



Characteristics of COPD phenotypes classified according to the findings of HRCT[☆]

Yoshiaki Kitaguchi^a, Keisaku Fujimoto^{a,*}, Keishi Kubo^a, Takayuki Honda^b

^aDepartment of Internal Medicine, Shinshu University School of Medicine, Matsumoto 390-8621, Japan

^bDepartment of Laboratory Medicine, Shinshu University School of Medicine, Matsumoto 390-8621, Japan

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Summary The present study was performed to clarify the clinical characteristics of chronic obstructive pulmonary disease (COPD) patients classified into phenotypes according to the dominancy of emphysema and the presence of bronchial wall thickening evaluated by chest high-resolution computed tomography (HRCT).

Eighty-five patients with stable COPD ($FEV_1 \leq 80\%$) were examined by chest HRCT. Emphysematous changes and bronchial wall thickening were evaluated visually, and COPD patients were classified into three phenotypes: absence of emphysema, with little emphysema with or without bronchial wall thickening (A phenotype), emphysema without bronchial wall thickening (E phenotype), and emphysema with bronchial wall thickening phenotype (M phenotype). Clinical characteristics were compared among the three phenotypes.

The A phenotype group showed a higher prevalence of subjects who had never smoked and patients with wheezing, higher values of body mass index (BMI) and DLco, milder lung hyperinflation, and greater reversibility of airflow limitation responsive to inhaled β_2 -agonist as compared with the other phenotypes. The degree of emphysema was significantly associated with Brinkman index, lower BMI, decrease in DLco, lower FEV_1/FVC . The presence of bronchial wall thickening in A- and M-phenotype was significantly associated with reversibility responsive to treatment with inhaled corticosteroid and sputum eosinophilia.

These findings suggest that the morphological phenotypes of COPD show several clinical characteristics and different responsiveness to treatment with bronchodilators and inhaled corticosteroids.

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*Corresponding author. Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. Tel.: +81 263 37 2631; fax: +81 263 36 3722.

E-mail address: keisaku@hsp.md.shinshu-u.ac.jp (K. Fujimoto).

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow limitation that is not fully reversible, and that is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases according to the GOLD guidelines.¹ Pathological changes characteristic of COPD are found in the central and peripheral airways, lung parenchyma, and pulmonary vasculature.^{2,3} The chronic airflow limitation is attributed to narrowing of the small airway lumen due to morphological changes and a decrease in lung elastic recoil due to parenchyma destruction. However, the relative contributions of these pathological changes of the large airway, small airway, and emphysema toward irreversible airflow limitation and clinical features vary between individuals, and the pathophysiological pathways that lead to emphysema and to small airway narrowing are independent of each other.^{4,5} For example, morphologically, some patients show severe emphysema accompanied with or without bronchial wall thickening. On the other hand, some patients do not show any apparent low attenuation areas (LAA) in the lung fields on chest high-resolution computed tomography (HRCT) but do show severe irreversible airflow limitation.⁵⁻⁷ Clinically, some patients show partial reversibility of airflow limitation in response to inhaled bronchodilators or inhaled corticosteroids (ICS), some patients show production of greater amounts of sputum and wheezing or sputum eosinophilia, and some complain of severe dyspnoea or mild hypoxemia.⁸⁻¹⁰

We hypothesised that the diversity of morphological changes may be associated with the differences in clinical features, including responsiveness to bronchodilators or ICS. To clarify the hypothesis, COPD was classified morphologically using HRCT into the three morphological phenotypes in accordance with the presence or absence of apparent emphysema and bronchial wall thickening, and examined the association with the morphological characteristics on HRCT and clinical characteristics including responsiveness to a bronchodilator or ICS and sputum eosinophilia in each phenotype. If the morphological phenotype will be associated with the characteristics of clinical features, we will be able to reconstruct the strategy for management of COPD in accordance with the each phenotype.

