	
Stage II: moderate	46.6
Stage III: severe	44.7
Stage IV: very severe	8.8
Medication use	
Any respiratory medication	93.1
Short-acting β-agonists	68.5
Any long-acting bronchodilator	60.5
Inhaled steroids	61.4
Short-acting inhaled anticholinergics	44.5
Xanthines	28.6
Oxygen	2.0

Data are presented as percentage of population or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; SGRQ: St George's Respiratory Questionnaire; FEV1: forced expiratory volume in one second; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Bronchodilator responsiveness

The mean pre-bronchodilator FEV1 and FVC were 1.10 and 2.63 L, respectively (fig. 1). Following bronchodilator administration, there was a 229 mL (23.4%) mean increase in FEV1 and a 471 mL (20.1%) mean increase in FVC ($p<0.001$ *versus* pre-bronchodilator value; fig. 1). This improvement corresponded to an increase in FEV1 from 39.3 to 47.6% pred, an absolute increase of 8.3%.

In order to examine responsiveness, the distributions of the post-bronchodilator percentage and absolute improvement in FEV1 and the absolute improvement in percentage predicted FEV1 are shown in figure 2. Overall, there were substantial improvements in FEV1, but the percentage of patients who could be characterised as responsive differed depending upon the criterion applied. In the cohort under study, 65.6% met the criterion of a ⩾15% increase in FEV1 (fig. 2a); 53.9% met the criterion of an increase in FEV1 of both ⩾12% and ⩾200 mL (73% of patients showed an increase of ⩾12% (fig. 2a), and 55% of ⩾200 mL (fig. 2b)); and 38.6% were characterised as reversible based on a ⩾10% absolute improvement in percentage predicted FEV1 (fig. 2c). If paradoxical bronchospasm is defined as a decrease in FEV1 of ⩾12% and ⩾200 mL, only a minute fraction (0.24%) of the subjects demonstrated this phenomenon.

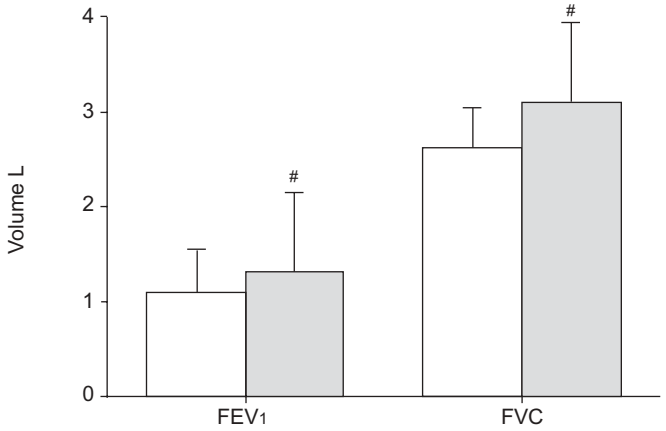

FIGURE 1. Results of pre- (□) and post-bronchodilator (■) spirometry at baseline (n=5,756). Data are presented as mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity. #: $p<0.0001$ *versus* pre-bronchodilator value.

Characteristics associated with bronchodilator responsiveness

The baseline characteristics, baseline lung function and COPD severity of patients who did or did not meet each of the three responsiveness criteria are shown in tables 2 and 3, respectively.

