Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma

L P Malmberg, A S Pelkonen, T Haaheta, M Turpeinen

Background: Respiratory function and airway inflammation can be evaluated in preschool children with special techniques, but their relative power in identifying young children with asthma has not been studied. This study was undertaken to compare the value of exhaled nitric oxide (FE_{NO}), baseline lung function, and bronchodilator responsiveness in identifying children with newly detected probable asthma.

Methods: Ninety six preschool children (age 3.8–7.5 years) with asthmatic symptoms or history and 62 age matched healthy non-atopic controls were studied. FE_{NO} was measured with the standard online single exhalation technique, and baseline lung function and bronchodilator responsiveness were measured using impulse oscillometry (IOS).

Results: Children with probable asthma (n=21), characterised by recent recurrent wheeze, had a significantly higher mean (SE) concentration of FE_{NO} than controls (22.1 (3.4) ppb v 5.3 (0.4) ppb; mean difference 16.8 ppb, 95% CI 12.0 to 21.5) and also had higher baseline respiratory resistance, lower reactance, and larger bronchodilator responses expressed as the change in resistance after inhalation of salbutamol. Children with chronic cough only (n=46) also had significantly raised mean FE_{NO} (9.2 (1.5) ppb; mean difference 3.9 ppb, 95% CI 0.8 to 7.0) but their lung function was not significantly reduced. Children on inhaled steroids due to previously diagnosed asthma (n=29) differed from the controls only in their baseline lung function. The analysis of receiver operating characteristics (ROC) showed that FE_{NO} provided the best power for discriminating between children with probable asthma and healthy controls, with a sensitivity of 86% and specificity of 92% at the cut off level of 1.5 SD above predicted.

Conclusions: FE_{NO} is superior to baseline respiratory function and bronchodilator responsiveness in identifying preschool children with probable asthma. The results emphasise the presence of airway inflammation in the early stages of asthma, even in young children.

Bronchial hyperresponsiveness, variable airway obstruction, typical symptoms, and airway inflammation are the manifestations which constitute the current definition of asthma. 

Because there is a lack of lung function methods suitable for use in young children, the diagnosis of asthma has largely been based on the clinical history, with recurrent wheezing being the most predictive symptom of asthma. The assessment of lung function in young children has recently become possible using methods which do not require active cooperation. The discriminative capacity of bronchodilator responsiveness, assessed by the interrupter technique, impulse oscillometry and whole body plethysmography—all of which can be used in young children—was recently compared in a series of asthmatic and healthy children. Differences between the techniques were small, which is not surprising since they all measure respiratory mechanics and the same manifestation of asthma—namely, variable airways obstruction.

The most common non-invasive methods currently available for measuring airway inflammation in asthma include induced sputum and exhaled nitric oxide (FE_{NO}), the latter being especially attractive in children because of the ease of measurement. However, there are only a limited number of reports on the use of FE_{NO} in preschool children with asthma. As airway inflammation seems to be present earlier than changes in lung function in patients with asthma-like symptoms, we hypothesised that the discriminative properties of estimates of airway inflammation might be even better than those of lung function in the assessment of newly detected asthma.

A study was therefore undertaken to compare measures of lung function (assessed by impulse oscillometry, IOS) and FE_{NO} measured by the standard single exhalation technique in preschool children with asthmatic symptoms or history. A sample of healthy non-atopic children was investigated to assess prediction intervals in oscillatory mechanics and FE_{NO} for this age group. Receiver operating characteristic (ROC) analyses were used to evaluate the discriminative power of the methods (IOS and FE_{NO}) to distinguish children with clinically probable asthma from healthy controls.

METHODS

Between September 1999 and November 2001 143 consecutive preschool children (age ≤ 7 years) referred to the unit of clinical physiology in the Division of Allergy, Helsinki University Central Hospital for the measurement of lung function (impulse oscillometry) and exhaled nitric oxide were studied. One hundred and thirty seven children (96%) had satisfactory IOS measurements and 102 (71%) performed acceptable FE_{NO} measurements. The proportion of successful measurements was strongly associated with the age of the children, and the age of the youngest children who performed the FE_{NO} measurement successfully was 3.8 years. Only those children who performed both tests satisfactorily were considered eligible for the study. In addition, the measurements from two children were discarded because of equipment failure and those from four children were discarded due to a history of chronic lung disease of prematurity.

