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Analysis of PC20-FEF25%-75% and ΔFVC in the Methacholine Bronchial Provocation Test

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Abstract

Purpose: Forced expiratory flow between 25% and 75% ($FEF_{25\%–75\%}$) is known to sensitively reflect bronchial obstruction. Methacholine challenge test (MCT) has shown varying reduction levels of forced vital capacity (FVC) with the reduction in forced expiratory volume in 1 second (FEV_1) in asthma. This study aimed to evaluate the clinical implication of provocative concentration causing a 20% fall in $FEF_{25\%–75\%}$ (PC_{20}-$FEF_{25\%–75\%}$) and the percentage fall in FVC at the PC_{20} dose of methacholine (ΔFVC). *Methods:* A total of 194 children who visited the hospital due to respiratory symptoms and underwent MCT were analyzed retrospectively. The patients were divided into 3 groups. Group I had both PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ above 16 mg/mL; group II had a PC_{20}-$FEF_{25\%–75\%}$ that fell below 16 mg/mL but PC_{20}-FEV_1 was 16 mg/mL or above; group III had a PC_{20}-FEV_1 and a PC_{20}-$FEF_{25\%–75\%}$ that both fell below 16 mg/mL. *Results:* In group II, PC_{20}-FEV_1 was lower ($P = 0.026$), and the rate of change in FEV_1 and $FEF_{25\%–75\%}$ from baseline to 16 mg/mL of methacholine concentration was greater than in group I (both $P < 0.001$). Levels of PC_{20}-$FEF_{25\%–75\%}$ were higher in group II compared to group III ($P < 0.001$). ΔFVC showed a correlation with PC_{20}-FEV_1 ($P < 0.001$) only in the whole group. *Conclusion:* In asthmatic children, PC_{20}-$FEF_{25\%–75\%}$ may be associated with bronchial hyperresponsiveness. ΔFVC was not associated with other parameters in either group. For subjects with a positive finding of PC_{20}-$FEF_{25\%–75\%}$ and a negative finding of MCT, the progression of asthma can be suspected.

Keywords

Methacholine challenge test
Asthma
Child
Vital capacity
Forced expiratory flow

1. Introduction

Asthma is one of the most common chronic diseases in children, causing frequent hospitalization and, in severe cases, respiratory distress and respiratory failure. It also causes airway remodeling, which can lead to irreversible changes, and bronchial hyperresponsiveness in bronchial provocation tests using inhaled methacholine, mannitol, and histamine [1]. Bronchial provocation testing with methacholine is the most commonly performed test and has been used primarily to assess forced expiratory volume in 1 second (FEV_1) as a reference marker of bronchial hyperresponsiveness, and PC_{20} (provocative concentration causing a 20% fall in FEV_1, PC_{20}-FEV_1), the concentration of methacholine that causes a 20% fall in FEV_1, as a diagnostic criterion for asthma [2]. However, PC_{20}-FEV_1 is not clinically used to predict exacerbations of asthma symptoms because it does not reflect worsening and remission of clinical symptoms in individual patients [3], has difficulty in determining the risk of asthma attacks [4], and does not reflect the maximal airway response, which indicates a moderate degree of bronchoconstriction and obstruction.

The percent fall in forced vital capacity (FVC) at the PC_{20} dose of methacholine has been proposed as a component of bronchial hyperresponsiveness. While FEV_1 primarily reflects airway tone, FVC is considered to reflect changes in peripheral bronchioles and the degree of stenosis [5], and Gibbons et al. reported that FVC is a useful indicator of maximal airway response [6]. FVC was significantly associated with the number of oral steroids prescribed in a month in asthmatic patients, suggesting that it is a more useful indicator of asthma moderation than PC_{20}-FEV_1. Lee et al. also suggested that FVC is useful for identifying symptomatic exacerbations in asthma and may be a novel marker for distinguishing moderate asthma [7].