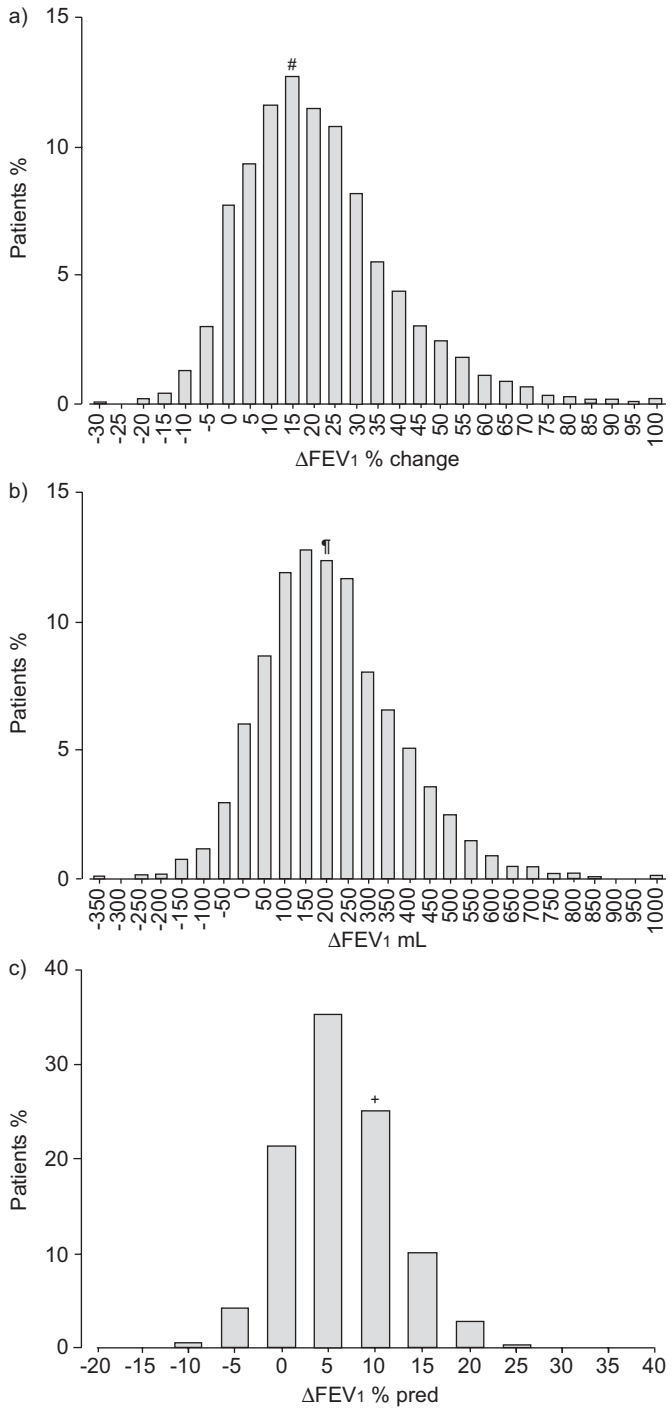

FIGURE 2. Proportion of patients (n=5,756) showing different changes in pre- to post-bronchodilator forced expiratory volume in one second (FEV_1): a) percentage change; b) absolute change; and c) absolute change in percentage predicted (% pred) value. Δ: change. #: 65.6% showed a ⩾15% increase in FEV_1; ¶: 55% showed a ⩾200 mL increase in FEV_1; +: 38.6% showed a ⩾10% absolute increase in percentage predicted FEV_1.

Certain characteristics of responsive relative to poorly responsive patients varied depending upon the criteria used. The significant variables from the multivariate logistic regression model are displayed in table 4. The odds for females tended to be higher than for males for meeting the criteria of a ⩾15% improvement in FEV_1 ($p<0.0001$) or a ⩾10% absolute increase in percentage predicted FEV_1 ($p<0.0001$); whereas the odds for males meeting the ⩾12% and ⩾200 mL increase threshold ($p<0.0001$) was higher than for females. Age was a significant factor only for the criterion of a ⩾12% and ⩾200 mL increase; a patient of older age tended to exhibit lower odds of being responsive under this criterion. A higher percentage of active smokers was poorly responsive using the criterion of a ⩾15% increase in FEV_1, but this did not show significance in the multivariate logistic regression model. Interestingly, the mean number of self-reported pack-years of cigarette use was lower, the duration of COPD was longer and the SGRQ total score was consistently higher in poorly responsive patients, regardless of which criterion was applied. The logistic regression model shows that higher odds of responsiveness are associated with a lower number of pack-years ($p<0.001$, $p=0.014$ and $p=0.006$ for the criteria ⩾12% and ⩾200 mL improvement in FEV_1, ⩾15% improvement in FEV_1, and ⩾10% absolute increase in percentage predicted FEV_1, respectively) and better SGRQ total score (*i.e.* lower scores; $p<0.0001$ for all criteria). However, the duration of COPD did not show significance in the logistic regression in all cases.

