

### Role of small airways in asthma: Investigation using high-resolution computed tomography

Tetsuya Ueda, MD,<sup>a</sup> Akio Niimi, MD, PhD,<sup>a</sup> Hisako Matsumoto, MD, PhD,<sup>a</sup>  
Masaya Takemura, MD,<sup>a</sup> Toyohiro Hirai, MD, PhD,<sup>a</sup> Masafumi Yamaguchi, MD,<sup>a</sup>  
Hirofumi Matsuoka, MD,<sup>a</sup> Makiko Jinnai, MD,<sup>a</sup> Shigeo Muro, MD, PhD,<sup>a</sup>  
Kazuo Chin, MD, PhD,<sup>b</sup> and Michiaki Mishima, MD, PhD<sup>a</sup> *Kyoto, Japan*

**Background:** Small airways may have an important role in asthma but are more difficult to assess pathologically than central airways. Computed tomographic indices of lung density are assumed to reflect air trapping and may be a useful noninvasive measure of small airways disease, but their pathophysiological relevance remains undetermined. **Objective:** To evaluate lung density on high-resolution computed tomography and examine its correlations with clinical and physiologic variables in 29 patients with stable asthma.

**Methods:** Both lungs were scanned at full-inspiratory and full-expiratory phases to quantify percentage of lung field occupied by low attenuation area (LAA %; < -960 Hounsfield units) and mean lung density. Asthma severity, pulmonary function, methacholine airway sensitivity and reactivity, and sputum eosinophil counts were evaluated.

**Results:** The mean lung density increased and LAA % decreased in all patients at expiratory phase compared with inspiratory phase. The inspiratory density indices and expiratory mean lung density correlated only with FEV<sub>1</sub>/forced vital capacity (FVC). Expiratory LAA % correlated more strongly than other variables with FEV<sub>1</sub>/FVC and with indices of peripheral airflow obstruction. Expiratory/inspiratory ratios of LAA % and mean lung density correlated, the former more strongly, with disease severity, residual volume/total lung capacity, and airway sensitivity, as well as with indices of global (FEV<sub>1</sub> and FEV<sub>1</sub>/FVC) and peripheral airflow obstruction.

**Conclusion:** Expiratory/inspiratory high-resolution computed tomography is useful for assessing small airways disease in asthma. Small airways involvement is associated with airflow obstruction, airway hypersensitivity, and more severe disease.

**Clinical implications:** Small airways are an important therapeutic target in asthma. (*J Allergy Clin Immunol* 2006;118:1019-25.)

**Key words:** Asthma, small airways, high-resolution computed tomography, lung density, airway responsiveness, airway inflammation, airway remodeling, air trapping

Chronic airway inflammation is a fundamental feature of asthma. Such inflammation is associated with airway remodeling, characterized by increases in smooth muscle and submucosal glands, thickening of reticular basement membranes, vascular proliferation, and airway wall thickening.<sup>1</sup> Autopsy studies of patients dying of episodes of asthma have shown that inflammation and remodeling involve both central and peripheral airways.<sup>2,3</sup> An important contribution of small airways to the pathogenesis of asthma has been suggested,<sup>4,5</sup> but methodologic difficulties have precluded detailed clinicopathological studies.

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 can be measured by helical or high-resolution CT (HRCT), either manually<sup>6-8</sup> or automatically.<sup>9,10</sup> These variables are considered indirect measures of airway remodeling.<sup>11,12</sup> Central 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,<sup>6-8</sup> and several biomarkers of airway inflammation and remodeling.<sup>13-15</sup> However, analysis of airway dimensions such as the wall area or luminal area of small airways (less than 1-2 mm in diameter) is beyond the spatial resolution limits of CT.<sup>9,11</sup> HRCT findings of air trapping, such as decreased lung attenuation or a so-called mosaic pattern, have therefore been used to assess small airway involvement in various lung diseases.<sup>16</sup>

Recently, HRCT indices of lung density, such as the percentage of lung field occupied by low attenuation area (LAA%) and mean lung density (MLD), have been quantitatively analyzed in patients with asthma.<sup>17-21</sup> These measures, especially those derived from full-expiratory

From <sup>a</sup>the Department of Respiratory Medicine and <sup>b</sup>the Department of Physical Therapy Respiratory Medicine, Kyoto University.

