

## ORIGINAL ARTICLE

# Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography

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## INTRODUCTION

COPD is a disease state characterized by airflow limitation that is not fully reversible, and that is usually progressive and associated with abnormal inflammatory responses of the lungs to noxious particles or

gases according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline.<sup>1</sup> Irreversible airflow limitation is defined as FEV<sub>1</sub>/FVC < 70% after inhalation of  $\beta_2$ -agonist. Prior to the GOLD guideline, COPD was classified into two phenotypes: emphysema type and chronic bronchitis type. However, emphysema was diagnosed based on the morphological and pathological features, but chronic bronchitis was defined based on the clinical symptomatic features, that is, cough and sputum. Therefore, COPD patients could not be classified completely into either phenotype. In the GOLD guideline, the terms 'emphysema' and 'chronic bronchitis' are no longer included in the definition of COPD.

Pathological changes characteristic of COPD are found in the central and peripheral airways, lung parenchyma and pulmonary vasculature.<sup>2</sup> The pathological changes of the central airway are characterized by increases in the number of epithelial goblet

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cells, enlarged submucosal mucous-secreting glands, increases in the amounts of smooth muscle and connective tissue in the airway wall, and airway cartilage degeneration. The pathological changes of the peripheral airways are characterized by goblet cell metaplasia of the epithelium, the presence of inflammatory exudates in the wall and lumen, reduced lumen, structural reorganization of the airway wall, increased smooth muscle and deposition of peribronchial connective tissue.<sup>3</sup> In COPD, the peripheral airways become the major site of airflow limitation together with the loss of lung elastic recoil.<sup>4</sup> However, the relative contributions of these pathological changes of the large airway, small airway, and emphysema towards 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.<sup>5,6</sup> Therefore, COPD is not a simple homogenous disease defined only as irreversible airflow limitation. Some patients show severe emphysema with irreversible airflow limitation, while some do not show any apparent low attenuation areas (LAA) in the lung fields on chest high-resolution CT (HRCT) despite severe irreversible airflow limitation.<sup>6</sup> In addition, some COPD patients show apparent bronchial wall thickening (BWT) on chest HRCT, while others do not. COPD could be classified into various phenotypes morphologically based on the findings of chest HRCT. Clinically, some patients show partial reversibility of airflow limitation in response to inhaled bronchodilator or corticosteroid, and some show production of large amounts of sputum, productive cough and wheezing on exertion.<sup>5,7</sup>

We hypothesized that the diversity of morphological changes may be associated with differences in clinical features, including responsiveness to bronchodilators or inhaled corticosteroids. To clarify the association between the morphological phenotypes and clinical features of COPD, we classified patients into three phenotypes according to the dominance of emphysema and BWT on chest HRCT and examined the clinical characteristics, including responsiveness to bronchodilator administration, in each phenotype.

## METHODS

### Subjects

A total of 180 patients with stable COPD, with FEV<sub>1</sub> values less than 80% of the predicted value (moderate to severe COPD), were recruited from the outpatient clinics of general hospitals belonging to the facilities involved in the investigation organized by the Ministry of Health, Labor, and Welfare, Japan, from September 2002 to September 2004. COPD was diagnosed based on clinical history and symptoms, including constant exertional dyspnoea and pulmonary function characterized by irreversible airflow limitation (FEV<sub>1</sub>/FVC < 70%) after inhalation of  $\beta_2$ -agonist in accordance with the GOLD guidelines.<sup>1</sup> Patients with late sequelae of pulmonary tuberculosis, diffuse pan-bronchiolitis, sinobronchitis, bronchiectasis or bron-

chiolitis obliterans due to autoimmune disease, or typical bronchial asthma that showed repeated episodes of paroxysmal dyspnoea characteristic of asthma and patients with a history of asthma were excluded from the study. Patients for whom a diagnosis of asthma/history of asthma could not be excluded were not included in the analysis. In addition, patients who 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 (regardless of the degree) in response to  $\beta_2$ -agonist inhalation, as long as their airflow limitation did not reach FEV<sub>1</sub>/FVC  $\geq$  70% and FEV<sub>1</sub>  $\geq$  80% of the predicted value after  $\beta_2$ -agonist treatment. The study was approved by the local research ethics committee, and all patients gave written informed consent to participate. This study was supported by the Ministry of Health, Labor, and Welfare of Japan.