As expected, the degree of improvement in FEV_1 was significantly greater in responsive than in poorly responsive subjects for all three threshold criteria. Interestingly, however, significant improvements in mean FEV_1 were observed after administration of bronchodilators in the poorly responsive, as well as the responsive, group regardless of threshold criteria, a finding facilitated by the large number of subjects studied. The mean baseline pre-bronchodilator percentage predicted FEV_1 was higher in the poorly responsive patients than in responsive patients for all criteria (table 3). However, the degree of difference in baseline percentage predicted FEV_1 between responsive and poorly responsive patients was greater using the criterion of a change in FEV_1 of ⩾15% (36.3 *versus* 45.2% pred; $p<0.001$) compared with the criteria of a change in FEV_1 of ⩾12% and ⩾200 mL (38.5 *versus* 40.3% pred; $p<0.001$) or a change in absolute percentage predicted FEV_1 of ⩾10% (38.8 *versus* 39.7% pred; $p=0.003$). When patients were characterised by COPD severity within each reversibility criterion, a markedly higher percentage of stage IV patients were poorly responsive than responsive for the reversibility criteria of change in FEV_1 of ⩾12% and ⩾200 mL and change in absolute percentage predicted FEV_1 of ⩾10% (table 3).

Bronchodilator responsiveness according to GOLD stage and consideration of whether flow (FEV_1) and volume (FVC) responses occur together or can occur independently are illustrated in figure 3. This figure displays the proportion of patients in GOLD stages II, III and IV achieving predefined criteria for responsiveness; GOLD stage I is not displayed since there were too few patients in this stage to provide meaningful data. The percentage of COPD patients exhibiting a flow response as judged by the ATS criteria of ⩾12% and ⩾200 mL improvement decreased progressively with increasing disease severity, whereas the percentages of those with a flow response by the ⩾15% increase criterion or a volume response by either of the two responsiveness criteria was affected relatively little by GOLD stage (fig. 3a and b). The percentage

TABLE 2 Patient characteristics by bronchodilator responsiveness at baseline

	ΔFEV1 ⩾12% and ⩾200 mL		ΔFEV1 ⩾15%		ΔFEV1 ⩾10% pred	
	Responsive	Poorly responsive	Responsive	Poorly responsive	Responsive	Poorly responsive
Patients	3103 (53.9)	2653 (46.1)	3776 (65.6)	1980 (34.4)	2224 (38.6)	3532 (61.4)
Age yrs	64.0±8.4#	65.1±8.4	64.5±8.5	64.4±8.5	64.5±8.6	64.5±8.4
Males	79.2#	69.2	73.8*	76.3	72.6	75.9
BMI kg·m^{-2}	26.1±5.0*	25.7±5.2	25.8±5.0#	26.3±5.2	26.1±5.0	25.9±5.1
Current smokers	30.7	30.5	28.9***	33.8	30.4	30.7
Smoking history pack-yrs	50.0±28.9#	47.1±26.5	49.4±28.3*	47.3±27.0	49.6±28.9*	48.1±27.2
Duration of COPD yrs	9.7±7.4	10.0±7.9	9.8±7.6	9.9±7.9	9.6±7.3	9.9±7.9
SGRQ total score	44.4±16.8#	47.7±17.3	45.8±16.7	46.1±17.7	44.0±16.8#	47.1±17.2

Data are presented as n (%), percentage or mean±SD. Δ: change; FEV1: forced expiratory volume in one second; % pred: % predicted; BMI: body mass index; COPD: chronic obstructive pulmonary disease; SGRQ: St George's Respiratory Questionnaire. *: p<0.05; ***: p<0.001; #: p<0.0001 *versus* poorly responsive patients.

of COPD patients who exhibited a volume response without a significant flow response (fig. 3d) ranged 5–49% depending upon the criteria and GOLD stage. The percentage of patients exhibiting volume responses without flow responses increased with the severity of airflow obstruction, particularly for the ATS criteria. If either an FEV1 or an FVC response was considered (fig. 3e), ~70% of patients exhibited a significant response regardless of GOLD stage.

