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Utility of a forced expiratory flow of 25 to 75 percent as a predictor in children with asthma

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= Abstract =

Purpose : Asthma is defined as chronic inflammation of the lower small airways, and bronchial hyperreactivity (BHR) is a pathophysiologic feature of asthma. It has been proposed that although there is no direct variable capable of assessing the small airways, a forced expiratory flow of between 25 and 75 percent (FEF_{25-75}) might be considered a more sensitive early marker of small airway obstruction than the forced expiratory volume in 1 second (FEV_1). Thus, we proposed that the presence and degree of positive responses to bronchial methacholine testing were related to the difference (DFF) and ratio (RFF) between FEV_1 and FEF_{25-75} in asthmatic children.

Methods : The subjects were 583 symptomatic children, including 324 children with BHR and 259 controls. Pulmonary function tests, methacholine challenge tests, and skin prick tests were performed, and the total eosinophil count, total serum IgE, and serum eosinophil cationic protein level were measured in all subjects. From a concentration-response curve, the methacholine concentration required to produce a decrease of 20% from post-saline FEV_1 was calculated (PC_{20}).

Results : The median DFF and RFF values decreased in controls compared to subjects with bronchial hyperresponsiveness, and this trend was found in groups ranked by its severity. PC_{20} had a negative correlation with DFF and RFF. Cutoff values of 0.5 for DFF and 1.042 for RFF were identified, and sensitivity and specificity were calculated.

Conclusion : This study revealed that DFF and RFF might be predictive of bronchial hyperresponsiveness in the context of normal FEV_1 in children. **(Korean J Pediatr 2008;51:323-328)**

Key Words : Asthma, Bronchial hyperresponsiveness, Forced expiratory flow between 25 and 75 percent, Forced expiratory volume in one second, Pulmonary function

Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. Chronic inflammation is associated with episodic airway obstruction characterized by expiratory airflow limitation[1]. Measurements of airflow limitation and reversibility are usually undertaken using forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF) or provocative concentration causing 20% fall in FEV_1 (PC_{20}), which is a concentration of methacholine inducing a 20% decrease in FEV_1[1].

The major site of airway inflammation has been controversial, but recent papers have focused on the importance of peripheral airway inflammation[2, 3]. It has been suggested that the inflammatory process is more severe in the peripheral than in the central airways of asthma patients, which is consistent with the fact that the smaller airways are a major site of obstruction in asthma[2].

Among respiratory indexes derived from the forced vital capacity maneuver, forced expiratory flow between 25% and 75% of the lung volume (FEF_{25-75}), which measures the average flow of gas through the middle lung volumes, was originally considered a more sensitive and earlier marker of obstruction in the small airways than FEV_1[4, 5]. However, FEF_{25-75} has not been accepted as an objective parameter because it is more variable and less reproducible than FEV_1. Recently, new parameters, the difference (DFF) and the ratio (RFF) between FEF_{25-75} and FEV_1, have been suggested in

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order to make up for the weakness of FEF_{25-75} as a predictor of bronchial hyperresponsiveness (BHR) in adult patients with asthma or allergic rhinitis[6]. Thus, we aimed to verify whether an association could be shown between the presence and degree of BHR and DFF and RFF in children.

Materials and Methods

1. Study Subjects

This study was performed with 583 subjects [384 males and 199 females; median (interquartile range) age 11.7 (8.9-13.0) years] who visited the allergy clinic for evaluation of nonspecific upper respiratory symptoms, typical symptoms of asthma or a general health workup at the Severance Childrens Hospital of Yonsei University. The control subjects were age-matched healthy children who had neither asthmatic symptoms nor a hypersensitive reaction to methacholine. The exclusion criteria consisted of acute and chronic upper and lower respiratory tract infections within 1 month before the study; use of intranasal, inhaled, or oral corticosteroids in the previous 4 weeks; and use of antileukotrienes, antihistamines, or long-acting β2-agonists in the previous week. Spirometry and methacholine challenge tests were performed, and total eosinophil count, total serum IgE, and eosinophil cationic protein (ECP) were measured in all participants. Informed written consent was obtained from all participants before inclusion in this study, which was approved by the Severance Hospital Institutional Review Board.

