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Responses to inhaled long-acting beta-agonist and corticosteroid according to COPD subtype☆

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Summary
Rationale: Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disorder in which a number of different pathological processes lead to recognition of patient subgroups that may have individual characteristics and distinct responses to treatment.
Objectives: We tested the hypothesis that responses of lung function to 3 months of combined inhalation of long-acting beta-agonist and corticosteroid might differ among patients with various COPD subtypes.
Methods: We classified 165 COPD patients into four subtypes according to the severity of emphysema and airflow obstruction: emphysema-dominant, obstruction-dominant, mild-mixed, and severe-mixed. The emphysema-dominant subtype was defined by an emphysema index on computed tomography of more than 20% and FEV_1 more than 45% of the predicted value. The obstruction-dominant subtype had an emphysema index $\leq$ 20% and $FEV_1 \leq 45\%$, the mild-mixed subtype had an emphysema index $\leq$ 20% and $FEV_1 > 45\%$, and the severe-mixed subtype had an emphysema index $>$ 20% and $FEV_1 \leq 45\%$. Patients were recruited prospectively and treated with 3 months of combined inhalation of long-acting beta-agonist and corticosteroid.
Results: After 3 months of combined inhalation of long-acting beta-agonist and corticosteroid, obstruction-dominant subtype patients showed a greater FEV_1 increase and more marked dyspnea improvement than did the emphysema-dominant subgroup. The mixed-subtype patients (both subgroups) also showed significant improvement in FEV_1 compared with the emphysema-dominant subgroup. Emphysema-dominant subtype patients showed no improvement in FEV_1 or dyspnea after the 3-month treatment period.
Conclusion: The responses to 3 months of combined inhalation of long-acting beta-agonist and corticosteroid differed according to COPD subtype.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible and is usually progressive.[1] Originally, COPD was classified into two phenotypes, emphysema and chronic bronchitis.[2] These phenotypes are considered to result from differences in sensitivity to noxious particles or gases, especially tobacco smoke, which may affect the development of emphysema or airway structural changes.[3] The pathophysiological pathways leading to emphysema and small airway narrowing are independent[4] but interact in a complex manner. In addition, the relative contributions toward irreversible airflow limitation caused by pathological changes in airways, and emphysema, vary among individuals,[5] and most patients with COPD cannot be clearly classified as showing either phenotype.

Chronic inflammation causes remodeling and narrowing of small airways, and, theoretically, airflow obstruction at such sites should respond to pharmacological agents such as bronchodilators and inhaled corticosteroids (ICS). Destruction of lung parenchyma leads to the loss of alveolar attachment to small airways and decreases lung elastic recoil; these pathological changes are considered to be unresponsive to pharmacological treatment.

Clinical responses to treatments such as bronchodilators and/or ICS may therefore vary among individuals according to the relative contributions of small airway disease and emphysema to airflow limitation. Indeed, significant reversibility of airflow limitation after use of bronchodilators and/or corticosteroids was noted in up to 30% of patients with stable COPD.[6]

If the severity of emphysema varies in patients showing the same degree of airflow limitation, it would be possible to compare drug responses of COPD patients in whom the relative contributions of small airway disease and emphysema differ. Patients displaying little evidence of emphysema despite the presence of severe airflow limitation might be considered as demonstrating a phenotype in which small airway disease is predominant.

Therefore, we classified COPD patients into four subtypes according to the quantitatively evaluated extent of emphysema on chest volumetric computed tomography (CT) scans and pre-bronchodilator forced expiratory volume in 1 second (FEV_1) data. We tested the hypothesis that responses of lung function to 3 months of combined inhalation of a long-acting beta-agonist (LABA) and a corticosteroid might differ among patients with various COPD subtypes.

Methods

Subjects and data acquisition

A total of 171 COPD subjects were included. The patients fulfilled all of three criteria, with a post-bronchodilator ratio of FEV_1 to forced vital capacity (FEV_1/FVC) of less than 0.7, more than 10 pack-years of smoking history, and no or minimal abnormality on chest radiography (Fig. 1). Among these 171 subjects, 165 patients were analyzed, because six CT scans were of poor quality.

