Influence of long-term cigarette smoking on changes of lung density by high-resolution computed tomography in asthmatics—4 years follow-up study—

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Abstract: Background - The influence of cigarette smoking on the pathogenesis of asthma in the elderly remains controversial. This study attempts to estimate longitudinal changes in HRCT (high resolution computed tomography) parameters and pulmonary function parameters obtained for ex-smokers and never-smokers in asthmatics during 4-yr follow-up period.

Methods - Fourteen asthmatics (6 ex-smokers and 8 never-smokers) were studied to determine the influence of aging and cigarette smoking on pulmonary function, and mean lung density (MLD) and the relative area of the lung showing attenuation values less than -950 HU (RA_{-950}) on HRCT scans.

Results - The values of FVC and FEV₁ were significantly more decreased in asthmatics without a smoking history during 4-yr follow-up period. The values of FVC, FEV₁, FEV₁/FVC and DLco/Vₜ were significantly increased in asthmatics with a smoking history over 4 years, and annual decline in FEV₁ ex-smokers was larger than that in never-smokers. In the upper lung field, inspiratory MLD was observed to shift in a negative direction and inspiratory RA_{-950} was found to increase during 4-yr observation period in ex-smokers, but not in never-smokers. In the middle lung field, inspiratory RA_{-950} was significantly enhanced in both two groups. Although expiratory MLD, expiratory RA_{-950} and exp RA_{-950}/ins RA_{-950} were observed to change significantly during the observation period in ex-smokers, no changes were observed in never-smokers.

Conclusion - These results suggest that aging augments airspace enlargement predominantly in the middle lung field, while long term cigarette smoking further worsens emphysematous alterations in the upper lung field.

Key words: lung density, high resolution computed tomography, asthma
Introduction

Asthma is considered a chronic inflammatory disease of the airways with participation of complex cellular and chemical mediators (1). It has become evident that the repair of the chronic inflammatory process can lead to various irreversible changes. Airway reconstruction, such as bronchial wall thickening, bronchiectasis, emphysematous changes, and mosaic patterns of lung attenuation has been demonstrated by high-resolution computed tomography (HRCT) in patients with asthma (2,3).

Smoking is closely related to the onset mechanism of COPD (4,5). It has been shown that 80-90% of all COPD patients have a history of smoking (6), and patients with mild COPD can reduce their symptoms by stopping smoking (7). With regard to adult asthma, a recent case-control study showed that adult onset of asthma was not associated with a history of smoking (8). In contrast, it has been demonstrated that current smoking increases asthma severity (9), and higher incidences of asthma are found in current and former smokers, compared with never-smokers (10-12). Our previous studies using the relative area of the lungs showing attenuation values less than -950 HU (RA950) on high resolution CT (HRCT) scans revealed that HRCT lung densitometry was influenced by aging and smoking (13,14). However, to the best of our knowledge, it remains unclear how the long-term cigarette smoking influence on the annual change of HRCT lung density as well as pulmonary function parameters in asthma.

In the present study, we attempted to estimate longitudinal changes in HRCT parameters and pulmonary function parameters obtained for ex-smokers and never-smokers in asthmatics during 4-yr follow-up period.

Methods

SUBJECTS

Fourteen asthmatic subjects were recruited from Misasa Medical Center. Among them, six subjects (all males, mean age=64.5±5.7 years; age at onset of the disease=51.5±21.0 years) were ex-smokers with a history of smoking>20 years (32.5±11.7 pack-years). The remaining 8 patients (2 males and 6 females, mean age=64.4±7.6 years; age at onset=55.2±10.4 years) were never-smokers. Asthma was diagnosed according to the definition proposed by the American Thoracic Society (15), as previously described (14). All asthmatic subjects were stable with no changes in asthma symptoms and medication for at least 2 month before pulmonary function tests and HRCT, except for the use of short acting β2 agonists. Pulmonary function tests and HRCT were annually performed at nearly the same period of time. Transitional variations of all parameters observed for various tests of pulmonary function and HRCT were assessed by estimating the annual change in each parameter. The annual change was calculated on the basis of the linear regression equation constructed using longitudinal data of each parameter obtained for each subjects.

