



The paradoxical response to short-acting bronchodilator administration in patients with chronic obstructive pulmonary disease

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Background: There are a few studies about paradoxical bronchodilator response (BDR), which means a decrease in forced expiratory volume in 1 second (FEV₁) or forced vital capacity (FVC) after short-acting bronchodilator administration in patients with chronic obstructive pulmonary disease (COPD). We evaluated the effect of paradoxical BDR on the clinical outcomes of COPD patients in South Korea.

Methods: We analyzed the KOREA COPd Subgroup Study team (KOCOSS) cohort data in South Korea between January 2012 and December 2017. BDR was defined as at least a 12% and 200-mL reduction in FEV₁ or FVC after bronchodilator administration.

Results: A total of 1,991 patients were included in this study. A paradoxical BDR was noted in 57 (2.9%) patients and was independently associated with worse dyspnea and poor quality of life. High C-reactive protein (CRP) levels were associated with a paradoxical BDR (OR, 1.05; 95% CI, 1.01–1.09; P=0.003). However, paradoxical BDR was not associated with severe acute exacerbations. Pre-bronchodilator FEV₁ (L) showed a higher area under the curve (AUC) for predicting severe acute exacerbations than the post-bronchodilator FEV₁ (L) in the paradoxical BDR group (0.788 vs. 0.752).

Conclusion: A paradoxical reduction of FEV₁ or FVC after bronchodilator administration may be associated with chronic inflammation in the airway and independently associated with worse respiratory symptoms and poor quality of life.

Keywords: Bronchodilator; chronic obstructive pulmonary disease (COPD); C-reactive protein (CRP); exacerbation; paradoxical

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Introduction

Post-bronchodilator spirometry is required for the diagnosis of chronic obstructive pulmonary disease (COPD), but the role of bronchodilator response (BDR) is unclear in COPD (1). Positive bronchodilator reversibility is no longer recommended as a treatment option for COPD, and there is no standard definition yet (2,3). In addition, positive bronchodilator reversibility does not predict the clinical outcomes of long-term use of bronchodilators and inhaled corticosteroid (ICS) (4). However, lung function may be paradoxically reduced after bronchodilator administration. In the previous study, COPD patients with paradoxical reductions in forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC) after bronchodilator spirometry had poor qualities of life and frequent severe exacerbations (5). The incorrect use of inhalers and bronchospasm in response to the ingredients in inhalers have been suggested, but the mechanism of paradoxical BDR is still unclear (6-8). To the best of our knowledge, no study has assessed paradoxical BDR and the clinical outcomes of COPD in an Asian population.

In this study, we aimed to evaluate the effect of paradoxical BDR on the clinical outcomes of COPD patients in the KOrea COPd Subgroup Study team (KOCOSS) cohort (NCT02800499).

Methods

Study design and patients

The KOCOSS cohort is an ongoing, longitudinal, prospective, non-interventional, and observational study within the South Korean patients with COPD. We recruited and analyzed cohort data between January 2012 and December 2017. Inclusion criteria were as follows: age >40 years; symptoms including cough, sputum, and dyspnea; and post-bronchodilator $FEV_1/FVC < 0.7$. Exclusion criteria were as follows: asthma; inability to complete pulmonary function test; myocardial infarction or cerebrovascular event within the previous 3 months; pregnancy; rheumatoid arthritis; malignancy (metastatic cancer, leukemia, lymphoma); irritable bowel syndrome; and use of systemic steroids over 8 weeks for a reason other than COPD.

The protocol which was conducted according to the principle expressed in the Declaration of Helsinki was approved by the institutional review board (IRB) at each participating center (CNUH-2012-070). All patients provided written informed consent for participation in the

study.

The initial evaluation for all patients included pulmonary function tests, 6-minute walk distance (6MWD), COPD Assessment Test (CAT), modified Medical Research Council (mMRC) dyspnea scale, COPD-specific version of St. George's Respiratory Questionnaire (SGRQ-C), exacerbations in the previous 12 months, smoking status, medications, and comorbidities. Acute exacerbation of COPD was defined as the worsening of any respiratory symptom, including increased sputum volume, purulence, or increased dyspnea. Severe exacerbation was defined as the need for hospitalization or visiting the emergency room due to acute exacerbation of COPD.

