



The airway hyperresponsiveness to methacholine may be predicted by impulse oscillometry and plethysmography in children with well-controlled asthma

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ABSTRACT

Objective: Airway hyperresponsiveness (AHR) is a hallmark of asthma. Methacholine challenge test which is mostly used to confirm AHR is not routinely available. The aim of this study was to investigate the predictive values of fractional exhaled nitric oxide (FeNO), impulse oscillometry (IOS), and plethysmography for the assessment of AHR in children with well-controlled asthma. **Methods:** 60 children with controlled allergic asthma aged 6–18 years participated in the study. FeNO measurement, spirometry, IOS, and plethysmography were performed. Methacholine challenge test was done to assess AHR. PC20 and dose response slope (DRS) of methacholine was calculated. **Results:** Mild to severe AHR with PC20 < 4 mg/ml was confirmed in 31 (51.7%) patients. Baseline FeNO and total specific airway resistance (SRtot)%pred and residual volume (RV)%pred levels in plethysmography were significantly higher and FEV1%pred, FEV1/FVC%pred, MMEF%pred values were lower in the group with PC20 < 4 mg/ml. FeNO, SRtot%pred, and RV%pred levels were found to be positively correlated with DRS methacholine. The higher baseline FeNO, frequency dependence of resistance (R5–R20) in IOS and SRtot%pred in plethysmography were found to be significantly related to DRS methacholine in linear regression analysis (β : 1.35, $p = 0.046$, β : 4.58, $p = 0.002$, and β : 0.78, $p = 0.035$, respectively). The cut-off points for FeNO and SRtot% for differentiating asthmatic children with PC20 < 4 mg/ml from those with PC20 \geq 4 mg/ml were 28 ppb (sensitivity: 67.7%, specificity: 72.4%, $p < 0.001$) and 294.9% (sensitivity: 35.5%, specificity: 96.6%, $p = 0.013$), respectively. **Conclusion:** IOS and plethysmography may serve as reliable and practical tools for prediction of mild to severe methacholine induced AHR in otherwise “seemingly well-controlled” asthma.

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Introduction

Airway hyperresponsiveness (AHR) is a prominent clinical feature of asthma. The measurement of AHR in children with asthma is important in monitoring the disease control and adjustment of asthma therapy [1,2]. Methacholine challenge test which is the most widely used direct bronchoprovocation test is highly sensitive for asthma [1]. However, the methodology is laborious, risky, and the utility of the test in most centers is low. Thus, a reliable and more practical alternative test would be useful for the assessment of AHR in controlled asthma.



A recent study demonstrated that the majority of patients with well-controlled asthma still had AHR [3]. Previous studies also showed that airway inflammation persisted in most of the controlled asthma patients despite the fact that their disease was under control [4]. Thus, the measurement of airway inflammation and AHR is useful to achieve adequate asthma control. Fractional exhaled nitric oxide (FeNO) has proven to be a reliable surrogate

marker for eosinophilic airway inflammation and also, it has been reported that FeNO has a significant predictive value for AHR in asthmatics [4,5].

Plethysmography has been introduced as an alternative technique to assess airway resistance in children with asthma. Specific airway resistance was reported to be a practical and reliable marker for detecting airway obstruction and classification of AHR [6,7].

Impulse oscillometry (IOS) which evaluates respiratory mechanics during tidal breathing can be easily applied even in young children [8,9]. It can be used in the assessment of patients with airway limitation and AHR and in predicting loss of asthma control. Also, IOS is reported to be more sensitive than spirometry for the assessment of peripheral airway disease [10].

The aim of this study was to investigate the diagnostic value of IOS and plethysmography for the prediction of the presence of AHR in children with controlled asthma.

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Methods

Study population

Children with allergic asthma aged 6–18 years were recruited from Pediatric Allergy and Immunology Department of Mersin University Hospital from July 2016 to January 2017. The patients were all sensitized to house dust mite and had intermittent and mild to moderate persistent controlled asthma. The controlled asthma was defined as the absence of the daytime symptoms, nocturnal symptoms, limitation of activities, and need for rescue treatment in the previous month according to the criteria of the Global Initiative for Asthma [11]. Inhaled corticosteroid usage was recorded in all patients. The exclusion criteria included a history of a respiratory tract infection in previous 4 weeks, an asthma attack or a history of systemic steroid usage in the last month, a pre-bronchodilator predictive value of forced expiratory volume in 1 second (FEV1) of <70%.

