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Bronchodilator Response in FVC Is Larger and More Relevant Than in FEV_1 in Severe Airflow Obstruction

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BACKGROUND: Recommendations on interpreting tests of bronchodilator responsiveness (BDR) are conflicting. We investigated the dependence of BDR criteria on sex, age, height, ethnicity, and severity of respiratory impairment.

METHODS: BDR test data were available from clinical patients in the Netherlands, New Zealand, and the United States (n = 15,278; female subjects, 51.7%) and from surveys in Canada, Norway, and five Latin-American countries (n = 16,250; female subjects, 54.7%). BDR calculated according to FEV_1, FVC, and FEV_1/FVC was expressed as absolute change, a percentage of the baseline level (% baseline), a percentage of the predicted value (% predicted), and *z* score.

RESULTS: Change (Δ) in FEV_1 and FVC, in milliliters, was unrelated to the baseline value but was biased toward age, height, sex, and level of airways obstruction; ΔFEV_1 was significantly lower in African Americans. In 1,106 subjects with low FEV_1 (200-1,621 mL) the FEV_1 increased by 12% to 44.7% relative to baseline but < 200 mL. Expressing BDR as a percentage of the predicted value or as a *z* score attenuated the bias and made the 200-mL criterion redundant, but reduced positive responses by half. ΔFEV_1 % baseline increased with the level of airflow obstruction but decreased with severe obstruction when expressed as *z* scores or % predicted; ΔFVC, however expressed, increased with the level of airflow obstruction.

CONCLUSIONS: Expressing FEV_1 responsiveness as % baseline spuriously suggests that responsiveness increases with the severity of respiratory impairment. Expressing change in FEV_1 or FVC as % predicted or as *z* scores eliminates this artifact and renders the required 200-mL minimum increase redundant. In severe airways obstruction ΔFVC should be critically evaluated as an index of clinically important relief of hyperinflation, with implications for bronchodilator drug trials. CHEST 2017; 151(5):1088-1098

KEY WORDS: airways obstruction; asthma; bronchodilator responsiveness; chronic obstructive pulmonary disease; respiratory physiology

ABBREVIATIONS: ANOVA = analysis of variance; ATS = American Thoracic Society; BD = bronchodilator; BDR = bronchodilator responsiveness; ECSC = European Community for Steel and Coal; ERS = European Respiratory Society

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Spirometry is the mainstay in diagnosing airways obstruction, and the response to a short-acting bronchodilator (BD) is an important aid in clinical decision-making. Recommendations about what constitutes a positive response have varied widely. It has been suggested that BD responsiveness (BDR) could be used to separate asthma from COPD.[1,2] However, BDR is not a dichotomous trait and poorly separates these diseases.[3-5] Early recommendations defined a positive response as an increase in FEV_1 of at least 15%[6] and a > 200-mL[7] increase from baseline. At present, the American Thoracic Society/European Respiratory Society (ATS/ERS) guideline recommends regarding a change in FEV_1 or FVC > 12% of baseline and >200 mL as significant bronchodilatation.[8] Because post-BD absolute change is independent of baseline FEV_1,[3,6,7,9] expressing change as a percentage of the initial value inflates the result in patients with low initial values and introduces vulnerability to regression to the mean.[10] Therefore, expressing the response as a percentage of the predicted value was advocated.[3,9,10]

The 200-mL minimum increase in FEV_1 or FVC requires a proportionately larger response in short vs tall people. Consequently, short individuals and those with very low initial values may not satisfy the 200-mL criterion, even if their change exceeds 12%. Therefore, the objectives of this study were to assess (1) how often an increase in FEV_1 or FVC of 12% of initial or predicted value and 200 mL post-BD occurred in patients with obstructive lung disease and in healthy subjects, and (2) how the different expressions of BDR according to FEV_1 and FVC varied in these groups. Expressing measured values or change as a percentage of the predicted value leads to an important age bias; hence they were expressed as *z* scores, which are free of any bias.[11,12]

Materials and Methods

Data on FEV_1, FVC, and FEV_1/FVC were obtained from patients in St. Louis University Hospital (St. Louis, MO), Erasmus Medical Center (Rotterdam, The Netherlands), and Christchurch Hospital (Christchurch, New Zealand) who were referred for BD testing. The St. Louis and Rotterdam data detailed the referring physician's tentative or confirmed diagnosis of asthma, COPD, or asthma/COPD overlap. Data from PLATINO (Proyecto Latino-americano de Investigación en Obstrucción Pulmonar), Norway, and CanCOLD (Canadian Cohort of Obstructive Lung Disease) published epidemiological studies[13-16] were also included. Measurements complied with contemporary international recommendations.[8,17,18]

All centers administered short-acting β_2-agonists via metered dose inhaler and spacer (see e-Appendix 1). Only data from subjects of self-reported European and African-American ancestry were included.

Anonymous data from clinical patients were routinely collected, obviating the need for approval by ethics committees. The regional ethics review boards previously approved the epidemiological studies.

