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Percentage Fall in FVC at the Provocative Concentration of Methacholine Causing a 20% Fall in FEV₁ in Symptomatic Asthma and Clinical Remission During Adolescence*

Young Yoo, MD; Jinho Yu, MD; Do Kyun Kim, MD; and Young Yull Koh, MD

**Background:** Many children with asthma go into long-term clinical remission at adolescence, but bronchial hyperresponsiveness (BHR) persists in approximately one half of these subjects. BHR is usually assessed by measuring the provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀). The percentage fall in FVC at the PC₂₀ (ΔFVC) has been suggested to be a more useful index of disease severity in asthma than PC₂₀.

**Study objective:** The aim of this study was to determine whether ΔFVC is higher in adolescents with symptomatic asthma than in those with clinical remission.

**Patients and methods:** Forty adolescents with symptomatic asthma and 80 adolescents with asthma remission underwent methacholine challenge testing. ΔFVC and PC₂₀ were measured on the methacholine dose-response curve.

**Results:** The mean (95% confidence interval [CI]) ΔFVC (15.5% [95% CI, 14.1 to 16.9%]) in the symptomatic group (n = 40) was significantly higher (p = 0.017) than that (12.8% [95% CI, 11.5 to 14.1%]) in the BHR-positive (PC₂₀ < 16 mg/mL) remission group (n = 44) or that (11.5% [95% CI, 10.2 to 12.8%]) of the BHR-negative remission group (n = 36), with no difference between the two latter groups (p = 0.581). No significant correlation was found between ΔFVC and PC₂₀ in the symptomatic group (r = -0.156, p = 0.336) or in the whole remission group (r = -0.187, p = 0.097).

**Conclusions:** Adolescents with symptomatic asthma had a higher ΔFVC than those with clinical remission, irrespective of the presence of BHR in the latter group. This finding suggests that ΔFVC may serve as an adjunct marker for differentiating between asthma persistence and remission during adolescence.

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**Key words:** adolescence; bronchial hyperresponsiveness; FVC; long-term clinical remission; provocative concentration of methacholine causing a 20% fall in FEV₁; symptomatic asthma

**Abbreviations:** ATS = American Thoracic Society; AUC = area under the curve; BHR = bronchial hyperresponsiveness; CI = confidence interval; ΔFVC = percentage fall in FVC at the provocative concentration of methacholine causing a 20% fall in FEV₁; PC₂₀ = provocative concentration of methacholine causing a 20% fall in FEV₁; ROC = receiver operator characteristic

Epidemiologic studies¹,² have demonstrated that many children with asthma go into long-lasting clinical remission at adolescence. Bronchial hyperresponsiveness (BHR) is a characteristic feature of asthma, and its measurement may provide a useful adjunct in the diagnosis of asthma.³ The correlation between the level of bronchial responsiveness and clinical severity of the disease, however, is not well established. While some workers⁴ have suggested that subjects with a greater degree of bronchial responsiveness have more severe asthma, others⁵ have disagreed. Several studies⁶,⁷ have shown that BHR persists in a considerable proportion of adolescents with asthma in long-term clinical remission, and therefore does not fully explain asthma symptomatology during adolescence.

BHR is usually defined as an increased sensitivity of the airways to inhaled nonsensitizing bronchocon-
strictors such as histamine or methacholine, and is assessed by measuring the concentration or dose of bronchoconstrictor that produces a 20% fall in FEV$_1$. However, this measure does not assess an absent or elevated maximal response plateau on the methacholine dose-response curve, which is presumably the most important pathophysiologic abnormality in asthma because it puts asthmatics at risk for serious illness. Thus, it is not surprising that only an imprecise relationship exists between the provocative concentration of methacholine causing a 20% fall in FEV$_1$ (PC$_{20}$) and the clinical expression of asthma.

The percentage fall in FVC at the PC$_{20}$ ($\Delta$FVC) has been proposed as an indirect index of gas trapping and therefore an expression of the risk of an absent or elevated maximal response plateau. Unlike the PC$_{20}$, $\Delta$FVC was found to be significantly related to the average number of oral corticosteroid prescriptions per month, which suggests that it may be a more useful index of disease severity in asthma than PC$_{20}$.

Little is known about the relationship between $\Delta$FVC and the clinical expression of asthma during adolescence; it is not known whether the level of $\Delta$FVC can distinguish between the persistence of asthma symptoms and clinical remission. In this report, we present the results of analyzing methacholine dose-response curves by measuring $\Delta$FVC as well as PC$_{20}$. If an absent or elevated maximal response plateau is an important determinant of asthma severity, we hypothesized that adolescents with symptomatic asthma would have higher $\Delta$FVC levels than those with clinical remission.