Methods

Subjects

One hundred and twenty-four stable COPD patients, with $FEV_1/FVC < 70\%$ and FEV_1 values less

than 80% of the predicted value after inhalation of a β_2 -agonist (moderate-to-severe COPD) were recruited from outpatient clinics of three general hospitals belonging to the investigation facilities organised by the Ministry of Health, Labour and Welfare in Japan from September 2002 to September 2004. COPD was diagnosed based on clinical history and symptoms including constant exertional dyspnoea, and pulmonary function characterised by irreversible airflow limitation ($FEV_1/FVC < 70\%$ after inhalation of a β_2 -agonist) in accordance with the GOLD guidelines.¹ Patients with late sequelae of pulmonary tuberculosis, diffuse panbronchiolitis, sinobronchitis, bronchiectasis or bronchiolitis obliterans due to autoimmune disease, severe cerebral-cardiovascular disease or events, or typical bronchial asthma who showed repeated episodes of paroxysmal dyspnoea characteristic of asthma and patients having a history of asthma were excluded from the study. We also left out of the analysis those patients for which the diagnosis of asthma/history of asthma could not be excluded. In addition, patients who had taken ICS or oral steroids, or had suffered from a respiratory tract infection or exacerbation of airway disease in the previous 6 weeks were also excluded. In the present study, we included COPD patients who had wheezing both at rest and on exertion or who showed partial reversibility of airflow limitation in response to β_2 -agonist inhalation or treatment with ICS,¹⁰ but their airflow limitation did not reach $FEV_1/FVC \geq 70\%$ and $FEV_1 \geq 80\%$ of predicted value after β_2 -agonist and ICS treatment. The study was approved by the local research ethics committee, and all patients gave their written informed consent to participation. This study was supported by the Ministry of Health, Labour and Welfare of Japan.

Protocol and measurements

During the first visit, the history of current illness, including complications and histories of smoking and exposure to noxious particles or gases other than tobacco, were obtained, and physical examination, laboratory examinations, including serum α_1 -antitrypsin, and chest X-ray, were performed. During the second visit, pulmonary function tests, including reversibility of airflow limitation by 20 μ g of inhaled procaterol hydrochloride, arterial blood gas analysis, and analysis of inflammatory cells in induced sputum, were examined. During the third visit, chest HRCT scanning was performed, and the patients were treated with 400 μ g/day of inhaled fluticasone propionate for 2-3 months.

After treatment, pulmonary measurements were again obtained by spirometry.

HRCT protocol and evaluation of the degree of emphysema and bronchial wall thickening

A helical CT scanner (Hi Speed Advantage; GE Medical Systems, Milwaukee, WI) was used for conventional contiguous scanning with a slice thickness of 10 mm to screen for chest abnormalities, followed by HRCT scanning at full inspiration (at TLC level) with 1-mm collimation of (120 kVp, 200 mA, pitch 1.0). Four slices 1 mm thick were obtained at three anatomic levels at full inspiration, i.e., near the superior margin of the aortic arch (level of the upper lung field), at the level of the carina (level of the middle lung field), and at the level of the orifice of the inferior pulmonary veins (level of the lower lung field). HRCT images were photographed with a window setting appropriate for the lungs (window level from -700 to -900 HU; width, from 800 to 1000 HU). Emphysema was scored visually as LAA in bilateral upper, middle, and lower lung fields according to the method of Goddard et al.¹¹ The score in each dimension was calculated according to the ratio of LAA to occupy in the lung field as follows: score 0, LAA < 5%; score 1, 5% ≤ LAA < 25%; score 2, 25% ≤ LAA < 50%; score 3, 50% ≤ LAA < 75%; score 4, 75% ≥ LAA. The severity of emphysema was graded in accordance with the sum of scores at 6 dimensions as follows: grade 0, total score = 0; grade 1, total score = 1–6; grade 2, total score = 7–12; grade 3, total score = 13–18; grade 4, total score = 19–24. Bronchial wall thickening in all lung fields was graded visually as reported previously¹² as follows: grade 0, bronchial wall < 30% adjacent pulmonary artery diameter; grade 1, 30% ≤ bronchial wall < 50% adjacent pulmonary artery diameter; grade 2, bronchial wall ≥ 50% adjacent pulmonary artery diameter. HRCT images were analyzed independently by two pulmonologists with no knowledge of the patients' clinical information.

Classification of COPD into three phenotypes according to the findings of HRCT

The patients were classified into the three phenotypes according to the visual HRCT findings as follows: A phenotype is characterized by the absence of emphysema or little emphysema showing LAA ≤ grade 1 regardless of having bronchial wall thickening. E phenotype is characterized by the presence of apparent emphysema of grade 2 and more than grade 2 (≥ grade 2) without

bronchial wall thickening. M phenotype is characterized by the combination with the presence of apparent emphysema ≥ grade 2 and bronchial wall thickening ≥ grade 1.

