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Paradoxical Lung Function Response to Beta2-agonists: Radiologic Correlates and Clinical Implications

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Abstract

Background—Bronchodilator response is seen in a significant proportion of patients with chronic obstructive pulmonary disease (COPD). However, there are also reports of a paradoxical response (PR) to beta2-agonists, resulting in bronchoconstriction. Asymptomatic bronchoconstriction is likely far more common but there has been no systematic study of this phenomenon.We assessed theprevalence of PR in current and former smokers with and without COPD, and its radiologic correlates and clinical implications.

Methods—Subjects from a large multicenter study (COPDGene) were categorized into two groups based on PR defined as at least a 12% and 200mLreduction in FEV_1 and/or FVC after administration of a short-acting beta2-agonist (180ucg albuterol). Predictors of PR and associations with respiratory morbidity and computed tomographic measures of emphysema and airway disease were assessed.

Findings—9986 subjects were included. PR was seen in 4.54% and the frequency was similar in those with COPD and smokers without airflow obstruction. Compared to Caucasians, PR was twice as common in African-Americans (6.9% vs. 3.4%;p <0.001). On multivariate analyses, African- American race (adjusted OR 1.89, 95%CI 1.50 to 2.39), lesspercent emphysema (OR 0.96, 95%CI 0.92 to 0.99) and increased wall-area% of segmental airways (OR 1.04,95%CI 1.01 to 1.08) were independently associated with PR.PR was independently associated with worse dyspnea, lower six-minute-walk distance, higher BODE index, and a greater frequency of exacerbations(increased by a factor of 1.35, 95%CI 1.003 to 1.81).

Interpretation—Paradoxical response to beta2-agonists is associated with respiratory morbidity and is more common in African Americans.

Keywords

Paradoxical; bronchodilator; beta 2-agonist; COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is not fully reversible.[1]However, improvements in lung function after short acting beta2-agonist and anticholinergic bronchodilators can be demonstrated in a significant proportion

of patients with COPD.[2]There are also reports of a paradoxical response to beta2-agonists, resulting in bronchoconstriction and significant respiratory distress[3-5] and it is likely that asymptomatic bronchoconstriction occurs more frequently[6,7] though there has been no systematic study of this phenomenon. There are several potential reasons for a paradoxical response including an adverse reaction to either the bronchodilator itself or to inhaled preservatives or propellants. The patient characteristics underlying a paradoxical response and its clinical implications remain unknown. We hypothesized that a paradoxical response to beta2-agonistsin patients enrolled in the Genetic Epidemiology of COPD Study (COPDGene®)would beassociated with distinct radiologic phenotypes and with worse clinical outcomes.

Methods

Study design

Protocols for COPDGene subject enrollment and testing have been described previously.[8] Briefly, non-Hispanic white and African-American current and former smokers aged 45 to 80 years were included in the study. Exclusion criteria included history of other lung diseases except asthma, prior lung surgery, pregnancy, active cancer undergoing treatment, and active or suspected lung cancer. Written informed consent was obtained from each subject and the COPDGene study was approved by the institutional review boards of all participating centers.

Spirometry—At study enrollment, each subject underwent pre- and post- bronchodilator spirometry using the ndd Easy-One spirometer (Andover, MA) before and 12-20 minutes afterinhalation of twopuffs of albuterol (90 mcg albuterol base per puff) with a spacer according to the American Thoracic Society (ATS) criteria.[9]Reference values were obtained from the National Health and Nutrition Examination Survey (NHANES) III data.[10]The diagnosis of COPD was made using a fixed post-bronchodilator cut-off of FEV_1/FVC of <0.70.[1] Details of spirometry procedures have been previously described.[11]

Bronchodilator response categorization—ATS criteria were adapted to define bronchodilator response.[12]Subjects were categorized into two groups based on a paradoxical response to beta 2-agonist (PR) defined as at least 12% *and*200 ml reduction in FEV_1 and/or FVC. Percent reduction was assessed by [(postbronchodilator – prebronchodilator)/ prebronchodilator] x 100. The volume criterion was included to account for a greater percent change in subjects with lower baseline lung function.[12] As previous studies examining bronchodilator responses have mostly used percent criteria for FEV_1, we also categorized subjects by 10% and 15% reduction in FEV_1 alone (without FVC criteria) into $PR_{10\%}$ and non-$PR_{10\%}$, and $PR_{15\%}$ and non-$PR_{15\%}$ groups.