In addition, the use of PC_{20}-FEV_1 to diagnose asthma has been reported to be negative in 27% of true asthma patients [8], and false negatives may occur in patients with mild asthma without severe airway hyperresponsiveness [9,10]. In comparison, forced expiratory flow between 25% and 75% of functional vital capacity ($FEF_{25\%–75\%}$) is a more sensitive indicator of small bronchial obstruction, and if FEV_1 is normal on pulmonary function tests in patients with early asthma but $FEF_{25\%–75\%}$ is reduced, a reduction in $FEF_{25\%–75\%}$ may be associated with bronchial hyperreactivity. It has been suggested that a decrease in $FEF_{25\%–75\%}$ may play an important role in the management of asthma when FEV_1 is normal [11,12], and it has been reported that the provocative concentration of methacholine causing a 20% fall in $FEF_{25\%–75\%}$ (PC_{20}-$FEF_{25\%–75\%}$) is a more sensitive reflection of bronchial hyperreactivity than PC_{20}-FEV_1 [13]. In studies of pediatric mild asthma patients, $FEF_{25\%–75\%}$ values are meaningful when PC_{20}-FEV_1 is normal [14], and although detailed studies on the cut-off values for $FEF_{25\%–75\%}$ decline are lacking, some studies suggest that a 25% decline in $FEF_{25\%–75\%}$ may be a more sensitive marker of suspected bronchial hyperresponsiveness than PC_{20}-FEV_1 [15].

Therefore, in this study, we aimed to determine the significance of PC_{20}-$FEF_{25\%–75\%}$ and ΔFVC as additional markers in addition to PC_{20}-FEV_1 in methacholine bronchial provocation testing and the correlation of these markers with various clinical tests.

2. Materials and methods

2.1. Research subjects

From May 2014 to July 2019, 194 children who visited the Department of Pediatrics, Kyungpook National University Children's Hospital, and underwent the methacholine bronchial provocation test were included. Patients were excluded if they had respiratory infections within the last 1 month or had chronic diseases. Skin prick tests were performed in all patients, and six inhalant antigens ImmunoCAP, serum total IgE, peripheral blood total eosinophil count, serum eosinophil protein (ECP), and sputum eosinophil count by induced sputum test were measured. This study was conducted following the guidelines of the Institutional Review Board (IRB) of Chilgok Kyungpook National

University Hospital and passed the review process (IRB number: 2019-11-001).

2.2. Classification of research subjects

2.2.1. Classification by diagnosis

The diagnosis of asthma was defined as the presence of characteristic clinical symptoms such as dyspnoea and wheezing, a positive bronchodilator response, or a PC_{20} of less than 16 mg/mL in a methacholine bronchial provocation test according to the American Thoracic Society criteria, 16 eosinophilic bronchitis was defined as a chronic cough of more than 4 weeks, FEV_1 >80% of predicted on pulmonary function tests, PC_{20} >16 mg/mL on methacholine bronchial provocation test, and sputum eosinophil count > 3% [17]. In addition, patients with a sputum eosinophil count of less than 3% and a PC_{20} of more than 16 mg/mL on the methacholine bronchial provocation test were classified as the other group.

2.2.2. Classification according to the results of the methacholine bronchial provocation test

Children were classified into three groups according to the results of the methacholine bronchial provocation test. Group I was classified as having both PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ above 16 mg/mL, group II as having PC_{20}-$FEF_{25\%–75\%}$ below 16 mg/mL but PC_{20}-FEV_1 above 16 mg/mL, and group III as having PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ below 16 mg/mL. If the PC_{20}-FEV_1 decreased to less than 16 mg/mL but the PC_{20}-$FEF_{25\%–75\%}$ was greater than 16 mg/mL, the patient met the criteria for asthma and was excluded from the study.

