Evaluation of low attenuation area (LAA) of the lungs in patients with reversible airway obstruction by high resolution computed tomography (HRCT).

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Abstract: The significance of the low attenuation area (LAA) of the lungs on high resolution computed tomography (HRCT) has not been determined in patients with asthma.

We examined the relationship between the percentage of lung area with CT numbers lower than $-950$HU (%LAA) and the mean CT number in 81 patients with reversible airway obstruction (asthma) and in 22 healthy subjects, as well as the relationship between maximal %LAA and various parameters of pulmonary function, smoking history, disease severity and allergic type in the asthmatic subjects. The mean CT number was obtained by scans at three anatomic levels, and maximal %LAA was the %LAA which had the largest value of those measured at the three anatomic levels of the lung.

We found that: 1. The mean CT number was closely related to the maximal %LAA of the lungs in all subjects studied ($r=-0.916$, $p<0.0001$). 2. The maximal %LAA in asthmatics with a previous smoking history (median: 20.1) was significantly larger than that in asthmatics without a smoking history (median: 10.8), and that in healthy subjects with (median: 8.8) and without a history of smoking (median: 10.4). 3. The maximal %LAA was significantly correlated with FEV1/FVC ($r=-0.611$, $p<0.0001$) and TLC ($r=0.391$, $p=0.0068$) in the asthmatic subjects. 4. The maximal %LAA was significantly correlated with the severity of asthma ($p<0.01$), but not with the etiology of asthma.

This study suggests that the maximal %LAA is influenced by disease severity in patients with asthma, and that a smoking history has a more significant effect on the pulmonary function of asthmatics than healthy individuals.

Key Words: low attenuation area, high resolution computed tomography, reversible airway obstruction
Introduction

Asthma is a disease characterized by chronic airway inflammation. Inflammatory cells, especially activated T cells and eosinophils, and chemical mediators such as histamine, leukotrienes and various cytokines released from these cells, play important roles at allergic reaction sites in the airway. This inflammation process leads to abnormalities of the airway including an increase in muscle mass, mucous gland hypertrophy, and reorganization of the extracellular matrix. Frequent airway and lung parenchymal changes in asthma are considered to be responsible for irreversibility of airway obstruction, which is observed in many severe asthmatics. Thus, features of airway reconstruction such as bronchial wall thickening, bronchiectasis, emphysema and mosaic patterns of lung attenuation, have been observed by high resolution computed tomography (HRCT) in patients with asthma. Patients with nonallergic asthma have more extensive remodelling of the airways than those with allergic asthma, and asthmatics with abnormal HRCT findings demonstrate poorer lung function and less hyperresponsive bronchi than those with normal HRCT findings.

The relative area of the lungs with attenuation values less than \(-950\) Hounsfield Units (LAA, low attenuation area) on high resolution CT scans obtained at full inspiration is an objective measure of the extent of pulmonary emphysema. A previous study suggested that the percentage of pixels below \(-900\) HU is significantly correlated with pulmonary function, and reflects air trapping in asthmatic patients. However, the significance of the %LAA of the lungs on HRCT scans has not been determined in patients with asthma. In the present study, we investigated the influence of smoking history and asthma type and severity to the percentage of lung area with CT numbers lower than \(-950\)HU (%LAA) in asthmatic patients.

Subjects and Methods

Subjects

The subjects in this study were 81 asthmatics (39 females and 42 males) who were 21 to 81 years of age (median, 65 years). Thirty-two of the asthmatics were former cigarette smokers with a smoking history of \(30.9 \pm 23.9\) pack-years (mean \(\pm\) SD). Asthma was diagnosed according to the criteria of the International Consensus on Diagnosis and Management of Asthma. All of the asthmatic subjects have episodic symptoms of wheezing and coughing, and experience symptomatic relief and reversible airway response with increases of forced expiratory volume in one second (FEV1) exceeding 15% upon treatment with beta-adrenergic agonists. The onset and duration of asthma were established on the basis of the patient’s history, followed by a careful examination. Allergy was diagnosed by clinical history, skin tests and the presence of serum IgE antibodies specific to common inhalant allergens. The serum level of total IgE was measured by a radioimmunosorbent test (RIST), and the presence of serum IgE antibodies specific to inhalant allergens was estimated by the Phadebas radioallergosorbent test [RAST®] of the CAP system® (Pharmacia Diagnostics AB, Uppsala, Sweden). IgE antibodies against inhalant allergens were found in 45 of the 81 asthmatic patients (55.6%). We defined allergic patients as those who had a positive skin test and/or IgE specific to the common
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Inhalant allergens. The other patients were classified as nonallergic.