The remaining 96 children were divided into three groups according to their history: The first group consisted of children...
The reaction was regarded as positive if testing using 10 common inhalant allergens (SQ, ALK, EITC, ALK, etc.) was performed. Based on clinical judgement, bronchoscopy was subsequently adopted also for children, who had satisfactory FENO and IOS measurements. The output pressure and flow signals were analysed for their amplitude and phase difference to determine the resistance (Rrs) and reactance (Xrs) of the respiratory system, components of the respiratory impedance (Zrs). The pneumotachograph of the standard single exhalation technique recommended by the American Thoracic Society, subsequently adopted also for children, was applied.

Exhaled nitric oxide was measured using a chemiluminescence analyser (CLD 77 AM, Eco Physics, Duernten, Switzerland) connected to a computerised system (Exhaled Breath Analyser, Aerocin AB, Stockholm, Sweden) and calibrated with a certified NO calibration gas mixture (AGA Gas BV, Amsterdam, Netherlands). The standard single exhalation technique recommended by the American Thoracic Society, subsequently adopted also for children, was applied. Children were seated without a nose clip and were asked to fill their lungs completely with NO-free air, and thereafter to exhale slowly against a calibrated resistor of 200 cm H2O/l/s (Hans Rudolf Inc, Kansas City, MO, USA) with a mean flow of approximately 50 ml/s for at least 6 seconds. The flow was measured with a heated pneumotachograph (Hans Rudolph Inc). A variation of 40–60 ml/s in mean and instantaneous exhaled flow was allowed. Measurements were repeated until 2–3 exhalations with specified flows and acceptable plateaus were obtained and the FE_{exo} values agreed within 10% or within 5% of their mean value. The mean value of these measurements was recorded as the final result.

Lung function was measured by impulse oscillometry (IOS; Jaeger, Wurzburg, Germany). The method and equipment have been previously described in detail. The output pressure and flow signals were analysed for their amplitude and phase difference to determine the resistance (Rrs) and reactance (Xrs) of the respiratory system, components of the respiratory impedance (Zrs). The pneumotachograph of the standard single exhalation technique recommended by the American Thoracic Society, subsequently adopted also for children, was applied.

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device was calibrated daily and the system was also checked against a reference impedance of 0.2 kPa/l.s. During the measurement the child was in a sitting position, breathing quietly through a mouthpiece. A nose clip was used and the cheeks were supported by the hands of the investigator. Measurements were repeated in order to obtain three acceptable data sets which were used to calculate the mean value for Rrs and Xrs at 5 Hz. After the baseline measurements, the children received salbutamol in a dose of 0.3 mg administered via a Babyhaler. The lung function measurements were repeated 15 minutes after inhalation to assess the bronchodilator response. In the group of healthy controls, 49 children took part in the bronchodilator test.

Linear regression methods were applied to the results in healthy children to create prediction intervals for the log transformed data of oscillometric parameters and FE\textsubscript{no}. Standing and sitting height, age, weight, body surface area (BSA), and sex were tested as possible predictors using stepwise regression analysis. Standing height was found to be the best independent variable for both tests. Sex was not a significant predictor in any of the measured variables. In patient groups the deviation from the predicted value was expressed as multiples of the residual standard deviation.\textsuperscript{15} The bronchodilator responses in Rrs5 and Xrs5 were expressed as the nominal change (post – prebronchodilator value, ΔRrs5 and ΔXrs5) or as the percentage change compared with the predicted baseline value (ΔRrs5\%\textsubscript{pred} and ΔXrs5\%\textsubscript{pred}).

The results in the clinical groups were compared with those of healthy controls using ANOVA and by calculating the mean differences with 95% confidence interval (CI). For post hoc comparisons of ANOVA, Fisher’s PLSD test was used. The discriminative usefulness of baseline lung function, bronchodilator responses, and FE\textsubscript{no} was evaluated and compared by constructing ROC curves\textsuperscript{16} where sensitivity versus 1 – specificity was plotted for each possible cut off level. For this analysis, the group with probable asthma was labelled as diseased compared with the group of healthy controls. For each variable the area under the curve (AUC) with 95% confidence interval was determined. From each ROC curve we determined the ideal cut off level which corresponds to the closest point to the top left hand corner and which discriminates between the absence or presence of disease most efficiently. The respective sensitivity, specificity, and predictive values were compared.

