Bronchial Dilatation in Asthma*
Relation to Clinical and Sputum Indices

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Background: Investigations using high-resolution CT (HRCT) show that bronchial dilatation (BD) is found in many patients with asthma. However, the pathogenesis and pathophysiologic relevance of BD in asthma are poorly understood. A balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) may control the remodeling of extracellular matrix, and excess MMPs have been associated with destruction or dilatation of airways in patients with bronchiectasis.

Objectives: To study the prevalence of BD as assessed by HRCT according to standard subjective criteria in 37 patients with stable asthma and 10 healthy control subjects, and to examine the relation of BD in asthmatic patients to clinical characteristics and sputum indices, including MMP-9 and TIMP-1 levels.

Design: A prospective cohort study.

Results: At least one dilated bronchus was present in 23 asthmatic subjects (62%) and 2 control subjects (20%) \( p = 0.030 \). The ratio of dilated bronchi to all eligible bronchi in each subject (individual BD%) was higher in the asthmatic patients than in the control subjects \( 11.4 \pm 16.1\% \) vs \( 1.3 \pm 3.0\% \), \( p = 0.011 \) [mean \( \pm SD \)]. Asthmatic patients with \( n = 23 \) and those without BD \( n = 14 \) were similar with regard to age, duration and severity of asthma, atopy, pulmonary function, sputum eosinophil or neutrophil count, and sputum levels of MMP-9 or TIMP-1 and their molar ratio. Individual BD% of asthmatic patients was also unrelated to these clinical and sputum variables. When analysis was confined to the 23 patients with BD, however, individual BD% correlated with the severity score of asthma \( r = 0.49 \), \( p = 0.023 \). The results of follow-up HRCT obtained from 19 patients suggested that BD was a fixed rather than transient phenomenon.

Conclusion: BD is more prevalent in asthmatic patients than in normal subjects and might be associated with the severity of asthma. Cellular inflammation or possible imbalance between MMP-9 and TIMP-1 was not demonstrated in this study to be related to BD in asthma.

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Key words: airway inflammation; airway remodeling; asthma; bronchial dilatation; high-resolution CT; induced sputum; matrix metalloproteinase 9; tissue inhibitor of matrix metalloproteinase 1

Abbreviations: BD = bronchial dilatation; BD + = at least one dilated bronchi at the initial CT examination; BD − = no bronchial dilatation; ELISA = enzyme-linked immunosorbent assay; FEF 25–75% = mid-forced expiratory flow; HRCT = high-resolution CT; individual BD% = ratio of dilated bronchi to all eligible bronchi in each subject; MMP = matrix metalloproteinase; PBS = phosphate-buffered saline solution; TIMP = tissue inhibitor of matrix metalloproteinase

Asthma is characterized by chronic inflammation and remodeling of the airways. High resolution CT (HRCT) has been used to indirectly assess asthmatic airway remodeling on the basis of findings such as airway wall thickening and airway trapping. Furthermore, bronchial dilatation (BD) is observed on HRCT in asthmatic patients. This work was supported by AstraZeneca Asthma Research Award 2000 (Japanese Society of Allergology and Japan Allergy Foundation).

Manuscript received February 24, 2003; revision accepted November 3, 2003. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org). Correspondence to: Akio Niimi, MD, Department of Respiratory Medicine, Postgraduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan; e-mail: niimi@kuhp.kyoto-u.ac.jp

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Clinical Investigations
However, the pathogenesis and pathophysiologic implications of BD in asthma are poorly understood. The balance between matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMPs) has recently received considerable attention with regard to tissue remodeling in a variety of disorders. An excess of MMPs, which degrade extracellular matrix, can cause tissue destruction of diseased organs. In contrast, an excess of TIMPs, which inhibit the activity of MMPs, may cause fibrosis or tissue stiffening. In cystic fibrosis and noncystic fibrosis bronchiectasis, overexpression of MMPs in the airways is associated with disease severity. These disorders are characterized by airway destruction and luminal dilatation.

