
Risk factors related to fixed airway obstruction in patients with asthma after antiasthma treatment

An-Soo Jang, MD, PhD; June-Hyuk Lee, MD, PhD; Sung Woo Park, MD, PhD; Jong-Sook Park, MD; Do-Jin Kim, MD, PhD; and Choon-Sik Park, MD, PhD

Background: There are many unanswered questions about the role of airway remodeling in asthma.

Objective: To evaluate the physiologic factors related to airway remodeling after antiasthma drug treatment for 1 year.

Methods: We gave 582 patients with asthma long-term control medication for 1 year according to the severity of their asthma. Airway remodeling was defined using forced expiratory volume in 1 second/forced vital capacity and a predicted forced expiratory volume in 1 second of less than 75% after antiasthma treatment.

Results: Of the 582 patients, 49 (8.4%) had airway remodeling. Severe asthma resulted in more airway remodeling than mild-to-moderate asthma. Asthmatic patients with airway remodeling were significantly older and had a longer duration of asthma. Asthmatic patients with airway remodeling had more emphysema on high-resolution computed tomography, a higher rate of near-fatal asthma attacks, a lower percentage of sputum eosinophils, a lower atopy frequency, a greater response to short-acting bronchodilators, and a lower body mass index (BMI) than those without airway remodeling. Age, asthma duration, and BMI were important discriminators of airway remodeling.

Conclusion: Nonatopy, asthma duration, emphysema on high-resolution computed tomography, sputum eosinophils, age, and BMI before antiasthma treatment are important factors related to airway remodeling in patients with asthma.

Ann Allergy Asthma Immunol. 2007;99:408–412.

INTRODUCTION

Airway remodeling involves long-term structural airway changes, including goblet cell metaplasia, the deposition of extracellular matrix in the submucosa, smooth muscle cell hypertrophy/hyperplasia, and hyperplasia of fibroblasts/myofibroblasts. Airway remodeling plays an important role in the pathogenesis of asthma phenotypes, such as airway hyperresponsiveness (AHR) and airway inflammation, in patients with asthma.^{1–4}

Airway remodeling is linked to AHR via diverse triggers and a steeper trajectory of the long-term decrease in lung function in asthmatic patients.⁵ Histologic examination is essential in the evaluation of remodeling. Examinations of autopsied or resected lung have enabled detailed morphologic and morphometric studies and have provided fundamental knowledge of airway remodeling in asthma. However, such materials are available only fortuitously, and clinical information may often be insufficient in autopsied cases. Bronchoscopic mucosal biopsy has been widely used since the 1980s and has contributed substantially to basic investiga-

tions of inflammation and remodeling. Nevertheless, such specimens are limited in size and depth and are restricted to the central airways, and the procedure might be too invasive to be repeated. Remodeling can also be evaluated indirectly. Pulmonary function tests to evaluate chronic airflow obstruction are available in a clinical setting and are suitable for screening or mass studies, although the results may be affected by concomitant disease or short-term asthma control.

High-resolution computed tomography (HRCT) has recently been used to evaluate remodeling. It cannot discern pathologic details, but it provides a broader range of airway/lung morphologic features and is less invasive than biopsy.^{6,7} Eosinophils contribute substantially to airway remodeling but are not obligatory for allergen-induced lung dysfunction.⁸ Although current therapies targeting airway inflammation and AHR effectively relieve and prevent symptoms in most patients, some patients experience persistent symptoms and a progressive decline in lung function, described as irreversible or refractory asthma.

Although several studies^{6,7,9–11} have suggested the association between structural changes and disease severity, the relationship between the actual extent of remodeling and pulmonary function decreasing has still to be well defined. Furthermore, pulmonary function testing still has to be defined as the ideal functional marker of remodeling before and after antiasthma treatment. Therefore, arbitrarily manifested airway remodeling as a functional marker was defined by forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) and a predicted FEV₁ of less than 75%. The

Asthma and Allergy Research Group, Division of Allergy and Respiratory Diseases, Soonchunhyang University Hospital, Bucheon, Republic of Korea. Authors have nothing to disclose.

