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Comparison of Airway Remodelling Assessed by Computed Tomography in Asthma and COPD

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Airway remodelling, Asthma, COPD, three-dimensional computed tomography

ABSTRACT (246/250words)

Background: Few studies have directly compared airway remodelling assessed by computed tomography (CT) between asthma and chronic obstructive pulmonary disease (COPD). The present study was conducted to determine whether there are any differences between the two diseases with similar levels of airflow limitation under clinically stable conditions.

Methods: Subjects included older male asthmatic patients (n=19) showing FEV_1/FVC <70% with smoking history less than 5-pack/year. Age- and sex-matched COPD patients (n=28) who demonstrated similar airflow limitation as asthmatic patients and age-matched healthy non-smokers (n=13) were recruited. Using proprietary software, eight airways were selected in the right lung, and wall area percent (WA%) and airway luminal area (Ai) were measured at the mid-portion of the 3rd to 6th generation of each airway. For comparison, the average of eight measurements per generation was recorded.

Results: FEV_1 % predicted and FEV_1/FVC was similar between asthma and COPD (82.3±3.3% vs. 77.6±1.8% and 57.7±1.6% vs. 57.9±1.4%). At any generation, WA% was larger and Ai was smaller in asthma, both followed by COPD and then controls. Significant differences were observed between asthma and controls in WA% of the 3rd to 5th generation and Ai of any generation airway, while no differences were seen between COPD and controls. There were significant differences in Ai of any generation between asthma and COPD.

Conclusions: Airway remodelling assessed by CT is more prominent in asthma compared with age- and sex-matched COPD subjects in the 3rd- to 6th-generation airways when airflow limitations were similar under stable clinical conditions.

Ai = inner luminal area

Ao= outer area of the bronchus

COPD = chronic obstructive pulmonary disease

CT = computed tomography

Di= inner diameter

DL_{CO}= carbon monoxide diffusing capacity

FEV_1= forced expiratory volume in 1 s

FRC= functional residual capacity

FVC= forced vital capacity

ICS = inhaled corticosteroid

IgE= Immunoglobulin E

LAV= low attenuation volume

MMF= maximum mid-expiratory flow rate

RV=residual volume

SEM=standard error of measurement

TLC= total lung capacity

VA= alveolar volume

VC= vital capacity

WA = airway wall area

3D = three-dimensional

INTRODUCTION

Bronchial asthma is characterized by reversible airflow limitation and airway hyper-responsiveness to constricting stimuli. Some asthmatic patients have irreversible airflow limitations despite treatment, possibly caused by airway remodelling[1-3]. In contrast, airflow limitation observed in chronic obstructive pulmonary disease (COPD) is by definition not fully reversible. In both diseases, airway inflammation is present, although the characteristics of the inflammation are different. Airway remodelling is also a common feature of both diseases, but the characteristics differ in nature as well as in severity.

The inflammation and remodelling in these two diseases have been described with regards to physiology[4-9], pathology[10-13] and biology[14-16]. Differences in airway inflammation have been well characterized between bronchial asthma and COPD[4,13].

However, few studies have directly compared airway remodelling assessed by computed tomography (CT) in asthma and COPD[17,18] despite the increasing use of this modality for the assessment of airway dimensions in these diseases[19,20]. Some investigators have speculated that airway wall area is increased without a decrease in luminal area in asthma, whereas increased airway wall area is associated with a decrease in luminal area in COPD[21,22]. However, this speculation is based on results of two independent studies in subjects with different levels of airflow limitation.

In the present study, possible differences in airway dimensions between the two diseases were investigated in clinically stable patients with similar levels of airflow limitation. Specifically, we assessed proximal airway remodelling by CT and compared between subjects with asthma and COPD. We hypothesized that airway remodelling estimated by CT scans would be more prominent in bronchial asthma, because the airways we could measure were located in the proximal, but not in the distal, by definition. Airflow limitation in bronchial asthma is characterized by airway remodelling in the proximal airways while that of COPD is

characterized by mixture of emphysema and airway remodelling in the small airways. Proprietary computer software enabling precise analysis of the short-axis image of the airways perpendicular to the long axis at the 3rd-to 6th-generation airways was used[23,24].

METHODS

Subjects

Subjects were recruited from the outpatient clinic of Hokkaido University Hospital from October 2006 through June 2009. First, asthmatic male patients who were older than 55 years and had poorly reversible airflow limitation of FEV_1/ FVC <70% despite appropriate drug therapy were recruited. Diagnosis of bronchial asthma was made based on the definition of American Thoracic Society, "Asthma is a chronic inflammatory disorder of the airways. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that in often reversible either spontaneously or with treatment".[25]. Additional entry criteria included: i) clinically stable (no asthma attacks or major changes in medication for more than 6 weeks before study entry); ii) life-long non-smokers or smokers with a lifetime smoking history less than 5-pack/year; and iii) no apparent emphysema on CT by visual assessment. Male patients with COPD were selected from subjects who participated in the Hokkaido COPD cohort study[26]. Subjects were chosen based on age and values of FEV_1/FVC, FEV_1% and all other data were blinded. Subjects in the COPD group who had apparent giant bulla and/or bronchiectasis which might have anatomically affected bronchial structure were excluded. Also recruited were age-matched male healthy volunteers as controls with normal pulmonary function who had no history of respiratory diseases or respiratory symptoms.

All the subjects underwent CT and pulmonary function tests sequentially on the same day. Asthmatic patients had taken their regular medications on the examination day. Patients with COPD had refrained from taking respiratory medications for 1-2 days, according to the protocol of the Hokkaido COPD cohort study[26].

The study protocols were approved by the Clinical Research Ethics Committee of Hokkaido University Hospital on 6th July 2006. Written informed consent was obtained from all the subjects.