Respiratory morbidity—The Modified Medical Research Council (MMRC) dyspnea score was used to quantify dyspnea [13] and the St George's Respiratory Questionnaire (SGRQ) scores to assess respiratory disease related health impairment and quality of life.[14]A standardized six minute walk test (6MWT) was performed according to ATS guidelines to assess functional capacity.[8]BODE (Body-Mass-Index, Airflow Obstruction,

Dyspnea, and Exercise Capacity) Index was calculated to predict COPD-related mortality.[15] Subjects were contacted every 3 to 6 months to obtain follow-up data on exacerbations, defined as episodes requiring use of either antibiotics and/or systemic steroids for acute worsening of respiratory symptoms, and severe exacerbations, defined as those requiring hospitalization.[16]

Imaging—Volumetric computed tomographic scans obtained at maximal inspiration (total lung capacity, TLC) and at end-tidal expiration (functional residual capacity, FRC) were analyzed for emphysema (% lung volume at TLC with attenuation less than -950 Hounsfield Units (HU), low attenuation area, $\%LAA950_{insp}$) and gas trapping (% lung volume at FRC with attenuation less than -856HU, $\%LAA856_{exp}$)using 3D Slicer software (www.airwayinspector.org).[8] Emphysema was also assessed by Perc15, the lung density cut-off at which 15% of all voxels have a lower value.[17]Airway wall thickness was measured by quantitating wall area (WA%) of segmental bronchi and the Pi10 (square root of the airway wall area of a standardized airway of 10 mm luminal perimeter) using Pulmonary Workstation 2 (VIDA Diagnostics, Coralville, IA, USA).[8]

Statistical analyses

All values are expressed as mean (+standard deviation, SD). Univariate comparisons were made between PR+ and PR- groups using Chi-squared test for categorical variables, and 2-tailed independent t-test for continuous variables. Analyses were performed for the entire cohort and separately for subjects with COPD and smokers without airflow obstruction. Bivariate and multivariate linear regression models were created to assess the independent effects of PR status in the entire cohort on respiratory morbidity such as MMRC, SGRQ and 6MWT, with age, gender, race, smoking burden, current smoking status, FEV_1, airway wall thickness and emphysema as covariates. Binary and multivariate logistic regression analyses were performed to assess the relationships betweenpatient demographics (such as age, race and gender), CT measures and FEV_1, and PR status. Similar models were created for $PR_{10\%}$and$PR_{15\%}$. Differences in exacerbations and severe exacerbations over time were assessed using negative binomial regression models with age, gender, race, smoking status and FEV_1 as covariates. No adjustments were made for multiple comparisons. P value <0.05 was considered statistically significant. For patients enrolled at the University of Alabama, general linear regression models were constructed to assess potential learning effects and fatigue associated with repeated efforts both pre- and post- bronchodilator. All analyses were performed using Statistical Package for the Social Sciences (SPSS 22.0, SPSS Inc., Chicago, IL, USA).

Role of the funding sources

The COPDGene study was funded by the National Institute of Health and ECLIPSE by GlaxoSmithKline.The sponsors of the two studieswere not involved in study design, data collection, data analysis, data interpretation, or writing of the report. SPB, YK and MTD had full access to the raw data, and the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Demographics and Lung Function

Of 10,364 subjects enrolled in COPDGene, we excluded 64 who had significant interstitial lung disease or bronchiectasis, 108 normal controls, 143who did not have adequate spirometry data and 63 who had inadequate data for bronchodilator reversibility. Baseline characteristics of the final population for analysis (n=9986)are summarized in Table 1. The mean age of included subjects was 59.6 (SD 9) years; 4661 (46.7%) were female, 3282 (32.9%) were African American, and52.8% were current smokers. Physician-diagnosed asthma was reported by 17.6% of subjects. 4439 (44.5%) had COPD by GOLD criteria. Of these, 794 had GOLD (Global Initiative for Chronic Obstructive Lung Disease)spirometric severity classification grade I (17.7%), 1922 had grade II (42.9%), 1162 had grade III (25.9%), and 606(13.5%) had grade IV airflow obstruction. 1238 (12.4%) were GOLD unclassified,with reduced FEV_1 (%predicted) but $FEV_1/FVC>0.70$ (GOLD-U).