2.3. Methods

2.3.1. Pulmonary function tests and methacholine bronchial provocation tests

Methacholine bronchial provocation test was performed according to the American Thoracic Society guidelines and was performed after confirming that FEV_1 was at least 70% of the normal predicted value [16]. Chronic cough for more than 4 weeks, pulmonary function test FEV_1 greater than or equal to 80% of predicted, a methacholine bronchial provocation test with a PC_{20} of 16 mg/mL or greater, and a sputum eosinophil count of 3% or greater are defined as eosinophilic bronchitis [17]. In the absence of symptoms of upper or lower respiratory tract infection within 4 weeks, antihistamines that may affect test results were discontinued for at least 72 hours, theophylline for at least 24 hours, inhaled long-acting β2-agonists for at least 48 hours, ipratropium for at least 24 hours, short-acting beta-agonists for at least 8 hours, leukotriene antagonists for at least 24 hours [18], and inhaled steroids for at least 24 hours before pulmonary function tests and bronchial provocation tests were performed [19]. Methacholine (provocholine; Methapharm Inc., Brantford, ON, Canada) was dissolved in buffered saline and diluted to the respective concentrations (0.0625, 0.25, 1, 4, 16, and 25 mg/mL) using a spirometer (spirolab III, Medical International Research, Rome, Italy) and inhaled in increasing concentrations. Each child inhaled five puffs of buffered normal saline and the maximum of at least three measurements of FEV_1 and FVC were collected at 60–90 seconds after inhalation of each concentration. Concentrations were increased until FEV_1 decreased by at least 20% of baseline and PC_{20}-FEV_1 was obtained by log-linear interpolation from the dose-response curve. For $FEF_{25\%–75\%}$, the concentration at which $FEF_{25\%–75\%}$ decreased by 20% (PC_{20}-$FEF_{25\%–75\%}$) was obtained in the same way.

FVC was calculated by log-linear interpolation from FVC measurements at two points before and after PC_{20} on the dose-response curve to obtain FVC at PC_{20}, and the difference was expressed as a percentage of the FVC value after inhalation of buffered normal saline. Tests were repeated up to 25 mg/mL if FEV_1 did not decrease by more than 20% from baseline, and methacholine PC_{20} was treated with 25 mg/mL if methacholine concentration did not decrease by more than 20% to 25 mg/mL.

The percentage change in FEV_1 and the percentage

change in $FEF_{25\%–75\%}$ were calculated as the difference between the respective values after inhalation of buffered saline and after inhalation of a methacholine concentration of 16 mg/mL, expressed as a percentage.

2.3.2. Blood tests

Serum total IgE, specific IgE antibodies, and eosinophil cationic protein tests were performed in all children using the CAP radioallergosorbent technique (UniCAP, Pharmacia, Uppsala, Sweden). Specific IgE antibodies were tested against *Dermatophagoides farinae* (*D. farinae*), *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), Alternaria, Aspergillus, cat dander, and dog dander, and were defined as positive if they were greater than or equal to 0.35 kU/L. Atopy was also defined if one or more specific IgE antibodies were positive.

2.3.3. Skin prick test

The skin prick test was performed on the back of the patient after bathing on the day of the test, and the antigen was applied to the test site at regular intervals, and the skin was lightly scratched without bleeding, and the results were read by a trained examiner after about 15 minutes. The test was performed with 17 antigens including *D. farinae*, *D. pteronyssinus*, *Acarus siro*, Tyrophagus, cat dander, dog dander, Alternaria, Aspergillus, birch, alder, hazel, pine, bermuda, timothy, orchard, ragweed, and mugwort. Histamine and saline were identified as positive and negative controls, and the size of the swelling and redness was expressed as the sum of the lengths of the long and short diameters divided by two, and the size of the swelling was considered positive if it was greater than 3 mm and greater than the positive control. In addition, if one or more test items were positive, it was defined as atopic.

2.3.4. Induced sputum test

Using the criteria of the Korean College of Asthma and Allergy 21 as a reference, 3% hypertonic saline was inhaled four times for 5 minutes (total of 20 minutes) using an ultrasonic nebulizer (OMRON NE-U17; OMRON Matsusaka Co., Ltd., Kyoto, Japan), and sputum was expectorated by coughing. The obtained sputum samples were mixed with four times the volume of 0.1% dithiothreitol by vortexing, and after 15 min, an equal volume of saline was added, mixed by vortexing for 15 s, and then separated into four centrifuge tubes and centrifuged at 2,000 rpm for 5 min. The supernatant was separated and frozen, and the cell precipitate was resuspended in physiological saline and cytospun at 450 rpm for 6 min to prepare slides, and slides were examined after Wright staining. A record of the cellular fraction of the induced sputum was made by counting the total number of cells and the number of each cell contained therein and its fraction in %.

