

Original article

The importance of maximal airway response to methacholine in the prediction of wheezing development in patients with cough-variant asthma

Background: A significant proportion of patients diagnosed with cough-variant asthma eventually manifest classic asthma signs, such as wheezing and dyspnea. The aim of this study was to investigate whether the degree of airway hypersensitivity and/or the level of maximal airway response can predict the development of wheezing in subjects with cough-variant asthma.

Methods: At study initiation, a high-dose methacholine inhalation test was performed to measure provocative concentration causing a 20% fall (PC_{20}) in forced expiratory volume in 1 s (FEV_1) and maximal airway response. Each person was evaluated regularly every 3 months for 4 years and also on the occasion of wheezing being perceived for the first time.

Results: Of the 48 patients available in the follow-up period, 21 (Group 1) developed clinical wheezing, while 27 (Group 2) did not. There was no significant difference in PC_{20} levels between the two groups. The level of maximal airway response, however, was significantly higher in Group 1 than in Group 2. The score test for trend revealed a significant association between the future development of wheezing and the level of maximal airway response ($P = 0.007$), but not the level of methacholine PC_{20} ($P = 0.423$).

Conclusions: The level of maximal airway response, rather than the degree of airway hypersensitivity, may be an important risk factor for the future development of classic asthma in patients with cough-variant asthma.

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Most clinicians are familiar with coughing as a symptom of asthma, concomitant with wheezing and dyspnea. However, cough may be the sole presenting symptom of asthma (1). This type of asthma, cough-variant asthma, was initially described as uncommon, but it now appears that cough-variant asthma is one of the most common causes of chronic cough in children (2), as well as in adults (3).

Some studies have indicated that cough-variant asthma may be a forerunner of classic asthma, i.e. many patients who initially present with cough-variant asthma eventually manifest classic signs of asthma (4–6). Follow-up of such patients has shown that between one-third (4) and two-thirds (6) go on to develop episodic wheeze and dyspnea. However, it is not known which patients with cough-variant asthma are at greater risk of developing these signs.

Airway hyperresponsiveness (AHR), often called “the hallmark of asthma”, is known to be an important risk factor for the development of asthma (7) and to be indicative of asthma severity with respect to symptomatic asthma (8). AHR is also reported to be a marker for the

subsequent development of asthma in patients with allergic rhinitis (9). It is tempting therefore to speculate that the degree of AHR in patients with cough-variant asthma may be an indication of increased susceptibility to the development of classic asthma.

AHR is usually defined as an increased sensitivity of the airways to inhaled histamine or methacholine (10). The sensitivity of the airways to these agents is commonly expressed as the provocative concentration causing a 20% fall (PC_{20}) in forced expiratory volume in 1 s (FEV_1). However, there is accumulating evidence that AHR is a more complex functional abnormality that comprises more than just hypersensitivity (11). When exposed to high concentrations of inhaled histamine or methacholine, asthmatic patients show excessive narrowing of the airway, as reflected by an elevated or absent maximal response plateau. It can be argued that the latter is clinically a more relevant component of AHR than the former *per se* because it reflects the potential severity of airway obstruction in each individual (12).

The aim of this study was to investigate whether the degree of airway hypersensitivity and/or the level of

maximal airway response on the dose-response curve to methacholine can predict the development of wheezing in subjects with cough-variant asthma.

Material and methods

Children diagnosed with cough-variant asthma were recruited from the allergy and pulmonary clinic at Seoul National University Children's Hospital. Initially, they were referred to our clinic for chronic cough that had persisted for a minimum of 2 months (range: 9 weeks–2 years). The cough was usually dry or productive with a scant amount of clear sputum, and was mostly nocturnal. None of the patients had a history of wheezing or dyspnea, nor was any wheeze or prolonged expiratory phase detected on physical examination. At the time of diagnosis, all had a methacholine PC₂₀ level of less than 18 mg/ml. The children studied were similar to those with asymptomatic AHR (13), but differed in having chronic cough. Bronchodilators (inhaled, β_2 -agonists and/or oral theophylline) were effective against these coughs, but they recurred when the medication was stopped. Normal results were found for the following tests: chest radiograph, spirometry, sinus films, and tuberculin skin tests. No other apparent causes of cough were present. Skin prick test was performed, and atopy was defined by the presence of at least one positive reaction (>3 mm wheal diameter) with a battery of 12 common airborne allergens.

