◎総 説

Cigarette smoking and pathophysiology of asthma and pulmonary emphysema

Fumihiro Mitsunobu, Yasuhiro Hosaki, Kozo Ashida, Masanori Hamada[1], Naofumi Iwagaki, Makoto Fujii, Shingo Takata, Yoshiro Tanizaki

Division of Medicine, [1]Division of Rehabilitation, Misasa Medical Center, Okayama University Medical and Dental School

Abstract : The influence of long-term cigarette smoking on the pathophysiology of chronic respiratory diseases with obstructive ventilatory dysfunction was discussed in patients with asthma and pulmonary emphysema (PE). 1. In patients with asthma, significant differences in the pathophysiology of the disease were observed between smokers and nonsmokers. A positive RAST score against inhalant allergens, bronchial hyperresponsiveness, and LTB4 generation by leucocytes were significantly more increased in smokers than in nonsmokers. The values of FEV1/FVC and DLco were significantly more decreased, and %RV was significantly more increased in smokers than in nonsmokers. 2. In comparison of asthma with PE, IgE-mediated allergy was significantly more increased in smokers with asthma than in nonsmokers with asthma and in smokers with PE. The values of %FEV1, FEV1%, and %DLco were significantly higher in nonsmokers with asthma than in smokers with PE, however, the %DLco and %RV were not significantly different between smokers with asthma and those with PE. The %LAA of the lungs on HRCT was larger in patients with PE than in smokers and nonsmokers with asthma. The results suggest that cigarette smoking influences the pathophysiology of asthma and PE.

Key words : cigarette smoking, pulmonary function, hyperinflation, asthma, pulmonary emphysema

Introduction

Cigarette smoking has been reported to be closely related to the onset mechanism of chronic obstructive pulmonary disease (COPD)[1,2]. It has been shown that 80−90% of all COPD patients have a history of smoking[3], and patients with mild COPD can reduce their symptoms by stopping smoking[4].

The influences of cigarette smoking on pathophysiology of asthma have been shown : adult onset of asthma is not associated with ever-smoking, however, current smoking is found to increase asthma severity[5]. Ever-smoking for 3 years is found to increase the risk of asthma two-fold[6]. The exposure to ETS (environmental tobacco smoke) causes the onset of childhood asthma and exacerbation of symptoms throughout life[7,8].

The possibility for risk of active smoking for developing adulthood asthma still remains controversial. Several studies have supported higher incidence of asthma in current and former smokers, compared with never-smokers[9,10].

Our previous studies have shown that long-term cigarette smoking influences the pathophysiology in elderly patients with asthma[11]. The ratio of expiratory low attenuation area (LAA) against inspiratory LAA (exp LAA/ins LAA) was significantly higher in ever-smokers than in never-smokers of asthmatics, and the ratio was less than 0.5 in all never-smokers, and the ratio was more than 0.5 in 10 of 20 ever-smokers of asthmatics and in all patients with pulmonary emphysema[11]. These results suggest that the pathophysiology is different between asthma and pulmonary emphysema, and the pathophysiology of asthma is influenced by cigarette smoking.

LAA of the lungs on HRCT

In recent years, it has been suggested that computed tomography (CT) scanning is a sensitive technique of detecting emphysematous lesions in patients with COPD. The relative areas of the lungs that has attenuation values lower than -950 Hounsfield Units (HU) on high-resolution CT (HRCT) scans obtained at full inspiration can be an objective measure of the extent of pulmonary emphysema[12,13]. Pulmonary emphysema is defined in structural terms as 'a condition of the lung characterized by abnormal enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls'[14]. Our previous studies have shown that spa therapy is effective in patients with pulmonary emphysema, evaluated by improvement of ventilatory function and hyperinflation of the lungs[15-18]. Subjective symptoms, ventilatory function are improved by spa therapy in patients with pulmonary emphysema. Furthermore, LAA $<$-950 HU of the lungs on HRCT, which is characteristic of pulmonary emphysema[12,13], and is associated with residual volume (RV), shows a tendency to decrease by spa therapy[17,18].

The LAA of the lungs on HRCT is also observed in patients with asthma closely associated with aging, and cigarette smoking. Spa therapy is also effective in patients with asthma accompanied with emphysematous changes[19-21]. Paganin et al. found that patients with asthma did develop emphysema and that the extent of permanent abnormalities increased as a function of the severity and duration of both allergic and nonallergic asthma[22]. In contrast, Mochizuki et al. found no patients with emphysema among nonsmokers, including those with severe asthma or asthma of long duration, suggesting that asthma alone does not lead to emphysema[23].

Despite the findings, the LAA of the lungs on HRCT[24], and a reduction in computed tomographic lung density[25] were observed in patients with asthma.

In our previous studies, we evaluated the presence and the severity of LAA of the lungs in patients with asthma and COPD using HRCT. The results suggest that LAA in asthma is more closely related to hyperinflation or non-emphysematous expiratory airflow limitation than to emphysematous changes, and that asthma does not lead to emphysema, however, asthma + smoking leads to emphysema.

Asthma and cigarette smoking

Ventilatory function

Long-term cigarette smoking influences ventilatory function in patients with asthma. The %FVC value was not significantly different between smokers and nonsmokers of asthmatics (Fig. 1). In contrast, the FEV1/FVC (FEV1%) value was significantly larger in nonsmokers than in smokers of asthmatics ($p<0.05$) (Fig. 2).