Predicted values for FEV_1, FVC, and FEV_1/FVC and their *z* scores ($zFEV_1$, zFVC, and $zFEV_1$/FVC) were calculated with GLI-2012 software.[19] The lower limit of normal was defined as a *z* score of −1.645, airways obstruction as a *z* score for FEV_1/FVC < −1.645; respiratory impairment was graded according to the ATS/ERS.[8]

Data were analyzed with the statistical software R [version 3.2.4; R Foundation,[20] using the Lambda-Mu-Sigma method implemented in the GAMLSS [Generalized Additive Models for Location, Scale and Shape] package [version 4.4-0]). Changes in FEV_1 and FVC and their *z* scores were regressed as a function of sex, age, height, ethnic group, and a spline for the FEV_1/FVC *z* score (e-Appendix). GLI-predicted values for children did not fit the FEV_1, FVC, and FEV_1/FVC in the PLATINO study,[12,21] and therefore equations were derived from healthy Latin-American nonsmokers with height and an age spline as independent variables. The model with the lowest Schwarz-Bayesian criterion was selected, and the goodness of fit judged from quantile-quantile (Q-Q) and worm plots. Linear regression was performed when appropriate, and analysis of variance (ANOVA) to test differences between centers. *P* values < .05 were regarded as statistically significant. Median values and 95th centiles were estimated from 5,000 bootstrap samples with replacement. Classification of subjects by diagnosis of asthma, COPD, or asthma/COPD was studied by linear discriminant analysis, using 50% of data as a training set.

Results

Healthy Adults

Predicted values provided a good fit to data from asymptomatic nonsmoking adults, a subset of the

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epidemiologic data (n = 16,250) with full data on health and smoking habits, aged 19.7 to 95.0 years (men, 32%), without a self-reported history of symptoms or disease (questionnaire assessed) that would adversely affect pulmonary function.[13-15] Median *z* scores for FEV_1, FVC, and FEV_1/FVC were 0.04, 0.04, and 0.0, respectively (Table 1), with 4.6%, 4.3%, and 5.1%, respectively, of observations below the 5th percentile. The 95th percentile for absolute FEV_1 and FVC change post-BD was 320 mL, and for *z* score changes were 0.78 and 0.64, respectively (Table 1). The FEV_1/FVC ratio increased from 0.78 to 0.81, $zFEV_1$/FVC by 0.42 units (Table 1). Post-BD FEV_1, FVC, and FEV_1/FVC fell in 22.6%, 45.8%, and 16.7% of cases, respectively (χ^2 test, $P < .0001$). Changes (Δ) in FEV_1 and FVC expressed in milliliters, *z* scores, percentage predicted, or percentage baseline, were associated with age and level of airflow limitation, those in FEV_1 (mL) additionally with sex and height (e-Table 1).

Collated Data

A total of 31,528 (male subjects, 46.7%) tests were available in the 4- to 95-year age range (Table 2, e-Table 2), including 2,371 healthy white nonsmokers (male subjects, 44.4%; 19.7-86.8 years), and 1,972 African-American patients (male subjects, 38.5%; 14-92 years). Of these subjects, 32.2% had obstruction with a pre-BD FEV_1/FVC *z* score < –1.645; one in four of these subjects (8.0%) had a post-BD FEV_1/FVC *z* score > –1.645 (Table 3, e-Table 3). Post-BD the FEV_1 increased by ≥ 12% of baseline in 18.2% of subjects, irrespective of the presence of airways obstruction; only 7.6% changed by both ≥ 12% and ≥ 200 mL (Table 2) (for FVC, 10.9% and 6.8%, respectively) (χ^2 test, $P < .0001$). In 1,106 children and elderly subjects (female subjects, 67.4%; age, 67.4 ± 14.1 years) the increase was ≥ 12% baseline but < 200 mL (e-Fig 1). Of note, the post-BD FEV_1, FVC, and FEV_1/FVC values fell in 17.7%, 39.8%, and 21.2% of cases, respectively (χ^2 test, $P < .001$). Elderly subjects generally had more severe airways obstruction (Table 4, e-Table 4). In clinical patients ΔFEV_1 and ΔFVC were associated with age, height, sex, and level of respiratory impairment; the association with ethnicity varied with how BDR was expressed (e-Table 1).

TABLE 1] Prebronchodilator Median and 5th and 95th Centiles of FEV_1, FVC, and FEV_1/FVC Expressed as *z* Scores, and Changes After Bronchodilation in 2,371 Healthy White Asymptomatic Nonsmokers

Index	Median	5th Centile	95th Centile
$zFEV_1$	0.04	−1.59	1.72
zFVC	0.04	−1.55	1.66
$zFEV_1$/FVC	0.00	−1.65	1.44
ΔFEV_1, mL	71	−118	320
ΔFVC, mL	−19	−324	320
ΔFEV_1/FVC	0.027	−0.04	0.09
$\Delta zFEV_1$	0.18	−0.29	0.78
ΔzFVC	−0.03	−0.63	0.64
$\Delta zFEV_1$/FVC	0.42	−0.61	1.44
ΔFEV_1, % pred	2.71	−4.36	11.6
ΔFVC, % pred	0.02	−9.75	10.2
ΔFEV_1, % init	2.7	−4.3	13.3
ΔFVC, % init	−0.51	−9.5	12.0

Δ = change; % init, percentage of the initial value; % pred, percentage of the predicted value; $zFEV_1$ = *z* score of FEV_1; $zFEV_1$/FVC = *z* score of FEV_1/FVC; zFVC = *z* score of FVC.

