Assessment of Small Airways with Computed Tomography: Mosaic Attenuation or Lung Density?

Tsuyoshi Oguma^a Akio Niimi^b Toyohiro Hirai^a Makiko Jinnai^a
Hisako Matsumoto^a Isao Ito^a Masafumi Yamaguchi^c Hirofumi Matsuoka^a
Kojiro Otsuka^a Tomoshi Takeda^a Hitoshi Nakaji^a Kazuo Chin^a
Michiaki Mishima^a

^aDepartment of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, ^bDepartment of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya, and ^cDivision of Respiratory Medicine, Department of Medicine, Shiga University of Medical Science, Ootsu, Japan

Key Words

Air trapping · Asthma · Computed tomography · Mosaic · Small airways

Abstract

Background: Computed tomography (CT) assessment of air trapping has been considered useful as a measure of small airway disease. Mean lung density (MLD) and the percentage of the lung field occupied by low attenuation area (LAA%) can be evaluated automatically, and their expiratory/inspiratory (E/I) ratios correlate with asthma severity and spirometry parameters. However, mosaic attenuation, another indicator of air trapping, has been assessed visually, and its functional relevance remains controversial. **Objectives:** This retrospective study was conducted to correlate mosaic attenuation, which was assessed visually and automatically, and the E/I ratios of MLD and LAA% (defined as areas <–960 Hounsfield units) with clinical and physiological variables, including impulse oscillometry (IOS) indices. **Material and Methods:** In 36 nonsmoking patients with stable asthma, the lungs were scanned at full inspiration and full expiration. Mosaic attenuation was measured visually and automatical-

ly, by counting areas with CT values higher than the surrounding areas. MLD and LAA% were measured using our validated method. Spirometry, IOS, exhaled NO and the sputum eosinophil count were evaluated. **Results:** The automatic results and visual scores of mosaic attenuation correlated well on expiratory scans ($r = 0.894$) and to a lesser degree on inspiratory scans ($r = 0.629$; $p < 0.0001$ for both). However, only the E/I ratios of MLD and LAA% correlated with forced expiratory volume in 1 s/forced vital capacity of spirometry and the IOS indices of resistance from 5 to 20 Hz and the integrated area of low-frequency reactance. **Conclusions:** Our automatic method for analysis of mosaic attenuation is likely useful, but the results themselves may not be reflecting small airway involvement of asthma, unlike the E/I ratios of MLD and LAA%.

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Introduction

Chronic inflammation and remodeling of the airways are fundamental features of asthma [1]. Autopsy studies of patients who died of acute asthma have shown that

these features involve both large and small airways [2, 3]. An important contribution of small airways to the pathophysiology of asthma has recently been suggested [4–6], but methodological difficulties have precluded detailed investigation.

Central airway dimensions of patients with asthma have recently been assessed quantitatively by computed tomography (CT). Total airway area, wall area, luminal area and wall thickness of cross-sectional airways, considered indirect measures of airway remodeling, can be measured automatically [7–9]. Large airway walls of patients with asthma are thicker than those of normal subjects, and the degree of wall thickening correlates with disease severity, airflow obstruction [10–12], and several biomarkers of airway inflammation and remodeling [13–16]. However, analysis of airway dimensions such as wall area or luminal area of smaller airways (distal to the sixth generation, or less than 1–2 mm in luminal diameter) is beyond the spatial resolution limits of CT [9, 17, 18].

The classical high-resolution CT finding of air trapping, decreased lung attenuation, has been assessed visually to investigate small airway involvement in various lung diseases [19–23]. However, the functional relevance of this assessment remains controversial. This may be due to the fact that the so-called mosaic attenuation pattern, which is used as a visual index of air trapping, may also be secondary to parenchymal disease (causing abnormal high attenuation areas), vascular disease or vasoconstriction resulting in mosaic perfusion (causing abnormal low attenuation due to hypoperfusion) [24]. Moreover, the limitations of semiquantitative visual assessment may be involved. Only one study conducted automatic and quantitative analysis of mosaic attenuation in patients with constrictive obliterative bronchiolitis and healthy subjects, but details of the methods and the functional relevance of the measurements were not reported [25].