2.4. Statistical methods

Statistical analysis was performed using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). PC_{20}-FEV_1, ΔFVC, and PC_{20}-$FEF_{25\%–75\%}$ were compared by taking the common logarithm. Spearman correlation analysis was used to analyze the correlation of variables, independent *t*-test, and chi-square test were used to compare the characteristics of classified patients, and one-way analysis of variance was used to compare the characteristics of the three groups, followed by post-hoc analysis. For each statistical analysis, a *P* value of less than 0.05 was considered statistically significant.

3. Result

3.1. Statistical and clinical characteristics of the target patients

A total of 194 patients who visited the Department of Paediatrics, Kyungpook National University Children's Hospital, and underwent methacholine bronchial provocation testing had a mean age of 10.18 ± 3.27 (mean ± standard deviation) years, with 121 boys and 73 girls. There were 114 and 124 patients who were positive for one or more antigens

Table 1. Demographics and clinical characteristics of the subjects (n = 194)

Characteristic	Value
Age (yr)	10.18 ± 3.27
Sex	
Male	121
Female	73
Patient group	
Asthma	89 (46)
Eosinophilc bronchitis	37 (19)
Etc.	68 (35)
Atopy	147 (76)
Positive skin prick test	114 (59)
Inhalant ImmunoCAP positive	124 (64)
Pulmonary function test	
FEV_1 (% predicted)	99.11 ± 13.99
FVC (% predicted)	101.53 ± 12.98
FEV_1/FVC (%)	83.46 ± 6.72
Methacholine PC_{20}-FEV_1 (mg/mL)	15.10 ± 10.52
△FVC (%) (n = 163)	9.66 ± 6.60
Combined allergic disease	
Allergic rhinitis	95 (49)
Atopic dermatitis	30 (15)
Food allergy	16 (8)

in the skin prick test and ImmunoCAP, respectively, representing 59% and 64% of the total (Table 1).

Values are presented as mean ± standard error of the mean or number (%). FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; PC_{20}: provocative concentration causing a 20% decline in forced expiratory volume in 1 second; ΔFVC: percent fall in forced vital capacity at the PC_{20} dose of methacholine.

3.2. Demographic and clinical characteristics of patients in each group

Of the total 194 patients, 89 (46%) were in the asthma group, 37 (19%) in the eosinophilic bronchitis group, and 68 (35%) in the others group. Other conditions included allergic rhinitis, habitual cough, gastroesophageal reflux disease, and adenoid hyperplasia. There were no significant differences in gender, age, or body mass index between the groups.

When the presence of atopy was determined by skin prick testing and immunoCAP to inhaled antigens, 75 (84.3%) of the asthma group, 29 (78.4%) of eosinophilic bronchitis, and 43 (63.2%) of the others group were found to have a significant rate of atopy (P = 0.008). Sputum eosinophil count (P < 0.001), peripheral blood total eosinophil count (P = 0.012), and serum total IgE (P < 0.001) were significantly higher in asthma and eosinophilic bronchitis groups than in the others group, but ECP did not show any difference between the groups. In the methacholine bronchial provocation test, FVC was significantly higher in the asthma group than in the others group, and the eosinophilic bronchitis group also showed significantly higher values than the others group (P < 0.001) (Table 2).

Values are presented as number (%) or mean ± standard error of the mean. EB: eosinophilic bronchitis; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; PC_{20}: provocative concentration causing a 20% decline in forced expiratory volume in 1 second; ΔFVC:

Table 2. Characteristics of the subjects

Characteristic	Asthma (n=89)	EB (n=37)	Others (n=68)	*P*-value
Male sex	52 (58)	27 (73)	42 (62)	0.305
Age (yr)	9.77±3.27	10.81±3.42	10.38±3.17	0.222
BMI (kg/m^2)	19.52±3.64	19.59±3.73	19.28±3.77	0.892
Atopy	75 (84)	29 (78)	43 (63)	0.008
Pulmonary function test				
FEV_1 (% predicted)	96.09±14.06	100.16±13.48	102.50±13.48	0.015
FVC (% predicted)	101.63±12.53	99.86±14.60	102.29±12.75	0.656
FEV_1/FVC (%)	80.94±7.19	86.12±5.62	85.31±5.43	<0.001
Methacholine PC_{20}-FEV_1 (mg/mL)	4.26±4.31	24.67±1.05	24.07±2.42	<0.001
△FVC (%)	12.89±4.29	6.15±6.76	5.18±6.93	<0.001
Sputum eosinophil (%)	12.42±20.76	14.30±14.56	0.09±0.38	<0.001
Peripheral blood total Eosinophil count (/mm^3)	497.56±464.83	403.71±246.40	280.57±389.97	0.012
ECP (μg/L)	44.86±46.75	40.74±40.34	29.27±36.77	0.164
Serum total IgE (IU/mL)	647.19±699.05	551.43±618.16	198.45±315.04	<0.001

Table 3. Characteristics of study subject according to $FEF_{25\%–75\%}$

Characteristics	Group I (n=56)	Group II (n=48)	Group III (n=90)	*P*-value
Mean age (yr)	11.41±3.31	9.57±2.91	9.75±3.26	0.003
Male sex	40 (71)	29 (60)	52 (58)	0.241
Pulmonary function test				
FEV_1 (%)	101.11±11.94	101.96±15.06	96.36±14.21	0.087
FVC (%)	102.07±13.44	100.23±13.19	101.88±12.69	0.740
FEV_1/FVC (%)	85.12±6.13	86.13±4.69	81.00±7.17	<0.001
$FEF_{25\%–75\%}$ (%)	106.20±25.60	113.29±34.69	94.20±33.86	0.003

percent fall in forced vital capacity at the PC_{20} dose of methacholine; ECP: eosinophil cationic protein; IgE: immunoglobulin E.

3.3. Relationship between change in $FEF_{25\%–75\%}$ and bronchial hyperreactivity

In the 3-group classification according to the methacholine bronchial provocation test, group I was 56 patients (29%), group II 48 patients (25%), and group III 90 patients (46%). In the comparison by group, the mean age of group I was significantly higher than that of groups II and III (P = 0.003). No significant differences in FEV_1, FVC were found in the baseline pulmonary function tests between the groups, and the FEV_1/FVC, $FEF_{25\%–75\%}$ were significantly higher in group II compared to group III (P < 0.001, P = 0.003) (Table 3).

Values are presented as mean±standard error of the mean or number (%). Group I, both PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ above 16 mg/mL; group II, PC_{20}-$FEF_{25\%–75\%}$ that fell below 16 mg/mL but PC_{20}-FEV_1 was 16 mg/mL or above; group III, both PC_{20}-FEV_1 and a PC_{20}-$FEF_{25\%–75\%}$ fell below 16 mg/mL. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $FEF_{25\%–75\%}$: forced expiratory flow between 25% and 75% of functional vital capacity.

In the comparison of groups I and II, the mean PC_{20}-FEV_1 of the methacholine bronchial provocation test was significantly lower (P = 0.026) in group II than in group I, at 23.76 ± 2.59 and 24.71 ± 1.37 mg/mL, respectively, indicating greater bronchial hyperreactivity in group II (Figure 1A). The percentage change in FEV_1 at methacholine concentration of 16 mg/mL was 5.01 ± 6.35% in group