The changes in *z* scores for FEV_1, FVC, and FEV_1/FVC were clearly related to the level of respiratory impairment (Fig 1). $\Delta zFEV_1$ peaked at mild and moderate airways obstruction and then declined, whereas ΔzFVC increased as airways obstruction became more severe (Table 4, Fig 1). The improvement in zFVC was less than in $zFEV_1$ for subjects with mild to moderately severe airways obstruction; in severe and very severe obstruction ΔzFVC exceeded $\Delta zFEV_1$ (Fig 1, e-Table 5). ΔFEV_1 declined with age and became slightly negative after age 50 years (e-Fig 2).

ΔFEV_1 % predicted was unrelated to a diagnosis of asthma, COPD, and asthma/COPD; and ΔFVC % predicted was marginally larger in COPD and asthma/COPD than in asthma (Fig 2; explained variance, 1%). In subjects with airways obstruction FEV_1 increased post-BD by ≥ 12% predicted in 14.9% of subjects; positive responses increased to 22.7% when including the ΔFVC response; in severe and very severe obstruction including the FVC response more than doubled the percentage of positive responses (e-Table 6).

The FEV_1 and FVC responses according to ATS/ERS criteria were positive in 14.4% and 10.5% (Table 2), compared with change expressed as a percentage of the predicted value in 7.5% and 6.8%, respectively. After adjusting for height, age, sex, ethnicity, and severity of respiratory impairment small but significant differences between centers remained in the BD response in $zFEV_1$ (ANOVA, Tukey's honestly significant difference test, $P < .001$), but the explained variance was trivial (0.2%).

TABLE 2] Characteristics of Male and Female Subjects in Collated Data, and BD Response in Various Subgroups[a]

Sex of Subjects	Data[b]	No.	Age (y)	ΔFEV$_1$, % init (%)	ΔFEV$_1$, % pred (%)	ΔFVC, % init (%)	ΔFVC, % pred (%)
Male	Clinical	7,375	4-94	28.2 (23.9)	9.4 (9.4)	16.2 (16.0)	10.0 (10.0)
	Epidemiological	7,354	19-93	11.6 (10.9)	6.0 (6.0)	6.4 (6.4)	4.5 (4.5)
Female	Clinical	7,903	5-95	23.7 (15.6)	8.8 (8.7)	14.7 (13.5)	8.2 (8.1)
	Epidemiological	8,896	20-95	10.5 (8.7)	6.1 (6.0)	6.7 (6.6)	4.9 (4.9)
Total		31,528	4-95	18.2 (14.4)	7.6 (7.5)	10.9 (10.5)	6.8 (6.8)

BD = bronchodilator. See Table 1 legend for expansion of other abbreviations.
[a]The figures in the last four columns indicate the proportion of members in each subgroup who exhibited a change of > 12% in either initial or predicted values. The figures in parentheses indicate the proportion of subjects who exhibited a change of > 12% in either initial or predicted values as well as an absolute change of > 200 mL.
[b]Clinical data: St. Louis, Rotterdam, and Christchurch. Epidemiological data: CanCOLD, Norway, and PLATINO studies.

Subjects With a Diagnosis

Data sets from Rotterdam and St. Louis provided a putative or confirmed diagnosis of asthma, asthma/COPD, or COPD. Age and the level of zFEV$_1$, zFVC, and zFEV$_1$/FVC (Table 4) were significantly associated ($P < .001$), with the poorest spirometric indices in subjects with COPD. The improvement in FEV$_1$ and FEV$_1$/FVC (Table 5), whether expressed in milliliters, *z* scores, or percentage of initial or predicted values, was smallest in COPD ($P < .001$); the FVC improved least in asthma (ANOVA; $P < .002$), but the explained variance was only 1%. The post-BD FEV$_1$ was smaller than the pre-BD FEV$_1$ in asthma, asthma/COPD, and COPD in, respectively, 22.5%, 13.3%, and 16.2% of cases, and for FVC, respectively, in 35.6%, 26.9%, and 25.7%. Discriminant analysis using various combinations of explanatory variables resulted in poor separation of asthma, COPD, and asthma/COPD (maximum overall accuracy, 69%).