We have reported that the percentage of the lung field occupied by low attenuation area (LAA%), which was defined as areas below –960 Hounsfield units (HU), and the mean lung density (MLD), especially the ratios of these values obtained at full expiration to those at full inspiration (E/I ratios) [26], correlated with disease severity, residual volume/total lung capacity, and airway sensitivity to inhaled methacholine, as well as with spirometric indices – forced expiratory volume in 1 s (FEV₁), FEV₁/forced vital capacity (FVC) and forced expiratory flow of 25–75% (FEF_{25–75}) – which reflect airflow obstruction in subjects with stable asthma [26]. FEV₁ and FEV₁/FVC are considered to reflect global airflow obstruction while FEF_{25–75} is to reflect peripheral airflow obstruction [27].

Impulse oscillometry (IOS) is a recently developed technique that allows for respiratory functional studies without forced maneuvers; it is performed with spontaneous breathing and, therefore, requires minimal cooperation. Some IOS parameters have been reported to reflect small airway disease [28–31], but their correlations with high-resolution CT indices of small airways remain poorly known [32].

The aim of this study was to analyze mosaic attenuation automatically and quantitatively on multidetector CT in patients with asthma, to compare with the results of visual scoring, and to correlate with clinical and functional variables including IOS indices. The E/I ratios of MLD and LAA% were also examined to correlate with these variables. We hypothesized that (1) our automatic and quantitative method to analyze mosaic attenuation would precisely reflect the visually assessed mosaic scores, (2) the results of the automatic analysis would correlate better with clinical and functional indices than those of the visual analysis and (3) the utility of the E/I ratios of MLD and LAA% as indicators of air trapping or small airway disease [26] would be confirmed.

Material and Methods

Subjects

In this retrospective study, 36 adult patients with asthma who underwent both inspiratory and expiratory CT scans at Kyoto University Hospital from June 2006 to June 2007 were included. They were diagnosed according to the American Thoracic Society criteria [33]. All patients were clinically stable and had not had disease exacerbations or respiratory infections within 4 weeks. Patients who had a smoking history of more than 5 pack-years or who had quit within 1 year were not included in this study. The severity of asthma based on the daily regimen and response to treatment was intermittent in 1 patient, mild persistent in 6, moderate persistent in 13 and severe persistent in 16, according to the Global Initiative for Asthma guidelines 2004 [34]. None had evidence of chronic obstructive pulmonary disease, such as typical emphysema on CT images.

All patients had joined our previous studies (unpublished), which were approved by the ethics committee at our institution, and written informed consent was obtained from all subjects.

Multidetector CT Image Acquisition

Multidetector CT scans (Aquilion 64; Toshiba, Tokyo, Japan) were acquired with 0.5-mm collimation, a scan time of 500 ms, 120-kV peak and autoexposure control. Full-inspiratory and full-expiratory scans of both lungs were performed from the top to the bottom of the lungs. Expiratory scans were followed by inspiratory scans to avoid the effects of deep inspiration. Inspiratory and expiratory maneuvers and breath holding were checked as previously described [26].

Fig. 1. **a, b** Detected airway lumina (red; colors refer to the online version only) and lung areas (blue and green). **c, d** Representative images of original CT (**c**) and automatically detected mosaic partitions (**d**). Red partitions correspond to those with a relatively high density and blue partitions to those with a relatively low density as compared with surrounding partitions.

CT Image Analysis

Major airway lumens were detected by threshold segmentation, using -600 HU as the threshold value, and the 3-dimensional 6-neighborhood region labeling algorithm. Next, after masking the bronchus area, lung areas were detected by the same method using -400 HU as the threshold value (fig. 1a, b). At each detected lung area, LAA% and MLD were calculated automatically [26, 35, 36]. LAAs were defined as areas below -960 HU [26, 35, 36]. LAA% was calculated as the percentage of the entire lung area occupied by LAAs. LAA% and MLD were measured on all slices, for an average 483.6 slices, and averaged.

The visual mosaic score was assessed based on the consensus of two specialists (T.O. and M.J.), as previously reported [18], except that whole lung images were used in the present study, while only 3 slices of CT images were used in the previous study [19]. The two observers quantified the decreased attenuation area of each lobe by using all the slices of CT images for both full inspiration and at full expiration images, and semiquantified it as follows: grade 0, none; grade 1, less than 50% of the volume of the lobe (limited), and grade 2, more than 50% of the lobe (extensive). The total extent of decreased attenuation in each patient was examined by adding the lobar scores (the lingula was counted as a separate lobe), which gave a 13-point scale (0–12) [19].

