Complexity of Terminal Airspace Geometry Assessed by Computed Tomography in Asthma

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Low attenuation areas in computed tomography images from patients with chronic obstructive pulmonary disease have been reported to represent macroscopic and/or microscopic emphysema. The cumulative size distribution of the clusters has been shown to follow a power law characterized by the exponent *D*, a measure of the complexity of the terminal airspace geometry. We have previously found increased low attenuation areas in nonsmoking subjects with asthma. We examined the size distribution of the clusters in nonsmoking subjects with asthma compared with both nonsmoking control subjects and subjects with asthma with a smoking history. The percentage of lung field occupied by low attenuation areas (LAA%) and *D* in subjects with asthma with a smoking history differed significantly from nonsmoking subjects with asthma and control subjects. In nonsmoking subjects with asthma, both parameters differed significantly between severe asthma and mild or moderate asthma. The LAA% differed significantly between moderate and mild asthma, but *D* did not. In mild and moderate asthma, a highly significant correlation between LAA% and *D* was observed in patients with a smoking history, but not in nonsmoking subjects with asthma. Our results suggest that decreased *D* is mostly related to emphysematous change, and both measurements of LAA% and *D* may provide useful information to characterize low attenuation areas in subjects with asthma.

Keywords: asthma; computed tomography; fractals

The nature of asthma as a chronic inflammatory disease of the airways has been well recognized (1). Asthma was considered an essentially reversible disorder, but chronic inflammation in asthma can also lead to structural alterations (2). Frequent airway and lung parenchymal changes associated with asthma are considered responsible for irreversible airway obstruction, an outcome that is frequently observed in subjects with severe asthma (3, 4).

Emphysema, on the other hand, is defined pathologically as a process resulting in the increase of distal airspaces with destruction of alveolar walls but without obvious fibrosis (5). Previous studies have demonstrated the utility of computed tomography (CT) and high-resolution CT (HRCT) for detecting and quantifying pulmonary emphysema in patients with chronic obstructive pulmonary disease (COPD) (6–18). Low attenuation areas (LAAs) on CT scans *in vivo* have been shown to represent macroscopic and/or microscopic emphysematous changes in the lungs of patients with COPD (6–18).

The concept of fractal geometry was developed by Mandelbrot (19) to describe quantitatively the variations in size and shape seen in natural objects. A fractal object is said to be scale free because its characteristics are invariant under isotropic scale transformations. Such scale invariance can be achieved if the object is formed by parts that are similar to the whole. In other words, fractals are self-similar and hence characterized by power law functions (the only mathematical functions obeying scale invariance). The *D* is the exponent of a distribution function that is a power low. Although *D* is not precisely equivalent to the fractal dimension, it is nevertheless closely related to the fractal dimension. *D* values tend to decrease as the structure becomes more complex. The method of characterizing fractals has been successfully applied to pulmonary physiology (20, 21). For example, Mishima and colleagues (17) determined that LAAs on CT scans display fractal properties, and the exponent *D* is useful in revealing terminal airspace enlargement in early emphysema.

In recent studies, we found that the relative area of the lung with attenuation values lower than −950 Hounsfield Units (HU) (RA_{950}) correlates with airflow limitation, lung volume, and disease severity of asthma, but not lung-diffusing capacity in nonsmoking patients with asthma (22, 23). The purpose of this study was to investigate whether asthma affects the size distribution of LAA clusters and the development of emphysema. We quantified the size distribution of LAA clusters in nonsmoking patients with asthma compared with both nonsmoking healthy subjects and patients with asthma with a smoking history. In addition, we examined how asthma severity influences LAA clusters.

METHODS

Subjects

The study group comprised 105 patients with asthma (30 smokers and 75 nonsmokers) and 23 nonsmoking healthy subjects recruited from Misasa Medical Branch. Asthma was diagnosed according to the definition proposed by the American Thoracic Society (24). All subjects with asthma demonstrated episodic symptoms of wheezing and coughing and experienced symptomatic relief and reversible airway response with an accompanying increase in FEV_1 exceeding 15% upon treatment with β_2-adrenergic agonists. No subjects reported a history of clinically demonstrable tuberculosis or allergic bronchopulmonary aspergillosis as defined by the criteria of Rosenberg and colleagues (25). All subjects with asthma with a smoking history were ex-smokers with a smoking history of more than 20 pack-years. Nonsmoking healthy subjects demonstrated no chest symptoms and an FEV_1 of more than 90% predicted. All subjects were studied at a time when there had been no evidence of asthma exacerbation or respiratory tract infection for at least 1 month before the study. The CT scan was performed on the same day as lung function measurements.