2. Spirometry and Methacholine Challenge Test

Lung function was measured by spirometry (Vmax encore; VIASYS Healthcare Inc., Conshohocken, PA, USA) and evaluated according to the American Thoracic Society standards[8]. BHR was assessed in all participants using a methacholine challenge test. Children were eligible if they could perform spirometry reproducibly and had an FEV_1 of at least 70% of the predicted value[7]. Briefly, after saline inhalation, doses of methacholine (Sigma-Aldrich; St. Louis, Mo, USA. 0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, 25 mg/mL) were delivered for 0.6 seconds through a DeVilbiss 646 nebulizer (DeVibiss Health Care, Inc., Somerset, PS, USA) using a Rosenthal-French dosimeter (Ferraris, Hertford, England) until either FEV_1 decreased by 20% or more, or the highest dose was administered[9, 10]. FEV_1 was measured within 60 to 90 seconds after each inhalation. The concentration of methacholine inducing a 20% decrease in FEV_1 (PC_{20}) was determined, and the challenge test was considered positive if the PC_{20} was 16 mg/mL or less. In accordance with ATS guidelines[8], the study population was divided into four groups in relation to PC_{20} values (Group 1, 1 mg/mL; Group 2, 1-4 mg/mL; Group 3, 4-16 mg/mL; Group 4, 16 mg/mL) for data analysis.

3. Measurement of Blood Eosinophils, Total Serum IgE, and ECP

An NE-8000 system (Sysmex, Kobe, Japan) was used to count eosinophils in peripheral blood, and serum IgE and ECP were measured using the CAP radioallergosorbent technique (UniCAP; Pharmacia and Upjohn, Uppsala, Sweden).

4. Statistical Analysis

Descriptive statistics were calculated as mean$\pm$SD or as median (interquartile range) for continuous variables and as frequencies for categorical variables. Comparisons between groups with and without BHR were made using an independent t-test or Mann-Whitney U test. DFF and RFF were generated as measures of pulmonary function. The association BHR test response with DFF or RFF was evaluated using the Kruskal-Wallis test and Spearman correlation test. To determine the optimal cutoff value allowing identification of patients with BHR, receiver operating characteristic (ROC) analysis was applied. The area under the ROC curve and its 95% CI were calculated. The Statistical Package for the Social Sciences Software (version 13.0, SPSS Inc., Chicago, IL) was used for all analyses. P-values <0.05 were considered statistically significant.

Results

1. Subject Characteristics

Study subjects included 324 children with BHR and 259 controls. As listed in Table 1, all mean FEV_1, FEF_{25-75}, and FVC values were found to be significantly lower in subjects with BHR compared to controls. When examined for atopy parameters, subjects with BHR showed higher eosinophil counts, total IgE, and ECP levels than controls.

Comparison of DFF and RFF between subjects with BHR and controls

Median (interquartile range) DFF values decreased in controls (-5.0 [-18.0-6.0]) compared to subjects with BHR

(4.0 [-6.0-13.0], P<.001). This trend was also observed in groups divided by BHR severity (Group 1, 12.0 [3.0-17.3]; Group 2, 5.0 [-6.3-13.0]; Group 3, -2.0 [-12.0-7.0]; Group 4, -5.0 [-18.0-6.0]; P<.001; Fig. 1).

Similarly, median (interquartile range) RFF values decreased from 1.07 (0.93-1.21) in subjects with BHR to 0.95 (0.84-1.07) in the control group (P<.001), and this trend was also demonstrated in the 4 groups (Group 1, 1.19 [1.04-1.30]; Group 2, 1.07 [0.93-1.20]; Group 3, 0.97 [0.87-1.09]; Group 4, 0.95 [0.84-1.07]; P<.001; Fig. 2).

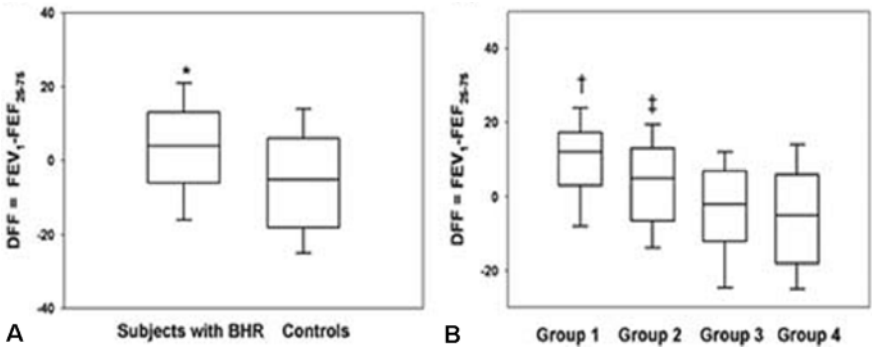

Fig. 1. Box plots comparing the difference between FEF_{25-75} and FEV_1 in subjects with bronchial hyperreactivity and controls (A), and among the groups divided by bronchial hyperreactivity degree (B). Horizontal lines indicate medians; boxes represent the 25th and 75th percentiles; bars represent the 10th and 90th percentiles. *P<0.001 compared to controls; †P<0.001 compared to group 2, 3 or 4; ‡P<0.001 compared to group 3 or 4.

