◎原　著

IgE antibodies against inhalant allergens in patients with pulmonary emphysema

Fumihiro Mitsunobu, Takashi Mifune, Yasuhiro Hosaki, Kozo Ashida, Hirofumi Tsugeno, Makoto Okamoto, Seishi Harada, Eiichiro Yumoto, Shingo Takata, Yoshiro Tanizaki, Koji Ochi[1], Hideo Harada[1], and Harumi Hasegawa[2]

Division of Medicine, Misasa Medical Branch, [1]Department of Laboratory Medicine, Okayama University Medical School, [2]Division of Medicine, Tottori City Hospital

Summary: To analyze the pathophysiological changes of the airways in emphysema, bronchial responsiveness and the generation of leukotrienes B4 (LTB4) and C4 (LTC4) by peripheral leucocytes were examined in 22 patients with emphysema. The subjects were divided into two groups according to the presence or absence of IgE antibodies against inhalant allergens; RAST positive group and RAST negative group. 1. Smoking history, mean CT number and mean maximum % low attenuation area (%LAA) <-950HU of the lung on high resolution computed tomography (HRCT), and DLco value suggested that there were emphysematous changes of the lung in all subjects . However, these findings were not different between the two groups. 2. The level of serum IgE was *significantly higher in RAST positive group than in RAST negative group*. 3. The mean %increase in FEV1. 0 after inhalation of β-agonists was higher in RAST positive group than in RAST negative group. The %increase more than 15% was found in 4 of the 9 subjects (44.4%) in RAST positive group and 2 of the 12 (16.7%) in RAST negative group. 4. The generation of LTC4 by leucocytes was significantly higher in RAST positive group than in RAST negative group ($p<0.01$). The generation of LTB4 was not significantly different between the two groups.

The results suggest that IgE-mediated allergy participates in the bronchial responsiveness of patients with emphysema.

Key words: emphysema, bronchial responsiveness, FEV1.0, LTB4, LTC4

Introduction

IgE-mediated allergy induces pathophysiological changes of the airways in asthma[1-3]. An asthma attack can be divided into two phases according to tne time it occurs after bronchial challenge with an allergen:

immediate asthmatic reaction (IAR) at about 30 min, and late asthmatic reaction (LAR) at 6-8 hours after the challenge. In the IAR, chemical mediators such as histamine and leukotrienes are released from tissue mast cells[5,6], while in the LAR, inflammatory cell infiltration is observed, accompanied by the release of various humoral factors including chemical mediators [7-10].

In asthma attacks, wheezing and dyspnea are characteristically observed due to bronchoconstriction, mucus hypersecretion, edema of mucous membrane,and bronchiolar obstruction[11,12]. In contrast, wheezing and exertional dyspnea are often observed in patients with pulmonary emphysema. Pulmonary emphysema is a disease accompanied with destruction of the lung. However, the pathophysiological changes in the airways of pulmonary emphysema is not well known.

In this study, to evaluate the airway response in pulmonary emphysema, the generation of leukotrienes B4 (LTB4) and C4 (LTC4) by leucocytes was examined in patients with the disease assessed by high resolution computed tomography (HRCT) and divided into the two groups according to IgE-mediated allergy.

Subjects and Methods

The subjects of this study was 22 patients (all males) with pulmonary emphysema. The mean age was 69.9 years (56-81years) and the mean age at onset of the disease was 62.8years (52-74years). The subjects were divided into two groups according to the presence or absence of IgE antibodies against inhalant allergens; house dust mite (HDm), cockroach, and Candida albicans. IgE antibodies were found in 9 patients (6 for HDm, 2 for Candida, and 1 for cockroach)(RAST possitive group), and not in residual 13 patients (RAST negative group).

CT scans were performed on a Toshiba Xpeed scanner (2.7s, 200mAs, 120Kvp) without infusion of contrast medium, using 2mm collimation (high resolution computed tomography: HRCT) in patients breath-holding at full inspiration. The lungs were scanned as preselected three anatomic levels; (1) top of the aortic arch, (2) origin of the lower lobe bronchus, (3) three cm above the top of the diaphragm, as reported by Miniati, et al.[13]. Inspiratory HRCT scans were evaluated quantitatively by measuring the percentage of lung area with CT number <-950 Hounsfield Unit (HU) (%low attenuation area; %LAA). The average of the CT numbers in three anatomic levels was expressed as the mean CT number. The maximum %LAA among the three anatomic levels of the lung was expressed as representative %LAA in each patient with pulmonary emohysema.