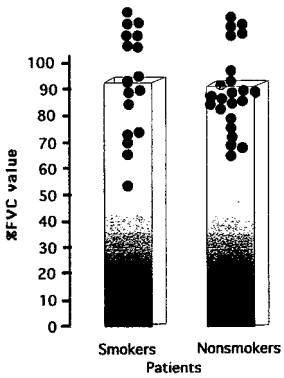

Fig.1. Comparison in %FVC value between smokers and nonsmokers of asthmatics

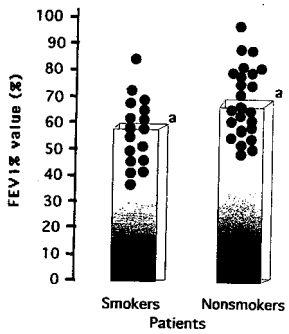

Fig.2. Comparison in FEV1.0% between smokers and nonsmokers of asthmatics. a:p<0.05.

The %FEV1 was not significantly different between smokers and nonsmokers of patients with asth-ma. The results suggest that cigarette smoking might be related to exacerbation of asthma symptoms.

Bronchial hyperresponsiveness

Bronchial hyperresponsiveness to methacholine was significantly increased in smokers compared with nonsmokers of asthmatics ($p<0.001$)[26,27] (Fig. 3). A correlation between serum IgE levels and bronchial hyperresponsiveness was not found in patients with asthma. In asthmatics with serum IgE levels between 0 and 150 IU/ml and between 151 and 350 IU/ml, bronchial hyperresponsiveness was significantly higher in smokers than in non-smokers, however, in

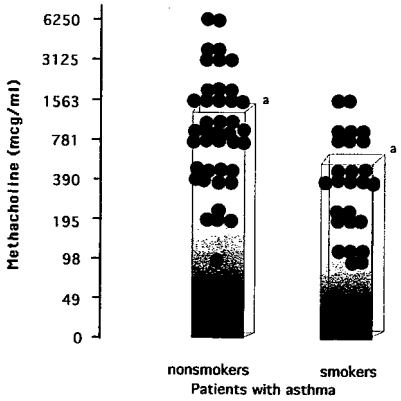

Fig.3. Comparison in bronchial hyperresponsiveness to methacholine between smokers and nonsmokers of asthmatics. a: p<0.001.

those with serum IgE more than 350 IU/ml, no significant difference was found between smokers and nonsmokers (Fig. 4). The results

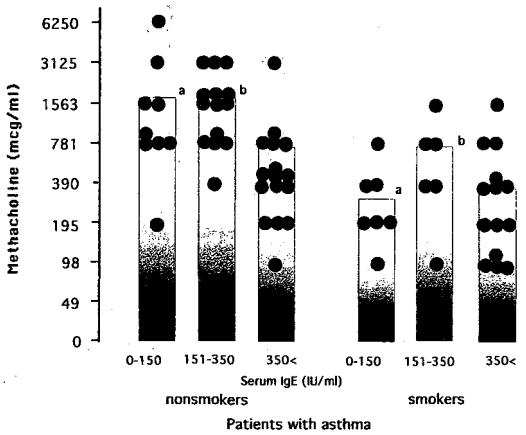

Fig.4. Comparison between bronchial hyperresponsiveness to methacholine and serum IgE level in patients with asthma in relation to cigarette smoking. a: p<0.001, b: p<0.01.

suggest that the influence of cigarette smoking on bronchial hyperresponsiveness was stronger than IgE-mediated allergy in patients with serum IgE level less than 350 IU/ml. In contrast, in those with serum IgE more than 350 IU/ml, the influence of IgE-mediated allergy on bronchial hyperresponsiveness might be stronger than that of cigarette smoking.

Bronchial hyperresponsiveness tended to decrease with aging both in smokers and nonsmokers of asthmatics. Bronchial hyperresponsiveness was significantly more increased in smokers than in nonsmokers in asthmatics between the ages of 60 and 69, and over age 70 years. However, bronchial hyperresponsiveness was not significantly different between the two groups in those between the ages of 50 and 59, and under age 49 years (Fig. 5).

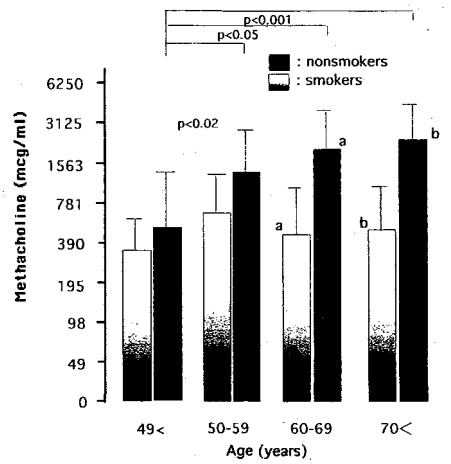

Fig.5. Comparison in bronchial hyperresponsiveness to methacholine between smokers and nonsmokers of asthmatics in relation to age. a : p<0.05, b: p<0.001.

Leukotriene B4 (LTB4) and C4 (LTC4) generation by leucocytes

Leukotrienes (LTs) are pro-inflammatory mediators that contribute to pathophysiology of asthma : LTC4 induces bronchoconstrictor effects, increases mucus formation, and induces bronchial wall edema, and LTB4 stimulates neutrophil chemotaxis and activates these cells, leading to the release of mediators and superoxides, and might be related to an increase in bronchial hyperresponsiveness[28].

The generation of LTB4 by leucocytes was significantly more increased in smokers than in nonsmokers of asthmatics ($p<0.001$) (Fig. 6).