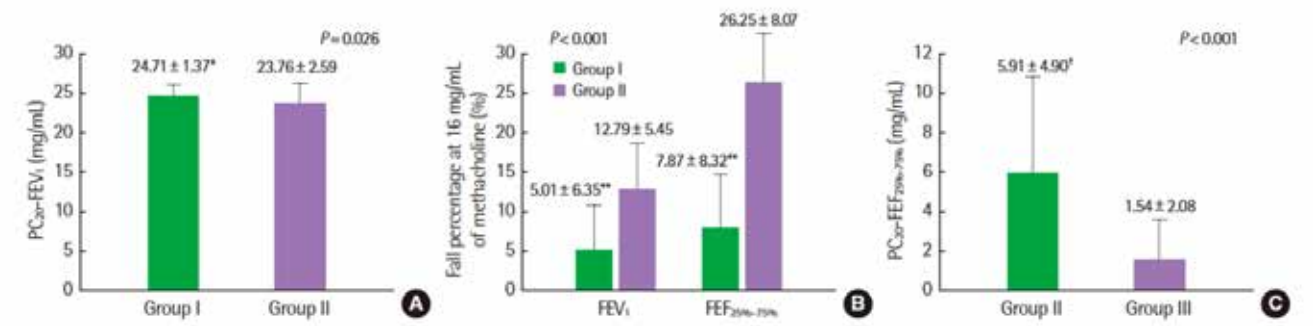

Figure 1. Comparison of bronchial hyperresponsiveness. (A) PC_{20}-FEV_1 was higher in group I compared with group II. (B) Group II children's percent falls of FEV1 and $FEF_{25\%–75\%}$ at 16 mg/mL of methacholine were higher than in group I. (C) PC_{20}-$FEF_{25\%–75\%}$ in group II was significantly higher than in group III. FEV_1: forced expiratory volume in 1 second; $FEF_{25\%–75\%}$: forced expiratory flow between 25% and 75% of functional vital capacity; PC_{20}-FEV_1: provocative concentration causing a 20% decline in forced expiratory volume in 1 second; PC_{20}-$FEF_{25\%–75\%}$: provocative concentration causing a 20% decline in forced expiratory flow between 25% and 75% of functional vital capacity. The results are expressed as mean±standard error of the mean. *$P \leq 0.05$ vs. group II. **$P \leq 0.001$ vs. group II. ‡$P \leq 0.001$ vs. group III.

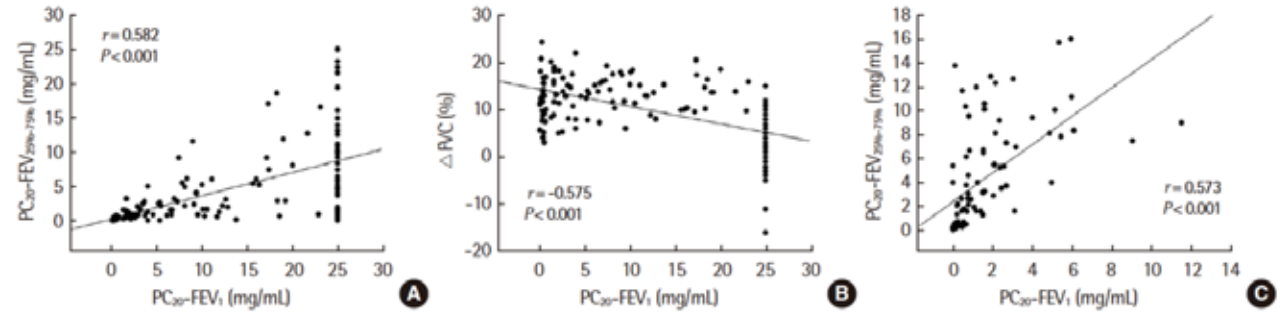

Figure 2. The relationship between parameter and ΔFVC (A) Correlation between PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ in the whole group (B) Correlation PC_{20}-FEV_1 and ΔFVC in the whole group (C) Correlation between PC_{20}-FEV_1 and PC_{20}-$FEF_{25\%–75\%}$ in the asthmatic group. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $FEF_{25\%–75\%}$: forced expiratory flow between 25% and 75% of functional vital capacity; FEV_1-PC_{20}: provocative concentration causing a 20% decline in forced expiratory volume in 1 second; ΔFVC: percent fall in forced vital capacity at the PC_{20} dose of methacholine.

I and 12.79 ± 5.45% in group II, and the percentage change in $FEF_{25\%–75\%}$ at a methacholine concentration of 16 mg/mL was 7.87% ± 8.32% in group I and 26.25% ± 8.07% in group II, which were significantly higher in group II ($P < 0.001$) (Figure 1B).

In the comparison of groups II and III, PC_{20}-$FEF_{25\%–75\%}$ was significantly higher in group II with 5.91 ± 4.90 mg/mL in group II and 1.54 ± 2.08 mg/mL in group III ($P < 0.001$) (Figure 1C).