The severity of asthma was classified by symptoms and treatment according to the National Institutes of Health/World Health Organization guidelines (26). Briefly, subjects with mild asthma were those experiencing symptoms twice a week or less who demonstrated an FEV_1 of 80% or more predicted before treatment and had been taking no regular medication but used inhaled β_2-agonists as needed for symptom relief. Subjects with moderate asthma were those who experienced daily symp-

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toms, used an inhaled short-acting β_2-agonist daily, demonstrated an FEV_1 between 60 and 80% predicted before treatment, and had been taking regular inhaled glucocorticoids. Subjects with severe asthma were those who experienced continual symptoms, limited physical activity, and frequent nocturnal asthma and demonstrated an FEV_1 of 60% or less predicted before treatment. Subjects with severe asthma were treated using oral prednisolone and inhaled steroids.

The onset and duration of asthma were established on the basis of a review of the patient's history after a careful physical examination. Allergy was diagnosed based on clinical history, skin tests, and the presence of serum immunoglobulin E antibodies specific to common inhalant allergens. Serum levels of total immunoglobulin E were measured using a radioimmunosorbent test, and the presence of serum immunoglobulin E antibodies specific to inhalant allergens was estimated based on results of the Phadebas radioallergosorbent test from the CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden). We defined atopic patients as those demonstrating a positive skin test and/or immunoglobulin E specific to the common inhalant allergens. All other patients were classified as nonatopic.

Informed consent to the study protocol was obtained from all subjects. The study protocol was approved by the ethics committee of our institution.

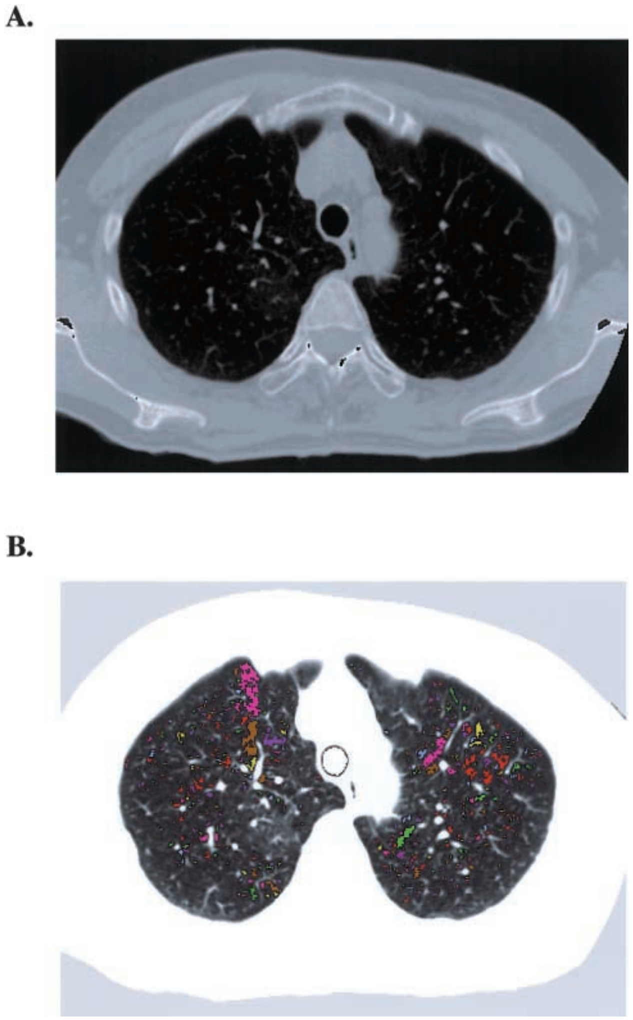

Figure 1. (*A*) Original CT image of the upper lung slice in a representative patient with asthma without smoking history. (*B*) The same image as in (*A*), but the individual *clusters* comprising contiguous LAA regions are shown in *contrasting colors*. The lung field was identified from the rest of the image, and the lumen of the trachea was excluded. LAA% is 6.5, and *D* is 1.17.

Pulmonary Function Tests

Pulmonary function tests were performed using a CHESTAC 33 (Chest Co., Tokyo, Japan). For all subjects, the following measurements were made using the FVC maneuver: FEV_1, FVC, FEV_1/FVC, $FEF_{25–75}$. Total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), and RV/TLC were measured using the helium dilution method. Diffusing capacity for carbon monoxide (D_{LCO}) per unit of alveolar volume (V_A) were measured according to the single-breath technique. FVC, FEV_1, $FEF_{25–75}$, FRC, and D_{LCO}/V_A measurements for each patient were expressed as a percentage of the predicted values (27).