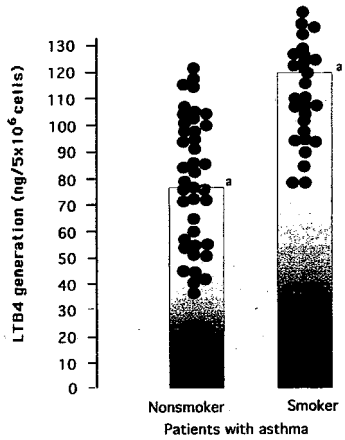

Fig.6. Comparison in leukotriene B4 generation by leucocytes between smokers and nonsmokers of patients with asthma. a : $p<0.001$.

The LTB4 generation was related to serum IgE levels in nonsmokers of asthmatics, and the LTB4 generation in patients with serum IgE more than 350 IU/ml was significantly larger than the generation in those with serum IgE between 151 and 350 IU/ml and less than 150 IU/ml, but not in smokers (Fig. 7).

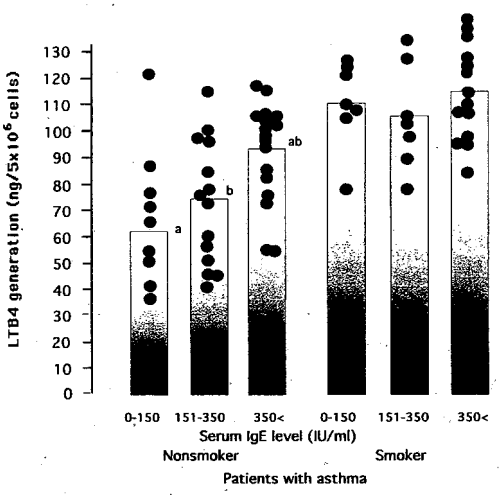

Fig.7. Comparison in leukotriene B4 generation by leucocytes between smokers and nonsmokers of patients with asthma in relation to serum IgE levels. a : $p<0.01$, b: $p<0.02$.

The LTB4 generation by leucocytes was not related to patient age. A significant difference between smokers and nonsmokers was found in patients between the ages of 60 and 69 ($p<0.01$), and over age 70 ($p<0.001$) years. However, the difference between the two groups was not significant in those between the ages of 50 and 59 and under age 49 years (Fig. 8).

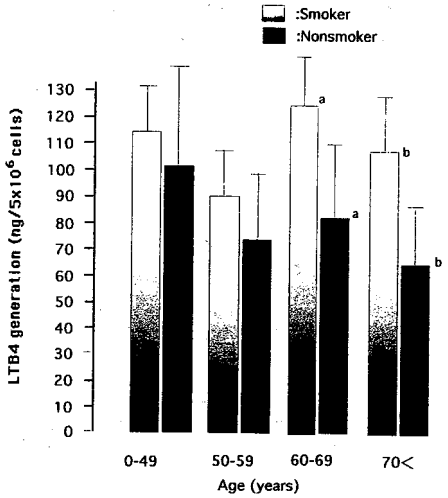

Fig.8 Comparison in leukotriene B4 generation by leucocytes between smokers and nonsmokers of patients with asthma in relation to age. a: $p<0.01$, b: $p<0.001$.

The generation of leukotriene C4 by leucocytes was not significantly different between smokers and nonsmokers of asthmatics (Fig. 9).

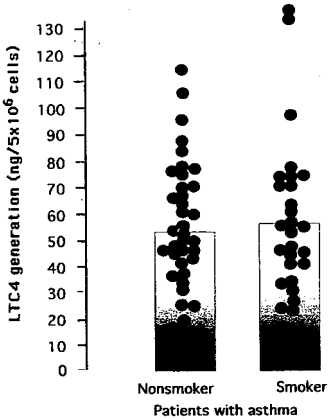

Fig.9. Comparison in leukotriene C4 generation by leucocytes between smokers and nonsmokers of patients with asthma.

The LTC4 generation showed a tendency to increase as serum IgE levels increased. The LTC4 generation by leucocytes from nonsmokers of asthmatics was significantly larger in patients with

serum IgE level more than 350 IU/ml than in those with serum IgE between 151 and 350 IU/ml ($p<0.05$) and less than 150 IU/ml ($p<0.05$). However , the LTC4 generation was not significantly different among smokers of asthmatics regardless of serum IgE levels (Fig. 10).

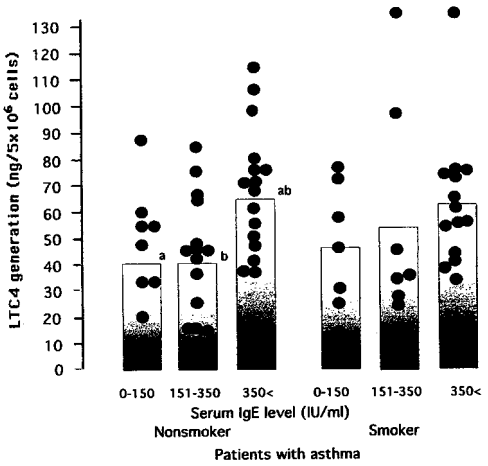

Fig.10. Comparison in leukotriene C4 generation by leucocytes between smokers and nonsmokers of patients with asthma in relation to serum IgE levels. a and b:p<0.05.

The generation of LTC4 by leucocytes was not related to patient age. A significant difference between smokers and nonsmokers was found in patients under age 49 years, and the generation was significantly larger in smokers than in nonsmokers ($p<0.01$). However, the difference between the two groups was not significant in patients over age 50 years (Fig. 11).