This work was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (01-PJ3-PG6-01GN04-003).

Received for publication September 25, 2006.

Received in revised form September 29, 2006.

Accepted for publication April 25, 2007.

aims of this study were (1) to estimate the effects of individual factors in terms of airway remodeling after 1 year of treatment with a recommended antiasthma drug according to asthma severity in patients with asthma and (2) to identify the factors that determine airway remodeling.

METHODS

Patients

We enrolled patients who visited the Department of Allergy and the Respiratory Department of Soonchunhyang University Hospital, Bucheon, Republic of Korea, because of asthma, defined as 1 or more asthma symptoms, and whose physical examination findings were compatible with the American Thoracic Society's definition of asthma.¹² Each patient showed airway reversibility, as documented by a positive bronchodilator response with a greater than 15% increase in FEV₁ or airway hyperreactivity to less than 10 mg/mL of methacholine.¹² The exclusion criteria included greater than 10 pack-years of smoking, younger than 20 years or older than 70 years, parenchymal lung disease apparent on chest radiography, diffusing capacity less than 80%, severe uncontrolled diabetes mellitus, and renal, hepatic, or cardiac failure. This study was performed with the approval of the ethics committee of Soonchunhyang University Hospital, and written informed consent was obtained from all the study participants.

Study Intervention

Study patients received long-term control medication consisting of inhaled glucocorticoids or inhaled glucocorticoids plus long-acting inhaled β_2 -agonists or sustained-release theophylline or a leukotriene modifier or oral glucocorticoids according to Global Initiative for Asthma guidelines¹³ and rapid-relief medication consisting of 2 puffs of inhaled salmeterol (100 μ g per dose) and 2 puffs of inhaled ipratropium bromide (20 μ g per dose) on an as-needed basis. Airway remodeling as a functional marker of remodeling was defined as FEV₁/FVC and a predicted FEV₁ of less than 75%. We also evaluated the effects of emphysema evident on chest radiographs or HRCT, near-fatal asthma attacks, asthma duration, atopy, sex, age, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) after antiasthma treatment for 1 year.

Lung Function Tests

Baseline FVC and FEV₁ measurements were obtained in the absence of recent bronchodilator use (within 8 hours) and were selected according to the American Thoracic Society criteria.¹² Basal and postbronchodilator FEV₁, FVC, and forced expiratory flow between 25% and 75% were measured between 1 and 4 PM. AHR was measured using methacholine challenge and was expressed as the provocation concentration that caused a decrease in FEV₁ of 20%, in noncumulative units.¹⁴

Sputum Examination

Sputum was induced using isotonic saline that contained a short-acting bronchodilator, as described by Norzila et al.¹⁵ Samples were treated within 2 hours of collection using the method of Pizzichini et al.¹⁶ with a minor modification. Briefly, all of the visible portions with greater solidity were carefully selected and placed in a preweighed Eppendorf tube. The samples were treated by adding 8 volumes of 0.05% dithiothreitol (Sputolysin; Calbiochem, San Diego, California) in Dulbecco phosphate-buffered saline. One volume of protease inhibitor (0.1M EDTA and 2 mg/mL of phenylmethylsulfonylfluoride) was added to 100 volumes of homogenized sputum, and the total cell count was determined by using a hemocytometer. The homogenized sputum was spun in a cytocentrifuge, and 500 cells were read on each sputum slide stained with Diff-Quick solution (American Scientific Products, Chicago, Illinois).