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Reprint requests: Akio Niimi, MD, PhD, Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: niimi@kuhp.kyoto-u.ac.jp.

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*Abbreviations used*

CT:	Computed tomography
Dmin:	Cumulative dose of methacholine at the inflection point at which simultaneous measurement of respiratory resistance begins to increase
E/I ratio:	Ratio of percentage of lung field occupied by low attenuation areas or mean lung density on expiratory scans to that on inspiratory scans
FEF <sub>25-75</sub> :	Midforced expiratory flow
FVC:	Forced vital capacity
HRCT:	High-resolution computed tomography
HU:	Hounsfield unit
LAA%:	Percentage of lung field occupied by low attenuation areas
MEF <sub>25</sub> :	Maximum expiratory flow at the quartile of forced vital capacity
MLD:	Mean lung density
Rrs:	Respiratory resistance
RV/TLC:	Residual volume/total lung capacity
SRrs:	Slope of the methacholine–respiratory resistance dose–response curve

**TABLE I.** Characteristics of patients with asthma\*

Female/male (n)	23/6
Age (y)	63 (26-75)
Height (cm)	154 (145-175)
Body weight (kg)	58 (37-92)
Atopy/nonatopy (n)	15/14
Asthma duration (y)	13.0 (0.7-65.0)
Exacerbation frequency (per y)	0.5 (0.0-3.0)
IgE (IU/mL)	120 (10-1830)
Sputum eosinophils (%)	2.8 (0.0-76.8)
FEV <sub>1</sub> (% predicted)	98.0 (50.6-137.5)
FEV <sub>1</sub> /FVC (%)	69.3 (47.3-83.5)
FEF <sub>25-75</sub> (% predicted)	68.7 (19.0-148.2)
MEF <sub>25</sub> (% predicted)	24.8 (8.6-63.2)
RV/TLC (%)	35.0 (22.8-52.2)
LAA% of inspiratory scans (%)	19.3 (1.1-49.5)
LAA% of expiratory scans (%)	2.2 (0.2-26.9)
E/I ratio of LAA%	0.09 (0.02-1.00)
MLD of inspiratory scans (HU)	−886 (−926 to −807)
MLD of expiratory scans (HU)	−769 (−897 to −649)
E/I ratio of MLD	0.87 (0.75-1.00)

\*Each value is the number of subjects or median, with range shown in parentheses.

scans, differ between patients and healthy controls, indicating the presence of air trapping in asthma.<sup>17,19,21</sup> LAA% and MLD on inspiratory and expiratory scans, and the ratios of these values at expiration to the respective values at inspiration (E/I ratios), are also considered CT indices of air trapping.<sup>18,22,23</sup> The relations of these CT indices to pulmonary function have been examined in asthma.<sup>17-21</sup> To our knowledge, however, a single study has not comprehensively evaluated which of these CT indices is the best index of lung function. More importantly, the relations of these indices to important pathophysiological variables in asthma, such as airway responsiveness and airway inflammation, remain to be evaluated.

We examined inspiratory and expiratory LAA% and MLD and their E/I ratios on HRCT in patients with asthma to investigate the relations of these indices to disease severity, pulmonary function measures of central and peripheral airway obstruction and air trapping, airway inflammation, and airway responsiveness.

## METHODS

### Subjects

We studied 29 patients with asthma diagnosed according to the American Thoracic Society criteria.<sup>24</sup> At study entry, all patients were clinically stable and had not had disease exacerbations or respiratory infections for at least 1 month. Severity of asthma was mild persistent (step 2) in 10 patients, moderate persistent (step 3) in 13, and severe persistent (step 4) in 6.<sup>25</sup> The quantitative index of asthma severity was defined according to this step classification (2, 3, or 4) of Global Initiative for Asthma guidelines.<sup>25</sup> Atopy was determined by the presence of specific serum IgE antibodies against at least 1 common inhalant allergen. The frequency of exacerbations, defined as annual episodes of increased symptoms requiring oral corticosteroids, emergency department visits, or hospitalization despite

maintenance therapy,<sup>26</sup> was determined over the course of 2 years (12 months before the study and 12 months after the study). Subjects were also compared according to the presence or absence of exacerbations. Twenty-five patients had never smoked. Four patients had smoked less than 5 pack-years, but had stopped smoking more than 12 months before study entry. None had evidence of chronic obstructive pulmonary disease (COPD). The research protocol was approved by the ethics committee of Kyoto University, and written informed consent was obtained from all subjects.