Pulmonary function, disease severity, and exercise assessments

Spirometry and 6MWD were performed according to previous studies (9,10). COPD severity was categorized using spirometry alone, in accordance with the 2017 GOLD guidelines. Stage I COPD: $FEV_1 \geq 80\%$ predicted; stage II: $FEV_1 \leq 50\%$ to 80% predicted; stage III: $FEV_1 \leq 30\%$ to 50% predicted; and stage IV: $FEV_1 < 30\%$ predicted. The paradoxical BDR was defined as $\geq 12\%$ and 200 mL reduction in FEV_1 or FVC, respectively, or in both, after the administration of a bronchodilator, as described by previous reports and modified from the adapted American Thoracic Society criteria for BDR (11). The reduction in percentage was assessed as follows (5):

$$\frac{\text{postbronchodilator } FEV_1 \text{ (L)} - \text{prebronchodilator } FEV_1 \text{ (L)}}{\text{prebronchodilator } FEV_1 \text{ (L)}} \times 100 \quad [1]$$

Statistical analyses

Descriptive statistics were reported as the mean and standard deviation for descriptive variables. For categorical variables, the number of patients per category and frequency of responses were recorded. Continuous variables with different severity classifications were analyzed using a two-sample *t*-test and χ^2 tests, and Fisher's exact test was used for comparing categorical variables. Bivariate and multivariate linear regression models were used to assess the independent effects of paradoxical BDR status in the cohort in relation to mMRC, CAT, SGRQ-C, and 6MWD, with age, sex, body mass index (BMI), smoking burden, and pre-bronchodilator FEV_1 as covariates. To identify the factors predictive of paradoxical BDR, the variables that differed significantly between the paradoxical BDR and no-paradoxical BDR

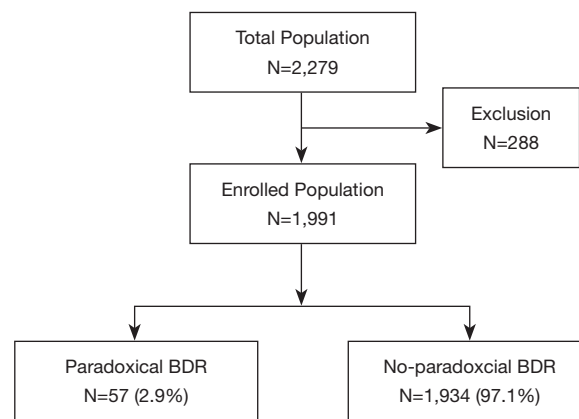


Figure 1 Study flow chart.

groups were included for univariate analysis with logistic regression. Subsequent multivariate logistic regression analysis using the backward method included variables with $P < 0.1$ in the univariate analysis. Pre-bronchodilator and post-bronchodilator FEV_1 (L) were assessed to predict acute severe exacerbations using the receiver operating characteristic curve and area under the curve (AUC) in paradoxical BDR groups. We evaluated the influence of paradoxical BDR on severe acute exacerbations by matching patients according to covariates of age, sex, current smoking status, BMI, pre-bronchodilator FEV_1 (% predicted), CAT, SGRQ-C, comorbid diseases (heart disease, diabetes, hypertension, and previous 1-year acute exacerbation), and previously used inhalers [long-acting muscarinic antagonist (LAMA), long-acting β_2 -agonist (LABA), and ICS]. Propensity score matching was performed with 1:3 nearest neighbor matching without replacement. The caliper was 0.05, and the absolute standardized differences of the mean were within 0.1 for all variables. Statistical analyses were performed using SPSS 23.0. Propensity score matching was performed using IBM SPSS 23.0 and R version R3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Results

We enrolled 1,991 patients in this study from 2,279 patients recruited during the cohort period (Figure 1). Two hundred and eighty-eight patients were excluded; 82 patients recorded FEV_1/FVC of >0.7 and 206 patients had missing FEV_1 or FVC data at the time of enrollment.

