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Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis

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On behalf of the NHLBI SubPopulations and InteRmediate Outcome Measures In COPD Study (SPIROMICS)

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Objective: Bronchodilator responsiveness (BDR) is prevalent in COPD, but its clinical implications remain unclear. We explored the significance of BDR, defined by post-bronchodilator change in FEV_1 (BDR_{FEV1}) as a measure reflecting the change in flow and in FVC (BDR_{FVC}) reflecting the change in volume.

Methods: We analyzed 2974 participants from a multicenter observational study designed to identify varying COPD phenotypes (SPIROMICS). We evaluated the association of BDR with baseline clinical characteristics, rate of prospective exacerbations and mortality using negative binomial regression and Cox proportional hazards models.

Results: A majority of COPD participants exhibited BDR (52.7%). BDR_{FEV1} occurred more often in earlier stages of COPD, while BDR_{FVC} occurred more frequently in more advanced disease. When defined by increases in either FEV_1 or FVC, BDR was associated with a self-reported history of asthma, but not with blood eosinophil counts. BDR_{FVC} was more prevalent in subjects with greater emphysema and small airway disease on CT. In a univariate analysis, BDR_{FVC} was associated with increased exacerbations and mortality, although no significance was found in a model adjusted for post-bronchodilator FEV_1.

Conclusion: With advanced airflow obstruction in COPD, BDR_{FVC} is more prevalent in comparison to BDR_{FEV1} and correlates with the extent of emphysema and degree of small airway disease. Since these associations appear to be related to the impairment of FEV_1, BDR_{FVC} itself does not define a distinct phenotype nor can it be more predictive of outcomes, but it can offer additional insights into the pathophysiologic mechanism in advanced COPD.

Clinical trials registration: ClinicalTrials.gov: NCT01969344T4.

Keywords: bronchodilator responsiveness, inspiratory capacity, FVC, FEV_1, SPIROMICS

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that persists after bronchodilator (BD) administration and is defined by the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) (FEV_1/FVC) <0.70.[1] Widely accepted guidelines define bronchodilator responsiveness (BDR) by the increase in FEV_1 or FVC of ≥200 mL and ≥12% relative to pre-BD values.[2,3] BDR is common in COPD patients,[4,5] but whether it defines a unique phenotype is incompletely understood. In contrast to BDR_{FEV1}, which represents a flow-based, time-limited response to bronchodilators, BDR_{FVC} evaluates the volumetric response and, together with other spirometry-measured capacities (slow vital capacity [SVC] and inspiratory capacity [IC]), evaluates a BD

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effect that is neither flow-dependent nor time-limited.[6] Studies of the response patterns to BD administration in COPD suggest that reduction in hyperinflation and air trapping, as reflected by increases in lung volumes, leads to improvement in symptoms.[6,7] Nevertheless, with conflicting data about the clinical relevance of BDRFVC in the assessment of COPD[8–11] and the lack of recommendations about the interpretability of BDR assessed by FVC and FEV_1,[12] a clear understanding of the clinical relevance of BDR in COPD has been largely missing.

Using data from a large cohort of longitudinally followed individuals, we evaluated the clinical significance of BDR in COPD and its relationship to the frequency of COPD exacerbations, which are associated with increased morbidity and mortality.[13,14] We compared flow- and volume-based responsiveness to BD administration and analyzed distinct clinical implications of FEV_{1BDR} and FVC_{BDR} and their association with various outcomes.

Methods

Study Design and Participants

Subpopulations and Intermediate Outcome Measures in COPD (SPIROMICS) is a multi-center observational study designed to identify different COPD phenotypes. SPIROMICS enrolled 2,974 participants, ages 40–80 years into four strata (non-smokers; current and former smokers without airflow obstruction; and current and former smokers with either mild/moderate COPD, or severe/very severe COPD).[15] Of these, 1,831 participants had COPD based on GOLD criteria.[12] Subjects with a current diagnosis of asthma or pulmonary comorbidities not related to COPD were excluded from participation in the study, although those with a prior history of asthma that was no longer active were eligible. Participants completed a baseline examination that comprised a detailed medical history; blood and sputum biomarker analysis; assessment of dyspnea by modified Medical Research Council (mMRC) scale, of symptoms by COPD assessment test (CAT), and of health status by St. George's Respiratory Questionnaire (SGRQ); spirometry before and after inhaled BD; and high resolution chest CT scan (HRCT). Enrolled subjects were classified using GOLD guidelines.[12,16]

Spirometry

Spirometry was performed using a centrally supplied pneumotachograph following current ATS/ERS recommendations and using reference values calculated from the Hankinson equation.[3] COPD was defined by a post-BD FEV_1/FVC<0.70. Prior to the testing, participants were asked to withhold bronchodilators for at least a period equal to twice the usual dosing frequency. BDR was tested 30 mins after four inhalations each of albuterol sulfate HFA (90 µg/actuation) and ipratropium bromide HFA (17 µg/actuation). We defined BDR as an increase in FEV_1, FVC, or IC of ≥12% and ≥200 mL.[2]

Chest CT Acquisition and Analysis

All SPIROMICS participants underwent HRCT on 64- or 128-slice helical scanners. Images were obtained at suspended full inhalation and on exhalation and data were analyzed by Apollo software (VIDA Diagnostics, Coralville, IA).[17] Emphysema scores were derived using percentages of low attenuation area below and including −950 Hounsfield units (HU). Parametric response mapping (PRM), a dynamic image registration technique that links inspiratory and expiratory features of CT lung scans, was used to assess functional small airway disease (fSAD) and emphysema.[18] PRM was performed on all CT data automatically using Lung Density Analysis (LDA™) software application (Imbio, LLC, Minneapolis, MN). The adopted nomenclature for these measures for normal lung parenchyma and fSAD is PRM^{Normal} and PRM^{fSAD}, respectively.