### CT analysis of lung density

High-resolution computed tomography scans (X-Vigor; Toshiba, Tokyo, Japan) were acquired with the use of 2-mm collimation, a scan time of 1.0 seconds, 120 kilovolts peak (kVp), and 200 milliamperes (mA), as previously described.<sup>9</sup> Full-inspiratory and full-expiratory scans of both lungs were performed at the carina, 4 cm above the carina, and 4 cm below the carina. Expiratory scans were followed by inspiratory scans to avoid effects of deep inspiration. An experienced technician instructed patients on how to inspire and expire correctly; the maneuver was practiced until the patient complied with the request to “breathe right out and hold it.” Moreover, during CT scanning, the technician closely observed patients for their inspiratory/expiratory maneuvers and breath holding. Scanning was finished only when these requirements were satisfactory achieved. These procedures were supervised by a physician. LAA% and MLD (Hounsfield units, HU) were calculated automatically.<sup>27,28</sup> Low attenuation areas were defined as areas below −960 HU.<sup>27,28</sup> LAA% was calculated as the low attenuation area percentage of the entire lung area. LAA% and MLD were measured at all 6 slices and averaged. The calculated LAA% and MLD values were considered representative of the whole lung, because a preliminary study in 8 patients showed that LAA% and MLD derived from the 3 lung levels used in this study were reproducible and did not significantly differ from the respective values derived from scans obtained at 10-mm or 20-mm intervals from the apex through the diaphragm (data not shown). This finding was consistent with the results of our previous study in chronic obstructive pulmonary disease.<sup>29</sup> LAA% and MLD on inspiratory and expiratory scans (inspiratory/expiratory

TABLE II. Spearman coefficients of correlation between clinical indices and CT indices\*

	Inspiratory scans				Expiratory scans				E/I ratio of LAA%		E/I ratio of MLD	
	LAA%		MLD		LAA%		MLD					
	r	P	r	P	r	P	r	P				
Age	0.18	.33	−0.16	.39	0.31	.12	−0.23	.25	0.21	.33	0.13	.51
Duration	−0.28	.14	0.25	.18	0.01	.96	0.02	.91	0.24	.26	0.14	.47
Severity	−0.06	.74	0.02	.90	0.23	.24	−0.28	.15	<b>0.47</b>	<b>.03</b>	<b>0.45</b>	<b>.02</b>
Exacerbation	−0.08	.68	0.13	.48	0.09	.64	−0.13	.50	0.26	.18	0.25	.20
IgE	−0.06	.75	0.08	.68	0.07	.71	−0.07	.91	0.23	.24	0.27	.16
Sputum eosinophils	−0.00	.99	0.14	.54	0.12	.60	−0.04	.86	0.25	.29	0.22	.36
FEV <sub>1</sub> †	0.21	.27	−0.21	.27	−0.25	.20	0.14	.49	<b>−0.63</b>	<b>.003</b>	<b>−0.39</b>	<b>.049</b>
FEV <sub>1</sub> /FVC	<b>−0.40</b>	<b>.04</b>	<b>0.38</b>	<b>.045</b>	<b>−0.74</b>	<b>.0002</b>	<b>0.54</b>	<b>.006</b>	<b>−0.68</b>	<b>.002</b>	−0.38	.06
FEF <sub>25-75</sub> †	−0.08	.69	0.07	.72	<b>−0.53</b>	<b>.008</b>	0.37	.06	<b>−0.73</b>	<b>.0006</b>	<b>−0.46</b>	<b>.02</b>
MEF <sub>25</sub> †	−0.24	.20	0.21	.26	<b>−0.56</b>	<b>.004</b>	0.34	.08	<b>−0.58</b>	<b>.007</b>	−0.29	.14
RV/TLC	−0.14	.45	0.15	.42	0.26	.19	−0.28	.15	<b>0.56</b>	<b>.009</b>	<b>0.53</b>	<b>.007</b>
Dmin	0.13	.54	−0.09	.66	−0.31	.15	0.41	.06	<b>−0.54</b>	<b>.02</b>	<b>−0.54</b>	<b>.01</b>
SRrs	0.10	.66	−0.08	.73	0.16	.50	0.06	.82	0.26	.32	−0.07	.78

\*Significant correlations are presented in boldface.  
†Percentage predicted.

