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Differences in radiological/HRCT findings in eosinophilic bronchitis compared to asthma: implication for bronchial responsiveness

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Key Words

Asthma, Eosinophilic Bronchitis, High-Resolution Computed Tomography, Airway hyperresponsiveness.

ABSTRACT

Background: Airway hyperresponsiveness (AHR) in asthmatics is considered to be one of the major consequences of airway inflammation and remodeling. Airway responsiveness is normal in patients with eosinophilic bronchitis (EB), despite eosinophilic inflammation of the airways comparable to that which occurs in asthmatics. Comparisons between asthma and EB should clarify the changes in airway morphology that are related specifically to AHR in asthmatics.

Methods: Eighteen asthmatics, 15 patients with EB, and 11 healthy subjects were recruited. We compared airway wall area percentage, centrilobular prominence, and air trapping in patients with EB, mild persistent asthmatics, and normal controls using thin-slice section computed tomography.

Results: Airway wall area percentage (WA%) was significantly greater in asthmatics than in EB patients (72 ± 3.1% vs. 54 ± 2.1%, p=0.032) and was similar in EB patients and controls(54 ± 2.1% vs. 57 ± 1.8%, p> 0.05). Centrilobular prominence and air trapping were similar in EB patients and asthmatics and were significantly greater than in controls.

Conclusion: Airway wall area percentage rather than air trapping or centrilobular prominence may be associated with the AHR that occurs in asthmatics but not in patients with EB.

INTRODUCTION

Asthma is a chronic airway inflammatory disease that is associated with an increased number of eosinophils, mast cells, and Th2 lymphocytes, which induce airway hyperresponsiveness (AHR) and a reversible airflow limitation.[1] In addition to airway inflammation, most asthmatics (even those with a mild condition) show evidence of remodeled airways, including goblet cell hyperplasia, reticular basement membrane thickening, vascular proliferation, and smooth muscle hypertrophy.[2] Thickening of the airway walls is attributed to inflammation and remodeling of the airways that occur during asthma.[3] The degree of thickening of the airway walls in asthmatics is correlated with the severity of the disease and airway flow limitation.[4 5] However, pathology studies have revealed that in asthmatics, the thickened airway wall extends through the small airways.[6]

Recently, morphological changes in the small airways have been indirectly analyzed using high-resolution computed tomography (HRCT). Obstruction of the small airways results in regional air trapping and an increased prominence of the centrilobular structure.[7 8] HRCT is an accurate and reproducible method for evaluating the small airways[8] and is more sensitive than spirometry.[7] Relatively few studies of the relationship between bronchial wall thickness and AHR have been conducted [4 9 10], and the results of these studies are inconsistent because subjects showed different degrees of airway inflammation or because the studies lacked appropriate control groups. In addition, there has been no study to investigate the contribution of small airway changes to AHR of asthma.

Eosinophilic bronchitis (EB) is an airway disease in which the microscopic pattern of inflammation of the large airways resembles that of asthma; however, patients with EB have normal airflow and show no signs of AHR.[11 12] In addition, there is no difference between the two conditions with respect to the expression of Th2 cytokines such as interleukin-4 and -5 and degranulation of eosinophils within the bronchial mucosa .[13 14] A macroscopic analysis of the morphology of the large and small airways has not been carried out in patients with EB. Furthermore, due to the similarity of airway inflammation in the two conditions, the effect of the airway inflammation contributing to AHR [9] could be eliminated if the two conditions were compared.

The aims of this study were (1) to examine the macroscopic changes in the airways of patients with EB and (2) to compare changes in the morphology of the airways of asthmatics and patients with EB in the thin-section CT.