**Materials and Methods**

A group of adolescents (aged 13 to 17 years) with current atopic asthma was recruited from the allergy clinic at Seoul National University Children’s Hospital. All subjects had a history of episodic wheezing and/or dyspnea, and had asthma diagnosed on the basis of airway reversibility (an increase in FEV$_1$ > 12% after bronchodilator administration) or PC$_{20}$ < 16 mg/mL. Atopy was defined as at least one positive skin-prick test result to a panel of 12 common airborne allergens in the presence of positive and negative controls. Forty patients who had experienced one or more episodes of wheezing during the previous year, as documented by a physician, were admitted consecutively. They had been medicated with inhaled $\beta_2$-agonists on demand in order to relieve symptoms, with or without inhaled corticosteroids. Those patients with a history of near-fatal asthma or major exacerbations necessitating the use of systemic corticosteroids were excluded.

A second group of 80 adolescents (aged 13 to 17 years) with long-term asthma remission was also recruited. They had received a diagnosis of atopic asthma according to the criteria used for those with current asthma. All subjects were being followed up at our clinic, with instructions to take $\beta_2$-agonists when asthmatic symptoms occurred. Long-term clinical remission was assumed if a subject reported a complete absence of wheezing and dyspnea at rest and on exertion, and had not received any medication in order to control asthmatic symptoms for at least 24 months before the study.

These two subject groups underwent a methacholine inhalation test. Patients with current asthma stopped using inhaled bronchodilators or other medications 48 h and inhaled corticosteroids 7 days before the test. None of the subjects had exhibited any symptoms of upper respiratory tract infections in the month preceding the test. Common exclusion criteria were an inability to perform lung function tests reproducibly, low FEV$_1$ (<70% of predicted), and illness that may have affected lung function.

Methacholine inhalation tests were carried out using a modification of the method described by Chai et al. Spirometric measurements (FEV$_1$ and FVC) were made using a computerized spirometer (Microspiro-HI 298; Chest; Tokyo, Japan), in accordance with the recommendations of the American Thoracic Society (ATS). The time course of the preceding inspiration was standardized, i.e., rapid maximal inspiration without end-inspiratory pause, and the FVC maneuver was continued until a pause in the forced expired volume curve was obvious by visual inspection. The minimum duration of the FVC maneuver was 6 s. Methacholine (Sigma Diagnostics; St. Louis, MO) solutions were prepared at different concentrations (0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, 25, 50, and 100 mg/mL) in buffered saline solution (pH 7.4). 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 an aerosol from a nebulizer (Devilbiss 646; Devilbiss Health Care; Somerset, PA), with pressurized air at 20 lb per square inch. Each subject 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 ± SD) per inhalation. FEV$_1$ and FVC were measured 90 s after inhalation at each concentration level, and the largest value of triplicate FEV$_1$ or FVC was used for the analysis. The procedure was terminated when the FEV$_1$ decreased by >20% of its post-saline solution value or when the highest methacholine concentration (100 mg/mL) was reached. The percentage decline of FEV$_1$ from the post-saline solution value was plotted against the log concentration of the inhaled methacholine. PC$_{20}$ was calculated by interpolating between two adjacent data points if the FEV$_1$ decreased by >20%. The $\Delta$FVC relative to baseline FVC after saline solution inhalation was also calculated using a log-linear interpolation. For subjects whose FEV$_1$ did not fall by 20% after inhalation of 100 mg/mL of methacholine, PC$_{20}$ was assumed to be 100 mg/mL and $\Delta$FVC was assumed to be the last data point of percentage fall in FVC.

Parents gave written informed consent for their children to participate in the study. The study protocol was approved by the Hospital Ethics Committee.
Statistical Analysis

The primary study outcome was ΔFVC, and a sample size calculation was based on previous data reported by Gibbons et al. A minimum of 37 subjects per group was required to detect a difference of 3.6% between two groups with 80% power and 5% statistical significance. In this study, we were intended to classify subjects with remission into BHR-positive and BHR-negative groups and to compare each group separately with the symptomatic group. Since approximately one half of subjects with remission were found to have BHR in our previous study, we planned to recruit 40 subjects with current asthma and 80 subjects with asthma remission.