LAA% and MLD) and the E/I ratios of LAA% and MLD were analyzed.<sup>18,22,23</sup>

Pulmonary function

Patients underwent pulmonary function tests on the same day as CT scanning, using a Chestac-55V unit (Chest, Tokyo, Japan) according to recommendations of the American Thoracic Society.<sup>30</sup> Forced vital capacity (FVC), FEV<sub>1</sub>, and residual volume/total lung capacity (RV/TLC), a functional parameter of air trapping, were measured. In addition, midforced expiratory flow (FEF<sub>25-75</sub>) and maximum expiratory flow at the quartile of the FVC (MEF<sub>25</sub>) were examined. These variables are considered to reflect airflow obstruction at the level of small airways.<sup>31,32</sup>

Methacholine challenge

Airway responsiveness was examined by continuous inhalation of methacholine, with simultaneous measurement of respiratory resistance (Rrs, cm H<sub>2</sub>O/L/s; Astograph; Chest).<sup>33</sup> As described and validated previously,<sup>10</sup> Dmin, the cumulative dose of methacholine at the inflection point at which Rrs begins to increase, was used as a marker of airway sensitivity, and the slope of the methacholine-Rrs dose-response curve (SRrs) was used as a measure of airway reactivity.

Sputum induction

After inhalation of salbutamol, sputum was induced as described previously.<sup>34</sup> Eosinophil percentage was determined using centrifuged preparations stained with May-Grünwald-Giemsa stain.

Statistical analysis

Data are expressed as medians (ranges). Differences between LAA% or MLD of inspiratory and expiratory HRCT scans were analyzed with the Wilcoxon signed-rank test. Effects of sex, atopy, and presence or absence of exacerbations on HRCT indices were analyzed with the Mann-Whitney *U* test. Relations between clinical variables and HRCT indices were evaluated with Spearman rank-correlation test. A *P* value < .05 was considered to indicate statistical significance.

RESULTS

Characteristics of patients with asthma

The characteristics of the subjects, including CT indices, are presented in Table I. On expiratory CT scans, LAA% decreased and MLD increased in all patients compared with the values on inspiratory scans (*P* < .0001 for both LAA% and MLD). All patients had received inhaled corticosteroids at daily doses equivalent to 800 μg (400-1600 μg) chlorofluorocarbon-beclomethasone dipropionate.

Relations between HRCT indices and clinical indices

Table II shows the coefficients of correlations between HRCT indices and clinical indices. All LAA% and MLD values at both inspiratory and expiratory phases significantly correlated with FEV<sub>1</sub>/FVC (Table II, Fig 1), consistently indicating an association between decreased lung attenuation and airflow obstruction. Correlations with FEV<sub>1</sub>/FVC were stronger for expiratory scans and LAA% than for inspiratory scans and MLD (Fig 1). There was no other correlations of clinical indices with inspiratory LAA% or with inspiratory or expiratory MLD (Table II). Expiratory LAA% also correlated negatively with FEF<sub>25-75</sub> and MEF<sub>25</sub> (Table II).

E/I ratio of MLD correlated positively with disease severity and RV/TLC, and negatively with FEV<sub>1</sub>, FEF<sub>25-75</sub>, and Dmin. E/I ratio of LAA% similarly correlated with all of these indices, generally more strongly than did E/I ratio of MLD, and correlated negatively with FEV<sub>1</sub>/FVC and MEF<sub>25</sub> (Table II, Fig 2).