Pulmonary function tests

Spirometry and measurement of DLco were performed with a pulmonary function testing system (Chestac-55V; Chest Co. Ltd., Tokyo, Japan). To evaluate the reversibility of airflow limitation, FEV₁ was measured before and 20 min after inhalation of β_2 -agonist (20 μ g of procaterol hydrochloride) by aerosol (metered-dose inhaler, MDI) with spacer. Functional residual capacity (FRC) was measured using a Body Box (Medgraphic, Ann Arbor, MI), after which the subjects immediately inspired to total lung capacity (TLC) and expired maximally to residual volume (RV), thus allowing calculation of lung volume and RV/TLC. Pulmonary function test was performed by two special technicians according to the ATS criterion. Two or three tests were repeated to guarantee repeatability.

Sputum collection and analysis

We collected sputum induced by the inhalation of hypertonic saline as described previously.⁹ Briefly, the method of sputum induction was as follows. Prior to the induction of sputum, all subjects inhaled a β_2 -agonist, and 3.5% hypertonic saline nebulised with an ultrasonic nebuliser (NE-V10B, Omron, Tokyo, Japan). If appropriate sputum could not be obtained, 4.5% hypertonic saline was nebulised for periods of 5 min. The nebulisation was continued for at least 10 min and stopped after 15 min or earlier if ≥ 2 ml of a sputum sample of good quality was obtained. The collected sputum was then separated from contaminating saliva by macroscopic examination, and the mucus plug was removed from the dish to a sterile plastic container, after which the volume of the sample was determined. The sample was incubated with an equal volume of Hank's balanced salt solution (HBSS) containing 1 mM dithiothreitol (Sigma Chemicals, Poole, UK) at 37 °C for 15 min. After removing the residual mucous, the eluent was used to obtain total and differential cell counts. The total cell count except that of squamous cells was determined with a standard haemocytometer, normalized for weight and expressed as cells × 10⁵/g wet weight of sputum. Cell smears were prepared with a centrifuge (Autosmear, Sakura, Tokyo) and stained with May-Grünwald-Giemsa for differential cell counting. The slides

were coded and 500 cells were counted for the differential leukocyte count.

Data analysis

The values shown in the text and tables are means \pm SEM. The data distribution of the variables in the various groups was first assessed with Bartlett's test. When the data for the variables showed a normal distribution, they were compared by one-way analysis of variance (ANOVA), followed by multiple comparisons with the Tukey–Kramer method. When the data for the variables did not show a normal distribution, the variables were compared with the Kruskal–Wallis test, followed by multiple comparisons among groups with the non-parametric Tukey–Kramer method. Simple correlations between variables were examined by calculating Pearson's product correlation coefficient. Multiple, stepwise, logistic regression analysis was performed to identify which variables were significantly responsible for the presence of emphysema \geq grade 2, or the presence of bronchial wall thickening. Multiple, stepwise, linear regression analysis was also performed to identify which variables were significantly associated with the reversibility in response to a β_2 -agonist or the treatment with ICS and the total score of LAA or the grade of bronchial wall thickening independently. The $P < 0.15$ was used first to identify candidate variables, and then removed variables from the regression model if P -value was more than 0.1. All statistical analyses were performed with the use of a Windows-compatible software program (Stat Flex ver. 5.0, Artech Ltd., Osaka, Japan). A P -value of less than 0.05 was considered significant for the results of all statistical analyses.

Results

Population of COPD phenotypes

Of one hundred and twenty-four patients recruited from our outpatient clinics, 7 patients complicated with pulmonary fibrosis, 2 patients complicated with late sequelae of pulmonary tuberculosis, 3 patients complicated with left-side heart failure, 2 patients complicated with lung cancer, and 3 patients complicated with sinobronchitis or bronchiectasis were excluded from this study. Seven patients who showed a history of asthma and/or repeated episodes of paroxysmal dyspnea characteristic of asthma were also excluded from this study. One patient whose FEV₁/FVC increased over

70% followed by the treatment with ICS was also excluded. Fourteen patients were missing because of failure to obtain appropriate sputum samples or to obtain agreement about the treatment with ICS or drop out during the treatment. Finally, eighty-five patients with moderate-to-severe COPD were examined in this study.

Eighty-five patients with COPD were classified into three phenotypes according to HRCT findings. Twenty-four patients with a mean LAA score of 0.1 ± 0.1 were classified into the A phenotype group (Fig. 1). Of the A phenotype group, 11 patients (12.9% of the total) showed no bronchial wall thickening, and 13 (15.3%) showed bronchial wall thickening (grade 1, 10 patients; grade 2, 3 patients). Thirty patients were classified into the E phenotype group. Thirty-one patients were classified into the M phenotype group (bronchial wall thickening grade 1, 28 patients; grade 2, 3 patients). There was no significant difference in total LAA score between the E phenotype and M phenotype groups (mean LAA score, 3.7 ± 0.1 in E phenotype and 3.5 ± 0.1 in M phenotype). The grade of bronchial wall thickening was significantly greater in the M phenotype group (1.1 ± 0.1 grade) than that in the A phenotype group (0.7 ± 0.1 grade).

