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New Guidelines for Bronchodilator Responsiveness in COPD: A Test in Search of a Use

To the Editor:

The usefulness of a positive bronchodilator response (BDR) in airway disease is controversial, especially in chronic obstructive pulmonary disease (COPD) (1). It has been used both for aiding diagnosis as well as for prognostication. The current recommended criteria for defining BDR is an increase in either FEV_1 and/or FVC by 12% and 200 mL (2). The percentage and volume criteria were combined to account for the possibility that individuals on the milder and more severe ends of the spectrum of airflow obstruction are likely to show a response by volume or percentage criteria, respectively. The new European Respiratory Society/American Thoracic Society (ERS/ATS) technical standard on interpretive strategies for lung function tests has made a significant change to the definition of BDR and has defined this as an at least 10% increase in either FEV_1% predicted or FVC % predicted, based on associations with all-cause mortality (3) We aimed to test the utility of this new definition in individuals with COPD, by testing associations of the old and new criteria with two important clinical outcomes, all-cause mortality and exacerbations.

Methods

We analyzed data from participants enrolled in the COPDGene (Genetic Epidemiology of COPD) study (4). Briefly, this is a multicenter cohort of current and former smokers, which excluded individuals with significant respiratory disease except for COPD and asthma. All subjects provided written informed consent prior to participation and the study was approved by the Institutional Review Boards of all 21 participating centers. Participants were enrolled from January 2008 to June 2011 and followed up longitudinally until September 2021. At enrollment, participants underwent spirometry according to the ATS guidelines, before and 15–20 minutes after administration of 180 mcg of inhaled albuterol (5). BDR was defined by both the 2005 ATS/ERS criteria: increase in FEV_1 and/or FVC by 12% and 200 ml (ATS-BDR) (2), as well as the proposed 2021 criteria (GLI-BDR) (3): a 10 unit increase in FEV_1% predicted or FVC % predicted using the Global Lung Function Initiative (GLI) reference equations (6). Participants were prospectively contacted every 3 to 6 months to ascertain exacerbations. Exacerbations were defined as worsening of respiratory symptoms requiring use of either antibiotics or systemic steroids; events resulting in hospitalization were

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Author Contributions: Study concept and design: S.P.B. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: S.P.B. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: S.P.B. Study supervision: all authors.

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Table 1. Baseline Characteristics of Participants by Presence and Absence of Bronchodilator Response by Old (2005) and New (2021) ATS/ERS Criteria

		2005 ATS/ERS		2021 ATS/ERS	
	Overall (*n* = 3,339)	**ATS-BDR+ (*n* = 1,084)**	**ATS-BDR− (*n* = 2,255)**	**GLI-BDR+ (*n* = 1,489)**	**GLI-BDR− (*n* = 1,850)**
Age, yr	63.5 (8.6)	63.7 (8.8)	63.5 (8.4)	63.9 (8.8)	63.3 (8.4)
F, *n* (%)	1,374 (41.2%)	452 (41.7%)	922 (40.9%)	475 (41.8%)	899 (40.8%)
Non-Hispanic White, *n* (%)	2,699 (80.8%)	887 (81.8%)	1,812 (80.4%)	943 (83.0%)	1,756 (79.7%)
Non-Hispanic Black, *n* (%)	640 (19.2%)	197 (18.2%)	443 (19.6%)	193 (17.0%)	447 (20.3%)
Body mass index, kg/m^2	27.6 (5.9)	27.6 (5.7)	27.6 (6.0)	27.7 (5.8)	27.6 (5.9)
Active smoker, *n* (%)	1,872 (56.1%)	611 (56.4%)	1,261 (55.9%)	694 (61.1%)	1,178 (53.5%)
Pack-years of smoking	52.7 (27.0)	52.9 (27.0)	52.7 (27.0)	52.8 (27.2)	52.7 (26.9)
GOLD Stage, *n* (%)					
1	660 (19.8%)	167 (15.4%)	493 (21.9%)	132 (11.6%)	528 (24.0%)
2	1,439 (43.1%)	483 (44.6%)	956 (42.4%)	485 (42.7%)	954 (43.3%)
3	828 (24.8%)	296 (27.3%)	532 (23.6%)	362 (31.9%)	466 (21.2%)
4	412 (12.3%)	138 (12.7%)	274 (12.2%)	157 (13.8%)	255 (11.6%)
FEV_1	1.7 (0.8)	1.6 (0.7)	1.8 (0.8)	1.6 (0.7)	1.8 (0.8)
FEV_1 %predicted	59.1 (23.1)	57.0 (22.0)	60.1 (23.5)	55.3 (22.2)	62.2 (23.3)
FVC	3.2 (1.0)	3.2 (0.9)	3.2 (1.1)	3.1 (1.0)	3.3 (1.1)
FVC %predicted	109.8 (26.4)	111.2 (25.6)	109.1 (26.8)	108.5 (26.3)	110.9 (26.5)
FEV_1/FVC	0.53 (0.13)	0.50 (0.13)	0.54 (0.13)	0.50 (0.13)	0.55 (0.13)
Total exacerbations (per 100 person-years)	45.9	50.1	43.9	50.4	42.3
Severe exacerbations (per 100 person-years)	16.4	18.2	15.5	18.7	14.5
Deaths, *n* (%)	1,142 (34.2%)	373 (34.4%)	769 (34.1%)	426 (37.5%)	716 (32.5%)

Definition of abbreviations: ATS = American Thoracic Society; ATS-BDR = BDR defined by the 2005 ATS/ERS criteria: increase in FEV_1 and/or FVC by 12% and 200 ml; BDR = bronchodilator response; ERS = European Respiratory Society; GLI-BDR = BDR defined by the 2021 criteria: a 10 unit increase in FEV_1% predicted or FVC % predicted using the Global Lung Function Initiative (GLI) reference equations; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

termed severe exacerbations. All-cause mortality was ascertained via 3–6 monthly follow-up contact.