Comparison of Criteria for Positive BD Response

Adopting the criterion that zFEV$_1$ should increase by > 0.78 units yielded a positive response in 7.9% of subjects, compared with 14.4% and 7.5% according to ATS/ERS and ECSC (European Community for Steel and Coal)/ERS criteria, respectively. Whereas application of the ATS/ERS criterion suggests greater responsiveness as the severity of respiratory impairment

TABLE 3] Mean (SD) of Pre-BD and Post-BD Characteristics in Collated Data of Male and Female Subjects in Various Subgroups

Baseline and Post-BD Data	Male Subjects		Female Subjects		Total (N = 31,528)
	Clinical[a] (n = 7,375)	Epidemiological[a] (n = 7,354)	Clinical[a] (n = 7,903)	Epidemiological[a] (n = 8,896)	
Baseline zFEV$_1$	−2.06 (1.36)	−0.60 (1.26)	−1.88 (1.40)	−0.42 (1.28)	−1.21 (1.52)
Baseline zFVC	−1.12 (1.35)	−0.17 (1.13)	−1.17 (1.33)	−0.09 (1.12)	−0.62 (1.34)
Baseline zFEV$_1$/FVC	−1.87 (1.57)	−0.79 (1.23)	−1.40 (1.54)	−0.62 (1.13)	−1.15 (1.46)
ΔFEV$_1$, mL	166 (184)	135 (199)	109 (151)	90 (149)	123 (173)
ΔFVC, mL	145 (266)	43 (296)	78 (196)	10 (220)	66 (245)
ΔzFEV$_1$	0.32 (0.38)	0.26 (0.38)	0.29 (0.41)	0.24 (0.40)	0.28 (0.39)
ΔzFVC	0.24 (0.44)	0.07 (0.43)	0.18 (0.45)	0.23 (0.48)	0.12 (0.46)
ΔFEV$_1$, % pred	8.8 (11.2)	4.9 (8.4)	7.6 (11.4)	4.6 (10.6)	6.4 (10.7)
ΔFVC, % pred	5.0 (9.8)	1.4 (7.4)	4.0 (10.1)	0.9 (11.2)	2.8 (10.0)
Obstruction pre-BD, %	53.3	21.5	40.9	16.2	32.2
Obstruction post-BD, %	44.9	15.3	34.1	10.6	25.6
Becomes obstructed post-BD, %	1.7	1.0	1.7	1.4	1.4
No longer obstructed post-BD, %	10.0	7.2	8.4	6.7	8.0

See Table 1 and 2 legends for expansion of abbreviations.
[a]Clinical data: St. Louis, Rotterdam, and Christchurch. Epidemiological data: CanCOLD, Norway, and PLATINO studies.

TABLE 4] Initial Mean Level (SD) in Collated Data of Spirometric Indices Expressed as *z* Scores, Percent Predicted, and Their Change Post-BD, Stratified by Sex and Level of Respiratory Impairment[a]

Baseline and Post-BD Data	No Obstruction ($zFEV_1/FVC > -1.64$)	Mild	Moderate	Moderately Severe	Severe	Very Severe
Male Subjects						
Age, mean (SD)	55.4 (15.4)	51.8 (18.1)	57.7 (17.5)	61.0 (16.0)	62.6 (15.9)	63.7 (13.1)
ΔFEV_1, mL	112 (176)	219 (215)	240 (220)	242 (220)	214 (207)	155 (200)
ΔFVC, mL	33 (224)	70 (271)	195 (292)	255 (305)	295 (344)	343 (412)
$\Delta FEV_1/FVC$	0.02 (0.03)	0.04 (0.04)	0.03 (0.05)	0.03 (0.05)	0.02 (0.05)	0.01 (0.05)
ΔFEV_1, % pred	3.2 (5.0)	6.2 (6.2)	7.0 (6.4)	7.3 (6.5)	6.7 (6.2)	4.8 (5.7)
ΔFVC, % pred	0.8 (5.2)	1.6 (6.3)	4.5 (7.0)	6.0 (7.3)	7.2 (8.4)	8.2 (9.5)
$zFEV_1$	−0.64 (1.17)	−1.17 (0.85)	−2.30 (0.38)	−2.82 (0.45)	−3.46 (0.58)	−4.22 (0.69)
zFVC	−0.47 (1.23)	0.34 (1.00)	−0.80 (0.73)	−1.24 (0.87)	−1.85 (1.00)	−2.71 (1.14)
$zFEV_1/FVC$	−0.38 (0.82)	−2.22 (0.48)	−2.59 (0.60)	−2.95 (0.74)	−3.46 (0.84)	−4.27 (0.84)
$\Delta zFEV_1$	0.22 (0.34)	0.45 (0.47)	0.45 (0.43)	0.45 (0.44)	0.38 (0.40)	0.24 (0.34)
ΔzFVC	0.05 (0.35)	0.11 (0.45)	0.31 (0.47)	0.41 (0.51)	0.49 (0.58)	0.55 (0.65)
$\Delta zFEV_1/FVC$	0.31 (0.52)	0.49 (0.56)	0.37 (0.53)	0.31 (0.51)	0.22 (0.47)	0.09 (0.45)
$\Delta FEV_1 > 12\%$,[b] %	7.1 (3.5)	22.1 (13.2)	40.5 (16.2)	46.8 (20.9)	44.5 (16.0)	27.9 (7.0)
$\Delta FVC > 12\%$,[b] %	4.3 (2.4)	4.0 (4.3)	17.2 (13.2)	27.0 (18.0)	39.2 (25.0)	47.9 (28.7)
ΔFEV_1, % pred > 8%,[c] %	12.9	31.7	39.6	40.5	36.7	17.4
% all male subjects	62.6	12.8	6.2	6.0	7.6	4.8
Female Subjects						
Age, mean (SD)	55.2 (15.3)	50.6 (18.0)	56.9 (17.3)	60.1 (15.8)	63.9 (13.7)	61.5 (13.4)
ΔFEV_1, mL	75 (139)	170 (178)	174 (167)	185 (187)	147 (158)	113 (154)
ΔFVC, mL	12 (190)	20 (251)	140 (210)	181 (231)	186 (239)	211 (273)
$\Delta FEV_1/FVC$	0.02 (0.04)	0.05 (0.05)	0.03 (0.04)	0.03 (0.05)	0.02 (0.05)	0.02 (0.06)
ΔFEV_1, % pred	3.0 (5.7)	8.4 (6.6)	6.9 (6.4)	7.5 (6.9)	6.4 (6.5)	4.8 (6.3)
ΔFVC, % pred	0.5 (6.3)	0.6 (9.2)	4.6 (6.0)	5.9 (7.6)	6.5 (8.3)	7.1 (9.2)
$zFEV_1$	−0.59 (1.22)	−1.12 (1.07)	−2.34 (0.35)	−2.91 (0.41)	−3.53 (0.51)	−4.49 (0.61)
zFVC	−0.46 (1.26)	0.34 (1.08)	−0.90 (0.64)	−1.36 (0.78)	−1.98 (0.92)	−2.91 (1.08)
$zFEV_1/FVC$	−0.30 (0.83)	−2.18 (0.45)	−2.49 (0.56)	−2.86 (0.68)	−3.28 (0.81)	−4.08 (0.86)
$\Delta zFEV_1$	0.21 (0.38)	0.46 (0.50)	0.46 (0.45)	0.48 (0.48)	0.38 (0.42)	0.27 (0.41)