The study was approved by the Institutional Ethical Committee of Mersin University. All patients provided written informed consent prior to taking part in the study.

Study protocol

The baseline lung functions were evaluated with IOS, spirometry, and plethysmography after measuring FeNO levels. AHR was assessed by a spirometric methacholine challenge test after basal respiratory functions were obtained.

Fractional exhaled nitric oxide (FeNO) measurement

FeNO measurement was performed with NIOX (Aerocrine AB, Sweden) system according to American Thoracic Society (ATS) guideline [12]. It was measured prior to lung function or methacholine challenge tests. The patients were instructed to exhale to residual volume. After mouthpiece was inserted, they were asked to inhale to total lung capacity. Finally, the patient exhaled for 10 seconds at a constant flow rate of 50 ml/s.

Pulmonary function tests

Spirometry

Spirometric indices were performed in compliance with ATS guideline by Master Screen Spirometry System (JaegerCO, Germany) [13]. The values of forced expiratory volume in 1 second (FEV1), FEV1 change in percentage predicted value (FEV1 $\Delta\%$ pred), forced vital capacity (FVC), the ratio FEV1/FVC and maximum mid-expiratory flow (MMEF) were recorded [14].

The results were expressed as the percentage of a predicted value. Reversibility test was evaluated after 200 mcg salbutamol administration by the percent change in FEV1 according to predicted value.

Impulse oscillometry

IOS was performed in accordance with European Respiratory Society/American Thoracic Society (ERS/ATS) guideline [15]. It was performed during spontaneous breathing by MasterScreen IOS system (JaegerCO, Germany). The IOS parameters obtained at the end of the application were resistances at 5–20 Hz (R5, 20), and reactance at 5 Hz (X5), area of reactance (AX), R5–R20 (resistance at 5 Hz minus resistance at 20 Hz).

Plethysmography

The measurements of lung volumes and airway resistance were obtained by whole-body plethysmography in compliance with ATS guideline [16]. Measurements were made using a MasterScope Body plethysmography system (Jaeger, Germany). During measurement the whole-body plethysmograph box is closed. One pressure transducer measured the pressure inside the box, another one recorded the mouth pressure during a shutter maneuver. Respiratory flow rate is recorded by pneumotachograph, which is calibrated regularly. Total specific airway resistance (SR_{tot}), total lung capacity (TLC), and RV/TLC (ratio of residual volume to total lung capacity) were recorded and the results were expressed as the percent predicted for age, sex, and height.

Methacholine challenge test

Methacholine challenge test by spirometry was performed according to ATS/ERS guideline [17]. Challenge test was done by 2-minute tidal breathing method. Each patient inhaled doubling increasing doses of methacholine. The provocative concentration of methacholine (PC20) producing a 20% decrease PC20-FEV1 and dose in FEV1 from baseline was determined. Dose response slope (DRS)-FEV1 was calculated to define the methacholine responsiveness. This allowed to use the data of methacholine response from all subjects, regardless of whether they met the conventional definition of AHR based on PC20 < 8 mg/mL. The DRS-FEV1 thus provided a continuous measure of AHR. DRS-FEV1 was defined as the percent decrease in FEV1 from the postsaline value to the last concentration of methacholine used in the challenge test divided by the cumulative dose of methacholine. In categorical classification, those with PC20 < 4 mg/ml included the children with mild, moderate, or severe AHR whereas those with PC20 \geq 4 mg/ml included the subjects

Table 1. The clinical and demographic characteristics and atopy markers of patients with PC20 < 4 mg/ml and PC20 ≥ 4 mg/ml.