The generation of leukotrienes, LTB4 and LTC4 ,by peripheral leucocytes was assessed by a HPLC method. Affer buffy coat was separated by adding a quater volume of 6% dextran, the number of the cells was adjusted to 5×10^6 cells /ml in Tris ACM, and then Ca ionophore A23187 ($1\mu g$) was added to the cell suspension. The mixed solution was incubated for 15 min at 37 ℃, after then, supernatant was taken into the syringe filter (Toyo Roshi Co, Japan). The HPLC analysis for LTB4 and LTC4 was performed by a method described by Lam et al.[14]. The results were expressed as ng/5×10^6cells.

Bronchial reactivity to methacholine was measured by an Astograph (TCK 6100, Chest Co, Japan). Different concentrations of methacholine (49, 98, 195, 390, 781, 1563, 3125, 6250, 12500, and 25000μg/ml) were prepared for bronchial challenge according to the method used by Chai et al.[15]. The increase of total respiratory resistance (Rrs) after methacholine inhalation was measured by the oscillation method[16]. A methacholine concentration causing a significant increase in Rrs was assessed as Cmin (minimum concentration)[17]. All medications were stopped 12 hours prior to the examination.

Pulmonary function test, forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0), and diffusing capacity for carbone monoxide (DLco) was measured in all patients using a

Chestac 33 (Chest Co, Japan).

IgE antibodies against inhalant allergens, house dust mite, cockroach, and Candida, were estimated by radioallergosorbent test (RAST), and serum IgE levels were evaluated by radioimmunosorbent test (RIST).

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

Results

Table 1 represents the characteristics of RAST positive and RAST negative group. Age and age at onset of the disease were not different between the two groups. Serum IgE level was significantly higher in RAST positive group than in RAST negative group. Smoking history was more than 40 pack-year and the mean CT number was less than -950HU in both groups Table[2].

Table 1. Characteristics of patients with pulmonary emphysema studied in relation to RAST score

RAST* score	No of patients	Age (years)	Age at onset (years)	Serum IgE (IU/ml)
−	13	70.5	53.5	86[a]
+	9	69.0	56.2	699[a]

*RAST score against inhalant allergens, a;p<0.01.

Table 2. Characteristics of patients with pulmonary emphysema studied in relation to smoking history and mean CT number on HRCT*

RAST score	No of patients	Smoking history (pack-year)	Mean CT number (HU)
−	13	45.7	937.6
+	9	40.7	933.1

*HRCT; high resolution computed tomography

The mean of maximum %LAA was rather higher in RAST positive group (60.4 ± 12.6%) (mean ± SD) compared to the mean in RAST negative group (55.8 ± 9.1%)(Fig.1). However, this was not significant. The DLco value was not different in the two groups; 65.7 ± 11.1% (%predicted) in RAST positive group and 65.9 ± 21.7% in RAST negative group (Fig.2).

The mean %increase in FEV1.0 after inhalation of β-receptor stimulating agents was higher in RAST positive group (13.2 ± 5.9%) than in RAST negative group (8.6 ± 7.0%). A large number of patients in the two groups showed the % increase in FEV1.0 value less than 15%. However, the %increase more than 15% was more frequently found in RAST positive group (4/9;44.4%) than in RAST negative group (2/12;16.7%)(Fig.3).

Bronchial hyperresponsiveness was not observed in all subjects except each one case in the two groups.

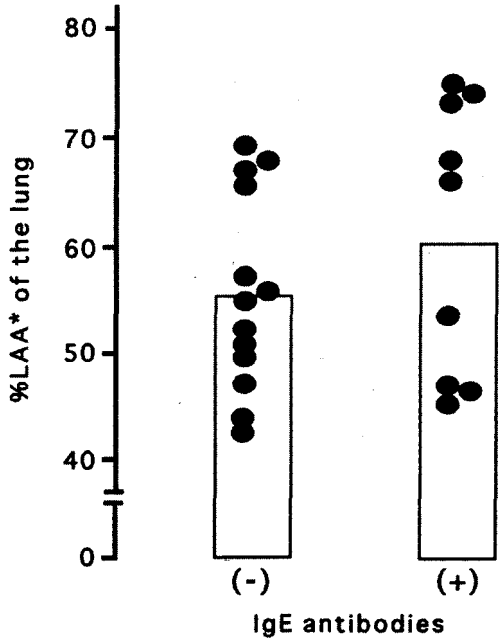

Fig.1. %LAA of the lung in patients with pulmonary emphysema in relation to IgE antibodies against inhalant allergens. LAA; low attenuation area