(Continued)

TABLE 4] (Continued)

	Female Subjects					
ΔzFVC	0.03 (0.42)	0.04 (0.54)	0.31 (0.46)	0.40 (0.52)	0.43 (0.56)	0.50 (0.66)
$\Delta zFEV_1/FVC$	0.33 (0.59)	0.58 (0.65)	0.35 (0.50)	0.32 (0.52)	0.23 (0.51)	0.13 (0.56)
$\Delta FEV_1 > 12\%$,[b] %	6.4 (4.1)	23.2 (15.0)	32.9 (17.7)	34.3 (19.2)	26.8 (15.8)	16.0 (8.3)
$\Delta FVC > 12\%$,[b] %	5.9 (3.7)	4.6 (5.0)	16.9 (12.0)	27.1 (18.2)	33.6 (20.7)	41.2 (24.1)
ΔFEV_1, % pred > 8%,[c] %	12.9	35.4	37.3	39.3	31.5	18.1
% all female subjects	72.2	10.0	4.6	4.4	5.7	3.1

See Table 1 and 2 legends for expansion of abbreviations.
[a]According to the American Thoracic Society/European Respiratory Society.[8]
[b]Percentage of subjects meeting this threshold as > 12% baseline and > 200 mL, within parentheses as > 12% predicted and > 200 mL.
[c]Percentage of subjects meeting this threshold.

increases, the ECSC/ERS criterion (ΔFEV_1 > 12% predicted value and > 200 mL) and the new criterion ($\Delta zFEV_1 > 0.78$) showed an opposite trend (Fig 2). The percentage of positive responses in FVC increased progressively with the level of respiratory impairment, being largest according to ATS/ERS and lowest for ECSC/ERS criteria (Fig 3).

Sensitivity Analysis

Analyses carried out on the collated data were repeated using only data from clinical subjects as well as from subjects in whom the FEV_1 and FVC did not fall post-BD (e-Fig 3). Predictably the regression coefficients differed somewhat, but the pattern was the same (see e-Appendix, e-Tables 7 and 8).

Discussion

To our knowledge, this is the first study that quantifies the progressively increasing BD response in FVC vs the declining absolute response in FEV_1 with increasing airflow limitation. Requiring a fixed minimum change in FEV_1 > 200 mL is unrealistic: in patients it varies with stature, age, sex, ethnic group, and the level or respiratory impairment, and a 12% response presupposes a baseline $FEV_1 \geq$ 1,667 mL (200/0.12). For example, in patients the mean post-BD increase in FEV_1 in a 40-year-old white man and a 75-year-old African-American woman, both of average height and with a *z* score of –2 for FEV_1/FVC, differed by 100 mL. In one-quarter of subjects with a low baseline FEV_1, comprising children and elderly adults, the FEV_1 increased ≥ 12% of baseline but < 200 mL (e-Fig 1). The 200-mL response is superfluous when expressing change as a percentage of predicted or *z* scores.