Paradoxical response (PR) was seen in 453 (4.54%) subjects. None of the subjects had symptomatic bronchoconstriction following administration of short acting beta2-agonist. Compared to Caucasians, African-Americans had twice the frequency of PR (6.9% vs. 3.4%; $p < 0.001$). There was no difference between genders (4.4% in males and 4.7% in females; $p = 0.53$). The frequency of PR was similar in subjects with and without COPD (4.46% vs. 4.60%; $p= 0.74$) however, the frequency of PR increased with GOLD stage (1.8%,4.2%, 5.1%, and 7.4% respectively, from GOLD stages 1 to 4; $p<0.001$). Among healthy smokers, 1.3% exhibited PR due to FEV_1 decline which was comparable to the frequency in those with GOLD stage 1 through 4 (2.4, 1.9, 1.2 and 3.2%, respectively). When PR was assessed by FVC decline, the rate was highest in those with GOLD 4 disease (6.5%) as compared to 3.2, 0.8, 2.1, and 3.9% in healthy smokers and GOLD stages 1 through 3 respectively. PR was noted in 8.6% of those with GOLD-U, of whom 0.7% had PR due to FEV_1 decline and 7.8% had PR due to FVC decline.In the entire cohort, those with PR were younger, more likely to be African-American, more likely to be current smokers but with similar smoking burden, and had more severe airflow obstructionthan those without PR (Table 1). The frequency of physician-diagnosed asthma was similar in the two groups. We did not find any evidence that a learning effect or fatigue influenced the prevalence of PR in either the COPD or healthy smoker groups (Supplement Figure 1).

Medication use

There was no difference in the use of long-acting bronchodilators or inhaled steroids as maintenance therapy between the PR+ and PR- groups (Table 1). However, there was a significant difference in respiratory medication use between Caucasians and African-Americans as African-Americans with COPD were less likely to be on long acting anticholinergics (29.4% vs. 35.7%; $p<0.001$), long-acting beta agonists without concomitant inhaled steroids (5.6% vs. 8.0%; $p=0.01$) as well as any maintenance long-acting medication (42.4% vs. 50.8%;$p<0.001$). No directions were given for washout of inhalers prior to BDR testing, however the time of last inhalation was recorded for patients taking these medications and it was determined whether BDR testing was performed within or outside the recommended washout period (i.e. short acting beta-agonists 6 hours, long acting beta

agonists 12 hours, etc.). There was no difference in the number of those who used an inhaler within the recommended washout period in the of PR+ and PR- patients (9.9% vs.8.8% for short acting beta agonists, 3.8% vs. 2.8% for long acting beta agonists, 14.1% vs. 15.2% for combined long acting beta agonists and inhaled corticosteroids, and 15.7% vs. 14.7% for long acting antimuscarinics; p not significant for all comparisons).

Imaging

Table 2 summarizes the radiologic comparisons between the PR groups for the entire cohort and also by presence or absence of COPD. For the entire cohort, those with PR had thicker airway walls but less percent emphysema (Table 2). Total lung capacity by CT was lower in those with PR, but there was no difference in functional residual capacity. On multivariate analyses, African-American race (adjusted odds ratio, OR = 1.89, 95%CI 1.50 to 2.39), percent emphysema (OR0.96,95%CI 0.92 to 0.99) and segmental wall area% (OR = 1.04, 95%CI 1.01 to 1.08) were independently associated with PR (Figure 1). When paradoxical response was defined by %FEV_1 reduction, African American race and segmental wall area % remained independentlyassociated with PR (Supplemental Tables 1 and 2).

