◎原 著

Characteristics of the elderly in high-resolution computed tomography lung densitometry

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ABSTRACT : To determine the characteristics of the elderly in high-resolution computed tomography (HRCT) lung densitometry, mean lung density (MLD) and relative area of the lungs showing attenuation values less than -950 HU (RA_{950}) on HRCT were evaluated in nonsmoking control subjects (n = 80) and patients with asthma (n = 80) in relation to their age and pulmonary function. MLD was significantly decreased, and RA_{950} was significantly increased with increasing age in both asthmatics and controls. The MLD values were significantly lower in asthmatics compared with controls in subjects aged between 60 and 69 years and over age 70. RA_{950} values were significantly higher in asthmatics compared with controls in subjects aged between 50 and 59 years, between 60 and 69, and over 70. %FEV_1 and FEV_1/FVC were significantly decreased in elderly asthmatic patients over 70 years of age compared with the values in those under 49. Percent residual volume (%RV) was significantly larger in patients over 70 years of age than in those between 50 and 59, and under 49 years. RA_{950} was significantly larger in patients with steroid-dependent intractable asthma (SDIA) between 50 and 59 years of age, and between 60 and 69 compared with RA 950 in those without SDIA. However, RA_{950} did not differ significantly between SDIA and non-SDIA in patients over age 70. The results suggested that in %LAA of the lungs on HRCT was significantly increased in the elderly subjects with and without asthma, and it was significantly higher in the elderly asthmatics than the elderly controls.

Keywords : aging, high-resolution computed tomography, low attenuation area, mean lung density, pulmonary function

Introduction

Asthma is characterized by airway inflammation, and an increase in airway smooth muscle[1,2], mucous gland hypertrophy[2], and reorganization of the extracellular matrix[3] have been observed in the inflammatory process. Furthermore, 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[4,5]. Asthmatics with abnormal HRCT findings have been shown to have poorer lung function and less hyperresponsive bronchi than those with normal HRCT findings[6].

In contrast, previous studies have shown that low attenuation areas (LAA) on CT scans *in vivo* represent macroscopic and/or microscopic emphysematous changes in the lungs of patients with chronic obstructive pulmonary disease (COPD)[7-15]. For the analysis of CT images, a quantitative method using digital data as well as a visual assessment of the scan is currently available[7-15]. Some studies have investigated the use of CT lung densitometry in nonsmoking asthmatic patients[16-21], and our previous study suggested that mean lung density (MLD) and relative area of the lungs showing attenuation values less than -950 HU (RA_{950}) are significantly correlated with pulmonary function, patient age, and disease severity in nonsmoking asthmatic patients[20]. We also reported that decreased CT lung density during asthma exacerbation is at least partially reversible, and changes of MLD and RA_{950} are related to the change in FEV_1 and residual volume[21]. However, to our knowledge, the characteristics of asthma in the elderly have not been determined using HRCT. The purpose of this study was to investigate the influence of aging on HRCT lung densitometry in patients with asthma and control subjects.

Subjects and Methods

Subjects

Eighty asthmatics (60 females and 20 males ; mean age 58 years, range 19−80 years) and eighty healthy controls (55 females and 25 males ; mean age 59 years, range 24−83 years) were recruited from Misasa Medical Center. Asthma was diagnosed according to the definition proposed by the American Thoracic Society[22]. All patients with asthma showed episodic symptoms of wheezing and coughing, and experienced symptomatic relief and reversible airway response with an accompanying increase in forced expiratory volume in one second (FEV_1) exceeding 15% upon treatment with β_2-adrenergic agonists. Asthmatics were stable with no changes in asthma symptoms and medication for at least 1 month, except for the use of short-acting inhaled β_2-agonists. None of the subjects had a history of upper respiratory tract infection within the month prior to entry. Twenty-four of 80 patients had steroid-dependent intractable asthma (SDIA) and had been treated with glucocorticoids for more than 2 years. Control subjects were randomly selected from those voluntarily visiting our hospital for an annual medical examination. They had no historical or clinical evidence of allergic, respiratory or cardiovascular disease, had a normal chest radiograph, and normal values for spirometry.