The automatic mosaic index was calculated as follows. First, lung areas were divided into square partitions composed of a predetermined number of CT pixels, and the average density of each partition was calculated. Then, partitions that had relatively high, low or similar densities as compared with up to 4 surrounding partitions were detected, according to a predetermined minimum significant difference in CT density between 2 partitions by Houns-

field units (fig. 1c, d; fig. 2). A partition was considered 'relatively low-density' when the number of surrounding partition(s) with a significantly higher density was greater than the number with a significantly lower density (fig. 2). The reverse was the case for 'relatively high-density' partitions. This rule was also applied to a case where the total number of surrounding (adjacent) partitions was less than 4. Finally, the percentage of each of the relatively high- or relatively low-density partitions occupying the whole lung area was calculated. The example presented in figure 2 applied a minimum significant difference of CT density between adjacent partitions of 50 HU.

To determine the optimal setting to automatically quantify mosaic attenuation, the above process was repeatedly performed by changing: (1) the square size of each partition from 2×2 pixels to 7×7 pixels by 1×1 pixel increments; (2) the minimum significant difference in lung density from 20 to 80 HU by 10-HU increments; (3) the targeted partitions to measure from those with a relatively low density to those with a relatively high density, and (4) the targeted partitions for comparison from the neighbor (adjacent) ones to next-to-neighbor ones (up to 4 partitions at maximum for each). The results that demonstrated the highest correlation with the visual mosaic score were used for the final analysis. Mixed data of both inspiratory and expiratory scans were used for these analyses.

Automatic analyses of MLD, LAA% and mosaic attenuation were done using a new software package developed in house.

Correlations of the automatic mosaic index and visual mosaic score with various clinical indices were examined for their expiratory values and inspiratory values. Moreover, for the automatic mosaic index, their ratio (E/I ratio) and difference (E–I gap) were also used for analysis.

Fig. 2. An example of the algorithm to determine relatively high- and low-density partitions compared with surrounding partitions, which applied a minimum significant difference in density of >50 HU. Each cell of the left panel represents a partition, and the values in the cells are the average CT value (in Hounsfield units) of each partition. For example, the circled cell with an average density of -840 HU is surrounded by 2 partitions with higher CT values (-700 and -720 HU), 1 with a lower CT value (-900 HU) and 1 with a similar CT value (-850 HU). As a result of 4 comparisons with surrounding partitions, the circled partition is therefore categorized as a relatively low-density partition and is colored in blue in the right panel. This algorithm was repeated for all partitions, which were accordingly colored in blue, red or uncolored in the right panel.

Impulse Oscillometry Analysis

Respiratory impedance was measured using a Jaeger Master-Screen IOS (Erich Jaeger, Hoechberg, Germany), as previously reported [29, 37], according to standard recommendations [38]. Rectangular mechanical impulses containing the whole frequency spectrum were applied to the respiratory system through a mouthpiece during quiet breathing. The resulting pressure and volume signals were analyzed for amplitude and phase differences to determine respiratory resistance (R) and respiratory reactance (X) of the total respiratory system. Impedance measurements included R and X from 5 to 35 Hz (R5–R35 and X5–X35) and frequency of resonance, which represents the point at which the usually negative reactance reaches 0. Pressure oscillations at frequencies >15 Hz are severely damped out before reaching peripheral airways, while those at frequencies <10–15 Hz penetrate much further into the lung periphery [39]. R5, R20 and R5–R20 were used as indices of total, large and small airway resistance, respectively [28–30, 39, 40]. In addition, the integrated area of low-frequency X (AX) was examined as a sensitive measure of small airway obstruction [28–30, 39, 40].

Spirometry

Patients underwent spirometry using a Chestac-55V unit (Chest, Tokyo, Japan) according to recent recommendations [41]. FVC, FEV₁ and FEF_{25–75} were examined.

Sputum Induction

After inhalation of salbutamol, sputum was induced as described previously [42]. The eosinophil percentage was determined by counting more than 400 cells using centrifuged preparations stained with May-Grünwald-Giemsa stain.