### Protocol and measurements

At the first visit, history of current illness, including complications, smoking history and exposure to noxious particles or gases other than tobacco, was obtained and physical examination, laboratory assessments, including serum  $\alpha_1$ -antitrypsin, and CXR, were performed. During the second visit, pulmonary function tests, including reversibility of airflow limitation by inhalation of  $\beta_2$ -agonist and arterial blood gas analysis, were examined. To evaluate the reversibility of airflow limitation, FEV<sub>1</sub> was measured before and 20 min after inhalation of  $\beta_2$ -agonist. FRC was measured by body plethysmography, after which the subjects immediately inspired to TLC and expired maximally to RV, thus allowing calculation of lung volume and RV/TLC. During the second or third visit, chest HRCT scanning was performed. The intervals from first to second and from second to third visit were 1–2 weeks. In 122 patients whose medical records extended over a period of at least 3 years, the mean exacerbation rate and hospitalization rate per year for the previous 3 years were calculated, and compared among the three phenotypes. Exacerbation of COPD was determined according to the definition and criteria of Anthonisen *et al.*<sup>8</sup>

### HRCT protocol and evaluation of the degree of emphysema and BWT

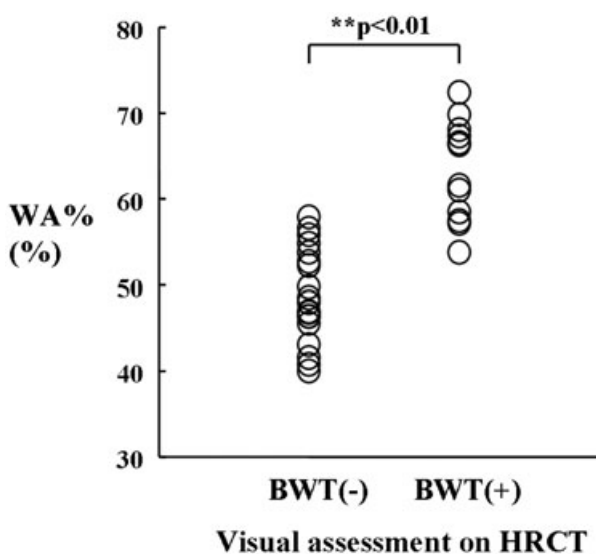
A helical CT scanner (Hi Speed Advantage; GE Medical Systems, Milwaukee, WI, USA) was used for conventional contiguous scanning with a slice thickness of 10 mm to screen for chest abnormalities, followed by HRCT scanning at full inspiration (at TLC level) with 1-mm collimation of (120 kVp, 200 mA, pitch 1.0). Four slices 1 mm thick were obtained at three anatomical levels at full inspiration, that is, 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). LAA were scored visually in each bilateral lung field according to the method of Goddard.<sup>9</sup> Total scores were calculated and the severity of emphysema was graded as follows: score 0, LAA < 5%; 1, 5% ≤ LAA < 25%; 2, 25% ≤ LAA < 50%; 3, 50% ≤ LAA < 75%; 4, 75% ≥ LAA. 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. BWT in all lung fields was graded visually as reported previously:<sup>10,11</sup> grade 0, none; grade 1, <50% adjacent pulmonary artery diameter; grade 2, ≥50% adjacent pulmonary artery diameter. HRCT images were analysed independently by two pulmonologists with no knowledge of the patients' clinical information. HRCT images are usually photographed with a window of -450 HU when evaluating BWT. Exactly, the wall area (WA) is underestimated when analysed HRCT images photographed with the window levels appropriate for the evaluation of LAA.<sup>12</sup> Prior to the study, we compared visual assessment of BWT at the trunk of the right B1 bronchus on HRCT images photographed with the window levels appropriate for the evaluation of LAA and WA% ( $WA\% = Aaw / (Aaw + Ai) \times 100$  with Aaw = airway wall area and Ai = airway luminal area) calculated with an electrical calliper using HRCT photographed with the window level of -450 HU in 31 individuals by a blind manner (Fig. 1). The mean values of WA% in COPD judged as having BWT and not having BWT were  $63.3\% \pm 1.7\%$  and  $48.8 \pm 1.3\%$ , respectively, and significantly increased in individuals judged as having BWT visually. The borderline of WA% separating BWT visually was approximately 57%, which is considered to be a proper value from previous reports.<sup>12</sup> Our preliminary observations suggested that HRCT images photographed with the same window levels when evaluating LAA can be used for visual assessment for BWT. Therefore, in the present study, BWT was evaluated using HRCT images similar to those used when evaluating LAA.

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

The patients were classified according to the visual HRCT findings as follows: absence of emphysema, which showed little emphysema and LAA ≤ grade 1 with and without BWT (A phenotype), emphysema without BWT phenotype, which showed apparent emphysema ≥ grade 2 without BWT (E phenotype), and emphysema with BWT phenotype that showed a combination of apparent emphysema = grade 2 and BWT of more than grade 1 (M phenotype).

