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Title	Airflow limitation and airway dimensions assessed per bronchial generation in older asthmatics
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Citation	Respiratory Medicine, 104(12), 1809-1816 https://doi.org/10.1016/j.rmed.2010.06.013
Issue Date	2010-12
Doc URL	http://hdl.handle.net/2115/44536
Type	article (author version)
Additional Information	There are other files related to this item in HUSCAP. Check the above URL.
File Information	RM104-12_1809-1816.pdf

Abstract word count: 248words

Airflow limitation and airway dimensions assessed per bronchial generation in older asthmatics (94/100words)

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Running title (50/50letters): Airflow limitation and airway dimensions in asthma

Key words: airway remodelling; HRCT; pulmonary function

ABSTRACT

Background: Computed tomography (CT) has been used for non-invasive quantitative assessment of airway dimensions, potentially showing airway remodeling, in asthma. However, most studies have examined either only one airway or only airways in anatomically unidentified cross-sections. Using software capable of precisely identifying the generation of airways and measuring airway dimensions perpendicular to the long axis of airways, we examined, in older patients with stable asthma, how inter-subject variation in airway dimensions correlated among the 3rd to 6th generation of airways, and then examined relationships between airway dimensions of each generation and indices of airflow limitation.

Methods: Subjects aged ≥ 55 years old comprised 59 asthmatic patients who underwent CT and pulmonary function tests on the same day. We measured airway wall area (WA%) and inner luminal area (Ai) from the 3rd to the 6th generation of eight bronchi in the right lung.

Results: Excellent correlations were identified for both WA% and Ai among the generations (r=0.744-0.930 for WA%) when we took the average of all measured bronchi per generation as a personal representative value. Significant correlations of airflow limitation indices with both WA% and Ai/BSA were found at each of the 3rd to 6th generations with similar correlation coefficients (WA% for FEV1%predicted, r= -0.410 to -0.556).

Conclusions: In older patients with stable asthma, airway wall thickening and narrowing might occur in a parallel manner through 3rd to 6th generation airways. Airway dimensions at these areas of airways may thus have significant and similar correlations with indices of airflow limitation.

ABBREVIATION LIST

Ai = inner luminal area

BSA = body surface area

COPD = chronic obstructive pulmonary disease

CT = computed tomography

Di= inner diameter

ICS = inhaled corticosteroid

IgE= Immunoglobulin E

WA = airway wall area

3D = 3-dimensional

INTRODUCTION

Bronchial asthma is characterized by reversible airflow limitation and hyperresponsiveness to constricting stimuli. Pulmonary function tests, however, have revealed that airflow limitations in some patients fail to reverse completely despite optimal treatment.[1,2] This phenomenon has been assumed to result from poorly reversible structural changes in airway remodeling, including increased airway smooth muscle mass and sub-epithelial thickening of the basement membrane.[3]

Computed tomography (CT) has been used for non-invasive quantitative assessment of airway dimensions, potentially indicating airway remodeling and providing valuable morphological information about the airways in vivo.[4-21] Airway wall thickening and airway narrowing have been repeatedly reported in patients with asthma compared with healthy controls.[4-6,8,16,22,23] However, only a few studies have attempted to examine relationships between indices of airflow limitation and airway wall dimensions detected on CT in stable asthmatic patients. In some reports, analyses have been limited to airway dimensions of only one airway or only of the third generation,[16,23] while other reports have attempted to analyze more distal airways, but have examined only airways cut in cross-section on CT, so airway dimensions were probably compared at anatomically different generations.[7,24,25] Only recently, Montaudon et al.[26] examined the relationship between morphometrically derived airway indices using 3-dimensional (3D)-CT and indices of airflow limitation. They introduced interesting parameters, namely slope of the wall area/lumen area and slope of wall area/total wall area as a function of generation, revealing that these parameters correlated significantly with some indices of airflow limitation. However, relationships of airway dimensions among bronchial generations or between airway dimensions at each generation and airflow limitation indices have not yet been explored.

The present study aimed to apply our 3D software (AZE, Tokyo, Japan) for a

structure-function study in older patients with stable asthma, by which we could identify the generation of airways and measure accurate cross-sectional images of airways until the 6th generation. The specific aims were to examine how inter-subject variations in airway dimensions correlated among the 3rd to 6th generation of airways, and to clarify relationships between airway dimensions of each generation and indices of airflow limitation in those patients.