Exhaled NO Analysis

The exhaled NO (eNO) levels were measured with a chemiluminescence analyzer (NOA 280, Sievers, Boulder, Colo., USA) as previously reported [43, 44] according to a recent guideline [45]. Briefly, the seated subject inserted a mouthpiece, inhaled orally to total lung capacity, exhaled immediately against a high resistance and maintained a mouth pressure at 20 cm H₂O. The steady-state NO plateau was taken as the eNO value. The eNO levels were measured at expiratory flow of 50 ml/s in this order, and the average of 3 measurements was taken as the final result.

Statistical Analysis

Data with a normal distribution were expressed as mean (with standard deviation), while data with a nonnormal distribution were expressed as median (with range). For correlation analysis, the former indices were analyzed with the parametric Pearson correlation test, while the latter indices were analyzed with the non-parametric Spearman rank correlation test, except for IOS indices, which showed log-normal distribution and were analyzed by the Pearson correlation test after log transformation. Effects of sex on CT indices were analyzed with the Mann-Whitney U test. Multiple linear regression analysis evaluated with the stepwise transformation method was performed as appropriate. p values of <0.05 were considered significant.

Results

Patient Characteristics

The characteristics of the subjects, including CT indices, are presented in table 1. On expiratory CT scans, LAA% decreased and MLD, the mosaic score and the mosaic index increased in all patients compared with the values on inspiratory scans. Of the 36 subjects, 33 had received inhaled corticosteroids at daily doses equivalent to 1,200 µg (400–2,400 µg) of chlorofluorocarbon-beclomethasone dipropionate.

Relationship between the Automatic Mosaic Index and the Visual Mosaic Score

Various settings were tried to calculate the mosaic index. With regard to the selection of targeted partitions, the count of partitions with relatively high density but not of those with low density, and comparison with next-to-neighbor partitions but not with neighbor partitions, showed a higher correlation with the visual mosaic score (table 2), almost consistently irrespective of pixel size and the minimum significant difference in lung density (data not shown). When these targeted partitions were used, a

partition size of 4×4 pixels and a minimum significant difference in lung density of 50 HU showed the highest correlation with the visual mosaic score (fig. 3a, b).

Using these best settings, the automatic mosaic index showed the best correlation with the visual score on the expiratory scans ($p < 0.0001$, $r = 0.867$; fig. 4b), while the correlation was lower on the inspiratory scans ($p < 0.0001$, $r = 0.656$; fig. 4a).

Relationships between the Mosaic Score or Index and Clinical or Functional Indices and the E/I Ratios of MLD or LAA%

Table 3 shows the correlation coefficients between the mosaic score, mosaic index, E/I ratio of mosaic index or expiratory-inspiratory (E/I) gap of mosaic index, which was calculated with expiratory mosaic index – inspiratory mosaic index, and clinical and functional indices. Both the expiratory mosaic score and mosaic index showed significant or marginally significant negative correlations with the E/I ratios of MLD or LAA%. There were no significant correlations with other clinical or functional indices for either the expiratory or inspiratory mosaic score or index (table 3; fig. 5).

Relationships between the E/I Ratios of MLD or LAA% and Clinical or Functional Indices

Table 4 and figure 5 show the relationships between the E/I ratios of MLD or LAA% values and various indices. The E/I ratios of LAA% or MLD values were significantly correlated with FEV₁/FVC, consistently indicating an association between air trapping and airflow obstruction. They were also significantly correlated with small airway indices of IOS, AX and R5–R20, and age. No CT index was related to the eNO level or sputum eosinophil count (table 4).

On the stepwise multiple regression analysis of the E/I ratios of MLD including age, FEV₁/FVC and AX, AX and FEV₁/FVC were entered to the regression equation and showed significant correlations. On the analysis of the E/I ratios of LAA% including the same indices, only AX was entered to the regression equation and resulted in a significant correlation (tables 5, 6).