Statistical Analysis

Demographic and clinical characteristics were tabulated, using mean and standard deviation for continuous variables, and frequency and percentages for categorical variables. We compared the clinical differences in clinical characteristics between BD responders and BD nonresponders using a two-sample *t*-test (or Wilcoxon rank sum test, if normality was not met) for continuous variables and a Chi-square test for categorical variables. PRM^{fSAD} scores between BD responders and nonresponders were compared by Wilcoxon rank sum test. To assess BDR repeatability measured by FEV_1, FVC, and IC, we calculated percentages of positive, negative, and total agreement, as well as Cohen's kappa.

We investigated if BDR_{FVC} was associated with exacerbations using univariate and multivariate negative binomial models and tested associations of BDR_{FVC} with 3-year survival by univariate and multivariate Cox proportional hazards models and Kaplan–Meier survival functions. For all multivariate modeling, stepwise model selections were performed to obtain the final parsimonious model. All tests for significance were two-tailed, using P-value less than 0.05 as the threshold for significance. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. 2013).

Ethics Statement

All investigations were conducted according to the principles of the Declaration of Helsinki. Protocols were reviewed and approved by institutional review boards in each participating site (detailed list of all approving ethics committees provided in the Supplemental data). All participants understood the purpose of the study, and all gave written informed consent before any procedures.

Results

Demographic Data

Of 2,974 participants, 202 (6.8%) were healthy never-smokers, 941 (31.6%) were current or former smokers without airflow obstruction, and 1,831 (61.6%) had COPD with one-third of those having severe or very severe disease defined by GOLD spirometric staging (Table 1). Mean smoking history among ever-smokers was 46 pack-years, and current smokers comprised 37% of the overall population.

Repeatability of BDR Measured by FEV_1, FVC, and IC

To assess BDR repeatability of flow-based versus volume-based measurements, we analyzed results of a published substudy of 98 participants who replicated their entire baseline evaluation (including spirometry) 2–6 weeks after their initial visit.[19] BDR_{FVC} had greatest repeatability (76.5%, k=0.53), in comparison to BDR_{FEV1} (72.4%, k=0.43) or BDR_{IC} (64.2%, k=0.27), Supplemental Table 1.

BDR in SPIROMICS Cohort

BDR was observed across all participant groups (Figure 1) and was similar for flow-based (FEV_1, 29.0%) and volume-based metrics, including FVC (26.3%) and SVC (26.5%) or IC (32.1%). Among participants without COPD, 7.1% of never-smokers and 13.7% of ever-smokers without obstruction demonstrated

Table 1 Demographic Data in SPIROMICS Cohort

Parameter	SPIROMICS Cohort (N=2974)	Healthy Controls (N=202)	Former or Current Smokers without COPD (N=941)	Mild/ Moderate COPD (N=1207)	Severe/Very Severe COPD (N=624)	COPD Total (N=1831)
Age (mean, SD)	63.01 (9.20)	56.5 (10.2)	60.3 (9.7)	65.6 (8.2)	64.3 (7.8)	65.1 (8.1)
Sex (male N, %)	1577 (53.0%)	79 (39.1%)	448 (47.6%)	701 (58.1%)	349 (55.9%)	1050 (57.4%)
Race						
White (N, % within the column)	2263 (76.1%)	140 (69.3%)	638 (67.8%)	995 (82.4%)	490 (78.5%)	1485 (81.1%)
Black	576 (19.4%)	46 (22.8%)	250 (26.6%)	169 (14.0%)	111 (17.8%)	280 (15.3%)
Asian	33 (1.1%)	4 (2.0%)	7 (0.7%)	15 (1.3%)	7 (1.1%)	22 (1.2%)
Others	102 (3.4%)	12 (5.9%)	46 (4.9%)	28 (2.3%)	16 (2.6%)	44 (2.4%)
Current smokers (%)	1093 (37.3%)	N/A	475 (51.0%)	460 (38.8%)	158 (25.7%)	618 (34.3%)
Cigarette Exposure - pY (ever smokers) (Mean, SD)	45.98 (28.76)	N/A	42.73 (24.28)	52.95 (29.57)	52.23 (23.07)	52.71 (27.52)
BMI (Mean, SD)	27.94 (5.27)	28.5 (5.0)	29.0 (5.1)	27.9 (5.2)	26.4 (5.4)	27.4 (5.3)
CBC eosinophil CNT at baseline (x10^9/L) [Mean, (SD)]	0.20 (0.17)	0.15 (0.13)	0.19 (0.15)	0.21 (0.19)	0.21 (0.18)	0.21 (0.19)
CBC eosinophil PCT at baseline [Mean, (SD)]	2.88 (2.08)	2.64 (2.17)	2.84 (2.12)	2.94 (1.93)	2.88 (2.26)	2.92 (2.04)
Chronic bronchitis at baseline (N, %)	596 (21.2%)	N/A	128 (14.1%)	251 (22.4%)	216 (37.0%)	467 (27.4%)
History of childhood asthma at baseline (N, %)	245 (8.2%)	4 (2.0%)	64 (6.8%)	115 (9.5%)	62 (9.9%)	177 (9.7%)
Reported history of asthma at baseline (N, %)	573 (19.3%)	10 (5.0%)	148 (15.7%)	264 (21.9%)	151 (24.2%)	415 (22.7%)
Post-BD FEV_1 percentage (mean, SD)	74.99 (26.75)	101.8 (11.6%)	96.8 (13.6)	74.0 (15.7)	35.4 (9.9)	60.9 (23.0)
SGRQ (mean, SD)	31.97 (20.99)	9.00 (9.99)	24.81 (19.34)	32.56 (19.07)	48.25 (16.91)	38.01 (19.81)
Use of inhaled bronchodilators (N, %)	1441 (49.0%)	N/A	223 (24.0%)	662 (55.4%)	547 (88.8%)	1209 (66.8%)
Use of inhaled steroids (N, %)	973 (33.1%)	N/A	111 (11.9%)	432 (36.1%)	425 (68.9%)	857 (47.3%)
Oral corticosteroid use at baseline (N, %)	71 (2.4%)	N/A	4 (0.4%)	16 (1.3%)	51 (8.3%)	67 (3.7%)
Cardiovascular condition at baseline (N, %)	1849 (63.0%)	93 (47.0%)	552 (59.3%)	811 (67.9%)	393 (64.3%)	1204 (66.7%)
Congestive heart failure (N, %)	71 (2.4%)	1 (0.5%)	14 (1.5%)	35 (2.9%)	21 (3.4%)	56 (3.1%)
Diabetes (N, %)	392 (13.3%)	19 (9.6%)	123 (13.2%)	178 (14.9%)	72 (11.8%)	250 (13.8%)
GERD (N, %)	865 (29.4%)	36 (18.2%)	264 (28.2%)	393 (32.8%)	172 (28.2%)	565 (31.2%)
Total exacerbations within 12 months at baseline (mean, SD)	0.42 (0.92)	0.04 (0.20)	0.22 (0.67)	0.39 (0.88)	0.89 (1.23)	0.56 (1.04)