METHODS

Subjects

Asthmatic patients who consented to participate in this study were prospectively recruited from Hokkaido University Hospital and Hokkaido Social Insurance Hospital from 2006 through 2009. Bronchial asthma was diagnosed based on the American Thoracic Society criteria.[27] Entry criteria were: i) clinically stable—that is, the patient had not experienced any asthma attacks or major changes in medication for >6 weeks before study entry; ii) age ≥ 55 years; iii) life-long non-smokers or smokers with a <10-pack/year lifetime smoking history; and iv) no obvious signs of emphysema on CT. Duration of disease was defined as the duration from when the patient first recollected wheezing to the time of examination.

All study protocols were approved by the Health Authority Research Ethics Committee of Hokkaido University School of Medicine.

CT Data Acquisition and Analysis

CT was performed using a multidetector-row spiral CT scanner with 64 detector arrays (Aquilion Multi, TSX-101A/6A; Toshiba Medical Systems, Gunma, Japan). Data were acquired with the following parameters: 120 kVp; 300 mA; 64 detector $\times$ 0.5-mm collimation; slice thickness, 0.5 mm; 0.5 s/rotation; helical pitch, 41. The entire lung was scanned with the

patient in a supine position, holding his or her breath in deep inspiration. On the study day,

the patients were asked to take their medications as usual. Data were transferred to a

workstation and then reconstructed into 3D images. The detailed process of CT data

acquisition and reconstruction has been described previously[28] and is available in the Online

Repository. Identification of the generation of bronchi relied on careful inspection,

simultaneously using longitudinal and short-axis images and searching for any bifurcations in

the entire circumference.We first define a segmental bronchus as the 3rd generation of bronchi,

and then proceed toward peripherally, using the longitudinal image and the short axis image

simultaneously and searching for any bifurcation all around circumference.

On the monitor of the work station, image interpretation was performed using window width

of 1,000 and a window level of -700. From the centroid point of the lumen, rays fanning out

over 360°were examined to determine airway wall thickness along the rays using the

full-width at half-maximum principle[29, 30]. After this process, if the outline of automatically

obtained airway walls was obviously out of contour, correction was made. Based on manual

plotting at several points, our software used cubic spline interpolation and built a new circle.

Finally, we obtained values for the inner luminal area (Ai) and the outer area of the bronchus

(Ao). At each bifurcation, we randomly selected one bronchus in general. In the case that

image of one bronchus is poor or one bronchus is obstructed, however, we then selected one

which would have been more easily identified until the 6th generation. We measured airway

dimensions of eight bronchi in the right lung; apical (B1), posterior (B2), and anterior (B3) of

the upper lobe; lateral (B4) and medial (B5) of the middle lobe; and anterior basal (B8),

lateral basal (B9), and posterior basal (B10) of the lower lobe, at the midpoint between

bifurcations, from the 3rd to 6th generation. A representative view of one airway for analysis is

shown in Figure 1. As shown in Figure 1c, Wall Area (WA) was calculated as (Ao-Ai). We

then determined wall area percent (WA%) defined as WA/Ao × 100 and Ai after correcting

for body surface area (Ai/BSA) for the parameters of airway dimensions. We took the average from all bronchi measured for comparison among generations and for comparison with airflow limitation indices. All measurements were performed by one of the authors (K.S.), who was blinded to any other subject information.

Pulmonary Function Tests

We conducted pulmonary function tests at 1-3 h after CT was performed. We measured spirometry, diffusing capacity for carbon monoxide, and lung volumes assessed by the helium closed-circuit method (CHESTAC-33; Chest M.I., Tokyo, Japan). Spirometric measurements included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and maximal mid-expiratory flow (MMF). Lung volume measurements included total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV). Details of procedures and prediction equations used are described in the Online Repository. Spirometry was repeated 30 min after inhalation of 200 μg of salbutamol to evaluate the remaining reversibility on the examination day. We used pre-bronchodilator values of pulmonary function parameters for comparison with the data obtained from CT.

Statistical Analysis

SPSS software (SPSS, Tokyo, Japan) was used for all statistical analyses. All the data are expressed as mean ± standard error of the mean for comparison. We used analysis of variance to analyze differences among lobes and among generations in mean values of WA% and of Ai/BSA. Pearson correlation coefficients were used to examine relationships among the 3rd to 6th generations of airways, and also relationships between airway dimensions and pulmonary function parameters. Values of $p<0.05$ were considered significant.

