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# %Low attenuation area (%LAA) of the lungs on high resolution computed tomography (HR CT), associated with pulmonary function in elderly patients with asthma

Fumihiro Mitsunobu, Yasuhiro Hosaki, Kozo Ashida, Hirofumi Tsugeno, Makoto Okamoto, Norikazu Nishida, Shingo Takata, Tadashi Yokoi, Mutsuo Nakai[1], and Yoshiro Tanizaki

Department of Medicine, [1]Division of Roentgenology, Misasa Medical Branch, Okayama University Medical School

**Abstract**: The clinical significance of low attenuation area <-950 HU of the lungs on high-resolution computed tomography (HRCT) was evaluated in 80 patients with asthma in relation to patient age, CT number, pulmonary function including %residusal volume (%RV) and %DLco, and generation of leukotrienes B4 and C4 by leucocytes. 1. The %LAA (<-950 HU) of the lungs showed a tendency to increase significantly with aging; the %LAA was significantly larger in elderly patients over the age of 60 years than in those under the age of 49 years. The CT number was also significantly increased with aging. 2. The values of %FVC, %FEV1.0, and FEV1.0% were significantly decreased in elderly patients over age 70 compared with the values in those under age 49. 3. The value of %residual volume (%RV) tended to increase significantly with aging; the value in patients over the age of 70 years was significantly larger in those between the ages of 50 and 59 ($p<0.001$), and under the age of 49 years ($p<0.001$). 4. The %DLco value significantly decreased with aging; the value in patients over age 70 was significantly lower than the value in those between the ages of 50 and 59 ($p<0.01$) and under age 49 ($p<0.001$). 5. A significant correlation was observed between %LAA of the lungs and %RV ($r=0.67$, $p<0.001$), however, any significant correlations were not observed between %LAA and the values of %FVC, %FEV1.0, and FEV1.0%. 6. The generation of LTB4 and LTC4 by leucocytes was not significantly related with patient age.

The results suggested that %LAA of the lungs on HRCT tended to increse with aging, accompanied with a significant increase in %RV.

**Key Words**: low attenuation area of the lung, CT number, residual volume, DLco, aging

## Introduction

Asthma is characterized by airway inflammation, and an increase in muscle mass[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 found by high resolution computed tomography (HRCT) in patients with asthma[4,5]. It has been shown that asthmatics with abnormal HRCT findings demonstrate poorer lung function and less hyperresponsive bronchi than those with normal HRCT findings[6].

In contrast, the relative area of the lungs with attenuation values $< -950$ Hounsfield Units (HU) (LAA, low attenuation area) on high resolution CT scans obtained at full inspiration is an objective measure of pulmonary emphysema[7,8]. A previous study suggested that the percentage of pixels below $-900$ HU is significantly correlated with pulmonary function, and reflects air trapping in patients with asthma[9]. However, the significance of the %LAA of the lungs on HRCT scans and effects of aging on the %LAA have not been determined.

In the present study, clinical significance of %LAA of the lungs on HRCT and the effects of aging on the %LAA were estimated in patients with asthma in relation to pulmonary function and generation of leukotrienes B4 (LTB4) and C4 (LTC4) by peripheral leucocytes.

## Subjects and Methods

The subjects in this study were 80 patients with asthma (58 females and 22 males), whose mean age was 57.4 years (range 19-80 years), and the mean serum IgE level was 551 IU/ml (range 10-5195 IU/ml). All subjects have episodic symptoms of wheezing and coughing, and experience symptomatic relief and reversible airway response with increase of forced expiratory volume in one second (FEV1.0) exceeding 15% upon treatment with beta-adrenergic agonists. All subjects were nonsmokers. The subjects were divided into 4 groups according to their age : $<49$, 50-59, 60-69, and $70<$.

All subjects had a modified HRCT scan of the chest with a TOSHIBA xpeed scanner using the thin section (2 ㎜ collimation) technique and a high resolution 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 performedin subjects holding their breath at full inspiration, and was reconstructed with a bone algorithm. End inspiratory scans were obtained at the following three selected anatomic levels as described by Miniati, et al.[10] : 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 mean %LAA was calculated from the %LAAs, and mean CT number from the CT numbers in three anatomical lung levels.