CT Data Acquisition and Analysis

CT was performed using a multidetector-row spiral CT scanner with a 64 detector array (Aquilion Multi, TSX-101A/6A; Toshiba Medical Systems, Gunma, Japan). Data were acquired with the following parameters: 120 kVp, 300 mA, 64 detector × 0.5-mm collimation, slice thickness 0.5 mm, 0.5 s/rotation, helical pitch 41. While subjects were in the supine position, holding their breath at deep inspiration, the entire lung was scanned. The data were transferred to a workstation and then reconstructed into three-dimensional (3D) images (AZE Ltd., Tokyo, Japan). The detailed process of CT data acquisition and reconstruction has been described previously[27].

First, a three-dimensional bronchial skeleton was automatically reconstructed using a certain threshold level, determined on an individual basis (-950HU to -980 HU) to obtain airway images as distal as possible. Any portions of lung parenchyma remaining with the skeleton were manually removed to prevent analysis error. Finally, we obtained a bronchial skeleton and were able to identify any bronchus in the source images of axial, sagittal, and coronal slices. The selected bronchial pathway was automatically converted to a curved multiplanar reconstruction image. As the automatically obtained bronchial skeleton often contained only up to the 3rd- (segmental) to 5th-generation airway, depending on the quality of the images, airways were selected and then extended to the 6th generation. Identification of the generation of bronchi was made by careful inspection while simultaneously using the longitudinal and short axis images and searching for any bifurcation in the entire circumference.

The bronchial long-axis image appeared as a straight pathway, and short-axis images from

the 3rd to the 6th generation, were identified (Figure 1). For measuring airway dimensions, the software used the full-width at half-maximum principle for defining the wall area. However, as the automatically obtained outline of airway walls was often out of contour, manual corrections were made as follows. Based on manual plotting at several points, the software used cubic spline interpolation and built a new circle. Finally, values were obtained for the inner luminal area (Ai) and the outer area of the bronchus (Ao) and wall area (WA) was calculated as (Ao – Ai). Wall area percent (WA%) was defined as (Ao - Ai) / Ao × 100. A total of eight airways per subject were chosen for the measurements, one airway from each of the following bronchi: the apical (B1), posterior (B2), and anterior (B3) of the upper lobe, the lateral (B4) and medial (B5) of the middle lobe, and the anterior basal (B8), lateral basal (B9), and posterior basal (B10) of the lower lobe in the right lung. The measurement site was generally at the midpoint between the bifurcations. All these measurements were done by one of the authors (K. S.) who was blinded to any of the subjects' characteristics and pulmonary function data.

Total lung volume and volume-based severity of emphysema were measured. In short, whole lung containing airways (A) were extracted from the 3D image of the thorax, resulting in deletion of the heart and major vessels in the lungs. Then the bronchial skeleton (B) was extracted from the whole lung, resulting in the lung consisting of parenchyma without either major vessels or proximal bronchial trees. Total lung volume was defined as (A) – (B). Severity of emphysema was assessed as low attenuation volume (LAV), based on the threshold value of -950 HU. LAV% was defined as lung low attenuation volume divided by total lung volume. All CT measurements were done by one author (KS) who was blinded to the subjects' information.

Pulmonary Function Tests

Spirometry, carbon monoxide diffusion capacity, and lung volume assessed by the helium closed-circuit method (CHESTAC-33, CHEST M. I., Inc., Tokyo, Japan) were measured. Spirometric measurements included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and maximal mid-expiratory flow (MMF). Lung volume measurements included total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV). We used the rolling seal type of spirometer, the CHESTAC-33 (CHEST MI, Inc., Tokyo, Japan). The procedures and results of pulmonary function tests met the requirements of the pulmonary function test guidelines of the Japanese Respiratory Society Guidelines[28], which are similar to those of the American Thoracic Society. The diffusing capacity of the lung for carbon monoxide (D_{LCO}), based on the single-breath method, was also measured in all subjects according to the pulmonary function test guidelines of the Japanese Respiratory Society. D_{LCO} divided by alveolar volume (V_A) was expressed as percentage of predicted values according to the prediction equations of Burrows[29]. Lung volumes (total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)) were measured by the helium closed-circuit method. Lung volumes were expressed as a percentage of predicted values according to the prediction equations of Nishida[30]. Spirometry was repeated 30 min after inhalation of salbutamol (200 μg for bronchial asthma, 400 μg for COPD, as determined by the Hokkaido COPD cohort study). Reversibility was defined as (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1) / post-bronchodilator $FEV_1 \times 100$. There were not significant differences between the asthma and COPD groups in any indices of pre-bronchodilator FEV1, post-bronchodilator FEV1, reversibility.

Statistical Analysis

SPSS was used for all statistical analyses (SPSS, Tokyo, Japan). All data are expressed as mean ± standard error of measurement (SEM) for comparison. For comparison of lung

volume, diffusing capacity, and %LAV between the asthmatic patients and the COPD patients the t-test was used, and analysis of variance was used for comparison of parameters between the three groups (age, pulmonary function tests, and airway dimensions). A p value <0.05 was considered statistically significant.

RESULTS

Characteristics in the three groups are summarized in Table 1. Nineteen asthmatic patients and twenty-eight patients with COPD and thirteen healthy controls fulfilled the criteria. Classification of asthma was based on the Global Initiative for Asthma 2005[31]. One subject was classified as mild persistent, 11 subjects were classified as moderate persistent and 7 subjects were classified as severe persistent. All subjects except one were taking inhaled corticosteroids. In asthmatic patients, 14 subjects were life-long non-smokers and 5 subjects were ex-smokers. Among the 28 COPD patients, 17 were classified as mild and 11 were classified as moderate, according to the GOLD stage[32]. Airflow limitation indices such as FEV_1% predicted (82.3±3.3 vs. 77.6±1.8) and FEV_1/FVC (57.7±1.6 vs. 57.9±1.4) were similar between the two disease groups. There were no significant differences either in the spirometric data or the data of lung volumes. The results of the reversibility test were similar in these two groups, because the asthmatic patients had taken regular medications and the COPD patients had refrained from taking respiratory medications for 1-2 days on the day(Table 2). DLco% predicted and DLco/VA% predicted were lower in the COPD group compared to the asthma group. Similarly, the severity of emphysema assessed as %LAV was significantly greater in COPD patients compared to asthmatic patients and controls (Fig. 1).