Zero-inflated negative binomial regression analyses were performed to test associations between each BDR status and the total number of exacerbations as well as severe exacerbations on follow-up, with adjustment for age, sex, race, height, pack-years of cigarette smoking, prior exacerbations, and post-bronchodilator FEV_1% predicted. Cox proportional hazards models were created to test the association between BDR status and survival, with adjustment for age, sex, race, height, smoking status, pack-years, and post-bronchodilator FEV_1% predicted. All analyses were performed using R statistical software (version 4.1.3), and a two-sided α of 0.05 was considered statistically significant for all analyses.

Results

Of 10,198 participants enrolled in COPDGene, we excluded 196 participants with inadequate spirometry data and 5,552 participants without airflow obstruction. We also excluded 1,111 participants with physician-diagnosed self-reported asthma. Participant characteristics at enrollment are shown in Table 1. The prevalence of ATS-BDR and GLI-BDR was 32.5% and 44.6%, respectively. The use of GLI-BDR resulted in the labeling of 405 (12%) additional participants as having BDR, and there was perfect concordance for absence of BDR. The percentage agreement was 87.9% and the Cohen's kappa was 0.75. The frequencies of ATS-BDR and GLI-BDR by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 through 4 was 25% versus 33%, 34% versus 44%, 36% versus 52%, and 33% versus 52%, respectively.

The median (25th–75th percentile) duration of follow-up for exacerbations was 9.3 (4.7–11.5) years. In unadjusted analyses, the incidence rate ratio (IRR) for the total number of exacerbations for participants who were ATS-BDR positive was 1.07; 95% confidence interval (CI), 0.94–1.23 and 1.14; 95% CI, 1.01–1.31 for those who were GLI-BDR positive. On multivariable analyses, there was no association between the total number of exacerbations and positivity by either BDR criteria (IRR for ATS-BDR 1.11; 95% CI, 0.99–1.24 and GLI-BDR 1.07; 95% CI, 0.96–1.19). The unadjusted IRR for severe exacerbations was 1.07; 95% CI, 0.90–1.27 for ATS-BDR and 1.21; 95% CI, 1.02–1.43 for GLI-BDR. On multivariable analyses, neither BDR criterion was associated with the frequency of severe exacerbations (ATS-BDR 1.14; 95% CI, 0.98–1.34 and GLI-BDR 1.15; 95% CI, 0.99–1.34).

The median (25th–75th percentile) duration of follow-up for survival was 8.7 (4.6–10.5) years. In unadjusted analyses, the hazards ratio (HR) for mortality was 1.04; 95% CI, 0.96–1.18 for ATS-BDR and 1.18; 95% CI, 1.05–1.32 for GLI-BDR. On multivariable analyses, these associations were not significant (adjusted HR for ATS-BDR 0.93; 95% CI, 0.82–1.05 and GLI-BDR 0.97; 95% CI, 0.86–1.09).

Discussion

In a cohort of current and former smokers with COPD, we found that once the severity of airflow obstruction was adjusted for, neither the old nor the new BDR criteria offered prognostic value for predicting exacerbation frequency and all-cause mortality.

BDR is often noted in adults with COPD but its utility remains unclear. A test is considered useful when it either helps detect a disease

and differentiate one disease from another, or when it offers prognostic information for predicting important clinical outcomes associated with a specific disease. BDR is most frequently used to support a diagnosis of asthma in the presence of airflow obstruction. The high prevalence of BDR in individuals with COPD, however, decreases the specificity for this indication significantly; indeed, approximately half met the new BDR criteria in the COPDGene cohort. The purported value of the new criterion is that the using the percentage predicted change in lung function would decrease the influence of the severity of lung disease on BDR. This consideration had resulted in the requirement for the combined absolute and relative change criteria in the 2005 ATS definition. The prognostic study cited to support the change in criteria adjusted for the FEV_1/FVC ratio which is not linearly associated with the severity of airflow obstruction, was conducted at a single center, and included only White individuals (7). Indeed, several studies have shown that a BDR response is not clinically useful when adjusted for the severity of underlying lung disease (8, 9). Hansen and colleagues showed that when models were adjusted for the best spirometry effort, which was often post-bronchodilator, the value of a positive BDR in predicting survival was erased (8). We recently showed that, compared with individuals with no BDR, those with a combined BDR (a positive response in percentage and volume criteria for both FEV_1 and FVC) have less emphysema and have more frequent moderate and severe exacerbations as well as lower mortality, compatible with an asthma-like phenotype (9). In the current study, we found that neither the current nor the proposed BDR criteria predicted exacerbations or mortality in COPD when adjusted for the severity of lung disease.

The strengths of the study include the stringent quality control of spirometry and the prospective collection of outcomes data. The study has a few limitations. Bronchodilators were not uniformly withheld prior to spirometry. This should not distract from the results as prior studies cited in the technical standard document also did not withhold bronchodilators. Furthermore, withholding bronchodilators is critical for documenting reversible versus irreversible airflow obstruction at the time of diagnosis but does not add much value for determining disease severity.

In conclusion, both the current and the proposed ERS/ATS criteria for bronchodilator responsiveness do not offer prognostic value in COPD. If the clinical application is to enhance diagnosis or prognostication, there is a need for increased specificity in the BDR criteria. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Care Fragmentation Is Associated with Increased Chronic Obstructive Pulmonary Disease Exacerbations in a U.S. Urban Care Setting

To the Editor:

Care fragmentation is associated with increased emergency department visits and greater healthcare spending among patients with several chronic conditions (1, 2). In patients with systemic lupus

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