Computed Tomography

HRCT scans were performed using a Toshiba Xpeed scanner (Toshiba, Tokyo, Japan) with a 2-mm slice thickness, a scanning time of 2.7

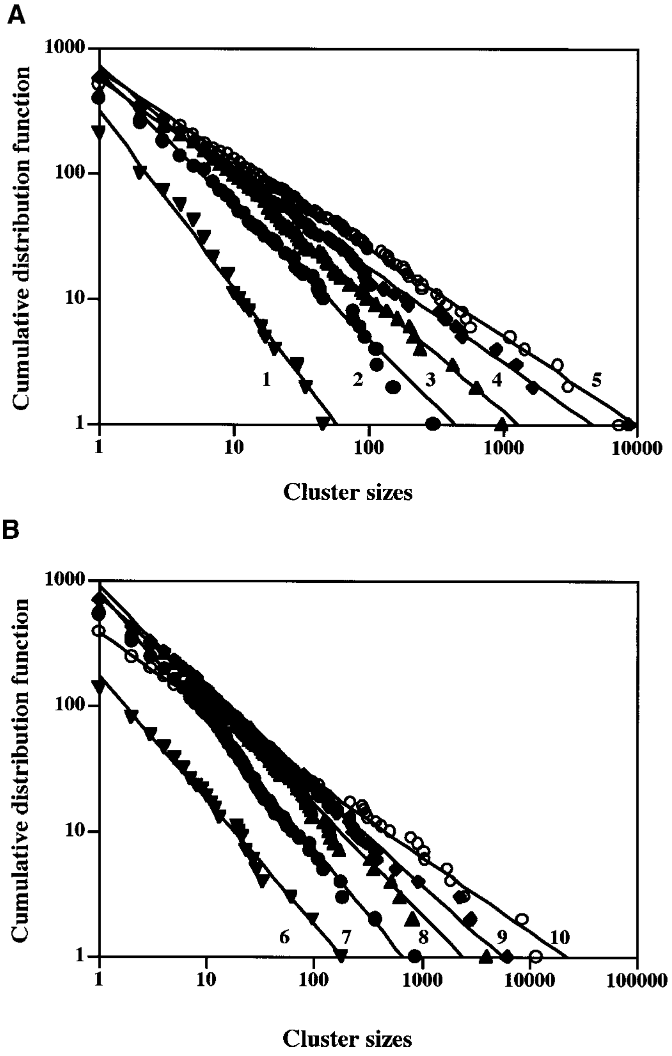

Figure 2. Log–log plot of representative cumulative frequency distributions of LAA size. In subjects with asthma without smoking history (*A*), the five lung slices analyzed had LAA% values of 1.4 (*1*), 7.5 (*2*), 9.9 (*3*), 24.2 (*4*), and 38.8 (*5*). In these five cases, r has a value of 0.992, 0.993, 0.996, 0.996, and 0.998, respectively. The corresponding *D* values are 1.42, 1.07, 0.92, 0.75, and 0.70, respectively. In subjects with asthma with a smoking history (*B*), the five lung slices analyzed had LAA% values of 2.9 (*6*), 8.2 (*7*), 16.7 (*8*), 23.6 (*9*), and 42.9 (*10*). In these five cases, r has a value of 0.995, 0.996, 0.995, 0.998, and 0.997, respectively. The corresponding *D* values are 0.99, 1.03, 0.87, 0.77, and 0.60, respectively.

seconds, a voltage of 120 kV, a tube current of 200 mA, and a field of view of 30 cm. All subjects were scanned in the supine position. During the scan, subjects held their breath after a deep inspiration. No intravenous contrast medium was administered. HRCT scans were obtained at the following three selected anatomic levels as described by Miniati and colleagues (28): (*1*) the top of the aortic arch, (*2*) the origin of the lower lobe bronchus, and (*3*) 3 cm above the top of the diaphragm. HRCT images of 512 × 512 pixels were calculated with a standard reconstruction algorithm (FC1). The percentage of low attenuation pixels (LAA%) was automatically calculated according to previously reported methods (12, 16–18). Our preliminary study revealed that one SD below the mean density of lungs from 15 control subjects who had never smoked was -949 HU, and we therefore defined the cutoff level between normal lung density and LAAs as -950 HU. A HRCT image and LAA (less than -950 HU) of a representative patient with asthma without smoking history are shown in Figure 1.

Figure 2 demonstrates that the cumulative frequency distributions of LAA sizes decrease linearly on log–log plots. The slopes of plots vary between subjects and as a function of LAA%. However, in each case, the cumulative frequency distribution, Y, can be described by a power law of size X of the form: $Y = K * X^{-D}$. Values of the exponent D were obtained by linear regression in the log–log domain, and correlation coefficients (r) were taken to indicate the goodness-of-fit of the power law. Values of D, r, and LAA% in three lung slices were then averaged for each subject. The mean ± SD values of r in subjects with asthma with and without smoking history and nonsmoking healthy control subjects were 0.985 ± 0.006, 0.983 ± 0.008, 0.982 ± 0.009, respectively, and were more than 0.949 in all subjects. No significant differences were observed between r values in subjects with asthma with or without smoking history and nonsmoking healthy control subjects, nor was any relationship between r and LAA% observed.

The presence of emphysema was estimated by the visual scoring method of Goddard and colleagues (29) for automatic comparisons with LAA% less than -950 HU. Each slice was evaluated individually, and the right and left lungs were graded separately according to the percentage of area demonstrating changes suggestive of emphysema. If less than 25% of the pulmonary emphysema in a slice was considered to reveal vascular disruption and low attenuation, the score was one; between 25 and 50%, the score was two; between 50 and 75%, the score was three; and more than 75%, the score was four. Therefore, the right and left lungs could each receive a maximal score of four, for maximal scores of 8 per slice and 24 for three slices. Each subject was evaluated independently on two separate occasions by three pulmonologists without the knowledge of the clinical data or results of pulmonary function tests.