Before and after the 3-month treatment with combined inhalation of LABA and corticosteroid, the extent of dyspnea (using the modified Medical Research Council [MMRC] scale[7]) spirometry data, and lung volume were evaluated in all patients. During 2 weeks of washout before the 3-month treatment period, only an inhaled short-acting beta-agonist (albuterol) was permitted until the day before baseline data were acquired. During the 3-month treatment period albuterol was allowed as needed.

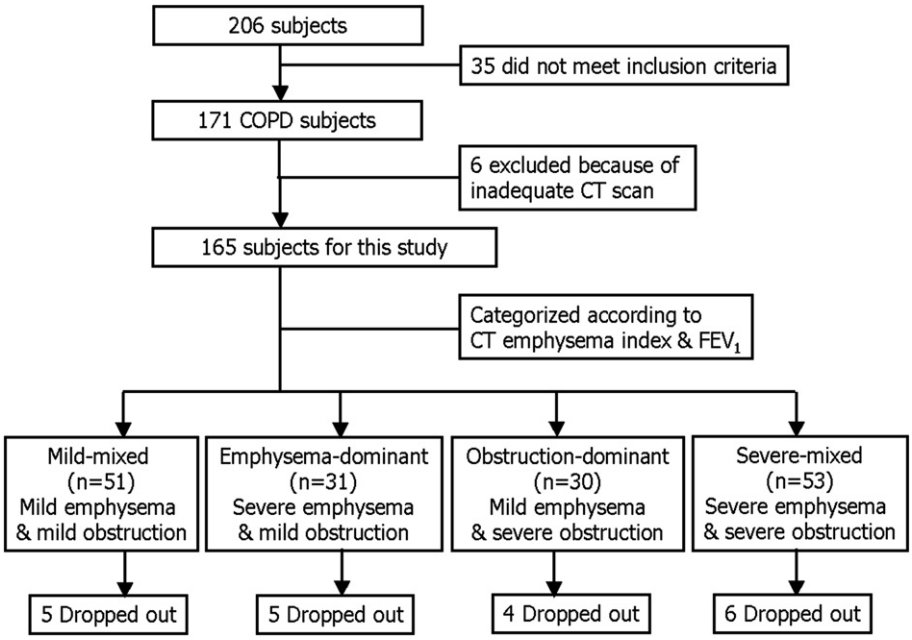

Figure 1 Study subjects and the four COPD subtypes. The subtypes of COPD were defined by CT emphysema index and FEV_1.

Before the 3-month treatment, a chest CT scan was obtained, a 6-minute walk distance (6MWD) test was performed,[8] and both diffusing capacity and body mass index (BMI) were evaluated, in addition to dyspnea scale scoring and collection of spirometry and lung volume data.

Our Institutional Review Board approved all of the procedures and written informed consent was obtained from all patients.

CT emphysema index (EI)

Volumetric CT scans were obtained using a 16-multidetector CT (MDCT) scanner (Somatom Sensation instrument; Siemens, Erlangen, Germany; GE Lightspeed Ultra instrument; General Electric Healthcare; Milwaukee, WI; Philips Brilliance instrument; Philips Medical Systems, Best, the Netherlands) as previously described.[9] From CT data, the volume fraction of the lung below −950 Hounsfield Units (HU) at full inspiration was calculated automatically and was termed the emphysema index (EI).

Lung function

Spirometry was performed as recommended by the American Thoracic Society (Vmax 22 instrument; SensorMedics, Yorba Linda, CA; PFDX instrument; MedGraphics, St. Paul, MN).[10] FVC, FEV_1, FEV_1/FVC, and mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) were evaluated before and after inhalation of 400 μg albuterol.

Lung volume[11] and diffusing capacity[12] were also measured. All values are expressed as percentages of predicted values.