Serum IgE was measured by radioimmunosorbent test (RIST), and IgE antibodies specific to 12 common aeroallergens including house dust mite, pollens, moulds, and animal danders were measured using the Pharmacia CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden).

Informed consent was obtained from all subjects and the study protocol was approved by the ethics committee of our institution. 

PULMONARY FUNCTION TESTS

Pulmonary function tests were performed with
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a Chestac 33 (Chest Co., Tokyo, Japan). The following measurements were performed on all subjects: forced vital capacity (FVC), FEV₁, and FEV₁/FVC. Total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and RV/TLC were measured using the helium dilution method. The DLco and DLco/VA (alveolar volume) were measured according to the single-breath technique. The FVC, FEV₁ and FRC measurements for each patient were expressed as a percentage of their predicted values (%FVC, %FEV₁ and %FRC, respectively) according to the prediction equations of the Japanese Society of Chest Diseases (16). DLco/VA was also expressed as a percentage of the predicted values following the method of Nishida (%DLco/VA). The ratio of FEV₁ to FVC (FEV₁/FVC) and RV to TLC (RV/TLC) were expressed as percentages.

COMPUTED TOMOGRAPHY

All subjects underwent a non-contrast HRCT scan of the lungs using a Toshiba Xspeed scanner (Toshiba, Tokyo, Japan) with 2 mm collimation, scanning time of 2.7 seconds, voltage of 120 kVp, and current of 200 mA. Maximal inspiratory and maximal expiratory HRCT scans were obtained at the following three selected anatomic levels, as described by Miniati et al. (17): (1) top of the aortic arch, (2) origin of the lower lobe bronchus, and (3) 3 cm above the top of the diaphragm. The mean lung density (MLD) and the relative area of the lungs with an attenuation value lower than -950 HU (RA₉₅₀) from each level were obtained both at full inspiration and full expiration. The ratio of expiratory RA₉₅₀ to inspiratory RA₉₅₀ (exp RA₉₅₀/ins RA₉₅₀) was also calculated.

STATISTICAL ANALYSIS

Results are expressed as mean±SD. Statistically significant differences of the two values were estimated using the unpaired Student's t test and χ² test. The difference in data at entry and those at 4 years later was judged with the paired t test. The significance of annual changes (i.e., changes in values against follow-up time, which were determined with the linear regression) in various parameters of pulmonary function tests and HRCT parameters was estimated on the assumption that the difference in slopes conforms to the t distribution. A p value of <0.05 was regarded as significant.

Results

PATIENT CHARACTERISTICS AT ENTRY

Patient characteristics at entry are shown in Table 1. There were no significant differences between ex-smokers and never-smokers in patient age and asthma duration. Serum IgE levels and frequency of atopy did not differ significantly between ex-smokers and never-smokers in subjects studied. The values of %FVC, %FEV₁ and FEV₁/FVC were significantly larger in never-smokers compared with ex-smokers (p<0.05). The RV/TLC value was significantly larger in asthmatics with a history of smoking than in never-smoking asthmatics (p<0.05). However the value of %FRC did not differ significantly between the two groups. The %DLco/VA was significantly more decreased in ex-smokers than in never-smokers in patients with asthma (p<0.05) (Table 1).

Initial inspiratory MLD values in three levels and expiratory MLD values in the middle lung field were significantly more negative in patients with a smoking history than those in the never-smokers. Initial inspiratory RA₉₅₀ values in three levels and expiratory RA₉₅₀ values in the middle lung field were significantly larger in patients with a smoking history than those in the never-smokers (Table 2).
Table 1. Patient characteristics at entry to the study