Statistical Analysis

All statistical analyses were performed using Stat View software (SAS Institute Inc., Cary, NC). Results were expressed as mean ± SD. Univariate (linear) regression analyses were used to evaluate the relationship between any two variables. One- and two-way analyses of variance with Bonferroni/Dunn correction were used to compare groups (23). Values of $p < 0.05$ were regarded as statistically significant.

RESULTS

Subject Characteristics

Subject characteristics, lung function data, and current medications are presented in Table 1. No significant differences in age or duration of asthma were observed between groups. The 75 subjects with asthma with no history of smoking consisted of 25 subjects with mild, 25 subjects with moderate, and 25 subjects with severe asthma. FEV$_1$ values (mean ± SD [range]) were as follows: 107.7 ± 15.6% (85.9–146.8%) for mild asthma; 70.2 ± 4.7% (60.6–79.2%) for moderate asthma; and 52.4 ± 5.1% (42.4–59.5%) for severe asthma. Thirty subjects with asthma reported a smoking history (43.2 ± 18.7 pack-years, 20–100 pack-years) and comprised 10 subjects with mild asthma, 10 subjects with moderate asthma, and 10 subjects with severe asthma. FEV$_1$ values were as follows: 89.9 ± 9.0% (80.9–103.1%) for mild asthma; 69.5 ± 4.7% (61.6–75.8%) for moderate asthma; and

TABLE 1. CHARACTERISTICS OF SUBJECTS WITH ASTHMA AND CONTROL SUBJECTS

	Nonsmoking Control Subjects	Asthma (*Nonsmoker*)	Asthma (*Smoker*)
Number of subjects	23	75	30
M/F	5/18	11/64	30/0
Mild/moderate/severe	NA	25/25/25	10/10/10
Mean age, yr[*]	64.0 (10.9)	61.1 (11.5)	66.4 (6.4)
Disease duration, yr[*]	NA	13.3 (10.9)	12.0 (11.4)
Atopy/nonatopy	0/23	39/36	22/8
Serum IgE, U/ml[†]	ND	166 (10–3,145)	357 (8–2,930)
FVC, % pred, %[*]	108.5 (15.6)	100.7 (18.3)	90.6 (13.2)[‡][§]
FEV$_1$, % pred, %[*]	115.4 (7.3)	76.8 (25.2)[‖]	70.5 (17.8)[‖]
FEV$_1$/FVC, %[*]	79.6 (4.0)	68.7 (11.9)[¶]	56.0 (11.0)[‖][**]
FEF$_{25–75}$, % pred, %[*]	100.7 (15.4)	59.8 (33.9)[‖]	33.8 (19.3)[‖][**]
FRC, % pred, %[*]	97.9 (8.7)	101.7 (20.6)	112.0 (18.6)[‡]
RV/TLC, %[*]	32.7 (4.5)	41.8 (8.2)[¶]	46.9 (7.7)[‖][††]
D$_{LCO}$/V$_A$, % pred, %[*]	107.4 (9.2)	113.3 (19.4)	90.7 (26.8)[‡][**]
Mean lung density, HU[*]	-818 (32)	-845 (29)[‖]	-868 (30)[‖][††]
LAA%[*]	3.6 (3.2)	11.0 (9.7)[‡]	23.8 (16.9)[‖][**]
D[*]	1.06 (0.16)	1.00 (0.15)	0.83 (0.18)[‖][††]
Inhaled BDP, μg/day[*]	0	568 (502)	473 (290)
Systemic corticosteroids, n	0	25	10

Definition of abbreviations: BDP = beclomethasone dipropionate; *D* = exponent of a distribution function of the low attenuation area size; D$_{LCO}$ = diffusing capacity for carbon monoxide; HU = Hounsfield Units; IgE = immunoglobulin E; LAA% = percentage of lung field occupied by low attenuation areas; NA = not applicable; ND = not determined; RV = residual volume; TLC = total lung capacity; V$_A$ = alveolar volume.

[*] Values are means with SD shown in parentheses.

[†] Values are geometric means of serum IgE levels with range shown in parentheses.

[‡] $p < 0.05$ compared with control subjects.

[§] $p < 0.05$ compared with asthma (nonsmoker).

[‖] $p < 0.001$ compared with control subjects.

[¶] $p < 0.01$ compared with control subjects.

[**] $p < 0.001$ compared with asthma (nonsmoker).

[††] $p < 0.01$ compared with asthma (nonsmoker).