Clinical features of each phenotype

There were no significant differences in age, sex, history of chronic sinusitis, age at starting smoking, and the prevalence of exposure to noxious particles or gases other than tobacco among the three phenotypes (Table 1). Body mass index (BMI) was significantly higher in the A phenotype group than in the E or M phenotype groups, and only 12.5% of patients in the A phenotype group showed BMI < 20 kg/m², whereas 46.7% and 51.6% of patients in the E phenotype and M phenotype groups, respectively, showed a decrease in BMI. The age at onset of exertional dyspnoea in the A phenotype group was significantly higher than that in the E phenotype group. The prevalence of those who had never smoked was significantly higher in the A phenotype group than in the other phenotype groups. Brinkman index in the E phenotype group was significantly increased as compared with those in the other phenotype groups. The number of patients receiving long-term oxygen therapy (LTOT) in the A phenotype group was significantly lower than that in the E phenotype group.

The prevalence of patients who complained of coughing and sputum production showed no

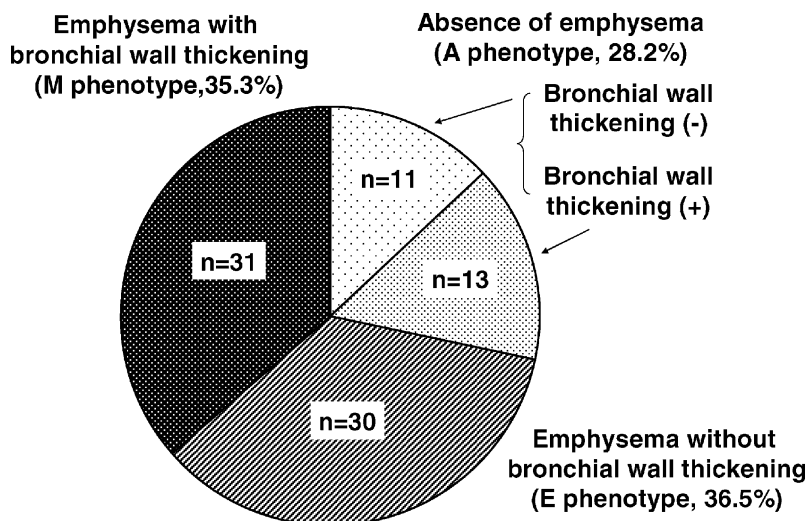


Figure 1 Constitution of the three phenotypes of COPD in the present study population classified according to the dominance of emphysema and bronchial wall thickening on chest HRCT findings. Absence of emphysema phenotype (A phenotype): little emphysema ($LAA \leq$ grade 1) with and without bronchial wall thickening. Emphysema without bronchial wall thickening phenotype (E phenotype): emphysema \geq grade 2 without bronchial wall thickening. Emphysema with bronchial wall thickening phenotype (M phenotype): combination of emphysema \geq grade 2 and bronchial wall thickening.

Table 1 Characteristics of three phenotypes of COPD.

	E phenotype (n = 30)	M phenotype (n = 31)	A phenotype (n = 24)
Age (yr)	70.7 ± 1.0	73.1 ± 1.0	69.9 ± 1.8
Sex (F/M)	3/27	4/27	6/18
Body mass index (kg/m ²)	20.3 ± 0.5	19.8 ± 0.6	23.2 ± 0.6 ^{**} , ^{††}
Age onset dyspnoea (yr)	61.8 ± 1.4	64.2 ± 1.4	65.7 ± 2.2 [*]
History of sinusitis, n	7(23.3%)	5(16.1%)	6(25.0%)
Never smoker, n	0(0.0%)	0(0.0%)	7(29.2%) ^{**}
Bl (packs-yr)	66.1 ± 4.7	51.8 ± 5.3	38.9 ± 6.9 ^{**} , ^{††}
Age at starting smoking	21.0 ± 0.5	21.2 ± 0.8 [*]	20.5 ± 0.7 ^{**}
History of noxious particles or gases other than tobacco, n	12 (41.4%)	14(50.0%)	10(43.8%)
LTOT, n	8(26.7%)	6(22.6%)	1(4.2%) [*]

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema; Bl, Brinkman index; LTOT, long-term oxygen therapy.