The representative airway images from two typical cases with similar airflow limitation are shown (Fig. 2) With regard to airway dimensions, WA% was larger and Ai was smaller at any generation of bronchi in the asthmatic group, both followed by the COPD group and then the controls (Fig. 3, 4). Significant differences were observed between the asthma and control groups in WA% of the 3^{rd} to 5^{th} generation ($p<0.01$) and Ai of any generation airway ($p<0.01$ for 4^{th}, $p<0.05$ for 3^{rd}, 5^{th}, 6^{th}), while no differences were seen between the COPD and control groups. There were significant differences in Ai of any generation between asthma and COPD ($p<0.01$ for 4^{th}, 5^{th}, $p<0.05$ for 3^{rd}, 6^{th}). The means of calculated calibers from Ai in the 3^{rd} to

the 6^{th} generation airways were 5.08mm, 3.94, 3.15, 2.57 in COPD, and 4.56, 3.39, 2.67, 2.26 in bronchial asthma.There were no differences in total lung volume determined by CT among the asthma, COPD, and control groups (4239.9±204.5, 4252.6±199.3, and 4223.8±251.7 cm^3, respectively).

DISCUSSION

In the present study, changes in airway dimensions at the 3rd to 6th generation airways assessed by 3D-CT were more prominent in older asthmatic patients compared with age-matched male COPD patients with clinically stable disease and similar levels of airflow limitation. At any generation, WA% was larger and Ai was smaller in the asthma group, followed by the COPD group and then the controls. Significant differences were observed only between the asthma and control groups in WA% of the 3rd to 5th generation airways and Ai of any generation airway, but not in any variable between the COPD and control groups. There were significant differences in Ai of any generation airway between the asthma and COPD groups.

Despite similar levels of FEV_1/FVC, FEV_1%, and lung volumes (including RV/TLC), there was a marked difference in DLco/VA between the asthma and COPD groups. In addition, %LAV assessed by CT showed a marked difference between the asthma and COPD groups. These data suggest that the presence of emphysema was significant and contributed to airflow limitation in COPD. Moreover, considering previous reports[13] on the airway pathology of asthma and COPD, it is likely that, under similar airflow limitations, airway inflammation and/or remodeling are more prominent in the proximal airways in asthma compared with in COPD. In COPD, the small airways and emphysema are likely to be significant contributing factors to airflow limitation. Thus, the present study clearly demonstrated that when airflow limitation is mild to moderate, 3D-CT has the capability to demonstrate differences in airway dimensions between asthma and COPD patients.

In the present study, subjects were selected so that patients with asthma and COPD were matched for airflow limitation parameters. To the best of our knowledge, only two previous studies have attempted to compare airway dimensions between asthma and COPD using CT data. In one study[17], subjects were not matched for age or sex, which could have caused

significant biases[32-35]. Furthermore, the asthma group included a substantial number of smokers. In the other study[18], all parameters of airway dimensions in HRCT analysis, including airway wall area, airway wall area %, inner luminal area, airway luminal diameter and wall thickness, were reported to be similar in the subjects with the two diseases and similar airflow limitations. However, only the airways in which the ratio of the diameter of the long axis to that of the short axis was less than 1.2 were measured, thus allowing inclusion of some airways cut obliquely on the CT slice. Additionally, random selection of airways might have led to comparison of airways of different generations and different sizes. Another explanation might be that the degree of airflow limitations in bronchial asthma was milder compared with that of COPD although not statistically significant, in other words, the two groups were not so exactly matched for airflow limitation indices as in our study, which might have obscured the difference. In the present study, lung volume when the CT was taken was considered as a possible confounding factor because it might be vitally important in measuring airway dimensions. Lung volume assessed by CT volumetric data demonstrated no significant differences between asthma and COPD, which again strengthened the results of the present study.

We have previously reported the relationships of airway dimensions, WA% and Ai, with airflow limitation indices such as FEV_1, % predicted in older patients with clinically-stable asthma[36] and also patients with COPD[23], in both of which the subjects displayed variable levels of airflow limitation. We found significant correlations of airflow limitation indices with airway dimensions in the 3rd to 6th generations with similar correlation coefficients in patients with bronchial asthma, and on the other hand, in patients with COPD, the correlation coefficients that we found similarly significant improved better as the airways became smaller in size from the 3rd to 6th generations. These study prompted us to examine the two diseases with similar levels of airflow limitation under stable conditions and we hypothesized that

airway remodelling estimated by CT scans would be more prominent in bronchial asthma.

Structural and/or pathological differences that may exist between subjects with the two diseases cannot be judged from the present study. However, considering previously reported pathology[13], it can be speculated that in asthma with poorly reversible airflow limitation there is remodelling consisting of increased airway smooth muscle mass[37]. On the other hand, in COPD with a mild to moderate degree of airflow limitation, airway inflammation and/or remodelling occurs mainly at the small airways rather than the proximal airways. This is particularly the case when few chronic bronchitis symptoms exist. Loss of lung elastic recoil as a result of established emphysema is another characteristic of COPD contributing to collapsing airways[37] and thus to airflow limitation.

Previous studies using CT assessment have suggested that, compared to healthy subjects, airways of patients with asthma were not narrowed despite the presence of airflow limitation and airway wall thickening[21,38]. This speculation was based on assessment of airway dimensions of 3rd generation airways. In the present study, airway narrowing was particularly detected in 4th and 5th generation airways in asthma patients.

