Air trapping is a major determinant of persistent airway obstruction in asthmatics

Sung-Woo Park a,g, Jai-Soung Park b,g, Sun Hye Jeong b, Yun Nah Lee c, Young Hwangbo d, Jong Sook Park a, June Hyuk Lee a, An-Soo Jang a, Do-Jin Kim a, Soo Taek Uh e, Yong Hoon Kim f, Choon-Sik Park a,*

a Genome Research Center for Allergy and Respiratory Disease, Soonchunhyang University Bucheon Hospital, 1174, Jung-Dong, Wonmi-Gu, Bucheon, Gyeonggi-Do 420-020, South Korea
b Department of Radiology, Soonchunhyang University Bucheon Hospital, 1174 Jung-Dong, Wonmi-Gu, Bucheon, Gyeonggi-Do 420-020, South Korea
c Department of Gastroenterology, Soonchunhyang University Bucheon Hospital, 1174 Jung-Dong, Wonmi-Gu, Bucheon, Gyeonggi-Do 420-020, South Korea
d Department of Preventive Medicine, Soonchunhyang University Bucheon Hospital, 1174 Jung-Dong, Wonmi-Gu, Bucheon, Gyeonggi-Do 420-020, South Korea
e Division of Allergy and Respiratory Medicine, Soonchunhyang University Hospital, 657, Hannam-Dong, Yongsan-Gu, Seoul 140-743, South Korea
f Division of Respiratory Medicine, Soonchunhyang University Chunan Hospital, South Korea

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KEYWORDS
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Persistence;
Air trapping;
Lung CT;
Inhaled corticosteroid

Summary
Chronic persistent airway obstruction has been observed in moderate-to-severe asthmatics despite treatment with inhaled corticosteroids. We investigated which airway changes were associated with this obstruction.

High-resolution computed tomography (HRCT) was performed at study entry and reexamined at the time of follow-up when the FEV1 reached a maximally constant level after treatment for 1 year or more with inhaled corticosteroids. Bronchial wall area and air trapping extent were compared in the recovered group (n = 18) and the persistent airway obstruction group (n = 14).

Bronchial wall area and air trapping of the initial HRCT were similar between the two groups. On follow-up HRCT, air trapping was markedly decreased in the recovered group compared to the persistent airway obstruction group.

Abbreviations: HRCT, high-resolution computed tomography; Post-BD FEV1, post-bronchodilator forced expiratory volume in 1 s; dAT, difference AT value between at initial and 2nd HRCT exam; d post-BD FEV1, difference post-BD FEV1 value between at initial and 2nd HRCT exam.

* Corresponding author. Tel.: +82 32 621 5024.
E-mail address: mdcspark@unitel.co.kr (C.-S. Park).
Sung-Woo Park and Jai-Soung Park contributed equally to this work as the first author.

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Asthma is a chronic inflammatory airway disease, characterized by airflow limitation and airway hyper-responsiveness. However, asthma patients consist of several subgroups defined by etiology, pathology, severity, and response to treatment. High doses of inhaled corticosteroids can relieve airflow obstruction in asthmatics. However, a proportion of patients fail to recover normal lung function. Such persistent airflow obstruction is one of the specific asthma phenotypes and comprises fewer than 5% of all asthmatics. This subgroup has several characteristics that differ from typical asthma. Eosinophilic airway inflammation is the characteristic abnormality in both atopic and nonatopic asthma. However, recent studies suggest that neutrophils are predominant in the airways of severely affected patients. Additionally, thickening of the reticular basement membrane and increased airway smooth muscle are associated with persistent airflow obstruction in severe asthma. Thus, the examining differences in airway inflammation and airway wall changes may help in predicting the effectiveness of asthma therapies including inhaled corticosteroids in asthma subgroups.

In evaluating airway structural changes in asthma, histological examinations using bronchoscopic biopsies are very useful, but availability is limited in severe asthmatics. For the past two decades, HRCT has been used as a noninvasive method to assess bronchial wall thickness and air trapping to reflect the changes in large and small airways. Severe asthma is characterized by thickened bronchial walls and increased air trapping on HRCT. These large and small airway changes are considered to be responsible for treatment-refractory, chronic, persistent airway obstructions. However, few studies have evaluated longitudinal morphological changes in these parameters. The purpose of this study was to evaluate large and small airway changes on HRCT for the structural characterization of the unresponsiveness to inhaled corticosteroids, leading to persistent airflow obstruction in patients with asthma.