<table>
<thead>
<tr>
<th>Asthmatic</th>
<th>Never-smokers (n=8)</th>
<th>Ex-smokers (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>5/3</td>
<td>6/0</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>64.4 (7.6)</td>
<td>64.6 (5.7)</td>
</tr>
<tr>
<td>Age at onset, years (SD)</td>
<td>53.6 (11.4)</td>
<td>51.5 (21.0)</td>
</tr>
<tr>
<td>Disease duration, years (SD)</td>
<td>9.5 (5.0)</td>
<td>13.0 (15.5)</td>
</tr>
<tr>
<td>Serum IgE, U/ml*</td>
<td>127 (25-787)</td>
<td>159 (29-1224)</td>
</tr>
<tr>
<td>Atopy/nonatopy, n</td>
<td>4/4</td>
<td>3/2</td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>0</td>
<td>32.5 (11.7)</td>
</tr>
<tr>
<td>FVC, %pred (SD)</td>
<td>104.3 (21.0)</td>
<td>80.3 (25.5)</td>
</tr>
<tr>
<td>FEV1, %pred (SD)</td>
<td>91.1 (29.3)</td>
<td>55.8 (22.8)</td>
</tr>
<tr>
<td>FEV1/VC (%pred)</td>
<td>91.6 (10.4)</td>
<td>91.1 (10.6)</td>
</tr>
<tr>
<td>FRC, %pred (SD)</td>
<td>132.2 (38.5)</td>
<td>96.2 (71.4)</td>
</tr>
</tbody>
</table>

Values are presented as mean and SD in parenthesis.
+ geometric mean and range in parenthesis.
FVC = forced vital capacity; Sex = sex of the predicted value
FEV1 = forced expiratory volume in one second
FRC = functional residual capacity; RV = residual volume;
TLC = total lung capacity
DLCO = diffusing capacity of the lung for carbon monoxide; VA = alveolar volume

Table 2. HRCT parameters at entry to the study

<table>
<thead>
<tr>
<th>Asthmatic</th>
<th>Never-smokers (n=8)</th>
<th>Ex-smokers (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper lung field (inspiratory)</td>
<td>-889 (14)</td>
<td>-922 (23)</td>
</tr>
<tr>
<td>R50% (SD)</td>
<td>6.9 (5.8)</td>
<td>33.3 (20.0)</td>
</tr>
<tr>
<td>Middle lung field (inspiratory)</td>
<td>-804 (15)</td>
<td>-922 (23)</td>
</tr>
<tr>
<td>R50% (SD)</td>
<td>12.7 (10.2)</td>
<td>33.3 (11.3)</td>
</tr>
<tr>
<td>Lower lung field (inspiratory)</td>
<td>-805 (15)</td>
<td>-922 (17)</td>
</tr>
<tr>
<td>R50% (SD)</td>
<td>13.2 (8.0)</td>
<td>34.0 (11.5)</td>
</tr>
<tr>
<td>Middle lung field (expiratory)</td>
<td>-864 (24)</td>
<td>-891 (45)</td>
</tr>
<tr>
<td>R50% (SD)</td>
<td>2.8 (5.9)</td>
<td>13.7 (9.3)</td>
</tr>
</tbody>
</table>

Values are presented as mean and SD in parenthesis.
MLD = mean lung density
R50% = the relative area of the lungs with an attenuation value lower than -900 HU

Annual changes in mean lung density of HRCT images

During the 4-yr follow-up period, inspiratory MLD in three levels did not change significantly in never-smokers (Figure 1). In ex-smokers,

Annual changes in pulmonary function parameters

The values of FVC and FEV1 (p<0.05) showed significant annual changes in nonsmoking asthmatics during 4-yr follow-up period (Table 3). In asthmatics with a smoking history, significant differences were observed in FVC, FEV1, FEV1/FVC, RV/TLC and DLco/VA (p<0.05). Annual decline in FEV1 was found to be -0.05 L/yr in nonsmoking asthmatics and -0.10 L/yr in asthmatics with a smoking history, and the annual decline in ex-smokers was larger than that in never-smokers (p<0.05).

Table 3. Pulmonary function parameters at study entry and annual changes*

<table>
<thead>
<tr>
<th></th>
<th>Never-smokers</th>
<th>Ex-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Change (per year)</td>
<td>Initial</td>
</tr>
<tr>
<td>FVC</td>
<td>-0.06 (0.05)</td>
<td>-0.10 (0.06)</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.47 (0.44)</td>
<td>1.30 (0.64)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.73 (0.81)</td>
<td>0.72 (0.81)</td>
</tr>
<tr>
<td>FRC</td>
<td>2.69 (0.59)</td>
<td>2.70 (0.60)</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>38.9 (2.6)</td>
<td>49.8 (6.0)</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td>6.71 (2.19)</td>
<td>4.14 (0.97)</td>
</tr>
</tbody>
</table>

Values are presented as mean and SD in parenthesis.
FVC = forced vital capacity; FEV1 = forced expiratory volume in one second
FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity
DLCO = diffusing capacity of the lung for carbon monoxide; VA = alveolar volume

Figure 1.