There were some limitations in the present study. 3D airway analysis has technological limitations; it adopts the full-width at half-maximum principle for determination of the airway wall, an algorithm that has been reported to underestimate airway luminal area and to overestimate airway wall thickness, particularly in small-diameter airways[39]. However, comparison of data from the same generation (i.e., similar-sized airways) between subjects might have minimized systemic errors. The same trend was observed among the 3rd to 6th generation bronchi, supporting the findings of this study. Second, only elderly male patients were selected for this study, and thus the results may not be extrapolated to female patients and/or young patients with asthma. In COPD, there have been some reports which have focused on gender differences in the contribution of airway disease and emphysema to airflow

limitation[33,35]. Third, patients were recruited only with mild to moderate degrees of airflow limitation. This is because few patients with clinically stable asthma showed severe airflow limitation under appropriate therapy. If we could recruit the old patients with severer asthma, they might share similarities with COPD particularly at the smaller airways. Finally, residual reversibility of airflow limitation was found both in the asthmatic and COPD groups when CT was performed. However, the magnitude of residual reversibility was small in both groups, and therefore probably did not significantly bias the main findings.

In conclusion, in older male patients with clinically stable disease and mild to moderate airflow limitation, airway remodeling at the 3rd to 6th generation bronchi assessed by 3D CT was more prominent in patients with bronchial asthma compared with age-matched COPD patients.

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FIGURE LEGENDS

Figure 1

Comparison of variables reflecting severity of emphysema between subjects with bronchial asthma and COPD.

DLco/VA% predicted were lower in the COPD group compared to the asthma group and the severity of emphysema assessed as %LAV was significantly greater in COPD patients compared to asthmatic patients.

Left panel: DLco/VA, % predicted; DLco: diffusion capacity of carbon monoxide, VA: alveolar volume at the measurement of DLco

Right panel: % lung attenuation volume (%LAV) assessed by whole lung CT data. See text for the assessment of %LAV.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$

Figure 2

The representative airway images from two typical cases with similar airflow limitation.

a. Images of a patient with bronchial asthma (FEV1,%predicted 63.2%, FEV1/FVC 52.4).

b Images of a patient with COPD (FEV1,%predicted 62.9%, FEV1/FVC 49.8%)

Short axis image of the bronchus in i) the third generation ii) the forth generation iii) the fifth generation iv) the sixth generation are shown. v) is the curved multiplanar reconstruction image image and gray lines and circles indicate the same sites analyzed. Short-axis images, obtained from a curved multiplanar reconstruction 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. Images of i), ii), iii), iv) in a, b are expressed by the same magnification.

Figure 3

Comparison of WA% among healthy controls, subjects with bronchial asthma, and subjects with COPD.

WA% was larger at any generation of bronchi in the asthmatic group, both followed by the COPD group and then the controls

Data expressed as the average per generation of eight bronchi in the right lung at the 3rd- to 6th-generation airways.

WA%: airway wall area divided by total airway area expressed as a percentage.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$

Figure 4

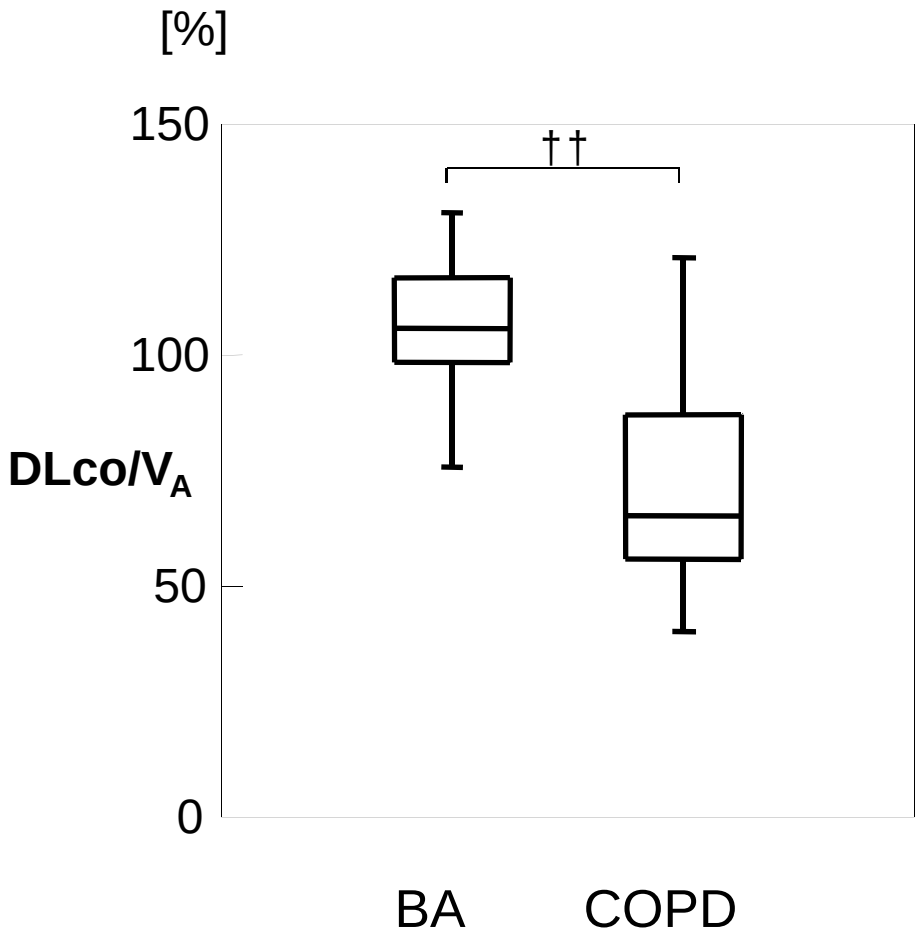
Comparison of Ai among healthy controls, subjects with bronchial asthma, and subjects with COPD.

Ai was smaller at any generation of bronchi in the asthmatic group, both followed by the COPD group and then the controls

Data expressed as the average per generation of eight bronchi in the right lung at the 3rd- to 6th-generation airways.