Materials and methods

Subjects

We enrolled patients with moderate or severe asthma according to the Global Initiative for Asthma (GINA) guidelines at a university hospital. Moderate-to-severe asthma was defined as post-bronchodilator forced expiratory volume in 1 s (post-BD FEV1) of <75% of the predicted value, two or more episodes of nocturnal symptoms per week, and limitation of activities with asthma symptoms present. Subjects had not taken any inhaled or systemic corticosteroid over the previous 4 weeks before the first HRCT examination. All subjects underwent a standardized assessment, which included complete blood count, total IgE, chest posteroanterior radiography, allergy skin-prick tests, and spirometry. Exclusion criteria included respiratory infections within 4 weeks of screening, smoking history of >10 packs per year, chronic obstructive pulmonary disease or post-BD FEV1 of >75% predicted value at screening.

This study was approved by the hospital ethics committee. Written consent was obtained from all patients.

Study design

At screening, the subjects underwent lung function tests and HRCT. Subjects with bronchiectasis, emphysema, or other parenchymal lung diseases on HRCT were excluded. Immediately after examination, systemic and/or inhaled corticosteroid treatment was started, according to GINA guidelines. During the study period, all subjects maintained higher doses of inhaled corticosteroids (>1000 μg fluticasone per day) combined with long-acting β-agonists and additional therapies to achieve optimal symptom relief and maximum FEV1 for 12 months or more. When the post-BD FEV1 level reached a maximum, HRCT was reevaluated. Maximal post-BD FEV1 level was defined as <10% variation observed on two or more consecutive FEV1 measurements with a 2-month interval after continuous medications for 12 months or more. Subjects were divided into two groups by post-BD FEV1 % levels: the recovered group with >75%, and the persistent airflow obstruction group with <75%.

Thin-slice CT scanning and radiological evaluation

All subjects underwent volumetric thin-section CT scanning of the chest using a 16-slice helical CT (Somatom Sensation 16, software version V20; Siemens Medical Solutions, Forchheim, Germany). The measurement of HRCT findings has been described previously. Inspiration and expiration scans were obtained at the end of full inspiration and at the end of full expiration. We used the following parameters:
120 kVp, 180 mAs, 1-mm table feed/rotation, 1-mm collimation, and a 0.5-mm interval. Image data were reconstructed with 1.0-mm thicknesses and 10-mm intervals using a bone algorithm.

Images were viewed at two window levels: −450 HU for bronchial wall area(%) and −700 HU for air trapping(%). All images were displayed at the lung window setting using a picture-archiving and communication system (PACS) work station (Starpacs, Infinit Technology). These findings were defined according to the glossary of terms recommended by the Fleischner Society.15 Airway images were viewed on a work station using a magnification of 5×, and measurements of outer (D) and internal (L) diameters of the bronchi were made using electronic calipers by two experienced thoracic radiologists. All bronchi with a D diameter of >1.5 mm and a ratio of the long-to-short D diameter < 1.5 were measured on each slice of the end-inspiration scans. Because oblique sections can influence wall thickness, bronchi showing a ratio of the long-to-short D diameter < 1.5 were analyzed.

Wall area(WA) was calculated as a percentage of total airway cross-sectional area according to the following formula:

\[
WA(\%) = \left(\frac{\pi(D/2)^2 - \pi (L/2)^2}{\pi(D/2)^2}\right) \times 100
\]

To measure air trapping, the lung was divided into six zones (right and left upper, middle, and lower) by one- and two-thirds of the vertical distance between the lung apices and the domes of the diaphragm. Air trapping was defined by the decreased attenuation of pulmonary parenchyma, manifested as a less-than-normal increase in attenuation during expiration, according to the definition of the Fleischner Society.15

Thus, lung attenuation and air trapping area measurements were performed on similar anatomical levels at inspiration and expiration. The reader selected HRCT sections according to anatomical landmarks and used the software to measure the difference between inspiratory and expiratory median lung attenuation, calculated for the whole lung, as described previously. Focal areas of relative lucency in the superior segments of the lower lobes were excluded from analysis because they can be seen in normal subjects on inspiratory scans.16 The low attenuation areas of emphysema and bullae were also excluded.