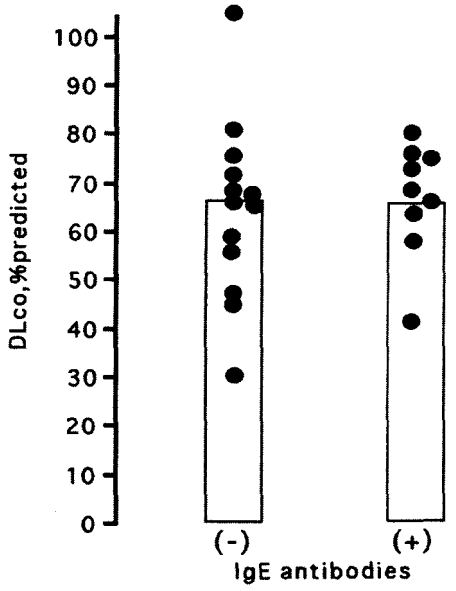

Fig.2. DLco value (%predicted) in patients with pulmonary emphysema in relation to IgE antibodies against Inhalant allergens.

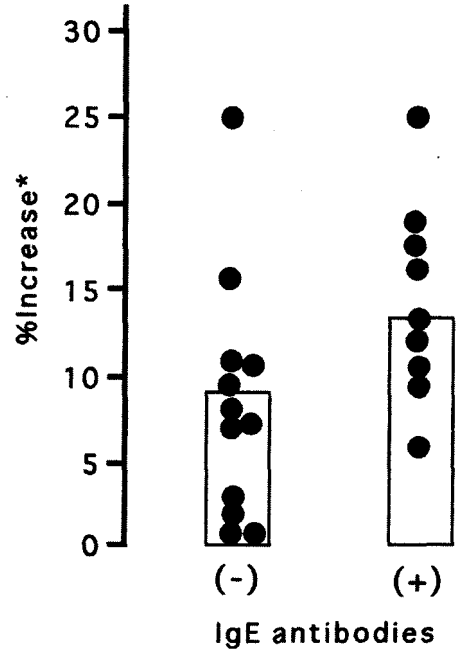

Fig.3. %Increase in FEV1.0 after β -agonists inhalation in patients with pulmonary emphysema in relation to IgE antibodies

The generation of LTB4 by leucocytes was 104.3 $\pm$ 36.5ng/5 $\times$ 10^6 cells in RAST positive group and 80.2 $\pm$43.9ng/5 $\times$ 10^6 cells in RAST negative group. There was no significant difference between the two groups. The production of LTC4 was significantly higher in RAST positive group (43.4 $\pm$ 30.1ng/5 $\times$ 10^6 cells) compared to the production in RAST negative group (10.9 $\pm$ 14.6ng/5 $\times$ 10^6cells) (p,0.01) (Fig.4).

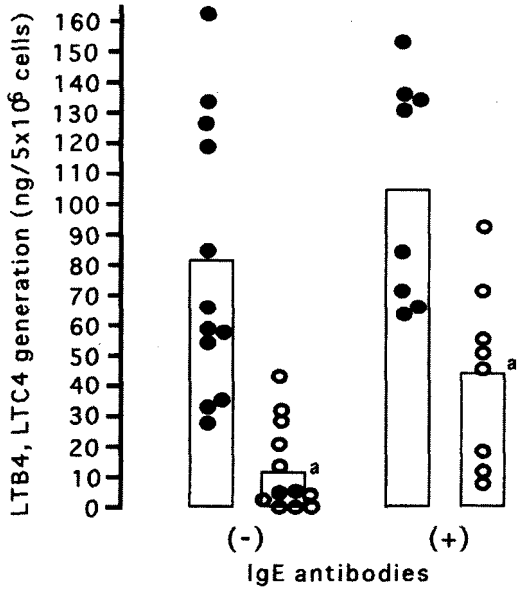

Fig.4. LTB4 (●) and LTC4 (○)generation by leucocytes in patients with pulmonary emphysema in relation to IgE antibodies against inhalant allergens. a; p<0.01.