3.4. Correlation of baseline pulmonary function tests with methacholine bronchial provocation tests

In the whole group, mean FEV_1 was 99.11% ± 13.99% and FVC was 101.53% ± 12.98% of the normal predicted values. FEV_1/FVC was 83.46% ± 6.72% and the mean PC_{20}-FEV_1 was 15.10 ± 10.52 mg/mL. For the methacholine bronchial provocation test, 163 patients had a measurable ΔFVC, and their mean ΔFVC was 9.66% ± 6.60% (Table 1). In all 194 patients, PC_{20}-$FEF_{25\%–75\%}$ and ΔFVC were significantly correlated with PC_{20}-FEV_1 ($r = 0.582$, $P < 0.001$; $r = -0.575$, $P < 0.001$) (Figure 2A, B). PC_{20}-$FEF_{25\%–75\%}$ and ΔFVC were not significantly correlated with blood total IgE, serum eosinophil count, sputum eosinophil count, and serum ECP. When analyzed in 89 asthmatic patients, ΔFVC was not significantly correlated with PC_{20}-FEV_1,

while PC_{20}-$FEF_{25\%–75\%}$ was significantly correlated with PC_{20}-FEV_1 (r = 0.573, P < 0.001) (Figure 2C). There was no significant correlation with blood total IgE, total eosinophil count in serum, total eosinophil count in sputum, serum ECP concentration, etc.

4. Discussion

In this study, PC_{20}-$FEF_{25\%–75\%}$ was significantly correlated with PC_{20}-FEV_1, a conventional index of bronchial hyperreactivity, in both the overall group of children and the asthmatic group of children, and the results of the methacholine bronchial provocation test were classified, where the percentage change in FEV_1 at a methacholine concentration of 16 mg/mL and the percentage change in $FEF_{25\%–75\%}$ were higher in group II, suggesting that bronchial sensitivity was more pronounced in group II, where PC_{20}-FEV_1 was not consistent with asthma and $FEF_{25\%–75\%}$ decreased by more than 20%.

Although the methacholine bronchial provocation test is a highly sensitive method to identify airway hyperresponsiveness and diagnose asthma in asthmatic patients, its specificity is limited, and a negative result does not necessarily indicate asthma [22], and there are reports of false negatives ranging from 27%–58% [22,23]. In addition, Kim reported that if the methacholine bronchial provocation test is followed up, some negative patients may be converted to positive, and it is recommended to repeat the test after a sufficient period, considering various factors affecting the methacholine bronchial provocation test, such as medication, when the test is repeated at regular intervals [24]. These studies suggest that there may be patients with asthma who have a negative methacholine bronchial provocation test, and in such cases, the diagnosis of asthma should not be completely excluded, but further testing and long-term maintenance treatment and observation may be required [25].

Previous studies have shown that $FEF_{25\%–75\%}$ is more sensitive than other variables in determining airway obstruction in asymptomatic pediatric asthma patients [26,27], and Park et al. suggested that patients with allergic rhinitis with a decrease in $FEF_{25\%–75\%}$ associated with bronchial hyperreactivity and should be monitored for possible progression to asthma and treated early [28]. In a study of adults, Son et al. reported that even with current or recent wheezing, only one-third of patients were diagnosed with asthma due to confirmed airway hyperresponsiveness by PC_{20}-FEV_1, suggesting that a more sensitive index is needed to identify mild airway hyperresponsiveness with PC_{20}-FEV_1 in potential asthmatic patients and that as many as 20% more patients could be diagnosed with asthma if PC_{20}-$FEF_{25\%–75\%}$ were considered as an index [13]. In children, there is a lack of detailed research on the cutoff for $FEF_{25\%–75\%}$ reduction, but a study by Rhee et al. suggests that a 25% reduction in $FEF_{25\%–75\%}$ in methacholine bronchial provocation test may be a more sensitive indicator of suspected bronchial hyperresponsiveness than PC_{20}-FEV_1 [15]. Based on these data, the rate of change of $FEF_{25\%–75\%}$ is associated with bronchial hyperresponsiveness and may be an additional marker in addition to PC_{20}-FEV_1. Baseline $FEF_{25\%–75\%}$ values and PC_{20}-$FEF_{25\%–75\%}$ should be considered when clinical signs of bronchial hyperresponsiveness suggest asthma, but FEV_1 and PC_{20}-FEV_1 values are normal on conventional pulmonary function tests and bronchial provocation tests with methacholine. Furthermore, if PC_{20}-$FEF_{25\%–75\%}$ is found to be significant, it can be inferred that it is a predictor of progression or a risk factor that may later be diagnosed as asthma, bearing in mind the possibility of very early mild asthma at this time. It is therefore considered that further research and monitoring of these children for progression to asthma may be beneficial for early intervention and treatment.