RESULTS
The concentration of FE\textsubscript{no}, respiratory resistance, and reactance measured with IOS were all significantly related to age and height of the healthy children. Standing height was the best independent variable, and introducing other factors (sitting height, age, weight or BSA) did not significantly improve the coefficient of determination of the predicted equations. With increasing height FE\textsubscript{no} increased slightly (r=0.29; p=0.02), Rrs5 decreased (r=0.50; p<0.0001), and Xrs5 increased (r=0.56; p<0.0001). In fig 1 FE\textsubscript{no} is shown as a function of standing height in healthy children with regression line and 95% prediction interval. Details of the regression equations for IOS variables have been described elsewhere.\textsuperscript{15} The bronchodilator response expressed as the nominal change (ΔRrs5 and ΔXrs5) was significantly related to age, height, and baseline value, but in terms of percentage change compared with the predicted values (ΔRrs5\%\textsubscript{pred} and ΔXrs5\%\textsubscript{pred}) independent of these factors.

Baseline lung function, bronchodilator responses, and FE\textsubscript{no} are shown in table 2. Children in the probable asthma group had the highest concentration of NO in exhaled air with a mean difference from healthy controls of 16.8 ppb (95% CI 12.0 to 21.5). Baseline lung function in this group was also significantly different from healthy controls, characterised by increased Rrs5 (mean difference 0.13 kPa/l.s, 95% CI 0.03 to 0.22) and decreased Xrs5 (mean difference –0.08 kPa/l.s, 95% CI 0.13 to –0.03), and the bronchodilator responses were significantly greater. FE\textsubscript{no} values in children in the treated asthma group were not significantly different from those in healthy children. However, they had significant changes in baseline lung function. In children with chronic cough FE\textsubscript{no} values were significantly higher than in healthy children (mean difference 3.9 ppb, 95% CI 0.8 to 7.0) but their baseline lung function was normal. The bronchodilator responses in the chronic cough and treated asthma groups were not significantly different from those in healthy children.

In the chronic cough group the mean (SE) concentration of FE\textsubscript{no} in atopic children was 14.0 (3.0) ppb which was significantly higher than in non-atopic children (mean difference 8.5 ppb, 95% CI 2.1 to 14.9). In children with probable or treated asthma FE\textsubscript{no} was not significantly associated with atopy. Compared with atopic children with probable asthma with mean (SE) FE\textsubscript{no} of 24.5 (3.7) ppb, atopic children with chronic cough (mean difference 10.5 ppb, 95% CI 0.7 to 21.7) and treated asthma (mean difference 15.9 ppb, 95% CI 6.3 to 25.6) had significantly lower FE\textsubscript{no}.

Boxplot presentations of Rrs5, Xrs5, ΔRrs5\%\textsubscript{pred}, and FE\textsubscript{no} in the study groups are shown in fig 2. In the combined clinical series of patients (n=96) the concentration of FE\textsubscript{no} was related to baseline Xrs5 (r=0.20, p=0.04) and to bronchodilator responses expressed as ΔRrs5 (r=0.31, p=0.002) and ΔXrs5\%\textsubscript{pred} (r=0.29, p=0.004) but not significantly to ΔRrs5\%\textsubscript{pred}. Within the separate patient groups the correlations were not significant.

Based on the distribution of the healthy controls, the 5th (for Xrs5, ΔRrs5\%\textsubscript{pred} and ΔXrs5\%\textsubscript{pred}) and 95th (for FE\textsubscript{no} and Rrs5) percentiles were determined and the numbers of abnormal test results in the study groups were calculated. In the probable asthma group 17 children (81%) had abnormal FE\textsubscript{no} concentrations but Rrs5 and Xrs5 were abnormal in only five (24%) and 11 (52%), respectively. Abnormal reversibility (ΔRrs5\%\textsubscript{pred} or ΔXrs5\%\textsubscript{pred}) was present in six children (29%) with probable asthma. The results of the discriminative properties of FE\textsubscript{no} and IOS variables are shown by ROC analysis in fig 3. FE\textsubscript{no} had the best discriminative capacity (AUC 0.91, 95% CI 0.83 to 0.96) followed by the lung function indices Rrs5 (AUC 0.77, 95% CI 0.67 to 0.86) and ΔXrs5\%\textsubscript{pred} (AUC 0.76, 95% CI 0.64 to 0.85; fig 3). The optimal cut off level for FE\textsubscript{no} was 1.5 SD above predicted, corresponding approximately to a value of 9.7 ppb giving a sensitivity of 86% and specificity of 92% (table 3). In particular, FE\textsubscript{no} had a high negative predictive value (95%).
Exhaled nitric oxide has been proposed as a non-invasive inflammatory marker of the airways. High concentrations have been found particularly in children with atopic asthma, while the role of \( \text{FE}_{\text{NO}} \) in reflecting airway inflammation of non-atopic asthma is still unclear. Non-atopic wheeze is common in early childhood, but the proportion of IgE associated wheeze becomes more dominant in new cases at the age group of the present study. This was reflected in our consecutive series of children with probable asthma who were mostly atopic. Furthermore, the institution where the study was performed specialises in allergic disorders which may have resulted in selection bias for the referring stage in favour of atopic children. The small number of non-atopic children with asthma did not allow subanalyses of ROC in the present study, so we were unable to determine the discriminative capacity of \( \text{FE}_{\text{NO}} \) in non-atopic asthma. Atopy alone does not seem to explain the variation in \( \text{FE}_{\text{NO}} \) since the atopic children with chronic cough had significantly lower values than atopic children with probable asthma.