RESULTS

Characteristics of the 59 subjects who met the entry criteria are presented in Table 1. The step classification of asthma was based on the Global Initiative for Asthma 2005.[31]

Most subjects were classified as moderate persistent or severe persistent. The majority of the subjects [55/59; 93%] were taking inhaled corticosteroids and 26 patients [44%] were taking long-acting β agonist inhalers and 28 patients [47%] were taking leukotriene receptor antagonists Results of pulmonary function tests are summarized in Table 3.Although all subjects were clinically stable, FEV1 %predicted varied from 49.7% to 112.5% (mean, 87.1 ± 2.1%). A similar wide variation was observed for other pulmonary function parameters, and FEV_1/FVC was <70% in 41 patients (69%). The reversibility of airflow limitation was 6.5 ± 0.8%. Nine patients increased their FEV1 by more than 200ml and 12% from the baseline after inhaling a bronchodilator.

Online Table E1 shows mean values for two airway parameters (Ai/BSA, WA%) at all 32 measurement sites, from the 3rd to 6th generation of eight bronchi in the right lung. We failed to obtain data at all 32 measurement sites in some subjects, as clear images of airways could not always be obtained. The number of subjects for whom measurements were available at each site is shown in Online Table E1; we missed data from a considerable number of subjects, particularly at the 5th and 6th generations of B4, B5, and B9 bronchi.

Averages were taken from all bronchi measured per generation for later analyses. Excellent correlations in inter-subject variations were seen for both mean WA% and mean Ai/BSA among generations (Table 2, E1).

We then examined relationships between mean WA% at each generation and pulmonary function parameters. Significant correlations were seen between airway dimensions at all generations and indices of airflow limitation, including FEV1 %predicted (Fig. 2), FEV1/FVC, and MMF %predicted (Table 4).

Of note, correlation coefficients were similar from the 3rd to 6th generations. Since mean values for WA% and Ai/BSA correlated well at all bronchial generations (3rd, r=-0.867; 4th, r=-0.857; 5th, r=-0.881; 6th, r=-0.870; p<0.01), similar relationships between structure and function were found also for Ai/BSA (Table 4). In other words, the more pulmonary function deteriorated, the thicker the airway wall and the narrower the airway caliber became at any generation.

Duration of asthma also correlated significantly with Ai/BSA and WA% at any generation, suggesting that patients with longer duration had thicker airway walls and narrower airway caliber (Table 4).

Finally, we performed a separate analysis by sex, as airway dimensions and airway remodeling may differ between men and women (Online Tables E2, E3). We generally found similar results in both groups and significant correlations of WA% with pulmonary function parameters, including FEV1 %predicted, FEV1/FVC, MMF %predicted, and FEV1 at the 3rd to 6th generations, with the exception of FEV1 %predicted at the 3rd generation in women.

DISCUSSION

This study simultaneously measured pulmonary function and airway dimensions from the 3rd to 6th generation of eight bronchi in the right lung of 59 older patients with clinically stable asthma. First, we found excellent correlations in inter-subject variation of both WA% and Ai/BSA among the 3rd to 6th generations when we took average data from all bronchi measured per generation. Second, significant correlations were noted between indices of airflow limitation and airway dimensions at any level from the 3rd to 6th generation with similar correlation coefficients. Interestingly, this contrasts with COPD, where airway dimensions from the 5th to 6th generation demonstrated better correlations with indices of airflow limitation than airway dimensions from the 3rd to 4th airways in our previous study.[32]

We chose either lifelong non-smokers or past smokers with a lifetime smoking history of <10 packs/year whose age was ≥55 years old. Furthermore, we excluded individuals with any evidence of apparent emphysema on lung CT. Consequently, subjects who showed airflow limitation in this study were likely to have poorly reversible airway remodeling, largely caused by long-standing bronchial asthma, which is concordant with the results of previous studies.[33-35] Another distinct reason for choosing only older subjects for the present study was that we were concerned about the risks of radiation exposure in younger subjects.[36]