^{*} $P < 0.05$.

^{**} $P < 0.01$ vs. E phenotype.

^{††} $P < 0.01$ vs. M phenotype.

significant differences among the three phenotypes (Table 2). The A phenotype group included many more patients who complained of wheezing both at rest and on exertion as compared with the other phenotype groups. Fletcher, Hugh-Jones dyspnoea score was significantly lower in the A phenotype group as compared with the other phenotype groups.

Pulmonary function tests and inflammatory cell analysis of induced sputum

In the A phenotype group, lung hyperinflation expressed by increased RV and TLC was significantly milder and FEV₁/FVC and DLco were significantly higher as compared with those in the other phenotype groups, although there was no

Table 2 Symptoms in the three phenotypes of COPD.

	E phenotype (n = 30)	M phenotype (n = 31)	A phenotype (n = 24)
Sputum			
None	22.3%	16.1%	12.5%
A little	50.5%	54.8%	58.3%
Large amount	26.7%	29.0%	29.2%
Cough			
None	50.0%	45.2%	45.8%
Productive cough	13.3%	12.9%	12.5%
Non-productive cough	36.7%	41.9%	41.7%
Wheezing			
None	53.3%	32.3%	20.8%*
On exertion	16.7%	19.3%	8.4%
Both exertion and rest	30.0%	48.4%	70.8%*,†
Dyspnea (F-H-J classification)	3.0 ± 0.2	3.2 ± 0.2	2.3 ± 0.2*,††

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema; F-H-J, Flether, Hugh-Jones.

* $P < 0.05$ vs. E phenotype.

† $P < 0.05$

†† $P < 0.01$ vs. M phenotype.

difference in FEV₁ among the three phenotypes (Table 3). Most of the patients in the A phenotype group showed DLco values within the normal range. Arterial blood gas analysis showed no significant differences among the three phenotypes. On laboratory analysis, there were no cases of α_1 -antitrypsin deficiency, and there were no significant differences in serum CRP, α_1 -antitrypsin or peripheral eosinophil counts among the three phenotypes.

The increases in FEV₁ in response to a β_2 -agonist were significantly higher in the A phenotype group as compared with the other phenotype groups and the increase in FEV₁ in response to treatment with 400 μ g/day of inhaled fluticasone propionate for 2–3 months were significantly higher in A and M phenotype groups than in the E phenotype group (Table 4). There were no significant differences in the total cell counts in induced sputum. However, eosinophil counts were significantly higher in the A- and M-phenotype groups as compared with the E phenotype group. When the patients were classified into two groups according to the reversibility of airflow limitation, defined as an increase in FEV₁ of >12% and 200 ml from baseline values, in response to inhaled β_2 -agonist or treatment with ICS for 2–3 months,¹¹ the prevalence of patients showing reversibility was significantly higher in the A phenotype group than in the E phenotype group (Table 5). The patients who showed reversibility in response to a β_2 -agonist also showed a significantly

greater increase in FEV₁ after ICS treatment, and there was a significant correlation between the reversibility in response to β_2 -agonist and the treatment with ICS ($r = 0.39$, $P < 0.01$). Furthermore, the reversibility in response to the treatment with an ICS was also significantly correlated with sputum eosinophilia ($r = 0.45$, $P < 0.01$). Multiple, stepwise, linear regression analysis showed that lower total LAA score ($P = 0.001$) and sputum eosinophil numbers ($P = 0.029$) were significant determinants for the reversibility in response to β_2 -agonist, and the symptom of wheezing both at rest and on exertion ($P = 0.047$), sputum eosinophil numbers ($P = 0.013$), and the grade of bronchial wall thickening ($P = 0.045$) were significant determinants for the reversibility in response to the treatment with ICS.

Characteristics of the patients with apparent emphysema or bronchial wall thickening among all COPD patients

When the patients in A phenotype were compared with the other patients in E and M phenotype, who showed apparent emphysema \geq grade 2 by the multiple, stepwise, logistic regression analysis, A phenotype was significantly characterized by lower Brinkman index ($P = 0.028$), no decreases in BMI ($P = 0.009$) and DLco ($P = 0.016$), and milder

Table 3 Pulmonary function and laboratory data in three phenotypes of COPD.

