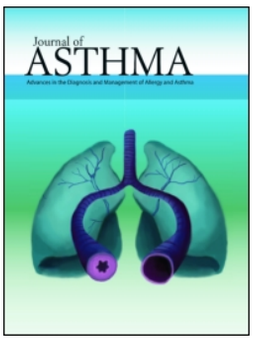

Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: http://www.tandfonline.com/loi/ijas20

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To cite this article: Tugba Arıkoglu, Ayyuce Unlu, Didem Derici Yıldırım & Semanur Kuyucu (2017): The airway hyperresponsiveness to methacholine may be predicted by impulse oscillometry and plethysmography in children with well-controlled asthma, Journal of Asthma

To link to this article: https://doi.org/10.1080/02770903.2017.1407337

Published online: 12 Dec 2017.

JOURNAL OF ASTHMA
https://doi.org/10.1080/02770903.2017.1407337

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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.

ARTICLE HISTORY
Received 18 September 2017
Revised 26 October 2017
Accepted 15 November 2017

KEYWORDS
Airway hyperresponsiveness; asthma; exhaled nitric oxide; impulse oscillometry; methacholine provocation test; plethysmography; spirometry

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, 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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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ijas.

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 Δ% 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 (SRtot), 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% decreasePC20-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 ≥ 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/m²)	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/mm³	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 (rs) 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.

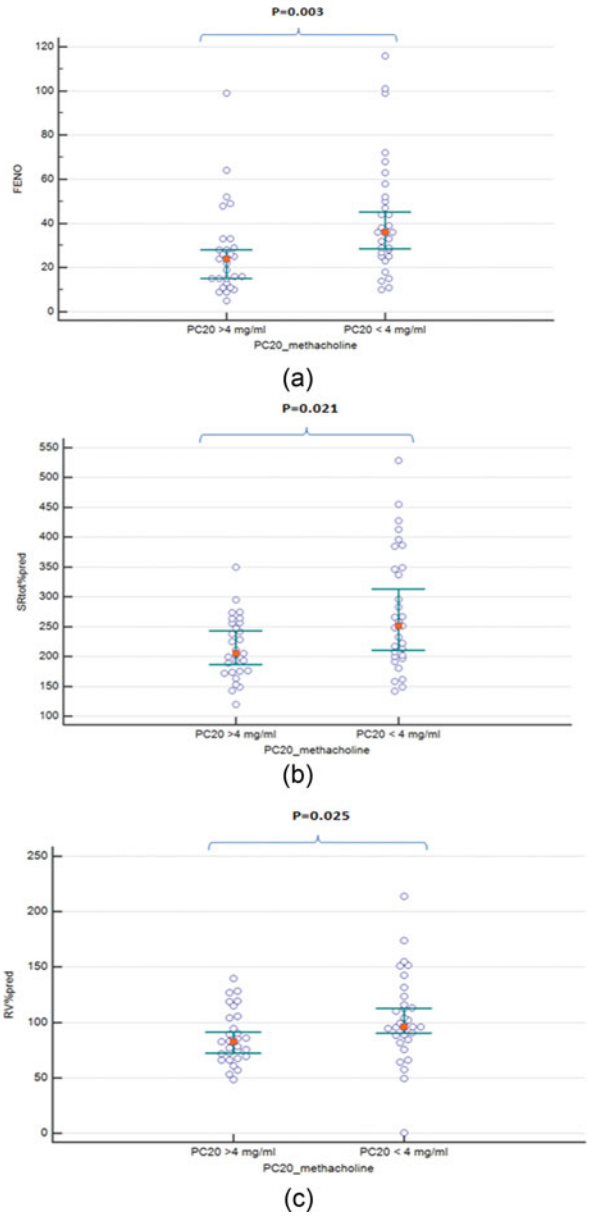

Figure 1. (a) FeNO levels (median, 95% CI) in patients with PC20 methacholine < 4 mg/ml and PC20 methacholine ≥ 4 mg/ml. (b) SRtot%pred levels (median, 95% CI) in patients with PC20 methacholine < 4 mg/ml and PC20 methacholine ≥ 4 mg/ml. (c) RV%pred levels (median, 95% CI) in patients with PC20 methacholine < 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% pred 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% pred 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 (β: 1.35, $p = 0.046$, β: 4.58, $p = 0.002$, and β: 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 ≥ 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.