MATERIALS AND METHODS

Subjects

Eighteen asthmatics, 15 patients with EB, and 11 healthy subjects (controls) were enrolled in the study. A clinical history was obtained using a physician-administered questionnaire[15] from subjects who had complained of chronic coughing for at least 4 weeks. EB was diagnosed on the basis of the following criteria: 1) FEV1% and FVC of greater than 75% of the predicted value without variable airway obstruction which could be demonstrated by negative response to a short - acting bronchodilator (increase of FEV1< 15%), 2) the absence of bronchial hyperreactivity (>10 mg/ml methacholine) and 3) sputum eosinophilia (>3%) 4) no abnormality in the lung parenchyma on simple chest posteroanterior radiograph. All of EB subjects were a part of ones in our previous publication.[16] None of the present study subjects developed into asthma or decline of FEV1 (%) during the follow up period ranged 6 to 24 months. Asthma was defined according to American Thoracic Society criteria[17] on the basis of clinical symptoms. The intermittent or mild persistent asthmatics with sputum eosinophilia (>3%) were included according to the clinical features and the daily medication required for symptomatic control. Each patient showed airway reversibility, as documented by a positive bronchodilator response of >15% increase in FEV_1 and/or airway hyperreactivity of <10 mg/ml methacholine. Normal healthy subjects were recruited from hospital personnel who answered negatively to a screening questionnaire for respiratory symptoms and had FEV1/FVC greater than 80%, FEV1 greater than 75% predicted, PC20 methacholine greater than 10 mg/ml and normal findings on chest radiographs. Exclusion criteria were current or ex-smokers, evidence of bacterial infections on chest radiographs, treatment with systemic or inhaled steroids, or hospitalization during the previous 6 weeks before this study. Subjects visited the laboratory on three occasions. On the first visits, the allergen skin prick test, the short-acting bronchodilator test, and sputum induction were performed. The study subjects produced sputum by the aerosol inhalation method of Pin and coworkers using hypertonic saline.[18] Sputum samples were examined and treated within 2 h of collection by using the method of Pizzichini and colleagues with minor modification.[19] On the second day of study, the subjects underwent PC_{20} methacholine challenge test. The PC_{20} methacholine challenge test was conducted using the method of Juniper *et al* [20], and the results are expressed as the provocation concentration required for a 20% reduction in FEV_1 (PC_{20}) in noncumulative units.[20] On the third study day, the subject underwent the thin-section CT. Atopy was determined by skin prick tests using 48 common inhalant allergens, including dust mites (*Dermatophagoides farinae and D. pteronyssinus*), cat

fur, dog fur, fungus, cockroach, grass, tree, and ragweed pollen (Bencard, Brentford, UK). The test was regarded as positive when the wheal diameter was ≥3 mm. This study was performed with the approval of the Ethics Committee of the University Hospital and informed written consent was obtained from all study subjects.

Thin-slice CT scan and radiological evaluation

All of the subjects underwent volumetric thin-section CT scans of the chest using a Somatom 4 scanner (Siemens Medical Systems, Forchheim, Germany). Patients were scanned caudocranially in one breath-hold. One-millimeter collimation was used at a table feed of 6 mm/0.75 sec scanner rotation (8 mm/sec) at 120 kV and 140 mAs. For the expiratory thin-section CT scan, all subjects were instructed to take a deep breath, exhale all the way, and hold their breath. Scanning was performed from the lung bases toward the apices. The volumetric axial images with 1-mm thickness and the 10-mm intervals were reconstructed with a high-spatial frequency algorithm on both end-inspiration and end-expiration scanning. All scans were obtained at suspended end-inspiratory volume because artifacts have been reported in scans obtained at functional residual capacity. [21]

The images were viewed at two window levels of –450 HU for accurate measurement of bronchial diameters and –700 HU for analysis of other HRCT features. All images were displayed at the lung window setting using a PACS (picture archiving and communication system) workstation (STARPACS, INFINITT TECHNOLOGY) .

The thin-section CT scans were evaluated for the presence and/or extent of the following features: (a) airway wall area percentage for bronchial wall thickening; (b) prominence of centrilobular structures for centrilobular nodule and branching linear structure; (c) air trapping on expiratory scan; (d) bronchiectasis; and (e) emphysema. These findings were defined according to the glossary of terms recommended by the Fleischner society .[22]

Prominence of centrilobular structures were defined as a dot-like, Y-shaped, or X-shaped opacity that lay in the region of the lobular core, adjacent to the centrilobular artery, or within a few millimeters away from the borders of the lobules, such as the interlobular septa or pleura.

Air trapping was defined as the abnormal retention of gas (<100 HU compared to normal lung parenchyma) within a lung or lung units at the end of exhalation. Air trapping can also be seen in normal subjects, although its extent is limited. Focal areas of relative lucency can be seen in normal subjects on expiratory scans in the superior segments of the lower lobes.[23] It is postulated that the slender segments may be less

well ventilated than adjacent lung, having a tendency to trap air during exhalation. Bronchiectasis was diagnosed as the cylindrical, varicose or cystic type. To diagnose bronchiectasis, the observers used not only the classical criterion based on the comparison of the diameters of the bronchial lumen and the homologous pulmonary artery, but also the absence of normal distal tapering of the bronchial lumen, as assessed on successive CT slices, and visualization of bronchi within 1 cm of the pleura.[24] Emphysema was defined as a focal area of very low attenuation, usually without definable wall, that was surrounded by higher attenuation normal lung parenchyma. Ground glass opacity was defined as an area of hazy increase in lung opacity on HRCT which is not associated with obscuration of underlying vessels.

The images were viewed on a work station using a magnification of ×5, and measurements of overall (D) and internal (L) diameter of the bronchi were made using electronic callipers, with wall thickness (T) being derived from these measurements (T = (D – L)/2). All bronchi of more than 1.5 mm in diameter clearly seen in cross section were measured in each slice of the inspiratory scans. Oblique sections influence wall thickness, and the long to short diameter ratio was used to assess "roundness" with an upper limit of 1.5 being permitted and measurements then being performed across the short diameter.[25]

The airway wall area percentage (WA%) was used to compare bronchial wall thickening between the groups. Wall area was calculated as a percentage of total airway cross sectional area (WA%; Fig. 2), thereby relating wall thickness to bronchial size, and a mean value was calculated for each patient for each observer from all the bronchi measured.[4] Given that two independent observers may identify a different position for the wall edge, we combined the data from the observers to obtain a consensus measurement of wall thickness, taking the mean of the average values obtained for the two observers for each assessment. Wall thickness was expressed as a consensus value for each patient was created in the same way, giving single measures of WA%.