| Variable | Patients with PC20 < 4 mg/ml n = 31 | Patients with PC20 ≥ 4 mg/ml n = 29 | p value |
|--|-------------------------------------|-------------------------------------|--------------|
| Age (years) | 12.0 (10.0–15.0) | 9.0 (8.0–13.0) | 0.072 |
| Male gender* | 25 (80.6%) | 15 (51.7%) | 0.018 |
| Height (cm) | 149.0 (137.0–165.0) | 136.0 (125.5–160.0) | 0.057 |
| BMI (kg/m ²) | 20.4 (16.9–22.1) | 17.0 (15.6–20.3) | 0.036 |
| ICS usage* | 16 (51.6%) | 24 (82.7%) | 0.742 |
| Blood eosinophil count cells/mm ³ | 500.0 (200.0–600.0) | 400.0 (200.0–700.0) | 0.557 |
| Total IgE IU/ml | 298.0 (146.0–1750.0) | 458.0 (260.0–750.0) | 0.657 |
| FeNO (ppb) | 36.0 (25.0–52.0) | 24.0 (14.0–31.0) | 0.003 |

Note. *The values were presented as number of patients (%). The other variables were presented as median (25p–75p).

with borderline or no AHR according to ATS guideline [18].

Statistical analysis

For the normally distributed variables means ± standard deviations (SD) were used, otherwise variables were presented as median (25p–75p) levels. The Chi-Square test was used for categorical endpoints. Mann–Whitney *U* test or Independent Sample *t*-test was used for comparison of two groups. Spearman's correlation coefficient (*r*_s) was used for the correlation analysis. Linear regression analysis was used to evaluate the associated factors for DRS-FEV1 methacholine. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value for FeNO and pulmonary indices to predict the patients with PC20 < 4 mg/ml. Beta coefficients (β) with their 95% confidence intervals (95% CI) were estimated. A *p* value of less than 0.05 was considered statistically significant.

Results

Sixty children aged 6–18 years participated in the study. The mean age was 11.4 ± 3.2 years. Forty (66.6%) of the patients were male. A total of 31 (51.7%) patients had a PC20 methacholine < 4 mg/ml. The body mass index (BMI) of patients with PC20 < 4 mg/ml was significantly higher than those with PC20 ≥ 4 mg/ml (*p* = 0.036). Forty (66.6%) of the subjects were using inhaled corticosteroids. There was no significant difference between groups with PC20 < 4 mg/ml and with PC20 ≥ 4 mg/ml in terms of age, ICS usage, blood eosinophil count, and serum IgE levels. FeNO levels were significantly higher in group with PC20 < 4 mg/ml than those with PC20 ≥ 4 mg/ml (*p* = 0.003) (Table 1 and Figure 1a). Fourteen patients with controlled asthma had PC20 methacholine > 16 mg/ml and they were all using inhaled corticosteroids. The clinical and demographic characteristics of patients are presented in Table 1.