Air trapping was calculated as the percentage of the involved area to the cross-sectional area from each zone. Intra- and inter-observer variation were assessed by plotting the difference between the two wall area and air trapping measurements against the mean value of each. To assess intra- and inter-observer variability of parameters, the kappa coefficient of agreement (κ) was computed.18

Statistical analysis

Data are expressed as means ± SEM or medians and inter-quartile ranges. The SPSS/PC + program (SPSS, Inc., Chicago, IL) was used for the statistical analyses. Mann–Whitney U test or the chi-squared test was used to compare differences between the recovered group and persistent airway obstruction group. Initial and follow-up differences in variables in the intra-group were determined by using the Wilcoxon signed rank test. Correlations between the data were assessed using Spearman’s rank test. Finally, multivariate log-binomial regression models were used because of the presence of common outcome variables to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the presence of persistent airflow obstruction by including the initial wall area (Model 1), the initial air trapping (Model 2), the difference between the initial and follow-up wall area (Model 3) and the difference between initial and follow-up air trapping (Model 4). Models 1 and 2 were adjusted for age, gender, smoking history, atopy, and symptom duration. Model 3 was further adjusted for initial wall area and Model 4 was further adjusted for initial air trapping. P values < 0.05 were considered to indicate statistical significance.

Results

Demographic and physiological characteristics of the study subjects

In total, 32 patients with moderate-to-severe asthma were enrolled; 14 patients developed persistent airway obstruction during treatment (Persistent airway obstruction group; Table 1). There was no significant difference in age, gender, frequency of atopy, smoking, or duration of asthma between the two groups. The mean length of follow-up duration was similar between the two groups (2.1 vs. 2.7 years). On the initial day of the study, all study subjects had post-BD FEV1s of <75% predicted. There was no significant difference in lung function, including FVC, FEV1, and FEV1/FVC values, between the two groups (Table 2). At the second HRCT examination, the post-BD FEV1 had not changed in the persistent airway obstruction group from that at the initial examination (55.2 ± 4.4% vs. 59.2 ± 3.0% of the predicted value; P = 0.37), whereas the recovered group showed a marked improvement in FEV1 (51.1 ± 5.4% vs. 86.6 ± 3.1% of the predicted value; P = 0.001). Changes in FVC and FEV1/FVC were comparable to changes in FEV1 in both groups (Table 2). Thus, the follow-up FEV1/FVC was significantly higher in the recovered group compared with the persistent airway obstruction group (73.4 ± 2.9% vs. 58.7 ± 4.1%; P = 0.002).

Comparison of parameters on HRCT findings between recovered group and persistent airway obstruction group

In total, 1092 bronchi were measured using thin-section CT scanning (630 in 18 patients in the recovered group, 462 in 14 patients in the persistent airway obstruction group; range, 16–21 bronchi on HRCT scanning per subject). The mean diameters of the outer airways of the measured bronchi were similar in the recovered group and persistent airway obstruction group (5.6 ± 0.24 vs. 5.7 ± 0.27 mm, respectively; P > 0.05). The κ values for inter- and intra-observer agreement of wall area were 68%
and 77%, respectively. Wall area at the initial HRCT was similar between the recovered group and persistent airway obstruction group (66.6 ± 1.5 vs. 65.6 ± 1.6%; \( P = 0.625 \)). Wall area values on the second HRCT were also similar between the recovered group and persistent airway obstruction group (65.1 ± 1.2 vs. 67.2 ± 1.8%; \( P = 0.568 \); Table 3). Air trapping values in the initial HRCT were comparable between the recovered group and persistent airway obstruction group (53.4 ± 4.2 vs. 50.7 ± 2.6%, \( P = 0.160 \)). However, air trapping was significantly decreased in the recovered group during the second HRCT compared with that of the initial HRCT (53.4 ± 4.2 vs. 41.6 ± 3.3%; \( P = 0.001 \)). In contrast, air trapping did not change in the persistent airway obstruction group despite treatment between the initial and second measurements (50.7 ± 2.6 vs. 54.2 ± 2.2%; \( P = 0.109 \)). The inter-observer agreement level was 73% for air trapping. The \( \kappa \) values for air trapping ranged from 0.48 to 0.60, indicating fair-to-good agreement. The intra-observer agreement rate was 86% for air trapping; all \( \kappa \) values were >0.75.