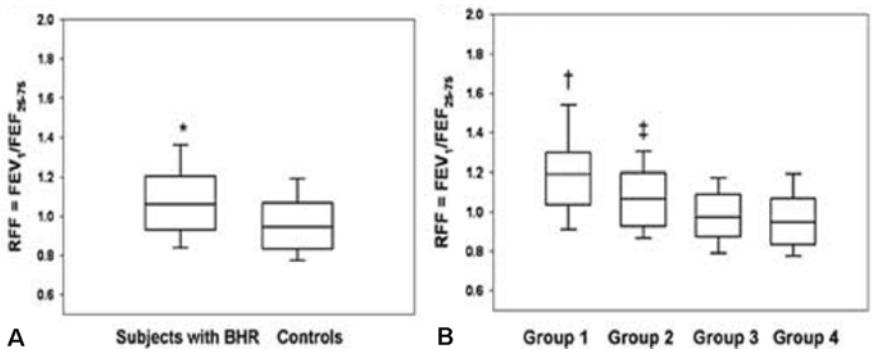

Fig. 2. Box plots comparing the ratio between FEF_{25-75} and FEV_1 in subjects with bronchial hyperreactivity and controls (A), and among the groups divided by bronchial hyperreactivity degree (B). Horizontal lines indicate medians; boxes represent the 25th and 75th percentiles; bars represent the 10th and 90th percentiles. *P<.001 compared to controls; †P<.001 compared to group 2, 3 or 4; ‡P<.001 compared to group 3 or 4.

Table 1. Characteristics of Subjects

Characteristics	Subjects with BHR	Controls
Sex (M:F)	226:98	158:101
Age (years)*	11.8 (8.9-13.2)	11.5 (8.4-12.8)
Severity (n)	Group 1/2/3 (107/106/111)	Group 4 (259)
Eosinophil counts (log μL^{-1})†	2.53±0.37	2.31±0.39
Total IgE (log U/mL)†	2.44±0.60	2.25±0.61
ECP (log μL/L)†	1.21±0.43	1.07±0.38
FEV_1 (% predicted)	81.42±12.47	92.46±14.82
FEF_{25-75} (% predicted)	78.34±21.51	92.03±20.92
FVC (% predicted)†	85.64±12.23	93.32±15.64

*median (interquartile range); †mean±SD, P<.001, Abbreviation : BHR, bronchial hyperresponsivesness

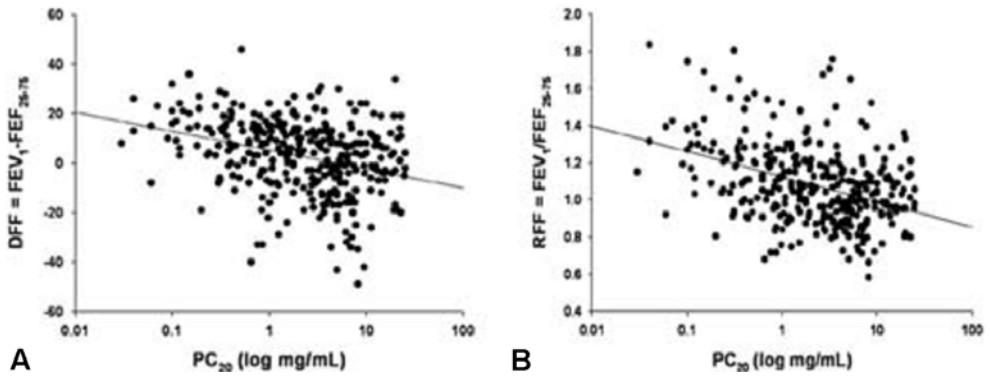

Fig. 3. Relationship of the difference between FEF_{25-75} and FEV_1 (A: γ =−0.337, P<.001) and the ratio between FEF_{25-75} and FEV_1 (B: γ =−0.362, P<.001) with PC_{20}.

2. Correlation between DFF or RFF, and BHR

As shown in Fig. 3, DFF and RFF were negatively correlated with PC_{20} (γ =−0.337, P<.001 and γ =−0.362, P<.001, respectively).