In both asthmatic patients and normal subjects, MMP-9 is the most prominently expressed MMP in BAL fluid and sputum. TIMP-1 is secreted in association with MMP-9 and binds noncovalently in a 1:1 proportion to MMP-9 or pro–MMP-9, inhibiting their enzymatic activity. Increased levels of MMP-9 and TIMP-1, and their imbalance, are found in the airway secretions of asthmatic patients, but relation of these enzymes to BD remains unknown. We investigated the prevalence of BD as assessed by HRCT in patients with stable asthma, as compared with that in healthy control subjects. We then examined the relation of BD to clinical characteristics and sputum indexes, including MMP-9 and TIMP-1 levels, in the asthmatic patients. Our hypothesis was that higher titers of MMP-9 or higher MMP-9/TIMP-1 ratios in sputum may be associated with an increased prevalence of BD.

**Materials and Methods**

**Subjects**

We studied 37 adult patients with asthma treated at the outpatient asthma clinic of Kyoto University Hospital. Asthma was diagnosed according to the American Thoracic Society criteria. All patients had stable disease for at least 2 months before study entry and were receiving short-acting inhaled β2-agonists as needed. Thirty-six patients (97%) were treated with inhaled corticosteroids (702 ± 273 μg/d as expressed in equivalent dose of beclomethasone dipropionate) [mean ± SD]. Fifteen patients (41%) were receiving sustained-release theophylline. The clinical severity of asthma was classified according to the Global Initiative for Asthma: step 2 (mild persistent, n = 11), step 3 (moderate persistent, n = 22), and step 4 (severe persistent, n = 4). The duration of asthma ranged from 3 months to 33 years, with an average of 9.1 years. Allergic bronchopulmonary aspergillosis was excluded clinically and serologically in all patients.

Ten healthy subjects were studied as controls. None of the asthmatic or normal subjects had ever smoked cigarettes or had a history of tuberculosis or bacterial pneumonia. CT scans, pulmonary function tests, and induced sputum examinations were performed in this order within a period of 2 weeks. Sputum induction was not done in control subjects. The study was approved by the Ethics Committee at our institution, and written informed consent was obtained from all participants.

**Radiologic Evaluation**

CT scans were performed with a Toshiba X-Vigor CT scanner (Toshiba; Tokyo, Japan). Axial HRCT sections with 3-mm collimation were acquired at 20-mm intervals from the apex to the dome of the diaphragm, at 120 kV, 200 mA, and a scan time of 1.0 s. All scans were obtained at full inspiration, and the images were obtained at a window level of –700 Hounsfield units and a window width of 900 Hounsfield units. All slices of the right lung (12 slices) were used for the measurement. The calculated radiation dose was approximately 1.8 to 1.9 millisieverts. The number of dilated bronchi was counted on printed HRCT films for all assessable cross sections of segmental, subsegmental, and smaller bronchi.

BD was considered present if the bronchial lumen was larger than the cross-section of the accompanying pulmonary artery. If bronchi or adjacent arteries were branching or not clearly identified, they were excluded from analysis. CT scans were evaluated by three respiratory physicians who were blinded to the clinical data. Discrepancies were resolved by consensus of at least two physicians. We did not assess the prevalence of varicose or cystic bronchiectasis, because longitudinal CT scans of bronchi could not be frequently obtained, and such findings were too rare for analysis.

The prevalence of BD was evaluated on the basis of two indices: whether the subject had at least one or more dilated bronchi, and the ratio of dilated bronchi to all assessable bronchi in each subject (individual BD%).

HRCT scanning was repeated in 19 asthmatic patients at an interval of 247 ± 59 days, when they were in stable condition, to clarify whether BD is a transient phenomenon or a persistent pathologic finding. The presence or absence of dilated bronchi was assessed in each patient. In addition, a subset of airways that could not be frequently obtained, and such findings were too rare for analysis.