The lung was divided six zones - upper, middle, and lower, right and left by one-third and two-third of vertical distance between the lung apices and the domes of diaphragm. Each of these zones was evaluated and scored separately for the presence and/ or extent of the thin-section CT features. Prominence of centrilobular structures and air trapping were scored in each of six zones according to the percentage of the involved area to cross-sectional area as follows; (0= no involvement, 1=1-25%, 2=26-50%, 3=51-75%, and 4=76-100% of cross-sectional area) as described in the other studies.[26 27] The scores of six zones were summated as the total scores for centrilobular structures and air trapping ranged from 0 to 24. They were expressed as semi-quantitative scale of grade

as follows; Grade 0 was defined for a total score of less than 1. Grade 1 was defined for a total score of 1 to 5. Grades 2, 3, and 4 were defined for total scores of 6 to 12, 13 to 18, and >18, respectively. The air trapping in the superior segments of the lower lobes and isolated pulmonary lobules were not scored due to the possibility of physiologic air trapping.[28] The remaining thin-section CT features of emphysema, and bronchiectasis were evaluated in terms of their presence or absence.

Reproducibility

Two experienced thoracic radiologists(J.P and Y.H), who were blinded to the clinical features of the study subjects measured independently overall (D) and internal (L) diameters of the bronchi using electronic calipers two times, separated by an interval of two weeks, and calculates the airway wall area percentage (WA%) . Intra-observer and inter-observer variation were assessed by plotting the difference between two WA% measurements against the mean value of the two.[29] To assess inter-observer and intra-observer variability of parameters, the kappa coefficient of agreement (*K*) was computed.[30]

Statistics

Characteristics of subjects were compared using descriptive statistics. Comparisons between the three groups (patients with EB, asthmatics, and controls) were made using a Kruskal-Wallis test. And if it found significant, Mann-Whitney U test was used to compare nonparametric data between two groups. An analysis (ANOVA) and Duncan's multiple range test were used to analyze parametric data. Spearman's rank correlation coefficient was calculated to evaluate the relationships between the physiological responses (FEV 1, FEF25-75% and PC20 methacholine) and radiological parameters. A p-value < 0.05 indicated statistical significance.

RESULTS

Thin-sliced CT scan findings

The characteristics of the subjects are shown in Table 1. Age, sex, FEV1 (% pred.), and sputum eosinophil content were matched between patients with EB and asthmatics. We found no difference in FEV1 (% pred.) among patients with EB, asthmatics, and controls. BA had a significantly lower levels of FEF25-75% predicted than NC group (p=0.028), but there was no statistical differences between EB and NC group even though former group showed lower trend than the latter group (83.8 ± 9.3 % vs. $94.6 \pm 3.6\%$, $p= 0.096$). The proportion of atopy was comparable between patients with EB and asthmatics. PC20 methacholine was significantly lower in asthmatics than in patients with EB and controls. The inter-observer agreement rate was 78% for centrilobular prominence and 72% for air trapping, and 84%, 76%, and 75% for the presence of bronchiectasis, emphysema, and ground glass opacities, respectively. The kappa value was >0.75 for centrilobular prominence, which represents excellent agreement. The kappa values for air trapping ranged from 0.45 to 0.59, which represents fair to good agreement.[31] The intra-observer agreement rate was 84% for centrilobular

prominence and 88% for air trapping and 86%, 90%, and 82% for the presence of bronchiectasis, emphysema, and ground glass opacities. All of their kappa values were > 0.75 .

The inter-observer and intra-observer agreement rates for airway wall percentage (WA%) were shown in Figure 4. In the each plot, every mean difference did not severely deviated from zero. The kappa value for inter-observer and intra-observer agreement of WA (%) were 64%, 76% respectively as which represents good to excellent agreement.

A total of 911 bronchi were measured using thin-section CT (264 in 15 patients with EB, 366 in 23 asthmatics, and 281 in 16 controls; range, 15–21 bronchi per subject). There was no difference in the mean number of bronchi measured in each study group. The mean diameters of the outer airway of the measured bronchi were similar in each group (5.4 ± 0.24, 5.5 ± 0.23, and 5.6 ± 0.26 mm in the controls, patients with EB, and asthmatics, respectively; $p > 0.05$).

The mean airway wall area percentage was significantly greater in asthmatics (72 ± 3.2 %) than in controls (57 ± 1.8 %) and EB patients (54 ± 2.1 %; $p = 0.032$ for each; Fig. 3A), but there was no difference of WA (%) between the latter two groups.

