

Review Article

Pathological and radiological approach to the small airway disease in asthma: Limitation of current inhaled corticosteroid therapy

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ABSTRACT

The small airway disease in asthma is characterized by airway wall thickening associated with eosinophilic inflammation and hypervascularity. In our study, predicted forced expiratory volume in 1 s (% FEV₁) correlated with the vascularity in the inner layers of large airways but not for small airways. High-resolution computed tomography (CT) scans of 0.5 mm collimation during acute mild exacerbations revealed mucus plugging, air-space nodules and ground-glass opacities. Mean lung density on CT in acute exacerbations was significantly increased compared with that in remission. These results suggest that the involvement of the small airways and lung parenchyma would be increased during exacerbations. Pathologically, eosinophils were significantly reduced by treatment with chlorofluorocarbon–beclomethasone dipropionate (BDP) in the large airways, but not in the small airways. New fine-particle inhaled corticosteroids (ICS), such as hydrofluoroalkane–BDP, can reach the small airways and lung parenchyma in asthmatic patients. From the results of peak inspiratory flow (PIF) through each dry powder inhaler in Japanese people, measurement of PIF should be recommended before the use of dry powder inhaler. In the present review, we address small airway disease in asthmatic patients using pathological and radiological

methods and discuss the critical problems of current ICS therapy.

Key words: asthma, eosinophil, high-resolution computed tomography, inhaled corticosteroid, small airway.

INTRODUCTION

Asthma is a chronic inflammatory disease affecting the whole bronchial tree, from large to small airways.^{1,2} However, information about the small airways and lung parenchyma in asthmatic patients and comparison of bronchial remodeling and inflammation between central and peripheral airways is lacking.³ The contribution of small airway involvement to acute exacerbations of asthma also remains unknown. High-resolution computed tomography (HRCT) has been useful for assessing structural changes in the asthmatic lung and permits investigation of the relationship between airway wall thickening and clinical parameters. Multidetector-row CT (MDCT) is now widely available and can scan the whole lung within a very short time compared with previous HRCT, enabling us to evaluate acute exacerbations with mild respiratory failure.

Inhaled corticosteroid (ICS) is a well-established anti-inflammatory therapy for asthma and steroid receptors are located throughout the bronchial tree.⁴ In general, the smaller particles can reach the more peripheral airways but, for an optimal therapeutic response to ICS, the inhaled particles should reach both large and small airways. Recently, a solution steroid aerosol, hydrofluoroalkane–beclomethasone dipropionate (HFA–BDP), was developed with a mass median aerodynamic diameter (MMAD) of 1.1 μm,⁵ raising the possibility that this extra-fine ICS may be more effective than

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conventional chlorofluorocarbon (CFC)-BDP, with an MMAD of 3.5 μm , in improving function in the small airways of asthmatic patients through more effective suppression of peripheral airway inflammation. We also address the problems regarding inhalation technique in patients with asthma and chronic obstructive pulmonary disease (COPD) and the significance of particle size of dry powder inhaler (DPI) and pressurized metered-dose inhaler (pMDI) of ICS. In the present review, we address small airway disease in asthmatic patients using pathological and radiological methods and discuss the critical problems of current ICS therapy.

PATHOLOGICAL APPROACH

Bronchial wall inflammation

Many investigators have reported inflammatory changes in the small airways in subjects with fatal and mild asthma using lung specimens obtained by operation. Saetta *et al.*⁶ found evidence of increased mucus plugging, airway smooth muscle thickening and infiltration of inflammatory cells, including eosinophils, in the small airways in fatal asthma. Kuwano *et al.*⁷ and Carroll *et al.*^{3,8} reported that remodeling also occurred in mild asthma. Hamid *et al.*² observed that inflammatory changes were more severe in small airways than in large airways of asthmatic patients who had undergone lung resection for tumor, whereas Kraft *et al.*⁹ reported that eosinophilic inflammation was greater in peripheral tissue than in the large bronchi in the early morning hours.