The present investigation took the average of all bronchi measured per generation as a representative value. Aysola et al.[23] recently used an automated, quantitative 3D approach to assess airway remodeling in bronchial asthma and measured airway dimensions at all segmental bronchi (comparable to the 3rd generation) from both lungs. They recognized the heterogeneity of airway dimensions among bronchi and thus took the average for comparison with pulmonary function. The present study demonstrated that the inter-subject variations in airway dimensions were very consistent among the generations form the 3rd to the 6th when we took the average per generation. These findings support the concept that airway disease—that is, wall thickening and/or airway narrowing—are likely to progress in a similar fashion from the 3rd to 6th bronchial generations at least in older asthmatics who are clinically stable. In other words, airway alteration at the 3rd generation could offer a good surrogate marker for changes in more distal airways of those asthmatic patients. This was echoed in COPD by Nakano et al.,[37] who demonstrated that mean WA% measured by CT for airways with a luminal perimeter >0.75 cm approximately predicted the mean dimensions of small airways with an internal diameter of 1.27 mm.[37] The equivalent diameter (Di) of an airway with a luminal perimeter of 0.75 cm is 2.39mm, which is almost equivalent diameter of airways from the 5th to 6th generation in our subjects.

Although numerous CT studies have been performed in bronchial asthma, only a few have

attempted to examine relationships between indices of airflow limitation and airway wall dimensions detected on CT in well-controlled asthmatic patients. Some investigators have examined only the segmental levels of bronchus.[16,22,23] Others have attempted to analyze more distal airways,[7,24,38,39] but had to choose only airways cut in cross-section on CT slices and to compare airway dimensions that were probably at different generations. While some found significant correlations of wall thickness with airflow limitation,[24,38] others failed to find such correlations.[7,39] We found significant relationships between indices of airflow limitation and airway dimensions at the 3rd to 6th airway generations in older patients with clinically stable asthma and, in addition, confirmed that correlation coefficients were very similar among generations.

In COPD, we and others have previously reported that correlation coefficients of airway dimensions with airflow limitation indices were better in distal airways than in proximal airways of the 3rd to the 6th generations.[20,39,40] In this study, however, we did not find such characteristics in terms of structure-function relationship. This may be explained by differences in the site of airway remodeling between diseases. Another explanation may lie in the effect of elastic recoil pressure surrounding the airway on inner luminal area. In COPD, not only airway disease but also emphysema is likely contribute to airway narrowing, thus causing Ai to be more closely correlated with function compared with WA%, whereas both Ai and WA% have similar relationships with function in bronchial asthma. The third explanation is that the degree of airflow limitation observed in this study population was not as severe as in COPD, so the involvement of small airway remodeling might not have been notable.

Of particular note, we found significant relationships of airflow limitation indices not only with WA%, but also with Ai/BSA. In contrast with airway wall thickening, which has been repeatedly reported in patients with bronchial asthma, controversy remains regarding airway luminal area. Although some studies have shown reduced airway luminal area in patients with

bronchial asthma compared with healthy controls,[8,17] other have found no such differences.[16,22] Our data suggest that airway wall thickening leads to airway narrowing, when the patients display airflow limitation.

Several limitations in this study require consideration. First, only older subjects with stable asthma were enrolled and most were classified as moderate persistent or severe persistent. Thus, the results in this study might not be applicable to younger patients nor patients who would be classified as intermittent and/or mild persistent. Second, as pulmonary function of the subjects overall was relatively preserved, it might be premature to compare the findings of this study with those of the past studies which had dealt with COPD. Comparison between the asthma and COPD would be highly interesting if the level of airflow limitation was comparable in the two groups. Third, sex-related differences have recently been reported not only in emphysema,[41] but also in airway disease in COPD.[42] Subjects in this study comprised 22 men and 37 women, so that the numbers may have been inadequate for comparison between sexes. Finally, we must also note technological limitations of our 3D airway analysis. As not all of the 5th and 6th generation of airways could be identified, there might have been selection bias of sampled airways. However, the advantage would be that we could compare the data per generation among the subjects, which could not have been performed in any of the past studies. Excellent correlations in airway dimensions among the generations of airways we found in this study may indicate superiority of our 3D analysis over other previously reported analyses, despite such bias. Another technical criticism might be use of the full-width-half-maximum method for determination of airway wall because this algorithm is reported to underestimate airway luminal area and to overestimate airway wall thickness particularly in airways of small diameters[43]. We, however, compared the data among the subjects, using the same generation of airways (i.e. the similar size of airways), which would minimize the potential systemic errors. Finally, even with progress in CT technology and the

present advanced algorithms, we cannot yet measure the airway dimensions of what we call "small airways," which are defined as those with diameters <2 mm.

