Cigarette smoking and pathophysiology of asthma and pulmonary emphysema

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

Division of Medicine, 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
Cigarette smoking, asthma and 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\(^10\). 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\(^10\). 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\(^11\). 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\(^19,20\). 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\(^20\).
Cigarette smoking, asthma and pulmonary emphysema

Despite the findings, the LAA of the lungs on HRCT and a reduction in computed tomographic lung density 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).

The %FEV1 was not significantly different between smokers and nonsmokers of patients with asthma. 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) (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
those with serum IgE more than 350 IU/ml, no significant difference was found between smokers and nonsmokers (Fig. 4). The results 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).

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 hyperresponsiveness⁹⁸.

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

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).

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

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
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\(^{30}\) as well as aging\(^{30}\). 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.

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).

**Figure 10.** Comparison in leukotriene C4 generation by leucocytes between smokers and nonsmokers of patients with asthma in relation to serum IgE levels. a: \(p<0.05\).

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

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).
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).

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).
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).

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).

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).
Cigarette smoking, asthma and pulmonary emphysema

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).

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).

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).
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. Spa therapy improves subjective and objective symptoms, ventilatory function, bronchial hyperresponsiveness as direct action of the therapy on airways, and furthermore improves suppressed function of adrenocortical glands as indirect action of the therapy in patients with asthma and pulmonary emphysema. 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. DeRaeve et al. demonstrated that the SOD activity in asthmatics not on inhaled corticosteroid was lower than asthmatics on inhaled corticosteroid and controls. 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. 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. 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


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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，保崎泰弘，芦田耕三，濱田全紀
岩垣尚史，藤井誠，高田真吾，谷崎勝朗

岡山大学医学部・薬学部附属病院三朝医療センター内科，11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の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いわゆる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