The FEV_1 increased by > 12% baseline in 20% of subjects with mild obstruction compared with 55% in very severe airways obstruction (Fig 3); this is inconsistent with structural changes of peripheral airways and lung parenchyma in fixed airways obstruction.[22] This paradox arises because the absolute BD response in FEV_1 is independent of the initial value (e-Fig 4A).[3,6,7,9,23-25] Therefore, expressing change as % baseline spuriously suggests that the poorest initial values are associated with the greatest reversibility (e-Fig 4B); this is attenuated by expressing change as a percentage of the predicted value (e-Fig 4C). Therefore, change in FEV_1 and FVC should preferably be expressed as a percentage of the predicted value[10,23-25] or as a change in *z* score. The latter are free of bias because they

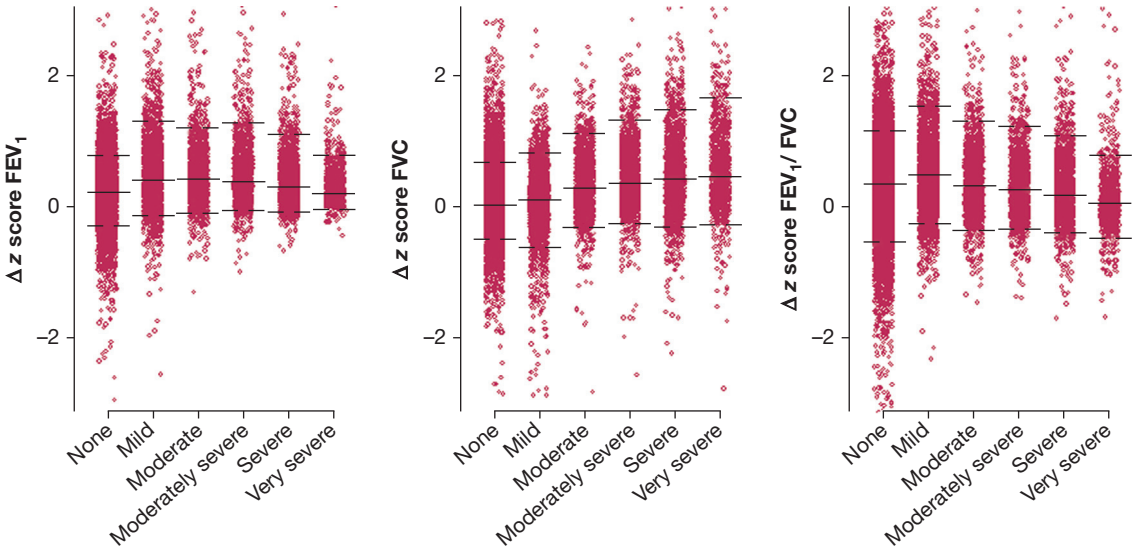

Figure 1 – *The post-bronchodilator (BD) change in z score for FEV_1 (left) is larger in mild, moderate, and moderately severe airways obstruction compared with no obstruction and then declines as obstruction becomes more severe. Conversely, the BD effect on FVC (middle) increases the more severe the respiratory impairment. The patterns for FEV_1 and FEV_1/FVC are similar. Dashed lines, 5th and 95th centiles; solid line, median.*

describe how much a measurement differs from the predicted mean, adjusted for age, height, sex, and ethnicity. These alternative ways of expressing change reduce the percentage of responders by about 50% (Table 2, e-Table 6).

It is noteworthy that FEV_1, FVC, and the FEV_1/FVC ratio fell in a large proportion of patients. This high frequency is unlikely to reflect paradoxical responses to the drug, particularly because the frequency was comparable in healthy subjects. It more likely represents variability of repeated measurements; positing an approximately equal percentage of increased values implies that about 35% of post-BD changes in FEV_1 reflect biological variability. While the scatter is the same, a small difference in the average FEV_1 and FVC response accounts for the larger percentage of lower FVC post-BD (e-Appendix, e-Fig 5).

The variability in FEV_1, combined with even greater variability in FVC, explains why a single BD result is poorly repeatable and may not be clinically meaningful.[4,26,27] Of the patients with asthma, 27.0% had airways obstruction pre-BD and 20.6% post-BD, confirming that it is often