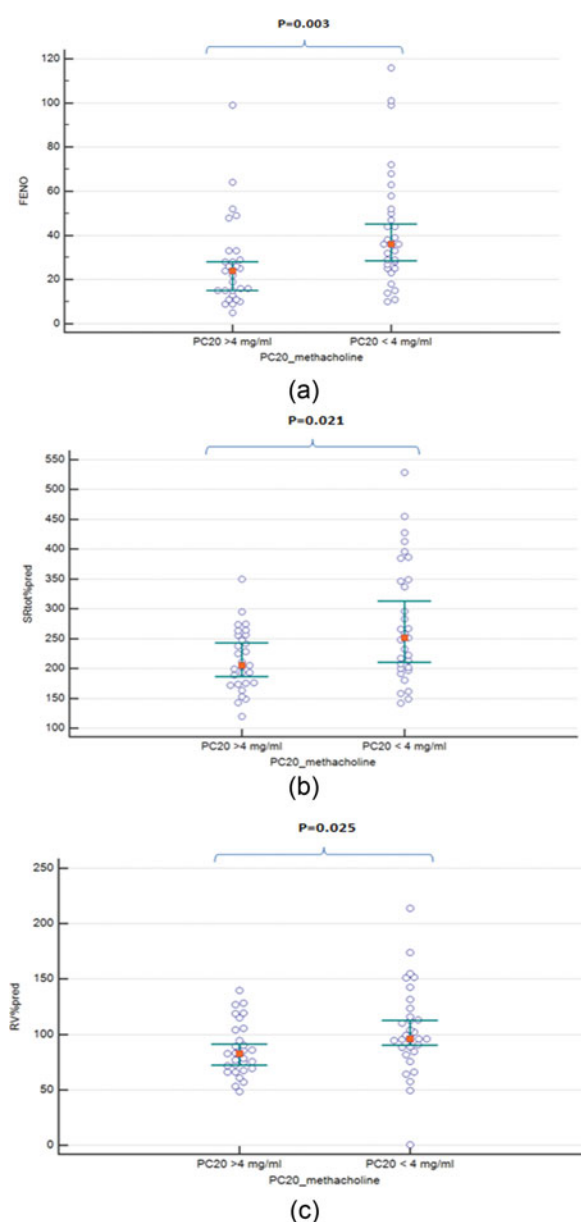


Figure 1. (a) FeNO levels (median, 95% CI) in patients with PC20 methacholine < 4 mg/ml and PC20 methacholine ≥ 4 mg/ml. (b) SRtot%pred levels (median, 95% CI) in patients with PC20 methacholine < 4 mg/ml and PC20 methacholine ≥ 4 mg/ml. (c) RV%pred levels (median, 95% CI) in patients with PC20 methacholine < 4 mg/ml and PC20 methacholine ≥ 4 mg/ml.

Table 2. The comparison of pulmonary function tests (spirometry, impulse oscillometry, and plethysmography) of patients with PC20 < 4 mg/ml and PC20 ≥ 4 mg/ml.

| Variable | Patients with PC20 < 4 mg/ml n = 31 | Patients with PC20 ≥ 4 mg/ml n = 29 | p value |
|-----------------------------|-------------------------------------|-------------------------------------|--------------|
| Spirometry | | | |
| FVC% pred.* | 99.9 ± 12.5 | 103.5 ± 9.9 | 0.226 |
| FEV1% pred.* | 93.2 ± 14.7 | 102.7 ± 12.0 | 0.009 |
| FEV1Δ% pred.* | 8.3 (5.1–12.9) | 5.8 (1.8–8.6) | 0.016 |
| FEV1/FVC% | 92.6 ± 9.5 | 99.4 ± 8.4 | 0.005 |
| MMEF% pred.* | 66.9 ± 21.3 | 83.4 ± 24.0 | 0.007 |
| Impulse oscillometry | | | |
| R5 Hz % pred. | 121.1 (107.2–142.7) | 110.1 (90.6–131.0) | 0.059 |
| ΔR5% pred. | –25.0 (–37.0–9.0) | –12.0 (–26.0–4.2) | 0.112 |
| R20Hz% pred.* | 119.6 ± 29.2 | 108.6 ± 27.4 | 0.102 |
| X5 | –0.19 (–0.31–0.13) | –0.22 (–0.34–0.14) | 0.579 |
| AX | 1.5 (0.9–3.1) | 1.4 (0.7–3.0) | 0.734 |
| ΔAX | –40.4 (–65.0–26.0) | –39.0 (–53.0–16.0) | 0.211 |
| R5–R20% pred. | 3.9 (–7.4–20.9) | 0.3 (–7.9–11.6) | 0.446 |
| Plethysmography | | | |
| SRtot% pred. | 251.7 (199.7–348.9) | 205.4 (174.2–256.0) | 0.021 |
| TLC% pred.* | 102.5 ± 10.2 | 99.2 ± 10.9 | 0.234 |
| RV% pred. | 95.9 (84.4–123.8) | 82.6 (68.4–104.7) | 0.025 |
| RV/TLC % | 95.9 (78.6–113.2) | 81.5 (65.9–107.1) | 0.078 |

Note. *The values were presented as mean ± SD. The other variables were presented as median (25p–75p).

Δ means the ratio of difference between the absolute values obtained before and after salbutamol inhalation to the absolute value before salbutamol and the result was multiplied by 100.

Δ% pred: change in percentage predicted value.