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**Induced-Sputum Production and Processing**

Sputum induction and processing were performed as described by Pin et al., with slight modification. Briefly, the subjects were premedicated with inhaled salbutamol (200 μg) and inhaled hypertonic (3%) saline solution, administered for 15 min by means of an ultrasonic nebulizer (MU-32; Azwell; Osaka, Japan). Patients were then asked to cough sputum into a plastic Petri dish.

All adequate plugs of sputum were separated from saliva and weighed. The plugs were treated with 0.1% dithiothreitol (Sputasol; OXOID; Hampshire, UK), two times the weight (milligrams) of the sputum sample, and then treated with the same volume of Dulbecco phosphate-buffered saline solution (PBS). After centrifugation at 1,000g for 10 min, the supernatants were collected and stored at –80°C.

The cell pellet was resuspended in PBS. The total cell count, excluding squamous cells, was determined with a standard hemocytometer and expressed as cell count times 10^7/grams wet-weight sputum. Then the cells were centrifuged and stained by the May-Grünwald-Giemsa method. Cell differential counts were determined by counting at least 400 nonsquamous cells.
Measurement of MMP-9 and TIMP-1 Levels in Sputum Supernatants

MMP-9 and TIMP-1 levels were measured with commercially available enzyme-linked-immunosorbent assay (ELISA) kits (MMP-9 and TIMP-1 Kit: Fuji Chemical Industries; Toyama, Japan). The MMP-9 ELISA recognizes human pro-MMP-9 (92 kd), intermediate MMP-9 (83 kd), and their complexes with TIMP-1 at the same immunoreactivity. The TIMP-1 ELISA recognizes free TIMP-1 and TIMP-1/MMPs complexes. The assay detection limit was 3.1 ng/mL for MMP-9 and 1.2 ng/mL for TIMP-1.

Zymography

MMPs present in sputum were detected by their capacity to degrade gelatin as described previously.21 Zymography on sodium dodecylsulfate-gelatin was used to determine the levels of gelatinase activity in the sputum samples. Each supernatant obtained from sputum was diluted (1:3) with PBS, and 30 μL of the sample was subjected to electrophoresis and further processing.

Pulmonary Function

FEV₁, FEV₁/FVC, and mid-forced expiratory flow (FEF₂₅₋₇₅%) were measured with the use of a Chestac-65V unit (Chest; Tokyo, Japan).

Statistical Analysis

Values are expressed as means ± SD or medians (range). Comparisons between groups were made with the unpaired t test, Mann-Whitney U test, or Fisher exact probability test. Correlations between data were analyzed by Spearman rank correlation test; p < 0.05 indicated statistical significance.

RESULTS

Comparison of Asthmatic Patients and Control Subjects

The characteristics of the asthmatic and control subjects are shown in Table 1. Age and sex did not differ between the two groups. The asthmatic patients had more obstructive airways than the control subjects, as demonstrated by lower FEV₁/FVC and FEF₂₅₋₇₅% values. The two indices used to evaluate the prevalence of BD were both significantly higher in the asthmatic patients than in the control subjects (Table 1, Fig 1). Figure 2 shows representative CT images obtained from a control subject and an asthmatic patient.

Sputum Analysis

Figure 3 shows examples of the results of zymography for an asthmatic patient and a healthy control subject. The major band of enzymatic activity was present at 92 kD, which corresponds to pro–MMP-9.21,22

Sputum MMP-9 and TIMP-1 levels in the asthmatic patients were 552.8 ± 385.7 ng/mL and 742.9 ± 479.1 ng/mL, respectively. The molar ratio of MMP-9 to TIMP-1 was 0.29 ± 0.19. Sputum MMP-9 levels correlated significantly with the number of neutrophils in sputum (r = 0.44, p < 0.01), but not with the numbers of macrophages, eosinophils, lymphocytes, or epithelial cells (data not shown). Sputum TIMP-1 levels were unrelated to the numbers of any of these cells (data not shown).