We also examined reproducibility of visual assessment on phenotype. Intra-observer error was tested by one observer (Y.K.) assessing the phenotype in 70 randomly selected COPD subjects two times, separated by an interval of more than 6 months (Fig. 2a). Inter-observer error was determined by two observers



**Figure 1** Comparison visual assessment of BWT at the trunk of the right B1 bronchus on HRCT images photographed with the window levels appropriate for the evaluation of LAA and WA% calculated with an electrical calliper using HRCT photographed with the window level of -450 HU in 31 individuals by a blind manner. The mean value of WA% visually judged as having BWT ( $n = 12$ ) was significantly larger than that not having BWT ( $n = 19$ ) (\*\* $P < 0.01$ ). BWT, bronchial wall thickness; HRCT, high-resolution CT; LAA, low attenuation area;  $WA\% = Aaw / (Aaw + Ai) \times 100$ ; Aaw, airway wall area; Ai, airway luminal area.

(Y.K. and S.K.) assessing the phenotype in 70 randomly selected COPD patients (Fig. 2b). The rates of concordance in both intra-observer and inter-observer were 94.3%.

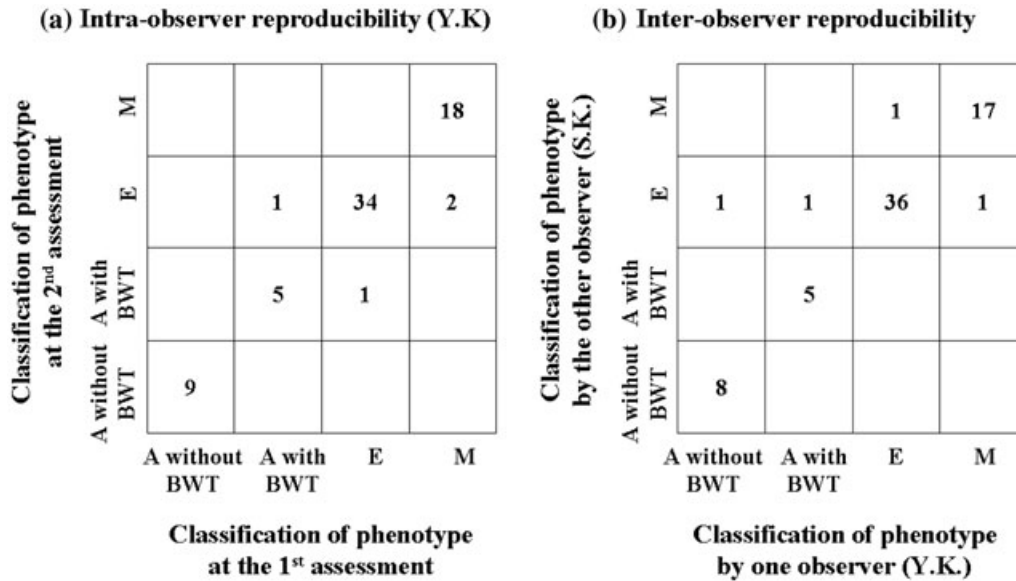
### Data analysis

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.  $P < 0.05$  was considered significant for all statistical analyses.

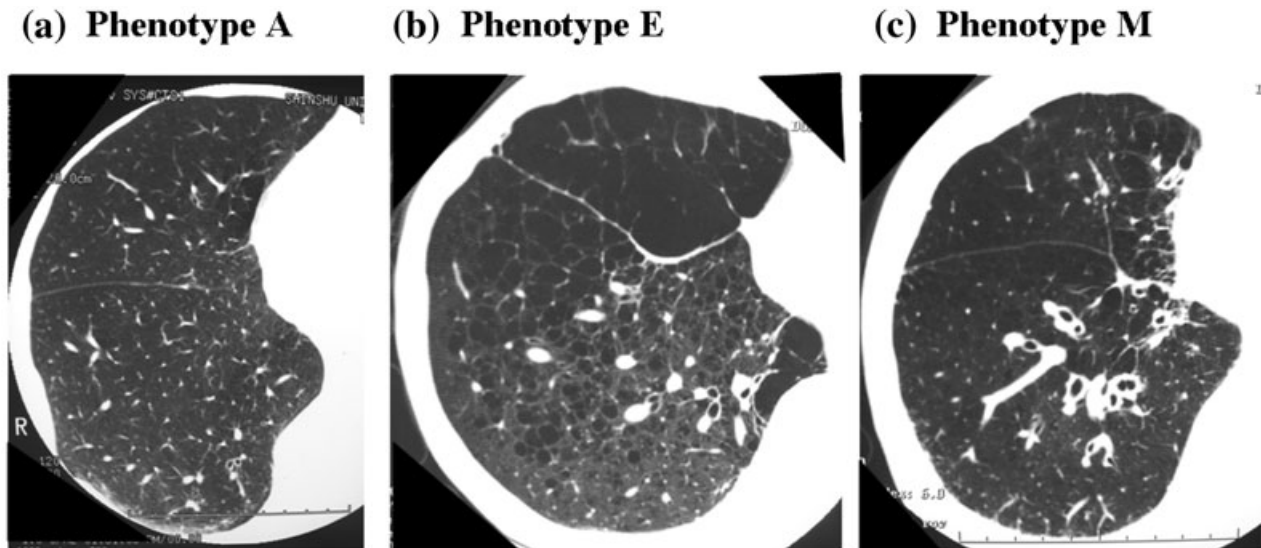
## RESULTS

### Population of COPD phenotypes

A total of 172 patients with COPD were classified into three phenotypes according to HRCT findings. The remaining eight patients with COPD showed severe