We analyzed the WA% by the inner diameter of 2 mm (small vs. large airways) in the three groups. WA% of small airway (1.5-2 mm in inner diameter) was greater than that of large airway in BA group (85±3.1 (%) vs. 68±3.2 (%), $p= 0.012$). But, there was no significant difference of the airway wall area percentage between large (>2 mm in inner diameter) and small airways in EB and control group. In the small airways, asthmatics have a significantly greater in WA (%) than that of normal or EB subjects ($p= 0.009$).

Centrilobular prominence was observed in 78% of the asthmatics and in 93% of the patients with EB, but was not observed in any of the controls. The grade of centrilobular prominence was significantly higher in asthmatics and patients with EB than in controls ($p = 0.024$, $p= 0.035$, respectively), but there was no difference between the former two groups ($p > 0.05$; Fig. 3B). Air trapping was observed in 83% of mild asthmatics and in 87% of patients with EB, but was not observed in controls. The grade of air trapping was significantly higher in asthmatics and patients with EB than in controls ($p = 0.025$, $p= 0.032$, respectively), but there was no difference between the former two groups ($p > 0.05$; Fig. 3C). None of the controls showed air trapping or centrilobular prominence. None of the patients with EB and none of the asthmatics had bronchiectasis or emphysema. Ground glass opacities were not observed in any of the subjects.

Correlation of airflow limitation and abnormal thin-sliced CT findings

We investigated the correlation between changes in the airway morphology observed using thin-section CT and the degree of airflow obstruction FEV1 (% pred.), FEV1/FVC (%), $FEF_{25-75\%}$ (%pred.) and AHR (PC20 methacholine) in asthmatics and EB patients. The airway wall area percentage was inversely correlated with FEV 1 and FEV1/FVC in the asthmatics ($r = –0.42$, $p = 0.026$ and $r = –0.54$, $p = 0.015$, respectively; Table 2, Fig. 5), but not in the patients with EB ($r = –0.04$, $p > 0.05$ and $r = –0.12$, $p > 0.05$ for FEV1 (% pred.) and FEV1/FVC (%), respectively). Other parameters including air trapping and centrilobular prominence were not correlated with FEV1 (% pred.) and FEV1/FVC (%) in either asthmatics or EB patients (Table 2). $FEF_{25-75\%}$ (% pred.) were not correlated with WA (%) or any other parameters in asthmatics or EB subjects ($r = –0.18$, $p > 0.05$, $r = –0.12$, $p > 0.05$, $r = -0.08$, $p > 0.05$ for the airway wall area percentage, centrilobular prominence, and air trapping, respectively). We also investigated the relationship between changes in the airways and AHR (PC20 methacholine) in asthmatics and found that none of the parameters related to morphological changes in the airways was correlated with AHR in this group ($r = –0.02$, $p > 0.05$, $r = –0.06$, $p > 0.05$, $r = 0.12$, $p > 0.05$ for the airway wall area percentage, centrilobular prominence, and air trapping, respectively).

DISCUSSION

AHR in asthma may be mainly attributed to the inflammation and remodeling of the airways as a consequence of epithelial damage, subepithelial fibrosis, increased airway vasculature, deposition of proteoglycans, and smooth muscle changes.[32] In this study, the relationship between airway morphology and AHR in patients with EB and asthmatics was compared using thin-section CT. We observed no thickening of the large airway walls in patients with EB, whereas paients with mild asthma had significantly thicker walls in the large airways compared to patients with EB. Given that the extent of airway inflammation is comparable between these two diseases, thickening of the large airways in asthmatics would appear to be due to airway remodeling rather than inflammation. In addition, we found that the amount of air-trapping and centrilobular prominence was similar in patients with EB and asthmatics. These results suggest that the absence of thickening of the walls of the large airways in patients with EB may be one of the reasons for the normal airway responsiveness to methacholine in these patients. Moreover, AHR in asthmatics may be attributed to thickened large airways, rather than to changes in the small airways.

To our knowledge, our study is the first in which patients with EB have been compared to asthmatics with a similar extent of airway inflammation. Therefore, the results of this study may be clearer than those of studies that compared asthmatics to normal control subjects, which produced conflicting results. For example, Boulet and coworkers[10] reported that airway wall thickness (measured using HRCT) was correlated with AHR in asthmatics with fixed airway obstructions. In contrast, Little and coworkers [4] failed to demonstrate a relationship between airway wall thickness and AHR in chronic asthmatics.