Discussion

In this study, an automatic method to analyze mosaic attenuation, which was especially useful for the quantitative assessment of expiratory scans, was developed. However, the results did not correlate with clinical and func-

Table 1. Characteristics of patients with asthma

Female/male	28/8
Age, years	63.4 (12.1)
Asthma duration, years	21.6 (15.9)
FVC, % predicted	85.9 (30.4)
FEV ₁ , % predicted	76.4 (27.7)
FEV ₁ /FVC, %	68.1 (11.6)
FEF _{25–75} , % predicted	48.9 (29.8)
Sputum eosinophils (n = 24), %	6.25 [0–54.8]
eNO, ppb	41.8 (28.5)
R5, kPa/l/s	0.40 [0.21–1.43]
R20, kPa/l/s	0.32 [0.19–0.69]
AX, kPa/l/s	0.76 [0.08–8.67]
LAA% of inspiratory scans, %	15.8 (5.8)
LAA% of expiratory scans, %	8.8 (4.1)
E/I ratio of LAA%	0.53 (0.12)
MLD of inspiratory scans, %	–860 (26.8)
MLD of expiratory scans, %	–803 (37.5)
E/I ratio of MLD	0.93 (0.03)
Inspiratory visual mosaic score	1.00 [0–12]
Expiratory visual mosaic score	7.00 [0–12]
Inspiratory automatic mosaic index, %	25.4 (2.7)
Expiratory automatic mosaic index, %	30.4 (3.0)
Dose of inhaled corticosteroids ¹ , µg	1,200 [0–2,400]
Use of oral corticosteroids (use/no use)	2/34
Use of long-acting β-agonists (use/no use)	20/16
Use of leukotriene receptor antagonists (use/no use)	14/22
Use of theophylline (use/no use)	11/25

Each value is the number of subjects, mean with standard deviation in parentheses, or the median with the range shown in square brackets.

¹ Converted into the equivalent dose of chlorofluorocarbon-beclomethasone dipropionate.

Table 2. Effect of selection of targeted partitions on correlation coefficients with the visual mosaic score

	Compared with neighbor partitions	Compared with next-to-neighbor partitions
Counted relatively high-density partitions	0.823	0.835
Counted relatively low-density partitions	0.628	0.680

The results obtained by using the best setting of partition size and minimum significant difference in lung density for each individual correlation analysis are presented.

Fig. 3. a Correlation coefficients between the automatic mosaic index and the visual mosaic score, comparing with next-to-neighbor partitions and counting partitions with a relatively high density. The correlation coefficient is highest when 4×4 pixels per partition and a minimum significant difference in density of 50 HU are used. **b** The correlation between the visual mosaic score

and the automatic mosaic index, when the best settings, namely partition size of 4×4 pixels, minimum significant difference of 50 HU, count of partitions with relatively high density and comparison with next-to-neighbor partitions, are used. x = Inspiratory scans; $\diamond$ = expiratory scans.

Fig. 4. Correlation between the visual mosaic score and the automatic mosaic index on inspiratory scans (**a**, $r = 0.666$, $p < 0.0001$) and expiratory scans (**b**, $r = 0.876$, $p < 0.0001$). The best setting of measurement as for figure 3b was used.

Fig. 5. Correlation between the automatic mosaic index (**a, b**) or the MLD E/I ratio (**c, d**) and FEV₁/FVC (**a, c**) or AX (**b, d**). The mosaic index does not correlate with either FEV₁/FVC (**a**, $r = 0.29$, $p = 0.203$) or AX (**b**, $r = -0.25$, $p = 0.178$), while the MLD E/I ratio correlates negatively with FEV₁/FVC (**c**, $r = -0.35$, $p = 0.047$) and positively with AX (**d**, $r = 0.49$, $p = 0.007$).

tional indices of asthma, including those associated with small airway involvement. In contrast, the E/I ratios of MLD and LAA% showed significant correlations with FEV₁/FVC, consistent with our previous study [28], and IOS indices of small airways (AX and R5–R20).

To the best of our knowledge, this is the first study to compare quantitative mosaic attenuation with clinical and functional indices and to show correlations of the E/I ratios of MLD and LAA% with the exact IOS values in adult asthma patients.

Expiratory mosaic attenuation was originally reported as a semiquantitative indicator of air trapping in bronchiectasis [19]. Inhomogeneous attenuation in the expira-

tory phase was scored (grade 0–2) in 6 lobes. The total score was inversely related to FEV₁ and FEV₁/FVC and positively related to residual volume. Since this pioneer study, mosaic attenuation scores have been examined in various respiratory diseases. In asthma, visual assessment of expiratory mosaic attenuation showed significant correlations with FEV₁, FEV₁/FVC, FEF_{25–75} and peak flow in some reports [20, 46], while not in others [21, 47]. The only report that assessed mosaic attenuation quantitatively showed a significant difference between patients with obliterative bronchiolitis and normal subjects, but it did not address its functional correlations [25].