**Figure 2** (a) Intra-observer and (b) inter-observer reproducibility of classification into each phenotype (phenotype A with and without BWT, E and M). Intra-observer reproducibility was tested by one observer (Y.K.) assessing the phenotype in 70 randomly selected COPD subjects two times, separated by an interval of more than 6 months. Inter-observer reproducibility was determined by two observers (Y.K. and S.K.) assessing the phenotype in 70 randomly selected COPD patients. The number in each square represents the number of patients classified into each phenotype. The rates of concordance in both intra-observer and inter-observer were 94.3%. BWT, bronchial wall thickness, see text for definition of Phenotype A, E and M.

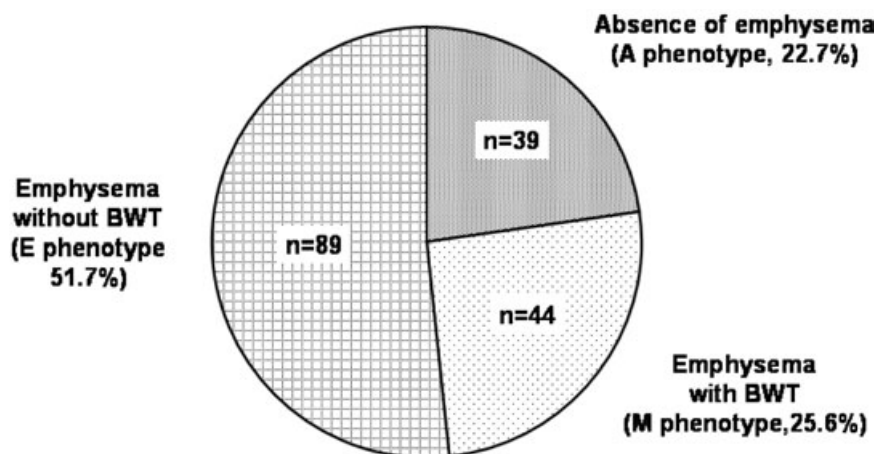


**Figure 3** Typical HRCT images in the (a) A phenotype, (b) E phenotype, and (c) M phenotype are shown. The A phenotype is defined as; absence or little emphysema (LAA grade 1) with or without bronchial wall thickening. The E phenotype is defined as emphysema grade 2 without bronchial wall thickening. The M phenotype is defined as combination of emphysema grade 2 and bronchial wall thickening. HRCT, high-resolution CT; LAA, low attenuation area.

emphysema with pulmonary fibrosis dominantly distributed in the bilateral lower lung fields. These patients were excluded from comparative analysis between COPD phenotypes. Figure 3 shows typical HRCT images in each phenotype. Thirty-nine patients with a mean LAA score of  $1.72 \pm 0.38$  were classified into the A phenotype (Fig. 4). In the A phenotype

group, 22 patients (12.8% of the total) showed no BWT, 17 (9.9%) showed BWT (grade 1, 14 patients; grade 2, three patients) and 23 patients (13.4%) showed no apparent emphysema (LAA grade 0). Eighty-nine patients were classified into the E phenotype, and their mean LAA score was  $21.0 \pm 0.5$ . Forty-four patients were classified into the M phenotype

**Figure 4** Constitution of the three phenotypes of COPD in the present study population classified according to the dominance of emphysema and bronchial wall thickening (BWT) on chest HRCT findings. Absence of emphysema (A phenotype): little emphysema (LAA grade 1) with or without BWT. Emphysema without BWT (E phenotype): emphysema grade 2 without BWT. Emphysema with BWT (M phenotype): combination of emphysema grade 2 and BWT. HRCT: high-resolution CT, LAA: low attenuation area.