Pulmonary function tests were carried out using a CHESTAC 33 (Chest Co. Tokyo) linked to a computer. All subjects underwent measurements of pulmonary function including : forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0), and flow-volume curve. Residual volume (RV) was

measured by the helium dilution method. The diffusing capacity for carbon monoxide (DLco) was measured by the single breath method.

The generation of leukotrienes B4 (LTB4) and C4 (LTC4) by leucocytes was measured by the method previously described[11]. Serum level of total IgE was measured by a radioimmunosorbent test (RIST).

Statistically significant differences of the mean were estimated using the unpaired Student't test. A p value of $<0.05$ was regarded as significant.

## Results

The attenuation area of the lung on HRCT was classified into three types as shown in Fig. 1[10]. The characteristics of low attenuation

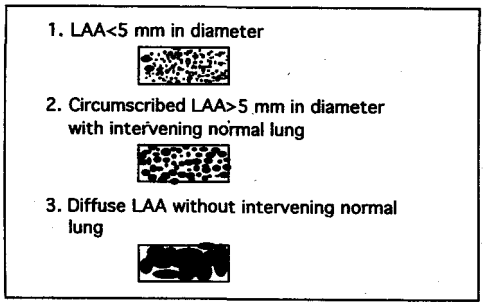


Fig.1. Characteristics of Low attenuation area (LAA)<-950HU of the lung on high resolution computed tomography (HRCT)

area (LAA) of the lung in patients with asthma were expressed as LAA <5㎜ in diameter, as shown in Fig. 1. Circumscribed LAA >5 ㎜ with intervening normal lung and diffuse LAA without intervening normal lung were not observed in patients with asthma. The low attenuation area of the lung on HRCT in patients with asthma showed a tendency to increase with aging. The %LAA in elderly patients over age 70 was significantly larger than the %LAAs in patients under age 49 and in those between the ages of 50 and 59. The %LAA in patients between the ages of 60 and 69 was also significantly higher than the %LAA in patients under age 49 and between the ages of 50 and 59. The CT number also increased with aging : the CT number in patients over age 70 was significantly higher than that in those under age 49 or between the ages of 50 and 59, as shown in Table 1.

Table 1. %Low attenuation area(LAA) of the lung and CT number on high resolution computed tomography in patients with asthma classified by age.

| Age, years | No of patients | %LAA | CT number (HU) |
|---|---|---|---|
| -49 | 20 | 5.8 ±5.4 $^{ab}$ | -901.8 ±22.7 $^{e}$ |
| 50-59 | 20 | 8.7 ±7.9 $^{cd}$ | -897.7 ±23.8 $^{f}$ |
| 60-69 | 20 | 16.0 ±14.7 $^{bd}$ | -881.5 ±28.7 |
| 70+ | 20 | 20.0 ±12.9 $^{ac}$ | -874.3 ±19.7 $^{ef}$ |

a:p<0.01, b, d and f:p<0.02, c:p<0.05, e:p<0.001.

The ventilatory parameters such as %FVC, %FEV1.0 and FEV1.0% were significantly lower in elderly patients over age 70 than in those under age 49 (Table 2).

Table 2. Ventilatory function in patients with asthma classified by age

| Age, years | No of patients | %FVC | %FEV1.0 | FEV1.0% |
|---|---|---|---|---|
| 70+ | 20 | 88.2±21.0 $^{ab}$ | 73.0±24.7 $^{c}$ | 63.2±12.1 $^{d}$ |
| 60-69 | 20 | 92.6±15.5 | 84.5±25.5 | 69.3±12.8 |
| 50-59 | 20 | 95.8±15.1 $^{b}$ | 80.0±21.8 | 69.1±12.7 |
| <49 | 20 | 105.4±15.4 $^{a}$ | 80.6±15.3 $^{c}$ | 75.1±13.5 $^{d}$ |

a:p<0.01, b :p<0.02, c and d:p<0.001.

The %residual volume (RV) of the lung tended to increase with aging. The %RV in elderly patients over age 70 was significantly larger than that in those under age 49 and between the ages of 50 and 59. The value of %RV was also significantly higher in patients between the

ages of 60 and 69 than in those under age 49. The value of %DLco was significantly lower in elderly patients over age 70 than in those under age 49 and between the ages of 50 and 59 (Table 3).