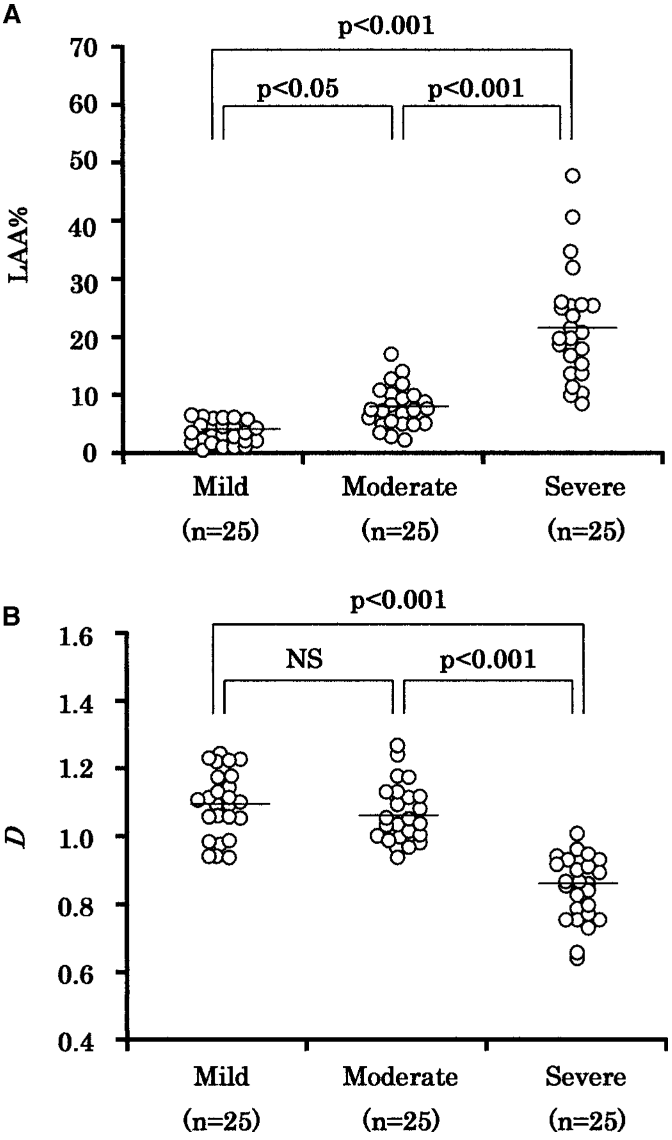

Figure 3. LAA% (*A*) and *D* (*B*) according to severity of asthma in subjects with asthma without smoking history. *Bars* represents mean ± SD.

52.4 ± 8.8% (37.4–59.5%) for severe asthma. All subjects with asthma were treated using inhaled β_2-agonists. No significant differences in lung function data were observed between nonsmoking control subjects and nonsmoking patients with mild asthma.

Size Distribution of LAA Clusters in Subjects With Asthma

LAA% values were significantly higher in subjects with asthma with a smoking history than in subjects with asthma without a smoking history ($p < 0.001$) or nonsmoking control subjects ($p < 0.001$) and were higher in subjects with asthma without a smoking history than in nonsmoking control subjects ($p < 0.05$) (Table 1). *D* values were significantly lower in subjects with asthma with a smoking history than in subjects with asthma without a smoking history ($p < 0.01$) or nonsmoking control subjects ($p < 0.001$). However, no significant difference was observed between subjects with asthma without a smoking history and nonsmoking control subjects (Table 1).