The values of FEV1 and FVC were expressed as percentages of predicted based on data from our local population. Subjects were considered to have BHR if they had a PC20 < 16 mg/mL. PC20 and serum total IgE values were logarithmically transformed before analysis and were expressed as geometric means with a antilog of 95% confidence intervals (CIs) of log IgE or log PC20 values. Other values were presented as means with 95% CIs. Screening of data for differences in the variables between the three groups was performed using analysis of variance. When significant differences were identified, individual groups were compared using the Student two-tailed, unpaired t test. Bonferroni multiple comparison tests were used to compare means. The ability of ΔFVC and PC20 to discriminate between symptomatic asthma and BHR-positive remission was evaluated and compared by constructing receiver operator characteristic (ROC) curves. For the two variables, the area under the curve (AUC) with 95% CI was determined. Correlations between ΔFVC and PC20 were examined using Pearson correlation tests. A p value ≤ 0.05 was taken to be significant.

RESULTS

Forty patients with symptomatic asthma and 80 patients with asthma remission completed the study. Two subjects in the symptomatic group had a PC20 < 16 mg/mL, but they were included in the study because they fulfilled the inclusion criteria. Of 80 subjects with asthma remission, 44 patients were found to have a PC20 < 16 mg/mL (BHR-positive remission group), and the remaining 36 patients had a PC20 > 16 mg/mL (BHR-negative remission group). The clinical characteristics of the three adolescent groups are shown in Table 1. There were no differences between the three groups in terms of age, sex ratio, atopic status as assessed by total serum IgE and patterns of positive skin response, or spirometric values (FEV1, FVC, or FEV1/FVC). PC20 was lower in the symptomatic group than in the BHR-positive remission group, but the difference was not statistically significant (p = 0.147).

The ΔFVC levels of the three study groups are shown in Figure 1. Nine participants in the BHR-negative remission group had a PC20 > 100 mg/mL, and for these subjects the ΔFVC after 100 mg/mL inhalation was used. The mean ΔFVC in the symptomatic group was 15.5% (95% CI, 14.1 to 16.9), which was significantly higher than that (12.8% [95% CI, 11.5 to 14.1%]; p = 0.017) in the BHR-positive remission group or that (11.5% [95% CI, 10.2 to 12.8%]; p = 0.000) in the BHR-negative remission group; the difference between the latter two groups was not significant (p = 0.581). After removing the nine subjects from the analysis, the mean ΔFVC level in the BHR-negative remission group was 12.3% (95% CI, 10.8 to 13.9%). However, omitting the data on these nine subjects did not materially change differences between the three groups.

ROC curves for the ability of ΔFVC and PC20 to discriminate between symptomatic asthma and BHR-positive remission are shown in Figure 2. The AUC-ROC for ΔFVC was 0.704 (95% CI, 0.509 to 0.817), whereas that for PC20 was 0.607 (95% CI, 0.485 to 0.730).

Scatter plots of ΔFVC against PC20 are shown in Figure 3. No significant correlation was found between ΔFVC and PC20 in the symptomatic group.

Table 1—Clinical Characteristics of the Three Adolescent Groups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Symptomatic Asthma (n = 40)</th>
<th>BHR-Positive Remission (n = 44)</th>
<th>BHR-Negative Remission (n = 36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr†</td>
<td>14.7 (13.1–16.8)</td>
<td>15.0 (13.3–16.7)</td>
<td>15.1 (13.4–16.7)</td>
<td>0.939</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>24/16</td>
<td>30/14</td>
<td>24/12</td>
<td>0.712</td>
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<tr>
<td>Serum IgE, IU/mL‡</td>
<td>354.8 (234.4–537.0)</td>
<td>323.6 (229.1–457.1)</td>
<td>309.0 (220.3–433.5)</td>
<td>0.481</td>
</tr>
<tr>
<td>Pattern of positive skin response§</td>
<td>39/15/8/5/12</td>
<td>100.7 (97.7–103.7)</td>
<td>101.9 (98.2–105.6)</td>
<td>0.377</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>94.8 (91.7–97.9)</td>
<td>96.2 (93.3–99.1)</td>
<td>98.0 (94.6–101.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>99.1 (95.9–102.3)</td>
<td>100.7 (97.7–103.7)</td>
<td>101.9 (98.2–105.6)</td>
<td>0.493</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>85.6 (84.2–87.0)</td>
<td>85.9 (84.1–87.7)</td>
<td>86.6 (85.0–88.2)</td>
<td>0.694</td>
</tr>
<tr>
<td>PC20, mg/mL§</td>
<td>2.88 (1.92–4.32)</td>
<td>4.46 (3.36–5.92)</td>
<td>All &gt; 16 mg/mL</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*p Data are presented as mean (95% CI) unless otherwise stated.
†Data are presented as geometric mean (antilog of 95% CI of log IgE or log PC20 values).
‡No. of cases positive to house dust mite (Dermatophagoides pteronyssinus and Dermatophagoides farinae)/animal dander (cat and dog)/mold (Aspergillus and Alternaria species)/pollen (oak, alder, rye grass, ragweed, and mugwort)/cockroach.
§p = 0.146 compared to symptomatic group.
Discussion

The present study shows that FVC is higher in adolescents with symptomatic asthma than in those with asthma remission. This is unlikely to be due to a difference in PC_{20} because FVC was no different between the BHR-positive and BHR-negative remission groups and because no correlation was found between FVC and PC_{20}.