Bronchial wall angiogenesis

Angiogenesis is characteristic of airway remodeling in asthma, but there have been few reports as to bronchial wall hypervascularity in the small airways. We found that the number of vessels and percent vascularity were increased in both large and small airways in patients with asthma compared with control subjects.¹⁰ Because previous *in vivo* quantitative studies used biopsy specimens obtained by fiberoptic bronchoscopy, the observations were limited to the large airways, whereas our data extend the finding of increased vascularity to small airways. Li *et al.*¹¹ did not find any relationship between clinical parameters and airway vascularity in patients with mild and moderate asthma, although Salvato¹² and Vrugt *et al.*¹³ showed that subjects with severe asthma had more vessels compared with mild to moderate

asthmatics. In contrast, vascularity is more prominent in the inner area,¹⁰ suggesting that airway edema due to plasma leakage from mucosal capillary vessels may increase the narrowing of the bronchial lumen and increase airway resistance. Our study showed that percentage forced expiratory volume in 1 s (%FEV₁) correlated with vascularity in the inner layer of the large airways, but not in the small airways.¹⁰ These results suggest that hypervascularity of the inner layer of large airways may contribute not only to disease severity, but also to airflow limitation in asthmatic patients.

RADIOLOGICAL APPROACH

High-resolution CT appearance at asthma exacerbation

High-resolution CT is one of the most useful tools for imaging the small airways and the direct signs are the result of changes in the airway wall or lumen. Teel *et al.*¹⁴ summarized small airway abnormalities as tubular, nodular or branching linear structures on HRCT scans and described indirect signs of small airway disease resulting from changes in the lung parenchyma distal to the diseased small airway due to air trapping, subsegmental atelectasis, centrilobular emphysema and air-space nodules. Niimi *et al.*¹⁵ reported that airway wall thickening measured by CT appeared in all degrees of asthma disease and suggested its magnitude may relate to the duration and degree of airflow limitation. To evaluate airway remodeling of the large and small airways and lung parenchyma during mild asthma exacerbations, we assessed the CT findings of the right upper lobe taken at 0.5 mm intervals and 0.5 mm collimation using MDCT. We examined the bronchial wall of generations 2–5 in stable asthmatic patients and patients with a mild exacerbation.¹⁶ We found that an increase of wall area of generation 4 bronchus was most responsible for airflow limitation (%FEV₁) in stable asthma, but found no relationship during mild exacerbation, suggesting that, during asthma exacerbation, airflow may be restricted not only by large airway narrowing and inflammation, but also by obstruction of the small airway by mucus plugging. Actually, air-space nodules and ground-glass opacities (GGO) appeared on 0.5 mm collimation HRCT during mild exacerbation (Fig. 1a,b). Micronodules also existed at the end of the bronchus and continued to the pulmonary artery, findings that appear in case of diffuse panbronchiolitis,

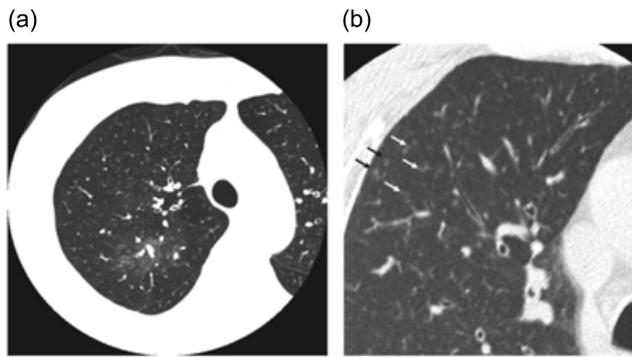


Fig. 1 High-resolution computed tomography of 0.5 mm collimation on asthma exacerbation. Ground glass opacities (a) and nodular opacities (arrows) connecting to the end of a bronchiole (b) are shown.

which suggest that these nodules may reflect small airway wall inflammation and mucus plugging. Ground-glass opacities during asthma exacerbation suggest eosinophil-dominant inflammation in the lung parenchyma.