All subjects were lifelong nonsmokers. The subjects underwent high-resolution chest CT scan and pulmonary function tests on the same day. Asthmatics and controls were classified into four groups according to their age : ≤49 years ; 50−59 years ; 60−69 years ; ≥70 years. Each age group consisted of 20 asthmatics and 20 controls.

Atopy was evaluated by a combination of history of allergies, skin tests and the presence of serum IgE antibodies specific to the 12 common aeroallergens, including dust mites, pollens, molds, and animal danders. Serum-specific IgE was measured using the Pharmacia CAP® System (Pharmacia Diagnostics AB, Uppsala, Sweden). Atopic patients were defined as those who had a positive skin test and/or the presence of allergen-specific IgE.

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

Pulmonary function tests

Pulmonary function tests were performed with a Chestac 33 (Chest Co., Tokyo, Japan). Forced vital capacity (FVC), FEV_1, FEV_1/FVC, residual volume (RV) using the helium dilution method and carbon monoxide diffusing capacity (DL_{CO}) using the single breath method were measured. The FVC, FEV_1 and RV measurements were expressed as a percentage of their predicted values (%FVC, %FEV_1 and %RV, respectively) according to the prediction equations of the Japanese Society of Chest Diseases[23]. DL_{CO} was also expressed as a percentage of the predicted values following the method of Nishida (%DL_{CO}). The ratio of FEV_1 to FVC (FEV_1/FVC) was expressed as a percentage.

Computed tomography

Each patient underwent noncontrast high-resolution computed tomography (HRCT) using a TOSHIBA Aquilion (TOSHIBA, Tokyo, Japan) scanner with 2-mm collimation, a scanning time of 1.0 seconds, a voltage of 120 kVp, and a current of 200 mA. All HRCTs were performed in supine patients following maximal inspiration. The images were reconstructed on a 32-cm field of view (FOV) using a standard algorithm (FC 10). Three HRCT scans were performed for determination of MLD and LAA ; an upper section was obtained at the top of the aortic arch, a middle section was taken at the origin of the lower lobe bronchus, and a lower section was taken 3 cm above the top of the diaphragm, as described by Miniati *et al.*[24]. The cut-off level between the normal lung density area and LAA was defined as -950 HU, and RA_{950} was calculated using a method previously reported[17-21]. The MLD was calculated from the total cross-sectional area of the six lung hemislices obtained at the three anatomical levels. Similarly, the lung area occupied by voxels with attenuation values lower than -950 HU (A_{950}), obtained by summing the values of A_{950} in each of the six hemislices, was expressed as a percentage of the total lung cross-sectional area (RA_{950}). HRCT lung densitometry was performed for each subject by means of a dedicated software program from TOSHIBA.

Statistical Analysis

All statistical analyses were carried out using Stat View software (SAS Institute Inc., NC, USA). Results were expressed as means ±SD. Serum IgE levels were given as the geometric mean and range. Analysis of variance (ANOVA) with Bonferroni/Dunn correction was used to compare groups. A p value <0.05 was regarded as statistically significant.

Results

Asthmatic patient characteristics

Asthmatic patient characteristics, pulmonary function tests, and current medications are shown in Table 1. Among the four groups, there were no statistically significant differences in disease duration, sex distribution, number of patients with SDIA or medications used. The

mean serum IgE level in patients under age 49 was the highest of the four groups. The prevalence of atopy was significantly higher in those under age 49 than in those aged between 60 and 69 ($p<0.05$). The %FVC was significantly lower in those over age 70 than in either those under age 49 ($p<0.01$) or aged between 50 and 59 ($p<0.05$), and was also significantly lower in those aged between 60 and 69 than in those under age 49 ($p<0.05$). The mean values of $\%FEV_1$ ($p<0.05$) and FEV_1/FVC ($p<0.01$) were significant lower in those over 70 years of age than in those under age 49. %RV was significantly higher in those over 70 years of age than in either those under age 49 ($p<0.01$) or aged between 50 and 59 ($p<0.05$).