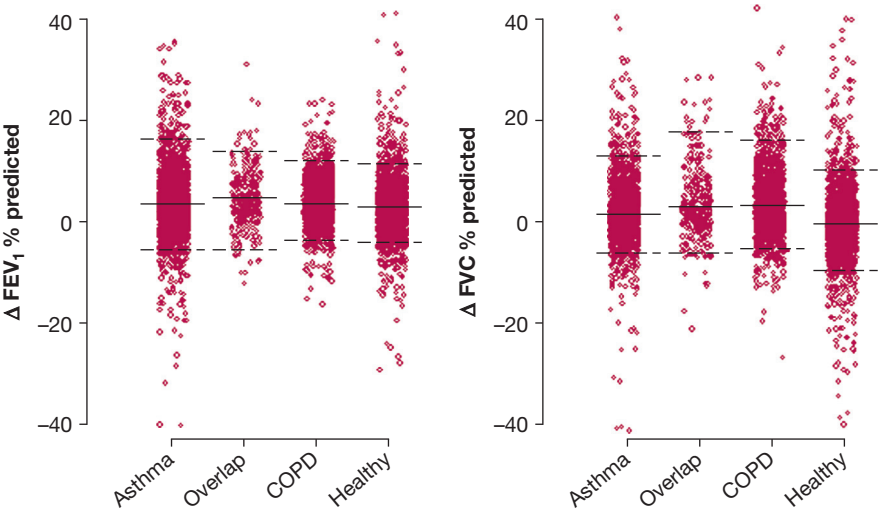

Figure 2 – *Patients with asthma have greater variability in FEV_1 and less variability in FVC response to bronchodilator than those with asthma/COPD overlap or COPD. Solid line, median; dotted lines, 5th and 95th centiles.*

TABLE 5] Initial Level of Spirometric Indices and Their Change Post-BD, Stratified by Sex and Diagnostic Category in Patients From St. Louis and Rotterdam

Index	Asthma (n = 1,946) Mean (SD)	Asthma/COPD (n = 331) Mean (SD)	Overlap COPD (n = 1,570) Mean (SD)
Age, y	41.8 (17.8)	56.7 (12.9)	63.1 (11.4)
Height, cm	166.9 (13.2)	167.8 (9.8)	169.2 (9.7)
FEV_1, L	2.58 (1.00)	1.92 (0.87)	1.72 (0.80)
FVC, L	4.43 (1.27)	3.01 (1.11)	2.87 (1.04)
FEV_1/FVC	0.75 (0.11)	0.64 (0.14)	0.60 (0.15)
$zFEV_1$	−1.39 (1.39)	−2.27 (1.33)	−2.48 (1.27)
zFVC	−0.94 (1.30)	−1.34 (1.22)	−1.52 (1.27)
$zFEV_1$/FVC	0.86 (1.43)	−1.90 (1.61)	−2.13 (1.62)
ΔFEV_1, L	0.13 (0.23)	0.14 (0.17)	0.12 (0.14)
ΔFVC, L	0.08 (0.24)	0.14 (0.26)	0.14 (0.24)
ΔFEV_1/FVC	0.02 (0.04)	0.02 (0.04)	0.01 (0.04)
$\Delta zFEV_1$	0.30 (0.52)	0.36 (0.36)	0.29 (0.29)
ΔzFVC	0.16 (0.49)	0.27 (0.50)	0.26 (0.44)
$\Delta zFEV_1$/FVC	0.32 (0.66)	0.24 (0.49)	0.14 (0.49)

See Table 1 and 2 legends for expansion of abbreviations.

difficult to distinguish between asthma and COPD on the basis of spirometric data alone.[28,29]

The $\Delta zFEV_1$ and $\Delta zFEV_1$/FVC first increase, and then decline, as airways obstruction becomes more pronounced (Fig 3, e-Figs 6 and 7); the response declines with age, becoming slightly negative after age 50 years (e-Fig 2). In contrast, ΔzFVC increases progressively from within the normal range of the FEV_1/FVC ratio to severe airflow limitation (Fig 3, e-Fig 8), exceeding the relative change in FEV_1 in severe and very severe obstruction (e-Table 5). This "volume response," that is, increasing improvement in FVC with the level of airflow limitation, confirms earlier reports[30-35]; this trend is likely to be more pronounced when measuring the slow expiratory or inspiratory vital capacity. The decline in the FEV_1 response as airways obstruction worsens might reflect a differential BD effect on hysteresis of airways