High-resolution CT lung density

The low-attenuation area (LAA) on CT has been shown to represent macroscopic or microscopic emphysema in patients with COPD and also has been used in the detection of airspace enlargement in patients with asthma. Mitsunobu *et al.*¹⁷ reported that LAA in non-smoking asthmatics ($11.0\% \pm 9.7$) was significantly increased compared with that in non-smoking controls ($3.6\% \pm 3.2$) and mean lung density (MLD) in non-smoking asthmatics (-845 ± 32 Hounsfield units (HU)) was significantly lower than that in non-smoking controls (-818 ± 29 HU). Mitsunobu *et al.*¹⁷ also reported that both MLD and LAA correlated with parameters of airflow limitation and lung volume, but not with the lung transfer factor in non-smoking asthmatic patients.¹⁸ We also measured CT lung density using MDCT in patients with stable asthma and with a mild exacerbation.¹⁹ In our study, LAA in non-smoking asthma ($10.3 \pm 5.4\%$) was increased, but not significantly, compared with non-smoking controls ($9.2 \pm 4.2\%$) and MLD in non-smoking asthma (-871 ± 31 HU) was higher, but not significantly, compared with non-smoking controls (-861 ± 31 HU). The different results may be explained by the selection of patients, because we excluded subjects with emphysematous change, giant bulla or cystic lesions on

CT,¹⁹ but Mitsunobu *et al.*^{17,18} did not. We also found that MLD in patients with mild exacerbations was significantly higher than in patients with stable asthma, whereas the LAA area in patients with mild exacerbation was significantly decreased compared with that in patients with stable asthma (S Sahara *et al.*, unpubl. obs., 2003). These results suggest that peripheral lung lesions may develop during asthma exacerbations. There has been no report about CT lung density during asthma exacerbation, but Kraft *et al.*²⁰ reported that lung biopsy specimens at 04.00 h in patients with nocturnal asthma demonstrated increased eosinophil infiltration into the lung parenchyma. We speculate that lung parenchyma lesions may be increased during asthma exacerbations.

The difference in peripheral lung density between inspiratory and expiratory CT is also useful for the detection of air trapping by small airway narrowing. Goldin *et al.*²¹ evaluated the efficacy of inhaled bronchoconstrictor (methacholine) and bronchodilator (albuterol) by assessing expiratory CT (at the residual volume level). They observed that the marked increase in LAA due to air trapping by inhalation of methacholine returned to baseline levels after inhalation of albuterol, suggesting that LAA on expiratory CT reflects prompt changes of small airway obstruction in asthmatic patients.

LIMITATION OF ICS THERAPY

Lung deposition of ICS

Inhaled corticosteroids are powerful anti-inflammatory drugs and, for optimal therapeutic response with ICS, the inhaled particles should reach both the large and small airways. Recently, a fine-particle ICS of HFA-BDP has become available with an MMAD of $1.1 \mu\text{m}$.⁵ Leach *et al.*²² reported that lung deposition, using gamma scintigraphy was greater with HFA-BDP (53%) compared with CFC-BDP (4%) in nine healthy non-smoking volunteers and that HFA-BDP was distributed diffusely throughout the lungs, whereas deposition of CFC-BDP was mainly in the large and intermediate airways. The pattern of lung deposition showed that HFA-BDP was spread diffusely through the lung airways, whereas CFC-BDP was confined to the large airways with little in the small airways. We evaluated lung specimens of mild and moderate asthma obtained at operation due to a small lung cancer¹⁰ and the number of eosinophils in the bronchial wall was significantly reduced by CFC-BDP $400\text{--}600 \mu\text{g/day}$ in the large airways, but not in the

small airways (Fig. 2). Possibly, the particle size of CFC-BDP (MMAD 3.5 μm) prevented it reaching to the small airways.