COPD subtypes

The emphysema-dominant subtype was defined when EI was more than 20% and FEV_1 was over 45% of the predicted value; obstruction-dominant subtype patients had EI $\leq$ 20% and $FEV_1 \leq$ 45% predicted; mild-mixed subtype patients had EI $\leq$ 20% and $FEV_1 >$ 45% predicted; severe-mixed subtype patients had EI > 20% and $FEV_1 \leq$ 45% predicted (Fig. 2). Cut-off values for EI and FEV_1 were determined arbitrarily, and were close to the median values.

Three-month treatment with combined inhalation of long-acting beta-agonist and corticosteroid

Among the 165 participants, 147 patients (89%) had been treated twice daily for 3 months with a combination of salmeterol (50 μg) and fluticasone propionate (500 μg), and 18 (11%) had been treated twice daily with a combination of formoterol (9 μg) and budesonide (320 μg). Ninety-one percent of subjects indicated that they had taken over 80% of the recommended medication dose.

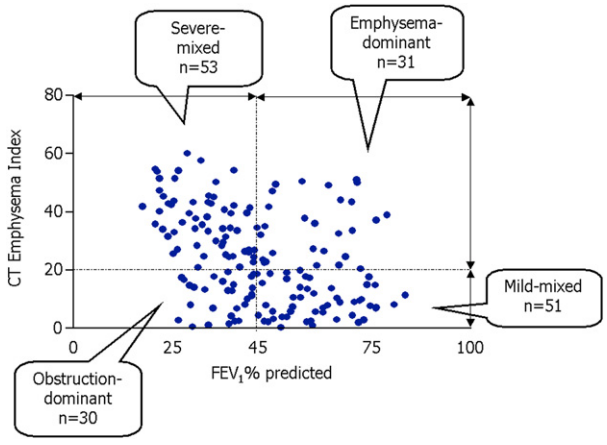

Figure 2 Distributions of FEV_1 and CT emphysema index. Each dot represents data from an individual patient.

Statistical analysis

All statistical analysis was performed using a statistical package (SPSS version 12.1.1; SPSS, Chicago, IL). All results are expressed as means ± standard deviations. Data from the four groups were compared by one-way analysis of variance (ANOVA), followed by multiple comparisons using the Bonferroni post-hoc test. Simple correlations between variables were examined by Spearman correlation analysis. A P value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Most patients had moderate-to-severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Of these, 1% were classified as GOLD 1 (mild COPD), 36% as GOLD 2 (moderate COPD), 48% as GOLD 3 (severe COPD), and 15% as GOLD 4 (very severe COPD).

Patients were classified into four subtypes according to EI values on CT scans and FEV_1 data. Fifty-one patients were classified as mild-mixed, 31 as emphysema-dominant, 30 as obstruction-dominant, and 53 as severe-mixed subtypes.

There was no death during the follow-up period. Five patients of both the mild-mixed and emphysema-dominant subtypes, four of the obstruction-dominant subtype, and six of the severe-mixed subtype, dropped out during follow-up. Thus, a total of 145 patients completed the study (Figs. 1 and 2).

The subjects consisted primarily of elderly patients (Table 1). The mean ages of the four subtypes of COPD patients were similar; no significant difference was apparent. Of all patients, 28–39% were current smokers. Smoking history, as measured by pack-years, was highest in the emphysema-dominant subgroup. Body mass index was lower in the emphysema-dominant and severe-mixed subgroups than in the mild-mixed or obstruction-dominant subgroups. The 6MWD was lower in the severe-mixed subgroup than in the mild-mixed or obstruction-dominant subgroups, and the MMRC dyspnea scale was higher in the severe-mixed subgroup than in the mild-mixed subgroup.

The EI was lowest in the emphysema-dominant subgroup and lower in the severe-mixed subgroup than in the mild-mixed or obstruction-dominant subgroups.