### Correlations of parameters on HRCT findings with lung function test in the patients

Bronchial wall area and air trapping were not correlated with post-BD FEV1% predicted values that were measured at initial examination (\( R = -0.336, P = 0.06; R = -0.337, P = 0.06 \)); respectively, Fig. 1). However, air trapping was

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### Table 1 Demographic characteristics of study subjects.

<table>
<thead>
<tr>
<th></th>
<th>Recovered group</th>
<th>Persistent airflow obstruction group</th>
<th>( p )-value, comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age (y)(^a)</td>
<td>58.4 ± 3.2</td>
<td>62.3 ± 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>11(61.1%)</td>
<td>8 (57.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up duration (y)(^a)</td>
<td>2.1 ± 0.4 (1.6–3.6)</td>
<td>2.7 ± 0.9 (1.6–4.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Asthma duration (y)(^a)</td>
<td>11.0 ± 2.7</td>
<td>13.7 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM (N)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ES (N)</td>
<td>8</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>NS (N)</td>
<td>8 (44.4%)</td>
<td>8 (57.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-ys(^b)</td>
<td>5 (0–10)</td>
<td>0 (0–10)</td>
<td>NS</td>
</tr>
<tr>
<td>Atopy (%)</td>
<td>6 (33.3%)</td>
<td>7 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Total IgE (IU)</td>
<td>358.8 ± 78.7</td>
<td>352.8 ± 96.1</td>
<td>NS</td>
</tr>
<tr>
<td>Dose of Inhaled Steroid (mg/day),(^a,c)</td>
<td>1375 ± 87</td>
<td>1367 ± 96</td>
<td>NS</td>
</tr>
<tr>
<td>Oral steroid (%)</td>
<td>61%</td>
<td>64%</td>
<td>NS</td>
</tr>
<tr>
<td>Leukotrien receptor antagonist (%)</td>
<td>35%</td>
<td>41%</td>
<td>NS</td>
</tr>
<tr>
<td>Exacerbation, number(^b)</td>
<td>1 (0–4)</td>
<td>2 (0–7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as \( N \), percentage.
\(^a\) Mean ± SEM.
\(^b\) Median (range).
\(^c\) Fluticasone equivalent SM: current smoker, ES: ex-smoker, NS: never smoker.

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### Table 2 Pulmonary function tests at initial and 2nd exam of HRCT.

<table>
<thead>
<tr>
<th></th>
<th>Recovered group</th>
<th>Persistent airflow obstruction group</th>
<th>Inter-group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>18</td>
<td>14</td>
<td>( p )-value</td>
</tr>
<tr>
<td>PFT % of predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDFVC Initial</td>
<td>68.6 ± 4.9</td>
<td>72.2 ± 4.9</td>
<td>0.703</td>
</tr>
<tr>
<td>2nd exam of HRCT</td>
<td>86.2 ± 2.5</td>
<td>77.0 ± 4.0</td>
<td>0.057</td>
</tr>
<tr>
<td>Intra-group comparison</td>
<td>&lt;0.001</td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>BDFEV1 Initial</td>
<td>51.1 ± 5.4</td>
<td>55.2 ± 4.4</td>
<td>0.493</td>
</tr>
<tr>
<td>2nd exam of HRCT</td>
<td>86.6 ± 3.1</td>
<td>59.2 ± 3.0</td>
<td>( &lt; 0.001 )</td>
</tr>
<tr>
<td>Intra-group comparison</td>
<td>&lt; 0.001</td>
<td>0.379</td>
<td></td>
</tr>
<tr>
<td>BDFEV1/FVC Initial</td>
<td>57.0 ± 2.7</td>
<td>54.3 ± 4.3</td>
<td>0.278</td>
</tr>
<tr>
<td>2nd exam of HRCT</td>
<td>73.4 ± 2.9</td>
<td>58.7 ± 4.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Intra-group comparison</td>
<td>&lt; 0.001</td>
<td>0.232</td>
<td></td>
</tr>
</tbody>
</table>
inversely correlated with post-BD FEV1% predicted that were measured at 2nd HRCT examination \((R = -0.397, P = 0.03, \text{Fig. 1})\). Differences in air trapping between the initial and second examination correlated well with post-BD FEV1 % of predicted between the initial and second examinations \((R = -0.440, P = 0.017; \text{Fig. 2})\).