Ai: inner luminal area of the airway; BSA: body mass index.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$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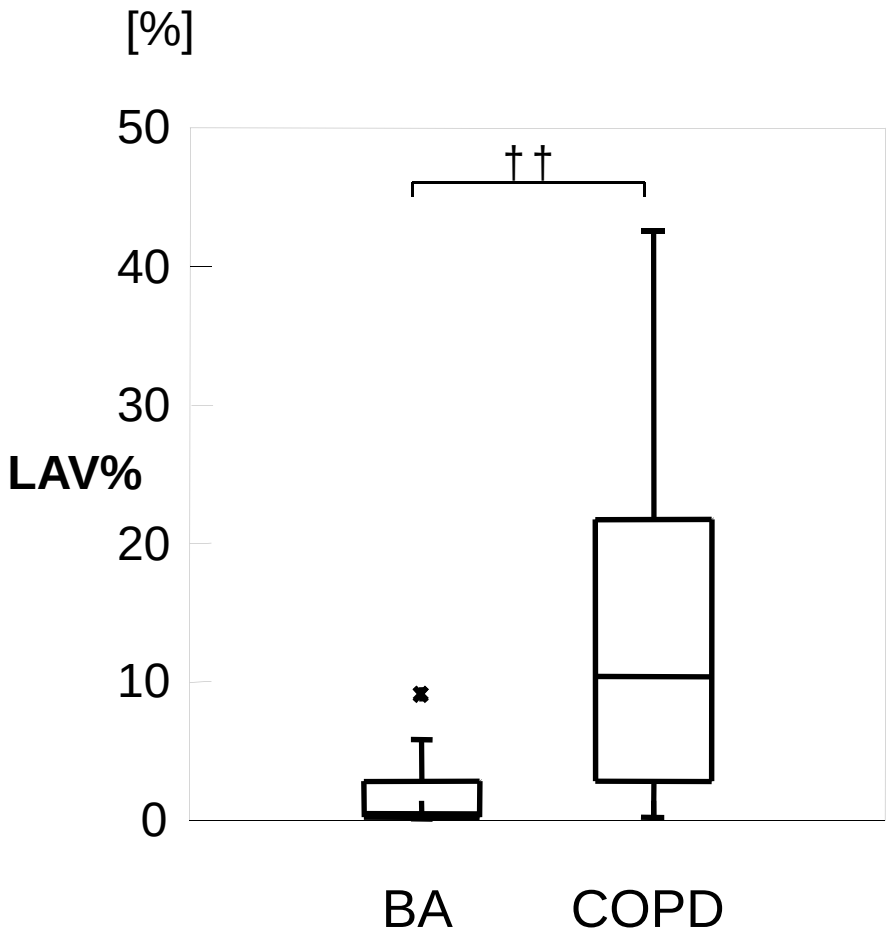
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30
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††
BA
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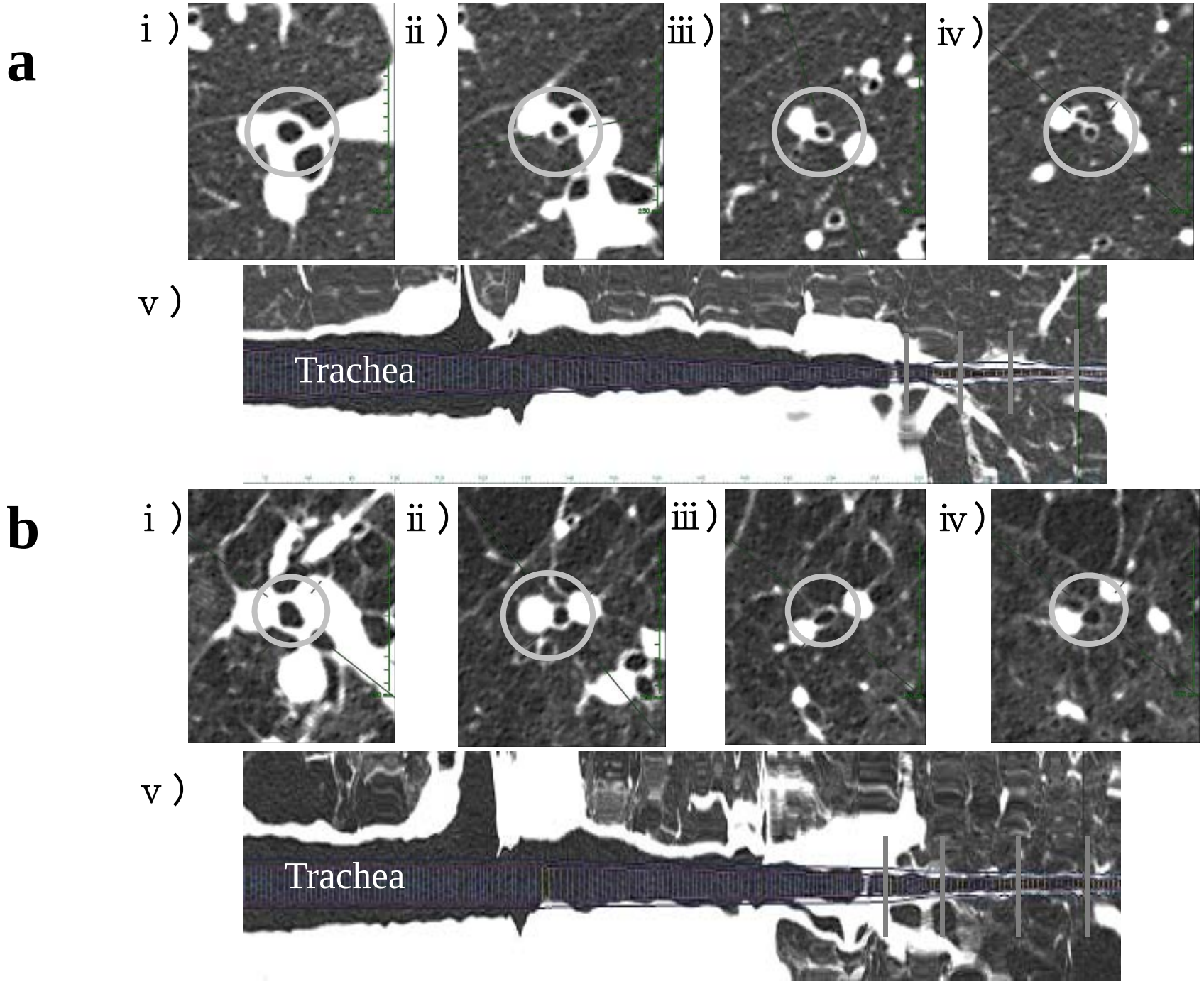
a
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ii)
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Trachea
b