No CT index was related to age, duration of asthma, serum IgE levels, or sputum eosinophil count (Table II) or was affected by sex or the presence of atopy (data not shown). CT indices were also unrelated to the frequency

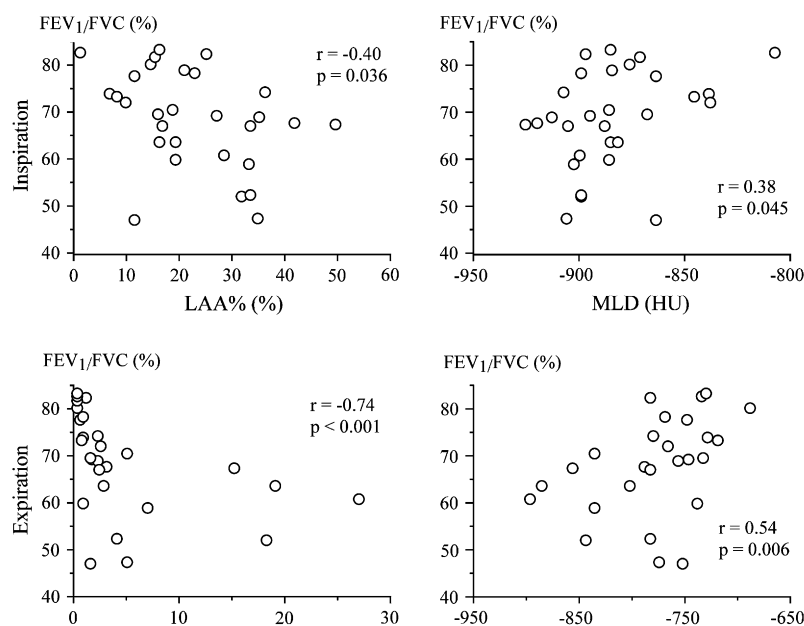


FIG 1. Correlation of inspiratory and expiratory CT indices with FEV<sub>1</sub>/FVC.

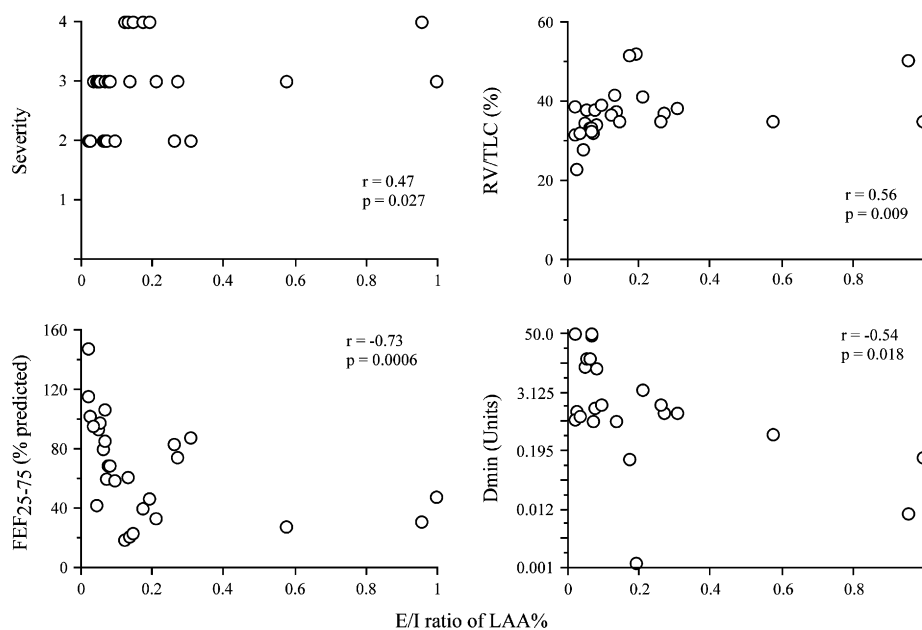


FIG 2. Correlation between E/I ratio of LAA% and clinical indices. The severity scores of 1, 2, 3, and 4 respectively represent intermittent, mild persistent, moderate persistent, and severe persistent disease according to the Global Initiative for Asthma guidelines.

of exacerbations, but 15 patients with 1 or more exacerbations over the course of 2 years had marginally higher E/I ratios of LAA% and MLD than did 14 patients without exacerbations ( $P = .073$  and  $.058$ , respectively).

When the 3 slice levels of CT (ie, upper, middle, and lower) were compared for each CT index, greater degrees of air trapping were consistently observed at lower lung levels (data not shown).