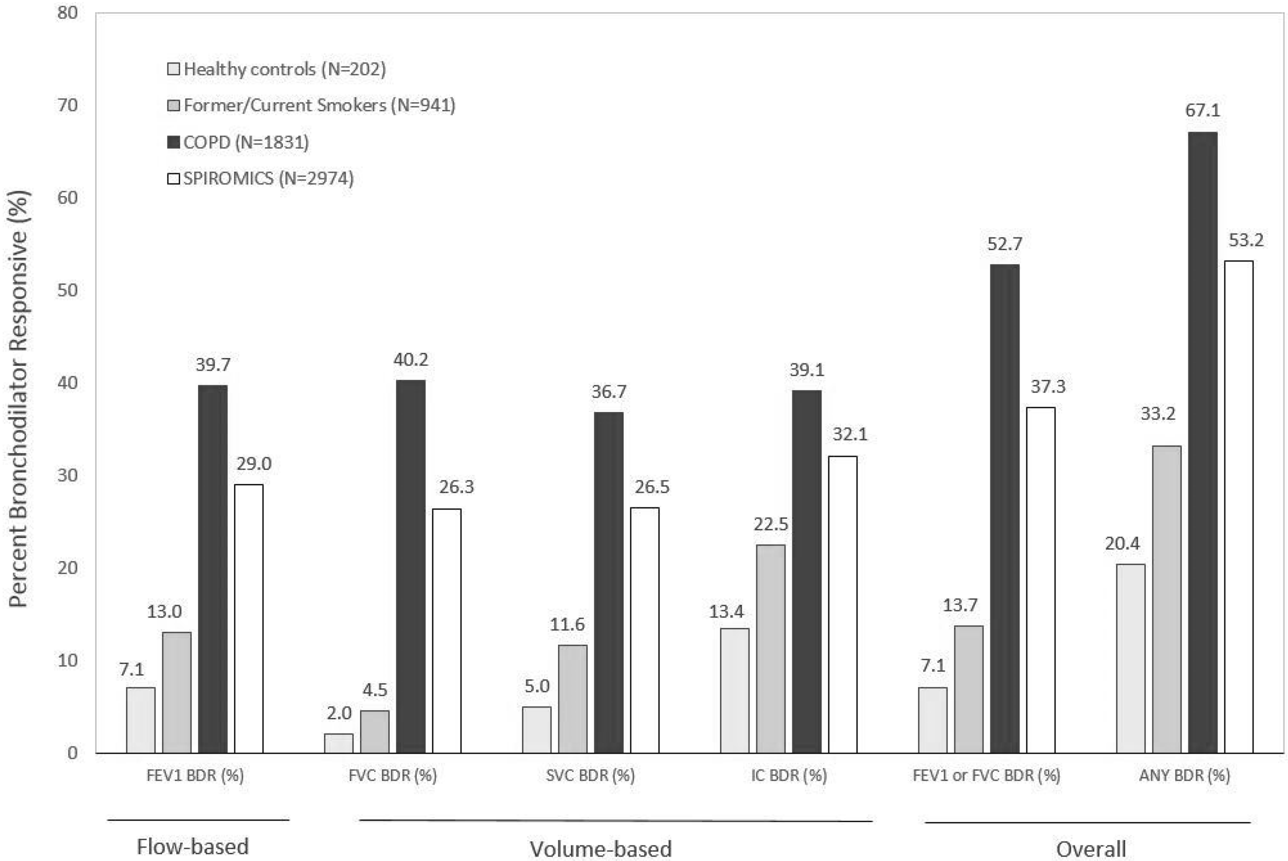

Figure 1 Overall BDR defined by different spirometric measures in the SPIROMICS cohort.