Table 1. Patient characteristics and medication use among groups classified by age

	Asthma			
	≤49 years (n=20)	50-59 years (n=20)	60-69 years (n=20)	70≤ years (n=20)
Male/female, n	7/13	2/18	5/15	6/14
Age at onset, years (SD)	22.7 (14.8)	39.3 (12.8)**	50.2 (12.3)**	58.3 (14.1)**,††
Disease duration, years (SD)	12.0 (7.9)	17.2 (13.7)	14.6 (12.0)	16.4 (13.3)
Patients with SDIA, n	5	7	6	6
Serum IgE, IU/ml (range)+	809 (45-5195)	182 (10-1124)**	250 (33-1648)**	101 (11-2918)*
Atopy/nonatopy, n	16/4	12/8	7/13*	10/10
FVC,%pred (SD)	105.6 (15.6)	100.0 (12.5)	91.1 (15.1)*	83.8 (16.6)**,†
FEV_1,%pred (SD)	90.3 (12.4)	83.9 (18.3)	81.5 (23.0)	73.3 (20.1)*
FEV_1/FVC, % (SD)	77.0 (11.0)	69.2 (11.9)	70.8 (12.8)	63.8 (12.6)**
RV,%pred (SD)	111.3 (22.9)	119.5 (28.4)	125.6 (26.2)	143.8 (32.6)**,†
DLCO,%pred (SD)	104.9 (13.0)	104.7 (17.3)	100.8 (11.9)	89.8 (15.7)*,†
Medication, n				
Inhaled steroids	18	17	18	19
Theophylline	12	12	12	14
LTRA	12	13	12	14

Values are presented as mean ± SD in parentheses.
+: geometric mean and range in parentheses.
SDIA = steroid-dependent intractable asthma
FVC = forced vital capacity; %pred = percentage of the predicted value
FEV_1 = forced expiratory volume in one second; RV = residual volume
DLCO = diffusing capacity of the lung for carbon monoxide
LTRA = leukotriene receptor antagonists
*,**: $p<0.05$, $p<0.01$ *versus* asthmatics under age 49
†,††: $p<0.05$, $p<0.01$ *versus* asthmatics between age 50 and 59

Patients over 70 showed the lowest $\%DL_{CO}$ values of all four age groups. All asthmatic patients were treated with inhaled β_2 agonists. The mean dose of inhaled BDP (beclomethasone dipropionate) was 530 μg/day for those under age 49, 580 μg/day for those aged between 50 and 59, 470 μg/day for those aged between 60 and 69, and 570 μg/day for those over age 70. In control subjects, %FVC was $110.0\pm17.8\%$, $\%FEV_1$ was $112.8\pm16.5\%$, and $\%FEV_1/FVC$ was $80.5\pm6.5\%$.

Correlation between age and HRCT lung densitometry in asthmatics and controls

Figures 1 and 2 show the correlations between subjects' age and HRCT measurements. Significant statistical negative correlations were observed in both asthmatics and controls between age and MLD (Figure 1). The RA_{950} had significant positive correlations with subjects' age in both asthmatics and controls (Figure 2).

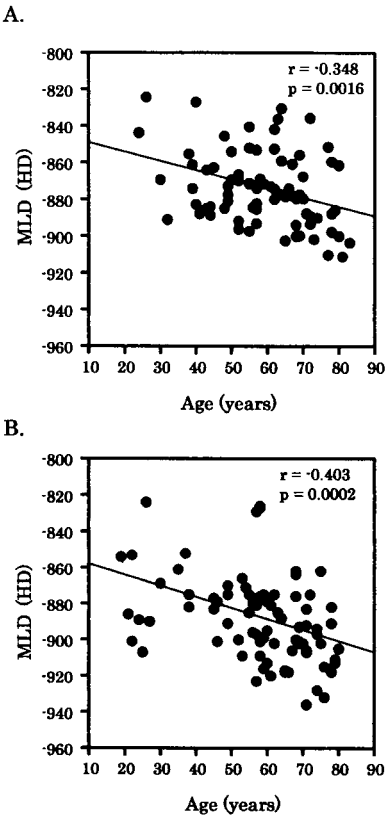

Figure 1.

Figure 1. Correlation between age and MLD in controls (A) and asthmatics (B).