FEV_1 values were lower in the obstruction-dominant and severe-mixed subgroups than in the mild-mixed or emphysema-dominant subgroups. FVC values were lowest in the obstruction-dominant subgroup and lower in the severe-mixed subgroup than in the mild-mixed or emphysema-dominant subgroups. FEV_1/FVC ratios were lowest in the severe-mixed subgroup, and lower in the emphysema-dominant and obstruction-dominant subgroups than in the mild-mixed subgroup. Bronchodilator response after short-acting beta-agonist inhalation showed no differences among subgroups. The diffusing capacity (DL_{CO}) was lower in the emphysema-dominant and severe-mixed subgroups than in the mild-mixed or obstruction-dominant subgroups. The obstruction-dominant subgroup also showed a lower DL_{CO} value than did the mild-mixed subgroup. Total lung capacity (TLC) was highest in the severe-mixed subgroup compared with the other three subgroups. Inspiratory capacity (IC) was lower in the obstruction-dominant and severe-mixed subgroups than in the mild-mixed and emphysema-dominant subgroups. Residual volume (RV) was higher in the obstruction-dominant and severe-mixed subgroups than in the mild-mixed and emphysema-dominant subgroups.

Responses in lung function and dyspnea scores from baseline, after 3 months of treatment with long-acting beta-agonist plus inhaled corticosteroid

The FEV_1 response after 3 months of treatment was significantly different among COPD subtype patients (Table 2). The emphysema-dominant subgroup showed the smallest improvement in FEV_1 (0.032 ± 0.263 liters) after 3 months of treatment, compared with the other three subgroups. The improvement in FEV_1 after 3 months of treatment was greatest in the obstruction-dominant subgroup (0.207 ± 0.223 liters) and the two mixed subgroups also showed intermediate but significant improvements in FEV_1 after 3 months of treatment, compared with the emphysema-dominant subgroup. There was no statistically significant difference among the obstruction-dominant and the two mixed subgroups. After 3 months of treatment, RV was significantly decreased in the obstruction-dominant subgroup compared with the mild-mixed and emphysema-dominant subgroups. Responses of other lung volume parameters after 3 months of treatment showed no significant differences among subgroups. The MMRC dyspnea score significantly decreased (patients thus improved) in the obstruction-dominant subgroup compared with the emphysema-dominant subgroup.

Correlation between baseline variables and changes in FEV_1 or dyspnea scores after 3 months of treatment with combined long-acting beta-agonist plus inhaled corticosteroid in patients with COPD

The change in FEV_1 after 3 months of treatment showed significant but weak correlations with pre-bronchodilator FEV_1 and DL_{CO} values, with correlation coefficients (r values) of -0.201 and 0.195, respectively. A better correlation was noted between the change in FEV_1 after 3 months of treatment and bronchodilator responses at baseline ($r = 0.37$, $p < 0.001$, Fig. 3). There was no significant correlation between change in FEV_1 and EI. Changes in the MMRC score showed weak correlation with EI ($r = 0.174$, $p = 0.038$), indicating that patients with lower EI values experienced more dyspnea relief (a greater negative value) after 3 months of treatment (Table 3).

Discussion

In the present study, we classified stable COPD patients into four subtypes according to EI value measured by CT scans, and FEV_1 measured by spirometry. Following 3 months of combined LABA and ICS treatment, emphysema-dominant patients showed the smallest improvement in FEV_1

Table 1 Baseline characteristics of COPD patients.