**Table 1** Characteristics of three phenotypes of COPD

	E phenotype (n = 89)	M phenotype (n = 44)	A phenotype (n = 39)
Age (years)	68.1 ± 1.1	68.4 ± 1.7	68.3 ± 1.8
Gender, F/M	24/65	10/34	14/25
BMI (kg/m <sup>2</sup> )	20.5 ± 0.4	21.0 ± 0.5	22.4 ± 0.6**
Age onset dyspnoea (years)	68.1 ± 1.1	60.7 ± 1.8	63.3 ± 1.9
History of sinusitis, n (%)	13 (14.8)	10 (22.2)	7 (17.9)
Never smoked, n (%)	1 (1.1)	2 (4.5)	7 (17.9)**
History of smoking (pack-years)	54.7 ± 3.0	46.6 ± 5.1	41.8 ± 5.6*
Age at starting smoking (years)	22.2 ± 0.6	21.3 ± 0.8	20.7 ± 0.8
History of noxious particles or gases other than tobacco, n (%)	25 (28.7)	17 (39.5)	9 (23.1)
α <sub>1</sub> -AT (mg/dL)	148.7 ± 5.8	230.0 ± 79.1	131.0 ± 10.7
P. eosinophil (/mm <sup>3</sup> )	213.1 ± 19.4	264.9 ± 44.1	167.0 ± 27.6

\* $P < 0.05$  and \*\* $P < 0.01$  versus E phenotype.

Values are means ± SEM. E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; A phenotype, absence of emphysema; α<sub>1</sub>-AT, α<sub>1</sub>-antitrypsin; P. eosinophil, peripheral eosinophil counts.

(BWT grade 1, 34 patients; grade 2, 10 patients). There was no significant difference in total LAA score between the E phenotype and M phenotype groups (mean LAA score, 20.5 ± 0.6 in E phenotype group and 18.7 ± 0.9 in M phenotype group). The mean grade of BWT was significantly greater in the M phenotype group (1.2 ± 0.1 grade) than that in the A phenotype group (0.5 ± 0.1 grade).

### Clinical features of each phenotype

There were no significant differences in age, gender, age at onset of exertional dyspnoea, history of chronic sinusitis, age at starting smoking, or the prevalence of exposure to noxious particles or gases other than tobacco among the three phenotypes (Table 1). BMI was significantly higher in the A phenotype group than in the E or M phenotype groups, and only 17.9% of patients in the A phenotype group showed BMI < 20 kg/m<sup>2</sup>, whereas 49.4% and 34.1% of patients in the E and M phenotype groups showed a decreased

BMI respectively. The prevalence of subjects who had never smoked was significantly higher in the A phenotype group than in the other groups. Brinkman index in the E phenotype group was significantly increased as compared with the A phenotype group. On laboratory analysis, there were no cases of α<sub>1</sub>-antitrypsin deficiency, and there were no significant differences in serum α<sub>1</sub>-antitrypsin or peripheral eosinophil counts among the three phenotypes.

The prevalence of patients who did not complain of coughing, sputum production and wheezing was significantly higher in the E phenotype group than that in the M phenotype group (Table 2), and the M phenotype group included many more patients who complained of large amounts of sputum, productive cough and wheezing on exertion or both on exertion and at rest. The patients in the A phenotype group also complained of much more of wheezing both on exertion and at rest as compared with the E phenotype group. Whereas there were no significant differences in Fletcher, Hugh-Jones dyspnoea score among the three phenotypes, the exacerbation rate and hos-

**Table 2** Symptoms in the three phenotypes of COPD

	E phenotype (n = 89)	M phenotype (n = 44)	A phenotype (n = 39)
Sputum (%)			
None	31.8	14.0*	25.6
A little	52.9	55.8	56.5
Large amount	15.3	30.2*	17.9
Cough (%)			
None	54.1	30.2*	48.7
Productive cough	29.4	46.5*	30.8
Non-productive cough	16.5	23.3	20.5
Wheezing (%)			
None	64.7	33.3**	46.2
On exertion	11.8	26.2*	10.2
Both exertion and rest	23.5	40.5*	43.6*
Dyspnoea (F-H-J classification)	30 ± 0.1	2.9 ± 0.2	2.6 ± 0.2
Exacerbation rate (events/year)	0.59 ± 0.13	1.36 ± 0.35*	0.70 ± 0.22
Hospitalization rate due to exacerbation (events/year)	0.19 ± 0.05	0.42 ± 0.12*	0.20 ± 0.09

\* $P < 0.05$  and \*\* $P < 0.01$  versus E phenotype.

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, Flecher, Hugh-Jones.