Allergy Skin Prick Tests

Allergy skin prick tests were performed using commercial inhalant allergens, which included dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) (CL Bencard, Devon, England) and histamine (1 mg/mL). None of the participants had received antihistamines orally in the 3 days preceding the study. All the tests included positive (1 mg/mL of histamine) and negative (diluent) controls. After 15 minutes the mean diameter of the wheals formed by the allergens was compared with that formed by histamine. When the former was the same size as or larger than the latter (allergen-histamine ratio ≥ 1.0), the reaction was deemed positive. Atopy was determined by the presence of an immediate skin reaction to 1 or more aeroallergens, as described previously.¹⁷

Statistical Analysis

The data were double-entered into a computer program (SPSS version 10.0; SPSS Inc, Chicago). Data are expressed as mean $\pm$ SEM. Descriptive statistics, frequency tables, and χ^2 tests were used. Multivariate logistic regression analysis with a stepwise selection method at $P < .05$ for entry into the model was used to obtain the independent effects of factors showing significant associations with airway remodeling despite antiasthma treatment for 1 year. $P < .05$ was considered statistically significant.

RESULTS

Airway remodeling as a functional marker of remodeling was defined as FEV₁/FVC and a predicted FEV₁ of less than 75%. Of 582 patients with asthma according to the guidelines of the Global Initiative for Asthma,¹³ 49 (8.4%) had airway remodeling (Table 1). Moderately to severely asthmatic patients had more airway remodeling than mildly asthmatic patients (mild vs moderate vs severe: airway remodeling group, 1 vs 14 vs 34; non-airway remodeling group, 376 vs 101 vs 56; $P < .001$, Table 1). Asthmatic patients with airway remodeling were significantly older and had a longer duration of asthma (50.8 ± 1.48 vs 44.1 ± 0.58 years and 12.2 ± 1.59 vs $5.30 \pm$

Table 1. Characteristics of 582 Patients With Asthma Before Treatment According to Airway Remodeling^a

Characteristics	Airway remodeling	
	Yes (n = 49)	No (n = 533)
Sex, M/F, No.	16/33	146/387
Severity, mild/moderate/severe, No.	1/14/34 ^b	376/101/56
Age, y	50.8 ± 1.48 ^b	44.1 ± 0.58
BMI	23.3 ± 0.38 ^c	24.2 ± 0.19
FEV ₁ , % predicted	60.0 ± 2.77 ^b	87.7 ± 0.92
FEV ₁ /FVC	63.1 ± 1.7 ^b	78.3 ± 0.46
FEF _{25%-75%}	38.8 ± 3.6 ^b	75.5 ± 1.95
Atopy, %	32.8 ^c	46.9
Duration of asthma, y	12.2 ± 1.59 ^b	5.3 ± 0.34
PC ₂₀ , mg/mL	8.45 ± 3.1	8.25 ± 0.79
Blood eosinophils, %	4.65 ± 0.58	4.55 ± 0.22
Sputum eosinophils, %	2.49 ± 0.67 ^c	5.6 ± 0.66
Total IgE, U	263.9 ± 59.8	313.6 ± 28.2

Abbreviations: BMI, body mass index; FEF_{25%-75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PC₂₀, provocation concentration of methacholine that caused a decrease in FEV₁ of 20%.

^a Data are given as mean ± SEM except where noted otherwise.

^b *P* < .001 compared with patients without airway remodeling.

^c *P* < .05 compared with patients without airway remodeling.

0.34 years, respectively; *P* < .001). Asthmatic patients with airway remodeling also had fewer sputum eosinophils (2.49% ± 0.67% vs 5.6% ± 0.66%; *P* < .032) and lower atopy (32.8% vs 46.9%; *P* < .05). Asthmatic patients with airway remodeling had more emphysema on HRCT (4/14 vs 2/54; *P* < .001), more near-fatal asthma attacks (3/73 vs 4/513; *P* < .05), and a greater postbronchodilator response (34/73 vs 108/513; *P* < .001) than asthmatic patients without airway remodeling (Table 2). Asthmatic patients with airway remodeling had a lower BMI than those without airway remodeling (23.3 ± 0.38 vs 24.2 ± 0.19; *P* < .05). Logistic regression was used to model the association between airway remodeling and no airway remodeling in patients with asthma while

Table 2. Comparison of Airway Remodeling Rates by Possible Predictors of Airway Remodeling

	Airway remodeling, No./total No. (%)	<i>P</i> value ^a
Emphysema on HRCT		
Yes	11/41 (26.8)	.001
No	9/92 (9.8)	
Near-fatal asthma		
Yes	3/73 (4.1)	<.05
No	4/513 (0.8)	
Postbronchodilator response		
Yes	34/73 (46.6)	<.001
No	108/513 (21.1)	

Abbreviation: HRCT, high-resolution computed tomography.