In conclusion, in clinically stable and older asthmatics, excellent correlations existed in inter-subject variation of airway dimensions measured by 3D-CT, among the 3rd to 6th generations, supporting the concept that airway wall thickening and airway narrowing occurs similarly at these areas of airways. Second, airway dimensions correlated significantly with indices of airflow limitation at any level from the 3rd to 6th generation of airways to a similar extent in those asthmatic population.

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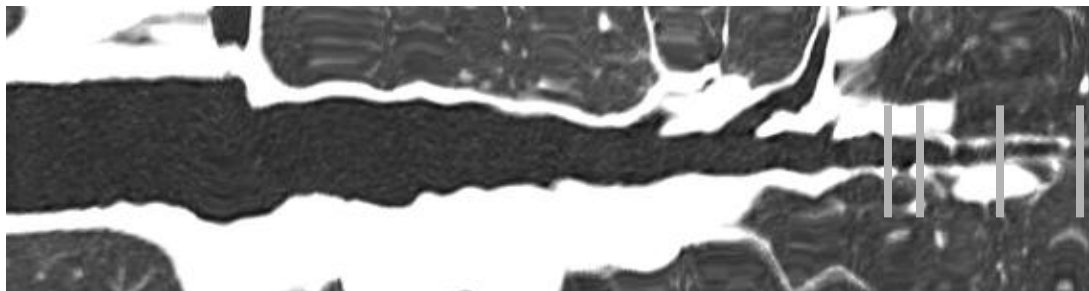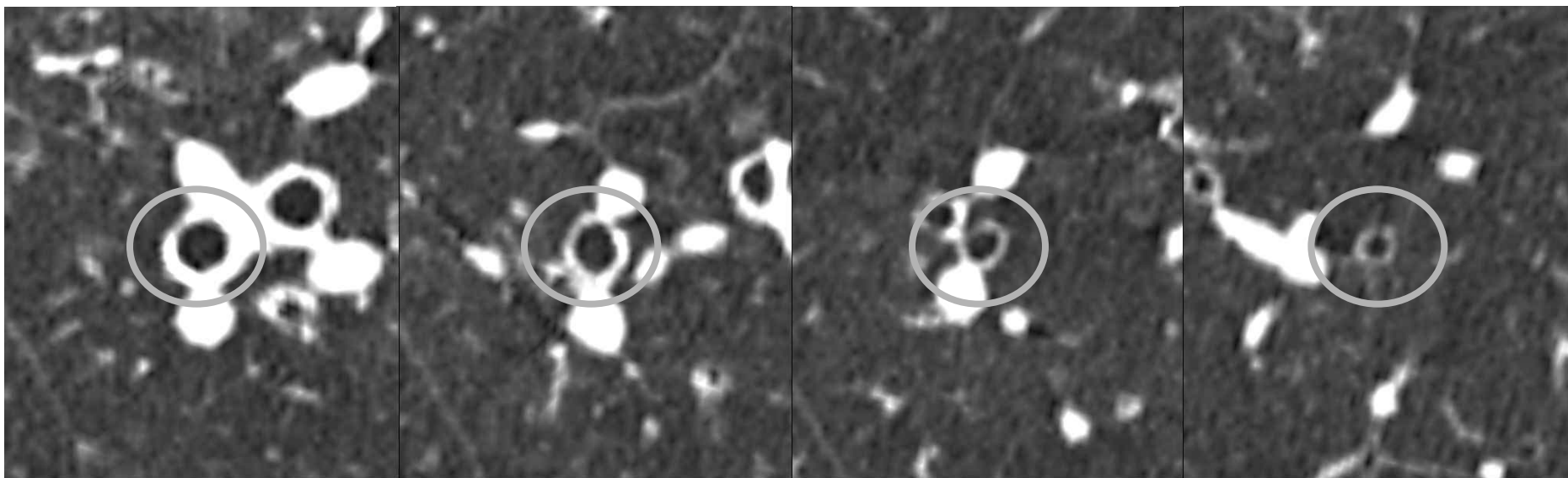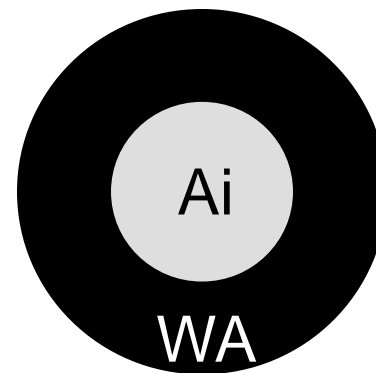
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FIGURE LEGENDS