The study was performed between December 1996 and February 2001. At the start of the study, high-dose methacholine inhalation tests were performed to measure the maximal airway response as well as the PC₂₀ level. The patients had to be capable of performing pulmonary function tests in a reproducible way (i.e. a coefficient of variation of FEV₁ in three consecutive flow-volume curves of $<5\%$) and needed to have an FEV₁ of at least 70% of the predicted value (14). Given that most of our atopic patients were sensitized predominantly to house-dust mites, we decided to perform the bronchial provocation test during the winter (December to February), when the levels of house-dust mites are the lowest, and the least changing, in our country (15). None of the children had symptoms of upper respiratory infection in the month preceding the test. They were excluded from the study if they could not tolerate the test, or if their PC₂₀ level was ≥ 18 mg/ml.

For the follow-up, children were asked to attend the clinic every 3 months if possible for clinical assessment and medication adjustment. At each visit, they were questioned about symptoms and signs during the preceding period, and they underwent physical examination as appropriate. Additional examinations were performed when the child or the parents perceived wheezing for the first time. Wheezing was defined as a whistling sound coming from the chest but not the throat, which had been demonstrated in the procedure of the initial bronchial provocation test. The development of wheezing was considered confirmed in each child when the claims of subjective wheezing were verified by the physician's careful auscultation. During the study, the children were instructed to control their cough symptoms by minimal use of inhaled bronchodilators. Those who developed wheezing were treated with an intermittent bronchodilator, and some were also given inhaled cromolyn sodium or inhaled corticosteroid according to National Institute of Health (NIH) guidelines (16).

Methacholine inhalation test

High-dose methacholine inhalation tests were carried out using a modification of the method described by Chai et al. (17). The

methacholine solutions (Sigma Diagnostics, St. Louis, MD) were prepared at different concentrations (0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, 25, 50, 100, 150, 200 mg/ml) in buffered saline (pH 7.4). Lung function was measured with a computerized spirometer (Microspiro-HI 298, Chest, Tokyo, Japan), and the largest value of triplicate FEV₁ at each time was used for analysis. A Rosenthal-French dosimeter (Laboratory for Applied Immunology; Baltimore, MD), triggered by a solenoid valve set to remain open for 0.6 s, was used to generate the aerosol from a DeVilbiss 646 nebulizer (DeVilbiss Health Care, Somerset, PA), with pressurized air at 20 psi. Each child inhaled five inspiratory capacity breaths of buffered saline solution and increasing concentrations of methacholine at 5-min intervals. This gave an output of 0.009 ± 0.0014 ml (mean $\pm$ standard deviation) per inhalation. FEV₁ was measured 60–90 s after inhalation at each concentration level. The procedure ended when either FEV₁ fell below 50% of the post-saline value, or when a maximal response plateau had been established. This was considered to occur if three or more data points at the highest concentrations fell within a 5% response range (18). An additional 5 or 10 inhalations of the 200 mg/ml solution were taken if the last three data points of less than 50% FEV₁ fall did not satisfy the above criteria. For safety reasons, children were permitted to stop the challenge test if they felt too much discomfort. Response was expressed as the percentage fall in FEV₁ from the post-saline solution value, and was plotted against the log of the concentrations of inhaled methacholine. The resulting dose-response curves were characterized by their position and maximal response. Position was expressed as PC₂₀, which was calculated by log linear interpolation between two adjacent data points. Maximal response was defined as either the level of the maximal response plateau by averaging three consecutive points on the plateau, or as the last data point of the dose-response curve if a plateau could not be obtained.

The study was approved by the Hospital Ethics Committee, and the parents of all children gave their informed consent.