Table 3. Correlation coefficients between mosaic and clinical variables

	Visual score		Automatic index			
	expiratory	inspiratory	expiratory	inspiratory	E/I ratio	E-I gap
Age	0.04	0.16	0.15	0.11	0.04	0.07
Asthma duration	-0.25	-0.10	-0.29	-0.32	0.07	0.00
Severity	0.00	0.03	-0.03	0.23	0.02	0.03
FVC	-0.24	-0.21	-0.09	-0.23	0.16	0.14
FEV ₁	-0.12	-0.06	-0.09	-0.08	0.13	0.13
FEV ₁ /FVC	0.23	0.29	0.29	0.28	-0.06	-0.02
FEF ₂₅₋₇₅	0.10	0.19	0.13	0.23	-0.09	-0.07
log R5	-0.04	0.29	-0.08	0.09	-0.23	-0.22
log R20	0.07	0.27	0.06	0.10	-0.06	-0.04
log AX	-0.08	0.32	-0.14	0.16	-0.15	-0.13
log R5-R20	-0.18	0.23	-0.28	0.01	-0.31	-0.31
Sputum eosinophils	-0.24	-0.10	-0.08	-0.22	0.05	0.03
eNO	-0.20	-0.28	-0.15	-0.23	0.15	0.10
E/I ratio of MLD	-0.59**	-0.09	-0.53**	-0.08	-0.55**	-0.60**
E/I ratio of LAA%	-0.37*	0.05	-0.30	0.08	-0.47**	-0.48**

* $p < 0.05$, ** $p < 0.01$.

Table 4. Correlation coefficients between the E/I ratios of MLD or LAA% and clinical variables (single regression analysis)

	MLD E/I ratio	LAA% E/I ratio
Age	0.42*	0.47*
Asthma duration	0.06	-0.07
Severity	0.20	0.15
FVC	0.33	0.32
FEV ₁	0.24	0.21
FEV ₁ /FVC	-0.35*	-0.39*
FEF ₂₅₋₇₅	0.07	0.06
log R5	0.22	0.24
log R20	-0.05	-0.06
log AX	0.37*	0.45*
log R5-R20	0.46*	0.43*
Sputum eosinophils	-0.01	0.04
eNO	0.17	0.11

* $p < 0.05$.

A previous report indicated that the mosaic attenuation pattern in the inspiratory phase may mainly reflect regional blood flow because it correlated with lung perfusion but not lung ventilation [48], while in the expiratory phase it reflected air trapping [49]. Thus, it is not at all surprising that no correlations were found for the inspira-

tory mosaic score or index in the present study (table 3). Even with expiratory scans, however, conflicting reports still exist regarding functional correlations (positive [20, 46] and negative [21, 47]), as described above. In a recent intervention study, mosaic attenuation on expiratory scans decreased after treatment with inhaled corticosteroids in asthma patients who initially had abnormal mosaic attenuation probably due to air trapping [50], but this report also showed no correlations between air trapping and small airway indices of spirometry or lung volume. We assume that such inconsistent results were due to the limitations of semiquantitative analysis. However, the present results failed to demonstrate any significant correlations even with the use of automatic quantification (table 3), which was contrary to our hypothesis. Therefore, mosaic attenuation, even on expiratory scans, does not appear to be a good indicator of small airway obstruction or disease severity.

In our automatic system, the count of partitions with a relatively high density showed a higher correlation with the visual mosaic score than the count of those with a relatively low density (table 2). These results are not easy to explain, but a possible reason may be as follows. Potential noise sources for automatic measurement, such as lung fissures and small vessels, have high density, while low-density noise may be rare unless emphysema is present, which is very unlikely in the present patients who

Table 5. Coefficients of determination between the E/I ratios of MLD or LAA% and clinical variables (step-wise multiple regression analysis)

	MLD E/I ratio				LAA% E/I ratio			
	R ²	unstandardized coefficients	standardized coefficients	p	R ²	unstandardized coefficients	standardized coefficients	p
Age	–	–	–	–	–	–	–	–
FEV ₁ /FVC	0.15	–0.001	–0.389	0.032	–	–	–	–
log AX	0.13	0.020	0.358	0.041	0.18	0.112	0.428	0.021

– = No significant correlations.