Relation Between the Presence or Prevalence of Dilated Bronchi and Clinical or Sputum Indexes in Asthmatic Patients

The characteristics of the asthmatic patients with and those without BD are shown in Table 2. The two

| Table 1—Characteristics of Asthmatic and Control Subjects* |
|-----------------------------|-----------------------------|-----------------------------|
| Characteristics            | Asthma (n = 37) | Control (n = 10) | p Value |
| Age, yr                    | 54 ± 17          | 49 ± 12          | 0.32    |
| Male/female gender, No.    | 17/20            | 2/8              | 0.17    |
| FEV₁, % predicted          | 96 ± 20          | 98 ± 6           | 0.79    |
| FEV₁/FVC, %                | 74 ± 11          | 85 ± 5           | 0.042   |
| FEF₂₅₋₇₅%, % predicted     | 62 ± 30          | 90 ± 24          | 0.031   |
| Evaluated bronchi, No.     | 12 (9–18)        | 10 (6–14)        | 0.051   |
| Individual BD%, % (range)  | 7.7 (0–75)       | 0 (0–9.1)        | 0.011   |

*Data are presented as mean ± SD unless otherwise indicated. BD + vs BD −.

Figure 1. The individual BD% in the asthmatic and control groups.
groups did not differ with regard to any of the clinical or sputum indices studied. The individual BD% was also unrelated to these indexes when all asthmatic patients (n = 37) were analyzed. The individual BD% did not correlate with sputum levels of MMP-9 ($r = -0.03$, $p = 0.86$), TIMP-1 ($r = 0.15$, $p = 0.36$), or their molar ratio ($r = -0.23$, $p = 0.18$) [other data not shown].

When analysis was confined to patients with one or more dilated bronchi (n = 23), however, individual BD% showed a significant positive correlation with the asthma severity score (Fig 4). No other index was related to individual BD% in this subgroup (data not shown).

Repeated CT Evaluation in Asthmatic Patients

Among the 19 patients who underwent follow-up CT evaluation, 10 patients had at least one dilated bronchi at the initial CT examination (BD +), whereas 9 patients did not have dilated bronchi (no BD [BD –]). The interval between the two HRCT scans was 262 ± 91 days in the BD + group and 229 ± 77 days in the BD – group ($p = 0.78$). Nine of the 10 patients who were initially BD + remained BD + at follow-up, and 8 of the 9 patients who were initially BD – remained BD –. A total of 32 pairs of “identical” bronchi were compared. Among 15 bronchi that were initially dilated, 13 remained dilated and 2 were undilated at the follow-up examination. Among 17 bronchi that were initially undilated or normal, 16 remained undilated or normal; only 1 bronchus was dilated at follow-up.

**DISCUSSION**

As reported by others, we showed that BD on HRCT was more common in asthmatic patients than in healthy control subjects. Individual BD% correlated with the severity of asthma in patients with at least one or more dilated bronchi. Contrary to our hypothesis, however, the prevalence of BD was not related to the sputum level of MMP-9 or the MMP-9/TIMP-1 molar ratio.

Several authors have examined the prevalence of BD on HRCT in asthmatic patients and healthy subjects.3,4,7 They used the same definition of BD as we used, which compares the luminal area of bronchi with the cross-section of the accompanying pulmonary artery.3,27 Lynch et al3 reported that 77% of