Statistical analysis

Results are expressed as mean $\pm$ SD unless otherwise stated. All PC₂₀ values were log-transformed before analysis and expressed as geometric mean and range of 1 SD. Values or prevalences of the two groups were compared by Student's *t*-test or the chi-square test. Score test for trend was used to evaluate potential relationships between the development of wheezing and either the levels of PC₂₀ or the maximal airway response. All analyses were made using STAT VIEW II (Abacus Concept, Berkeley, CA, USA) on a Macintosh computer (Apple Computer, Cupertino, CA, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

Of the 57 children enrolled in the study, nine were lost to follow-up in spite of every effort being made to continue the regular check-ups. Four patients dropped out of the study in the second year, three in the third year, and two in the fourth year. The characteristics of those who completed the study, and of those who dropped out, are summarized in Table 1. Those who developed wheezing during the course of follow-up ($n = 21$) were designated as Group 1, and those who did not ($n = 27$) were designated as Group 2. In Group 1, five children devel-

Table 1. Baseline characteristics of study groups at initiation

	Group 1	Group 2	Dropped-out
Number	21	27	9
Age (years)*	11.8 ± 2.1	11.1 ± 2.6	11.6 ± 3.2
Sex (M/F)	13/8	15/12	6/3
Atopy, n (%)	14 (66.7)	13 (48.1)	5 (55.5)
FVC (% predicted)†	96.7 (84.6–106.2)	98.1 (85.2–104.6)	95.4 (88.1–103.7)
FEV ₁ (% Predicted)†	98.0 (86.3–107.5)	97.5 (82.4–106.5)	96.7 (84.6–101.8)
FEV ₁ /FVC (%)†	88.1 (80.4–93.3)	87.8 (79.1–92.9)	88.4 (82.3–92.7)

* Mean ± SD.

† Mean (range).

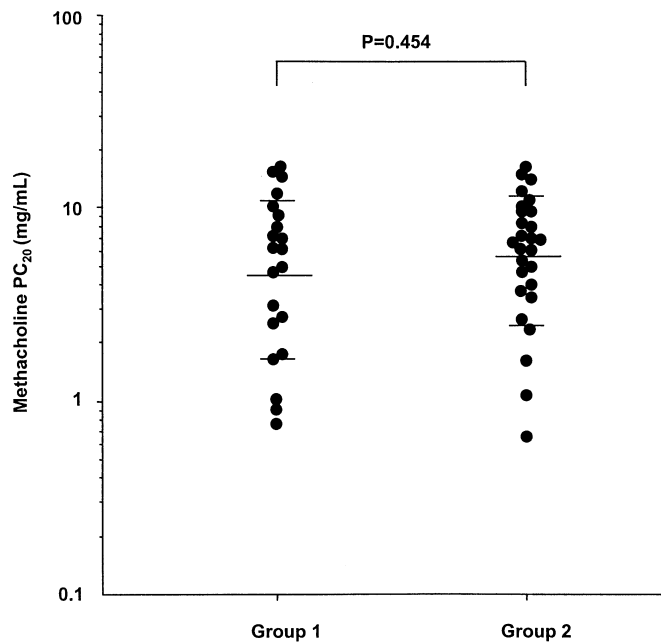
FEV₁, forced expiratory volume in 1 s.

Figure 1. Comparison of methacholine PC₂₀ level in children who developed wheezing during follow-up (Group 1, *n* = 21) and those who did not (Group 2, *n* = 27). Horizontal bars represent mean ± SD.

oped wheezing in the first year, seven in the second year, five in the third year, and four in the fourth year. In Group 2, 12 children continued to suffer from persistent cough for at least 2 weeks of every year, nine alternated between a “cough” year and a symptom-free year during the follow-up, and six were symptom-free during the last two or three years. The two groups did not exhibit any significant difference with respect to age, sex, prevalence of atopy, or spirometric values.