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

	E phenotype (n = 89)	M phenotype (n = 44)	A phenotype (n = 39)
VC (% of pred.)	90.7 ± 1.8	90.0 ± 2.7	83.2 ± 3.3
FEV <sub>1</sub> (% of pred.)	46.4 ± 1.8	42.0 ± 2.2	47.5 ± 2.5 <sup>†</sup>
FEV <sub>1</sub> /FVC (%)	44.1 ± 1.3	43.5 ± 1.6	51.6 ± 1.8** <sup>†</sup>
RV (% of pred.)	188.0 ± 7.1	175.4 ± 7.3	166.6 ± 6.9*
RV/TLC (%)	50.3 ± 1.3	52.5 ± 1.4	51.8 ± 1.8
FRC (% of pred.)	124.3 ± 3.7	116.4 ± 5.1	116.7 ± 5.4
TLC (% of pred.)	122.1 ± 1.9	112.1 ± 2.2**	110.3 ± 3.1**
DL <sub>CO</sub> (% of pred.)	49.3 ± 2.1	61.6 ± 2.8**	78.2 ± 3.5** <sup>†</sup>
PaO <sub>2</sub> (mm Hg)	69.2 ± 1.3	69.1 ± 2.0	69.0 ± 2.0
PaCO <sub>2</sub> (mm Hg)	41.4 ± 0.6	42.8 ± 1.0	42.7 ± 0.9
Response to β <sub>2</sub> -agonist			
ΔFEV <sub>1</sub> (mL)	102.0 ± 12.2	154.2 ± 20.7*	153.8 ± 23.9*
% Change of FEV <sub>1</sub>	10.7 ± 1.5	16.8 ± 2.4*	13.1 ± 1.9

\* $P < 0.05$  and \*\* $P < 0.01$  versus E phenotype, <sup>†</sup> $P < 0.05$  and <sup>‡</sup> $P < 0.01$  versus M phenotype.

Values are means ± SEM. A phenotype, absence of emphysema; DL<sub>CO</sub>, diffusing capacity for carbon monoxide; E phenotype, emphysema without bronchial wall thickening; M phenotype, emphysema with bronchial wall thickening; pred., predicted.

pitalization rates were significantly higher in the M phenotype group than in the E phenotype group.

When comparing the patients with and without BWT in the A phenotype group, there were no significant differences in the prevalence of subjects who had never smoked (four without BWT and three with BWT), the history of exposure to noxious particles or gases other than tobacco, or clinical features between the two groups in the A phenotype. However, the patients with BWT in the A phenotype group were significantly older (65.0 ± 2.7 years without BWT vs. 72.5 ± 1.7 years with BWT) and had a later age at onset of dyspnoea (59.2 ± 2.8 years without BWT vs. 68.5 ± 1.9 years with BWT), and higher hospitalization

rate (0.01 ± 0.01 events/year with BWT vs. 0.38 ± 0.16 events/year) as compared with patients without BWT in the A phenotype group.

### Pulmonary function tests and reversibility in response to β<sub>2</sub>-agonist

In the A phenotype group, lung hyperinflation expressed by increased RV and TLC was milder and FEV<sub>1</sub>/FVC and diffusing capacity for carbon monoxide (DL<sub>CO</sub>) were significantly higher as compared with those in the other phenotype groups, although there was no difference in FEV<sub>1</sub> between A and E phenotype

groups (Table 3). Most of the patients in the A phenotype group showed DL<sub>CO</sub> values within the normal range. In addition, TLC and DL<sub>CO</sub> were significantly lower and higher, respectively, in the M as compared with the E phenotype group. Arterial blood gas analysis showed no significant differences among the three phenotypes. The increases in FEV<sub>1</sub> in response to  $\beta_2$ -agonist were significantly higher in the A and M phenotype groups as compared with the E phenotype group. The patients were classified into two groups according to the reversibility of airflow limitation, defined as an increase in FEV<sub>1</sub> of >12% and 200 mL from baseline values in response to inhaled  $\beta_2$ -agonist.<sup>7</sup> In the present study, 12 patients in the A phenotype group (30.8%), 14 in the M phenotype group (32.4%), and 10 in the E phenotype group (11.3%) showed partial reversibility in response to treatment with  $\beta_2$ -agonist. The prevalence of patients showing partial reversibility was significantly higher in the A and M phenotype groups than in the E phenotype group.

There were no significant differences in FEV<sub>1</sub> ( $47.6 \pm 3.9\%$  without BWT vs.  $47.3 \pm 3.1\%$  with BWT) or the reversibility in response to a  $\beta_2$ -agonist ( $\Delta$ FEV<sub>1</sub>;  $152.0 \pm 31.4$  mL without BWT vs.  $156.4 \pm 38.6$  mL with BWT, % $\Delta$ FEV<sub>1</sub>;  $13.3 \pm 2.4\%$  without BWT vs.  $12.6 \pm 3.3\%$  with BWT) between patients with and without BWT in the phenotype A group.