BDR defined by either FEV_1 or FVC. Among those with BDR, a response was detected more often by BDR_{FEV1} than by BDR_{FVC} (7.1% vs 2% never smokers; 13% vs 4.5% ever-smokers without obstruction). Comparing BDR for FVC to BDR for SVC and IC, a lower prevalence of BDR_{FVC} was evident in both healthy never-smokers (BDR_{FVC} 2% vs BDR_{SVC} 5.0% and BDR_{IC} 13.4%) and ever-smokers without obstruction (BDR_{FVC} 4.5% vs BDR_{SVC} 11.6% and BDR_{IC} 22.5%), suggesting greater ability of BDR_{FVC} parameter to discriminate between healthy and diseased airways.

Over half of the subjects with COPD displayed FEV_1- or FVC-defined BDR (52.7%) with similar overall frequencies of BDR_{FEV1} (39.7%) and BDR_{FVC} (40.2%). In contrast to other groups, COPD subjects showed a greater prevalence of BDR_{FVC} than BDR_{IC} or BDR_{SVC} (39.1% and 36.7%, respectively). Accepting categorization of subjects as BD responsive if any of the these four metrics indicated BDR, we found 67.1% of the participants with COPD to be BD responders.

BDR Relates to a Reported History of Asthma but Not to Blood Eosinophil Counts

Although individuals with currently active non-COPD obstructive lung disease were not included in SPIROMICS cohort, participants with COPD had a self-reported previous history of asthma more frequently than healthy nonsmokers or former/current smokers (Table 1). A self-reported history of asthma was significantly more common in participants who were FEV_1- or FVC-BD responders (Table 2). Neither BDR_{FVC} nor BDR_{FEV1} was associated with blood eosinophil counts (BEC), relative to nonresponders (Table 2).

Volume Responsiveness Increases as COPD Progresses

Mild COPD (spirometric GOLD grade 1) was characterized by greater BDR_{FEV1} than BDR_{FVC} (35.6% vs 19.2%), a difference that was less marked in GOLD grades 2 and 3 (Figure 2A). In very severe COPD (spirometric GOLD

Table 2 Baseline Clinical Characteristics of FVC-BD Responders and FVC-BD Nonresponders

Parameter	FEV1-BD Responders (n=724)	FEV1-BD Nonresponders (n=1102)	P-Value	FVC-BD Responders (n=734)	FVC-BD Nonresponders (n=1092)	P-Value
Age (mean,SD)	64.36 (7.99)	65.63 (8.06)	0.001*	65.0 (7.9)	65.2 (8.2)	0.59
Sex (male N, %)	439 (60.6%)	610 (55.4%)	0.03*	407 (55.5%)	642 (58.8%)	0.16
Current smokers (%)	271 (37.9%)	346 (32.0%)	0.01*	256 (35.4%)	361 (33.7%)	0.46
Cigarette Exposure - pY (ever smokers) (mean, SD)	53.37 (26.98)	52.25 (27.88)	0.40	53.6 (24.5)	52.1 (29.4)	0.25
BMI (mean,SD)	27.65 (5.44)	27.15 (5.23)	0.05	27.4 (5.3)	27.3 (5.4)	0.76
Post-BD FEV1 percentage (mean, SD)	62.08 (18.53)	60.08 (25.53)	0.07	53.1 (19.7)	66.1 (23.6)	<0.0001*
History of childhood asthma (N, %)	82 (11.3%)	94 (8.5%)	0.048*	83 (11.3%)	93 (8.5%)	0.048*
Reported history of asthma (N, %)	191 (26.4%)	222 (20.2%)	0.002*	188 (26.6%)	225 (20.6%)	0.012*
SGRQ (mean, SD)	37.74 (19.09)	38.16 (20.31)	0.66	41.4 (19.3)	35.7 (19.9)	<0.0001*
CBC eosinophil count (×10^9/L) (mean, SD)	0.21 (0.23)	0.21 (0.15)	0.49	0.21 (0.16)	0.21 (0.21)	0.56
CBC eosinophil percent (mean, SD)	2.97 (2.10)	2.88 (2.00)	0.36	2.82 (2.02)	2.95 (2.06)	0.39
Use of inhaled bronchodilators (N, %)	492 (68.6%)	713 (65.5%)	0.17	545 (75.3%)	660 (61.0%)	<0.0001*
Use of inhaled steroids (N, %)	345 (48.0%)	508 (46.7%)	0.58	384 (52.8%)	469 (43.4%)	<0.0001*
Emph % (log-transformed)	1.70 (1.25)	1.81(1.34)	0.03*	1.98 (1.28)	1.62(1.31)	<0.0001*
PRM fsad	27.72 (13.43)	26.67 (14.45)	0.07	31.38 (13.36)	24.21 (13.78)	<0.0001*
PRM emph	8.34 (10.35)	10.44 (12.71)	0.07	11.6 (12.64)	8.2 (11.12)	<0.0001*
Total exacerbations within 12 months at baseline (mean, SD)	0.49 (0.98)	0.60 (1.06)	0.01*	0.57 (1.02)	0.54 (1.04)	0.53

grade 4), BDR_{FEV1} was infrequent (11.3%). By contrast, BDR_{FVC} prevalence increased with advanced obstruction and was observed most frequently (54.3%) in spirometric GOLD grade 4.

