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 (FFE25-75) might be considered a more sensitive early marker of small airway obstruction than the forced expiratory volume in 1 second (FEV1). 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 FEV1 and FFE25-75 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 FEV1 was calculated (PC20).

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. PC20 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 FEV1 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 limitation1. Measurements of airflow limitation and reversibility are usually undertaken using forced expiratory volume in one second (FEV1), peak expiratory flow (PEF) or provocative concentration causing 20% fall in FEV1 (PC20), which is a concentration of methacholine inducing a 20% decrease in FEV11.

The major site of airway inflammation has been controversial, but recent papers have focused on the importance of peripheral airway inflammation2,3. 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 asthma3.

Among respiratory indexes derived from the forced vital capacity maneuver, forced expiratory flow between 25% and 75% of the lung volume (FEF25-75), 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 FEV14,5. However, FEF25-75 has not been accepted as an objective parameter because it is more variable and less reproducible than FEV1. Recently, new parameters, the difference (DFF) and the ratio (RFF) between FEF25-75 and FEV1, have been suggested in...
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. Thus, we aimed to verify whether an association could be shown between the presence and degree of BHR and DFF and RFF in children.

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. 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. 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 (DeVibbiss 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. 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, 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±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
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(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<sub>25-75</sub> and FEV<sub>1</sub> 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 25<sup>th</sup> and 75<sup>th</sup> percentiles; bars represent the 10<sup>th</sup> and 90<sup>th</sup> percentiles. * P<.001 compared to controls: † P<.001 compared to group 2, 3 or 4; ‡ P<.001 compared to group 3 or 4.](image1)

![Fig. 2. Box plots comparing the ratio between FEF<sub>25-75</sub> and FEV<sub>1</sub> 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 25<sup>th</sup> and 75<sup>th</sup> percentiles; bars represent the 10<sup>th</sup> and 90<sup>th</sup> percentiles. * P<.001 compared to controls: † P<.001 compared to group 2, 3 or 4; ‡ P<.001 compared to group 3 or 4.](image2)

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<td>FVC (% predicted)†</td>
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*median (interquartile range); †mean±SD, P<.001, Abbreviation: BHR, bronchial hyperresponsiveness
2. Correlation between DFF or RFF, and BHR

As shown in Fig. 3, DFF and RFF were negatively correlated with PC_{20} (\( \gamma = -0.337, P < .001 \) and \( \gamma = -0.362, P < .001 \), 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 54.3% 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.

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. 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. 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.

Recently, it has been reported that asthmatic children without symptoms have decreased FEV_{25-75} in a larger proportion of patients than have peak expiratory flow rate or FEV_{1}, suggesting that FEV_{25-75} is a more sensitive indicator of chronic airflow obstruction. 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. FEV_{25-75} has been also reported to decrease in response to exercise without changes in FEV_{1}, mainly in children with mild asthma. In addition, it has been shown that a FEV_{25-75} less than 60% of the predicted value might be used to predict the presence of BHR.

On the other hand, FEV_{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. In addition, because full vital capacity may not be delivered in a forced expiratory
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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. Therefore, we selected the DFF and RFF, which have been recently reported to predict the presence and degree of BHR in allergic adults. 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}. 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.

한글 요약
소아 천식에서 최대호기중간유량의 기관지
과민성 예측인자로서의 의의

소아천식의 왜연의 연세대학교 의과대학 소아과학과 김규원

목적: 천식의 하부기도의 만성 염증으로 경화될 수 있으며, 기관지과민성은 천식의 복잡성의 특징이다. 하부기도의 지적, Torrent 155, 2016 25 and 75 percent, FEF_{25-75} is a higher degree of market

대한기한되어야 할지 여부로 결정한 것으로 알려져 있다. 본 연구에서는 1초

기간기한(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 기관지과민성의 판단을 알아보

고찰 하였다.

방법: 만 6세에서 15세 사이의 583명을 대상으로 하였다. 전

체 대상자에서 폐기능 검사, 에타플린 흡입 유발시험을 시행하였고, 혈액 내 호산구수, 혈청 중 IgE 농도, 혈청 ECP 농도를 측정

하였다. 에타플린 흡입 유발시험으로 얻어진 PC_{20}을 기준으로 기관지과민성 양성군(PE_{20}=16 mg/mL)과 응성군(PE_{20}=16 mg/mL)을 정의하였으며, 그 중간수에 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.

결과: DFF는 기관지과민성 양성군에서 4.0 (~6.0-13.0), 응

성군에서 5.5 (~18.0-6.0)로 양성군에서 응성군에 비해 유의하게 높게 나타났다(\textit{p}<0.001). RFF도 기관지과민성 양성군에서 1.07

(0.93–1.21), 응성군에서 0.95 (0.84–1.07)로 양성군에서 응성군에 비하여 의미있게 높았다(\textit{p}<0.001). 또한 기관지과민성 중증도에 따라 나눈 4군 사이에서도 DFF (\textit{p}<0.001)와 RFF (\textit{p}<0.001) 모두 유의한 차이를 나타내었다. PC_{20}은 DFF (\gamma =0.337, P<

0.001) 및 RFF (\gamma =0.337, P<0.001)와 의의있는 음의 상관 관계를 보였다.

결론: FEF_{25-75}를 이용하여 얻어진 DFF와 RFF는 기관지과

민성과 밀접한 연관성을 보였고 이를 반영하는 지표가 될 수 있

는 가능성을 보여주었다.

References