3. Identification of Cutoff Values for BHR

Cutoff values of 0.5 for DFF and 1.042 for RFF were identified by means of ROC analysis for discriminating between subjects with BHR and controls. The area under the ROC curve for DFF was 0.662, and its sensitivity and specificity were 59.6% and 63.7%, respectively (OR [95% CI], 2.59 [1.85-3.63]). The area under the ROC curve for RFF was 0.667, and its sensitivity and specificity were 53.4 % and 68.7% (OR [95% CI], 2.52 [1.79-3.55]).

Discussion

We focused on DFF and RFF as predictive indexes of BHR in this study. DFF and RFF values increased in subjects with BHR compared to controls, and this increasing trend was found in groups divided by BHR severity. DFF and RFF also correlated negatively with PC_{20}.

BHR, which is associated with chronic inflammation, is a pathophysiological feature of asthma and may be evaluated by nonspecific challenge, including methacholine. Nonspecific bronchial provocation testing is clinically useful and widely used in the evaluation of patients with symptoms suggestive of asthma. Although bronchial provocation testing is safe and widely available, the protocol is time consuming and difficult for children to perform, especially for preschool children. In addition, the testing is usually reserved for those with normal or near normal baseline spirometry[8].

The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2 Guidelines recommend spirometric measures, principally FEV_1, for diagnosis and severity assessment of asthma in designing appropriate therapeutic plans[11]. However, the evidence for a relationship between FEV_1 and the risk for asthma outcomes is mixed. It has been reported that predicted FEV_1% is independently associated with clinically important outcomes in children with asthma, asthma symptoms, and health care utilization [12]. Conversely, children with mild, intermittent asthma constitute more than half of all cases of childhood asthma, and asthma severity classified by symptom frequency or medication usage did not correlate with FEV_1, which was generally normal, even in severe persistent asthma[13]. Recently, it has been reported that asthmatic children without symptoms have decreased FEF_{25-75} in a larger proportion of patients than have peak expiratory flow rate or FEV_1, suggesting that FEF_{25-75} is a more sensitive indicator of chronic airflow obstruction[4]. This variable was originally considered to differentiate the most effort-independent portion of the curve, and thus that portion most sensitive to obstructive disease of the small airways[14]. FEF_{25-75} has been also reported to decrease in response to exercise without changes in FEV_1, mainly in children with mild asthma[15]. In addition, it has been shown that a FEF_{25-75} less than 60% of the predicted value might be used to predict the presence of BHR[16].

On the other hand, FEF_{25-75} has been shown to be more variable and less reproducible than FEV_1 because it is influenced by changes in lung volume and the shape of the flow-volume loop, and this is only partially corrected by calculating flow rates at isovolume[17]. In addition, because full vital capacity may not be delivered in a forced expiratory

maneuver in the presence of severe airway obstruction, FEF_{25-75} may underestimate the degree of airway obstruction. The advantages of FEV_1 as a marker of asthma severity include its objectivity and reproducibility[18, 19]. Therefore, we selected the DFF and RFF, which have been recently reported to predict the presence and degree of BHR in allergic adults[6]. Results of the present study correspond well with an earlier study which reported that DFF and RFF are well associated with BHR and its severity. Cutoff values for DFF and RFF, however, are not in accord with the results in allergic adults. Cutoff values had relatively low sensitivity and specificity for confirmative diagnosis in childhood asthma in this study, as well as in adults in the earlier study. Individual differences in DFF and RFF might not be enough to differentiate the presence of BHR. Because FEV_1 and FEF_{25-75} are known to decrease in severe asthma, the DFF and RFF, contrary to expectation, decrease in severe asthma patients with abnormal FEV_1[15]. Our study, nevertheless, is the first report that DFF and RFF is correlated with BHR in children regardless of the presence of allergy.

In conclusion, we suggest that DFF and RFF may be considered an approximate predictor of BHR in the context of a normal FEV_1 in children. In particular, these predictors could be used as good supportive and complementary diagnostic tools for children who cannot perform bronchial provocation testing.

한 글 요 약

소아 천식에서 최대호기중간유량의 기관지 과민성 예측인자로서의 의의

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목 적 : 천식은 하부기도의 만성 염증으로 정의될 수 있으며, 기관지과민성은 천식의 병태생리적인 특징이다. 하부기도를 직접적으로 평가할 수는 없지만 최대호기중간유량(forced expiratory flow between 25 and 75 percent, FEF_{25-75})이 하부기도의 직경을 비교적 잘 반영하는 것으로 알려져 있다. 본 연구에서는 1초간호기량(forced expiratory volume in 1 second, FEV_1)과 FEF_{25-75}를 이용하여 얻어진 이들의 차이(difference between FEV_1 and FEF_{25-75}, DFF)와 비(ratio between FEV_1 and FEF_{25-75}, RFF)를 분석하여 기관지과민성과의 연관성을 알아보고자 하였다.