## DISCUSSION

In the current study, we assessed LAA% and MLD on inspiratory and expiratory HRCT scans and calculated the expiratory/inspiratory ratios of these variables in patients with stable asthma. To our knowledge, this is the first study to examine the relations of lung density on CT with airway inflammation and airway responsiveness.

Inspiratory LAA% and MLD weakly correlated only with  $FEV_1/FVC$ . Expiratory LAA% and MLD more strongly correlated with  $FEV_1/FVC$ , and the former also correlated with indices of peripheral airflow obstruction. The E/I ratio of LAA% or MLD was related to disease severity, airway sensitivity, and RV/TLC, as well as to indices of airflow obstruction. These results indicate considerable pathophysiologic involvement of small airways in asthma.

Several groups have assessed LAA% and MLD on inspiratory scans, expiratory scans, or both and analyzed the relations of these variables to pulmonary function in patients with stable asthma. LAA% ( $< -900$  HU) on conventional CT or HRCT at full expiration, but not at full inspiration, has been shown to correlate with  $FEV_1$  and residual volume.<sup>21</sup> Expiratory scans are superior to inspiratory scans for discriminating patients with asthma from controls on both conventional CT and HRCT.<sup>21</sup> Lung density at full inspiration on conventional CT has been found not to correlate with  $FEV_1$  or RV/TLC in patients with asthma.<sup>35</sup> An HRCT study found no difference in inspiratory MLD or LAA% ( $< -950$  HU) between patients with asthma with chronic hyperinflation and healthy controls.<sup>36</sup> That study even failed to show a decrease in these values after antigen challenge in patients with asthma, despite a marked ( $>20\%$ ) decrease in the  $FEV_1$ .<sup>36</sup> Our results are generally consistent with the findings of these studies.<sup>21,35,36</sup> Inspiratory CT indices may thus reflect regional blood flow rather than air trapping.<sup>37</sup> Mitsunobu et al<sup>17-19</sup> recently evaluated inspiratory HRCT lung density in non-smoking patients with asthma. They found that MLD and LAA% ( $< -950$  HU) in patients differ from those in healthy controls and correlate closely with  $FEV_1$  and  $FEV_1/FVC$ . The underlying reason for the difference between our results and those of Mitsunobu et al,<sup>17-19</sup> who used an HRCT protocol similar to ours, is difficult to explain, but may be related to more severe disease in their subjects.

The E/I ratio of MLD is also considered to reflect air trapping, as demonstrated in patients with pulmonary emphysema<sup>22</sup> and *Mycobacterium avium* complex disease.<sup>23</sup> Gono et al<sup>20</sup> have recently reported that the E/I ratio of MLD was significantly higher in 14 patients with asthma with chronic airflow limitation than in 10 patients with asthma with normal lung function and 7 healthy controls. In our study, E/I ratios of LAA% and MLD in the patients with asthma both correlated with many of the clinical indices examined (Table II). These variables may thus be more useful markers of small airways disease in asthma, compared with absolute lung density measures on inspiratory or expiratory scans. The absolute value of expiratory LAA% or MLD simply reflects how much air is contained in the lungs at full expiration. The E/I ratio of LAA% or MLD might reflect the degree to which fully inhaled air is effectively exhaled at full expiration. We believe that E/I ratios have a more dynamic nature than absolute expiratory values, which are static measures. E/I ratios may thus more accurately reflect the degree of air trapping, a dynamic phenomenon occurring in the lungs of patients with asthma. Compared with the E/I ratio of

MLD, the E/I ratio of LAA% correlated more strongly not only with RV/TLC, a functional measure of air trapping, but also with the severity score, obstruction of global ( $FEV_1$  and  $FEV_1/FVC$ ) and peripheral airways, and airway sensitivity. These results suggest that the E/I ratio of LAA% is the most sensitive and useful marker of small airways abnormalities in patients with asthma. Asthma may involve pathologic changes of lung parenchyma such as cellular infiltrates,<sup>38,39</sup> which might affect lung density. LAA% and particularly the E/I ratio of LAA% may more closely reflect small airways abnormalities than MLD because these variables are less likely to be affected by parenchymal abnormalities.