We found 57 (2.9%) patients had a paradoxical BDR. Mean age was 68.8 years in the paradoxical BDR and

69.2 years in the no-paradoxical BDR group (Table 1). The male sex was predominant representing 87.7% of the paradoxical BDR group and 90.8% of the no-paradoxical BDR group. There were no differences in underlying diseases between groups. Pre-bronchodilator FEV_1 (L) was higher in the paradoxical BDR group than the no-paradoxical BDR group. However, post-bronchodilator FEV_1 and FVC were significantly higher in the no-paradoxical BDR group than the paradoxical BDR group.

A multivariate analysis that adjusted for age, sex, BMI, pack-years of smoking, and pre-bronchodilator FEV_1 (L), showed that the paradoxical BDR was independently associated with higher mMRC, CAT, and SGRQ-C scores (Table 2).

To identify the factors predictive of paradoxical BDR, the variables that differed significantly between the two groups in Table 1 were selected; these were DL_{CO} (% predicted), vital capacity, CRP, and pre-bronchodilator FEV_1 (L). DL_{CO} (% predicted), vital capacity, CRP, and pre-bronchodilator FEV_1 (L) were associated with paradoxical BDR in the univariate logistic regression analysis. However, multivariate logistic regression analysis using the backward method revealed that high CRP [odds ratio (OR), 1.05; 95% confidence interval (CI), 1.01–1.09; $P = 0.003$] and DL_{CO} (% predicted) (OR, 0.95; 95% CI, 0.92–0.98; $P = 0.004$) were significantly associated with paradoxical BDR as shown in Table 3 (Nagelkerke $R^2 = 0.218$).

A paradoxical BDR was not associated with severe acute exacerbation during the 1-year period after logistic regression analysis with adjusting for confounding factors (Table 4). In addition, we used propensity score matching with variables to assess whether a paradoxical BDR was associated with severe acute exacerbation of COPD within

Table 1 Baseline characteristics of the no-paradoxical and paradoxical BDR groups

	Paradoxical BDR, (N=57)	No-paradoxical BDR, (N=1,934)	P value
Age, years	68.8±8.2	69.2±7.8	0.664
Sex, male	50 (87.7%)	1757 (90.8%)	0.274
Smoking history, pack-years	43.9±20.1	44.3±20.1	0.928
Current smokers	11 (20.0%)	512 (26.7%)	0.352
Body weight, kg	60.7±1.6	62.4±0.5	0.591
Height, meter	1.63±0.01	1.64±0.01	0.522
Body mass index, kg/m ²	22.5±3.5	22.9±3.3	0.421
mMRC Score	1.3±0.9	1.4±0.9	0.733
CAT score	14.9±6.8	14.8±7.9	0.975
SGRQ-C total score	34.6±18.9	32.7±18.5	0.484
Heart disease	146 (7.5%)	6 (10.5%)	0.441
Diabetes mellitus	11 (19.6%)	313 (16.3%)	0.467
Hypertension	21 (37.5%)	747 (39.0%)	0.890
Pre-bronchodilator FEV ₁			
Value, L	2.25±2.50	1.53±0.55	0.035
Percent of predicted value, %	57.17±16.68	57.87±26.25	0.843
Pre-bronchodilator FVC			
Value, L	3.18±0.88	3.12±0.80	0.582
Percent of predicted value, %	78.4±19.2	82.1±17.4	0.121
Pre-bronchodilator FEV ₁ /FVC, % measure	53.6±15.5	49.0±11.8	0.006
Post-bronchodilator FEV ₁			
Value, L	1.41±0.62	1.62±0.56	0.005
Percent of predicted value, %	55.6±17.8	60.7±19.1	0.049
Post-bronchodilator FVC			
Value, L	2.67±0.84	3.23±0.80	<0.000
Percent of predicted value, %	74.6±22.1	84.9±18.1	0.001
Post-bronchodilator FEV ₁ /FVC, % measure	51.3±9.7	53.5±15.8	0.912
FEV ₁ change, mL	-83.9±31.7	93.5±0.2	0.005
FEV ₁ change, %	-25.3±4.0	6.9±0.2	<0.000
FVC change, mL	-60.3±15.4	11.8±0.5	<0.000
FVC change, %	-14.6±4.4	4.5±0.2	<0.000
DL _{CO}	11.89±4.69	13.45±5.53	0.090
DL _{CO} , % predicted	62.2±21.3	73.9±23.4	0.003
Total lung capacity, L	6.05±1.80	6.04±1.31	0.979