DISCUSSION

The most important finding of the present study of a large cohort of patients with severe and very severe COPD is that the magnitude of bronchodilator responsiveness was greater than expected. In addition, the prevalence of significant responses varied according to the criteria used. Until recently, COPD had been characterised as a disease with largely irreversible airflow obstruction. Methodological issues (class and dose of acute bronchodilators, timing of post-bronchodilator spirometry following bronchodilator administration, suboptimal inhaler technique and insufficient wash-out period to minimise residual effects of previous bronchodilator therapy) [1], as well as criteria for responsiveness, may have resulted in misclassification of reversibility. Although it is now widely accepted that COPD is characterised by partially reversible airflow obstruction, the degree of acute responsiveness to bronchodilators in general use for COPD has not been rigorously analysed. The UPLIFT trial provided the opportunity to investigate the degree of acute responsiveness to large doses of two different classes of inhaled bronchodilator in a large cohort of patients with moderate-to-very-severe COPD.

Following administration of ipratropium and salbutamol timed to achieve maximal or near-maximal bronchodilation, the majority of COPD patients achieved significant improvements in FEV1 over pre-bronchodilator values (23.4% increase from pre- to post-bronchodilator values). Up to 65.6% of patients met at least one common criterion for FEV1 responsiveness following acute administration of bronchodilators. However, when the three criteria (⩾12% and ⩾200 mL improvement in FEV1, ⩾15% improvement in FEV1, or ⩾10% absolute increase in percentage predicted FEV1) were evaluated

TABLE 3 Baseline spirometric parameters and severity of chronic obstructive pulmonary disease by bronchodilator responsiveness at baseline

	ΔFEV1 ⩾12% and ⩾200 mL		ΔFEV1 ⩾15%		ΔFEV1 ⩾10% pred	
	Responsive	Poorly responsive	Responsive	Poorly responsive	Responsive	Poorly responsive
FEV1 % pred						
Pre-bronchodilator	38.5±10.5¶	40.3±13.4	36.3±10.6¶	45.2±12.2	38.8±10.0*	39.7±13.0
Post-bronchodilator	50.6±11.20¶	44.0±13.3	47.4±12.4	47.9±13.1	52.6±10.3¶	44.4±13.0
GOLD stage %						
Stage II: moderate	56.0	35.4	45.7	48.1	62.7	36.3
Stage III: severe	40.6	49.5	45.9	42.5	36.0	50.2
Stage IV: very severe	3.3	15.2	8.4	9.4	1.3	13.5
p-value#	<0.0001		<0.001		<0.0001	

Data are presented as mean±SD, unless otherwise indicated. Δ: change; FEV1: forced expiratory volume in one second; % pred: % predicted; GOLD: Global Initiative for Chronic Obstructive Lung Disease. #: across all GOLD stages shown (*versus* poorly responsive). *: p<0.05; ¶: p<0.0001 *versus* poorly responsive patients.

independently, the percentage of patients considered to show reversible airflow obstruction differed substantially (53.9 *versus* 65.6 *versus* 38.6%, respectively). Females were less likely to exhibit responsiveness to bronchodilators than males using percentage plus absolute volume improvement (*i.e.* ⩾12% and ⩾200 mL above baseline) to measure response but more likely than males using percentage or percentage predicted improvement alone. Lower percentage predicted pre-bronchodilator FEV1 values were also associated with a greater likelihood of a positive bronchodilator response for all three criteria, although the association was strongest for the criterion based on ⩾15% improvement over baseline FEV1, which is most influenced by the baseline value. The biasing influence of the baseline value can be obviated to some extent either by including an absolute level of improvement in FEV1 in the criterion for a positive response or by expressing the response in terms of absolute improvement in percentage predicted FEV1.