To investigate whether the observed low frequency of BDR_{FEV1} in very severe disease was simply a consequence of low (<30% predicted) baseline FEV_1, we performed sensitivity analyses of BDR_{FEV1} and BDR_{FVC} by dividing

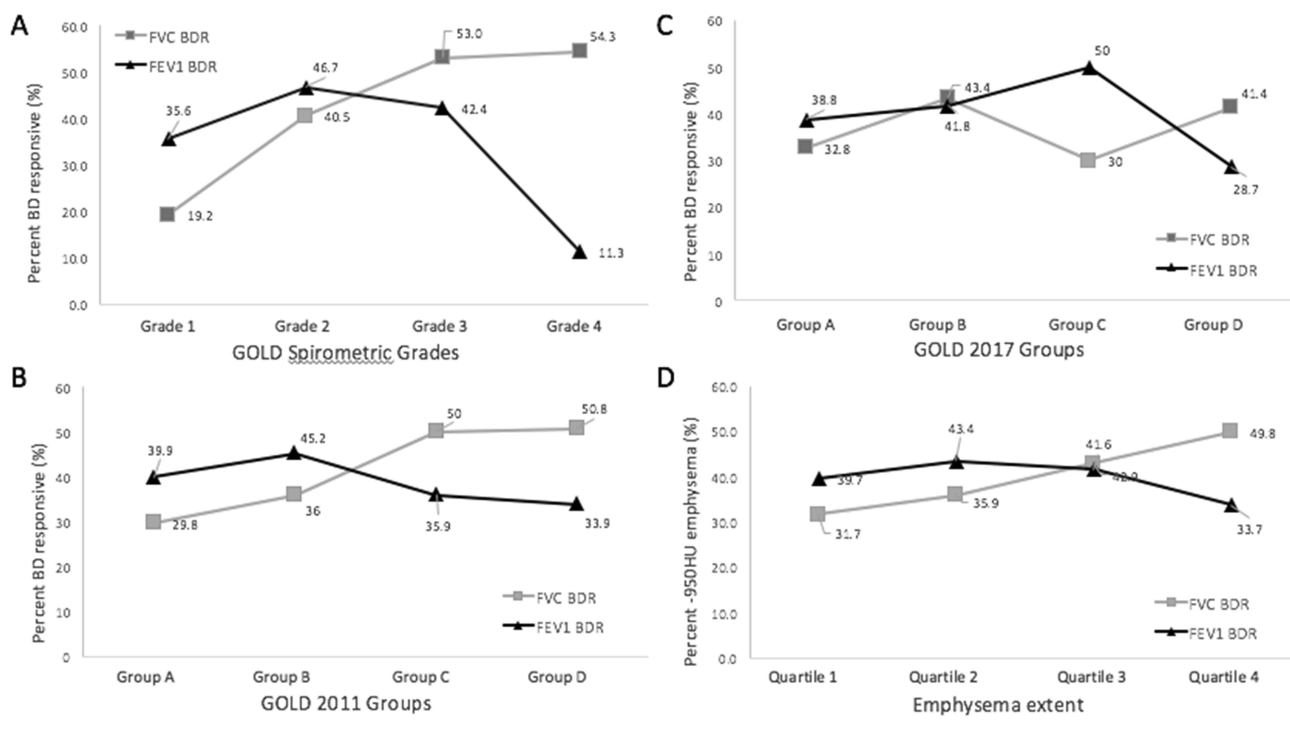

Figure 2 Distribution of flow (FEV_1) and volume (FVC) BDR in COPD based on (**A**) spirometric GOLD grades, (**B**) GOLD groups defined by symptoms, exacerbations, and spirometric grades (revision 2011), (**C**) GOLD groups defined by symptoms and exacerbations only (revision 2019), and (**D**) percentage emphysema <−950 HU.

subjects with COPD into four GOLD groups (A through D), defined by either combining spirometric grades with exacerbation frequency and symptoms (GOLD revision 2011), (Figure 2B) or by only exacerbation frequency and symptoms without spirometry (GOLD revision 2019) (Figure 2C). In both classification systems, advanced disease (Group D) was characterized by a greater prevalence of BDR_{FVC} (50.8% and 41.4%, respectively) than BDR_{FEV1} (33.9% and 28.7%, respectively).

To assess the relationship of BDR to radiographic emphysema (CT density ≤−950 HU), we divided COPD subjects into quartiles by quantity of emphysema observed on HRCT (Figure 2D). Subject age did not differ significantly across the quartiles. BDR_{FVC} was more prevalent in those with more emphysema (Quartile 4, 49.8 versus 33.7%), in contrast to those with less emphysema (Quartiles 1 and 2) where BDR_{FEV1} was more prevalent.

Volume Responsiveness Correlates with PRM Analysis of Small Airway Disease and Emphysema

To evaluate whether BD responders have more small airway disease in comparison to BD nonresponders, we analyzed parametric response mapping (PRM) in relationship to FVC and FEV_1 BDR status. PRM analysis demonstrated significantly more functional small airway disease (PRM^{fSAD}) which is equivalent to air trapping in FVC-BD responders compared with FVC-BD nonresponders, but showed no difference between FEV_1-BD responders and nonresponders (Figure 3).

Clinical relevance of BDR_{FVC}

FVC-BD responders had lower post-BD FEV_1, more emphysema, more small airway disease, and poorer health-related quality of life measured by SGRQ compared to nonresponders. FVC-BD responders also had more self-reported use of inhaled bronchodilators and inhaled steroids relative to FVC-BD nonresponders. By contrast, FEV_1 BD-responders were associated with current smoking status and fewer exacerbations reported at baseline (Table 2).