Table 1 (continued)

Table 1 (continued)

	Paradoxical BDR, (N=57)	No-paradoxical BDR, (N=1,934)	P value
Total lung capacity, % predicted	106.4±33.9	108.5±23.5	0.650
Vital capacity, L	2.92±0.77	3.27±0.79	0.030
Vital capacity, % predicted	79.2±16.7	92.2±45.6	0.154
Inspiratory capacity, L	2.22±1.15	1.84±0.60	0.135
Inspiratory capacity, % predicted	83.6±41.9	74.9±23.6	0.369
Functional residual capacity	84.05±0.95	4.15±1.19	0.695
Functional residual capacity, % predicted	124.5±27.2	129.2±42.6	0.605
Residual volume, L	2.85±1.15	2.77±2.07	0.857
Residual volume, % predicted	132.3±48.0	125.3±58.3	0.560
Residual volume/total lung capacity	48.3±15.9	44.6±14.4	0.255
GOLD stage			
I	5 (8.8%)	281 (14.5%)	0.195
II	30 (52.6%)	1083 (56.0%)	
III	17 (29.8%)	491 (25.4%)	
IV	5 (8.8%)	79 (4.1%)	
6MWD, meter	383.2±127.6	377.3±116.8	0.779
Eosinophil, %	3.23±3.59	3.35±3.41	0.818
C-reactive protein, mg/dL	11.6±18.2	2.7±7.5	0.055
Acute exacerbation			
Acute exacerbations in prior year	16 (28.6%)	435 (22.8%)	0.333
Severe acute exacerbation in 1 year	5 (9.6%)	317 (23.5%)	1.000
Baseline drugs			
Long-acting muscarinic antagonist	30 (52.6%)	1168 (60.4%)	0.272
Long-acting β_2 agonist	25 (43.9%)	1,095 (56.6%)	0.059
Inhaled corticosteroid	20 (35.1%)	756 (39.1%)	0.584

Data are presented as number (%) or mean (SD). BDR, bronchodilator response; mMRC, modified Medical Research Council; CAT, COPD assessment test; SGRQ-C, COPD-specific version of St. George's Respiratory Questionnaire; FEV₁, forced expiratory volume in 1 second; L, liters; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide; GOLD, global initiative for chronic obstructive lung disease; 6MWD, 6-minute walk distance. Missing values [n]; smoking history [747], current smokers [20], body mass index [6], mMRC score [17], CAT score [77], SGRQ-C total score [46], diabetes mellitus [15], hypertension [19], DL_{CO} [393], total lung capacity [690], vital capacity [687], inspiratory capacity [848], functional residual capacity [777], residual volume [682], residual volume/total lung capacity [752], 6MWD [493], eosinophil [394], C-reactive protein [1,074].

1 year. After 1:3 matching analysis, a paradoxical BDR was not associated with severe acute exacerbations of COPD.

The receiver operating characteristic curve predicting severe acute exacerbation during 1 year showed that pre-bronchodilator FEV₁ (L) had a higher AUC than post-bronchodilator FEV₁ (L) in the paradoxical BDR group

(AUC, 0.788; 95% CI, 0.649–0.927; P=0.040 *vs.* AUC, 0.752; 95% CI, 0.567–0.936; P=0.094, respectively).