The levels of PC₂₀ (Fig. 1) and maximal airway response (Fig. 2) on the initial methacholine challenge test were compared between the two groups. There was no significant difference in PC₂₀ between Group 1 (geometric mean 4.57 mg/ml, range of 1 SD 1.78–11.75) and Group 2 (5.62 mg/ml, 2.57–12.30; *P* = 0.454). Twelve

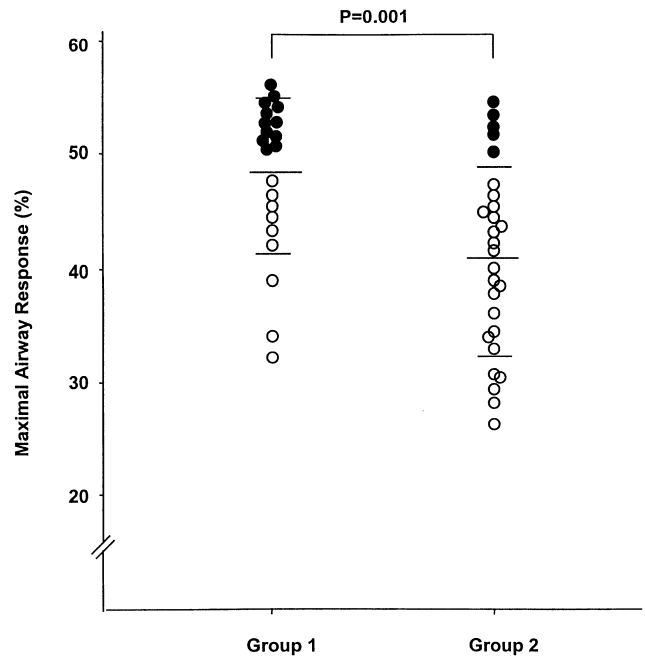


Figure 2. Comparison of maximal airway response to methacholine in children who developed wheezing during follow-up (Group 1, *n* = 21) and those who did not (Group 2, *n* = 27): (○) with a maximal response plateau; (●) with forced expiratory volume in 1 s (FEV₁) fall > 50% without a plateau. Horizontal bars represent mean ± SD.

children (57.1%) in Group 1 showed FEV₁ falls of more than 50% without evidence of plateau, compared to five (18.5%) from Group 2 (chi-square test, *P* = 0.006). When the percentage decline in FEV₁ at the end of the protocol in the children without a plateau was taken as the maximal response in order to allow comparison between all members of both groups, the level of maximal airway response was significantly higher in Group 1 (48.3 ± 6.8%) than in Group 2 (41.0 ± 8.1%; *P* = 0.001).

To evaluate further the association between the development of wheezing and either airway sensitivity or maximal response, the risk for developing wheezing was assessed with children classified according to the levels of PC₂₀ or maximal airway response (Fig. 3). In the analysis of groups with different levels of PC₂₀, five (62.5%) out of eight with moderate-to-severe hypersensitivity (PC₂₀ < 2 mg/ml) developed wheezing, compared to nine (39.1%) of the 23 who had mild hypersensitivity (2 mg/ml ≤ PC₂₀ < 8 mg/ml), and seven (41.2%) out of 17 with borderline hypersensitivity (PC₂₀ ≥ 8 mg/ml) (score test for trend *P* = 0.423). In the analysis of groups with different levels of maximal response, 12 (70.6%) of the 17 children without a measurable maximal response due to the absence of a plateau developed wheezing, compared to seven (33.3%) out of 21 with a maximal response plateau ≥ 35%, and two (20%) out of 10 with a plateau < 35% (score test for trend, *P* = 0.007).