It has been reported that FVC is significantly increased in patients with severe asthma compared to those with mild asthma [29], and correlates more strongly with asthma severity than PC_{20}-FEV_1 as a useful marker of maximal airway response [6]. In addition, in a study of asthmatic children aged 6–8 years, FVC was significantly correlated with the duration of asthma,

making it more significant than PC_{20}-FEV_1 as a marker of decreased bronchial responsiveness due to prolonged asthma in children [30], and in adolescent asthmatic patients aged 13–17 years, FVC was significantly increased in symptomatic patients compared with those in clinical remission, suggesting that FVC may be a novel marker for distinguishing between exacerbations and remissions of disease and for deciding whether to continue treatment [31].

In this study, FVC was significantly correlated with PC_{20}-FEV_1 in the overall group of children, but not in the asthma group, and no correlation was found with other markers such as total IgE, peripheral blood total eosinophil count, or ECP. In a previous correlational study of FVC, Yoo et al. reported that an increase or loss of peak response plateau was associated with an increase in sputum eosinophil percentage and ECP concentration, and there was an association between peak airway response and FVC in 41 patients with cough variant asthma [32]. Suh et al. also reported a correlation between FVC and serum ECP concentration, which was different from this study [33]. This may be caused by the effect of increased ECP due to comorbidities, as the subjects in this study included patients with other conditions (e.g., allergic rhinitis, atopic dermatitis, food allergies). In addition, ΔFVC was not significantly correlated with PC_{20}-FEV_1 in children with asthma, a finding that is consistent with previous studies, which suggest that FEV_1 primarily reflects airway tone when indicating bronchial hyperresponsiveness, whereas a decrease in FVC primarily reflects changes in the peripheral airways. In addition, the finding that ΔFVC was significantly correlated with PC_{20}-FEV_1 in the whole group of children and that the means of ΔFVC in the asthma, eosinophilic bronchitis, and others groups were significantly different, with the others group having a significantly lower mean value than the rest, which led to a consideration that ΔFVC could predict bronchial hyperreactivity.

Limitations of this study include the fact that it was a retrospective study and excluded patients with severe chronic diseases but included patients with other mild to moderate diseases (e.g., allergic rhinitis, atopic dermatitis, food allergies, etc.) that may affect allergy testing. Therefore, the results may reflect the effects of comorbidities. Secondly, $FEF_{25\%–75\%}$ is a difficult metric to standardize as it is highly variable even in normal individuals, with poor reproducibility and large inter-individual variation, so it is difficult to say that it currently has direct clinical significance. In addition, in the case of PC_{20}-FEV_1, it has recently been recommended that asthma that is negative for PC_{20}-FEV_1 should be diagnosed by further retesting, so further studies should be conducted to confirm the usefulness of $FEF_{25\%–75\%}$ before it can be considered as clinically useful as PC_{20}-FEV_1. Thirdly, the number of patients in this study was small, and although there were significant differences between the groups, the differences between the groups were negligible. In addition, there was a lack of information on the severity of asthma, which could not be considered in this study.

In conclusion, in addition to PC_{20}-FEV_1, PC_{20}-$FEF_{25\%–75\%}$ can be considered as one of the indicators of bronchial hyperresponsiveness and may be more sensitive than PC_{20}-FEV_1. FVC was not significantly associated with other indices in children with asthma. Further studies are needed to address the limitations of this study.

Disclosure statement

The authors declare no conflict of interest.

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