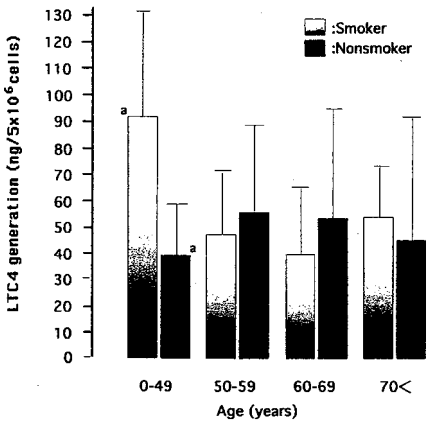

Fig.11. Comparison in leukotriene C4 generation by leucocytes between smokers and nonsmokers of patients with asthma in relation to age. a: p<0.01.

Characteristics of asthma with a long history of smoking

The pathophysiology of asthma is influenced by long-term cigarette smoking. IgE-mediated allergy is enhanced by cigarette smoking[29]. Exposure to cigarette smoke increased sensitization to food allergens in the few years of life[30], but not associated with sensitization to inhaled allergens[7]. Our previous studies have shown that IgE-mediated allergy is affected by cigarette smoking[31] as well as aging[32]. Table 1 shows the pathophysiological characteristics in asthmatics with a long history of cigarette smoking. The frequency of patients with positive RAST score against inhalant allergens was significantly larger in smokers than in nonsmokers of asthmatics. Bronchial hyperresponsiveness to methacholine was significantly more increased in smokers than in nonsmokers. The generation of LTB4 by leucocytes was significantly larger in smokers compared with nonsmokers, but the LTC4 generation was not significantly different between smokers and nonsmokers. Regarding pulmonary function, the values of FEV1%, %RV, %DLco, and %LAA of the lungs on HRCT were significantly different between smokers and nonsmokers, as shown in Table 1 .

Table 1. Characteristics of asthmatics with a history of smoking more than 20 years

	Smoking +	Smoking -	Differences
Smoking (pack-year)	49.1	-	-
IgE (IU/ml)	451 (9-2929)	440 (11-2918)	NS
RAST*(%)	88.0	52.2	p<0.05
C min**	949	1677	P<0.02
LTB4 !	107.7	77.3	p<0.001
LTC4 !	48.8	46.3	NS
%FVC	80.1	84.0	NS
%FEV1	68.7	77.2	NS
FEV1/FVC	59.1	65.8	p<0.05
%RV	170.1	131.1	p<0.001
%DLco	70.1	88.4	p<0.001
%LAA***	25.6	12.6	p<0.001

*Frequency of positive RAST against inhalant allergens. **Minimum concentartion of methacholine causing bronchospasm. ***Low attenuation area <-950 HU of the lungs on HRCT. !: ng/5x10^{5}cells. NS: not significant.

Asthma and pulmonary emphysema

IgE-mediated allergy

The frequency of patients with serum IgE level more than 200 IU/ml was significantly larger in smokers than in nonsmokers of asthmatics ($p<0.01$). The frequency of these patients was also significantly larger in smokers with asthma compared with those with pulmonary emphysema ($p<0.001$). The results suggest that cigarette smoking enhances IgE-mediated allergic reaction, but does not induce the allergic reaction (Fig. 12). The frequency of

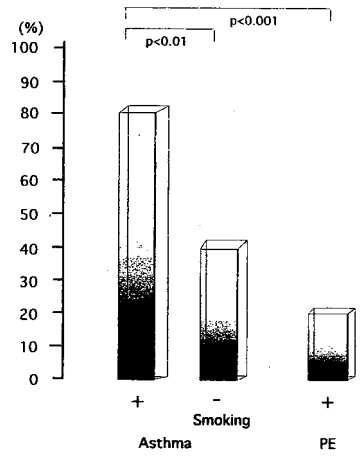

Fig.12. Frequency of patients with serum IgE over 200 IU/ml in asthma and pulmonary emphysema (PE)

patients with a positive RAST score against inhalant allergens was significantly larger in smokers with asthma than in nonsmokers with asthma ($p<0.02$) and than in smokers with pulmonary emphysema ($p<0.001$) (Fig. 13).

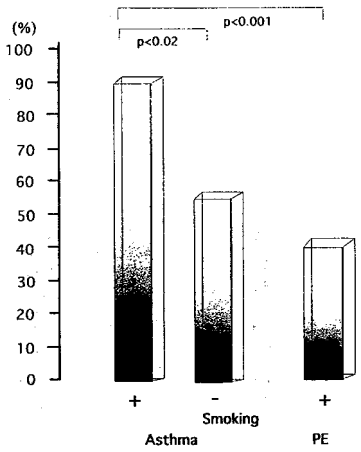

Fig.13. Frequency of patients with a positive RAST score against inhalant allergens in asthma and pulmonary emphysema (PE)

Regarding each inhalant allergen such as house dust mites (HDm), cockroach, and Candida albicans (Cand), frequency of positive RAST score against each allergen was higher in smokers than in nonsmokers with asthma, and the difference in RAST score against Cand was significant between smokers and nonsmokers ($p<0.02$) (Fig. 14).

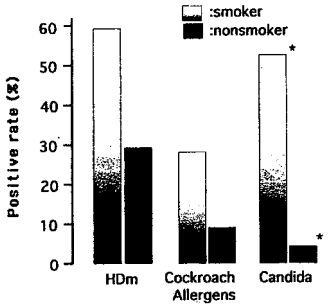

Fig.14. Positive RAST score for inhalant allergens in patients with asthma in relation to smoking. HDm: house dust mite, *p<0.02.