Comparison of baseline pulmonary function tests of patients with PC20 methacholine < 4 mg/ml and PC20 ≥ 4 mg/ml in patients with controlled asthma

The values of FEV1%pred ($p = 0.009$), FEV1/FVC%pred ($p = 0.005$), MMEF%pred ($p = 0.007$) were significantly lower in the group with PC20 methacholine < 4 mg/ml than those with PC20 methacholine level ≥ 4 mg/ml. (FEV1 Δ% pred) ($p = 0.016$), total specific airway resistance (SRtot%pred) ($p = 0.021$) (Figure 1b), and residual volume (RV%pred) ($p = 0.025$) (Figure 1c) were significantly higher in children with PC20 methacholine < 4 mg/ml than those with PC20 methacholine ≥ 4 mg/ml (Table 2). No significant difference was found between groups in terms of FVC%pred ($p = 0.226$), resistance at 5 Hz (R5%pred) ($p = 0.059$), ΔR5%pred ($p = 0.112$), resistance at 20 Hz (R20%pred) ($p = 0.102$), frequency dependence of resistance (R5–R20)%pred ($p = 0.446$), reactance at 5 Hz (X5) ($p = 0.579$), area of reactance (AX) ($p = 0.734$), ΔAX ($p = 0.211$), total lung capacity (TLC% pred) ($p = 0.234$), and RV/TLC% ($p = 0.078$) levels (Table 2).

Correlation analysis of FeNO and pulmonary function tests with DRS-FEV1 methacholine in patients with controlled asthma

In Spearman correlation analysis, FEV1%pred ($r_s: -0.33$, $p = 0.009$), FEV1/FVC%pred ($r_s: -0.39$, $p = 0.002$), and MMEF%pred ($r_s: -0.38$, $p = 0.002$) levels were found to be negatively correlated with DRS-FEV1 methacholine whereas FeNO ($r_s: 0.41$, $p = 0.001$),

SRtot%pred ($r_s: 0.33$, $p = 0.010$), and RV%pred ($r_s: 0.32$, $p = 0.013$) values were positively correlated (Table 3).

Also, R5–R20% predicted levels were found to be positively correlated with SRtot% pred ($r_s: 0.38$, $p = 0.003$), RV% pred ($r_s: 0.29$, $p = 0.027$), and RV/TLC ($r_s: 0.30$, $p = 0.020$) in correlation analysis. RV% predicted levels were also found to be positively correlated with SRtot% pred ($r_s: 0.35$, $p = 0.007$).

Linear regression and ROC analysis of factors that are related to DRS-FEV1 methacholine in patients with controlled asthma

The higher FeNO, R5–R20%pred and SRtot%pred values were found to be significantly related to DRS-FEV1 methacholine in linear regression analysis ($\beta: 1.35$, $p = 0.046$, $\beta: 4.58$, $p = 0.002$, and $\beta: 0.78$, $p = 0.035$,

Table 3. Correlation analysis of pulmonary function tests and DRS methacholine.

| Variable | Spearman correlation coefficient (r_s) | p value |
|------------------------|--|--------------|
| FEV1% pred. | –0.33 | 0.009 |
| FEV1/FVC% pred. | –0.39 | 0.002 |
| MMEF% pred. | –0.38 | 0.002 |
| R5% pred. | 0.20 | 0.118 |
| R20% pred. | 0.12 | 0.344 |
| R5–R20% | 0.12 | 0.342 |
| X5 | –0.02 | 0.874 |
| AX | 0.11 | 0.380 |
| SRtot% pred. | 0.33 | 0.010 |
| TLC% pred. | 0.23 | 0.082 |
| RV% pred. | 0.32 | 0.013 |
| RV/TLC% | 0.25 | 0.051 |
| FeNO (ppb) | 0.41 | 0.001 |
| Blood eosinophil count | 0.23 | 0.080 |

respectively) independent of age, gender, BMI, ICS usage, and blood eosinophil count (Table 4).