It has been suggested that, even in mild asthma, monitoring of airway inflammation and bronchial hyperresponsiveness would be useful for determining the control

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

Variable	Beta coefficient (95% CI)	*p* value
Age (years)	12.28 (−7.61–32.18)	0.221
Gender	61.09 (−61.09–183.27)	0.321
BMI (kg/m²)	− 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/mm³	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**

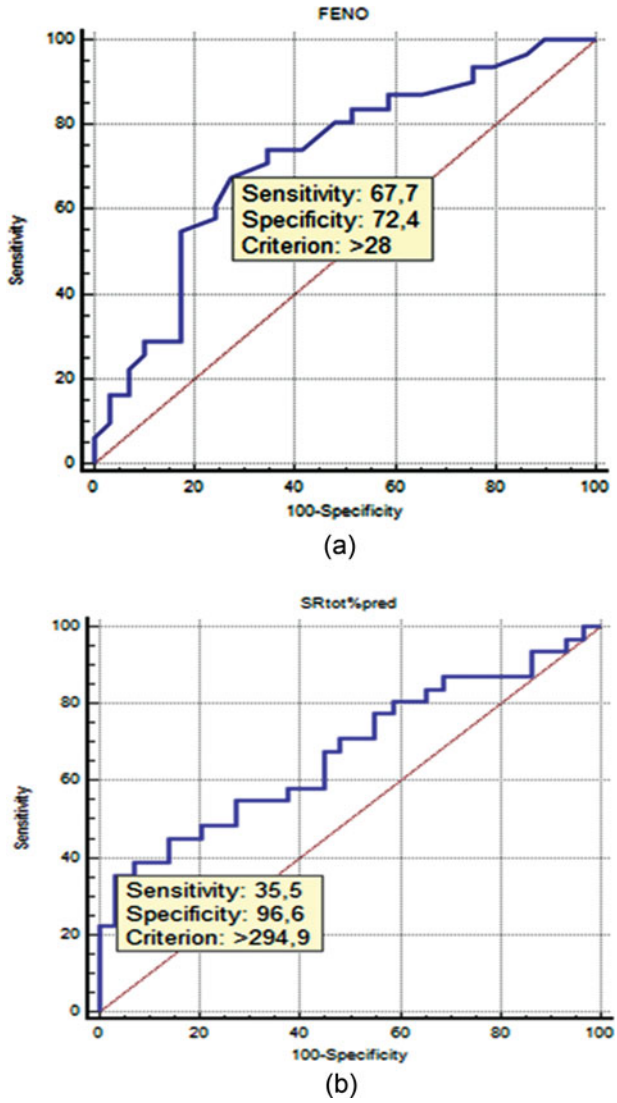

Figure 2. (a) The receiver operating characteristic curve for FeNO to predict PC20 methacholine < 4 mg/ml (AUC: 0.723, $p < 0.001$). (b) The receiver operating characteristic curve for SRtot%pred to predict PC20 methacholine < 4 mg/ml (AUC: 0.674, $p = 0.013$).

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 relativeley 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.

Funding

There is no funding

References

1. Cockcroft D, Davis B. Direct and indirect challenges in the clinical assessment of asthma. Ann Allergy Asthma Immunol 2009;103:363–369. doi:10.1016/S1081-1206(10)60353-5.
2. Galera R, Casitas R, Martínez-Cerón E, Romero D, García-Río F. Does airway hyperresponsiveness monitoring lead to improved asthma control? Clin Exp Allergy 2015;45(9):1396–1405. doi:10.1111/cea.12539.
3. Huang J, Zhang M, Zhang X, Wang L. Airway hyperresponsiveness and small airway function in children with well-controlled asthma. Pediatr Res 2015;77:819–822. doi:10.1038/pr.2015.42.
4. Muñoz X, Sanchez-Vidaurre S, Roca O, Torres F, Morell F, Cruz MJ. Bronchial inflammation and hyperresponsiveness in well-controlled asthma. Clin Exp Allergy 2012;42:1321–1328. doi:10.1111/j.1365-2222.2012.04004.x.
5. Barreto M, Zambardi R, Villa MP. Exhaled nitric oxide and other exhaled biomarkers in bronchial challenge with exercise in asthmatic children: current knowledge. Paediatr Respir Rev 2015;16:68–74.
6. Nensa F, Marek W, Marek E, Smith HJ, Kohlhäufl M. Assessment of airway hyperreactivity: comparison of forced spirometry and body plethysmography for methacholine challenge tests. Eur J Med Res 2009;14(Suppl 4):170–176.
7. Naji N, Keung E, Kane J, Watson RM, Killian KJ, Gauvreau GM. Comparison of changes in lung function measured by plethymography and IOS after bronchoprovocation. Respir Med 2013;107:503–510. doi:10.1016/j.rmed.2012.12.022.
8. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. Chest 2014;146:841–847. doi:10.1378/chest.13-1875.
9. Komarow HD, Myles IA, Uzzaman A, Metcalfe DD. Impulse oscillometry in the evaluation of diseases of the airways in children. Ann Allergy Asthma Immunol 2011;106:191–199. doi:10.1016/j.anai.2010.11.011.
10. Desiraju K, Agrawal A. Impulse oscillometry: the state-of-art for lung function testing. Lung India 2016;33(4):410–416. doi:10.4103/0970-2113.184875.
11. Global Strategy for Asthma Management and Prevention. Global İnitiative for Asthma (GINA) 2011. Accessed 2012 July 1 Available from: http://www.ginaasthma.org.
12. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602–615. doi:10.1164/rccm.9120-11ST.
13. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J 2005;26:153–161. doi:10.1183/09031936.05.00034505.
14. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948–968. doi:10.1183/09031936.05.00035205.
15. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007;175:1304–1345. doi:10.1164/rccm.200605-642ST.

16. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS task force on standards for infant respiratory function testing. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17:302–312. doi:10.1183/09031936.01.17203020.
17. 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(1):309–329.
18. Coates AL, Wanger J, Cockcroft DW, Culver BH, Kai-Håkon C, Diamant Z, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017;49(5). doi:10.1183/13993003.01526-2016.
19. Sverrild A, Porsbjerg C, Thomsen SF, Backer V. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study. J Allergy Clin Immunol 2010;126(5):952–958. doi:10.1016/j.jaci.2010.08.028.
20. Grzelewski T, Grzelewska A, Majak P, Stelmach W, Kowalska A, Stelmach R, et al. Fractional exhaled nitric oxide (FeNO) may predict exercise-induced bronchoconstriction (EIB) in schoolchildren with atopic asthma. Nitric Oxide 2012;27(2):82–87. doi:10.1016/j.niox.2012.05.002.
21. Park YA, Park HB, Kim YH, Sul IS, Yoon SH, Kim HR. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide in children with asthma. J Asthma 2017;54(6):644–51. doi:10.1080/02770903.2016.1255751.
22. Kim YH, Sol IS, Yoon SH, Kim MJ, Kim KW, Sohn M, et al. Association of extended nitric oxide parameters with bronchial hyperresponsiveness and bronchodilator response in children with asthma. J Breath Res 2017;11(4):046003. doi:10.1088/1752-7163/aa7c1f.
23. Silvestri M, Spallarossa D, Battistini E, Brusasco V, Rossi GA. Dissociation between exhaled nitric oxide and hyperresponsiveness in children with mild intermittent asthma. Thorax 2000;55(6):484–488. doi:10.1136/thorax.55.6.484.
24. Kaminsky DA, Daud A, Chapman DG. Relationship between the baseline alveolar volume-to-total lung capacity ratio and airway responsiveness. Respirology 2014;19(7):1046–1051. doi:10.1111/resp.12347.
25. Telenga ED, van den Berge M, Ten Hacken NH, Riemersma RA, van der Molen T, Postma DS. Small airways in asthma: their independent contribution to the severity of hyperresponsiveness. Eur Respir J 2013;41(3):752–754. doi:10.1183/09031936.00170912.
26. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. Lancet Respir Med 2014;2(6):497–506. doi:10.1016/S2213-2600(14)70103-1.
27. Alfieri V, Aiello M, Pisi R, Tzani P, Mariani E, Marangio E, et al. Small airway dysfunction is associated to excessive bronchoconstriction in asthmatic patients. Respir Res 2014;15:86 doi:10.1186/s12931-014-0086-1.
28. Short PM, Anderson WJ, Manoharan A, Lipworth BJ. Usefulness of impulse oscillometry for the assessment of airway hyperresponsiveness in mild-to-moderate adult asthma. Ann Allergy Asthma Immunol 2015;115:17–20. doi:10.1016/j.anai.2015.04.022.
29. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003;22(6):1026–1041. doi:10.1183/09031936.03.00089403.
30. Merget R, Nensa F, Heinze E, Taeger D, Bruening T. Spirometry or body plethysmography for the assessment of bronchial hyperresponsiveness? Adv Exp Med Biol 2016;921:1–10.
31. Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, et al. Working group for body plethysmography of the German Society for Pneumology and Respiratory Care, body plethysmography–its principles and clinical use. Respir Med 2011;105:959–971. doi:10.1016/j.rmed.2011.02.006.
32. Urbankowski T, Przybyłowski T. Methods of airway resistance assessment. Pneumonol Allergol Pol 2016;84:134–141. doi:10.5603/PiAP.2016.0014.
33. Kaminsky DA. What does airway resistance tell us about lung function? Respir Care 2012;57:85–96. doi:10.4187/respcare.01411.
34. McNulty W, Usmani OS. Techniques of assessing small airways dysfunction. Eur Clin Respir J 2014;1. doi:10.3402/ecrj.v1.25898.
35. Perez T, Chanez P, Dusser D, Devillier P. Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction. Respir Med 2013;107:1667–1674. doi:10.1016/j.rmed.2013.08.009.
36. Jain VV, Abejie B, Bashir MH, Tyner T, Vempilly J. Lung volume abnormalities and its correlation to spirometric and demographic variables in adult asthma. J Asthma 2013;50:600–605. doi:10.3109/02770903.2013.789058.
37. Stanbrook MB, Chapman KR, Kesten S. Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest 1995;107(4):992–995. doi:10.1378/chest.107.4.992.
38. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. Am J Respir Crit Care Med 1999;160:594–599. doi:10.1164/ajrccm.160.2.9811100.
39. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010;138:11S–17S. doi:10.1378/chest.10-0231.
40. Nuijsink M, Hop WC, Sterk PJ, Duiverman EJ, de Jongste JC. Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial. Eur Respir J 2007;30(3):457–466. doi:10.1183/09031936.00111806.
41. Koenig SM, Murray JJ, Wolfe J, Andersen L, Yancey S, Prillaman B, et al. Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma? Respir Med 2008;102(5):665–673. doi:10.1016/j.rmed.2007.12.023.