The clinical severity of asthma was evaluated by the Aas scoring system, which is used to grade chronic asthma from very mild to severe forms. It has been reported that the Aas score is significantly correlated with the value of FEV1, and with airway inflammation in asthma.

We also studied 22 adult control subjects who had no history of allergic or respiratory disease. They included 12 male subjects who had a smoking history ranging between 15 and 150 pack-years (mean ± SD: 48.6 ± 37.3 pack-years), and 10 female subjects who had never smoked.

Informed consent for the study protocol was obtained from all subjects. The study protocol was approved by the Ethics Committee of our institution. All patients were studied at a time when there was no evidence of asthma exacerbation or respiratory tract infection.

Study design

The CT scan study was performed on the same day as lung function measurements. The value of the maximal %LAA was compared with various parameters of pulmonary function, disease severity and allergic type in the asthmatic subjects.

Pulmonary function tests

All pulmonary function tests were performed using a CHESTAC 33 (Chest Co., Tokyo, Japan) linked to a computer. All subjects underwent measurements of pulmonary function including: forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and flow-volume curve. Total lung capacity (TLC) was measured by the helium dilution method. The diffusing capacity for carbon monoxide (DLco) was measured by the single breath method.

Computed tomography

All subjects had a modified HRCT scan of the chest with a TOSHIBA Xpeed scanner (TOSHIBA, Tokyo, Japan) using the thin section (2 mm collimation) technique and a high resolution (bone) reconstruction algorithm. An intravenous contrast medium was not administered. The scanning time was 2.7 seconds, tube current was 200 mAs, and voltage was 120 kVp. HRCT was performed in subjects holding their breath at full inspiration, and was reconstructed with a bone algorithm. End inspiratory scans were obtained at the following three selected anatomical levels as described by Miniati, et al.: 1) top of the aortic arch, 2) origin of the lower lobe bronchus, and 3) 3 cm above the top of the diaphragm. Each inspiratory HRCT scan was evaluated quantitatively by measuring the percentage of lung area with CT number < -950 HU (%LAA), and the mean CT number expressed in HU. The low attenuation area (< -950 HU) which had the largest value among those at the three different levels of the lung, was taken to be the maximal %LAA in each subject. The mean CT number was calculated from the CT numbers at the three anatomical lung levels.

Statistical Analysis

Correlation between any two variables was determined using the nonparametric Spearman's correlation coefficient when possible. Differences between medians were tested with the Mann-Whitney U test for two independent samples. One-and two-way analyses of variance (ANOVA) were used to compare the maximal %LAA of the asthmatic patients classified by the severity of asthma (Aas score) and allergic type. A p value of < 0.05 was regarded as significant.
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Results

Table 1 shows the characteristics of the subjects classified by smoking history and asthma type. The asthma patients were classified into 4 groups according to smoking history and asthma type. Among the asthmatics without a smoking history, the patients with allergic asthma were significantly younger than those with nonallergic asthma (median: 57.0 and 67.0 years, respectively; p<0.05). The age of onset of asthma was also significantly younger in patients with allergic asthma than in those with nonallergic asthma (median: 45.0 and 55.0 years, respectively; p<0.01). The duration of asthma was not significantly different among the allergic and nonallergic asthmatics with and without a smoking history. The age of the asthmatic and healthy subjects did not differ significantly.

Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Smoking History</th>
<th>Asthma Type</th>
<th>Patients (n)</th>
<th>Age* (yr)</th>
<th>Age at onset* (yr)</th>
<th>Duration of asthma* (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial asthma</td>
<td>Non-smoker Atopy</td>
<td>22</td>
<td>57 (21-78)</td>
<td>45 (4-49)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Non-smoker Non-atopy</td>
<td>27</td>
<td>67 (47-81)</td>
<td>55 (28-75)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Smoker Atopy</td>
<td>23</td>
<td>66 (47-79)</td>
<td>52 (4-71)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Smoker Non-atopy</td>
<td>9</td>
<td>64 (53-72)</td>
<td>53 (22-71)</td>
<td>12</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>Non-smoker</td>
<td>10</td>
<td>68.5 (59-71)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Smoker</td>
<td>12</td>
<td>67.5 (59-71)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA = not available
* Results are expressed as median and range.
*p<0.05
^p<0.01