Over the 3-year study period, FVC-BD responders had reduced survival in comparison to FVC-BD nonresponders (88.1% vs 91.7%, P<0.05) (Figure 4). This difference was significant in a univariable Cox proportional hazards model (HR=1.46, CI: 1.02–2.08). In an univariable negative binomial model, BDR_{FVC} was associated with an increased incidence rate ratio (RR) for exacerbations, relative to FVC-BD nonresponders (RR=1.30, CI:1.12–1.52). However, in multivariate models adjusted for known risk factors, including post-BD FEV_1, these associations were no longer significant for either exacerbation (RR=1.12, CI: 0.96–1.31) or mortality (HR=1.03, CI=0.71–1.47), Supplemental Table 2.

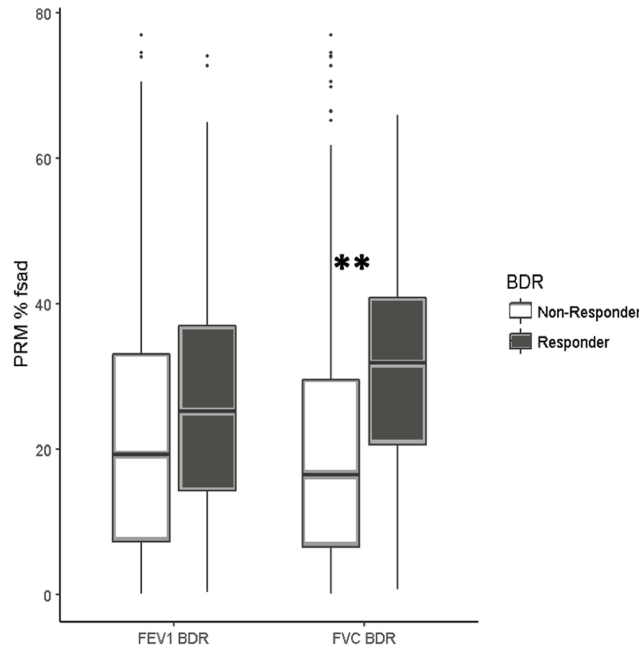

Figure 3 Parametric Response Mapping analysis. The extent of small airway disease (PRM^{fSAD}) shows that FVC-BD responders have more PRM^{fSAD} on functional imaging in comparison to FVC-BD nonresponders. There is no difference between FEV_1 BD responders and nonresponders in the extent pf PRM^{fsad}.

Finally, to understand the diverging proportions of flow-based versus volume-based BDR in advanced COPD, we analyzed subjects who demonstrated BDR_{FVC} but not BDR_{FEV1}. These subjects represented 32% of all FVC-BD responders (N=238), and in comparison to individuals who demonstrated both BDR_{FEV1} and BDR_{FVC} (N=496), they had more emphysema (Figure 5A) and more exacerbations during the follow-up period (Figure 5B). A higher risk of exacerbations was observed in isolated BDR_{FVC} relative to other COPD subjects who were not isolated FVC-BD responders (HR 1.71, CI: 1.09–2.67) (Supplemental Table 3). Isolated BDR_{FVC} was characterized by a higher 3-year mortality relative to other COPD participants. Nevertheless, stratified by post-BD FEV_1 in a multivariate model, there was no association between isolated BDR_{FVC} and exacerbations or mortality risk (Supplemental Figure 1).

Discussion

In a longitudinal analysis of 2,974 individuals with and without COPD, we evaluated the prevalence and clinical