Recently, Niimi and coworkers[9] evaluated the relationship between airway sensitivity and airway reactivity versus bronchial wall thickness and airway inflammation. They found that airway reactivity was correlated negatively with airway wall thickness, while airway sensitivity was related to the degree of airway inflammation but not to airway wall thickness. However, dissociation of eosinophilic inflammation from AHR has been observed in asthmatics undergoing treatment with inhaled steroids. For instance, the elimination of inflammation by glucocorticoids was reported to improve but not to eliminate AHR.[33] In our study, the effect of airway inflammation on AHR could be excluded because asthma and EB are both associated with a similar degree of sputum eosinophilia (Table 1). We did not measure airway inflammation using mucosal biopsies. However, airway inflammation can be assessed by measuring the cellular components of sputum.[18] In addition, because asthma and EB are pathologically similar eosinophilic

inflammatory airway diseases,[12] it seems reasonable to compare asthma with EB to exclude the effect of airway eosinophilia on AHR.

In this study, airway wall area was similar in patients with EB and in normal control subjects. In our previous long-term study of patients with EB[16], most EB patients exhibited transient sputum eosinophilia that persisted for less than two months and showed no derangement of airflow rate and associated symptoms. Based on our previous observations and the findings of the present study, absence of airway wall thickening may be associated with transient airway inflammation as reflected by the relatively short-term eosinophilia within the airways of patients with EB.

AHR may develop when airway inflammation and remodeling have increased progressively over months or years. This causes the recruitment of inflammatory cells and the release of mediators over the short term. However, over the long term, underlying structural changes (e.g., subepithelial fibrosis, extracellular matrix deposition) cause irreversible airway remodeling.[34] Thickening of the airway smooth muscle layer[35] abnormality in autonomic neuronal control[36]and vascular factor such as vascular endothelial growth factor (VEGF)[37] also had potential to contribute to AHR in the asthma. It has been well documented that there were some differences and similarities between BA and EB in the aspect of immunopathology by biopsy or sputum study. Previous studies of asthma have reported thickening of the basement membrane layer, reduction in epithelial integrity, increased iNOS expression.[38, 39] Using bronchial biopsy, bronchoalveolar lavage, and induced sputum, Brightling et al. have shown that asthma and EB are similar immunopathology findings except mast cell infiltration into the smooth muscle of asthma.[40]

A morphometric and cellular analysis revealed the same degree of basement membrane thickening and cellular infiltration in patients with EB and asthmatics.[12,40] Recently, Kanazawa and coworkers [41] found that the production of VEGF and airway permeability were increased in asthmatics but not in patients with EB. Brittling and coworkers [42] also found that infiltration of airway smooth muscle by mast cells that expressed interleukin-4 and -13 was characteristic of asthma but not of EB. IL-13 was highly detected in the sputum and mucosa of asthmatics than EB[42,43], and sputum IL-13 levels were inversely correlated with PC20 methacholine value in asthma.[43] These findings raise the possibility that interactions between mast cells and airway smooth muscle and the overproduction of cytokines may contribute to the thickening of the bronchial walls and to the development of AHR.

It is certain that the results obtained from the microscopic evaluation using these procedures give us many important information in the aspect of

immunopathophysiology of asthma and EB. However, the aforementioned studies compared asthma and EB microscopically, rather than grossly. Moreover, thickening of whole bronchial walls, small airway abnormalities, or any other gross morphology can not be precisely evaluated with these procedures. Our gross examination of airway morphology using thin-section CT revealed that EB is associated with normal airway wall thickness despite the presence of eosinophilic airway inflammation.

In our study, air trapping and centrilobular prominence were shown 83% and 78% of asthmatics. These values are higher than those reported from the other investigators.[31, 44, 45] The different results between the studies might be due to different methodology of CT scaning, different scoring system, and ethnic differences.

We analyzed the WA% by the inner diameter of 2 mm (small vs. large airways) in the three groups. WA% of small airway (1.5-2 mm in inner diameter) was greater than that of large airway in BA (85±3.1 (%) vs. 68±3.2 (%), p= 0.012) . However, we found no significant difference of the airway wall area percentage between large (>2 mm in inner diameter) and small airways (1.5-2 mm in inner diameter) in EB group. In addition to greater degree of centrilobular prominence and air trapping, this result suggests that small airways of diameter less than 1.5 mm may be a major site at which eosinophilic inflammation occurs during EB.

The small airway abnormalities such as prominence of centrilobular structures and air trapping were partially reversible in the both near fatal asthma and non-near fatal asthma groups following steroid treatment.[46] However, it is not known whether the changes that occur in the small airways of patients with EB have reversibility over time after anti-inflammatory drugs. Further studies are needed to investigate change of small airways over time in eosinophilic bronchitis.

In conclusion, EB causes remarkable changes in the small airways that are reflected by an increase in air trapping and centrilobular prominence, which resembles the changes that occur in asthmatics. However, the thickness of the large airway was normal in patients with EB, which may explain the normal responsiveness of such patients to methacholine. Moreover, this finding implicates bronchial wall thickening in the AHR that characterizes asthmatics. Finally, increased air trapping and centrilobular prominence may be indicative of the presence of diseased small airways in patients with EB.