Computed Tomography

There was a significant correlation between the maximal %LAA and the mean CT number among the normal and asthmatic subjects, as shown in Figure 1 (Spearman's rank correlation coefficient: r = -0.916, p<0.0001). The maximal %LAA in the asthmatics with a previous smoking history (median: 20.1, range: 2.0 to 41.7) was significantly higher than that in asthmatics without a smoking history (median: 10.8, range: 0.1 to 36.6), and that in healthy subjects with (median: 8.8, range: 2.0 to 36.1) and without a history of smoking (median: 10.4, range: 1.1 to 18.8), as shown in Figure 2. These results suggest that a smoking history has a significant effect on the maximal %LAA of asthmatics.

We observed significant correlations between maximal %LAA on HRCT and various pulmonary function tests in the asthmatic subjects. In particular, maximal %LAA was closely correlated with FEV1/FVC (r = -0.611, p<0.0001) (Figure 3-a) and TLC...
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(r = 0.391, p = 0.0068) (Figure 3-b), but was not correlated with %FVC (Figure 3-c) nor DLco (Figure 3-d) in patients with asthma.

Fig. 2. Comparison of the maximal %LAA on the inspiratory CT scans of 22 control subjects and 81 patients with asthma, according to smoking history. The solid horizontal line indicates the median of maximal %LAA in each group. * p < 0.01.

There was a significant correlation between maximal %LAA and disease severity as assessed by the Aas score among the allergic asthma patients and among the nonallergic asthma patients (ANOVA, p < 0.01). Among the allergic asthma cases, the maximal %LAA in patients with severe asthma (median: 16.8, range: 3.7 to 36.6) was significantly larger than that in patients with mild asthma (median: 6.0, range: 0.1 to 13.7) (p < 0.01). There was also a significant relationship between the maximal %LAA and the pulmonary function of asthmatics. Maximal %LAA was significantly correlated with (a) FEV1/FVC and (b) TLC, but not with (c) %FVC, or (d) DLco among all asthmatics.
Maximal %LAA showed significant correlation with the severity of asthma \( (p<0.01) \), but not with the type of asthma. However, no significant difference in maximal %LAA was found between allergic and nonallergic asthmatic subjects with the same severity of asthma (Figure 4).

The solid horizontal line indicates the median of maximal %LAA in each group. The correlation was analyzed by ANOVA (analysis of variance).
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Discussion

Comparison of computed tomography (CT) images with pathologic features of emphysema in autopsy and surgical lung specimens has strongly suggested that CT is the most accurate imaging method for diagnosing emphysema\textsuperscript{18-23}. The relative area of the lung with attenuation values \(< -950\) HU on HRCT scans can be used for evaluation and diagnosis of emphysema\textsuperscript{18-23}. Thus, it is generally agreed that CT scanning is a sensitive technique for detecting emphysematous lesions\textsuperscript{24}; however, CT quantification of pulmonary emphysema may be affected by hyperinflation and nonemphysematous expiratory airflow limitation, factors which have not yet been investigated\textsuperscript{25}.

Patients with asthma show more abnormalities related to airways remodelling on HRCT than normal subjects\textsuperscript{6,7}. Airways remodelling is more often found in patients with nonallergic asthma than in those with allergic asthma\textsuperscript{7}. The significance of the size of the low attenuation area of the lungs on HRCT has been controversial in asthma. Gevenois, et al., did not find any significant change in CT lung density parameters with respect to the size of the low attenuation area (LAA) of the lungs (\(< -950\) HU) during allergic challenge tests, despite a decrease in FEV\textsubscript{1} of 0.91 associated with an increase in residual volume (RV) and functional residual capacity (FRC) of about the same volume. They concluded that hyperinflation and airflow obstruction without emphysematous lung destruction would not influence densitometric measurements obtained from inspiratory scans\textsuperscript{26}. Newman, et al., found that inspiratory HRCT scans obtained in the lower area (the level of the diaphragm, \(\text{LAA} \text{<} -900\) HU) in asthmatics and nonasthmatic subjects, did not differ significantly; however, those obtained in the upper area (the level of the transverse aorta, \(\text{LAA} \text{<} -900\) HU) did differ significantly\textsuperscript{27}.