Respiratory outcomes

Respiratory morbidity was greater in those with PR as measured by a higher MMRC (1.61±1.48 vs. 1.35±1.45; p<0.001), higher SGRQ (31.0±23.2 vs. 27.2±22.9; p<0.001), and lower 6MWD (1250±416 vs. 1356±397 ft;p<0.001) (Table 1). PR status was also associated with a greater BODE index (1.87±1.95 vs. 1.43±1.84;p<0.001) (Table 1). On multivariate analysesadjusting for age, gender, race, smoking burden and smoking status, airflow obstruction, and CT indices of emphysema and airway wall thickness, PR was independently associated with a lower 6MWD and higher MMRC scores (Table 3). On univariate analysis, there was a significant association between PR and greater SGRQ scores, but this was not significant on multivariate analysis (Table 3). PR was also independently associated with a greater BODE index which in turn is a predictor of COPD related mortality (Table 3).

For patients with COPD, PR status was also associated with a significantly higher risk of total exacerbations (an increase by a factor of 1.33, 95%CI 1.06 to 1.66; p=0.01) and severe exacerbations on follow up (an increase by a factor of1.35, 95%CI 1.003 to 1.81; p=0.048), after adjustment for age, race, gender, FEV_1 and smoking status.

Discussion

Panel: Research in context

Systematic Review—We searched Pubmed and Google Scholar for publications related to “Paradoxical Response”, “Paradoxical bronchoconstriction”, “Paradoxical bronchospasm”, and “albuterol, bronchoconstriction” to identify relevant studies. We also identified pertinent references from the bibliographies of these publications. Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is not fully reversible. While bronchodilator responsiveness can be demonstrated in a significant proportion of patients with COPD, some patients have a paradoxical reduction in lung

function following beta2-agonist administration. There has been no systematic study of this phenomenon.

Interpretation—This is the first systematic study describing the prevalence of a paradoxical response (PR) to beta2 agonists in smokers with and without COPD. This phenomenon is more common in African-Americans possibly explaining some of the poor outcomes seen in this population, and is independently associated with greater wall thickness and less emphysema on CT. PR is associated with worse respiratory outcomes including greater dyspnea and more frequent exacerbations.

We have demonstratedthat a paradoxical response to beta2-agonistsoccurs in smokers with and without airflow obstructionand that this phenomenonoccurs more frequently in AfricanAmericans and is associated with more severe airway disease and less percent emphysema as assessed by CT. This paradoxical response is also associated with respiratory morbidity including a greater risk of both moderate and severe COPD exacerbations.

Bronchodilator response (BDR) has long been assessed but its implications and clinical significance are unclear. Though lack of BDR has traditionally been deemed evidence of irreversible airflow obstruction,[1] it is not specific in differentiating asthma from COPD[7] anddoes not predict a therapeutic response to the regular administration of long acting bronchodilators.[2] It is pertinent to note that BDR criteria are based on arbitrary spirometric thresholds and responses less than these cutoffs that might also have clinical implications. In this context, we explored the implications of a paradoxical worsening of lung function in response to beta2-agonists and found that this identifies a distinct subset of subjects with worse outcomes. Interestingly, all smokers seemed to be at risk for PR though its frequency tended to increase with increasing COPD severity.

In the absence of literature to guide us, we adapted the ATS criteria for BDR to define PR and used a 12% reduction in FEV_1 or FVC as well as a 200 mL volume reduction.[12] The latter was to account for those with more severe airflow obstruction who are expected to more easily meet PR criteria based solely on a percent change from baseline.[19] It is generally accepted that a 100 mL change in FEV_1 is clinically significant as this can often be perceived by patients.[19] As these cut-offs remain somewhat arbitrary, we also defined PR using 10% and 15% thresholds for change in FEV_1[20] and found similar predictors of PR.

The mechanisms underlying PR remain unknown. Acute bronchoconstriction following administration of bronchodilators has been described in case reports[3-5]andseveral mechanisms have been proposed including an adverse reaction to propellants used in metered dose inhalers,[21] an immunoglobulin E mediated reaction to soy or lecithin containing excipients in the inhaler,[22] as well as bronchial irritation due to preservatives or turbulent airflow resulting from inappropriate inhaler technique.[21]Preservatives such as sodium metabisulfite and benzalkonium chloride as well as hyperosmolality and acidity of the solutions have also been implicated in bronchoconstriction following nebulization of bronchodilators.[23-25]None of these reports were in patients with COPD. Previous use of bronchodilators can also lead to a lack of BDR due to down-regulation of receptors and development of airway subsensitivity,[26]but this is unlikely to lead to a paradoxical response.