	E phenotype (n = 30)	M phenotype (n = 31)	A phenotype (n = 24)
VC (% of pred.)	97.3±3.4	90.4±2.7	86.1±4.1*
FEV ₁ (%of pred.)	47.4±3.6	46.1±2.8	51.0±2.9
FEV ₁ /FVC (%)	42.7±2.2	46.1±2.0	55.2±2.0**,*†
RV (% of pred.)	242.6±14.3	209.9±11.4	205.6±11.7*
RV/TLC (%)	56.3±1.9	56.2±2.3	56.9±2.0
FRC (% of pred.)	145.2±6.6	137.4±6.9	136.8±7.9
TLC (% of pred.)	139.7±4.4	123.3±3.1*	120.7±3.8**,*†
DLco (% of pred.)	51.3±3.5	60.6±3.6	84.9±4.3**,*†
PaO ₂ (torr)	67.4±2.4	71.8±1.9	70.3±2.2
PaCO ₂ (torr)	41.0±0.9	41.7±0.9	42.0±1.1
CRP (mg/dl)	0.36±0.10	0.21±0.04	0.47±0.17
α ₁ -AT (mg/dl)	154.0±10.0	148.0±4.7	137.0±14.1
P. eosinophil (/mm ³)	164.3±59.0	299.7±56.5	254.4±47.5

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema; CRP, C reactive protein; α₁-AT, α₁-antitrypsin; P. eosinophil, peripheral eosinophil counts.

*P<0.05.

**P<0.05 vs. E phenotype.

††P<0.01 vs. M phenotype.

Table 4 Responses to β₂-agonist and inhaled corticosteroid, and cell analysis in induced sputum.

	E phenotype (n = 30)	M phenotype (n = 31)	A phenotype (n = 24)
Response to β ₂ agonist			
ΔFEV ₁ (ml)	94.0±18.1	133.7±21.6	253.3±42.4**,*†
%Change of FEV ₁ (%)	11.1±2.7	13.5±2.6	19.3±3.1*
Response to treatment with inhaled corticosteroid			
ΔFEV ₁ (ml)	116.2±26.9	247.9±43.6*	313.9±74.4*
% Change of FEV ₁ (%)	15.4±3.3	24.6±5.2	28.8±7.1
Sputum cell differentiation			
Total cell (×10 ⁵ /g)	104.1±38.6	157.0±42.4	82.3±23.5
Macrophage (%)	10.4±1.8	10.0±0.8	12.2±3.7
Lymphocyte (%)	3.6±0.7	3.6±0.7	4.1±0.7
Neutrophil (%)	83.6±2.4	79.0±4.7	74.0±5.6
Eosinophil (%)	2.4±0.7	7.5±2.4*	9.7±3.3*

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema.

*P<0.05

**P<0.05 vs. E phenotype.

†P<0.01 vs. M phenotype.

airflow limitation. When compared the patients in A phenotype with and without bronchial wall thickening, Fletcher, Hugh-Jones dyspnoea score (1.8±0.3 vs. 2.7±0.2, P<0.05) and peripheral eosinophil numbers (122±25 vs. 353±69/mm³, P<0.05) were significantly higher in the patients

with bronchial wall thickening. However, there were no significant differences in provocation of noxious particles or gases, pulmonary function, reversibility, and sputum findings

Multiple, stepwise, logistic regression analysis revealed that the presence of emphysema ≥ grade

Table 5 Comparison of patients who showed partial reversibility [increase in FEV₁ > 200 ml and 12%] in response to β_2 -agonist or inhaled corticosteroid.

	Reversibility [–]	Reversibility (+)
(A) Responsiveness to β_2 -agonist		
E/M/A phenotype, <i>n</i>	27/26/13	3*/5/11**
Response to β_2 -agonist		
Δ FEV ₁ (ml)	81.8 ± 8.2	358.0 ± 31.3**
% change of FEV ₁ (%)	8.5 ± 1.0	31.9 ± 3.9**
Response to inhaled corticosteroid		
Δ FEV ₁ (ml)	167.8 ± 27.0	358.8 ± 70.8*
% change of FEV ₁ (%)	16.7 ± 2.2	40.4 ± 9.3*
Sputum eosinophils (%)	4.2 ± 1.1	12.2 ± 3.9
(B) Responsiveness to inhaled corticosteroid		
E/M/A phenotype, <i>n</i>	23/2/12	7/10/12*
Response to β_2 -agonist		
Δ FEV ₁ (ml)	102.1 ± 14.2	232.8 ± 32.7**
% change of FEV ₁ (%)	9.1 ± 1.2	23.4 ± 3.5**
Response to inhaled corticosteroid		
Δ FEV ₁ (ml)	67.9 ± 14.4	418.6 ± 40.7**
% change of FEV ₁ (%)	8.4 ± 1.5	41.2 ± 4.8**
Sputum eosinophils (%)	2.2 ± 0.5	14.3 ± 3.3**

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema.