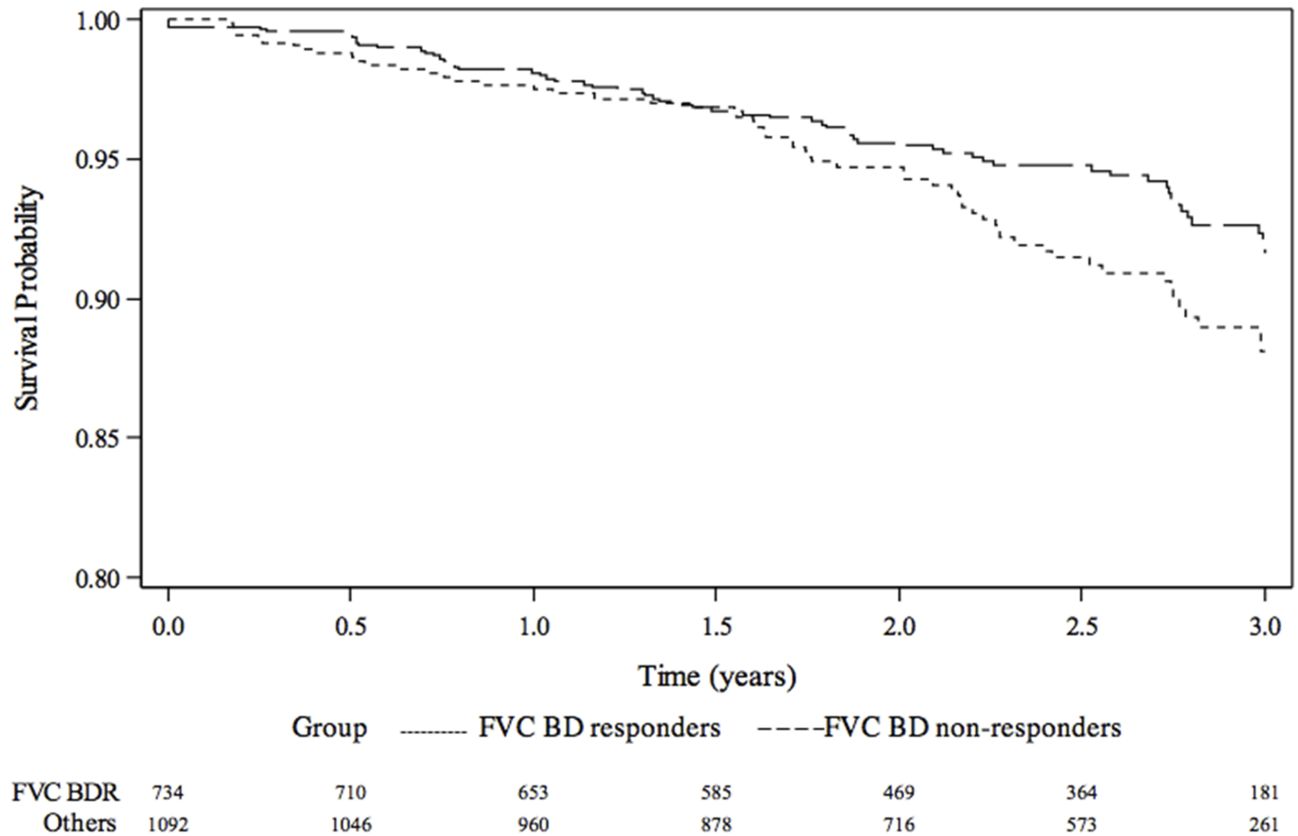

Figure 4 Kaplan–Meier plot of overall survival up to 3 years: FVC-BD responders (88.1%) vs FVC-BD nonresponders (91.7%) (P<0.05).

implications of BDR. Focused on distinctions between BDR_{FEV1} and BDR_{FVC}, our study revealed several interesting observations.

As reported previously,[4,6,11,20] BDR is present in a majority of participants with COPD. Despite being a common feature of this disease, it is still often misinterpreted as a hallmark of asthma, a misconception originating in part by COPD being defined by "persistent airflow limitation".[12] Reversibility of airflow obstruction or, normalization of FEV_1/FVC ratio after BD administration, is absent in COPD, but BDR, a measure of BD-induced change in lung volumes rather than ratios, is frequent and does not necessarily imply the coexistence of asthma.[21] While the self-reported history of asthma in our cohort was associated with BDR, this parameter cannot be used to differentiate between or define asthma or COPD, since it is frequently observed in both conditions.[22] Analyzing BDR among healthy never-smokers without an asthma history showed that a significant proportion of these individuals showed either flow-based or volume-based BDR with frequencies similar to reported values,[23] indicating that BDR also poorly discriminates diseased from healthy airways.[24] Our data add to the evidence of the lack of association of BDR with blood eosinophils,[25] and we show that average blood eosinophil counts (BEC) were similar among BD responders and BD nonresponders, with both FEV_1 and FVC-BD responders having similar BEC compared to FEV_1 and FVC nonresponders, respectively.

Despite such limitations, the clinical significance of BDR increases when its pattern is analyzed with regard to changes in both FEV_1 and FVC. This is particularly important in advanced COPD, where distal airway remodeling and emphysema with loss of alveolar attachments may lead to an early expiratory collapse of small airways with subsequent air trapping and dynamic hyperinflation,[26,27] resulting in a less significant impact on the post-bronchodilator change in FEV_1 in comparison to the change in FVC. The increase in the prevalence of BDR_{FVC} closely reflected the progression of emphysema and small airway disease, as demonstrated in the present study by quantitative HRCT and PRM. Small airway disease, one of the key features of COPD, may lead to air-trapping and hyperinflation with an increase in functional residual capacity (FRC) and a corresponding decrease in IC. BD administration can induce