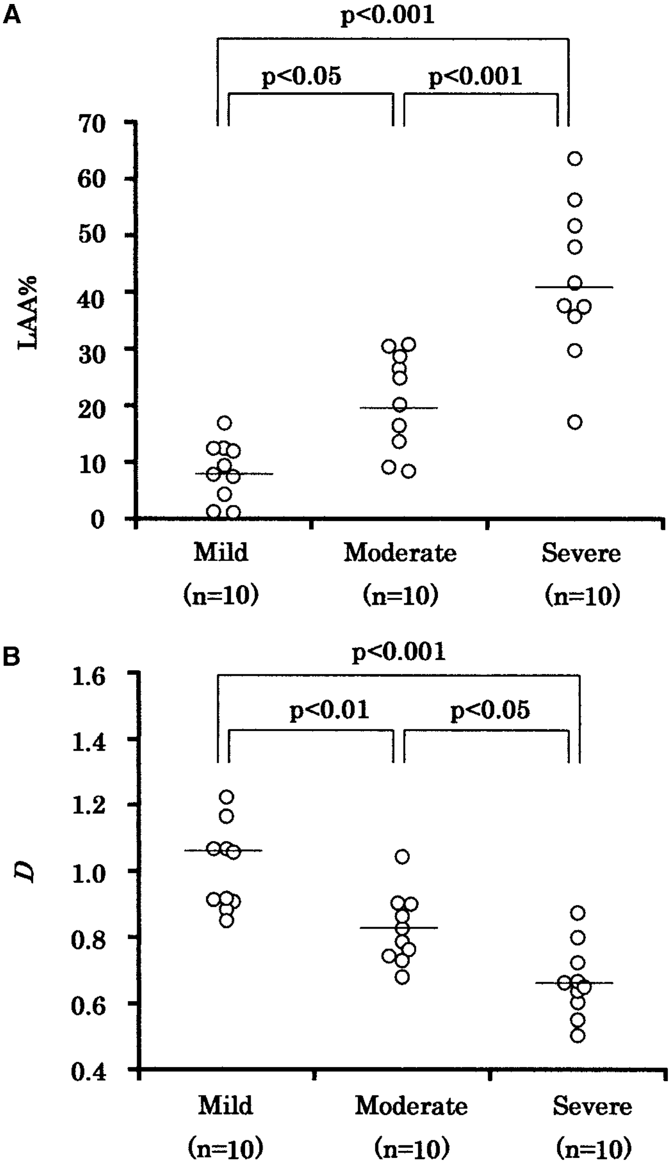

Figure 4. LAA% (*A*) and *D* (*B*) according to severity of asthma in subjects with asthma with a smoking history. *Bars* represents mean ± SD.

Relationship between Size Distribution of LAA Clusters and Asthma Severity

Both LAA% and *D* significantly correlated with disease severity and smoking history ($p < 0.001$, two-way factorial analysis of variance).

Figure 3 shows the relationships between disease severity and LAA% or *D* in subjects with asthma without a smoking history. LAA% values were significantly higher in severe asthma than in mild ($p < 0.001$) and moderate ($p < 0.001$) asthma and in moderate asthma than in mild asthma ($p < 0.05$). *D* values were significantly lower in severe asthma than in mild ($p < 0.001$) or moderate asthma ($p < 0.001$). However, no significant difference was observed between mild and moderate asthma.

Figure 4 shows the relationships between asthma severity and LAA% or *D* in subjects with asthma with a smoking history. LAA% values were significantly higher in severe asthma than in mild ($p < 0.001$) or moderate ($p < 0.001$) asthma and in

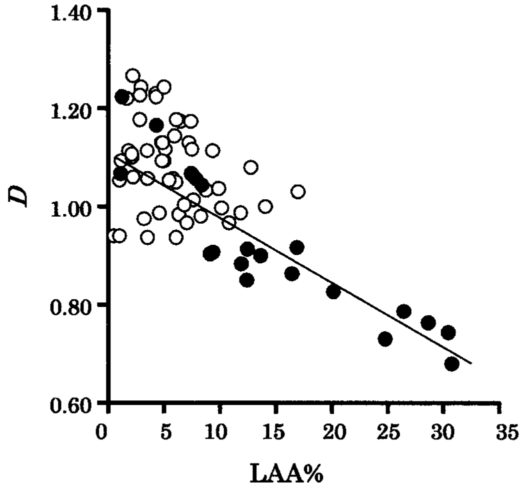

Figure 5. Relationship between LAA% and *D* in patients with mild and moderate asthma. *Open circles* and *closed circles* represent patients without and with a smoking history, respectively. There was a highly significant correlation between LAA% and *D* ($r = -0.907$, $p < 0.0001$) in patients with a smoking history, but not in those without smoking history.

moderate asthma than in mild asthma ($p < 0.05$). *D* values were significantly lower in severe asthma than in mild ($p < 0.001$) or moderate asthma ($p < 0.05$) and in moderate asthma than in mild asthma ($p < 0.01$).

We also examined the relationship between LAA% and *D* in subjects with mild and moderate asthma (Figure 5). A highly significant correlation between LAA% and *D* ($r = -0.907$, $p < 0.0001$) was observed in subjects with asthma with a smoking history. However, there was no significant correlation between LAA% and *D* in subjects with asthma without smoking history.

Nonsmoking subjects with asthma demonstrated no findings of emphysema on visual assessment (Table 2). Significant differences were observed among groups in subjects with asthma with a smoking history ($p < 0.001$).

Relationship between Size Distribution of LAA Clusters and Pulmonary Function Data

We observed a significant negative relationship between LAA% and %FEV_1 ($r = -0.626$, $p < 0.0001$) and a significant positive relationship between *D* and %FEV_1 ($r = 0.600$, $p < 0.0001$). LAA% and *D* correlated significantly with %FEV_1, FEV_1/FVC, %$FEF_{25\text{–}75}$, %FRC, and RV/TLC but not %$\mathrm{DL_{CO}/VA}$ (Table 3). These data reveal that both LAA% and *D* bear significant correlations with parameters regarding flow limitation and lung volume but not with diffusion capacity of the lung in nonsmoking subjects with asthma.

TABLE 2. VISUAL ASSESSMENT OF EMPHYSEMA IN SUBJECTS WITH ASTHMA

	Mild	Moderate	Severe
Asthma (nonsmoker)	0	0	0
Asthma (smoker)	0.6 (0.8)	5.2 (3.5)*	11.8 (5.6)†‡

Values are means with SD shown in parentheses.

* $p < 0.05$ compared with mild asthma (smoker).

† $p < 0.001$ compared with mild asthma (smoker).

‡ $p < 0.01$ compared with moderate asthma (smoker).