Pulmonary function

The values representing ventilatory function such as %FVC, %FEV1, and FEV1% were not significantly different between smokers and nonsmokers with asthma. A significant difference between smokers with asthma and those with pulmonary emphysema was found in the values of %FEV1 and FEV1%, but not in %FVC (Fig. 15).

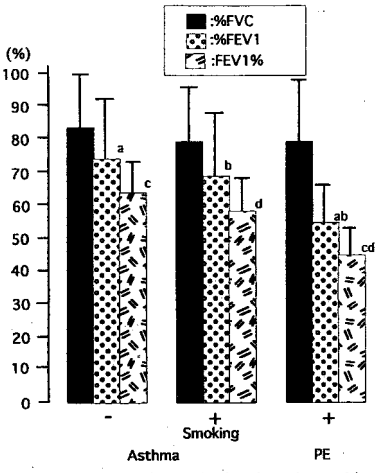

Fig.15. %FVC, %FEV1, and FEV1% values in patients with asthma and pulmonary emphysema (PE). a,c, and d:p<0.001, b:P,0.01.

The value of %DLco in nonsmokers with asthma was significantly higher compared with the value in smokers with asthma ($p<0.001$) and in smokers with pulmonary emphysema ($p<0.001$) (Fig. 16).

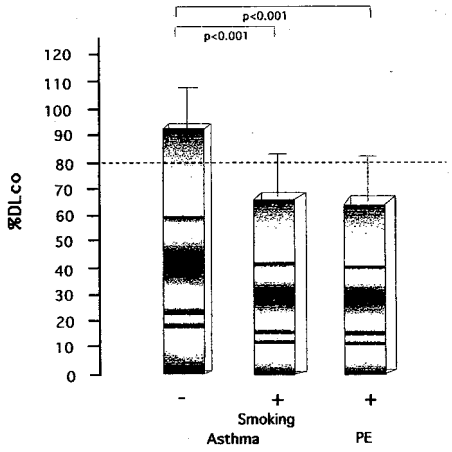

Fig.16. %DLco in asthma and pulmoanry emphysema (PE) in relation to smoking

Hyperinflation of the lungs

The %RV value is closely related to % low attenuation area (%LAA) of the lungs on HRCT. The value of %RV was significantly higher in smokers with pulmonary emphysema than in nonsmokers with asthma. The value was also significantly higher in asthmatics with $0.5 <$ LAA ratio (expiratory LAA/ inspiratory LAA) than in those with LAA ratio <0.5 ($p<0.05$), however, the difference between patients with pulmonary emphysema of $0.5 <$ LAA and those with asthma of $0.5 <$ LAA was not significant (Fig. 17)[33].

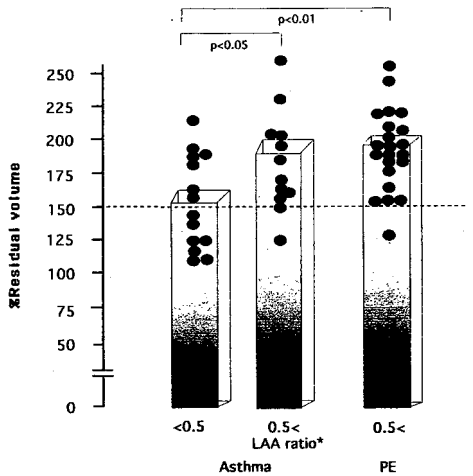

Fig.17. %Residual volume (RV) in patients with asthma and pulmonary emphysema (PE).
*Ratio of LAA in expiration /LAA in inspiration

The %LAA value of the lungs on HRCT was significantly larger in smokers with pulmonary emphysema than in smokers with asthma ($p<0.001$) and than in nonsmokers with asthma ($p<0.001$). A significant difference was observed in %LAA between smokers and nonsmokers with asthma ($p<0.001$). These results demonstrate that cigarette smoking leads to hyperinflation of the lungs expressed as an increase in %RV and %LAA of the lungs (Fig. 18).

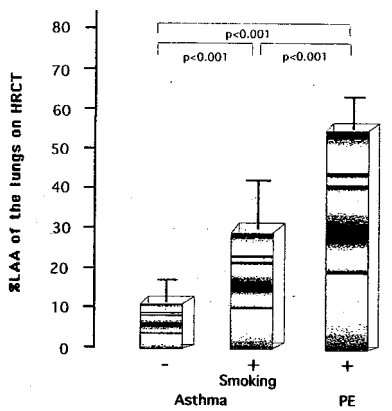

Fig.18. %LAA of the lungs on HRCT in patients with asthma and pulmonary emphysema (PE) in relation to smoking.

The ratio of expiratory LAA/ inspiratory LAA was significantly higher in smokers with pulmonary emphysema than in smokers with asthma ($p<0.001$) and in nonsmokers with asthma ($p<0.001$). Furthermore, the ratio was significantly more increased in smokers than in nonsmokers with asthma ($p<0.001$) (Fig. 19).