Subclinical bronchoconstriction is likely considerably more common than symptomatic bronchospasm, as evidenced by our study. We found a prevalence of PR much higher than the 0.24% reported in the UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) study[7]though this could be partly explained by the greater number ofAfrican-Americans enrolled in COPDGene and by the concurrent use of ipratropium for BDR testing in UPLIFT.It is not clear if adapting the UPLIFT protocol for bronchodilator responsiveness testing would have altered our findings.

Identification of PR has significant clinical implicationsasit is independently associated with worse respiratory outcomes.We found that PR status is not only associated with worse exercise tolerance and dyspnea, but is also a predictor of total and severe exacerbations. Paradoxical response was twice as common in African-Americans as in Caucasians. This is a novel finding that we speculate might explain some of the poor outcomes seen in African-Americans with COPDthat have often been explained by poor socioeconomic status,[27] lower heath care utilization,[28] and genetic susceptibility to greater airflow obstruction and emphysema for similar smoking burden.[29] Though respiratory medication use was lower in African-Americans in our study suggesting disparities in care, this was not a predictor of PR status.Recent advances in genetics have also identified beta receptor polymorphisms as a potential source of differential response to beta agonists in African-Americans and our findings support the assertion that this is clinically relevant.[30-32]These findings imply that some subjects might do better with discontinuation of beta2-agonists, and further research is needed to test this hypothesis. Whether PR is modifiable or if it could be used to help select different therapies for this subset of patients is also unknown. Interestingly, we found a high frequency of PR in the GOLD-U group. This group is heterogeneous and is made up of patients with restrictive disorders as well as patients with less air trapping and bronchodilator responsiveness as well as thicker airway walls compared to patients with COPD.[18] These characteristics would appear to predispose this population to a paradoxical response.

We found that PR is associated with distinct radiologic findings, though the differences in airway wall thickness and emphysema were modest. Increased airway thickness could be due to a combination of chronic bronchitis with mucus and smooth muscle hypertrophy[33]that could in turn be the result or cause of a poor response to bronchodilators. Increased airway thickness has been shown to correlate with symptoms independent of the degree of emphysema[34,35]and our results demonstrate that PR further predictspoor outcomes. We also found a weak inverse association between PR and the degree of emphysema. As flow limitation in COPD results from a combination of bronchoconstriction and decreased elastic recoil, we speculate that PR is more likely due to airway characteristics than reduced elastic recoil.

Our study has some limitations. We enrolled subjects who were current or former smokers, and thus our results might not be generalizable to populations at low risk for COPD. While there appear to be significant racial differences, the relatively small number of subjects with PR precluded meaningful genetic analyses. While learning effects and fatigue can potentially impact post bronchodilator values, these did not impact PR status in our study (Supplemental Figure 1). Subjects on long acting anti-muscarinics require a long washout

period prior to bronchodilator reversibility testing which was not feasible in this study. Whilethe lack of instructions for medication withholding may have introduced bias, there was no difference in maintenance medication use between those with and without PR nor any difference in the number of subjects who used an inhaler during the washout period between these two groups. CT scans were not spirometrically gated which can affect measurements of emphysema, however detailed instructions were given to subjects to maximize the probability of obtaining scans at full inspiration (TLC) and at end expiration. Finally, we did aim to validate these findings by examining data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort.[36] However we found a lower rate of PR [47 (1.9%) of the 2493 patients], perhaps due to the low number of individuals of African descent enrolled (44 of the 2493), and this precluded meaningful analysis. Additional studies are needed to determine if PR+ is a clinically stable phenotypeand to confirm if it is a feature that identifies a set of African Americans with specific clinical features.