Selection of bronchodilator class, as well as dose and timing, may affect the degree of responsiveness observed in a study population. Although responses to β-agonists are frequently used to characterise bronchodilator responsiveness in asthma, COPD patients may manifest more pronounced improvements following administration of anticholinergics [15]. The timing of spirometry to coincide with the expected time of peak bronchodilation ensures that the optimal response to a bronchodilator is captured. Time–response curves for short-acting β-agonists and cholinergic antagonists have demonstrated peak responses to these two classes of bronchodilator at ~30–60 and ~60–90 min, respectively [1]. As already noted, combining bronchodilators with different mechanisms of action may increase the maximum degree of bronchodilation achievable with either drug alone [16].

In the UPLIFT trial, therefore, the administration of double the standard dose of both salbutamol and ipratropium, the withholding of previous bronchodilator agents for periods exceeding their known duration of action (to avoid confounding by residual effects of previous bronchodilator therapy), the performance of post-bronchodilator spirometry at the expected time of peak or near-peak bronchodilation of each of the two agents (30 min after salbutamol and 90 min after ipratropium) and the use of centralised spirometry with rigorous quality control provide the best opportunity for determining optimal bronchodilator responsiveness in patients with COPD.

Even when performing methodologically optimised bronchodilator testing, as in the UPLIFT trial, the threshold criteria selected for the definition of responsiveness may further confound the assessment. There is no complete agreement as to the recommended criteria for judging a short-term response to a bronchodilator to be significant, partly due to the lack of consensus concerning how the bronchodilator response should be expressed [8, 17]. Currently, the three most widely used methods of expressing the response to a bronchodilator are: ⩾15% improvement over pre-bronchodilator FEV1 [11]; ⩾12% improvement plus an absolute volume increase of ⩾200 mL over pre-bronchodilator FEV1 [8, 9]; and an absolute improvement over pre-bronchodilator FEV1 of ⩾10% pred [2, 13, 14]. Although the selection of these recommended criteria is somewhat arbitrary, the rationale for the 12–15% improvement over the pre-bronchodilator FEV1 is supported by some evidence indicating that these thresholds exceed normal within-trial variability [18] and responses to placebo inhalation [19], at least in asthmatic subjects. A low denominator (*i.e.* a low pre-bronchodilator FEV1) can magnify the response when expressed as percentage above baseline; however, the ATS criteria include the requirement for an additional increment in absolute volume (⩾200 mL), which would offset the influence of the pre-bronchodilator FEV1 on percentage improvement [8] and take into consideration the limits of measurement reproducibility. Conversely, a pre-specified absolute increase in FEV1 tends to minimise what may be clinically meaningful improvements in patients with very severe COPD, who may experience perceptible benefit from relatively modest absolute improvement in FEV1 above a very low baseline value. The criterion of a 10% absolute improvement in percentage predicted FEV1 represents another strategy for minimising the influence of a low denominator [2, 14, 20] and, in one study of patients with obstructive airways disease, proved to be the most useful method for expressing bronchodilator response [14].

In the present study, it was demonstrated that the application of different criteria to post-bronchodilator improvements in FEV1 results in differing prevalences of responsiveness. Patients may manifest post-bronchodilator improvements in airflow that meet one of these criteria, but may not meet all three. Hence,

TABLE 4 Logistic regression with stepwise selection procedure for each reversibility criterion

Variables#	OR (95% CI)	p-value
ΔFEV1 ⩾12% and ⩾200 mL		
Sex	0.610 (0.538–0.691)	<0.0001
Age yrs	0.978 (0.971–0.984)	<0.0001
Smoking history pack-yrs	1.003 (1.001–1.005)	00.0006
SGRQ	0.985 (0.982–0.989)	<0.0001
FEV1	0.982 (0.978–0.987)	<0.0001
ΔFEV1 ⩾15%		
Sex	1.371 (1.191–1.578)	<0.0001
Smoking history pack-yrs	1.003 (1.001–1.005)	0.0135
SGRQ	0.984 (0.981–0.988)	<0.0001
FEV1	0.926 (0.921–0.931)	<0.0001
ΔFEV1 ⩾10% pred		
Sex	1.314 (1.159–1.490)	<0.0001
Smoking history pack-yrs	1.003 (1.001–1.005)	0.0063
SGRQ	0.986 (0.983–0.990)	<0.0001
FEV1	0.988 (0.983–0.992)	<0.0001

An event in the definition of the odds ratio (OR) is a responsive patient according to one of the reversibility criteria. The ORs for the continuous variables (age, percentage predicted forced expiratory volume in one second (FEV1), St George's Respiratory Questionnaire (SGRQ) total score and smoking history) are calculated according to a one-unit increase in these variables. CI: confidence interval; Δ: change; % pred: % predicted. #: selected from age, sex (female *versus* male), smoking status, smoking history, chronic obstructive pulmonary disease duration (in years), baseline percentage predicted FEV1 before bronchodilators and SGRQ total score. Variables with a p-value of <0.05 were kept in the model.