In the present study, subjects were regarded to be in clinical remission when they reported the complete absence of symptoms and had received no treatment for at least 2 years preceding the study. Despite the strict criteria used for clinical remission, the frequency of BHR (55%) was relatively high, compared to other studies. This may be explained by our recruiting subjects from a specialized allergy clinic, which may have caused bias toward the more severe end of the asthma spectrum, and by the fact that only atopic subjects were selected, in order to avoid the confounding effect of atopy on the persistence of BHR. A PC_{20} of 16 mg/mL was chosen as the BHR cutoff. This may appear high, but it is considered clinically relevant, since “borderline” BHR (PC_{20} of 4 to 16 mg/mL), defined according to the ATS guidelines, was shown by a considerable proportion (40%) of the symptomatic group. The inhalation of methacholine was extended to 50 mg/mL and 100 mg/mL when the FEV_{1} did not fall by 20% after inhaling up to 25 mg/mL, to allow FVC to be measured in as many subjects as possible.

In the present study, FVC in the symptomatic group was significantly higher than in the BHR-positive remission group or BHR-negative remission group. The FVC may have been underestimated in the latter group because nine subjects had PC_{20} values above the upper limit of measurement.
PC$_{20}$ > 100 mg/mL. The exclusion of these subjects from the analysis, however, did not change our findings. Although inhaled corticosteroids had been discontinued in the symptomatic group at least 1 week before the study, they may have had carryover effects. However, corticosteroids would rather decrease than increase $\Delta$FVC, and therefore cannot account for the higher $\Delta$FVC observed in the symptomatic group. Increased $\Delta$FVC might be a consequence of progressive shortening in expiration during bronchoprovocation testing, leading to incomplete emptying of the lung. However, this is thought unlikely, since compliance with ATS criteria, including the occurrence of an expiratory plateau, was checked on all occasions. ROC curves constructing from the data of the symptomatic vs BHR-positive remission group showed that the AUC for $\Delta$FVC was 0.704, whereas that for PC$_{20}$ was 0.607 (Fig 2). Generally, a test is considered discriminating if the AUC is > 0.70. Our results suggest that $\Delta$FVC could contribute to better discrimination between persistence and remission of asthma during adolescence, and raise the hypothesis that $\Delta$FVC is an important confounder in the relationship between airway sensitivity and the clinical expression of asthma.

The lack of a difference between the BHR-positive remission and BHR-negative remission groups with respect to $\Delta$FVC suggests that the higher $\Delta$FVC in patients with symptomatic asthma than in patients with asthma remission is not due to a difference in PC$_{20}$. This interpretation is further supported by the lack of significant correlation between $\Delta$FVC and PC$_{20}$ in the symptomatic and in the whole remission group (Fig 3). Our findings are similar to those described by other investigators and imply that the ease of bronchoconstriction, as measured by PC$_{20}$, and the degree of gas trapping or propensity for excessive bronchoconstriction, as reflected by $\Delta$FVC, might be due to different mechanisms.

Excessive bronchoconstriction, as reflected by an absent or elevated maximal response plateau on the methacholine dose-response curve, is clinically a more relevant component of BHR than the PC$_{20}$, because it indicates the potential severity of airways obstruction in the individual patients. However, the measurement of excessive bronchoconstriction is neither safe nor easy to perform because of problems inherent in provoking an excessive fall in FEV$_1$. Gibbons et al suggested that $\Delta$FVC reflects gas trapped due to excessive bronchoconstriction. We have shown that the levels of maximal airway response on the methacholine dose-response were significantly lower in adolescents with asthma remission than in symptomatic asthmatic adolescents with a similar degree of airway hypersensitivity.

In conclusion, adolescents with symptomatic asthma had a higher level of $\Delta$FVC than those with clinical remission, irrespective of the presence of BHR in the latter group. This suggests that $\Delta$FVC may serve as an adjunct marker for differentiating between asthma persistence and remission during adolescence.

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