Subtype	Mild-mixed	Emphysema-dominant	Obstruction-dominant	Severe-mixed
Number of patients	46	26	26	47
Age, years	65.8 ± 8.2	68.0 ± 7.4	65.4 ± 5.3	66.2 ± 7.0
Male	46 (100%)	26 (100%)	25 (96%)	46 (98%)
Smoking, pack-years	43.0 ± 20.0	60.1 ± 436.2*	43.6 ± 19.8§	46.0 ± 22.4¶
Current smokers [n, (%)]	18 (39%)	9 (35%)	10 (39%)	13 (28%)
BMI, kg/m^2	24.7 ± 3.1	21.7 ± 2.8*	23.9 ± 3.7§	21.6 ± 3.4‡**
6MWD, meters	464.3 ± 70.5	434.5 ± 84.0	458.0 ± 54.1	404.5 ± 88.3‡**
MMRC score	1.32 ± 1.10	1.58 ± 0.95	1.77 ± 1.00	2.04 ± 1.00‡
Emphysema index	9.1 ± 5.7	33.1 ± 9.9*	10.2 ± 6.0§	37.3 ± 10.2‡¶**
FEV_1, liters	1.93 ± 0.43	1.66 ± 0.33	1.11 ± 0.20†§	1.00 ± 0.27‡¶
(% predicted)	(61.0 ± 10.4)	(57.2 ± 10.1)	(37.3 ± 6.0†§)	(32.3 ± 7.3‡¶**)
FVC, liters	3.67 ± 0.75	3.48 ± 0.71	2.51 ± 0.59†§	2.86 ± 0.63‡¶**
(% predicted)	(83.4 ± 14.0)	(86.1 ± 15.8)	(61.4 ± 13.8†§)	(71.0 ± 15.2‡¶**)
FEV_1/FVC, %	53.0 ± 7.8	48.2 ± 7.0*	45.3 ± 8.3†	34.1 ± 7.6‡¶**
BDR, mL	194 ± 156	147 ± 136	207 ± 171	163 ± 125
(%)	(5.98 ± 4.63)	(5.04 ± 4.68)	(6.77 ± 5.46)	(5.28 ± 4.06)
DL_{CO}, % predicted	98.5 ± 24.5	65.8 ± 14.7*	85.6 ± 27.5†§	61.2 ± 20.8‡**
TLC, liters	6.40 ± 0.95	6.50 ± 1.17	6.37 ± 1.67	7.16 ± 1.219‡¶**
(% predicted)	(110.1 ± 12.7)	(125.5 ± 23.7*)	(120.3 ± 36.6)	(128.6 ± 19.6‡)
IC, liters	2.37 ± 0.52	2.18 ± 0.56	1.73 ± 0.37†§	1.69 ± 0.48‡¶
(% predicted)	(86.3 ± 18.2)	(88.9 ± 21.8)	(68.2 ± 12.3†§)	(64.2 ± 16.5‡¶)
RV, liters	2.64 ± 0.78	2.96 ± 1.13	3.69 ± 1.59†§	4.01 ± 1.26‡¶
(% predicted)	(122.0 ± 34.5)	(139.4 ± 51.2)	(179.5 ± 78.9†§)	(185.6 ± 58.0‡¶)

6MWD, 6-minute walk distance; BDR, bronchodilator response; BMI, body mass index; DL_{CO}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; IC, inspiratory capacity; MMRC, modified Medical Research Council dyspnea score; RV, residual volume; TLC, total lung capacity.
Data are shown as means ± standard deviations.
* Mild-mixed vs. Emphysema-dominant, $p < 0.05$.
† Mild-mixed vs. Obstruction-dominant, $p < 0.05$.
‡ Mild-mixed vs. Severe-mixed, $p < 0.05$.
§ Emphysema-dominant vs. Obstruction-dominant, $p < 0.05$.
¶ Emphysema-dominant vs. Severe-mixed, $p < 0.05$
** Obstruction-dominant vs. Severe-mixed, $p < 0.05$.

compared with those of the other three subgroups. Improvement in FEV_1 after 3 months of treatment was greatest in the obstruction-dominant subgroup, and the two mixed subgroups also showed intermediate but significant improvement in FEV_1 after 3 months of treatment, compared with the emphysema-dominant subgroup. Airflow obstruction in the emphysema-dominant subgroup, as measured by FEV_1 and dyspnea scale scores, showed no

Table 2 Responses in lung function and dyspnea score following 3 months of treatment with combined long-acting beta-agonist and inhaled corticosteroid.