In the ROC analysis, FeNO level higher than 28 ppb was found to be significantly related to the risk of having a PC20 level < 4 mg/ml (AUC: 0.723, $p < 0.001$, sensitivity: 67.7%, and specificity: 72.4%) (Figure 2a). SRtot level higher than 294.9% was found to be significantly related to the risk of having a PC20 level < 4 mg/ml (AUC: 0.674, $p = 0.013$, sensitivity: 35.5%, and specificity: 96.6%) (Figure 2b). The combination of these two markers yielded more powerful specificity; if the level of SRtot $\geq 294.9\%$ with the level of FeNO ≥ 28 ppb, the specificity increased to 100% but the sensitivity decreased to 32.3%.

Discussion

AHR is a major characteristic of asthma. The evaluation of AHR is used for the diagnosis of asthma and also monitoring disease control [2]. Methacholine challenge test is one of the standard bronchoprovocation techniques for the assessment of AHR and diagnosis of asthma [1]. Unfortunately, methacholine challenge test is not easy to perform especially in children and takes considerable time. For practical purposes it would be of great importance to know whether airway hyperresponsiveness can be predicted by non-invasive and well tolerated tools. Thus, simple and accurate measurement techniques to assess AHR would be more valuable and practical.

We found that 51.7% of the patients had mild to severe AHR with PC20 < 4mg/ml despite the fact that 51.6% of these subjects were using ICS and they all had clinically well-controlled asthma. FeNO, total specific airway resistance (SRtot), and residual volume (RV%) levels were significantly higher in asthmatic children with mild to severe AHR than those with borderline or no AHR. In addition, the higher FeNO, R5–R20%pred and SRtot%pred values were found to be significantly associated to DRS-FEV1 methacholine levels in patients with controlled asthma.

Table 4. Linear regression analysis of factors that are related to DRS methacholine.

| Variable | Beta coefficient (95% CI) | <i>p</i> value |
|--|---------------------------|----------------|
| Age (years) | 12.28 (−7.61–32.18) | 0.221 |
| Gender | 61.09 (−61.09–183.27) | 0.321 |
| BMI (kg/m ²) | −9.57 (−25.07–5.94) | 0.221 |
| ICS usage | −17.80 (−143.52–107.90) | 0.777 |
| FeNO (ppb) | 1.35 (1.01–1.79) | 0.046 |
| Blood eosinophil count cells/mm ³ | 0.12 (−0.08–0.33) | 0.223 |
| FEV1% pred. | −1.03 (−5.83–3.76) | 0.668 |
| MMEF% pred. | 1.38 (−3.08–5.84) | 0.537 |
| R5–R20% pred. | 4.58 (1.81–7.35) | 0.002 |
| SRtot% pred. | 0.78 (0.06–1.49) | 0.035 |