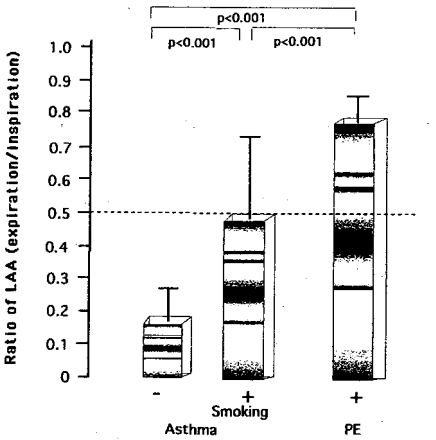

Fig.19. Ratio of expiratory LAA/Inspiratory LAA in patients with asthma and pulmonary emphysema (PE) in relation to smoking

LTB4 and LTC4 generation by leucocytes

The LTB4 generation by leucocytes is influenced by cigarette smoking, but not LTC4 generation. The generation of LTB4 was significantly smaller in nonsmokers with asthma compared with smokers with asthma ($p<0.001$) and those with pulmonary emphysema ($p<0.01$) (Fig. 20).

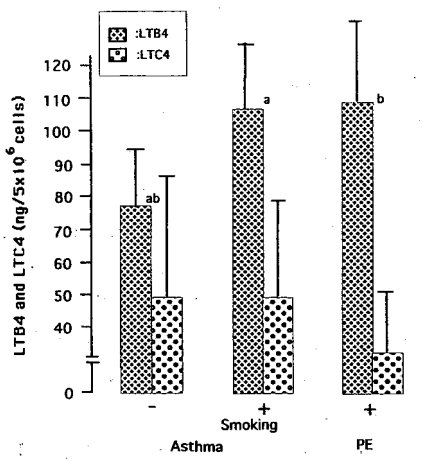

Fig.20. Generation of leukotrienes B4 and C4 by leucocytes in patients with asthma and pulmonary emphysema (PE).
a:p<0.001, b:p<0.01.

Spa therapy, asthma, and pulmonary emphysema

Cigarette smoking induces hyperinflation of the lungs which is expressed by %RV and %LAA of the lungs on HRCT. Spa therapy is clinically effective for patients with asthma and those with pulmonary emphysema. Furthermore, spa therapy improves hyperinflation of the lungs in patients with asthma and pulmonary emphysema[21,34,35]. Spa therapy improves subjective[36,37] and objective symptoms, ventilatory function[16,38], bronchial hyperresponsiveness[39] as direct action of the therapy on airways, and furthermore improves suppressed function of adrenocortical glands[40], and increases superoxide dismutase (SOD) activity[41-46] as indirect action of the therapy in patients with asthma[19-21] and pulmonary emphysema[15,18]. Regarding major enzymatic antioxidants such as SOD and catarase (CAT) activity in asthma, it has been reported that antioxidant capacity is reduced in patients with asthma[47-50].

DeRaeve et al. demanstrated that the SOD activity in asthmatics not on inhaled corticosteroid was lower than asthmatics on inhaled corticosteroid and controls[47]. Comhair et al. showed that loss of SOD activity in bronchoalveolar lavage fluid (BALF) occurs within minutes of an acute asthmatic response to segmental antigen instillation into the lung of individuals with atopic asthma[48]. It has been represented that SOD activity of asthmatics was significantly lower than that of the controls, and that the activity of SOD and CAT in blood were significantly lower in children with asthma, even during resting conditions[49,50]. They also showed that the lipid peroxide levels in plasma and erythrocytes were significantly elevated in asthma. Spa therapy seems to act on enzymatic antioxidants and improve decreased activity of SOD and CAT in patients with asthma.

References

1. Siafakas NM, Vermeire P, Pride N, et al. : Optimal assessment and management of chronic obstructive pulmonary disease (COPD) : a consensus statement of the European Respiratory Society. Eur Respir J 8 : 1398-1420, 1995.
2. British Thoracic Society. BTS Guideline for the management of chronic obstructive pulmonary disease. Thorax 52 (Suppl 5) : S1-28, 1997.
3. U. S. Department of Health and Human Services. The Health Benefits of Smoking Cessation. A report on the Surgeon General. U. S. Government Priting Office. Washington, DC. 1990.
4. Kanner RE, Anthonisen NR, Connett JE, et al. : Lower respiratory illness promote FEV1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease. Results from the lung health study. Am J Respir Crit Care Med 164 : 258-364, 2001.
5. Troisi RJ, Speizer FE, Rosner B, et al. : Cigarette smoking and incidence of chronic bronchitis and asthma in women. Chest 108 : 1557-1561, 1995.
6. Flodin U, Jonsson P, Zeigler J et al. : An epidemiologic study of bronchial asthma and smoking. Epidemiology 6 : 503-505, 1995.
7. Strachan DP, Cook DG : Health effects of passive smoking. 6. Parental smoking and childhood asthma : longitudial and case-control studies. Thorax 53 : 204-212, 1998.
8. Schwartz J, Timonen KL, Rekkanen J : Respiratory effects of environmental tobacco smoke in panel study of asthmatic and symptomatic children. Am J Respir Crit Care Med