The pathogenesis of airway hyperresponsiveness in asthma is a crucial yet unresolved issue. Various inflammatory cells, mediators, and pathologic changes have been implicated. We have recently shown that the thickness of the central airway wall on helical CT scans negatively correlates with airway reactivity, but is unrelated to airway sensitivity.<sup>10</sup> Central airway wall thickening or remodeling may thus protect against excessive airway narrowing, possibly by stiffening the airway wall.<sup>10</sup> Changes in lung density in response to allergen or methacholine inhalation have been investigated,<sup>36,40,41</sup> but the relation between airway responsiveness and lung density remains unknown. In our patients, the E/I ratios of both LAA% and MLD correlated with airway sensitivity, but not with airway reactivity, indicating that pathologic changes of the peripheral airways or associated air trapping is related to airway hypersensitivity. This notion is consistent with evidence showing that closure of small airways during stable episodes, as indicated by an increase in closing volume, is associated with more frequent exacerbations of asthma.<sup>42</sup> Indeed, although we found no significant correlation between the frequency of exacerbations and the E/I ratio of LAA% or MLD (Table II), 15 patients with 1 or more exacerbations over the course of 2 years had marginally higher E/I ratios of LAA% and MLD than did 14 patients without exacerbations. Thickening of the outer airway wall, caused by factors such as extracellular matrix deposition, may attenuate transmission of the distending force generated by the surrounding lung parenchyma to oppose smooth muscle shortening, making the airways more likely to narrow.<sup>43</sup> Such effects may be much more pronounced in distal airways, which have a smaller internal diameter and may lack cartilage.<sup>44</sup> Damaged alveolar attachments and decreased elastic fiber content in the adventitia of small airways and peribronchial alveolar septa, confirmed in patients with fatal asthma, may also promote airway-parenchymal uncoupling by decreasing the tethering mechanical forces exerted by the surrounding parenchyma, as well as lead to excessive narrowing of smooth muscle.<sup>45</sup> The roles of central<sup>10</sup> and peripheral airways in the pathophysiology of asthma may thus differ. Treatment approaches specifically targeting small airways should thus be considered in the future.

Inflammation of peripheral or distal airways in asthma has recently been investigated by transbronchial<sup>39,46,47</sup>



and surgical<sup>5</sup> biopsy. Inflammation may be more intense in the peripheral airways than in the central airways.<sup>5</sup> We found no correlation between HRCT indices and inflammation as assessed by sputum eosinophilia, perhaps because induced sputum is derived more from central rather than peripheral airways.<sup>48</sup> The use of late-phase samples of sequentially induced sputum might have yielded significant correlations.<sup>49</sup>

We did not perform spirometric control of specific lung volumes for CT scanning. This may be a limitation of our study, but the required techniques are not widely available. Our patients were cooperative and were carefully instructed to breathe in deeply for inspiratory CT scans and to breathe out completely for expiratory CT scans. In several previous HRCT studies using similar scanning methods but not spirometric gating,<sup>18,21,22</sup> the CT indices of air trapping clearly discriminated patients with various respiratory diseases from healthy controls and strongly correlated with pulmonary function or severity markers, in agreement with our results. These findings support the validity of the conventional CT methods we used.

Full-inspiratory and full-expiratory scans were performed at the carina, 4 cm above the carina, and 4 cm below the carina. This procedure may have resulted in different absolute levels of the lungs between full inspiration and full expiration. However, this is unlikely to have affected our final results significantly. To calculate LAA% or MLD, we averaged the 6 values of LAA% or MLD, derived from the 3 CT slices from each of the lungs, on the inspiratory or expiratory CT scans. The calculated LAA% and MLD were considered representative of the entire lung, as described in Methods. The E/I ratio of LAA% or MLD was obtained by dividing the average expiratory LAA% or MLD value by the average inspiratory LAA% or MLD value, not by averaging the 6 E/I values for each CT slice. A similar analytical strategy has been used by other groups.<sup>18,20</sup>

We conclude that expiratory/inspiratory HRCT is a useful research tool for assessing small airways disease in asthma. Small airways involvement is associated with airflow obstruction, airway hypersensitivity, and more severe disease. It may therefore be an important therapeutic target. Because HRCT might also be sensitive enough to evaluate response to interventions<sup>50,51</sup> and is less invasive than transbronchial biopsy,<sup>38,39,52</sup> expiratory/inspiratory HRCT may have an important role in future research on asthma treatment.

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