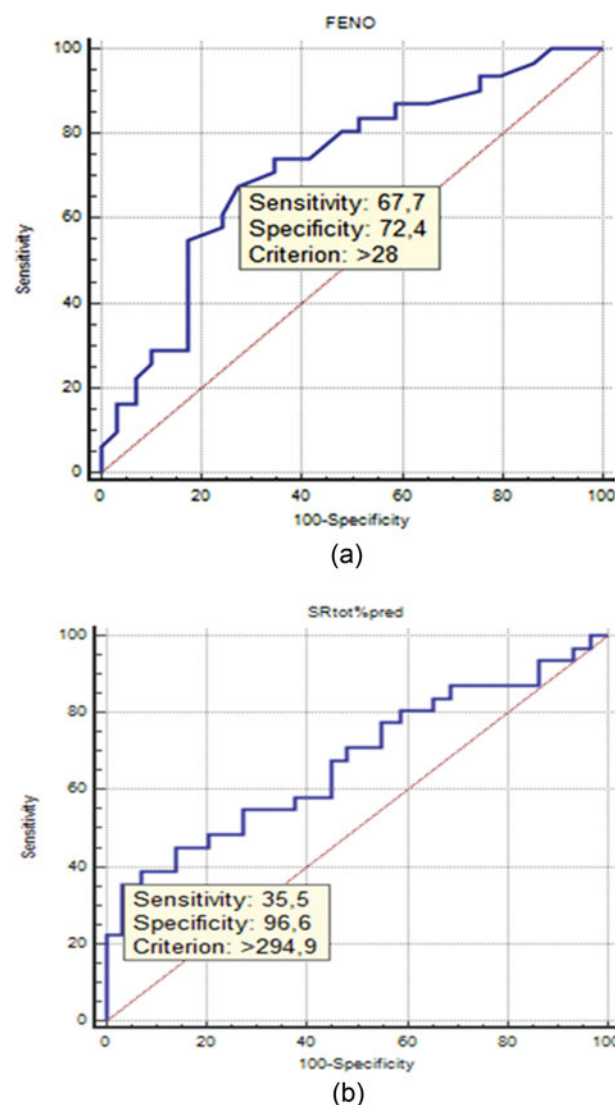


Figure 2. (a) The receiver operating characteristic curve for FeNO to predict PC20 methacholine < 4 mg/ml (AUC: 0.723, $p < 0.001$). (b) The receiver operating characteristic curve for SRtot%pred to predict PC20 methacholine < 4 mg/ml (AUC: 0.674, $p = 0.013$).

It has been suggested that, even in mild asthma, monitoring of airway inflammation and bronchial hyperresponsiveness would be useful for determining the control of the disease and the efficacy of anti-inflammatory treatment [11]. Bronchoprovocation tests can be categorized as direct or indirect. Methacholine challenge test is the most often used direct bronchoprovocation test in the clinical assessment of asthma. A negative methacholine challenge test has a high predictive value to exclude current asthma with reasonable certainty whereas a positive challenge test is consistent with but not diagnostic of asthma [1]. To date, numerous studies of patients with asthma have identified association between AHR to indirect stimulus and FeNO than with direct stimulus in this population [5,19–21].

FeNO is currently used as a non-invasive and reliable indicator of the airway inflammatory status in patients with asthma. Previous studies reported that patients with well-controlled asthma still had airway inflammation or AHR although the asthma was under control [3,4]. Consistent with these results, we found that a total of 31 (51.7%) patients had mild to severe AHR although they had well-controlled asthma. In this aspect, FeNO may have a predictive value as a non-invasive marker to assess AHR in controlled asthma. In the present study, FeNO levels were significantly higher in asthmatic children with mild to moderate AHR than with borderline or no AHR. Recent studies investigated the predictive value of FeNO for methacholine induced AHR [21,22]. It was shown that dose response ratio of methacholine challenge test was correlated positively with bronchial and airway tissue nitric oxide in asthmatic children [22]. However, a previous study suggested that levels of exhaled NO were not accurate predictors of the degree of airway responsiveness to inhaled methacholine in children with mild intermittent asthma [23]. We demonstrated that a FeNO level higher than 28 ppb was significantly related to mild to severe AHR among asthmatic children who were otherwise well controlled.

In the present study, FEV1%, FEV1/FVC%, and MMEF% levels in spirometry were found to be significantly lower in the group with mild to severe AHR than those with borderline AHR or no AHR. Since the response to methacholine has been shown to depend partly on airway caliber [17], this result was not unexpected. It has been investigated whether spirometry indices measured at baseline may allow predicting AHR. Comparing baseline FEV1 and forced expiratory flow between 25 and 75% of vital capacity (FEF 25%–75%) between patients with methacholine induced AHR and without AHR, only FEF 25%–75% levels were significantly lower in group with methacholine induced AHR [3]. Kaminsky et al. demonstrated that mean baseline FEV1 and FVC levels of asthmatic patients with methacholine induced AHR were significantly lower than those without, but FEV1/FVC levels were not so different [24].