161 : 802－806, 2000.
9. Ronmark E, Lundback B, Jonsson E, et al. : Incidence of asthma-report from the Obstructive Lung Disease in Northern Sweden Study. Allergy 53 : 1071－1078, 1997.
10. Toren K, Hermansson BA : Incidence rate of adult-onset asthma in relation to age, sex, atopy and smoking : a Swedish population-based study of 15813 aduls. Int Tuberc Lung Dis 3 : 192－197, 1999.
11. Mitsunobu F, Hosaki Y, Ashida K, et al. : Long-term cigarette smoking influences low attenuation area of the lungs on high-resolution CT in elderly patients with asthma, compared with pulmonary emphysema. Ann Rep Misasa Med Center, Okayama Univ Med Sch 73 : 19－24, 2003.
12. Gevenois PA, deMaertelaer, De Vuyst P, et al. : Comparison of computed density and macroscopic morphology in pulmonary emphysema. Am J Respir Crit Care Med 152 : 653－657, 1995.
13. Gevenois PA, DeVuyst P, deMaertelaer V, et al. : Comparison of computed density and microscopic morphology in pulmonary emphysema. Am J Respir Crit Care Med 154 : 187－192, 1996.
14. Ciba Guest Symposium Report : Termiology, difinitions, and classification of chronic pulmonary emphysema and related conditions. Thorax 14 : 86－299, 1959.
15. Mitsunobu F, Mifune T, Hosali Y, et al. : Effects of spa therapy on patients with pulmonary emphysema. Relationship to disease severity evaluated by low attenuation area of the lung on high resolution computed tomography. J Jpn Assoc Phys Med Balneol Climatol 61 : 79－86, 1998.
16. Mitsunobu F, Mifune T, Hosaki Y, et al. : Improvement of pulmonary function by spa therapy in patients with emphysema, evaluated by residual volume (RV) and low attenuation area (LAA) of high-resolution computed tomography (HRCT). J Jpn Assoc Phys Med Balneol Climatol 62 : 121－128, 1999.
17. Mitsunobu F, Mifune T, Hosaki Y, et al. : Effects of spa therapy on pulmonary emphysema in relation to IgE-mediated allergy. J Jpn Assoc Phys Med Balneol Climatol 63 : 120－126, 2000.
18. Mitsunobu F, Hosaki Y, Ashida K, et al. : Long-term spa therapy prevents the progressive pathological changes of the lung in patients with pulmonary emphysema. J Jpn Assoc Phys Med Balneol Climatol 66 : 91－98, 2003.
19. Ashida K, Mitsunobu F, Mifune T, et al. : Clinical effects of spa therapy on patients with asthma accompanied by emphysematous changes. J Jpn Assoc Phys Med Balneol Climatol 63 : 113－119, 2000.
20. Ashida K, Mitsunobu F, Mifune T, et al. : Effect of spa therapy on low attenuation area (LAA) of the lungs on high-resolution computed tompography (HRCT) and pulmonary function in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 64 : 203－209, 2001.
21. Ashida K, Mitsunobu F, Hosaki Y, et al, : Decrease in low attenuation area (LAA) of the lungs on high resolution computed tomography (HRCT) by long-term spa therapy in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 66 : 115－122, 2003.
22. Paganin F, Senettere E, Chanez P, et al. : Computed tomography of the lungs in asthma : Influence of disease severity and etiologyy. Am J Respir Crit Care Med 153 : 110－114, 1996.
23. Mochizuki T, Nakajima H, Kokubu F, Kushihashi T, Adachi M : Evaluation of emphysema in patients with reversible airway

obstruction using high-resolution CT. Chest 112 : 1522－1526, 1997.

24. Gevenois PA, Scillia P, deMaertelaer V, Michils A, Vuyst PD, Yemaut JC : The effects of age, sex, lung size, and hyperinflation on CT lung densitometory. Am J Roentgenol 167 : 1169－1173, 1996.

25. Biernacki W. Redpath AT, Best JJ, MacNec W : Measurement of CT lung density in patients with chronic asthma. Eur Respir J 10 : 2455－2459, 1997.

26. Mitsunobu F, Ashida K, Hosaki Y, et al. : An increase in bronchial hyperresponsiveness by cigarette smoking in elderly patients with asthma. Ann Rep Misasa Med Center, Okayama Univ Med Sch73 : 25－30, 2003.

27. Mitsunobu F, Hosaki Y, Ashida K, et al. : Cigarette smoking enhancesLTB4 generation by leucocytes associated with bronchial hyperresponsiveness in asthma in the elderly. Ann Rep Misasa Med Center, Okayama Univ Med Dent Sch 74 : 18－24, 2004.

28. Mistunobu F, Mifune T, Hosaki Y, et al. : Enhanced peripheral leukocyte leukotriene production and bronchial hyperresponsiveness in asthmatics. Eur Respir J 16 : 504－508, 2000.

29. Ashida K, Mitsunobu F, Hosaki Y, et al. : IgE-mediated allergy and cigarette smoking enhance the generation of leukotrienes B4 (LTB4) and C4 (LTC4) by leucocytes and bronchial hyperresponsiveness in patients with atopic asthma. Ann Rep Misasa Med Center, Okayama Univ Med Dent Sch 74 : 42－47, 2004.

30. Kulig M, Luck W, Lau S, et al. : Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Allergy 54 : 220－228, 1999.

31. Mitsunobu F, Ashida K, Hosaki Y, et al. : Influence of long-term cigarette smoking on immunoglobulin E-mediated allergy, pulmonary function, and high-resolution computed tomography lung densitometry in elderly patients with asthma. Clin Exp Allergy 34 : 59－64, 2004.

32. Mitsunobu F, Mifune T, Hosaki Y, et al. : IgE-mediated allergy in elderly patients with asthma. Allergology International 46 : 237－241, 1997.

33. Mitsunobu F, Hosaki Y, Ashida K, et al. : Difference in low attenuation area (LAA) of the lungs on high resolution computed tomography (HRCT) between asthma and pulmonary emphysema in relation to cigarette smoking. Ann Rep Misasa Med Center, Okayama Univ Med Dent Sch 74 : 35－41, 2004.