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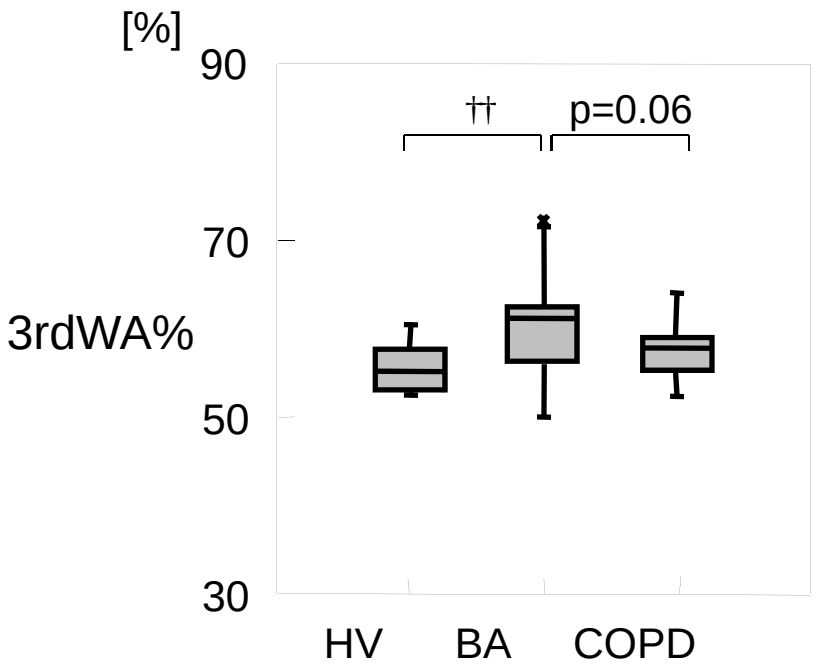
Trachea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3rdWA%
††
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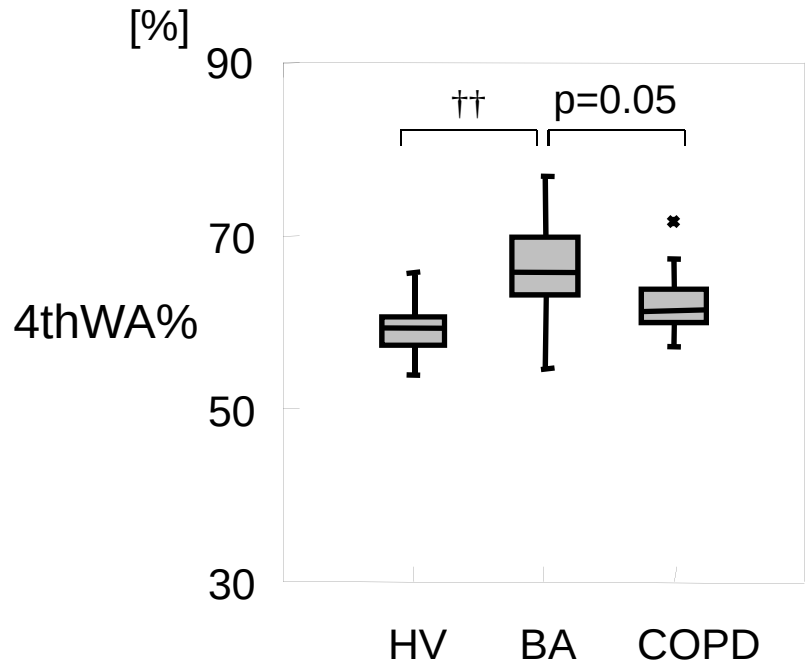
HV
BA
COPD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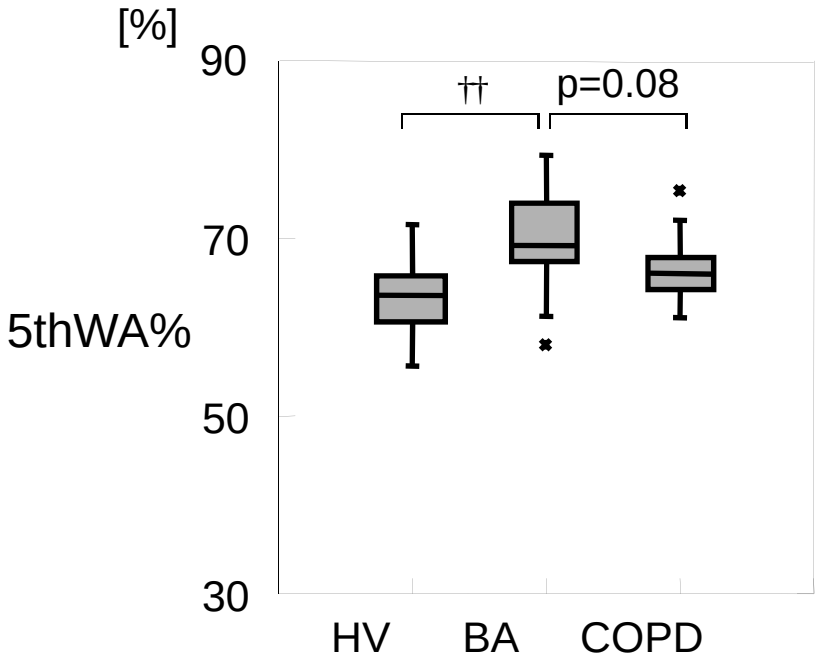
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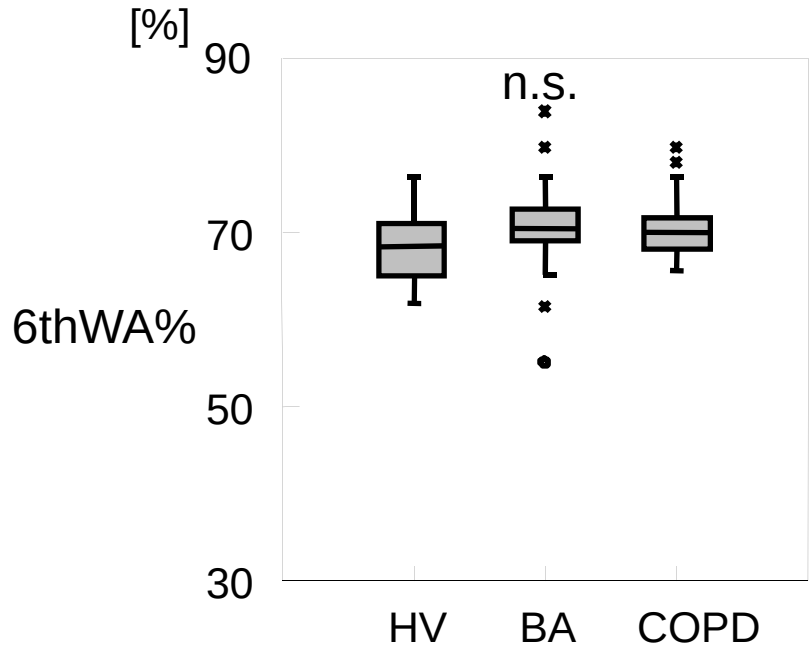
COPD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HV