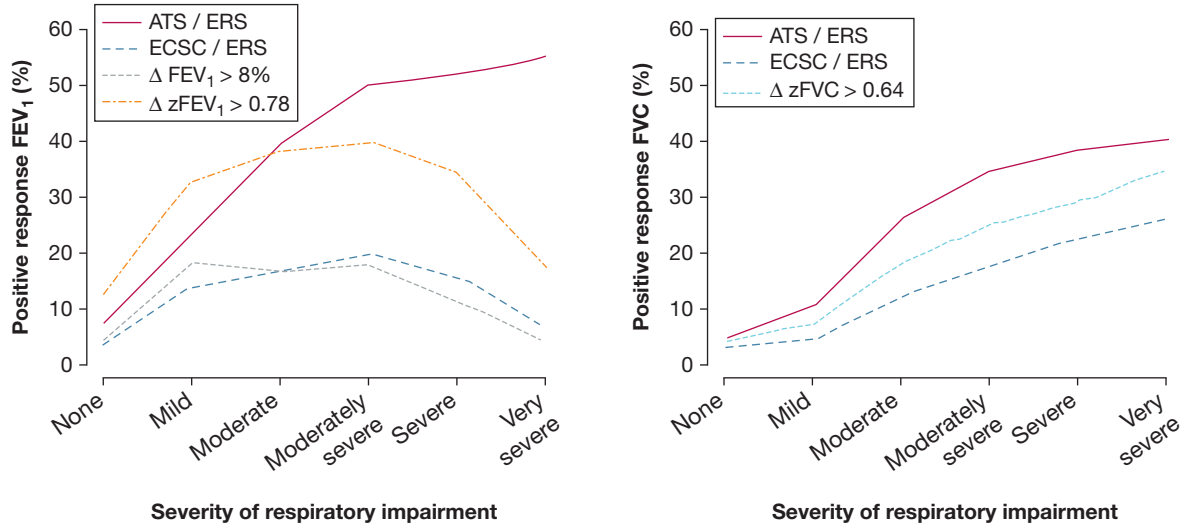

Figure 3 – *Percentage of subjects with a positive bronchodilator response (left, FEV_1; right, FVC) according to different criteria: increase > 12% initial value and ≥ 200 mL (ATS/ERS[8]), > 12% predicted value, and ≥ 200 mL (ECSC/ERS[10]), ΔFEV_1 > 8% predicted value,[25] or z score of FEV_1 or FVC increases by > 0.78 or > 0.64 units, respectively.*

and parenchyma,[36,37] but probably reflects the effects of thoracic gas compression on the FEV_1.[38-41] The higher the expiratory flow resistance, the more the intrathoracic gas volume is reduced by such high pressures; this diminishes lung elastic recoil pressure, intrathoracic airway dimensions, and the pressure/area characteristics of airways, key determinants of forced expiratory flow. Thus, FEV_1 measured at the mouth progressively underestimates the true change in lung volume as airways obstruction increases. The improvement in FEV_1 declines because the more severe and the more fixed airways resistance becomes, such as in elderly patients (Table 4), the less the improvement, due to diminished thoracic gas compression. Our findings are compatible with previous studies,[42,43] which found that a predominant volume response occurred in patients with lung emphysema and severe airways obstruction and was associated with little if any change in small airway diameter post-BD.

Recommendations on what constitutes a positive BD response are generally based on statistical rather than clinical criteria. Yet, a response not meeting recommended criteria may be clinically relevant, particularly in a patient with poor lung function[44]; indeed, a 5% to 10% change from baseline in FEV_1 is regarded as clinically meaningful,[45] and an FEV_1 change $>$ 8% predicted is associated with an optimal survival advantage.[25] Ideally, criteria for a positive BDR should be based on clinical outcome, such as exacerbations, hospitalization, quality of life, and so on. This also holds for categorizing respiratory impairment, where the use of percent predicted FEV_1 leads to a significant age bias that can be circumvented by the use of z scores,[11] but does not yet form part of international recommendations; hence we followed the ATS/ERS recommendation.[8] Spirometric reversibility testing is generally not necessary to establish a diagnosis or to plan maintenance therapy and may be misleading because of poor reproducibility.[4,26,27] Therefore, clinical judgment should prevail over statistical considerations. Whereas the emphasis is often still on evaluating the BD response in FEV_1,[8,25,46] the progressively larger FVC response as airflow limitation becomes more pronounced points to a clinically important reduction of hyperinflation with beneficial effects on dyspnea, exercise performance, and gas exchange.[38,45,47] Including the FVC response increases the number of positive responses in those with airways obstruction by $>$ 50%, and is particularly relevant in elderly patients with severe airways obstruction.

A strength of this study is the consistent pattern of BDR across multiple large data sets from patients referred for suspected obstructive lung disease and random population samples. However, unlike in the epidemiological studies, the spirometric measurements in clinical patients were made routinely, so that in that group the BDR may have been underestimated if medication was not withheld prior to testing. Although various bronchodilators and dosages were used, no clinically relevant differences were observed between centers. The data reflect common daily clinical practice, which underscores the clinical usefulness of our findings. The diagnoses of physicians who referred patients to the lung function laboratory might change following completion of supplementary investigations. Regardless, the trends in responsiveness suggest the credibility of the diagnostic classifications.

Conclusions

Post-BD change in FEV_1 expressed relative to baseline erroneously suggests that bronchial responsiveness increases with poorer initial pulmonary function. Expressing the change in FEV_1 or FVC as a percentage of the predicted value, or as a change in z score, eliminates this artifact and obviates the requirement for an increase in FEV_1 or FVC of $\geq$ 200 mL, which introduces a bias associated with age, height, sex, ethnicity, and the level of respiratory impairment. A critical evaluation of the FVC response is recommended in patients with severe airways obstruction. A fall in FEV_1 or FVC post-BD is common and likely related to spontaneous variability in repeated measurements. Therefore, drawing conclusions from a single BD test may often be misleading. This underpins the role of clinical judgment when treating patients.

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Additional information: The e-Appendix, e-Figures and e-Tables can be found in the Supplemental Materials section of the online article.

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