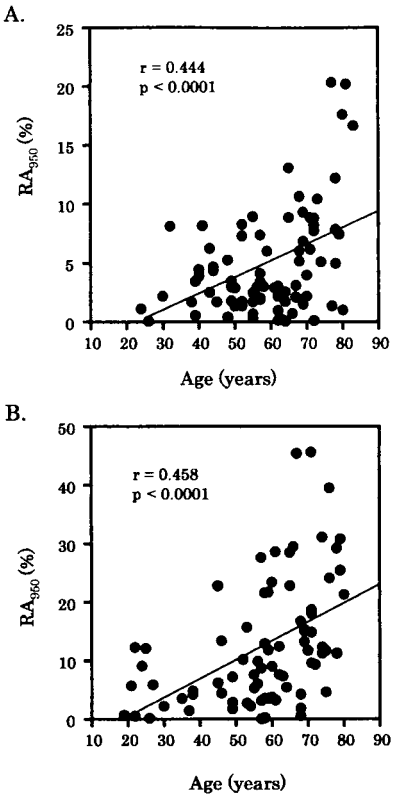

Figure 2.

Figure 2. Correlation between age and RA_{950} in controls (A) and asthmatics (B).

Comparison of HRCT lung densitometry between age groups

The results of HRCT lung densitometry in each age group are shown in Table 2. The MLD values were significantly lower in asthmatics compared with controls in subjects aged between 60 and 69 and over age 70. RA_{950} values were significantly higher in asthmatics compared with controls in subjects aged between 50 and 59, aged between 60 and 69, and over age 70.

Table 2 Comparison between controls and asthmatics in HRCT lung densitometry classified by age

	MLD (HU)			RA_{950} (%)		
	control	asthma	p	control	asthma	p
≤49 years	-868 (20)	-876 (20)	NS	3.4 (2.4)	6.1 (5.6)	NS
50-59 years	-873 (16)	-882 (28)	NS	3.5 (2.6)	8.7 (7.9)	<0.05
60-69 years	-871 (21)	-895 (18)	<0.001	4.1 (3.8)	14.7 (11.8)	<0.001
70≤ years	-885 (20)	-903 (19)	<0.01	3.6 (6.1)	19.6 (11.1)	<0.001

Values are presented as mean and SD in parenthesis.
MLD = mean lung density
RA_{950} = relative area of the lungs showing attenuation values less than -950 HU
HU = Hounsfield Units
NS = not significant

RA_{950} in patients with SDIA

RA_{950} was significantly larger in patients with SDIA aged between 50 and 59 ($p<0.001$), and between 60 and 69 ($p<0.05$), compared with the RA_{950} in those without SDIA from the same age group. However, RA_{950} did not differ significantly between SDIA and non-SDIA in patients over age 70 (Fig. 3).

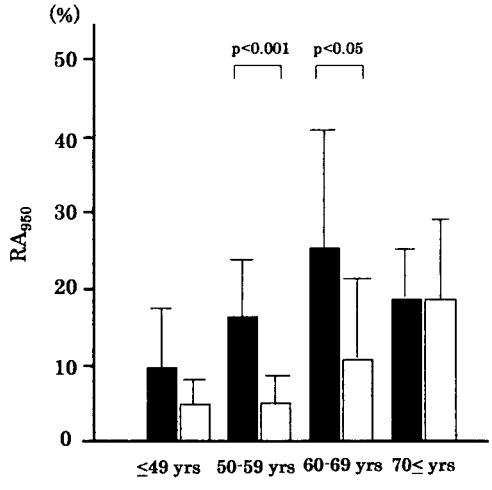

Figure 3.

Figure 3. RA_{950} in patients with steroid-dependent intractable asthma (SDIA) (■) and non-SDIA (□) in four groups classified by age.

Discussion

To clarify the characteristics of the elderly, HRCT lung densitometry (MLD and RA_{950}) and pulmonary function (%FEV_1 and %RV) were examined in healthy controls and stable asthmatics classified into four groups according to age ($\leq$49, 50−59, 60−69, $\geq$70 years). In terms of pulmonary function, measurements of airflow limitation (%FEV_1, FEV_1/FVC) and %DL_{CO} were significantly decreased, and %RV was significantly increased in stable asthmatics over 70 years of age compared with the values in those under age 49. The results suggest that pulmonary function (%FVC, %FEV_1, FEV_1/FVC, and DL_{CO}) is clearly decreased in asthmatics over 70 years old.