Subtype	Mild-mixed	Emphysema-dominant	Obstruction-dominant	Severe-mixed
ΔFEV_1, liters	0.169 ± 0.218	0.032 ± 0.263*	0.207 ± 0.223§	0.155 ± 0.166¶
(% predicted)	(5.1 ± 6.4)	(0.9 ± 9.3*)	(6.7 ± 7.3§)	(5.1 ± 5.5¶)
ΔTLC, liters	−0.09 ± 0.52	0.09 ± 0.57	−0.41 ± 1.11	−0.16 ± 0.56
ΔIC, liters	0.07 ± 0.47	0.22 ± 0.48	0.11 ± 0.30	0.11 ± 0.33
ΔRV, liters	−0.20 ± 0.64	−0.11 ± 0.85	−0.63 ± 1.26†§	−0.31 ± 0.77
ΔMMRC score	−0.39 ± 1.02	−0.16 ± 0.55	−0.68 ± 1.03§	−0.26 ± 0.74

FEV_1, forced expiratory volume in 1 sec; IC, inspiratory capacity; MMRC, modified Medical Research Council dyspnea scale measurement; RV, residual volume; TLC, total lung capacity.
Data are shown as means ± standard deviations. One-way analysis of variance for quantitative variables with Bonferroni's test was used for multiple comparisons.
* Mild-mixed vs. Emphysema-dominant, $p < 0.05$.
† Mild-mixed vs. Obstruction-dominant, $p < 0.05$.
‡ Mild-mixed vs. Severe-mixed, $p < 0.05$.
§ Emphysema-dominant vs. Obstruction-dominant, $p < 0.05$.
¶ Emphysema-dominant vs. Severe-mixed, $p < 0.05$.
** Obstruction-dominant vs. Severe-mixed, $p < 0.05$.

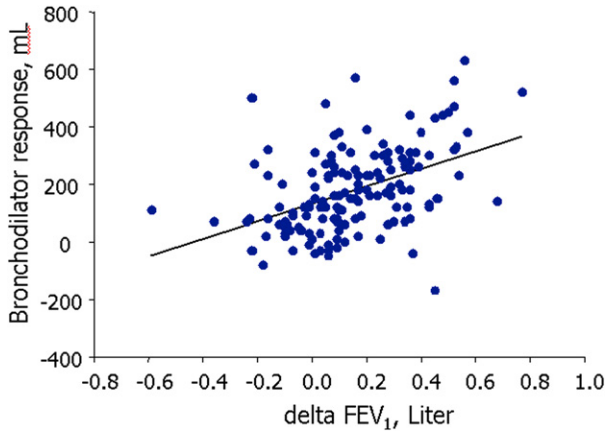

Figure 3 The correlation between bronchodilator response and change in FEV_1 after 3 months of treatment with long-acting beta-agonist and inhaled corticosteroid (deltaFEV$_1$) was significant, with a correlation coefficient of 0.37 ($p < 0.001$). Bronchodilator response was measured as the increase in FEV_1 after inhalation of 400 μg albuterol.

Table 3 Correlation between baseline variables and change in FEV_1 or dyspnea scores after 3 months of treatment with combined long-acting beta-agonist plus inhaled corticosteroid in patients with COPD[a].

Baseline variables	Change in FEV_1		Change in MMRC score	
	r value	*p* value	*r* value	*p* value
FEV_1, % predicted	−0.201	0.015	0.069	0.401
BDR[b], mL	0.37	<0.001	0.117	0.164
DL_{CO}, % predicted	0.195	0.019	−0.115	0.171
Emphysema index	−0.150	0.072	0.174	0.038

BDR, bronchodilator response; DL_{CO}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 sec; MMRC, modified Medical Research Council dyspnea scale measurement; *r*, correlation coefficient.

[a] All patients of the four COPD subtypes were analyzed together.