TABLE 3. CORRELATION COEFFICIENTS OF UNIVARIATE REGRESSION ANALYSES FOR PULMONARY FUNCTION TESTS USING LAA% AND *D* IN NONSMOKING PATIENTS WITH ASTHMA (n = 75)

	LAA%		*D*	
	r	p Value	*r*	p Value
FEV_1, % pred	−0.626	< 0.0001	0.600	< 0.0001
FEV1/FVC, %	−0.603	< 0.0001	0.643	< 0.0001
$FEF_{25\text{–}75}$, % pred	−0.496	< 0.0001	0.539	< 0.0001
FRC, % pred	0.516	< 0.0001	−0.461	< 0.0001
RV/TLC, %	0.447	< 0.0001	−0.366	0.0013
$\mathrm{DL_{CO}/VA}$, % pred	−0.187	0.1138	0.152	0.1994

Definition of abbreviations: *D* = exponent of a distribution function of the low attenuation area size; $\mathrm{DL_{CO}/VA}$ = carbon monoxide diffusing capacity per unit of alveolar volume; LAA% = percentage of the low attenuation area of three lung levels; RV = residual volume; TLC = total lung capacity.

As seen in Table 4, LAA% was found to show highly significant negative correlations with %FEV_1 ($r = -0.789$, $p < 0.0001$) and %$\mathrm{DL_{CO}/VA}$ ($r = -0.775$, $p < 0.0001$). *D* was likewise found to show highly significant negative correlations with %FEV_1 ($r = 0.772$, $p < 0.0001$) and %$\mathrm{DL_{CO}/VA}$ ($r = 0.783$, $p < 0.0001$). LAA% and *D* correlated significantly with %FEV_1, FEV_1/FVC, %$FEF_{25\text{–}75}$, %FRC, RV/TLC, and %$\mathrm{DL_{CO}/VA}$. These data reveal that both LAA% and *D* possess significant correlations with parameters regarding flow limitation and lung volume, in addition to diffusion capacity of the lung in smoking subjects with asthma.

DISCUSSION

Our study demonstrated that the size distribution of LAA clusters can be affected by the smoking history and disease severity in patients with asthma.

LAAs on CT scans *in vivo* have been reported to represent macroscopic and/or microscopic emphysematous changes in the lungs of patients with COPD (6–18). Some studies have investigated the use of CT lung densitometry in nonsmoking patients with asthma (30–32). Gevenois and colleagues (30) failed to find any significant changes in CT lung density parameters with respect to the RA_{950} during allergic challenge tests. This was despite a decrease in FEV_1 accompanied by an increase in RV and FRC of approximately the same volume. They concluded that hyperinflation and airflow obstruction without emphysematous lung destruction do not influence densitometric measure-

TABLE 4. CORRELATION COEFFICIENTS OF UNIVARIATE REGRESSION ANALYSES FOR PULMONARY FUNCTION TESTS USING LAA% AND *D* IN SMOKING PATIENTS WITH ASTHMA (n = 30)

	LAA%		*D*	
	r	p Value	*r*	p Value
FEV_1, % pred	−0.789	< 0.0001	0.772	< 0.0001
FEV_1/FVC, %	−0.768	< 0.0001	0.712	< 0.0001
$FEF_{25\text{–}75}$, % pred	−0.754	< 0.0001	0.731	< 0.0001
FRC, % pred	0.545	0.0033	−0.538	0.0038
RV/TLC, %	0.504	0.0045	−0.553	0.0015
$\mathrm{DL_{CO}/VA}$, % pred	−0.775	< 0.0001	0.783	< 0.0001

Definition of abbreviations: *D* = exponent of a distribution function of the low attenuation area size; $\mathrm{DL_{CO}/VA}$ = diffusing capacity for carbon monoxide per unit of alveolar volume; LAA% = percentage of lung field occupied by low attenuation areas; RV = residual volume; TLC = total lung capacity.

ments obtained from inspiratory scans. Conversely, Newman and colleagues observed that the percentage of pixels below −900 HU on CT and HRCT was indicative of air trapping and airflow limitation, particularly on expiratory scans (31). Biernacki and colleagues (32) reported that a low CT lung density, with values similar to those of patients with chronic bronchitis and emphysema, occurs in chronic asthma. They concluded that the cause is chronic overinflation, which is difficult to differentiate pathologically from early microscopic emphysema. We recently reported that the LAA% represented by RA_{950} in nonsmoking subjects with asthma increased in comparison with nonsmoking control subjects and was related to airflow limitation, hyperinflation, and disease severity but not to lung diffusion capacity at full inspiration (23).

In this study, we obtained images after deep inspiration. Gevenois and colleagues (30) reported that inspiratory CT images are more accurate than expiratory images for quantifying pulmonary emphysema. They speculated that abnormalities in the expiratory CT are more reflective of air trapping than of a reduction in terminal airspace volume. Eda and colleagues (33) found that the helical CT images acquired at maximal expiration reflect air trapping, whereas CT visual scores at full inspiration demonstrate significant correlations with emphysema. We therefore consider inspiratory CT to be more suitable than expiratory CT for determining the presence of emphysema in asthma.