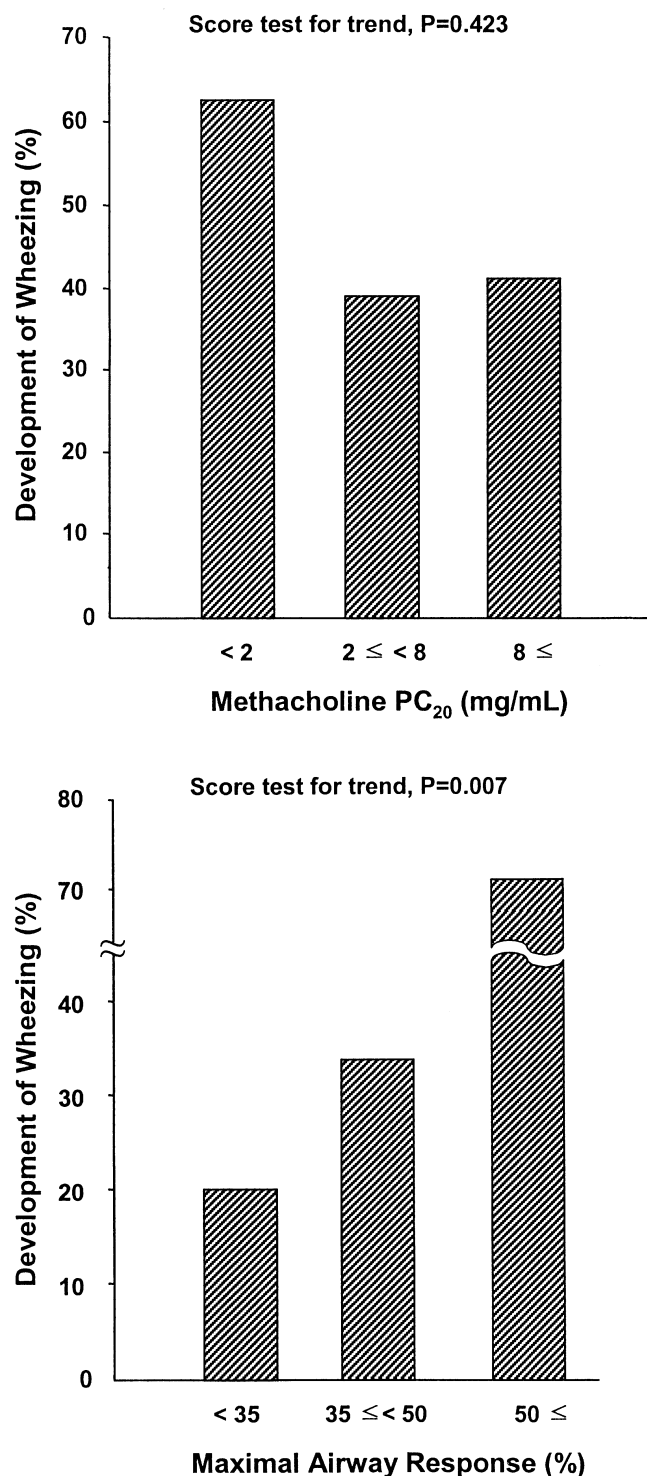


Figure 3. The risk for developing wheezing according to the level of methacholine PC₂₀ (upper panel) or the level of maximal airway response (lower panel) at the initiation of study. The development of wheezing was not significantly associated with the level of methacholine PC₂₀ (score test for trend: $P = 0.423$), but with the level of maximal airway response ($P = 0.007$).

Discussion

Our results show that an absent or elevated maximal response plateau on the dose-response curve to methacholine may be a reliable marker for the subsequent development of wheezing in patients with cough-variant asthma. In contrast, the degree of airway hypersensitivity was unable to predict which patients with cough-variant asthma would develop wheezing. To our knowledge, this is the first study that has addressed the importance of maximal airway response for predicting the future development of classic asthma in patients with cough-variant asthma.