[b] Bronchodilator response was measured as the increase in FEV_1 after inhalation of 400 μg albuterol.

improvement after treatment. Also, the bronchodilator response after short-acting beta-agonist treatment correlated positively with response after 3 months of treatment with combined LABA and ICS; although the bronchodilator response showed no statistically significant difference among the four subtypes. These findings indicate that the best treatment response to combined LABA and ICS may be expected in patients with the airway obstruction-dominant phenotype of COPD, who show a relatively high degree of airway reversibility. The worst responses may be expected in patients with the emphysema-dominant phenotype.

To the best of our knowledge, this is the first study to show that treatment responses to combined LABA and ICS differ significantly among patients with various subtypes of COPD.

To date, guidelines for therapy selection have been based on a one-dimensional scale of disease severity.[1] An important challenge in COPD research is the development of more powerful, multivariate methods for predicting individual outcomes and personal responsiveness to particular therapies, using clinical and laboratory characteristics.

It is well known that, in a susceptible host, small airway inflammation primarily contributes to airflow limitation by narrowing or obliterating the airway lumen and by actively constricting the airway.[4] Patients with chronic bronchitis showed higher levels of eosinophils and macrophages in sputum than did normal controls, indicating that chronic bronchitis reflects an inflammatory sub-phenotype among patients with COPD.[13] These findings may indicate that bronchodilator and/or anti-inflammatory treatment is indicated for COPD patients with an airway-dominant phenotype, but not for those with an emphysema-dominant phenotype.

Recently, Kitaguchi and colleagues showed that airway disease-dominant COPD patients, who demonstrated bronchial wall thickening on high-resolution CT (HRCT), showed greater reversibility of airflow limitation in response to short-acting bronchodilator or ICS treatment compared with patients with either the mixed form of COPD or emphysema-dominant patients.[14] Thus, recent work has attempted to divide COPD patients into subgroups and to analyze clinical between-subgroup differences.[14–17] However, the available reports show some inconsistencies in the description of clinical manifestations, which may be related to the absence of consensus guidelines for differentiating emphysema-dominant and bronchitis-(airway-) dominant subtypes of COPD. To date, the modes of differentiation used have been arbitrary, and have thus varied among reports.[14,15,17] The availability of consensus methodology to differentiate COPD subgroups will lead to a revision of some original concepts of the natural history of COPD, which will finally enable clinicians to precisely characterize and understand the disease.

Originally, symptoms of chronic bronchitis were used to identify a subgroup of COPD patients. According to results of the Lung Health Study, the prevalence of respiratory symptoms decreased by 80% after 5 years of smoking cessation.[18] Therefore, many patients with COPD may not show symptoms of chronic bronchitis even though they also display little evidence of emphysema. Thus, we did not use such symptoms as indicators of airway involvement.

Recently, CT has become popular for noninvasive assessment of airway disease in COPD patients,[19–21] particularly with the development of multi-slice CT scanning techniques. However, CT scans are still limited by a pixel size of approximately 0.5 mm, which makes measurements on small airways, in particular, prone to error.[22] However, quantification of emphysema by CT can be objectively performed using computer-based analysis, which has been validated by pathologic correlation.[23–26] One of the major advantages of computer-based quantification is that the results are of high reproducibility, because little or no human intervention is involved. The software used in the present study was developed by our research group, and has been validated in our previous study.[9]

A low attenuation area on CT may reflect hyperlucency resulting from air trapping, rather than emphysema *per se*, thus confounding the assumption that a CT score simply indicates the extent of emphysema. However, in the present study, as in many similar studies, EI on CT scan

correlated well with DL_{CO}, with an r-value of -0.623 ($p < 0.001$). DL_{CO} is thus another indicator of the degree of emphysema.[17,27]

Although diffusing capacity is less sensitive than a CT scan to diagnose mild emphysema,[28] and although diffusing capacity may decrease in patients with severe airway obstruction, it may be valuable to assess emphysema and to divide patients into COPD subtypes using DL_{CO} instead of EI because CT instruments may not always be readily available. Therefore, we used DL_{CO} values rather than CT EI to divide patients into four subgroups using FEV_1 and DL_{CO}. With cut-off values for FEV_1 of 45% and for DL_{CO} of 75% (these are the median values), treatment response expressed as changes in FEV_1 and dyspnea index was similar to the results obtained using FEV_1 and EI analysis (data not shown). Because chest CT is not routinely used in clinical settings to evaluate patients with COPD, DL_{CO} may serve as a useful surrogate for EI in categorization of the four subtypes.