방 법 : 만 6세에서 15세 사이의 583명을 대상으로 하였다. 전체 대상자에서 폐기능 검사, 메타콜린 흡입 유발시험을 시행하였고, 혈액 내 호산구수, 혈청 총 IgE 농도, 혈청 ECP 농도를 측정하였다. 메타콜린 흡입 유발시험으로 얻어진 PC_{20}을 기준으로 기관지과민성 양성군(PC_{20}>16 mg/mL)과 음성군(PC_{20}=16 mg/mL)을 정의하였으며, 그 중증도에 따라 4군으로(Group 1: <1 mg/mL; Group 2: 1-4 mg/mL; Group 3: 4-16 mg/mL; Group 4: >16 mg/mL, by American Thoracic Society, 1999) 분류하여 분석하였다.

결 과 : DFF는 기관지과민성 양성군에서 4.0 (-6.0-13.0), 음성군에서 -5 (-18.0-6.0)로 양성군에서 음성군에비해 유의하게 높게 나타났다 (P<.001). RFF도 기관지과민성 양성군에서 1.07 (0.93-1.21), 음성군에서 0.95 (0.84-1.07)로 양성군에시 음성군과 비교하여 의미있게 높았다(P<.001). 또한 기관지과민성 중증도에 따라 나눈 4군 사이에서도 DFF (P<.001)와 RFF (P<.001) 모두 유의한 차이를 나타내었다. PC_{20}은 DFF (γ=0.337, P<.001) 및 RFF (γ=0.337, P<.001)와 의미있는 음의 상관 관계를 보였다.

결 론 : FEF_{25-75}를 이용하여 얻어진 DFF와 RFF는 기관지과민성과 밀접한 연관성을 보였고 이를 반영하는 지표가 될 수 있는 가능성을 보여주었다.

References

1) Global Initiative for Asthma. Global strategy for asthma management and prevention. Revised 2006. National Institutes of Health Publication No 95-3659 1995. [accessed 10 January 2006) Available from: URL://http://www. ginasthma.org
2) Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, et al. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997;100:44-51.
3) Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996;154:1505-10.
4) Ferguson AC. Persisting airway obstruction in asymptomatic children with asthma with normal peak expiratory flow rates. J Allergy Clin Immunol 1988;82:19-22.
5) McFadden ER, Jr., Linden DA. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. Am J Med 1972;52:725-37.
6) Cirillo I, Klersy C, Marseglia GL, Vizzaccaro A, Pallestrini E, Tosca M, et al. Role of $FEF_{25\%-75\%}$ as a predictor of bronchial hyperreactivity in allergic patients. Ann Allergy Asthma Immunol 2006;96:692-700.
7) Yoon KA, Lim HS, Kim H, Koh YY. Normal predicted values of pulmonary function test in Korean school-aged children. J Korean Pediatr Soc 1993;36:25-37.
8) Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000;161:309-29.

9) Kang H, Kang EK, Nah KM, Yoo Y, Koh YY. Comparison of Obesity between children with asthma and healthy children. Pediatr Allergy Respir Dis (Korea) 2003;13:17-25.
10) Chai H, Farr RS, Froehlich LA, Mathison DA, McLean JA, Rosenthal RR, et al. Standarization of bronchial inhalation challenge procedure. J Allergy Clin Immunol 1975;56:323-7.
11) National Asthma Education and Prevention Program Expert Panel Report 2: Guidelines for the diagnosis and management of asthma.: Bethesda, MD: NIH publication 96-3659B
12) Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. Pediatrics 2006;118:e347-55.
13) Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr., Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170:426-32.
14) Leuallen EC, Fowler WS. Maximal midexpiratory flow. Am Rev Tuberc 1955;72:783-800.
15) Fonseca-Guedes CH, Cabral AL, Martins MA. Exercise-induced bronchospasm in children: comparison of FEV1 and $FEF_{25-75\%}$ responses. Pediatr Pulmonol 2003;36:49-54.
16) Alberts WM, Ferris MC, Brooks SM, Goldman AL. The $FEF_{25-75\%}$ and the clinical diagnosis of asthma. Ann Allergy 1994;73:221-5.
17) Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis 1991;144:1202-18.
18) Enright PL, Lebowitz MD, Cockroft DW. Physiologic measures: pulmonary function tests. Asthma outcome. Am J Respir Crit Care Med 1994;149:S9-18.
19) Enright PL, Johnson LR, Connett JE, Voelker H, Buist AS. Spirometry in the lung health study. 1. Methods and quality control. Am Rev Respir Dis 1991;143:1215-23.