## DISCUSSION

In the present study, 172 patients with stable moderate-to-severe COPD were classified into three groups showing the absence of emphysema (A phenotype), emphysema without BWT phenotype (E phenotype), or emphysema with BWT (M phenotype) according to the findings of HRCT. The A phenotype showed a higher prevalence of subjects who had never smoked and of patients with wheezing both on exertion and at rest, higher values of BMI and DL<sub>CO</sub>, milder lung hyperinflation, and greater reversibility of  $\beta_2$ -agonist-responsive airflow limitation as compared with the E phenotype. The M phenotype group showed a higher prevalence of patients who complained of large amounts of sputum, productive cough and wheezing not only on exertion but also at rest, higher rates of exacerbation or hospitalization, and greater reversibility of airflow limitation responsive to inhaled  $\beta_2$ -agonist as compared with the E phenotype. These findings suggested that the morphological phenotypes of COPD classified according to dominance of emphysema and the presence of BWT show several clinical characteristics and different responses to treatment with a bronchodilator.

In this study, the presence of emphysematous changes and BWT were evaluated by semi-quantitative instead of quantitative methods. LAA% is usually used to evaluate emphysematous changes quantitatively. However, the critical value of LAA% = 30% can be used to differentiate between normal or mildly diseased lungs and those with very severe disease.<sup>6</sup> The LAA% on its own is not sufficient to distinguish reliably between normal subjects and mild emphysema-

tous patients because the large variation in LAA% between individuals creates substantial overlap between these two groups. In addition, the decrease in attenuation of the lung field due to obliterative bronchiolitis could not be differentiated from LAA due to emphysema. Mishima *et al.*<sup>13</sup> demonstrated that the complexity of the terminal airspace geometry is a sensitive and powerful parameter for the detection of the terminal airspace enlargement that occurs in early emphysema. The BWT is usually evaluated as WA% or T/D ratio, defined as wall thickness (T) divided by the total diameter of the bronchus (D), at the right apical segmental bronchus measured automatically on the computer or with electrical callipers,<sup>6</sup> especially in patients with asthma.<sup>14</sup> However, WA% and lumen area vary with anatomical location in the tracheobronchial tree.<sup>15</sup> Nakano *et al.* reported the highly significant relationship between WA% in the apical segmental bronchus and the additional airways in smokers;<sup>6</sup> however, the intercept was not zero and the slope was not unity. It has also been suggested that visual scoring is nearly precise and clinically more practical than quantitative assessment in patients with emphysema.<sup>16</sup> Prior to the study, the visual assessment of BWT at trunk of the right apical bronchus and WA% were compared and confirmed that visual scoring can be used for assessment of BWT. Therefore, we evaluated the presence of emphysematous changes and BWT by semi-quantitative instead of quantitative methods in the present study.

In COPD, airflow limitation is due mainly to loss of elastic recoil and narrowing of small airways.<sup>4</sup> In the A phenotype, the structural changes at the site of the small airway are the most important causes of airflow limitation. The A phenotype is not a feature at an early stage of COPD because the severity of airflow limitation was the same as in the emphysema-dominant phenotype. These phenotypes may be the result of differences in sensitivity to smoking for developing emphysema or airway structural changes or to differences in noxious particles or gases to which the subjects were exposed.<sup>17</sup> The A phenotype group was characterized by an increased prevalence of subjects who had never smoked and patients with wheezing not only on exertion but also at rest, better partial improvement in airflow limitation in response to inhaled  $\beta_2$ -agonist, and small decreases in DL<sub>CO</sub>.<sup>5</sup> DL<sub>CO</sub>, an index of gas exchange in alveolar capillary areas, is lowered in the emphysema-dominant phenotype reflecting alveolar destruction,<sup>18</sup> and reduction of DL<sub>CO</sub> is correlated more strongly with the severity of emphysema, as determined by HRCT analysis.<sup>19</sup> Therefore, it is reasonable that DL<sub>CO</sub> in the A phenotype was not decreased as markedly as in the emphysema-dominant phenotype. Twelve of 39 patients in the A phenotype group showed partial reversibility, and three of these patients complained of wheezing not only on exertion but also at rest. Complete reversibility of airflow limitation is typical of asthma, but partially reversible airflow limitation may be present in patients with remodelled airway asthma or in patients with COPD who have no evidence of asthma or atopy.<sup>20</sup> 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.<sup>21</sup> Most patients with asthma with irreversible airflow limitation have BWT on chest HRCT.<sup>14</sup> Seventeen of the patients in the A phenotype group showed BWT, but 22 did not. However, there were no significant differences in symptoms or pulmonary function, including reversibility of airflow limitation, between the two groups, and the patients with BWT and had a symptom onset at an elder age, and higher hospitalization rate as compared with patients without BWT. It is possible that long-standing persistent airway inflammation may result in BWT. The irreversible airflow limitation in phenotype A, especially in patients without BWT, may be due to narrowing of the small airways as described in obliterative bronchiolitis. It may be difficult to distinguish COPD from asthma without typical asthma symptoms showing irreversible airflow limitation due to airway remodelling secondary to long-standing asthma over time, especially in subjects who have never smoked in the A phenotype group.<sup>22</sup>

Of seven subjects who had never smoked in the A phenotype group, three had a long-standing history of passive smoking, and three had a history of long-term exposure to occupational dust (a boiler operator, a mushroom cultivator and a worker using chemicals, such as isocyanates). The irreversible airflow limitation in these patients may have been associated with passive smoking and occupational exposure to dust.