Figure 1 a) A curved multiplanar reconstruction (MPR) image of the anterior basal bronchus from the right lower lobe. **b)** Short-axis images, obtained from the curved MPR image, are precisely perpendicular to the long axis of the airway. Identification of the generation of bronchi relied on careful inspection, simultaneously using longitudinal and short-axis images and searching for any bifurcations in the entire circumference. At each bifurcation, we randomly selected one bronchus. Red lines and circles indicate the same sites analyzed. **c)** We measured inner luminal area (Ai), outer area of the bronchus (Ao). Wall Area (WA) was calculated as (Ao-Ai) and Wall area corrected for the size of the bronchus was calculated as WA/Ao (WA%)

Figure 2. Relationships between FEV1, %predicted and mean WA% of all bronchi measured. Significant correlations were seen between WA% and FEV1 %predicted at all airway generations. Data from men and women are separately shown in Online E2, E3, respectively. Wall area corrected for the size of the bronchus was calculated as WA/Ao (WA%)

a

c

Inner luminal area (Ai)
Wall area (WA)
Ao = Ai+WA
WA% = WA / Ao × 100

b

3rd generation   4th generation   5th generation   6th generation
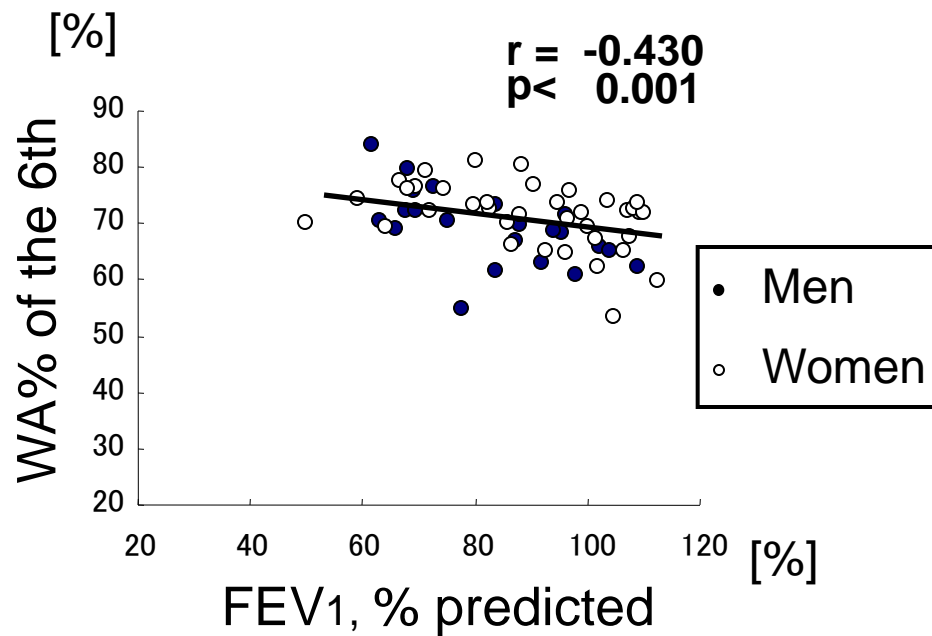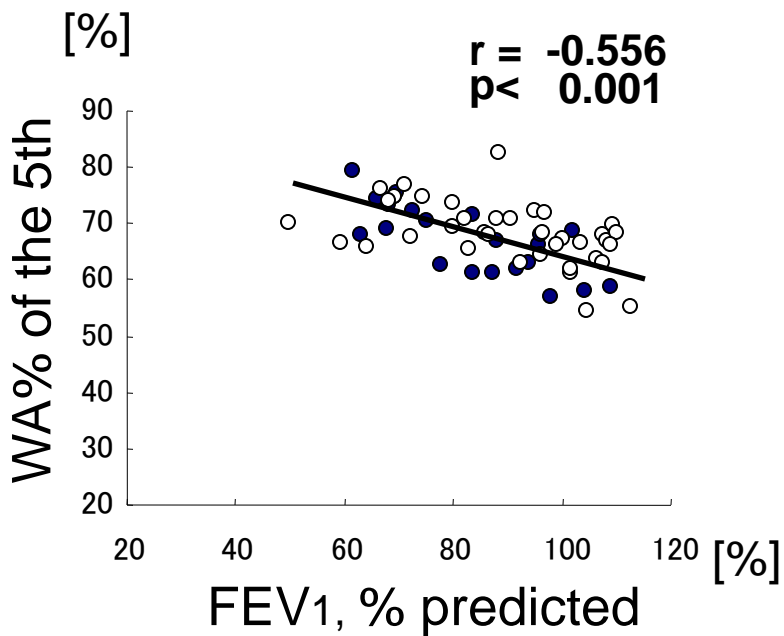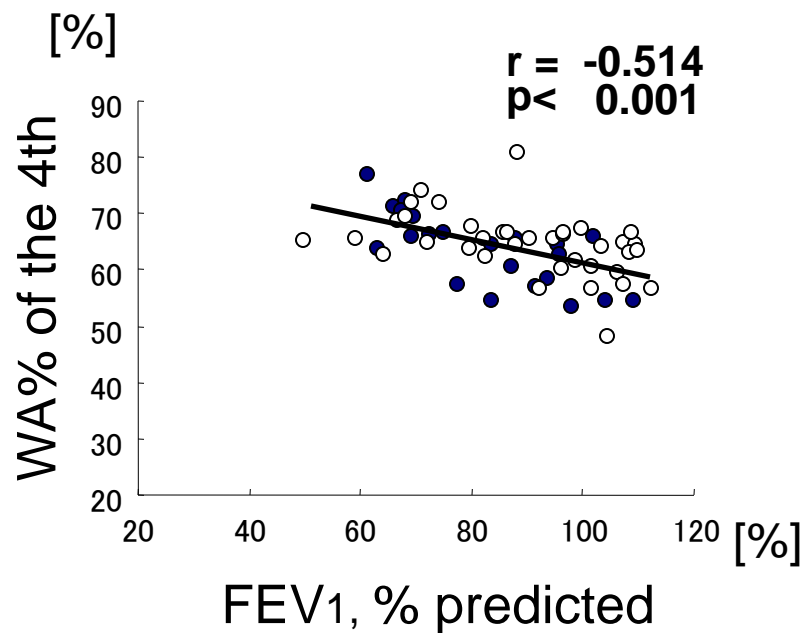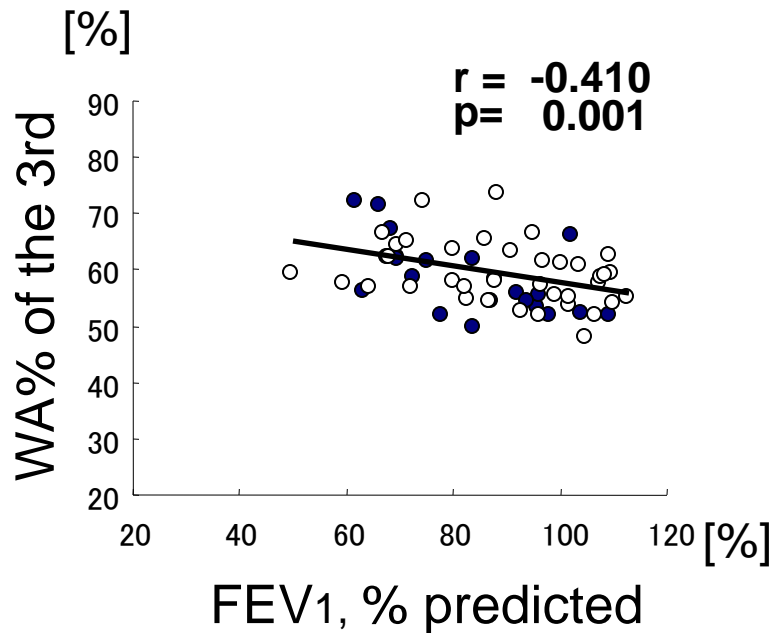
Table 1. Characteristics of subjects

n (male/female)	59 (22/37)
Age, years	67.4 ± 0.9 (55-86)
Hight m	1.56 ± 0.01 (1.37-1.70)
Weight kg	59.1 ± 1.1 (43-77)
BMI kg/m^2	24.4 ± 0.4 (19.1-32.4)
BSA m^2	1.58± 0.02 (1.31-1.87)
STEP (intermittent/mild persistent/ moderate persistent/severe persistent)	0/5/16/38
Duration of asthma, years	17.6 ± 2.1 (1-62)
Blood eosinophils per µl	302.5 ± 29.7 (12-1031)
Total IgE IU/ml	243.3 ± 64.1 (0-2902.8)

Data are shown as means ± standard error. BMI: body mass index BSA: body surface area IgE: Immunoglobulin E

The step classification of asthma was based on the Global Initiative for Asthma 2005.