**P* < 0.05.

***P* < 0.01 vs. Reversibility(—).

2 was significantly associated with Brinkman index (*P* = 0.028), lower BMI (*P* = 0.009), decrease in DLco (*P* = 0.016), and lower FEV₁/FVC (*P* = 0.007), and the presence of bronchial wall thickening was significantly associated with Brinkman index (*P* = 0.032), Fletcher, Hugh-Jones dyspnoea score (*P* = 0.005), and reversibility in response to the treatment with ICS (*P* = 0.019) independently. Multiple, stepwise, linear regression analysis also showed a significant regression model for the total score of LAA (*r* = 0.79) comprised of Brinkman index (*P* = 0.046), without wheezing both at rest and on exertion (*P* = 0.036), lower BMI (*P* = 0.003), lower FEV₁/FVC (*P* < 0.001), and decrease in DLco (*P* < 0.001). This model accounted for 62.1% of total score of LAA. The regression model for the grade of bronchial wall thickening was significant (*r* = 0.51) and comprised of the following determinants; Fletcher, Hugh-Jones dyspnoea score (*P* = 0.013), reversibility in response to the treatment with ICS (*P* = 0.099), and sputum eosinophilia (*P* = 0.002). However, there was a significant correlation between reversibility in response to the treatment with an inhaled corticosteroid and sputum eosinophilia (*r* = 0.45, *P* < 0.01). If sputum eosinophilia was removed, the regression model was also significant (*r* = 0.44, *P* < 0.01) and reversibility in

response to the treatment with ICS became more significant (*P* = 0.004).

Discussion

In the present study, 85 stable moderate-to-severe COPD patients were classified into groups showing absence or less of emphysema phenotype (A phenotype), emphysema without bronchial wall thickening phenotype (E phenotype) and emphysema with bronchial wall thickening phenotype (M phenotype) in accordance with the findings of HRCT. In the A phenotype group, the prevalence of those who had never smoked and patients with wheezing not only on exertion but also at rest, and the reversibility of airflow limitation in response to inhaled β_2 agonist were significantly greater as compared with those in the other phenotype groups. Patients with the A phenotype also showed significantly greater reversibility of airflow limitation in response to treatment with ICS, and a significant increase in sputum eosinophil counts as compared with those in the E phenotype group. In the M phenotype group, the reversibility of airflow limitation in response to ICS was also significantly greater and the eosinophil

counts in sputum were higher than those in the E phenotype group. Multiple, stepwise, linear regression analysis revealed that Brinkman index, lower BMI, decrease in DLco, lower FEV₁/FVC, and no symptom of wheezes both at rest and on exertion were significant determinants for the total score of LAA. When all patients were classified into the two groups according to the presence or absence of bronchial wall thickening, dyspnoea score, reversibility in response to the treatment with ICS, and sputum eosinophilia were significant determinants for the presence of bronchial wall thickening. These findings suggested that the morphological phenotypes of COPD classified according to dominance of emphysema and the presence of bronchial wall thickening show several clinical characteristics and different responses to the treatment with bronchodilators and ICS.

COPD is a disease state characterized by airflow limitation that is not fully reversible. However, the degree of reversibility of the airflow limitation in response to bronchodilators or treatment with ICS varies among individuals.^{9,13,14} We have shown that, in patients with COPD, airway eosinophilia is related to reversibility of airflow limitation after a short course of oral steroids.⁹ It has also been demonstrated that COPD patients with partial reversibility of airflow limitation in response to a β_2 -agonist show sputum eosinophilia as compared with healthy controls.¹⁰ In the present study, the patients who showed reversibility in response to a β_2 -agonist or treatment with ICS showed higher eosinophil counts in induced sputum as compared with those who showed no reversibility, and there was a significant correlation between the reversibility in response to ICS and sputum eosinophilia. Complete reversibility of airflow limitation is typical of asthma, but partially reversible airflow limitation may be present in patients with COPD who have no evidence of asthma or atopy.¹⁵ Indeed, significant reversibility of airflow limitation after use of bronchodilators and/or corticosteroids may be present in up to 30% of stable patients with COPD.¹⁶ However, there have been no previous reports about the characteristics on chest HRCT imaging of patients with COPD showing partial reversibility of airflow limitation. The present study indicated that the prevalence of patients showing partial reversibility of airflow limitation in response to a β_2 -agonist or treatment with ICS was higher in A phenotype or M phenotype as compared with E phenotype. Multiple, stepwise, linear regression analysis also showed that the reversibility in response to a bronchodilator was significantly associated with lower emphysema score and increased eosinophils in sputum, and the presence of