In summary, we demonstrate that PR is more common in African Americans and is associated with significantly worse respiratory outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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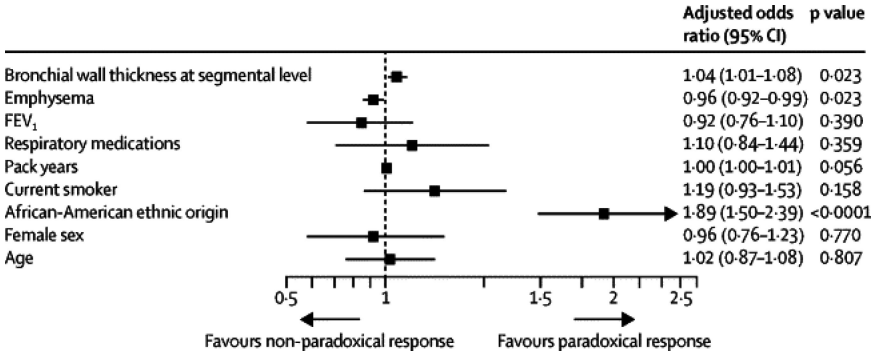

Figure 1.

Multivariate logistic regression model showing adjusted odds ratios for predictors of Paradoxical Response. FEV_1 = Pre-bronchodilator Forced Expiratory Volume in the first second. Perc15 = the density of lung in HU below which 15% of the voxels had the lowest attenuation numbers at full inspiration.Wallarea% = Bronchial wall area at segmental level. #Respiratory medications include one or more of inhaled long acting beta agonists, long acting antimuscarinic agents or a combination of inhaled corticosteroids/long acting beta agonists and theophylline. Odds Ratios depicted for every 10 HU change in Perc15, and for every 10 year change in age.

*p<0.05. †p<0.001

Table 1

Baseline characteristics of patients

	All		COPD		Smokers	
	PR+ (n=453)	**Non-PR (n=9533)**	**PR+ (n=198)**	**Non-PR (n=4241)**	**PR+ (n=255)**	**Non-PR (n=5292)**
Demographics						
Age (years)	58.4 (8.9)**	59.7 (9.0)	62.2 (8.9)	63.1 (8.6)	55.5 (7.8)*	56.9 (8.4)
Sex (%female)	218 (48.1)	4443 (46.6)	77 (38.9)	1885 (44.4)	141 (55.3)*	2558 (48.3)
Race (%African American)	227 (50.1)†	3055 (32.0)	80 (40.4)†	921 (21.7)	147 (57.6)†	2134 (40.3)
BMI (kg/m^2)	29.2 (6.5)	28.8 (6.3)	27.6 (6.1)	27.9 (6.1)	30.5 (6.6)*	29.5 (6.3)
Pack-years	45.5 (28.5)	44.2 (24.7)	53.1 (34.4)	51.5 (26.8)	39.5 (21.1.)	38.4 (21.2)
Current smoker (%)	289 (63.8)†	4986 (52.3)	102 (51.5)*	1824 (43.0)	187 (73.3)†	3162 (59.8)
Asthma (%)	75 (16.6)	1679 (17.6)	38 (19.2)	964 (22.7)	37 (14.5)	715 (13.5)
Long acting antimuscarinic (%)	82 (18.3)	1582 (16.9)	73 (37.6)	1417 (34.3)	9 (3.6)	165 (3.2)
Long acting beta agonist (%)	21 (4.7)	330 (3.5)	17 98.8)	307 (7.5)	4 (1.6)*	23 (0.4)
Inhaled corticosteroids/Long acting beta agonist (%)	86 (19.1)	1841 (19.6)	67 (34.2)	1530 (36.8)	19 (7.5)	311 (6.0)
Spirometry						
Pre-bronchodilator FEV_1 (L)	2.07 (0.86)*	2.15 (0.92)	1.57 (0.77)	1.56 (0.77)	2.45 (0.72)†	2.63 (0.73)
Pre-bronchodilator FVC (L)	3.22 (0.95)	3.22 (1.03)	2.96 (0.90)	2.90 (1.03)	3.43 (0.94)	3.47 (0.95)
Pre-bronchodilator FEV_1/FVC	0.63(0.17)**	0.65 (0.16)	0.52 (0.18)	0.52 (0.14)	0.72 (0.09)†	0.76 (0.06)
FEV_1 %change	−7.6 (11.6)†	6.3 (9.4)	−10.4 (13.4)†	9.0 (11.3)	−5.4 (9.5)†	4.1 (6.9)
FEV_1 volume change (ml)	−173 (254)†	105 (150)	−201 (272)†	115 (144)	−151 (238)†	97 (154)
FVC %change	−14.9 (9.1)†	4.6 (10.3)	−12.8 (11.6)†	8.8 (12.2)	−16.5 (5.9)†	1.2 (6.9)
FVC volume change (ml)	−474 (321)f	112 (269)	−361 (363)†	215 (292)	−562 (252)†	28 (2150

All values expressed as mean (SD), unless otherwise specified. PR = Paradoxical response to bronchodilator. BMI = Body Mass Index. FEVi = Forced Expiratory Volume in the first second. FVC = Forced Vital Capacity.