The value of the bronchodilator response after administration of short-acting beta-agonists in predicting patient response after long-acting bronchodilator (and ICS) treatment remains controversial.[29–31] However, bronchodilator response seems to be useful in assessing treatment response to LABA and/or ICS in patients with COPD. In the present study, an improvement in FEV_1 after 3 months of combined LABA and ICS treatment correlated positively with bronchodilator response after administration of a short-acting beta-agonist. Considering that the correlation coefficient was relatively low ($r = 0.37$) and that there was no significant difference in bronchodilator response among subgroups, it may be unreliable to seek to predict the response to long-term treatment using only bronchodilator response data.

Because the majority of our COPD patients showed a mixed form of emphysema and bronchiolitis, and because the mixed-form subgroup included patients with a wide range of airflow obstruction, from mild to severe, we divided patients into four subgroups, including mild-mixed and severe-mixed. Although FEV_1 improved most in the obstruction-dominant subgroup, the mixed subgroups showed an intermediate improvement in FEV_1, compared with the emphysema-dominant subgroup. It is important to note that mild-mixed subgroup patients, with an average FEV_1 value of 61%, also showed a significant FEV_1 increase and dyspnea improvement after treatment, as did the severe-mixed subgroup. According to GOLD guidelines, regular treatment with ICS is recommended for symptomatic COPD patients with $FEV_1 < 50\%$ of predicted value, who also show repeated exacerbation.[1] However, considering the similar improvement in lung function and dyspnea in the two mixed subgroups, and the fact that almost 80% of patients (excluding the 20% of emphysema-dominant patients) demonstrated some improvement after treatment, combined LABA and ICS should be considered even for mild symptomatic COPD patients, especially if there is little evidence of emphysema.

Our study had some limitations. First, we did not separately analyze responses to LABA and ICS because we did not compare response to the combined LABA/ICS treatment with the effects of treatment with either LABA or ICS alone. However, other clinical studies have shown that combined LABA/ICS treatment may be superior to use of LABA or ICS alone.[32,33]

Second, we diagnosed and enrolled patients with COPD using GOLD guidelines,[1] although it is known that these guidelines (airway obstruction that is not fully reversible) lack precision in differentiating asthma from COPD. It is difficult to distinguish the two diseases in particular patients, especially smokers and/or the elderly. Also, the short-acting bronchodilator response is of limited value in differentiating between the two conditions. We excluded doctor-diagnosed asthma patients. To the best of our knowledge, this is the optimal method for differentiation of the two diseases in clinical practice.

Finally, our cut-off values for classifying patients into subgroups were arbitrary. We also used the mean values of FEV_1 and EI, an FEV_1 of 50% and an EI of 20%, in statistical analysis, and found that the principal results of the present study were not affected by such data manipulation. This means that even though our subgrouping was somewhat arbitrary, and although most COPD patients showed a mixed phenotype of airway obstruction and emphysema, the relative contribution of emphysema and airway obstruction in each patient is nonetheless important in the prediction of response to treatment.

In conclusion, it is important to examine between-patient differences to determine who will benefit from bronchodilators and/or ICS treatment. Patient subgrouping using FEV_1 and EI obtained by CT scanning may help to identify those who will respond to selective therapy. In the present study, we showed that the response to 3 months of LABA and ICS treatment varied with COPD subtype. Obstruction-dominant COPD patients showed the best response and emphysema-dominant patients the worst. Further studies on standardized identification of predominant phenotypes may improve our understanding of underlying COPD pathophysiology and should facilitate development of selective treatments for the complex disease labeled, in an over-simplification, as COPD.

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Conflicts of interest

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