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Figure legends

Figure 1. A 45-year-old man with mild persistent bronchial asthma. a) Inspiratory thin-section CT scan shows diffuse bronchial wall thickening (arrows) and prominence of centrilobular structure (arrowheads, score 1) in the right lower lobe. b) Expiratory thin-section CT scan shows geographic air trapping (arrows, score 2) at the same level of the right lower lobe.

Figure 2. Schematic explanation about measurement of airway wall area percentage (WA%). D: Outer diameter of bronchus, L: Inner diameter of bronchus

Figure 3. Comparison of airway wall area percentage (WA%) (A), prominence of centrilobular structure (B), air trapping (C) on HRCT between eosinophilic bronchitis group (EB), mild asthma group and normal controls.
Airway wall area percentage was higher in group of asthma than group of EB or normal controls (A). Prominence of centrilobular structure was higher in EB than group of asthma, but the difference was not statistically significant ($p > 0.05$) (B). Air trapping was higher in group of asthma than EB, but there was no statistical difference ($p > 0.05$). Group of EB and asthma had a greater air trapping than that of normal controls (C).
Bar represents mean ± SEM.
*: $p = 0.032$ compared with EB and normal controls.
**: $p < 0.05$ compared with normal controls.
WA (%): Airway wall area percentage.

Figure 4. Inter-observer and intra-observer variances for the measurement of airway wall area percentage (WA%). The mean of and difference between two measurements are plotted. The dotted and dashed lines represent the mean and mean ± 2SD of the difference, respectively.

Figure 5. Correlation between airway wall area percentage (WA%) and FEV1 (% pred.) in the group of mild asthmatics. WA% was inversely correlated with FEV_1 (% pred) ($r = -0.42$, $p = 0.026$).

Table 1.

	Normal Control	Eosinophilic Bronchitis	Mild Asthma
Sex (M/F)	4/7	6/9	7/11
Age (years)	46.2 ± 3.23	51.8 ± 4.74	49.3 ± 4.44
FVC(% pred.)	98.6 ± 3.16	91.7 ± 2.15	94.3 ± 3.24
FEV1(% pred.)	95.3 ± 4.05	93.5 ± 2.18	88.5 ± 6.16
FEV1/FVC(%)	94.2 ± 4.24	89.4 ± 2.72	85.6 ± 5.36
FEF_{25-75}(% pred.)	94.6 ± 3.61	83.8±9.32	64.4 ± 8.21*
PC_{20}(mg/ml)	24.5 ± 1.0	20.8 ± 1.17	1.62 ± 1.23†
Atopy (n)	2	7†	11†
Serum IgE (u/ml)	64.9 ± 17.04	135.2 ± 123.6	337.7 ± 104.3†
Sputum cell profile			
Total cell count x 10^6 /ml	3.23 ± 2.09	7.98 ± 1.52*	10.34 ± 2.43*
Viability (%)	90.2 ± 2.7	84.8 ± 1.7	83.9 ± 2.6
Macrophage (%)	54.7 ± 3.4	67.5 ± 4.6	72.8 ± 5.2
Neutrophil (%)	34.9 ± 6.4	12.8 ± 6.1*	10.96 ± 4.2*
Lymphocyte(%)	1.9 ± 0.6	2.7 ± 0.4	1.8 ± 0.3
Eosinophil (%)	0.5 ± 0.2	10.9 ± 1.3†	12.2 ± 4.6†
Bronchial epithelial cells (%)	5.3 ± 2.7	7.6 ± 3.1	8.2 ± 1.6
Squamous Cell (%)	5.1 ± 0.6	4 ± 0.4	3.2 ± 1.2

Data are presents as mean ± SEM

*: **p < 0.05 compared with normal control**

†: p < 0.01 compared with normal control

PC20 values are expressed as geometric means

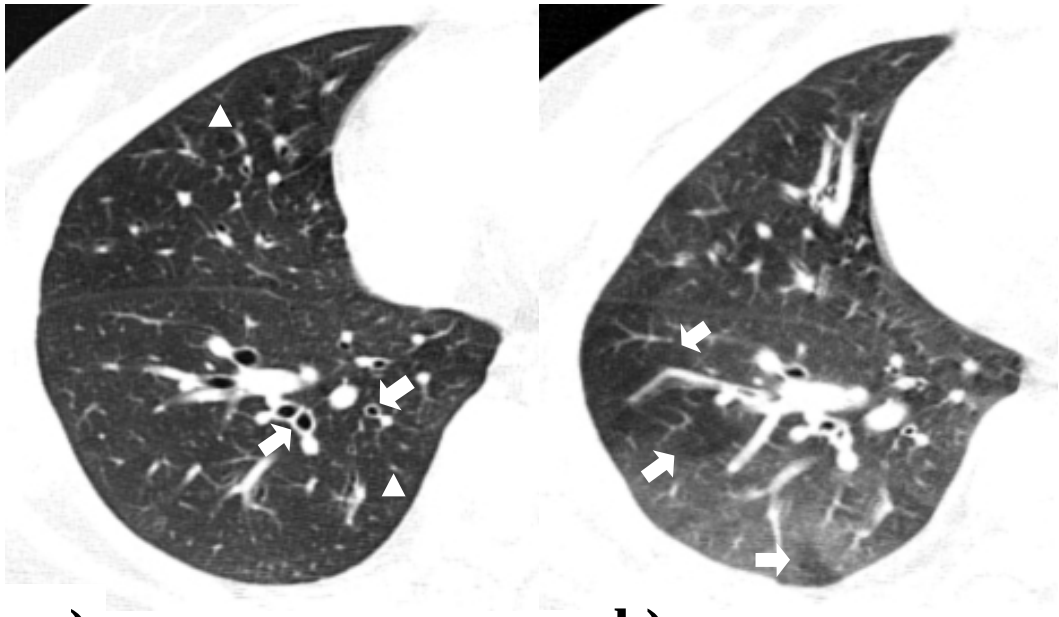
Table 2. Correlation coefficient between the abnormality on thin-section CT and the degree of airway obstruction [FEV1 (% pred.) / FEV1/FVC (%)]