bronchial wall thickening was significantly associated with the reversibility in response to the treatment with ICS being correlated with sputum eosinophilia, and twenty-three of 46 patients who showed bronchial wall thickening demonstrated reversibility in response to β_2 -agonist or ICS therapy. Therefore, bronchial wall thickening and/or sputum eosinophilia may be one indicator for predicting the better responsive to the treatment with ICS. Although increased airway wall thickening in the small airways, but not in the large airway, mainly contributes to airflow limitation in COPD,¹⁷ it has been demonstrated that the wall thickening in large or intermediate airways reflects the wall thickening in smaller airways.¹⁸ Therefore, patients who show bronchial wall thickening in large or intermediate airways on HRCT may also have increased airway inflammation and wall thickening in the small airway. The airway inflammation at small airways may be implicated in the reversibility by bronchodilators or ICS. On the contrary, in the E phenotype, the airway wall thickening in the small airway may be mild, and the airflow limitation is thought to be mainly due to the decreased elastic recoil. Therefore, it may be reasonable that patients in the E phenotype group hardly show reversibility in response to treatment with a bronchodilator or ICS. Reversibility in response to bronchodilators or the treatment with ICS and sputum eosinophilia are one of the typical characteristics of asthma, and bronchial wall thickening has been commonly observed in asthma developed airway remodelling secondary to long-standing asthma over time.¹⁹ However, it can not be concluded that these COPD patients were complicated with asthma, but these COPD patients may have an asthmatic component. It may become difficult to distinguish COPD from asthma showing irreversible airflow limitation due to airway remodelling in phenotype A, especially in never smokers.²⁰ Four subjects of seven never smokers in A phenotype showed sputum eosinophilia and partial reversibility in response to a β_2 -agonist and ICS (Δ FEV₁: 320, 360, 390, 1190 ml). Three of these subjects showed bronchial wall thickening. We cannot exclude the possibility that these patients may be asthma with fixed airflow limitation due to airway remodelling. However, these patients complained of coughing and dyspnoea on exertion, but did not have asthma history and show typical asthma symptoms, such as repeated episodes of paroxysmal dyspnoea. It is also possible that these patients with sputum eosinophilia can be diagnosed as having eosinophilic bronchitis, because some eosinophilic bronchitis patients develop irreversible airflow limitation.²¹ These findings may suggest

that some asthmatics with fixed airflow limitation due to airway remodelling and without typical asthma symptoms or eosinophilic bronchitis may be diagnosed as phenotype A in COPD. However, even if the four never smokers in A phenotype were excluded from the analysis, the reversibility in response to β_2 -agonist and ICS treatment was still significantly greater than that in E phenotype. Epidemiological studies have shown that 5–12% of patients with a diagnosis of COPD have never smoked,²² and these subjects are predominantly female and can be divided into at least two pathological subgroups, one of which may be associated with organ-specific autoimmune disease, while the other shows sputum eosinophilia.²³ In the present study, none of the patients had organ-specific autoimmune disease. Three of 7 never smokers in A phenotype had no sputum eosinophilia and did have sputum neutrophilia. Two of these patients had been exposed to passive smoking for a long time at home. Four patients had a history of long-standing provocation of noxious particles or gases other than tobacco, such as organic solvents, mushroom spores, and carbon dust from boiler. When compared the patients with and without bronchial wall thickening, there were no significant differences in provocation of noxious particles or gases, pulmonary function, reversibility, and sputum findings because of small numbers. It may be interesting the difference between the patients with and without bronchial wall thickening in phenotype A, further study will be needed.

It is important to determine the differences between patients who will benefit from bronchodilators or inhaled corticosteroid treatment and those who will not. Sputum inflammation parameters and morphological phenotypes assessed by HRCT may help in identifying those patients who will respond to selective therapy.

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H. Kimura, MD (Department of Internal Medicine II, Nara Medical University), and T. Horie (First, Department of Medicine, Nihon University), M. Sakatani, MD (Kinki Central Hospital).

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