![Figure 2. Representative HRCT images (right lower lobe) of (top) a control subject and (bottom) a patient with asthma.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22007/)
asthmatic patients and 59% of healthy control subjects had one or more dilated bronchi. The presence or absence of BD in asthmatic patients was not related to clinical characteristics such as age, pulmonary function, or medication. Park et al. demonstrated that one or more dilated bronchi were present at a prevalence of 31% in asthmatic patients as compared with 7% in healthy subjects (\( p < 0.001 \)). However, the presence or absence of BD was not related to the degree of airflow obstruction in the asthmatic patients. Paganin et al. showed that one or more dilated bronchi or cylindrical bronchiectasis was present in 32 of 57 asthmatic subjects (56%) and in none of 10 normal control subjects. Another study by the same authors failed to show a relation of this finding to the severity of asthma. Harmanci et al. reported an association between an increased severity of asthma and a higher prevalence of bronchiectasis (cylindrical, varicose, or cystic) as assessed by HRCT. This finding of HRCT was observed in 8 of 18 patients (44%) with severe asthma. Healthy control subjects were not included in their study. We have confirmed that the prevalence of BD in patients with asthma was higher than that in healthy control subjects, and suggested that BD may be related to the severity of disease. The different prevalences of BD among these studies may have resulted from differences in the window settings used for HRCT scanning, incomplete and varying techniques for HRCT, especially the technical parameters, or differences in the clinical severity of asthma.

We examined whether BD was consistently found in 19 patients, examined at a mean interval of 8 months. The presence or absence of at least one dilated bronchus was consistently confirmed at the two examinations in 17 patients. Among 15 bronchi that were initially dilated, 13 remained dilated at follow-up. These results indicate that BD in asthma

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**Table 2—Characteristics of Asthmatic Subjects With and Without BD***

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BD +</th>
<th>BD −</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>23</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>58 ± 15</td>
<td>48 ± 20</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of asthma, yr</td>
<td>7 ± 8</td>
<td>12 ± 9</td>
<td>0.10</td>
</tr>
<tr>
<td>Atopy/no atopy, No.</td>
<td>12/11</td>
<td>11/3</td>
<td>0.17</td>
</tr>
<tr>
<td>Log IgE, IU/L</td>
<td>2.3 ± 0.7</td>
<td>2.4 ± 0.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Severity score (1–4)</td>
<td>2 (2–4)</td>
<td>2 (2–4)</td>
<td>0.83</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>99 ± 21</td>
<td>88 ± 17</td>
<td>0.08</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>74 ± 19</td>
<td>74 ± 11</td>
<td>0.34</td>
</tr>
<tr>
<td>FEF₂₅–₇₅%, % predicted</td>
<td>63 ± 30</td>
<td>56 ± 27</td>
<td>0.37</td>
</tr>
<tr>
<td>Sputum indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils, ( \times 10^⁷/g )</td>
<td>16.6 ± 49.2</td>
<td>11.5 ± 2.7</td>
<td>0.71</td>
</tr>
<tr>
<td>Eosinophils, ( \times 10^⁷/g )</td>
<td>7.8 ± 13.7</td>
<td>8.4 ± 20.7</td>
<td>0.92</td>
</tr>
<tr>
<td>MMP-9, ng/mL</td>
<td>534 ± 374</td>
<td>385 ± 416</td>
<td>0.70</td>
</tr>
<tr>
<td>TIMP-1, ng/mL</td>
<td>810 ± 511</td>
<td>632 ± 415</td>
<td>0.28</td>
</tr>
<tr>
<td>MMP-9/TIMP-1 molar ratio</td>
<td>0.26 ± 0.20</td>
<td>0.33 ± 0.16</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.

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**Figure 3. A representative zymographic analysis of sputum supernatants obtained from an asthmatic patient and a control subject.**

**Figure 4. Relationship between the severity score of asthma and individual BD% in patients with one or more dilated bronchi.**
is a persistent or fixed pathologic finding and may be considered a structural change or remodeling. Our results may be consistent with those of Paganin et al., who showed that cylindrical or varicose bronchiectasis was not reversible after 2 weeks of treatment with systemic corticosteroids in 10 asthmatic patients with acute exacerbation.