In children with asthma \( \text{FE}_{\text{NO}} \) has been found to correlate with sputum eosinophilia as well as eosinophilia in biopsy specimens, and it is also associated with other clinical characteristics of asthma such as airway hyperresponsiveness, bronchodilator responses, and exercise induced bronchoconstriction. In our patients \( \text{FE}_{\text{NO}} \) was significantly associated with baseline lung function and with bronchodilator responses, although within the groups the correlations were not statistically significant. This loose association probably reflects the fact that lung function changes and airway inflammation are different aspects of asthma and do not necessarily co-exist in individual children.

Only a few reports of \( \text{FE}_{\text{NO}} \) in preschool asthmatic or healthy children are available. \( \text{FE}_{\text{NO}} \) is commonly used as a marker of airway inflammation in children with asthma. The diagnostic value of \( \text{FE}_{\text{NO}} \) and the oscillometric method have been previously studied in preschool children with probable asthma. The diagnostic value of \( \text{FE}_{\text{NO}} \) in distinguishing preschool children with probable asthma was superior to measures of lung function assessed by the oscillometric technique in distinguishing preschool children with probable asthma. The diagnostic value of \( \text{FE}_{\text{NO}} \) in distinguishing preschool children with probable asthma was superior to measures of lung function assessed by the oscillometric technique in distinguishing preschool children with probable asthma.
online exhalation method was restricted to children aged ≥4 years because of problems with cooperation which is a limitation of the technique. Only 71% of the children aged 4–7 years were capable of performing acceptable measurements. The mean FE\textsubscript{NO} observed in the healthy children studied (5.3 ppb) was slightly less than that reported by Baraldi \textit{et al}\textsuperscript{27} in healthy children aged 4–13 years using a special flow driven method (9.6 ppb), and slightly higher than that reported by Buchvald and Bisgaard\textsuperscript{18} in healthy children aged 2–5 years using controlled tidal breathing at a fixed flow rate (3 ppb). The observed age and height dependency of FE\textsubscript{NO} in the present study is in agreement with the findings of Franklin \textit{et al}\textsuperscript{19}.

The oscillometric technique has been found to be a useful method for assessing lung function and bronchodilator responsiveness in young children.\textsuperscript{5,12–14} This technique was chosen for the present study because it is particularly suitable for young children as it requires less cooperation than spirometry and can be performed in most preschool children. This was confirmed by the high success rate (96%) of IOS measurements in the present study. Previously, Hellinckx \textit{et al}\textsuperscript{5} were unable to find differences between healthy children and those with stable asthma when baseline lung function and bronchodilator responses were investigated with IOS. In contrast, we in the present study and Nielsen and Bisgaard\textsuperscript{18} have found significant differences between similar groups. This is probably explained by differences in selection criteria. In young children there is no lung function method that would be regarded as the gold standard in the diagnosis of asthma. In the present study of preschool children we chose the history of recent recurrent wheeze relieved by \(\beta_2\) agonists as an indication of probable asthma. Although in infancy wheeze may not accurately predict the development of asthma, recurrent wheezing in children of preschool to school age is highly predictive of asthma and constitutes the basis for the diagnosis in settings where other causes have been excluded and the presence of asthma is likely.\textsuperscript{13} Therefore, in our children (age 4–7 years) with recurrent wheezing the diagnosis of asthma may be regarded as highly probable. We chose to use the group with probable asthma for discrimination analysis rather than the treated asthma group because these children were not on anti-inflammatory medication which could have confounded the results. Furthermore, the children in the probable asthma group had recent symptoms and were referred for the first time with suspected asthma. We therefore believe that they represent more closely the population in whom the diagnostic methodologies are applied and should be evaluated.