MLD tended to decrease significantly and RA_{950} showed a tendency to increase with aging in both asthmatics and controls. RA_{950} was significantly higher in asthmatics compared with controls in subjects between 50 and 59, between 60 and 69, and over age 70. RA_{950} was also significantly larger in patients with SDIA aged between 50 and 59, and between 60 and 69 years, compared with RA_{950} in those without SDIA from the same age groups ; however, a significant difference was not found in RA_{950} between SDIA and non-SDIA in elderly patients over 70 years old. The results suggest that RA_{950} is mainly influenced by aging in patients over 70. In contrast, RA_{950} is affected by severity of the disease as well as aging in patients aged between 50 and 59, and between 69 and 69. The relationship between RA_{950} and %FEV_1 or %RV was statistically significant in asthmatics over 50 years of age, but not in those under 49.

Some studies have demonstrated that the duration of asthma is associated with airflow limitation and hyperinflation[25-28]. We previously demonstrated that HRCT lung densitometry was correlated with patient age and severity of asthma[20], and that RA_{950} in asthmatics with a smoking history indicates the presence of emphysema, whereas in nonsmoking asthmatics it reflects hyperinflation and nonemphysematous expiratory airflow limitation rather than emphysematous lesions[19]. In the present study, we found significantly decreased %FEV_1 and significantly increased %RV and RA_{950} in patients over 70 years old compared with the values in those under 49. The results show that airflow limitation and hyperinflation as expressed by RA_{950} were mainly associated with aging in patients aged over 70, and partially associated with disease severity in those between the ages of 50 and 69, but not with disease duration. However, Quadrelli *et al.* demonstrated that airflow impairment is related not to age itself, but to the duration of asthma[25]. The discrepancy between their study and the current study may be explained by disease severity. Twenty-four patients with SDIA (30%) were included in our study, whereas none were included in their study. The subjects in our study therefore had a higher disease severity than those in their study.

We used -950HU as the cut-off level between normal lung density area and LAA. Previous studies have used variable levels ranging from -900 to -960 HU[7-15,24,29]. This discrepancy may be attributed to variations between the CT scanning techniques (equipment and 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.

Gevenois *et al.* reported that both MLD and RA_{950} are influenced by TLC, and to a lesser extent by age in healthy subjects[17]. This was further supported by a longitudinal study from Soejima *et al.* who studied images of

nonsmoking subjects over a study period of 5 years[30]. The present study revealed that an increased RA_{950} may be largely influenced by age in patients over 70 years old. In contrast, the present results also show that RA_{950} is affected by both aging and disease severity in patients between the ages of 50 and 69.

We conclude that decreased HRCT lung density, airflow limitation and hyperinflation are closely related to age in nonsmoking asthmatics over age 70. The decreased HRCT lung density may represent chronic overinflation in elderly patients with asthma. These results suggest that HRCT scanning may be a useful tool to determine functional characteristics, especially in elderly patients with asthma.

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高分解能CT lung densitometryにおける高齢者の臨床的特徴

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高齢者の病態的特徴を明らかにするために，健常者80例および非喫煙喘息患者80例を対象として，平均肺CT値(MLD)ならびに高分解能CT(HRCT)による－950HU以下の肺 low attenuation area (RA_{950})を評価し，年齢及び肺機能との関連を検討した。1．健常者，喘息患者いずれにおいても年齢とともにMLDは有意に減少し，RA_{950}は有意に増加した。MLDは，60－69歳と70歳以上の年齢層において，健常者に比して喘息患者で有意に低値を示した。RA_{950}は，50－59歳・60－69歳・70歳以上の年齢層において，健常者に比して喘息患者で有意に高値を示した。2．喘息患者において，1秒量(%FEV_1)および1秒率(FEV_1／FVC)は，49歳以下の年齢層に比して70歳以上の年齢層で有意に低値を示した。一方，残気量(%RV)は，50－59歳ならびに49歳以下の年齢層に比して70歳以上の年齢層で有意に高値を示した。3．50－59歳および60－69歳の年齢層では，RA_{950}は，ステロイド依存性重症難治性喘息（SDIA）患者において非SDIA患者に比して有意に高値を示した。しかし，70歳以上の年齢層では両者に有意の差は認められなかった。これらの結果より，HRCT上の肺low attenuation areaは高齢者において有意に増加すること，さらに喘息患者の方が健常者に比してより高値を示すことが示唆された。

索引用語：加齢，高分解能CT，低吸収域，平均CT値，肺機能