Studies have indicated that many patients who initially present with cough-variant asthma eventually develop mild to moderately severe manifestations of classic asthma. Corrao et al. (4) noted that two of their six adult patients began to wheeze within a few years. König (5) reported that in eight of 10 children with cough-variant asthma, wheezing and dyspnea associated with typical asthma attacks eventually developed. In another study on children with cough-variant asthma, Hannaway and Hopper (6) showed that 18 of 24 patients available for long-term follow-up developed classic asthma with wheezing and dyspnea of mild-to-moderate severity. The proportion of subjects who developed wheezing in our study (43.8%) cannot be compared directly with those of the studies described above because of differences in subject recruitment, wheezing documentation, and follow-up period. The inclusion criteria for this study included the complete absence of any incidence of wheezing, whether reported or heard, and the presence of bronchial hyperreactivity, defined as PC₂₀ less than 18 mg/ml. This last criterion was chosen because we found previously that a PC₂₀ level greater than 18 mg/ml virtually rules out the possibility of current symptomatic asthma (19). Another prerequisite was that cough ceased with antiasthma medication but recurred when medication was stopped. The development of wheezing was accepted only if the wheezing recognized by the children or their parents was verified by the physician's careful auscultation. These strict criteria undoubtedly excluded some mild episodes of classic asthma, but greatly reduced the chance of misidentifying nonspecific respiratory symptoms, or doubtful occasions as the development of wheezing.

A 4-year period was chosen for follow-up. It is possible that follow-up beyond this period may have revealed additional cases of wheezing development, and that other prognostic factors could have been identified. Despite this possible deficiency, we believe that the results of this study provide valuable information on prognostic factors for the development of wheezing.

AHR is known to be an important risk factor for the development of asthma. One study examining airway hypersensitivity before and after asthma diagnosis indicated that airway hypersensitivity preexisted in children

who went on to become asthmatic (7). In follow-up studies of people with allergic rhinitis (9, 20), it has been shown that those with methacholine hypersensitivity are more likely to develop asthma. Similarly, previous investigations (21, 22) have suggested that AHR in early life is strongly predictive of the later emergence of asthma and other respiratory symptoms, and may thus be an important marker of those infants at risk of developing asthma and persistent wheezing in childhood. In our previous longitudinal study (23), the development of wheezing in patients with cough-variant asthma was associated with an increase in airway hypersensitivity. It is tempting, therefore, to speculate that the degree of airway hypersensitivity may be a reliable marker for the subsequent development of classic signs of asthma, such as wheezing. In this study, the baseline methacholine PC₂₀ level was not statistically different between those who developed wheezing and those who did not. Furthermore, the analysis between groups with different PC₂₀ levels revealed no significant association between the degree of airway hypersensitivity and the development of wheezing at follow-up. These observations suggest that the degree of airway hypersensitivity cannot predict which patients with cough-variant asthma will develop wheezing.

In normal people, the dose-response curve to methacholine reaches a plateau at a mild degree of airway narrowing, whereas in asthmatic people it shows an excessive airway narrowing, as reflected by an elevated or absent maximal response plateau (12). Excessive airway narrowing without evidence of a plateau was observed in 35.4% of our children with cough-variant asthma. Neither the presence of a maximal response plateau nor the severity of excessive airway narrowing has been investigated so far in patients with cough-variant asthma. In this study, the proportion of children without evidence of a plateau was higher among those who developed wheezing than among those who did not. Furthermore, a

significant association was found between the level of maximal airway response and the development of wheezing at follow-up, whether the response was evaluated as a dichotomous (presence/absence of maximal response plateau) variable, or as a stratified (three groups of different maximal response levels) one. These results suggest that subjects with an elevated or absent maximal response plateau are at increased risk for developing wheezing.

The maximal airway response on the dose-response curve to methacholine is assumed to reflect the potential degree of airway obstruction in individual patients irrespective of the level of sensitivity (12, 24). Indeed, it has been demonstrated that the maximal degree of airway narrowing is associated with the severity of asthma symptoms (25). In nonasthmatic subjects with allergic rhinitis, it was the maximal airway response, rather than airway sensitivity, which was found to be correlated with peak expiratory flow rate variation (26), and natural allergenic exposure may lead to an increase in maximal airway response in a significant number of patients with allergic rhinitis (27). We speculate that people with an elevated or absent maximal response plateau have greater variability in peak expiratory flow rate, and thus have an increased chance of developing wheezing, if they experience such a degree of airflow obstruction as to bring on wheezing, on exposure to allergic or nonallergic stimuli.

In conclusion, the level of maximal airway response, rather than the degree of airway hypersensitivity, may be an important risk factor for the future development of classic asthma (28) in patients with cough-variant asthma.

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