### Table 3  HRCT findings at initial and 2nd exam.

<table>
<thead>
<tr>
<th></th>
<th>Recovered group</th>
<th>Persistent airflow obstruction group</th>
<th>Inter-group comparison (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 14)</td>
<td></td>
</tr>
<tr>
<td><strong>Bronchial wall area (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>66.6 ± 1.5</td>
<td>65.6 ± 1.6</td>
<td>0.513</td>
</tr>
<tr>
<td>2nd exam</td>
<td>65.1 ± 1.2</td>
<td>67.2 ± 1.8</td>
<td>0.568</td>
</tr>
<tr>
<td><strong>Intra-group comparison (p-value)</strong></td>
<td>0.304</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td><strong>Air trapping (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>53.4 ± 4.2</td>
<td>50.7 ± 2.6</td>
<td>0.16</td>
</tr>
<tr>
<td>2nd exam</td>
<td>41.6 ± 3.3</td>
<td>54.2 ± 2.2</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Intra-group comparison (p-value)</strong></td>
<td>0.007</td>
<td>0.109</td>
<td></td>
</tr>
</tbody>
</table>

Prediction models for the presence of persistent airflow obstruction in response to maximal steroid treatment in the HRCT findings

After adjusting for age, gender, atopy, smoking, asthma duration, and initial air trapping (%), the log-binomial

![Figure 1](image1.png)  
**Figure 1** Correlation between parameters on HRCT findings and Post-BD FEV1(%) at the initial and 2nd exam of HRCT. Air trapping(%)_I, bronchial wall area_I, and post-bronchodilator FEV1(%)_I means the values of these parameters measured at initial visit. Air trapping(%)_F, bronchial wall area_F, and post-bronchodilator FEV1(%)_F means the values of these parameters measured at 2nd HRCT exam. Air trapping at 2nd HRCT exam (air trapping(%)_F) is inversely correlated with Post-BD FEV1(%) \((R = -0.397, P = 0.03)\). Open and closed circles represent persistent airway obstruction group and recovered group, respectively.
Discussion

In the present study, we found that changes in small airways, but not large airways, may have an impact on the unresponsiveness to treatment with higher doses of inhaled corticosteroids. Air trapping was significantly decreased in the recovered group, but was not changed in the persistent airway obstruction group at the second HRCT compared with the initial HRCT. This suggests that persistent airflow limitation, despite intensive asthma treatment, is primarily due to the persistence of small airway changes. Small airway changes have been observed in several subtypes of asthma. The duration of this study was over 1 year for two reasons. First, treatment duration of 1 year properly reflects seasonal variation in environmental factors (allergens, air pollutants, infection) that could affect asthma control. Second, extensive evaluation and proper treatment of asthma over a 6-month period by specialists is required to define chronic severe refractory asthma. To our knowledge, air trapping on HRCT scans has not previously been longitudinally analyzed with anti-asthma treatments for a more than 1 year in moderate-to-severe asthmatics, although a 3-month follow-up study has been reported. Tunon-de-Lala et al. reported that air trapping measured using HRCT was partially diminished after 3 months of treatment with inhaled corticosteroids in patients with uncontrolled mild-to-moderate asthma. The discrepancy between the results in this study and ours may be due to a milder degree of airway obstruction (89.2% of FEV₁ predicted) and a younger age group (35.3 ± 10.7 years) in the Lara study.

Air trapping on HRCT may be produced by a combination of multiple factors, including intrabroncholar mucoid impaction, peribroncholar inflammation, and bronchiolar wall remodeling, which includes muscular hypertrophy on pathology. Inflammatory debris consists of plasma exudates and inflammatory cells, particularly eosinophils and epithelial cells, that are sloughed from the airway surface. In addition to airway inflammation, remodeling with collagen deposition and smooth muscle hypertrophy were also found throughout the peripheral airways. The pattern of inflammation and structural changes in small airways may vary according to the severity and duration of asthma. Pagani and colleagues reported on the evolution of CT abnormalities after antiasthmatic therapy. Within 1–2 weeks, mucoid impaction, acinar patterns, and lobar collapse could be reversed, whereas bronchial wall thickness, bronchiectasis, and emphysema were unchanged. The reversibility of remodeled airways is supported, in part, by a pathological study showing that subepithelial collagen deposition, one component of bronchial wall thickening, was reduced significantly in asthmatic patients who had received intensive anti-inflammatory therapy for 6 months.