Imbalance between MMP and TIMP activities has been implicated in a number of pathologic conditions. The messenger RNA expression of MMPs and the MMPs/TIMPs ratio of messenger RNA expression are significantly higher in tissue of abdominal aortic aneurysms than in normal aorta. MMP-9 messenger RNA expression is also significantly higher in moderate-diameter aneurysms than in small aneurysms. MMPs may thus play a role in the development of abdominal aortic aneurysms, possibly by degrading extracellular matrix with consequent tissue thinning and luminal dilatation. Zheng et al. reported that patients with bronchiectasis have significantly higher densities of MMP-8-positive and MMP-9-positive cells in the lamina propria of the airways than control subjects. Moreover, Sepper et al. found that MMP-8 and MMP-9 are overexpressed in BAL fluid obtained from patients with bronchiectasis. The activity of these MMPs strongly correlates with disease severity. Delacourt et al. also showed a relation between free gelatinolytic activity in sputum supernatant and disease severity in patients with cystic fibrosis. These results indicate a causal relationship between the overexpression of MMPs and airway destruction in ectatic airway diseases. In asthmatic patients, absolute increases in TIMP-1 or relative excess of TIMP-1 over MMP-9 is associated with chronic airflow obstruction. This association is attributed to airway fibrosis or deposition of extracellular matrix, similar to other disorders characterized by tissue fibrosis.

Since MMP-9 and TIMP-1 levels in sputum and their molar ratio vary considerably among patients with asthma, we hypothesized that patients who show relatively higher titers of MMP-9 or higher MMP-9/TIMP-1 ratios may be more prone to BD. However, we found no relation between the prevalence of BD and sputum MMP-9 and TIMP-1 levels, their molar ratio, or inflammatory-cell differential count.

The increased prevalence of BD in more severe asthma, which Harmanci et al. and we have demonstrated, is not easy to interpret. BD may be induced by intense airway inflammation with consequent tissue destruction or remodeling. It thus could merely be an epiphenomenon of severe asthma. However, destructed and dilated airways might be less elastic and more collapsible when exposed to certain stimuli, leading to more severe disease. We had expected that excess MMP-9 could explain this scenario, but our results do not support this hypothesis. More local sampling of airway constituents, such as those obtained by BAL, might have revealed a positive relationship. Another possibility is that BD might be triggered by a different mechanism, and the MMP-9 and TIMP-1 step might become important at a later stage of the disease.

Our study had several limitations. Since nearly all asthmatic subjects were receiving inhaled corticosteroids, the levels of MMP-9 and TIMP-1 might have been affected, although some authors negate this possibility. We used a qualitative method to assess BD on HRCT. Although this was a standard method used in most previous studies, pulmonar artery diameter may be affected by blood volume or local hypoxia. These factors might lead to misinterpretation of results. Because 3-mm collimation was used in our study, smaller bronchi and adjacent vessels might not have been precisely displayed. However, when the airways were separately analyzed according to their luminal diameter (≥4 mm or <4 mm), larger and smaller bronchi both showed a significantly or marginally higher prevalence of BD in asthmatic patients as compared with control subjects (data not shown). In patients with bronchiectasis, HRCT with 3-mm to 4-mm collimation shows excellent diagnostic accuracy when findings of bronchography are used as the “gold standard” for diagnosis of bronchiectasis or BD. Such validation studies are difficult to perform in asthmatic patients because of the potential risk of bronchoconstriction being induced by bronchography. Moreover, other proteases, such as neutrophil elastase, should have been examined. However, the number of sputum neutrophils, the cellular source of this proteolytic enzyme, was unrelated to the prevalence of BD in our study.

In conclusion, BD as assessed by HRCT is more prevalent in asthmatic patients than in healthy subjects. BD in asthma might be related to the severity of disease, but its pathogenesis and pathophysiologic relevance remain controversial. Longitudinal studies of inflammatory indices in sputum and the development of BD may shed further light on the roles of these phenomena in the pathophysiology of asthma.

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