*p<0.05.

**p,0.01.

†p<0.001

Table 2

Comparison of computed tomographic imaging and indices of respiratory morbidity

	All		COPD		Smokers	
	PR+ (n=453)	**Non-PR (n=9533)**	**PR+ (n=198)**	**Non-PR (n=4241)**	**PR+ (n=255)**	**Non-PR (n=5292)**
CT						
TLC (L)	5.2 (1.5)†	5.5 (1.4)	5.8 (1.5)*	6.0 (1.4)	4.6 (1.2)†	5.2 (1.3)
FRC (L)	3.3 (1.3)	3.2 (1.1)	4.0 (1.4)	3.9 (1.2)	2.7 (0.8)	2.7 (0.7)
%LAA<-950insp	5.5 (9.5)	6.2 (9.6)	10.6 (12.2)	11.6 (12.2)	1.5 (2.4)*	1.9 (2.5)
Emphysema (Perc15)	−910.4 (34.3)†	−917.9 (31.6)	−930.9 (30.3)*	−935.8 (28.3)	−893.9 (27.7)†	−903.4 (26.2)
Gas trapping (%LAA<-856exp)	22.9 (21.5)	21.9 (19.9)	37.7 (23.0)	35.7 (20.7)	11.2 (10.1)	10.8 (9.6)
Wall Thickness (Wallarea% of segmental airways)	62.1 (3.3)†	61.4 (3.3)	62.8 (3.2)	62.4 (3.2)	61.6 (3.2)†	60.5 (3.1)
Pi10	3.71 (0.13)†	3.68 (0.13)	3.72 (0.14)	3.70 (0.14)	3.70 (0.12)†	3.66 (0.12)
QoL						
MMRC	1.61 (1.48)†	1.35 (1.45)	2.05 (1.46)	1.89 (1.47)	1.27 (1.41)†	0.92 (1.28)
6MWD (m)	381 (127)†	413 (121)	343 (127)†	377 (124)	410 (118)†	442 (111)
SGRQ	31.0 (23.2)†	27.2 (22.9)	38.8 (22.7)	36.8 (22.9)	25.0 (21.8)†	19.5 (19.8)
BODE index	1.87 (1.95)†	1.43 (1.84)	2.94 (2.12)**	2.47 (2.11)	1.04 (1.32)†	0.62 (1.02)

All values expressed as mean (SD), unless otherwise specified. PR = Paradoxical response to bronchodilator. TLC = Total Lung Capacity on computed tomography. FRC = Functional Residual Capacity on computed tomography. %LAA<950insp = %Low Attenuation Area below a threshold of −950 Hounsfield Units at end inspiration. Perc15 = the density of lung in HU below which 15% of the voxels had the lowest attenuation numbers at full inspiration. %LAA<856exp = %Low Attenuation Area below a threshold of −856 Hounsfield Units at end tidal expiration. Wallarea% = Bronchial wall area at segmental level. Pi10 = Square root of the airway wall area of a standardized airway of 10 mm luminal perimeter. MMRC = Modified Medical Research Council Dyspnea Scale. 6MWD = Six Minute Walk Distance. SQRQ = St. George's Respiratory Questionnaire.BODE = Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index.

* p<0.05.