Discussion

In this cohort study, we described the characteristics of

Table 2 Univariate and multivariate analysis of the paradoxical response and respiratory symptoms

	Unadjusted		Adjusted		r ²
	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value	
6-minute walk distance					
					0.149
Age	-3.80 (-4.55, -3.06)	<0.000	-3.66 (-4.70, -2.62)	<0.000	
Sex, male	20.72 (-1.65, 43.11)	0.070	3.93 (-43.81, 51.68)	0.872	
BMI	4.27 (2.49, 6.05)	<0.000	2.95 (0.65, 5.24)	0.011	
Pack-years	-0.53 (-0.83, -0.23)	0.001	-0.39 (-0.68, -0.10)	0.008	
FEV ₁ (L)	61.25 (51.09, 71.71)	<0.000	49.33 (35.39, 63.27)	<0.000	
Paradoxical BDR	5.87 (-35.16, 46.91)	0.779	-20.39 (-40.72, -0.05)	0.951	
Modified Medical Research Council score					
					0.109
Age	0.01 (0.01, 0.02)	<0.000	0.01 (0.00, 0.02)	<0.000	
Sex, male	-0.19 (-0.34, -0.04)	0.013	-0.04 (-0.37, 0.29)	0.814	
BMI	-0.02 (-0.03, -0.01)	<0.000	-0.01 (-0.03, 0.00)	0.063	
Pack-years	0.002 (0.000, 0.004)	0.014	0.002 (0.000, 0.004)	0.078	
FEV ₁ (L)	-0.41 (-0.47, -0.36)	<0.000	-0.32 (-0.39, -0.25)	<0.000	
Paradoxical BDR	-0.04 (-0.29, 0.20)	0.730	0.33 (0.02, 0.64)	0.034	
COPD assessment test score					
					0.072
Age	0.04 (-0.00, 0.08)	0.084	0.02 (-0.04, 0.08)	0.564	
Sex, male	-1.50 (-2.84, -0.16)	0.028	-3.29 (-6.29, -0.29)	0.031	
BMI	-0.29 (-0.40, -0.19)	<0.000	-0.25 (-0.39, -0.12)	<0.000	
Pack-years	0.02 (0.01, 0.04)	0.001	0.02 (0.01, 0.04)	0.002	
FEV ₁ (L)	-2.60 (-3.10, -2.11)	<0.000	-2.03 (-2.63, -1.44)	<0.000	
Paradoxical BDR	0.03 (-0.29, 2.16)	0.975	2.85 (0.11, 5.58)	0.041	
St. George's Respiratory Questionnaire					
					0.176
Age	0.25 (0.14, 0.36)	<0.000	0.05 (-0.08, 0.19)	0.466	
Sex, male	-3.43 (-6.58, -0.28)	0.033	-2.71 (-9.61, 3.78)	0.426	
BMI	-0.76 (-1.01, -0.51)	<0.000	-0.28 (-0.59, 0.32)	0.079	
Pack-years	0.04 (0.00, 0.08)	0.044	0.03 (-0.00, 0.06)	0.114	
FEV ₁ (L)	-12.61 (-13.99, -11.23)	<0.000	-13.40 (-15.32, -11.47)	<0.000	
Paradoxical BDR	1.85 (-3.34, 7.05)	0.484	11.01 (4.71, 17.31)	0.001	

BMI, body mass index; FEV₁, forced expiratory volume in 1 second; L, liters; BDR, bronchodilator response; COPD, chronic obstructive pulmonary disease; CI, confidence interval.

patients with COPD who exhibit a paradoxically reduced FEV₁ or FVC after bronchodilator administration. We found that the paradoxical BDR was independently associated with higher mMRC, CAT, and SGRQ-C scores, and an elevated CRP level was associated with

paradoxical BDR after bronchodilator administration. Pre-bronchodilator FEV₁ (L) was more predictive of severe acute exacerbations of COPD than post-bronchodilator FEV₁ (L) in the paradoxical BDR group.