Wheeze is a sign of airflow limitation so it is not surprising that children in the probable asthma group had the highest degree of airway obstruction (increased resistance). As in the present study, preschool wheezing has been associated with increased responses to bronchodilators in earlier studies.\textsuperscript{5} In preschool children wheeze is also associated with signs of airway inflammation expressed as high concentrations of NO in exhaled air.\textsuperscript{17}

Our study is the first to combine lung function data with FE\textsubscript{NO} values in a clinical group of preschool children. The most important finding was that, in the group of children with probable asthma characterised by recent wheeze, signs of airway inflammation (as expressed by FE\textsubscript{NO}) were more constantly present than changes in lung function, and FE\textsubscript{NO} could discriminate between these children and healthy children better than any of the lung function indices. In particular, bronchodilator responsiveness, considered one of the hallmarks of asthma diagnosis, was present less frequently than high levels of FE\textsubscript{NO}. This is probably due to the variable nature of bronchial obstruction in asthma; in a cross sectional analysis such as the present study some asthmatic subjects are likely to have normal lung function. Alternatively, it may be that, in the early stages of the disease, signs of airway inflammation and symptoms precede those of abnormal lung function as we have shown in adults with asthma-like symptoms.\textsuperscript{11}

Persistent cough is one of the cardinal symptoms of asthma, but it may be associated with many other disorders. Some investigators argue that asthma is rarely the cause of persistent cough.\textsuperscript{18} In most children with recurrent cough the symptoms are probably reflections of recurrent respiratory infections, although at the time of testing no acute infection was present. In some children chronic cough may have been a sign of cough variant asthma. We therefore consider that the aetiology of the symptoms in the group with chronic cough was heterogenous. In agreement with this, we found signs of airway inflammation and abnormal lung function only in a few of these children. In our series the lung function of children with chronic cough was not significantly altered, although some authors have reported increased bronchodilator responsiveness in patients with cough alone.\textsuperscript{29} No reports on FE\textsubscript{NO} in preschool children with persistent cough have previously been published. We found significantly raised FE\textsubscript{NO} values in some of these children, suggesting airway inflammation. FE\textsubscript{NO} in this group was significantly associated with atopy, assessed by skin prick tests. The young children with recurrent and persistent cough constitute a large but difficult diagnostic challenge. For these children, objective measures of lung function and airway inflammation are urgently needed for targeting anti-inflammatory therapy. Reports on adult patients with persistent cough suggest that FE\textsubscript{NO} may be a promising tool in identifying subjects with asthma.\textsuperscript{11}

We conclude that FE\textsubscript{NO} is superior to baseline lung function measures or indices of bronchodilator responsiveness assessed by the oscillometric technique in identifying preschool children with predominantly atopic probable asthma. The discriminative properties of FE\textsubscript{NO} in non-atopic preschool children with wheeze still need to be clarified. The results emphasise the presence of airway inflammation in the early stages of asthma, even in young children.

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The work of the personnel in the unit of clinical physiology in performing the tests of the present study is acknowledged. The study

### Table 3

<table>
<thead>
<tr>
<th>Test parameter (cut off)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
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<tbody>
<tr>
<td>FE\textsubscript{NO}&gt;1.5SD</td>
<td>86</td>
<td>92</td>
<td>78</td>
<td>95</td>
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<tr>
<td>Rs5 (&gt;0.3SD)</td>
<td>90</td>
<td>53</td>
<td>40</td>
<td>94</td>
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<tr>
<td>Xrs5 (&lt;–1.5SD)</td>
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<td>91</td>
<td>70</td>
<td>86</td>
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<tr>
<td>ΔXrs5%pred (&lt;–21.2%)</td>
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<td>93</td>
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<tr>
<td>ΔXrs5%pred (&lt;–55.3%)</td>
<td>38</td>
<td>91</td>
<td>67</td>
<td>77</td>
</tr>
</tbody>
</table>

Rs5=resistance at 5 Hz; Xrs5=reactance at 5 Hz; FE\textsubscript{NO}=exhaled nitric oxide.
Exhaled NO in preschool children with probable asthma

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REFERENCES
1 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225–44.

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