** p,0.01.

† p<0.001

Table 3

Univariate and Multivariate Associations between Paradoxical Response and respiratory morbidity

	Unadjusted beta regression co-efficient	95% CI	Adjusted betaregression co-efficient	95% CI
6MWD				
Age (years)	−7.02 †	−7.88 to −6.17	−2.38 †	−3.40 to −1.36
Female gender	−85.4 †	−101.0 to −69.8	33.9 †	17.2 to 50.5
African American Race	−130.5 †	−146.9 to −114.1	−162.9 †	−179.9 to −146.0
Current smoking	0.91 †	0.65 to 1.16	−22.62 **	−39.15 to −6.10
Packyears	−3.27 †	−3.58 to −2.96	−1.83 †	−2.13 to −1.54
Pre-bronchodilator FEV_1	213.2 †	205.7 to 220.7	183.4 †	171.7 to 195.2
Emphysema (Perc 15)	0.91 †	0.65 to 1.16	−0.21	−0.48 to 0.06
Wall Area%	−39.0 †	−41.3 to −36.7	−14.0 †	−16.6 to −11.5
PR	−106.3 †	−144.1 to −68.5	−45.8 **	−78.5 to −13.2
				$R^2 = 0.30$
MMRC				
Age (years)	0.01 †	0.007 to 0.01	−0.030 †	−0.033 to −0.026
Female gender	0.29 †	0.23 to 0.35	0.20 †	0.14 to 0.26
African American Race	0.19 †	0.13 to 0.25	−0.18 †	−0.24 to −0.12
Current smoking	−0.09 **	−0.15 to −0.03	−0.04	−0.10 to 0.02
Packyears	0.012 †	0.011 to 0.013	0.007 †	0.006 to 0.008
Pre-bronchodilator FEV_1	−0.77 †	−0.80 to −0.75	−0.80 †	−0.84 to −0.76
Emphysema (Perc 15)	−0.007 †	−0.008 to −0.006	−0.003 †	−0.004 to −0.002
Wall Area%	0.14 †	0.13 to 0.15	0.034 †	0.025 to 0.044
PR	0.26 †	0.12 to 0.39	0.12 *	0.00 to 0.24
				$R^2 = 0.29$
SGRQ				
Age (years)	0.05	−0.004 to 0.01	−0.62 †	−0.68 to −0.56
Female gender	2.40 †	1.50 to 3.29	−5.92 †	−6.83 to −5.0
African American Race	2.37 †	1.42 to 3.32	0.13	−0.80 to 1.07
Current smoking	1.60 †	0.71 to 2.50	2.47 †	1.56 to 3.38
Packyears	0.23 †	0.21 to 0.24	0.14 †	0.12 to 0.16
Pre-bronchodilator FEV_1	−12.4 †	−12.8 to −12.0	−13.7 †	−14.4 to −13.1

	Unadjusted beta regression co-efficient	95% CI	Adjusted betaregression co-efficient	95% CI
Emphysema (Perc 15)	−0.12 †	−0.13 to −0.10	−0.05 †	−0.07 to −0.04
Wall Area%	2.52 †	2.39 to 2.65	0.76 †	0.62 to 0.90
PR	3.84 †	1.68 to 6.0	1.32	−0.47 to 3.12
				R^2 = 0.35
BODE Index				
Age (years)	0.033 †	0.029 to 0.037	−0.048 †	−0.052 to −0.044
Female gender	0.15 †	0.08 to 0.23	−0.70 †	−0.77 to −0.64
African American Race	−0.04	−0.12 to 0.03	0.30	−0.03 to 0.09
Current smoking	−0.44 †	−0.51 to −0.37	−0.06	−0.12 to 0.003
Packyears	0.018 †	0.016 to 0.019	0.006 †	0.005 to 0.007
Pre-bronchodilator FEV_1	−1.36 †	−1.39 to −1.33	−1.46 †	−1.50 to −1.41
Emphysema (Perc 15)	−0.022 †	−0.023 to −0.021	−0.012 †	−0.013 to −0.011
Wall Area%	0.20 †	0.19 to 0.21	0.04 †	0.03 to 0.05
PR	0.43 †	0.26 to 0.61	0.31 †	0.19 to 0.43
				R^2 = 0.56

FEV_1 = Forced Expiratory Volume in the first second. Perc15 = the density of lung in HU below which 15% of the voxels had the lowest attenuation numbers at full inspiration. Wallarea% = Bronchial wall area at segmental level. PR = Paradoxical response to beta2-agonists. BODE = Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index. All variables significant on bivariate analyses were entered into a multivariate model to assess independent associations.

* p<0.05.

** p,0.01.

† p<0.001