Our results reveal that bronchial wall thickening was not reversed in asthmatic patients, even in the recovered group, members of which showed improvements in FEV₁. This may be because the subjects had no reversible bronchial wall component at the initial HRCT examination because many of them had been on inhaled corticosteroids therapy during the 4 weeks prior to the initial HRCT examination. It may also possible that such a difference in Wall thickening could not be detected between the two groups because of the small sample size. However, air trapping was improved in more than half of the study subjects, suggesting that anatomical changes in small

Table 4 Multivariate log-binomial regression models for the presence of persistent airflow obstruction response to over 12 months of treatment with maximal dose of inhaled steroid.

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Initial bronchial wall area (%)</td>
<td>1.01</td>
<td>(0.91–1.13)</td>
<td>0.79</td>
</tr>
<tr>
<td>Model 2: Initial air trapping (%)</td>
<td>1.01</td>
<td>(0.97–1.05)</td>
<td>0.62</td>
</tr>
<tr>
<td>Model 3: Difference bronchial wall area (%)</td>
<td>1.04</td>
<td>(0.92–1.19)</td>
<td>0.515</td>
</tr>
<tr>
<td>Model 4: Difference air trapping (%)</td>
<td>1.7</td>
<td>(1.09–2.64)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Model 1 and 2 were adjusted for age, sex, smoking (ever/never), atopy and symptom duration. Model 3 included variables in Model 1 and initial bronchial wall area. Model 4 included variables in Model 2 and initial air trapping.

a Difference was calculated by initial minus 2nd HRCT exam.
airways still had reversible components in these moderate-to-severe asthmatics in the present study.

A few studies have found risk or predictive factors for the development of fixed airflow obstruction in asthmatics. Lee et al. reported that sputum eosinophilia, smoking, longer asthma duration, and older age were associated with persistent airflow obstruction in patients with asthma. The lack of impact of inhaled corticosteroid treatment on air trapping in the chronic persistent airway obstruction group may not be due to the duration of treatment in the present study, because the two groups had similar durations. Smoking has been considered to be one of the main risk factors for the development of fixed airflow obstruction or persistent airflow limitation that is refractory to treatment. In the present study, smoking may not have been related to steroid treatment under-responsiveness because smoker and ex-smoker prevalences were comparable between the two study groups, and smokers who smoked less than 10 packs per year were included in the study. Although we exclude the possibility of COPD from our study asthmatics by smoking history and emphysema by HRCT, it still possible that some of patients might have overlap syndrome caused by other than cigarette smoking because some phenotype of COPD have only air trapping without emphysema by HRCT analysis. Ten Brinke et al. reported that adult onset of disease, sputum eosinophilia, and airway hyper-responsiveness were associated with persistent airflow limitation.29 Other reports have shown that patients with severe asthma with irreversible airflow obstruction had high levels of peripheral eosinophilia, and high degrees of bronchial wall thickening on HRCT scans.30 Additionally, different types of airway inflammation may be related to different responses to steroid treatment. Eosinophilic asthma responds well to inhaled corticosteroids. In contrast, neutrophilic asthma appears to be relatively corticosteroid-resistant. Recently, Choi et al. reported that patients with persistent airflow obstruction due to refractory asthma have neutrophil-dominant airway inflammation.31 Busacker et al. reported that a high level of airway neutrophils was a risk factor associated with air trapping in patients with severe asthma.32 Thus, the relationship between neutrophilic inflammation and small airway changes in moderate-to-severe asthma unresponsive to steroid treatment should be evaluated in the future. In our study, the frequency of persistent airflow obstruction was 44% (14 from 32 subjects), which is higher than 5% of all asthmatics.3 This may be derived from the different population of study subjects. The present study was investigated in moderate-to-severe asthmatics on long term — high dose asthma medication while the latter was observed in all subjects of mild to very severe asthma. A limitation of this study was the small number of patients. However, strengths of the study include that it was prospectively and longitudinally performed over 12 months to measure HRCT and lung function test over the same time interval.

In summary, in this study, we showed that the development of persistent airflow obstruction was associated with small airway changes, as reflected in persistent air trapping in adult moderate-to-severe asthma even after prolonged treatment with high doses of inhaled corticosteroid. This impairment should be a therapeutic target in future studies so that specific rationales can be developed for treatment or prevention of persistent airflow obstruction in moderate-to-severe persistent asthma.

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**Conflict of interest statement**

None declared.

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Air trapping on airway obstruction in asthma

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