We found that 57 (2.9%) of 1,991 patients with COPD

Table 3 Predictive factors for a paradoxical bronchodilator response

Variables	Odds ratio	95% CI	P value
Univariate analysis			
DL _{CO} (% predicted)	0.97	0.96–0.99	0.003
Vital capacity	0.56	0.33–0.94	0.031
C-reactive protein	1.04	1.02–1.07	<0.000
Long-acting β_2 agonist	0.59	0.35–1.01	0.058
Pre-bronchodilator FEV ₁ (L)	3.07	2.00–4.72	<0.000
Multivariate analysis			
C-reactive protein	1.05	1.01–1.09	0.003
DL _{CO} (% predicted)	0.95	0.92–0.98	0.004

DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 second; L, liters; CI, confidence interval.

Table 4 Predictive factors for severe 1-year acute exacerbation

Variables	Odds ratio	95% CI	P value
Paradoxical BDR (crude)	0.49	0.19–1.27	0.145
Paradoxical BDR ^a	0.51	0.19–1.34	0.176
Paradoxical BDR ^b	0.51	0.19–1.37	0.187
Paradoxical BDR (propensity score matching analysis)	0.54	0.19–1.57	0.264

^a, adjusted for age and sex; ^b, adjusted for age, male sex, CAT score, SGRQ-C score, and previous 1-year acute exacerbation. CI, confidence interval; BDR, bronchodilator response; CAT, COPD assessment test; SGRQ-C, COPD-specific version of St. George's Respiratory Questionnaire.

exhibited a paradoxical BDR, following the definition of a paradoxical BDR as described by a previous study (5). Previous studies have reported a paradoxical BDR incidence rate of 4% of all patients with COPD in the COPD Gene cohort. However, the ECLIPSE cohort reported that 47 (2%) of 2493 patients showed a paradoxical BDR (5,12). In contrast, the UPLIFT cohort reported a very low incidence of 0.24%, wherein the paradoxical BDR was measured based on GOLD criteria (13). Racial differences may contribute to the differences in incidence of paradoxical BDR (5). In this Asian cohort study, the rate of paradoxical BDR was similar to the results of the ECLIPSE cohort. Further research is needed to determine whether racial differences influence the paradoxical BDR.

The mechanisms associated with a paradoxical BDR after bronchodilator administration have not been fully elucidated. Several possible hypotheses include incorrect inhaler use, bronchospasm from the propellant or the benzalkonium chloride, chlorofluorocarbons, and oleic

acid contained in inhalers (6-8). Population differences are observed in the paradoxical response, which might be associated with β -receptor polymorphism (5). In this study, higher CRP expression was associated with the paradoxical BDR. Elevated CRP level is associated with reductions in FEV₁ and worse outcomes in COPD (14,15). A smaller increase in FEV₁ after administration of a bronchodilator is associated with elevated CRP levels in patients with COPD (16). CRP is associated with chronic respiratory inflammation in COPD; therefore, the deterioration of chronic inflammation may be associated with the paradoxical BDR to bronchodilator administration.

In this study, the paradoxical BDR was independently associated with worse dyspnea and a poorer quality of life. In line with this, Bhatt *et al.* reported that a paradoxical BDR was associated with lower 6MWD and higher mMRC scores (5). Emphysema and airway thickness are independently associated with airway obstruction in patients with COPD (17). Airway thickness but not emphysema

is significantly increased in the paradoxical BDR group (5). The increased airway thickness may have reduced the response to bronchodilators, consequently contributing to worse dyspnea and poor quality of life. However, paradoxical BDR was not associated with severe acute exacerbations in the present study. In contrast, Bhatt *et al.* reported that there was an increase in the frequency of severe exacerbation in a paradoxical BDR group after adjusting for confounding factors (5). Bhatt *et al.* explained that the incidence of severe acute exacerbation was increased in the paradoxical group because there were more African-Americans than whites in the paradoxical BDR group (5). African-Americans with COPD have poorer outcomes than whites (18). Considering racial differences, the present study suggests that Asian populations associated with paradoxical BDR are not prone to acute exacerbations of COPD.