Peak inspiratory flow in DPI

Three devices of DPI, namely Diskhaler®, Diskus® (GlaxoSmithkline, Brentford, UK) and Turbuhaler® (AstraZeneca, Lund, Sweden), are currently available in Japan. They are increasingly being used in preference to

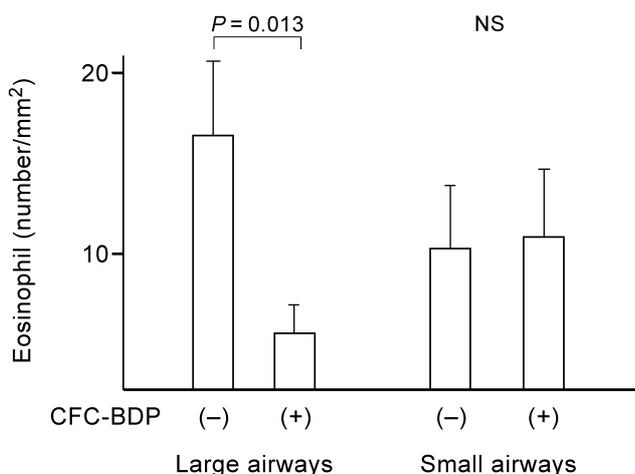


Fig. 2 Number of eosinophils at the inner layer of large airways (inner diameter 2–5 mm) and small airways (inner diameter < 2 mm) in lung specimens obtained by operation due to a peripheral small malignant tumor. In the large airways, the number of eosinophils in patients treated with chlorofluorocarbon–beclomethasone dipropionate (CFC-BDP) was significantly ($P = 0.013$) decreased compared with subjects without CFC-BDP treatment; however, this sort of reduction in eosinophil numbers was not seen in the small airways.

Table 1 Patient characteristics

	Asthma	COPD
No. patients	223	43
Sex (M/F)	90/133	38/5
Age (years)	53 ± 16	71 ± 8
PEF (L/min)	361 ± 121	225 ± 101
PIF (L/min)	230 ± 73	165 ± 65
Inhaled corticosteroids (no. patients)		
CFC-BDP	95	5
DPI-FP (diskhaler)	106	10
None	22	28

Where appropriate, data are given as the mean ± SD.

COPD, chronic obstructive pulmonary disease; PEF, peak expiratory flow; PIF, peak inspiratory flow; CFC, chlorofluorocarbon; BDP, beclomethasone dipropionate; DPI, dry powder inhaler; FP, fluticasone.

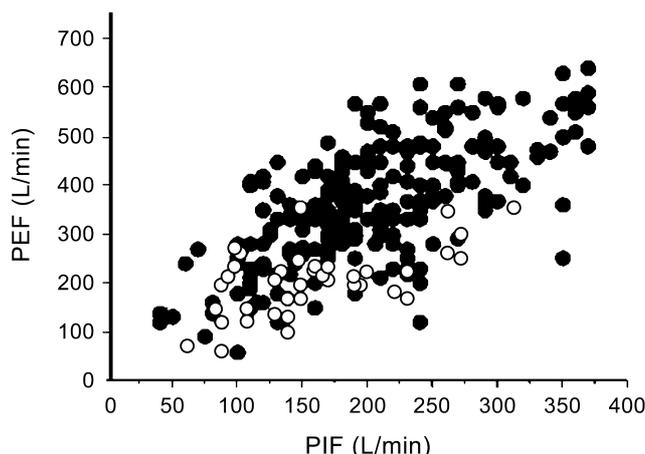


Fig. 3 Correlation between peak expiratory flow (PEF) and peak inspiratory flow (PIF) measured using In-Check® (Clement Clarke, Harlow, Essex, UK) in patients with asthma (λ; $n = 223$; $r = 0.67$; $P < 0.0001$) and chronic obstructive pulmonary disease (COPD; ○; $n = 43$; $r = 0.69$; $P < 0.0001$). The PIF in COPD is relatively higher than that in asthma compared with the value of PEF.