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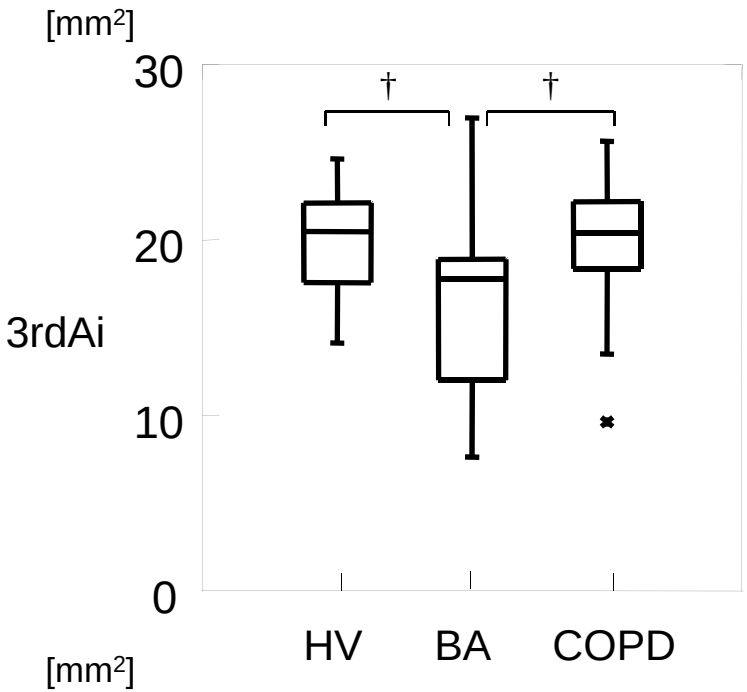
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3rdAi
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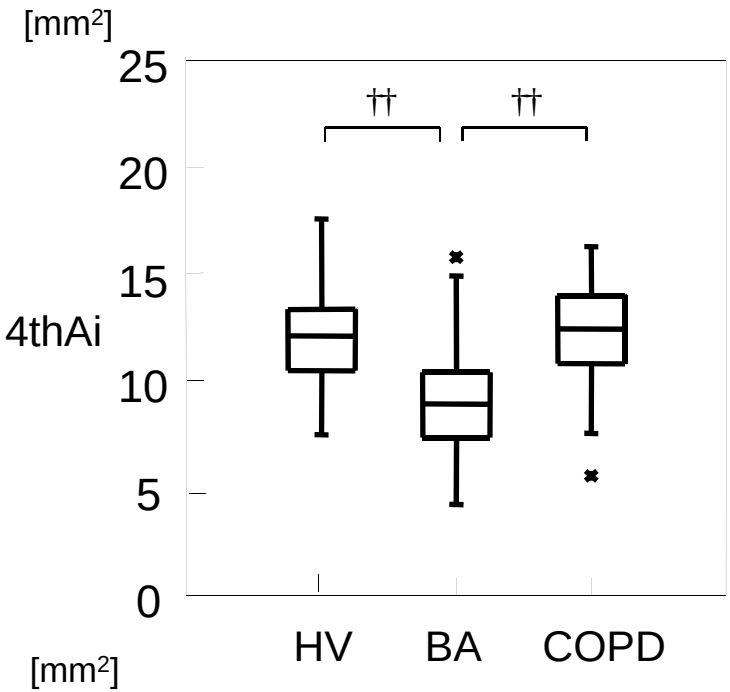
HV
BA
COPD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4thAi
††
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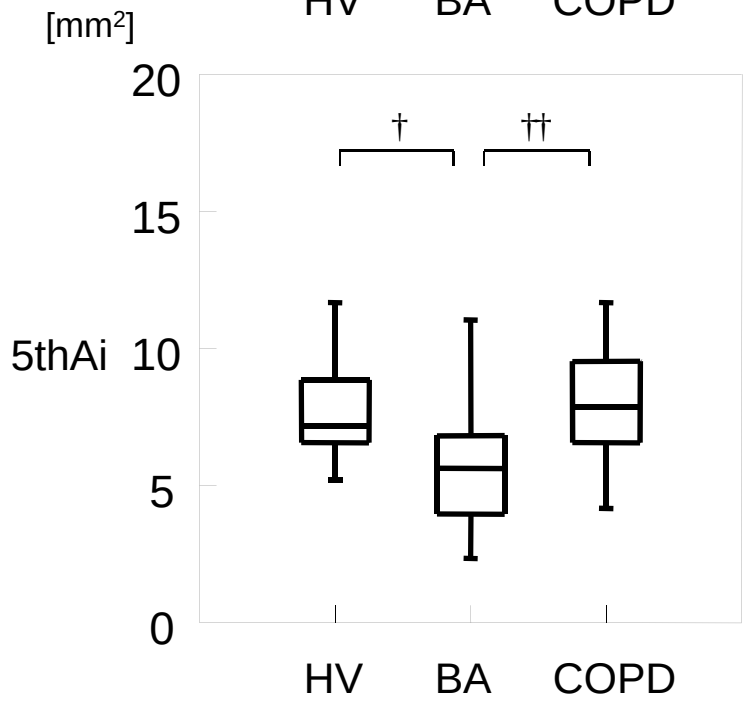
HV
BA
COPD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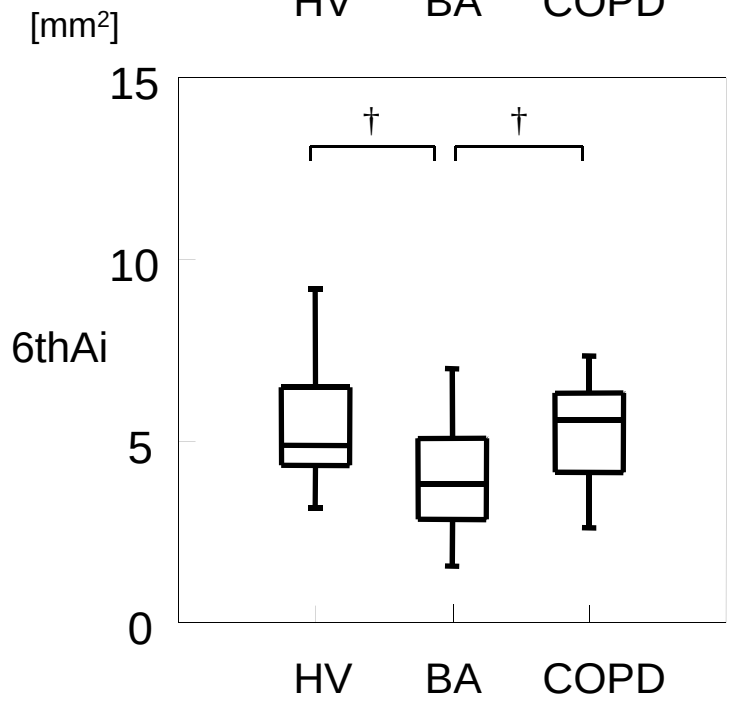
[mm2]
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COPD