34. Mitsunobu F, Hosaki Y, Ashida K, et al. : Improvement of hyperinflation of the lungs by spa therapy in patients with asthma. J Jpn Assoc Phys Med Balneol Climatol 67 : 195－201, 2004.

35. Mitsunobu F, Hosaki Y, Ashida K, et al. : Five-year observation of the effects of spa therapy for patients with pulmonary emphysema, evaluated by %low attenuation area (%LAA) of the lungs on high resolution CT, %DLco and %residual volume (RV). J Jpn Assoc Phys Med Balneol Climatol 67 : 148－154, 2004.

36. Tanizaki Y, Kitani H, Okazaki M, et al. : Clinical effects of spa therapy on bronchial asthma. 1. Relationship to clinical asthma types andpatient age. J Jpn Assoc Phys Med Balneol Climatol 55 : 77－81, 1992.

37. Tanizaki Y, Kitani H, Okazaki M, et al. : Ten-year study on spa therapyin 329 patients with bronchial asthha. J Jpn Assoc Phys Med Balneol Cllimatol 57 : 142－150, 1994.

38. Tanizaki Y, Kitani H, Okazaki M, ert al. : Clinical effects of spa therapy on bronchial

asthma. 2. Relationship to ventilatory function. J Jpn Assoc Phys Med Balneol Climatol 55 : 82-86, 1992.
39. Tanizaki Y, Kitani H, Okazaki M, et al. : Clinical effects of spa therapy on bronchial asthma. 9. Suppression of bronchial hyperresponsiveness. J Jpn Assoc Phys Med Balneol Climatol 56 : 135-142, 1993.
40. Tanizaki Y, Kitani H, Okazaki M, et al. : Clinical effects of spa therapy on bronchial asthma. 8. Effects on suppressed function of adrenocortical glands. J Jpn Assoc Phys Med Balneol Climatol 56 : 87-94, 1993.
41. Yamaoka K, Komoto Y, Suzuka I, Edamatsu R, Mori A : Effects of radon inhalation on biological function-lipid peroxide level, superoxide dismutase activity, and membrane fluidity. Arch Biochem Biophys 302 : 37-41, 1993.
42. Ma J, Yonehara H, Ikebuchi M, Aoyama T : Effect of radon exposureon superoxide dismutase (SOD) activity in rats. J Radiat Res 37 : 12-19, 1996.
43. Yamaoka K, Mifune T, Mitsunobu F, et al. : Basic study on radoneffects and thermal effects on humans in radon therapy. Physiol Chem Phys Med N. M. R. 33 : 133-138, 2001.
44. Mitsunobu F, Yamaoka K, Hanamoto K, et al. : Elevation of antioxidant enzymes in the clinical effects of radon and thermal therapy for bronchial asthma. J Radiat Res 44 : 95-99, 2003.
45. Yamaoka K, Mitsunobu F, Hanamoto K, et al. : Study on biologic effects of radon and thermal therapy on osteoarthritis. J Pain 5 : 20-25, 2004.
46. Yamaoka K, Mitsunobu F, Hanamoto K, et al. : Biochemical comparison between radon effects and thermal effects on humans in radon hot spring therapy. J Radiat Res 45 : 83-88, 2004.
47. DeRaeve HR, Thunissen FB, Kaneko FT, et al. : Decreased Cu, Zn-SOD activity in asthmatic airway epithelium : correction by inhaled corticosteroid in vivo. J Physiol 272 : L148-154, 1997.
48. Comhair SA, Bhathena PR, Dweik RA, Kavuru M, Erzurum SC : Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response. Lencet 355 : 624-624, 2000.
49. Tekin D, Sin BA, Mungan D, Misirligil Z, Yavuzer S : The antioxidative defense in asthma. J Asthma 37 : 59-63, 2000.
50. Shanmugasubdaram KR, Kumar SS, Rajajee S : Excessive free radical generation in the blood of children suffering from asthma. Clin Chim Acta 305 : 107-114, 2001.

長期間喫煙による気管支喘息，肺気腫の病態的変化

光延文裕，保﨑泰弘，芦田耕三，濱田全紀[1)]，
岩垣尚史，藤井　誠，高田真吾，谷崎勝朗

岡山大学医学部・歯学部附属病院三朝医療センター内科，[1)]リハビリテーション科

長期間喫煙による気管支喘息および肺気腫の病態的変化について若干の検討を加えた。1．気管支喘息に関しては，喫煙例と非喫煙例との間に以下のような病態的特徴に差が見られた。吸入抗原に対する特異的IgE抗体の陽性率，気道過敏性，白血球のLTB4産生能はいずれも，喫煙例で非喫煙例に比べ有意の亢進を示した。また，喫煙例では，非喫煙例に比べ，FEV1%や%DLcoは有意の低下，%RVは有意の増加傾向を示した。2．喘息と肺気腫の比較では，IgE にmediateされるアレルギー反応は，喘息の非喫煙例や肺気腫（全て喫煙例）に比べ，喘息の喫煙例で有意の亢進が見られた。%FEV1，FEV1，%DLco値はいずれも喘息の非喫煙例で，肺気腫と比べ有意に高い値を示したが，%DLcoと%RV値には，喘息の喫煙例と肺気腫の間に有意の差は見られなかった。また，肺のHRCT上の%LAAは，肺気腫において，喘息の喫煙例，非喫煙例いずれよりも有意に高い値を示した。以上の結果より，長期間の喫煙が喘息や肺気腫の病態に影響を与えることが示された。

キーワード：喫煙，肺機能，肺の過膨張，喘息，肺気腫