Table 2. Relationships of mean WA% in all bronchi among the 3rd to 6th generations.

Correlation coefficients	3rd	4th	5th	6th
3rd	-	0.863**	0.834**	0.744**
4th	-	-	0.930**	0.844**
5th	-	-	-	0.864**
6th	-	-	-	-

**p<0.01

Table 3. Pulmonary function tests before and after salbutamol

Pulmonary function tests	Baseline*	Add-on**
VC, l	3.03 ± 0.09 (1.71-4.44)	3.11 ± 0.09 (1.81-4.73)
VC, %predicted	106.7 ± 1.50 (76.7-132.8)	109.1 ± 1.62 (81.2-137.4)
FEV_1, l	1.90 ± 0.06 (0.78-3.01)	2.03 ± 0.06 (0.86-3.24)
FEV_1, %predicted	87.1 ± 2.1 (49.7-112.5)	93.7 ± 2.06 (54.9-123.8)
FEV_1/FVC, %	64.3 ± 1.3 (41.4-83.3)	66.4 ± 1.3 (44.1-84.7)
MMF, %predicted	60.2 ± 4.2 (11.0-162.2)	65.3 ± 4.5 (15.6-162.2)
DL_{CO}, %predicted	109.8 ± 2.5 (71.4-161.6)	
DL_{CO}/V_A, %predicted	114.2 ± 2.6 (75.8-189.7)	
TLC, %predicted	110.6 ± 1.5 (74.0-131.1)	
FRC, %predicted	92.1 ± 2.2 (57.9-127.8)	
RV, %predicted	105.8 ± 2.4 (68.1-165.5)	
RV/TLC, %	37.1 ± 0.7 (26.1-51.3)	

VC, vital capacity; FEV_1, forced expiratory volume in 1 s; MMF, maximum mid-expiratory flow rate; DL_{CO}, carbon monoxide diffusing capacity; V_A, alveolar volume; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume.

Data are shown as means $\pm$ standard error.

Baseline*: with usual medication

Add-on**: after inhaling 200 μg of salbutamol

Table 4. Correlation coefficients of the mean airway dimensions of eight bronchi with pulmonary function tests and duration of asthma

a) Ai/BSA

Pulmonary function tests	3rd	4th	5th	6th
VC, %predicted	0.021	0.075	0.045	0.098
FEV1, l	0.419**	0.438**	0.354**	0.326*
FEV1, %predicted	0.299*	0.445**	0.508**	0.482**
FEV1/FVC, %	0.324*	0.461**	0.519**	0.446**
MMF, %predicted	0.347**	0.483**	0.544**	0.491**
TLC, %predicted	-0.193	-0.221	-0.227	-0.174
FRC, %predicted	-0.023	-0.150	-0.231	-0.217
RV, %predicted	-0.246	-0.316*	-0.340**	-0.348**
RV/TLC, %	-0.344**	-0.350**	-0.296*	-0.288*
Duration of asthma	-0.290*	-0.355**	-0.352**	-0.353**

b) WA%

Pulmonary function tests	3rd	4th	5th	6th
VC, %predicted	0.006	-0.009	0.007	-0.017
FEV1, l	-0.419**	-0.472**	-0.463**	-0.462**
FEV1, %predicted	-0.410**	-0.514**	-0.556**	-0.430**
FEV1/FVC, %	-0.413**	-0.529**	-0.575**	-0.424**
MMF, %predicted	-0.409**	-0.497**	-0.541**	-0.398**
TLC, %predicted	0.084	0.205	0.223	0.242
FRC, %predicted	-0.018	0.184	0.219	0.158

RV, %predicted	0.150	0.292*	0.323*	0.375**
RV/TLC, %	0.228	0.308*	0.284*	0.337**
Duration of asthma	0.348**	0.410**	0.372**	0.346**

VC, vital capacity; FEV_1, forced expiratory volume in 1 s; MMF, maximum mid-expiratory

flow rate; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume.

*$p<0.05$; **$p<0.01$