^a By χ^2 test.

adjusting for potential confounders. A main-effects model that included risk factors for asthma, such as age, asthma duration, BMI, and sputum eosinophils, was fit initially. In a multiple logistic regression model, independent associations with airway remodeling were seen with age (odds ratio [OR], 1.037; 95% confidence interval [CI], 1.009–1.066; *P* = .008), asthma duration (OR, 1.052; 95% CI, 1.022–1.083; *P* = .001), and BMI (OR, 0.891; 95% CI, 0.807–0.984; *P* = .02) but not with sputum eosinophils (OR, 0.976; 95% CI, 0.934–1.019; *P* = .27). The results show that age, asthma duration, and BMI were important discriminators of airway remodeling.

DISCUSSION

These results support the hypothesis that airway wall remodeling contributes to airway narrowing, which is a characteristic abnormality in asthma. Age, atopy, duration of asthma, emphysema, sputum eosinophils, and obesity are important risk factors for fixed airway obstruction and airway remodeling.

The process of aging and prolonged exposure to disease effects are important factors in determining the functional characteristics of chronic asthma. In particular, aging is associated with not only reduced acute responsiveness to bronchodilators but also a reduced slope of the relationship between duration and mean FEV₁ attainable after treatment, suggesting a slowing of the rate of loss of reversibility of uncertain biological meaning.¹⁸ Aging contributes to increased variability in airway caliber in asthma. Aged patients are potentially at risk because functional evidence of nocturnal asthma may frequently be accompanied by poor subjective awareness.¹⁹ Serum levels of interferon- γ were associated with the subsequent rate of change in lung function among asthmatic patients in a cohort of middle-aged and older men.²⁰ In the present study, asthmatic patients with airway remodeling were older than those without airway remodeling, suggesting that aging is a risk factor related to severe asthma and airway remodeling, in agreement with previous studies.^{18–23} In addition, asthmatic patients with airway remodeling had a higher prevalence of near-fatal asthma attacks than those without airway remodeling, indicating that airway remodeling is an important risk factor for severe asthma.

The presence of atopy was not a significant risk factor for airway remodeling, despite a trend toward increased atopy in study members with a persistent low ratio.²³ In contrast to a previous study,²³ we found that nonatopy was a risk factor for airway remodeling. Airway and alveolar inflammation have been described in asthma. Prolonged inflammation may lead to airway remodeling, which can result in physiologic abnormalities. The duration of asthma is associated with the degree of airflow limitation and hyperinflation. Furthermore, these abnormalities can become irreversible across time and may reflect distal airway or parenchymal changes and proximal airway remodeling.^{18,24} There is an increase in airway wall area, including smooth muscle, and airway narrowing with

increasing duration of severe asthma or with older age.²⁵ The present study is in agreement with previous studies^{24,25} in finding that the duration of asthma is an important risk factor for airway remodeling and severe asthma.

Airway reactivity was negatively correlated with airway wall thickness, indicating that airway wall thickening attenuates airway reactivity in patients with asthma.²⁶ Laprise et al²⁷ reported increased subepithelial fibrosis and an increased number of cytokines in individuals with asymptomatic AHR before asthma had developed. Rather than considering AHR as a marker of asthma, it might be regarded as a parallel pathologic process.²⁸ In the present study, AHR was not related to airway remodeling, indicating that AHR is not a marker of airway remodeling or severe asthma before asthma treatment.