Recent studies suggested that asthmatics with AHR have more severe small airway obstruction and inversely, small airway obstruction seems to significantly contribute to the degree of severity of AHR [25]. Furthermore, small airway dysfunction in asthma is becoming recognized as a distinct clinical phenotype related with poor asthma control [26]. The increased sensitivity of IOS gives promise for the measurement of small airway function as well as AHR in asthmatics [27,28]. Short et al. demonstrated that the magnitude of changes seen with IOS parameters including peripheral airway resistance, area under the curve, and resonant frequency during methacholine

challenge test was greater compared with spirometry [28]. Naji et al. reported that other IOS parameters (R5–R20, AX, X5) were more sensitive than spirometry and plethysmography measurements in detecting methacholine induced bronchoconstriction [7]. IOS measurements have shown to reliably reflect the changes in lung function during bronchial challenge in children with sensitivity comparable to spirometry and plethysmography [29]. However, most IOS studies in pediatric stable asthma assess the airway obstruction during bronchoprovocation test and relatively few data are available regarding the assessment of baseline airway parameters. In the present study, the level of baseline R5–R20 which reflects the resistance in peripheral airways was found to be significantly related to DRS-methacholine suggesting the relation between small airway dysfunction and AHR to methacholine.

There is accumulating evidence that body plethysmography has a higher sensitivity than spirometry for detecting methacholine induced AHR [30,31]. Plethysmography has been introduced as an alternative technique to measure the respiratory mechanics in children with asthma [32]. If body plethysmography is used in combination with spirometry in routine bronchial inhalation challenges, experience shows that up to 20% of patients demonstrate a positive response in specific airway resistance (sRaw) without sufficient response in FEV1 [31]. SRtot is reported to be a reliable indicator for the assessment of small airway obstruction [32,33]. We showed that baseline SRtot levels were significantly higher in asthmatic children with PC20 < 4 mg/ml than those without. This data suggested that the presence of small airway dysfunction would be associated with an increased AHR as measured by methacholine challenge test. Furthermore, SRtot level higher than 294.9% was found to be significantly related to the severity of AHR with a sensitivity of 35.5% and a specificity of 96.6%. Nensa et al. found the specific airway resistance to be the most sensitive parameter to detect AHR during methacholine challenge test [6]. Plethysmography also gives valuable information regarding the air trapping [34]. RV in plethysmography is a reliable marker for small airway dysfunction [35,36]. It has been investigated whether AHR can be predicted by a surrogate test such as plethysmography in adults. RV/TLC was reported to be the best predictor of a positive methacholine challenge test [37]. In accordance with this data, we found that RV level, a reliable marker of small airway dysfunction, was higher in the group with mild to severe AHR than those without.

We showed that plethysmography had a greater specificity (95%) in relation to presence of mild to severe AHR in controlled asthma. In addition, combining the markers, FeNO and SRtot, yielded more powerful specificity.

Furthermore, if levels of SRtot greater than 294.9% and levels of FeNO greater than 28 ppb were present, the specificity increased to 100% but the sensitivity decreased to 32.3%.

In accordance with current guidelines, measures of airway caliber and symptoms allow clinicians to assess the degree of asthma control. However, these parameters fail to reflect the extent of underlying endobronchial inflammation and airway hyperresponsiveness. It was shown that asthmatic patients with an adequate control of their symptoms might be still at risk of exacerbations associated with underlying airway inflammation [38]. The increased AHR may indicate the presence of under-treated airway inflammation and thus be a useful therapeutic target in asthma [39]. However, some studies reported that AHR is weakly associated with asthma symptoms, the need for medications and lung function [40,41]. Nuijsink and colleagues found no increase in the number of symptom-free days using the AHR strategy in children over a 2-year period [40]. Also, a previous study in adults also found no advantage in using a AHR strategy with methacholine in terms of improvements in symptoms, peak expiratory flow, or beta-2-agonist use [41].

The shortcoming of the present study was the relatively small sample size. However, the strengths of this study were the demonstration of the association between baseline SRtot and direct AHR in children with well-controlled asthma and the comparison of different markers for direct AHR. In addition, a cut-off point for baseline SRtot to predict the severity of AHR was not reported in controlled asthmatic children in the literature.

Conclusions

In conclusion, this study suggested that FeNO, R5–R20 in IOS, and SRtot in plethysmography are reliable and practical markers for prediction of mild to severe methacholine induced AHR in well-controlled asthma. In addition, the detection of AHR and markers of small airway dysfunction in children who had otherwise “seemingly well-controlled” asthma may provide optimal treatment of this disease.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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