Table 1

Characteristics of the subjects

Characteristic	Control	Bronchial asthma	COPD
N	13	19	28
Age (y)	67.4 ± 2.6	71.1 ± 1.9	70.4 ± 1.4
Height(cm)	163.0 ±.2.2	162.0 ± 1.2	164.4 ± 1.3
Weight(kg)	62.9 ± 3.2	62.9 ± 1.7	63.7 ± 2.1
Body Surface Area (m^2)	1.7 ± 0.1	1.7 ± 0.0	1.7 ± 0.0
Smokers			
Non-smokers	13	14	0
Ex-smokers	0	5	24
Current smokers	0	0	4
Smoking history (pack-years)	0	3.6 ± 0.8	65.4 ± 5.9
Asthma duration (y)		20.0 ± 4.0	
Treatment			
Inhaled corticosteroids (%)		94.7	0
Long-acting β2-agonist			
Inhaler (%)		36.8	10.7
Transdermal patch (%)		21.1	3.6
Inhaled anticholinergics (%)		0	10.7
Theophylline (%)		15.8	21.4
Leukotriene receptor antagonists (%)		42.1	0

Oral steroids (%)	0	0
Blood eosinophils (/μl)(normal range:70-440)	304.7 ± 52.3	227.9 ± 30.1
Total IgE (IU/ml)	371.9 ± 159.0	222.8 ± 67.3

All the subjects were male.

Data are shown as mean ± standard deviation

Table 2

The results of pulmonary function tests

	Control	Bronchial asthma	COPD
N	13	19	28
Pulmonary function tests			
VC, l	3.8 ± 0.2	3.8 ± 0.1	3.8 ± 0.1
VC (% predicted)	113.5 ± 3.5	111.1 ± 3.2	108.0 ± 2.0
FEV_1, l	2.9 ± 0.1	2.1 ± 0.1†	2.2 ± 0.1†
Post-bronchodilator FEV_1, l		2.2 ± 0.1	2.3 ± 0.1
Reversibility * (%)		6.9 ± 1.8	5.2 ± 0.9
FEV_1 (% predicted)	102.2 ± 2.5	82.3 ± 3.3†	77.6 ±1.8†
FEV_1/FVC (% predicted)	78.0 ± 1.4	57.7 ± 1.6†	57.9 ± 1.4†
MMF (% predicted)		44.3 ± 4.0	44.5 ± 2.7
DL_{CO} (% predicted)		124.7 ± 5.0	86.7 ± 4.6§
TLC (% predicted)		105.6 ± 2.7	106.5 ± 2.3
FRC (% predicted)		98.9 ±3.7	103.7 ± 3.2
RV (% predicted)		104.1 ± 4.4	104.5 ± 3.6
RV/TLC (%)		36.6 ± 1.3	40.0 ± 2.6

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

* Reversibility(%) is defined as (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1) / post-bronchodilator FEV_1 × 100.All the subjects were male. Asthmatic patients had taken their regular medications prior to the reversibility test on the examination day. Patients with COPD had refrained from taking respiratory medications for 1-2 days, according to the protocol of the Hokkaido COPD cohort study

Data are shown as mean ± standard deviation

Significantly different from controls: $^{\dagger}p<0.05$

Significantly different from bronchial asthma: $^{\S}p<0.05$