Humbles et al⁸ reported that increases in AHR and mucous secretion in mice with total ablation of the eosinophil lineage were similar to those observed in wild-type mice, whereas eosinophil-deficient mice were significantly protected from peribronchiolar collagen deposition and increases in airway smooth muscle. Those results suggested that eosinophils contribute substantially to airway remodeling but are not obligatory for allergen-induced lung dysfunction. The present finding that the airway remodeling group had fewer sputum eosinophils suggests that eosinophils are markers for asthma therapy that suppresses airway inflammation. Further studies are needed to clarify the role of airway remodeling. Neutrophils may be involved in the airway remodeling process in asthmatic patients.^{29,30} Although the airway remodeling group had more sputum neutrophils (data not shown), they were not a risk factor for airway remodeling in the logistic regression model. The role of neutrophils in airway remodeling remains to be determined.

Airway distensibility is related to airway remodeling, such as reticular basement thickening and airflow limitation.³¹ The airway is exposed to a variety of mechanical stimuli, the most prominent of which is the acute compressive stress caused by bronchoconstriction. The folding of the airway wall into a rosette pattern during bronchoconstriction creates a complex stress field, with the greatest stresses compressing the epithelial layer at the inner surface of the airway wall. The epithelial cells lining the airway possess the capacity to modulate the inflammatory environment of the airway wall and produce factors that affect the recruitment, proliferation, and activity of fibroblasts and smooth muscle cells. These findings suggest that mechanical stress contributes to remodeling of the asthmatic airway.³² We found that asthmatic patients with postbronchodilator responses had higher rates of airway remodeling than those without postbronchodilator responses, which suggests that the tone of the airway smooth muscle is an important factor in determining airway remodeling.

Recently, CT been used to evaluate remodeling. Although it cannot discern pathologic details, CT provides a broader range of airway/lung morphologic features and is less invasive than biopsy. In addition to classic subjective evaluations, quantitative evaluation has been reported for central airway

dimensions, such as the airway wall area, luminal area, and wall thickness, and for peripheral airway abnormalities or air trapping, as measured by decreased lung attenuation or increased mosaic perfusion.^{6,7,9} Abnormal HRCT findings are more prominent with increased severity of asthma, decreased FEV₁ values, and a longer duration of asthma.¹⁰ Asthmatic patients with airway remodeling had a higher rate of emphysema evident on HRCT than those without airway remodeling, suggesting that emphysema on HRCT is an important risk factor for severe asthma and airway remodeling.

Changes in airway structure and function have been associated with obesity.³³ Studies have produced inconsistent findings regarding the association of AHR and obesity. Litonjua et al³⁴ reported an association between increased BMI and the onset of AHR in a longitudinal study of aging in male subjects in the United States. Two other large cross-sectional studies^{35,36} confirmed these observations. Asthmatic patients with airway remodeling had a lower BMI than those without airway remodeling, suggesting that severely asthmatic patients have decreased food intake, which contributes to loss of body weight and decreased pulmonary function.

Current strategies for managing asthma focus on suppressing airway inflammation. Other characteristic features of human asthma, such as AHR and the structural changes collectively referred to as airway remodeling, are largely ignored in existing guidelines for monitoring the effectiveness of treatment. Evidence is accumulating that pharmacologic therapy targeting airway wall remodeling is valuable in treating asthma. However, the development of appropriate therapeutic agents requires a better understanding of the pathogenesis of remodeling, which seems to be regulated by a variety of cytokines and growth factors produced by inflammatory, epithelial, and stromal cells.³⁷

In summary, these data suggest that long-standing asthma results in irreversible decrements in lung function, which may manifest as airway remodeling. Based on multiple physiologic outcomes, the results of this study support the proposal that the development of fixed airway obstruction might result from airway remodeling caused by decades of persistent airway inflammation. Furthermore, these results suggest that prolonged asthma is associated with decreases in FEV₁/FVC and FEV₁, defined as airway remodeling. Long-term prospective studies correlating physiologic variables with histologic findings from lung biopsy samples are necessary to explore airway remodeling further.

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Requests for reprints should be addressed to:
 Choon-Sik Park
 Division of Allergy and Respiratory Diseases
 Department of Internal Medicine
 Soonchunhyang University Hospital
 1174, Jung-dong, Wonmi-gu
 Bucheon-si, Gyeonggi-do 420–767, Republic of Korea
 E-mail: mdcsppark@unitel.co.kr