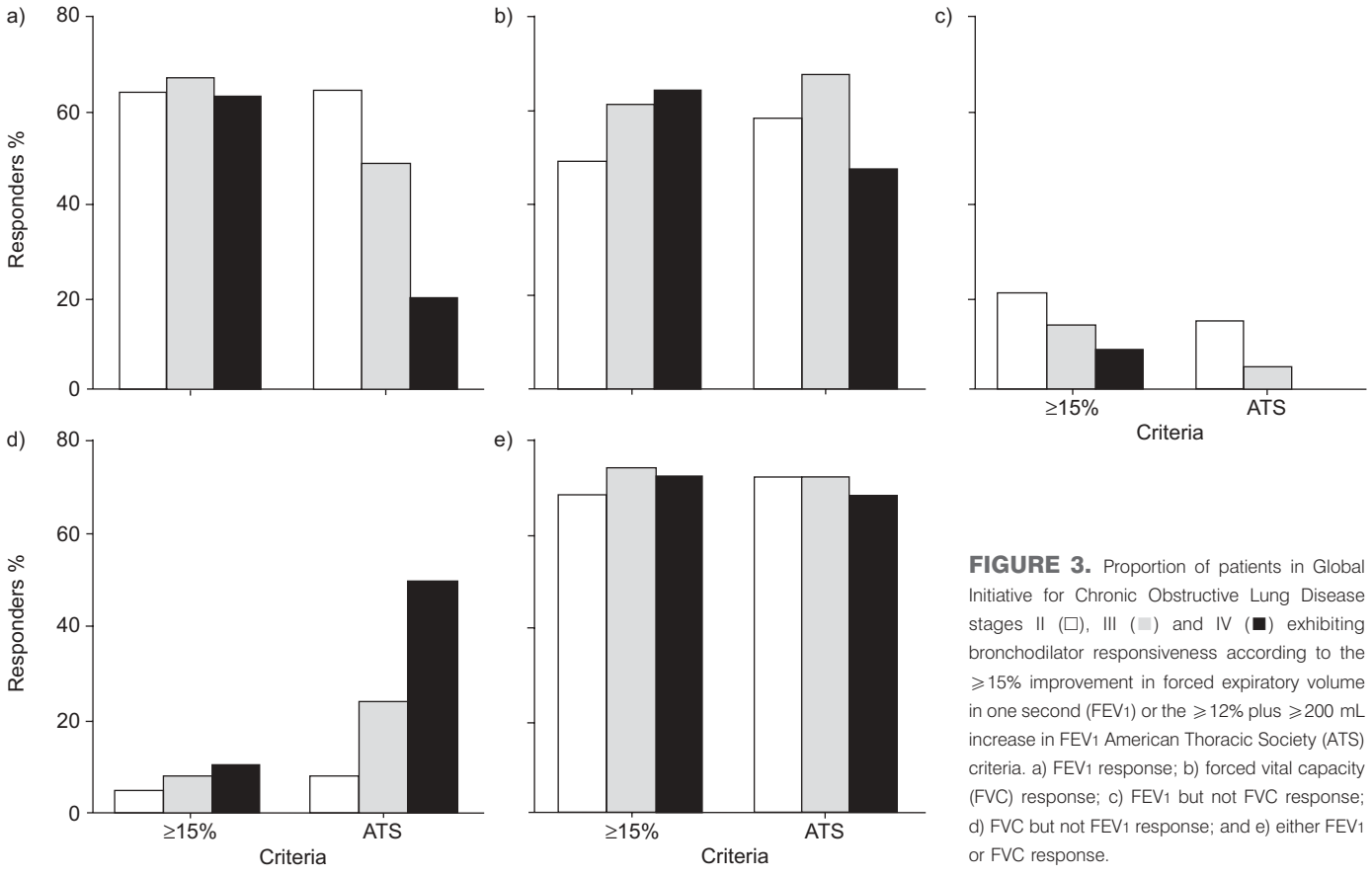

FIGURE 3. Proportion of patients in Global Initiative for Chronic Obstructive Lung Disease stages II (□), III (▒) and IV (■) exhibiting bronchodilator responsiveness according to the ⩾15% improvement in forced expiratory volume in one second (FEV_1) or the ⩾12% plus ⩾200 mL increase in FEV_1 American Thoracic Society (ATS) criteria. a) FEV_1 response; b) forced vital capacity (FVC) response; c) FEV_1 but not FVC response; d) FVC but not FEV_1 response; and e) either FEV_1 or FVC response.

classifications of responsiveness (*i.e.* responsive *versus* nonresponsive) are dependent upon the criteria applied. In addition, it was noted that significant improvements in FEV_1 were observed after administration of bronchodilators in both the responsive and poorly responsive subgroups, regardless of which criteria were applied, indicating that each method of expressing reversibility is a continuous variable, and underscoring the importance of distinguishing between significant and clinically meaningful changes. Dichotomisation using the absolute terms responsive and nonresponsive may not be clinically useful in the management of patients with COPD.

Some of the baseline characteristics of the patient population appeared to be associated with such classifications of responsiveness. Males appeared to be more often responsive than females based on certain responsiveness criteria. A higher percentage of active than of former smokers were not reversible using the criterion of a ⩾15% increase in FEV_1. Poorly responsive patients generally exhibited a lower self-reported cigarette use (in pack-yrs), a longer duration of COPD and a higher SGRQ total score regardless of which criterion was applied. However, these apparent associations should be viewed with caution given the wide range of values and inherent biases (*e.g.* females have smaller lung volumes than males and ex-smokers may have lower lung function than current smokers who can more readily tolerate continued smoking), which may not necessarily be adequately adjusted for in the multivariate analysis.