Fig. 1. Longitudinal changes in inspiratory MLD for upper (UL), middle (ML), and lower (LL) lung fields during 4-yr follow-up period. Open circle = never-smokers with asthma, closed circle = ex-smokers with asthma. Values are means±SD. *Significant increase over 4 yr (p<0.01).
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inspiratory MLD estimated in the upper lung field shifted significantly negative direction \((p<0.01)\), but not in middle and lower lung fields. Expiratory MLD at the middle portion of the lung in ex-smokers was found to shift significantly in a negative direction \((p<0.05)\), whereas that in never-smokers did not show any significant change (Figure 2).

**Figure 2.**

Fig. 2. Longitudinal changes in inspiratory MLD for middle (ML) lung fields during 4-yr follow-up period. Open circle=never-smokers with asthma, closed circle=ex-smokers with asthma. Values are means \(\pm SD\). *Significant increase over 4 yr \((p<0.05)\).

ANNUAL CHANGES IN RELATIVE AREA WITH LOW ATTENUATION OF HRCT IMAGES

Although significant increase in inspiratory \(RA_{950}\) in the upper lung field was investigated for ex-smokers \((p<0.01)\), upper lung inspiratory \(RA_{950}\) for never-smokers was not altered during follow-up period. (Figure 3). In the middle lung field, inspiratory \(RA_{950}\) was significantly enhanced in both two groups \((p<0.05)\). Inspiratory \(RA_{950}\) at lower lung region did not change over 4 years in never-smokers and ex-smokers. Expiratory \(RA_{950}\) in the middle lung field exhibited significant change in ex-smokers \((p<0.05)\), whereas that in never-smokers showed no significant change during the observation period (Figure 4).

**Figure 3.**

Fig. 3. Longitudinal changes in inspiratory \(RA_{950}\) for upper (UL), middle (ML), and lower (LL) lung fields during 4-yr follow-up period. Open circle=never-smokers with asthma, closed circle=ex-smokers with asthma. Values are means \(\pm SD\). *Significant increase over 4 yr \((p<0.01)\); †, ‡Significant increase over 4 yr \((p<0.05)\).

**Figure 4.**

Fig. 4. Longitudinal changes in expiratory \(RA_{950}\) for middle (ML) lung fields during 4-yr follow-up period. Open circle=never-smokers with asthma, closed circle=ex-smokers with asthma. Values are means \(\pm SD\). *Significant increase over 4 yr \((p<0.05)\).
We also found that the value of exp \( \frac{RA_{950}}{ins} \) \( RA_{950} \) significantly moved to a positive value in ex-smokers over 4 years, but not in never-smokers (Figure 5).

**Figure 5.**

Fig. 5. Longitudinal changes in exp \( \frac{RA_{950}}{ins} \) \( RA_{950} \) during 4-yr follow-up period. Open circle=never-smokers with asthma, closed circle=ex-smokers with asthma. Values are means±SD. *Significant increase over 4 yr \( (p<0.05) \).

**Discussion**

To investigate the influence of long term cigarette smoking on asthmatics, pulmonary function parameters and HRCT lung densitometry (MLD and \( RA_{950} \)) were followed for 4 years in ex-smokers and never-smokers in patients with asthma.

In efforts to minimize radiation exposure, we calculated both MLD and \( RA_{950} \) using three cross sections of the lung (upper, middle, and lower). This was considered adequate as Mishima et al described an accurate correlation between the percentage of low attenuation area (LAA) detected from 10 sections (from apex to base of the lung) versus three sections in patients with COPD (18).

We used -950 HU as the cut-off level between the normal lung density area and LAA. Previous studies have used variable levels ranging from -900 to -960 HU (17-24). This discrepancy may be attributed to variations between the CT scanning techniques (equipment & reconstruction of images) as well as CT images (conventional vs. high resolution). In our study, using HRCT of 15 healthy controls, we found the mean MLD minus 1 SD to be -949 HU.