Post-bronchodilator FEV₁ and FVC are key values in diagnosing COPD and assessing the prognosis. However, if the post-bronchodilator FEV₁ is used for assessing the prognosis of COPD, airway obstruction can be overestimated. In this study, pre-bronchodilator FEV₁ (L) is higher in the paradoxical BDR group than in the non-paradoxical BDR group. However, post-bronchodilator FEV₁ and FVC are significantly higher in the non-paradoxical BDR group than in the paradoxical BDR group. We found that pre-bronchodilator FEV₁ (L) had a higher AUC for predicting severe acute exacerbations than post-bronchodilator FEV₁ (L) in the paradoxical BDR group. While there was no difference between the pre-bronchodilator and post-bronchodilator FEV₁ (% predicted) AUC at predicting severe acute exacerbations, pre-bronchodilator FEV₁ measurements may be helpful in assessing disease prognosis in patients with a paradoxical BDR.

There are several limitations to this study. First, we did not assess the serial reversibility tests. Several studies showed that measurements are not consistent when repeated serial BDR tests are administered (19,20). Further study including analysis of the serial measurements is required. Second, there is no validated definition for paradoxical BDR; therefore, we used the definition from a previous study, which defined paradoxical BDR based on the American Thoracic Society criteria (5). Therefore, further studies are necessary to identify whether this definition yields meaningful results in other cohorts. Third, while we found that increased CRP was an independent factor to predict a paradoxical BDR in this study, we cannot exclude the influence of other chronic inflammatory conditions. To reduce this influence, we adjusted for other chronic

inflammatory diseases, such as heart disease, diabetes mellitus, and hypertension. After adjusting for these variables, higher CRP was significantly associated with a paradoxical BDR (OR, 1.06; 95% CI, 1.02–1.10; P=0.001). Fourth, although patients with asthma were excluded, some of them may have been included among patients with positive bronchodilator reversibility. It is also possible that these patients underused ICS.

Conclusions

A paradoxical reduction of FEV₁ or FVC after bronchodilator administration is independently associated with worse respiratory symptoms and a poor quality of life in patients with COPD and may be associated with chronic inflammation in the airway. While paradoxical BDR was not associated with severe acute exacerbations, pre-bronchodilator FEV₁ (L) may be a useful measure for predicting severe acute exacerbations in patients with paradoxical BDR.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol which was conducted according to the principle expressed in the Declaration of Helsinki (as revised in 2013) was approved

by the IRB at each participating center including Seoul National University Hospital IRB, Catholic Medical Center Central IRB, Yonsei University Wonju College of Medicine IRB, Severance Hospital IRB, Soonchunhyang University Cheonan Hospital IRB, Ajou University Hospital IRB, Hallym University Dongtan Sacred Heart Hospital IRB, Hallym University Chuncheon Sacred Heart Hospital IRB, Hallym University Pyeongchon Sacred Heart Hospital IRB, Hanyang University Guri Hospital IRB, Konkuk University Hospital IRB, Konkuk University Chungju Hospital IRB, Hallym University Kangdong Sacred Heart Hospital IRB, Hallym University Kangnam Sacred Heart Hospital IRB, Seoul National University Boramae Medical Center IRB, Korea University Guro Hospital IRB, Korea University Anam Hospital IRB, Dongguk University Gyeongju Hospital IRB, Dong-A University Hospital IRB, Gachon University Gil Medical Center IRB, Gangnam Severance Hospital IRB, Kyung Hee University Hospital at Gangdong IRB, Kangbuk Samsung Hospital IRB, Kangwon National University Hospital IRB, Kyungpook National University Hospital IRB, Gyeongsang National University Hospital IRB, Pusan National University Hospital IRB, Soonchunhyang University Bucheon Hospital IRB, Seoul National University Bundang Hospital IRB, CHA Bundang Medical Center, CHA University IRB, Asan Medical Center IRB, Inje University Ilsan Paik Hospital IRB, Eulji General Hospital IRB, Samsung Medical Center IRB, Ulsan University Hospital IRB, Soonchunhyang University Seoul Hospital IRB, Yeungnam University Hospital IRB, Ewha Womans University Mokdong Hospital IRB, Inha University Hospital IRB, Chonbuk National University Hospital IRB, and Jeju National University Hospital IRB. All patients provided written informed consent for participation from each center.

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