In this study, we used the mean values from three HRCT slices to reflect the condition of the whole lung field. This was considered adequate as Mishima and colleagues (18) described an accurate correlation between the percentage of LAA detected from 10 sections (from apex to base of the lung) versus 3 sections in patients with COPD.

Cumulative size distributions of LAA clusters have been shown to follow a power law characterized by an exponent *D*, which is a measure of the complexity of the airspace terminal geometry on HRCT images of the lungs in patients with COPD (17). Thus, a decrease in *D* represents increased clustering of LAAs and consequently an enlargement in the terminal airspace area. In this study, we observed that LAA% was significantly higher and *D* was significantly lower in subjects with asthma with a smoking history than in subjects with asthma without a smoking history or nonsmoking control subjects. In addition, a significant difference was found in LAA% between nonsmoking subjects with asthma and nonsmoking control subjects, but not in *D*. In summary, LAA% increases concomitantly with decreases of *D* in subjects with asthma with a smoking history. However, LAA% increases without a concomitant decrease of *D* in nonsmoking subjects with asthma. These results suggest that the increase of LAA% in subjects with asthma with a smoking history is derived not only from airway obstruction but also from pulmonary emphysema.

In subjects with asthma with a smoking history, the relationship between LAA% and disease severity was similar to that between *D* and disease severity. Visual scores likewise differed among groups, suggesting that the degree of emphysema correlates with asthma severity. In addition, we observed that both LAA% and *D* significantly correlated with lung-diffusing capacity and parameters regarding airflow limitation and lung volume. These observations are consistent with the concept that increasing LAA implies progression of emphysema. Mishima and colleagues found that neither LAA% nor *D* correlated with FEV_1/FVC in COPD subjects, and *D* significantly correlated with $D_{L_{CO}}/V_A$, whereas LAA% showed a much weaker correlation with $D_{L_{CO}}/V_A$ (17). We found no significant difference between LAA% and *D* in relationship to pulmonary function in subjects with asthma. The subjects in our study included those with asthma, whereas their study included patients with COPD, which might explain the discrepancies between our findings and theirs.

In nonsmoking subjects with asthma, the relationship between LAA% and disease severity differs from that between *D* and disease severity. Although LAA% differed significantly among subgroups, *D* values were significantly lower in severe asthma than in mild or moderate asthma but were not significantly different between mild and moderate asthma. This result supports the interpretation that the cluster number of small LAAs increases in mild to moderate asthma, and the cluster size of LAAs increases in severe asthma. LAAs in nonsmoking subjects with asthma appear to reflect factors other than emphysema, such as hyperinflation. Our study demonstrated that neither LAA% nor *D* displayed significant correlations with $\%D_{L_{CO}}/V_A$, which have been shown to correlate most closely in previous structure/function studies with emphysema. Both LAA% and *D* display significant correlations with airflow limitation ($\%FEV_1$, $\%FEV_1/FVC$, $\%FEF_{25-75}$) and lung volume (%FRC, RV/TLC) in nonsmoking subjects with asthma. This study revealed that nonsmoking subjects with asthma displayed no findings of emphysema on visual assessment. Mochizuki and colleagues likewise reported that none of the nonsmoking patients with asthma, including those with severe asthma or asthma of long duration, presented with emphysema (34). This is consistent with our results. However, it is still unclear whether LAA in nonsmoking subjects with severe asthma is caused by chronic overinflation or early microscopic emphysema.

In this study, we observed a highly significant negative correlation between LAA% and *D* in subjects with mild and moderate asthma with a smoking history but not in those without a smoking history. For the reason that LAA% increases without a decrease in *D* in nonsmoking patients with mild and moderate asthma, we speculate that the new clusters themselves would have the same distribution as the old ones because the total number of clusters significantly increased with increasing severity in nonsmoking subjects with asthma by analysis of variance ($p < 0.001$) (data not shown). Nevertheless, clusters cannot increase by merging smaller clusters because that would definitely change *D*.

Although we have previously reported that the LAA% represented by RA_{950} increases in nonsmoking subjects with asthma compared with healthy control subjects, the properties of LAA clusters in nonsmoking subjects with asthma have not been examined. Our results demonstrated that the values of *D* calculated from CT images seem to be sensitive to emphysematous changes in subjects with asthma with a smoking history in the same manner as patients with COPD. In addition, the degree of emphysema has been suggested to correlate with asthma severity in subjects with asthma with a smoking history. We suggest that LAA in nonsmoking subjects with mild or moderate asthma may be caused by hyperinflation, not emphysema. However, further investigation of LAA in nonsmoking subjects is necessary from a pathologic basis. We have concluded that *D* is a sensitive and powerful parameter for detecting emphysema, and both measurements of LAA% and *D* may provide useful information to discriminate between hyperinflation and emphysema in subjects with asthma.

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