Table 3. %Residual volume (RV) and %DL co in patients with asthma classified by age

| Age, years | No of patients | %RV | %DLco |
|---|---|---|---|
| -49 | 20 | 106.2 ±31.9 [ac] | 104.9 ±13.0 [d] |
| 50-59 | 20 | 120.6 ±29.7 [b] | 105.0 ±17.4 [e] |
| 60-69 | 20 | 130.0 ±28.8 [c] | 99.9 ±12.8 |
| 70+ | 20 | 145.2 ±38.4 [ab] | 89.2 ±17.2 [de] |

a, b, c, and d:p<0.001, e:p<0.01.

A significant correlation between %RV and %LAA of the lung on HRCT was found in all subjects with asthma studied, as shown in Fig. 2.

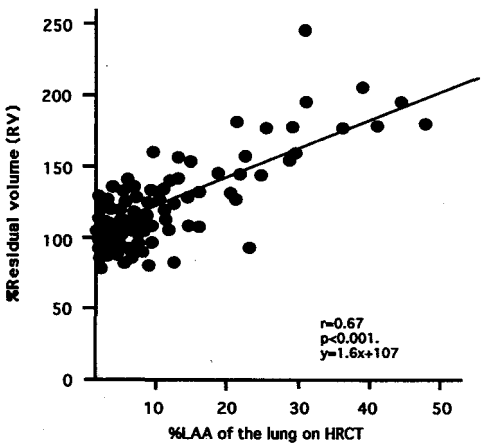


Fig.2. Correlation between %LAA of the lung on HRCT and %residual volume (RV) in ventilatory function in patients with asthma classified.

Any correlations were not observed between %LAA and a ventilatory parameter such as %F VC, %FEV1.0, and FEV1.0%, and between %LAA and %DLco.

The generation of leukotriene B4 (LTB4) was higher in patients under age 49 compared with the generation in those over age 70. However, a significant difference was not found between the two age groups. The generation of leukotriene C4 (LTC4) by leucocytes was not significantly diferent among the four age groups (Fig. 3).

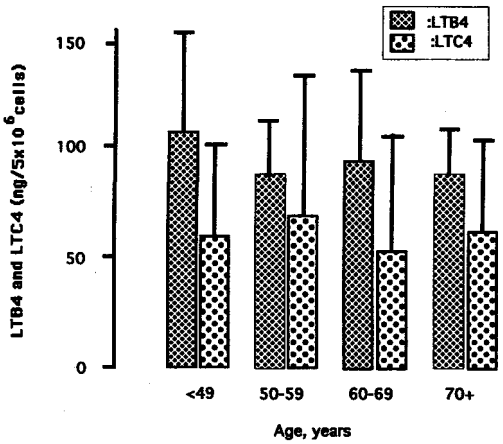


Fig.3. Generation of leukotrienes B4 and C4 by leucocytes in patients with asthma classified by age

## Discussion

Asthma is characterized by transient dyspnea with wheezing, related to airway inflammation[12]. Patients with asthma show more abnormalities related to airways remodelling on high resolution computed tomography (HRCT) than normal subjects[4,5]. Airways remodelling is more often observed in patients with nonallergic asthma than in those with allergic asthma[13]. In contrast, it has been shown that diagnosis of emphysema by pathologic examinations is related with high resolution CT scan findings[14,15]. The low attenuation area (LAA) <950 Houunsfield Unit (HU) of the lung on HRCT scans at full inspiration is an objective measure of the extent of pulmonary emphysema[4,5]. However, the influences of hyperinflation and nonemphysematous expiratory airflow limitation on the CT quantification of pulmonary emphysema are still unclear[13].

In contrast, emphysematous changes of the lung on HRCT have been observed in patients with asthma in relation to smoking and severity of the disease. A previous studies suggetsted that the percentage of pixels below −900 HU is significantly correlated with pulmonary function, and reflects air trapping in asthmatic patients[17]. However, the significance of the %LAA of the lung on HRCT scans has not been determined in patients with asthma.