Although the purpose of the present report was to assess bronchodilator responsiveness in COPD, as commonly defined by published criteria regarding changes in FEV_1 [2, 8–14], it has long been recognised that a large proportion of COPD patients who fail to exhibit the requisite threshold increase in FEV_1 according to one or more of these criteria nonetheless demonstrate a substantial post-bronchodilator improvement in FVC or vital capacity, which can be considered an isolated volume response [1, 21]. NEWTON *et al.* [22] reported substantial increases in FVC following salbutamol (336 and 204 mL in severely and moderately hyperinflated COPD patients, respectively), as well as parallel improvements in inspiratory capacity and reductions in functional residual capacity and residual volume, despite significant improvements in FEV_1 in only a minority of patients. The clinical significance of these changes in lung volume has been underscored by the observation that improvements in exercise endurance and dyspnoea during exercise following bronchodilator therapy correlate better with increases in inspiratory capacity than with increases in FEV_1 [23]. In the present study, mean FVC improved by 20.1% and 471 mL over baseline, consistent with these earlier observations. It is also worth noting that ⩽49% of the patients with very severe COPD showed a volume response without a flow response to the bronchodilators when the ⩾12% and ⩾200 mL increase over baseline criterion was applied to both FEV_1 and FVC, and that the percentage of patients with an isolated volume response increased with the severity of airflow obstruction (fig. 3d). At the present time, however,

bronchodilator responsiveness is formally defined only by improvements in FEV1, although a compelling argument could be made for redefining bronchodilator responsiveness to include improvements not only in FEV1 but also in lung volumes alone and in addition to increases in FEV1, especially in COPD patients, who are more likely to exhibit an isolated volume response than patients with asthma.