Discussion

Emphysema is defined as a condition of the lung characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls[18]. Pulmonary emphysema is diagnosed by sujective and objective symptoms, and clinical findings including chest X ray and pulmonary function such as forced expiratory

volume in one second (FEV1.0), residual volume (RV), and DLco. In recent years, it has become clear that computed tomography (CT) is the most accurate imaging method for diagnosing emphysema in vivo. It has been shown that the relative areas of the lungs that has attenuation values lower than -950HU on high resolution CT scans obtained at full inspiration is an objective measure of the extent of pulmonary emphysema[19,20].

Emphysematous changes on chest X ray films, FEV1.0<80%, and DLco<80% were observed in all subjects studied. Furthermore, the results of mean CT number and maximum %LAA suggest that all subjects had emphysematous changes of the lung. The extent of emphysematous changes of the lung can be analyzed by pulmonary function and mean CT number and %LAA of the lung. However, airway responsiveness of pulmonary emphysema is not well known despite wheezing offen accompanied with exertional dyspnea.

In this study, airway responsiveness was analyzed in patients with emphysema in relation to IgE-mediated allergy. The mean of %increase in FEV1.0 after inhalation of β-agonists was low in RAST positive group (8.6%)and RAST negative group (13.2%). However, the %increase in FEV1.0 exceeding 15% was more frequently observed in RAST positive group (44.4%) compared to the %increase in RAST negative group (16.7%). The results suggest that airway responsivness to β-agonists is higer in RAST positive group than in RAST negative group.

Cysteinyl leukotrienes, LTC4, LTD4, and LTE4, have bronchoconstrictory action[21], increase mucus formation[22], and bronchial wall edema[23]. It has been shown that the generation of LTC4 by leucocytes was significantly higher in asthmatic children than in healthy controls[24]. The report also demonstrated that leucocytes from patients with a history of severe asthma displayed a higher LTC4 formation than leucocytes from patients with less severe disease. Our results on pulmonary emphysema revealed that the generation of LTC4 by leucocytes was significantly higher in patients of RAST positive group than in those of RAST negative group.

The data from %increase in FEV1.0 after β-agonists inhalation and LTC4 generation by leucocytes might suggest that airways dysfunction in pulmonary emphysema is more frequently and more strongly observed in patients with IgE-mediated allergy than in those without the allergy.

Leukotriene B4 (LTB4) stimulates neutrophil chemotaxis and activation of the cells, leading to the release of mediators, enzymes, and superoxide[25]. It has been reported that neutrophil inflammation enhances bronchial hyperresponsiveness[26,27]. Our results in this study on pulmonary emphysema demonstrated that the generation of LTB4 by leucocytes was higher in patients with IgE-mediated allergy than in those without the allergy. However, this was not significant.

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肺気腫患者における吸入抗原に対するIgE抗体

光延文裕，御舩尚志，保崎泰弘，芦田耕三，柘野浩史，岡本　誠，原田誠之，湯本英一郎，高田眞吾，谷崎勝朗，越智浩二[1)]，原田英雄[1)]，長谷川晴巳[2)]

岡山大学医学部附属病院三朝分院内科
[1)]医学部臨床検査医学
[2)]鳥取市立病院内科

肺気腫患者の気道病変を解析する目的で，22例の肺気腫患者を対象に，その気道反応および白血球のロイコトリエンB4，C4産生能について検討を加えた。この際対象症例はIgE抗体の有無によってRAST陽性症例RAST陰性症例に分類された。1. 喫煙歴，平均ＣＴ値，high resolution computed tomography (HRCT) 上の-950HU以下の%low attenuation area(%LAA)，DLcoなどの値は，いずれも対象症例が高度な気腫化病変を有していることを示した。2. 血清IgE値は，RAST陽性例で陰性例に比べ有意の高値を示した。3. β受容体刺激薬吸入後のFEV1.0の増加は，RAST陽性例で陰性例に比べ高度であった。そして，吸入後のFEV1.0が15%以上の増加を示した症例は，RAST陽性例では9例中4例(44.4%)，陰性例では12例中2例(16.7%)であった。4. 白血球のLTC4産生量は，RAST陽性例で陰性例に比べ有意に高い値であったが，LTB4産生は両者間に有意の差は見られなかった。以上の結果より，IgEにmediateされるアレルギー反応が，肺気腫患者の気道反応に関与している可能性が示唆された。