	EB (n=15)	Asthma (n=18)	NC (n=11)
Airway wall area percentage (WA %)	-0.04/-0.08	-0.42* / -0.54**	-0.02/-0.14
Prominence of centrilobular structure (grade)	-0.21/-0.12	-0.04/-0.11	0
Air trapping (%)	0	-0.26/-0.22	0

*: p=0.026 correlation from FEV1 (% pred.).

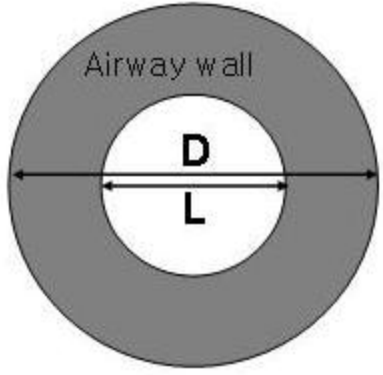
**: p= 0.015 correlation from FEV1/FVC (%).

Figure 1



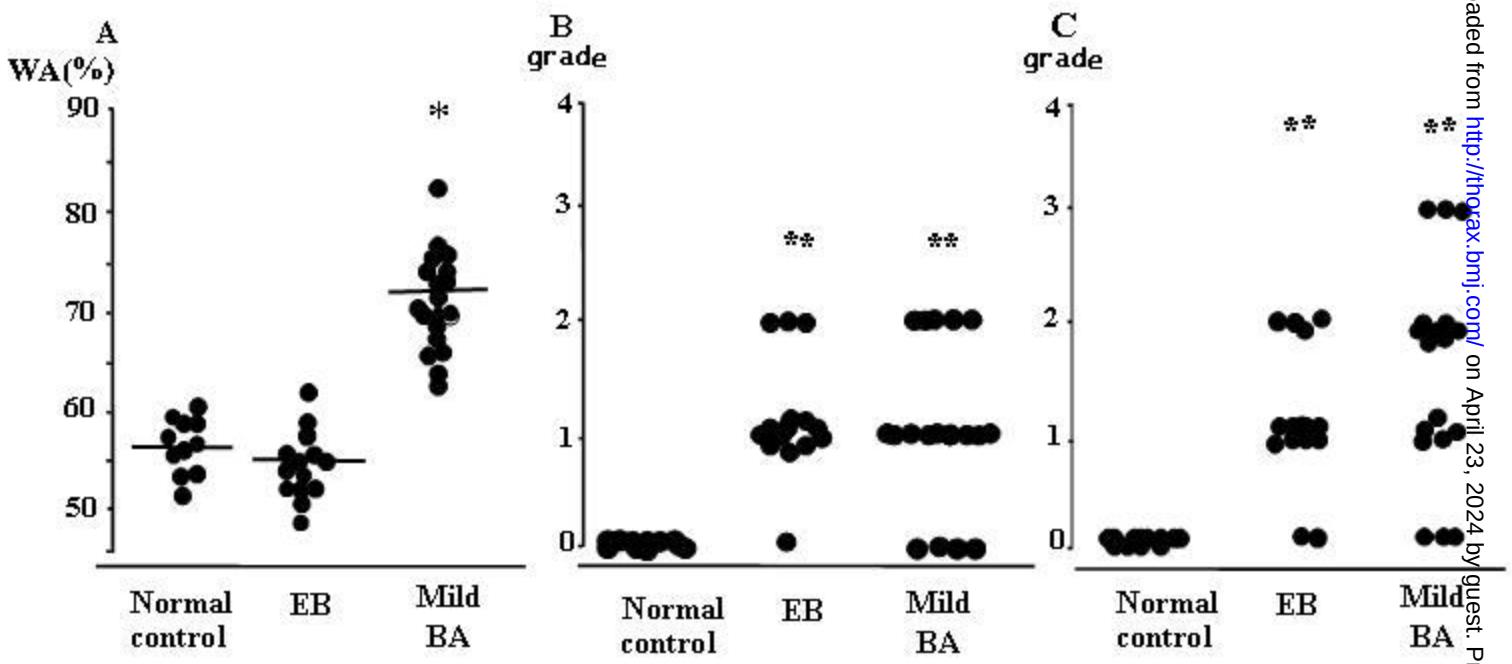
a) b)