Table 6. Hierarchical multiple regression change in the R² value with step-wise multiple regression analysis shown in table 5

	MLD E/I ratio				LAA% E/I ratio			
	parameter	action	R ²	p	parameter	action	R ²	p
Step 1	FEV ₁ /FVC	added	0.15	0.032	log AX	added	0.18	0.021
Step 2	log AX	added	0.28	0.041				

were never smokers or were very light ex-smokers. When we employ the count of partitions with a relatively low density for the automatic analysis, even one relatively high-density partition caused by such high-density noise may affect all of the surrounding partitions and may erroneously increase up to 4 relatively low-density partitions. On the other hand, if we employ the count of partitions with a relatively high density, such a high-density noise partition may result in only 1 erroneously counted partition (namely the noise partition itself). Therefore the count of relatively low-density partitions is more likely to result in an error than the count of relatively high-density partitions.

It has been reported that MLD and LAA% of CT and their E/I ratios correlate with spirometry indices, disease severity and airway hyperresponsiveness in asthma patients [26, 51]. Only one report showed relationships between MLD or LAA% and IOS indices [32]; it showed a correlation between LAA% on expiratory scans and IOS bronchodilator reversibility of R5, R10 and X5 with albuterol in children with mild to moderate asthma.

In the present study, the E/I ratios of MLD and LAA% showed significant correlations with FEV₁/FVC of spirometry indices, consistent with our previous report [26]. In addition, they showed a positive correlation with age

in this study and in the literature [52], whereas this was not the case in our previous report [26]. With advancing age, elastic fibers in the lung parenchyma decrease. These changes may alter the elastic properties of the airways, resulting in a loss of elastic recoil [53]. Thus, in elderly subjects, small airways may tend to collapse during expiration, possibly leading to air trapping. The inconsistent results may have been caused by differences in asthma severity or the CT scanner. Indeed, subjects involved in the present study seemed to have severer disease than those of the previous report [26].

The E/I ratios of MLD and LAA% showed positive correlations with the IOS indices of AX and R5–R20. These indices have been reported to reflect small airway obstruction [28, 30] and are used in clinical studies [29, 54]. On the other hand, they showed no correlations with R5 and R20, reflecting total and central airway resistance, respectively. On multiple regression analysis, only AX and FEV₁/FVC showed significant correlations with these ratios; thus, it is considered that they reflect airway disease rather than an aging effect. As mentioned above, the E/I ratios of MLD and LAA% reflect mainly small airway disease.

In the present study, the visual mosaic score and automatic mosaic index on expiratory scans showed unex-

pected negative correlations with the E/I ratios of MLD and LAA%. This would be due to the fact that both the expiratory mosaic score and the E/I ratios of MLD or LAA% depend on the difference in lung density between inspiratory and expiratory scans. Namely, the attenuated change (increase) of lung density from inspiratory to expiratory scans results in higher E/I ratios (closer to 1.0) and lower mosaic scores. In this study, none of the CT indices correlated with inflammation markers, eNO or sputum eosinophils. This was also the case in our previous study [26]. We considered that the CT indices used in these studies are unlikely to reflect airway inflammation.

CT scanning of specific lung volumes was not performed under spirometric control in the present study. This may be a limitation, but in several previous high-resolution CT studies using similar scanning methods but not spirometric gating [26, 55–57], the CT indices of air trapping clearly discriminated patients with various respiratory diseases from healthy controls and were strongly correlated with pulmonary function or severity markers, in agreement with the present results. These findings

may support the validity of the conventional CT methods used, though it would be desirable to perform expiratory CT scans under spirometric control in the future.

In the present study, the relevance of the mosaic attenuation pattern could not be determined, although it is reportedly sensitive to interventions [50]. The E/I ratios of MLD and LAA% showed their usefulness in the assessment of small airways, as in our previous report [26], by showing significant correlations with the IOS indices of AX and R5–R20, which were not included in our previous study.

In conclusion, the E/I ratios of MLD and LAA% may be useful tools to assess small airways in asthma. Thus, these parameters might have an important role in future research on asthma treatment. However, the mosaic attenuation pattern must be carefully interpreted.

Financial Disclosure and Conflicts of Interest

There are no conflicts of interest.

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