Regarding the relationship between pulmonary function and cigarette smoking, although no significant correlation was found between the frequency of lower respiratory illness (LRI) and decrease in FEV\(_1\) in sustained quitters, the frequency of LRI had an adverse effect on the 5-yr averaged annual rate of decline of FEV\(_1\) in intermittent and continuing smokers of patients with mild COPD (7). In the present study, FVC and FEV\(_1\) were significantly more decreased in asthmatics without a smoking history during 4-yr follow-up period, whereas RV/TLC and \( %DLco/V_a \) did not show any significant change. We also observed that FVC, FEV\(_1\), FEV\(_1\)/FVC and \( %DLco/V_a \) were significantly decreased and RV/TLC were significantly increased in asthmatics with a smoking history over 4 years, and annual decline in FEV\(_1\) ex-smokers was larger than that in never-smokers. The results suggested that cigarette smoking enhances hyperinflation and/or emphysematous change of the lungs expressed by an increase in \( RA_{950} \) in patients with asthma.

The relative area of the lungs with attenuation values less than -950 HU (\( RA_{950} \)) on HRCT scans obtained at full inspiration has been shown to be an objective measure of the extent of pulmonary emphysema by comparison with histopathologic data (20, 21). Previous studies have demonstrated that \( RA_{950} \) was significantly larger in asthmatics with a smoking history compared with those without a smoking history (13). \( RA_{950} \) is also influenced by aging and disease severity in asthmatics without a smoking history (14). Here, at the upper portion of the
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lung, inspiratory MLD was observed to shift in a negative direction and inspiratory RA960 was found to increase during 4-yr observation period in ex-smokers, but not in never-smokers. In contrast, at the middle and lower portion, inspiratory MLD and RA960 did not show any significant change. Although expiratory MLD, expiratory RA960 and exp RA960/ins RA960 significantly were observed to change during the observation period in ex-smokers, no changes were observed in never-smokers. These results demonstrated that the cigarette smoking influenced on HRCT lung densitometry especially in upper lung field and at full expiration.

In this study, we found RA960 at the middle portion of the lung was significantly enhanced over 4 years in nonsmoking asthmatics. Our previous study suggested that MLD and RA960 are significantly correlated with pulmonary function, patient age and disease severity in nonsmoking asthmatic patients (14). Soejima et al (25) demonstrated that aging influenced airspace enlargement predominantly in the middle and lower lung field. The difference between the findings of their study and ours may be due to the fact that that our subjects are asthmatics but not theirs.

In conclusion, HRCT is superior to pulmonary function measurements in detecting subtle longitudinal changes caused by aging and smoking in asthma. These results suggest that aging augments airspace enlargement predominantly in the middle lung field, while long term cigarette smoking further worsens emphysematous alterations in the upper lung field.

References


気管支喘息のlow attenuation area（LAA）に対する長期喫煙の影響—4年間の経過観察—

光延文裕，芦田耕三，保崎整弘，松野浩史，
岡本 誠，西田典数，永田拓也，高田真吾，
中井隆郎11，谷崎勝朗，谷本光音22

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気管支喘息患者の肺高解能CT所見に対する長期喫煙の影響を検討することを目的とした。非喫煙喘息患者8名，喫煙歴を有する喘息患者6名を対象として，肺機能，肺平均CT値（MLD）, -950HU以下のlow attenuation area（RA950）について4年間の経過観察を行った。

4年間の観察中，非喫煙喘息患者では努力肺活量，1秒量の低下を認めた。喫煙歴を有する喘息患者では努力肺活量，1秒量，1秒率，肺拡散能の低下および残気率の増加を認めた。喫煙歴を有する喘息患者では吸気において，上肺野MLDの有意の低下，RA950の有意の上昇を認めたが，非喫煙喘息患者では有意の変化は認めなかった。中肺野RA950は喫煙歴を有する喘息患者，非喫煙喘息患者ともに有意の上昇を認めた。また，呼気において，喫煙歴を有する喘息患者でMLDの有意の低下，RA950の有意の上昇を認めたが，非喫煙喘息患者では有意の変化は認めなかった。

喘息患者において，加齢は主に中肺野のlow attenuation area，喫煙は上肺野のlow attenuation areaに影響を及ぼすことが示唆された。