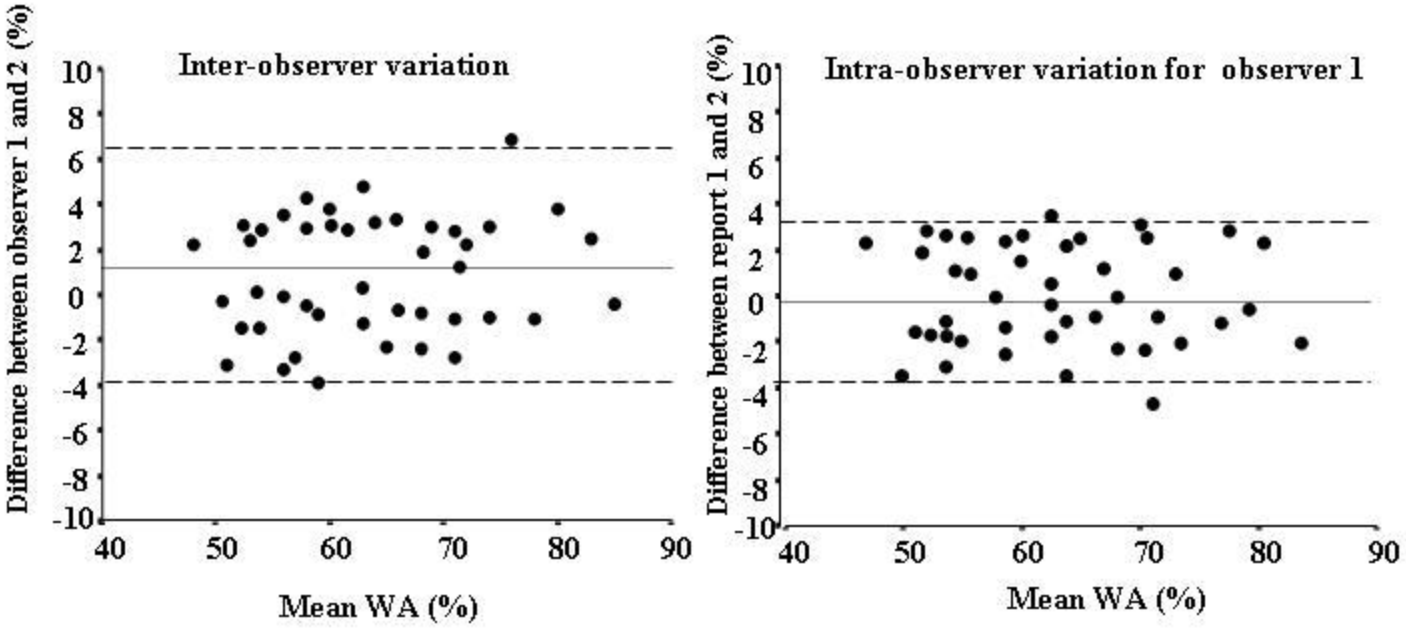
Figure 2.



$$WA\ (\%) = \left(\frac{\pi(D/2)^2 - \pi(L/2)^2}{\pi(D/2)^2} \right) * 100$$

Figure 3.





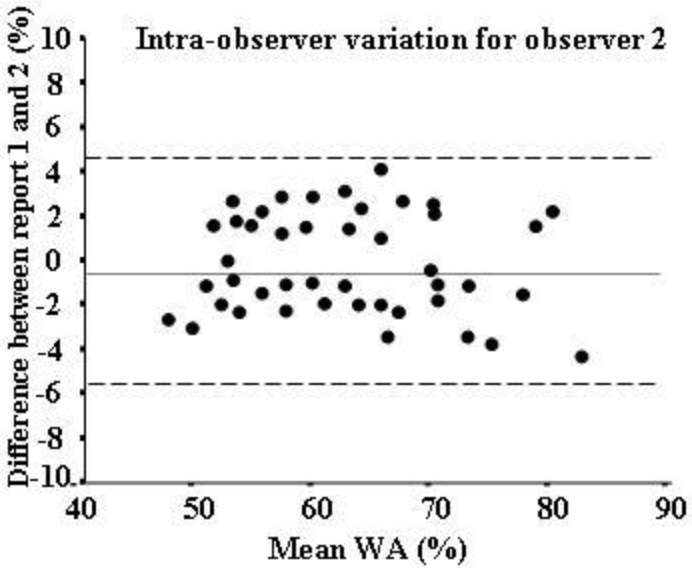


Figure 4.

Figure 5.