In the present study, the effect of aging on %LAA of the lung on HRCT and pulmonary function were examined in patients with asthma. The results demonstrated that %LAA of the lung on HRCT in patients with asthma tended to increase with aging. The %residual volume (RV) of the lung in asthmatics also showed a tendency to increase with aging. A significant correlation between the two parameters was observed in patients with asthma. The results suggest that %LAA of the lung on HRCT in patients with asthma is closely correlated with hyperinflation of the lung, but not with emphysematous changes of the lung.

In elderly patients with asthma over age 70, a significant devrease in DLco, and ventilatory parameters such as %FVC, %FEV1.0 and FEV1.0% were observed. However, any significant correlations were not observed bwteen %LAA and %DLco, and between %LAA and each ventilatory parameter. The results obtained here show that such findings as a significant increase in %LAA of the lung and %RV, and a significant decrease in DLco and ventilatory parameters (%FVC, %FEV1.0 and FEV1.0%) are characteristics of elderly patients with asthma.

Leukotriene B4 and cys LTs, LTC4, LTD4, and LTE4, play an important role in pathophysiology of the airways of bronchial asthma. A number of factors can influence LTB4 production as well as cysLTs. LTB4 has a chemotactic action for neutrophils as well as interleukin 8 (IL8), which causes bronchial hyperresponsiveness and airway neutrophil accumulation[18]. LTC4production is almostly exclusively due to eosinophils[19]. Eosinophils appear to be important in asthma pathophysiology. Accumulation of the cells into the airways often associated with increased production of LTC4[20]. The amount of LTC4 production by eosinophils depends not only on the number of the cells but also on the degree of activation[21]. Our previous studies demonstrated that the release of histamine from bronchoalveolar lavage (BAL) cells was significantly larger in younger patients with atopic asthma compared to the release in older patients with atopic asthma and in those with nonatopic asthma[22], suggesting that histamine largely participate in attacks of younger patients with atopic asthma, and that the participation of histamine tends to decrease with aging. In contrast, the generation of LTC4 is increased in both atopic and nonatopic asthma and is not affected by aging. In this study, the generation of LTB4 and LTC4 by leucocytes was compared among four age groups. The generation of LTB4 was larger in younger patients under age 49 compared to the generation in those over age 70, however, there was not significant difference between the two age groups. The generation of LTC4 was not different among the four age groups.

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**HRCT上の肺のLow Attenuation Area および肺機能により評価された高齢者善喘息の特徴**

光延文裕，保崎泰弘，芦田耕三，柘野浩史，
岡本　誠，西田典数，高田眞吾，横井　正，
中井睦郎[1)]，谷崎勝朗

岡山大学医学部附属病院三朝分院内科，
[1)]放射線室

気管支喘息80例（全例非喫煙者）を対象に，high resolution computed tomography (HRCT) 上の肺の-950HU以下のLow attenuation area (LAA) の臨床的意義について，患者年齢，CT number，残気率(%RV)，拡散能(%DLco)を含む肺機能検査，白血球のコイコトリエンB4，C4の産生能などとの関連のもとに検討を加えた。1．%LAAは，年齢が高くなるにつれて増加する傾向を示し，60才以上の症例の%LAAは，49歳以下の症例に比べ有意に高い値を示した。また，CT number も，年齢が高くなるにつれて有意の増加を示した。2．%FVC，%FEV1.0およびFEV1.0%値は，いずれも70才以上の症例で49歳以下の症例に比べ有意に低い値を示した。3．残気率(%RV) は，年齢が高くなるにつれて増加する傾向を示し，70才以上の症例の%RVは，50－59才および49才以下の症例の%RVに比べ有意に高い値を示した。4．一方，拡散能(%DLco)は，年齢が高くなるにつれて有意に低下する傾向を示し，70才以上の症例の%DLcoは，50－59才および49才以下の症例のDLcoに比べ有意に低い値を示した。5．%LAAと%RVとの間には有意の相関が見られたが，%LAAと%DLco，および%LAAと換気機能（%FVC，%FEV1.0，FEV1.0%）との間には関連は見られなかった。6．白血球のLTB4およびLTC4の産生能においては年齢による差は見られなかった。

これらの結果は，%LAAが年齢とともに増加すること，そして%LAAは%RVと密接な関連を有していることを示している。