Of 17 patients in the A phenotype group with BWT, three who had never smoked and one ex-smoker who had peripheral eosinophilia showed partial reversibility in response to bronchodilator treatment. We cannot exclude the possibility that these four patients may have had asthma with fixed airflow limitation due to airway remodelling. We treated these patients with an inhaled corticosteroid for at least 2 months, but their FEV<sub>1</sub>/FVC did not reach more than 70% and the mean increase in FEV<sub>1</sub> was 298.2 ± 56.9 mL. Furthermore, the results were similar if these four subjects were excluded from the study.

The M phenotype group also showed a greater increase in FEV<sub>1</sub> in response to β<sub>2</sub>-agonist treatment as compared with the E phenotype. Increased airway wall thickening in the small airways, but not in the large airway, contributes mainly to airflow limitation in COPD. However, it has been demonstrated that wall thickening in large or intermediate airways reflects the wall thickening in smaller airways.<sup>23</sup> Patients who show BWT in large or intermediate airways on HRCT may also have increased BWT in the small airway. On the other hand, in the emphysema without BWT phenotype, the BWT in the small airway may be mild, and the airflow limitation is thought to be due mainly to the decreased elastic recoil. Therefore, it is reasonable that patients with the E phenotype showed little reversibility of airflow limitation in response to bronchodilator treatment.

The BWT on chest HRCT in the M phenotype group may reflect enlarged submucosal mucus-secreting glands and increases in the amounts of smooth muscle, and it is not surprising that patients with BWT complained of large amounts of sputum, productive

cough and wheezing. O'Brien and colleagues reported HRCT evidence of bronchiectasis in 29% of COPD patients, and patients with bronchiectasis showed increased evidence of sputum.<sup>24</sup> In the present study, most of the patients showing BWT on HRCT also showed bronchiectatic changes. It is of interest that the M phenotype showed the highest rate of exacerbation or hospitalization among the three phenotypes. Exacerbation is associated with increases in airway inflammation due to various causes, such as viral or bacterial infection or environmental factors.<sup>25</sup> It has been demonstrated that the exacerbation frequency is associated with the severity of COPD.<sup>26</sup> However, there were no significant differences in severity of COPD between the M and E phenotypes in the present study.

There is some evidence that exacerbation is more frequent in subjects with regular sputum production.<sup>27</sup> Patients with M phenotype had more sputum and wheezing, and may have a greater increase in airway inflammation. Tiddens and colleagues<sup>28</sup> reported that the increase in cartilaginous airway wall area was correlated significantly with a semi-quantitative measure of peripheral airway inflammation. Bhowmik *et al.* also demonstrated that patients with more frequent exacerbation have higher baseline sputum IL-6 and IL-8 levels.<sup>29</sup> Therefore, it is reasonable that COPD patients with BWT show more sputum production and increased airway inflammation, which may be associated with the increased rate of exacerbation and hospitalization due to exacerbation.

Weight loss, muscle wasting and tissue depletion are commonly seen in COPD patients. It has been demonstrated that pink puffers become more cachectic, whereas blue bloaters do not.<sup>30</sup> Pink puffers and blue bloaters are not the same as emphysema-dominant phenotype and airway disease-dominant COPD. In the present study, BMI was significantly lower in the E phenotype than the A phenotype. The mechanisms underlying weight loss are not yet completely understood, but likely involve an imbalance in ongoing processes of protein degradation and replacement, including alterations in the relative levels or activities of endocrine hormones, inflammatory cytokines and programmed cell death.<sup>31</sup> The biological contribution of the tumour necrosis factor (TNF) family as candidate genes in COPD has already been discussed,<sup>32</sup> and weight loss in COPD has been shown to be associated with increased levels of circulating TNF-α.<sup>33</sup> TNF-α levels are elevated in pink puffers with tissue hypoxia and may be a factor contributing to weight loss in these patients.<sup>34</sup> TNF-α gene polymorphisms in the Japanese population are genetic risk factors for emphysema.<sup>35</sup> In this study, BMI was significantly lower in the E and M phenotypes than in the A phenotype, and it was suggested that weight loss is a characteristic feature of severe emphysema.

The morphological phenotypes of COPD evaluated by HRCT show several clinical characteristics and differences in responsiveness to treatment with inhaled bronchodilators. Classification of COPD into morphological phenotypes using HRCT may help in identifying those patients who will respond to selective

therapy and in determining the pathophysiology associated with each phenotype.

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