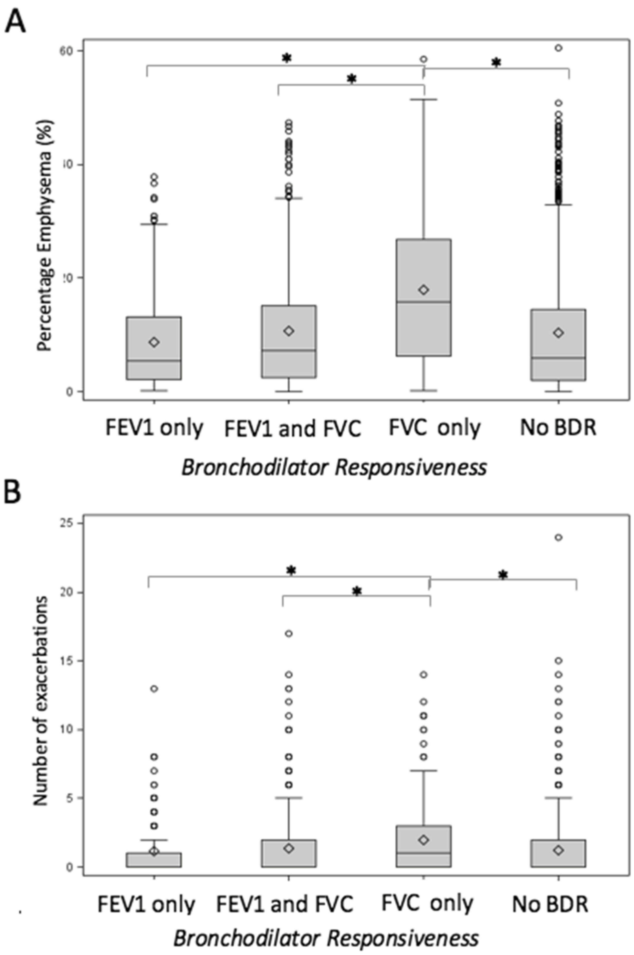

Figure 5 Comparison of isolated BDR_{FVC} among individuals with COPD in comparison to dual FVC and FEV_1 BDR, isolated BDR_{FEV1} without BDR_{FVC} and complete nonresponsiveness by either FEV_1 or FVC: (**A**) FVC-BD responders who do not show BDR_{FEV1} have more emphysema in comparison to the other three groups, (**B**) FVC-BD responders who do not show BDR_{FEV1} have a higher median rate of exacerbations in comparison to the other groups.

significant reductions in lung hyperinflation, manifested by a response in FVC or IC even in the absence of significant improvement in FEV_1 in a majority of individuals with advanced emphysema, and the benefit may be greatest in those with the most severe disease. These findings suggest that BDR_{FVC} offers an insight into pathophysiologic processes in advanced airway disease, which have been previously described.[10,11]

The distribution pattern of BDR_{FVC} was, in agreement with that reported previously,[10,28] infrequent in healthy subjects and ever-smokers without COPD. In early COPD, BDR_{FVC} was uncommon relative to BDR_{FEV1}, but became more prevalent as the disease progressed, being highest in the most advanced disease, whether defined spirometrically or by the GOLD grading system.[12] In contrast, BDR_{FEV1} was rare in subjects with spirometrically very severe COPD, thus failing to identify the actual prevalence of BD responsiveness in these individuals. This observation can also explain why FVC-BD responsiveness in the absence of BDR_{FEV1} is associated with a higher risk of exacerbations in univariate analysis while this effect is lost in a model adjusted for FEV_1.

Does BDR_{FVC} have other relevant clinical implications in COPD management? We found that FVC-BD responders with COPD had lower post-BD FEV_1% predicted, more often used steroids and inhaled BD, and had more respiratory symptoms than FVC-BD nonresponders, despite similar age, sex, smoking history and BMI, all results suggesting more advanced or active disease. Although our FVC-BD responsive participants reported the same frequency of exacerbations in the year before enrollment as nonresponders, they were more likely to exacerbate during the 3-year follow-up period and their mortality was significantly worse than FVC-BD nonresponders. However, these findings were no longer significant in a multivariate model adjusted for post-BD FEV_1% predicted. Similar findings were reported in a study where BDR was tested using salbutamol only,[9] in which BDR identified frequent exacerbators, with the lack of statistical significance after the inclusion of pre-BD FEV_1 as a covariate. In a different COPD cohort,[29] baseline BDR was predictive of a greater mean rate of FEV_1 decline over 3 years than observed in the entire cohort (33 mL/year vs 17 mL/year); however, the mean baseline FEV_1 was substantially higher among BD responders compared to BD nonresponders. In small randomized controlled trials, BDR correlated with lower exercise capacity and worse quality-of-life scores.[30]

While this study is in agreement with other studies that failed to demonstrate that BDR represents a distinct clinical phenotype predictive of outcomes,[4,8,9] our findings suggest that, in appropriate clinical settings, analyzing BDR_{FVC} and BDR_{FEV1} status may offer treating physicians additional insights about their patients, particularly with regard to the presence of hyperinflation.

Our study has several limitations. We did not analyze the actual values of post-BD changes in FEV_1 or FVC, but instead followed the accepted practice of a categorical classification of BD responsiveness versus and BD nonresponsiveness.[3] We applied one among several existing criteria proposed to define BDR[4] and thus cannot extend our findings to universal clinical settings or other definitions. Since the current diagnosis of asthma represented one of the exclusion criteria for the enrollment in the study, the possible presence of asthma–COPD overlap syndrome cannot be precisely analyzed in this report.[31] We have also analyzed only currently available data for subjects who continue to be followed through the SPIROMICS study cohort, so that the reported associations with outcomes cannot be considered final. These limitations are balanced by our goal to relate a common use of spirometry to clinical management.

Several strengths merit emphasis. One is our large cohort of ever-smokers without and with COPD, whose clinical characteristics were well described at baseline and longitudinally, allowing for the adequate association of BDR with multiple clinical outcomes. We analyzed several metrics that reflect BDR, including comprehensive imaging assessment and novel biometric measures such as PRM, which offered additional insight into pathophysiologic processes in COPD. Unlike other studies evaluating BDR in COPD,[9] we attempted optimal BDR testing, via higher doses of both a short-acting beta-agonist and a short-acting muscarinic antagonist, and allowed sufficient time for the nearly full medication effect. Using different classes of short-acting inhaled agents at twice their usual recommended dose is supported by established evidence of their additive effect.[32]

Conclusion

BDR was highly prevalent among COPD subjects in the SPIROMICS cohort. Defined using standard criteria, BDR_{FEV1} was observed more often in subpopulations of healthy subjects and ever-smokers either without airflow obstruction or with early stages of COPD. In contrast, BDR_{FVC} was more prevalent in advanced COPD and associated with increases in emphysema and small airway disease measured by HRCT. BDR_{FVC} status correlated with increased exacerbations and mortality, although this association may partly be a consequence of the markedly reduced FEV_1 in individuals with advanced COPD.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

IB and CBC had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. IB, CBC, SH, XW, RGB, DT contributed to the conception and design of the study. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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