In this study, the maximal \%LAA of three anatomic lung levels was examined in patients with reversible airway obstruction. The results obtained here demonstrate that maximal \%LAA is closely related to the mean CT number not only in asthma patients but also in normal subjects. The mean CT number is linearly related to the fraction of air in the lungs, i.e., the ratio of the volume of air to the volume of air plus the volume of tissue\textsuperscript{27}. The maximal \%LAA in asthmatic patients with a history of smoking was significantly larger than that in asthmatics without a history of smoking and those of the control subjects. In contrast, there was no significant difference between the maximal \%LAA of the control subjects with and without a history of smoking. A smoking history had a significant effect on the maximal \%LAA of the asthmatics, but not the normal subjects. These results suggest that smoking affects the maximal \%LAA of the lungs of asthmatic patients more significantly than that of healthy subjects. Maximal \%LAA was also correlated with FEV\textsubscript{1}/FVC (\(r = -0.611, p < 0.0001\)) and total lung capacity (TLC) (\(r = 0.391, p = 0.0068\)) in the asthmatics, which suggests that the percentage of lung area with attenuation values \(< -950\) HU can be used for evaluating the pathophysiology of asthma. However, the correlation between maximal \%LAA and TLC was significant, but not highly significant, perhaps because TLC was measured by the helium dilution method. Since a significant correlation did not exist between maximal
%LAA and DLco in the asthmatics, this suggests that the value of the maximal %LAA does not directly implicate the presence of emphysematous lesions.

Gevenois, et al., showed that aging was significantly related to an increase in %LAA <−950 HU; however, they did not find a significant correlation between an increase in %LAA and changes in total lung capacity (TLC)\(^9\). In the present study, it can be speculated that aging did not influence the results because a significant difference in maximal %LAA was not found between the allergic asthma patients and the nonallergic asthma patients, although the mean age of these two groups of patients differed significantly. The value of the maximal %LAA was found to be associated with the severity of asthma, but not with the type of asthma. These results suggest that in asthma, a high %LAA value on HRCT indicates more extensive remodelling of the airways than a low %LAA value.

The presence of emphysema in patients with asthma is controversial. One recent report suggested that none of the nonsmoking asthma patients, including those with severe asthma and those with asthma of long duration, had emphysema\(^9\). Another report indicated that at least some patients with chronic, stable asthma develop a reduction in computed tomography lung density, similar to that in patients with emphysema\(^9\). It is still unclear whether high %LAA in asthma is due to hyperinflation and non-emphysematous expiratory airflow limitation, or to emphysematous lesions. However, we speculate that both expiratory airflow limitation and emphysematous lesions contribute to the %LAA in asthmatics. Although the subjects in our study are very old for a study of asthmatics, we demonstrated that the maximal %LAA is closely related with the severity of asthma, even in subjects which may include those with chronic obstructive pulmonary disease (COPD) and emphysema. Further studies are necessary to clarify the effects of hyperinflation and airflow limitation on the CT quantification of asthma.

References


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気管支喘息における胸部HRCT所見の臨床 [光延文裕]の意義

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【目的】気管支喘息症例において胸部HRCTを用いて％LAA (Low attenuation area) を評価し、臨床病態との関連を検討する。
【対象と方法】気管支喘息症例81例ならびに健康者22例を対象とした。大動脈弓部, 下葉分岐部, 横隔膜上3cmの3スライスを撮影し、胸部CT値の演算によりCT値が－960HU以下の％LAA, さらに3スライス中の最大％LAAと3スライスの平均CT値を算出した。その値と年齢, 発症年齢, 禍病期間, 性別, 喫煙歴, 重症度, 病型, 肺機能との関連を検討した。
【結果】1. 最大％LAAは平均CT値と強い相関を示した(\(r = -0.916, p<0.0001\))。2. 最大％LAAは喫煙者喘息者において非喫煙喘息者, 喫煙ならびに非喫煙健常者に比較して喘息者において有意に高値を示した。％LAAは喫煙者, 非喫煙者ともに重症例において有意に高値を示した。3. 最大％LAAは肺機能では1秒率(\(r = -0.611, p<0.0001\)), 全肺気量(\(r = -0.391, p<0.0001\)) と有意な相関を示した。4. 最大％LAAは喘息の重症度とは有意の関係を示したが, 病型とは関連は見られなかった。
【考察】喘息患者におけるHRCTによる最大％LAAは喫煙, 重症度, 肺機能と関連を示しており, 気管支喘息の臨床病態を反映する可能性が示唆された。