In summary, the present results in 5,756 COPD patients confirm and extend previous reports of substantial acute bronchodilator reversibility in patients with COPD who had no other features of asthma, regardless of the method used to define reversibility. Findings indicated that, at study entry, patients with moderate-to-very-severe COPD participating in the global clinical trial UPLIFT were responsive to near-maximal doses of two different classes of inhaled bronchodilator, as evidenced by increases over baseline in FEV1 and percentage predicted FEV1. Over a half to almost two-thirds of the subjects met the most commonly used criteria for acute bronchodilator responsiveness, and more than a third showed acute responsiveness by the increase in percentage predicted criterion. It should not be surprising that the effect of baseline characteristics on responsiveness varies depending upon the criterion used for defining reversibility. In the present study, it was also demonstrated that patients with COPD can exhibit a volume response to short-acting bronchodilators without a significant flow response and that the proportion of patients exhibiting volume responses without flow responses increases with the severity of airflow obstruction.

The major conclusion of the present study is that the method of assessing near-maximal bronchodilator responsiveness used in the Understanding Potential Long-term Impacts on Function with Tiotropium trial, although difficult to implement in clinical practice, shows more reversibility in chronic obstructive pulmonary disease patients than has generally been thought and can be used in research.

ACKNOWLEDGEMENTS

The authors would like to acknowledge T. Keyser (Boehringer Ingelheim, Ridgefield, CT, USA) for editorial support in the preparation of this manuscript.

REFERENCES

1 Tashkin DP. Measurement and significance of the bronchodilator response. *In*: Jenne JW, Murphy S, eds. Drug Therapy for Asthma: Research and Clinical Practice. Lung Biology in Health and Disease. New York, Marcel Dekker, Inc, 1987; pp. 535–613.
2 Anthonisen NR, Wright EC. Bronchodilator response in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 814–819.
3 Dorinsky PM, Reisner C, Ferguson GT, Menjoge SS, Serby CW, Witek TJ Jr. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. *Chest* 1999; 115: 966–971.
4 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Guidelines: workshop report. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated September, 2005. www.goldcopd.com/GuidelineList.asp?!1=2&!2=1 Date last accessed: January 13, 2007.
5 Celli BR, MacNee W, committee members. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
6 Kesten S, Rebuck AS. Is the short-term response to inhaled β-adrenergic agonist sensitive or specific for distinguishing between asthma and COPD? *Chest* 1994; 105: 1042–1045.
7 Decramer M, Celli B, Tashkin DP, *et al*. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *J COPD* 2004; 1: 303–312.
8 American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144: 1202–1228.
9 Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
10 Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest* 2003; 123: 1441–1449.
11 Criteria for the assessment of reversibility in airways obstruction. Report of the Committee on Emphysema, American College of Chest Physicians. *Chest* 1974; 65: 552–553.
12 Routine nebulized ipratropium and albuterol together are better than either alone in COPD. The COMBIVENT Inhalation Solution Study Group. *Chest* 1997; 112: 1514–1521.
13 Eliasson O, Degraff AC Jr. The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Influence of clinical diagnosis, spirometric, and anthropometric variables. *Am Rev Respir Dis* 1985; 132: 858–864.
14 Brand PL, Quanjer PH, Postma DS, *et al*. Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. *Thorax* 1992; 47: 429–436.
15 Chapman KR. Anticholinergic bronchodilators for adult obstructive airways disease. *Am J Med* 1991; 91: Suppl. 4A, 13S–16S.
16 In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group. *Chest* 1994; 105: 1411–1419.
17 Hansen JE, Casaburi R, Goldberg AS. A statistical approach for assessment of bronchodilator responsiveness in pulmonary function testing. *Chest* 1993; 104: 1119–1126.
18 Pennock BE, Rogers RM, McCaffree DR. Changes in measured spirometric indices. What is significant? *Chest* 1981; 80: 97–99.
19 Sourk RL, Nugent KM. Bronchodilator testing: confidence intervals derived from placebo inhalations. *Am Rev Respir Dis* 1983; 128: 153–157.
20 Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
21 Ransdell JW, Tisi GM. Determination of bronchodilatation in the clinical pulmonary function laboratory. Role of static changes in lung volumes. *Chest* 1979; 76: 622–628.

22 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.

23 O'Donnell D, Flüge T, Gerken F, *et al*. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004; 23: 832–840.