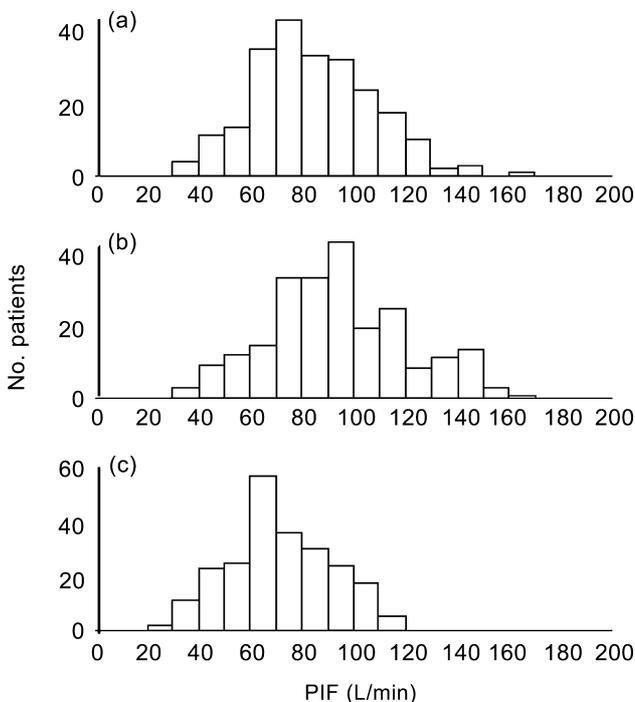


Fig. 4 Histograms of peak inspiratory flow (PIF) in 223 asthmatic patients determined using In-Check® (Clement Clarke, Harlow, Essex, UK) through each adaptor: (a) Diskhaler®; (b) Diskus®; (c) Turbuhaler®.

the conventional aerosol pMDI, because patients find them easier to use and, furthermore, they do not contain CFC. However, a potentially serious disadvantage is that their efficient use is dependent on the generation of an adequate inspiratory flow. Although the effect of PIF on drug delivery through the DPI inhalation device is well known, there have been few studies using Diskhaler[®], Diskus[®] and Turbuhaler[®] in Japanese people.²³ Therefore, we evaluated peak expiratory flow (PEF) using a Mini-Wright[®] peak expiratory flow meter (Clement Clarke, Harlow, Essex, UK) and PIF using an In-Check[®] peak inspiratory flow meter (Clement Clarke) in 266 outpatients; 223 patients with asthma and 43 subjects with COPD (Table 1). A significant correlation between PEF and PIF existed in patients with asthma and those with COPD, but PEF was extremely low compared with PIF in subjects with COPD (Fig. 3). This fact showed that expiratory airflow may be limited in patients with COPD, but the limitation of inspiratory airflow was slight, suggesting that COPD patients can use the DPI as well as asthmatic patients. Next, PIF through Diskhaler[®], Diskus[®] or Turbuhaler[®] was measured at a maximal forced inspiration using another In-check[®] attached to each inhaler adaptor. Histograms of PIF for each device adaptor in the 223 asthmatic patients are shown in Fig. 4. For optimal lung deposition, patients with PIF values of 60–90 L/min are recommended to use the Diskhaler[®], whereas those with PIF values of 30–90 L/min are recommended to use the Diskus[®] or the Turbuhaler[®]. In measuring PIF through the Diskhaler[®], 28 asthmatic patients had a low PIF under 60 mL/min and although these patients were almost all women, it did not appear that the result was age dependent (age range 25–76 years). It is suggested that PIF should be measured before the use of DPI.

CONCLUSION

Newly refined morphometric and immunohistochemical techniques have been used to detect asthma inflammation in the small airways and these technological changes have had a profound clinical impact. Now, it is understood that the eosinophilic infiltration occurs throughout the asthmatic lung. The contribution of small airway inflammation to deficits in pulmonary function has been clarified by HRCT imaging. Current treatment with CFC-BDP by pMDI or DPI can suppress the inflammation in the large airways but a

little in the small airways. In contrast, new formulations of fine-particle ICS, such as HFA-BDP, can penetrate into the small airways and lung parenchyma. Their potential to treat inflammation at the level of the small airway may lead to significant improvements in asthma outcome.

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