ASTHMA

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

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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.[1] 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.[2] The assessment of lung function in young children has recently become possible using methods which do not require active cooperation.[3–7] 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.[8] 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.[9 10] 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,[11] 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

Table 1 Demographic characteristics of study groups and healthy children

	Treated asthma (n=29)	Probable asthma (n=21)	Chronic cough (n=46)	Healthy children (n=62)
Boys/girls	19/10	11/10	26/20	30/32
Age (years)*	5.6 (3.8–7.4)	5.7 (4.0–7.3)	5.6 (4.2–7.5)	5.8 (4.1–7.0)
Height (cm)*	112 (99–131)	114 (102–127)	114 (101–132)	115 (98–129)
Weight (kg)*	21 (15–35)	20 (14–31)	20 (15–28)	22 (16–31)
Skin prick test positive (%)	66	86	43	0
History of atopic excema (%)	62	57	41	11
Family history of asthma/atopy (%)	86	76	61	29
Family history of smoking (%)	7	5	13	10

*Mean (range).

Table 2 Mean (SE) baseline lung function, bronchodilator responses, and exhaled nitric oxide in the treated asthma (n=29), probable asthma (n=21) and chronic cough (n=46) groups and healthy children (n=62)

	Treated asthma	p value	Probable asthma	p value	Chronic cough	p value	Healthy children
Rrs5 (kPa/l.s)	0.95 (0.04)	0.002	1.01 (0.05)	<0.0001	0.87 (0.03)	NS	0.83 (0.02)
Rrs5 (SD)	0.5 (0.3)	NS	1.1 (0.3)	0.0003	0.1 (0.2)	NS	0 (0.1)
Xrs5 (kPa/l.s)	–0.32 (0.03)	<0.0001	–0.33 (0.03)	<0.0001	–0.27 (0.01)	NS	–0.24 (0.01)
Xrs5 (SD)	–1.1 (0.4)	0.002	–1.5 (0.4)	0.0002	–0.4 (0.2)	NS	0 (0.1)
ΔRrs5 (kPa/l.s)	–0.18 (0.03)	NS	–0.29 (0.03)	<0.0001	–0.16 (0.01)	NS	–0.16 (0.01)
ΔRrs5%pred (%)	–20.6 (2.9)	NS	–34.8 (3.8)	<0.0001	–19.4 (1.6)	NS	–19.6 (1.6)
ΔXrs5 (kPa/l.s)	–0.09 (0.02)	NS	–0.10 (0.02)	0.01	–0.06 (0.01)	NS	–0.06 (0.01)
ΔXrs5%pred (%)	–32.7 (5.9)	NS	–39.8 (6.9)	0.01	–26.1 (3.0)	NS	–23.5 (3.0)
FE_{NO} (ppb)	7.7 (1.4)	NS	22.1 (3.4)	<0.0001	9.2 (1.5)	0.02	5.3 (0.4)
FE_{NO} (SD)	0.4 (0.3)	NS	2.6 (0.3)	<0.0001	0.8 (0.2)	0.002	0 (0.1)

Rrs5=resistance at 5 Hz; Xrs5=reactance at 5 Hz; FE_{NO}=exhaled nitric oxide.
p values refer to comparison with healthy children (ANOVA).

with previously diagnosed asthma on regular medication—that is, treated asthma (n=25). The diagnosis had been based on typical clinical history, symptoms, and signs according to consensus statements.[12] The second group (n=21) consisted of children with persistent or recurrent respiratory symptoms associated with recent (within the previous 3 months) wheezing relieved by β_2 agonist therapy. Clinical examination and chest radiographs were performed to exclude acute infections and rare causes of wheeze before the lung function tests were performed. Based on clinical judgement, bronchoscopy was not considered to be indicated in any of these children with late onset wheeze. We considered that these children had probable asthma.[12] The third clinical group (n=46) consisted of children with chronic (persistent or recurrent) cough only, without wheezing episodes. The symptoms had lasted at least 6 weeks and acute or chronic respiratory infections were excluded, based on clinical examination, chest or sinus radiographs, before lung function tests were performed. The children in the probable asthma and chronic cough groups were referred for the first time because of a suspicion of asthma and had not used any anti-inflammatory medication (corticosteroids, cromones or antileukotriene drugs) for at least 2 months before the study. All the children in the group with treated asthma were on inhaled steroids at the time of the study. The demographic characteristics of the study groups are shown in table 1.

Control subjects were chosen from a sample of 62 age matched (4.0–7.0 years) healthy non-atopic children attending kindergartens[13] who had satisfactory FE_{NO} and IOS measurements. They did not have any present or chronic respiratory symptoms, asthma or atopic disease, and their skin prick tests for common respiratory allergens were negative. With regard to demographic data, there were no significant differences between the study groups and healthy controls.

The definition of atopy in this study was based on skin prick testing using 10 common inhalant allergens (SQ, ALK, Horsholm, Denmark). The reaction was regarded as positive if the wheal diameter was 3 mm or more and the control solutions gave expected results. At the time of testing none of the children had experienced a respiratory tract infection in the preceding 2 weeks or showed signs of clinical obstruction (wheeze or shortness of breath). Short acting β_2 agonists were withheld for at least 12 hours preceding the test. The study was approved by the institutional ethics committees of Helsinki University Hospital and Espoo Social and Health Care Center, and written informed consent was obtained from the parents of all participating children.

Exhaled nitric oxide was measured using a chemiluminescence analyser (CLD 77 AM, Eco Physics, Duernten, Switzerland) connected to a computerised system (Exhaled Breath Analyzer, Aerocrine 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,[14] subsequently adopted also for children,[10] 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 H_2O/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_{NO} 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, Würzburg, Germany). The method and equipment have been previously described in detail.[6 13] 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

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_{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.[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%pred and ΔXrs5%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_{NO} was evaluated and compared by constructing ROC curves[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_{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_{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_{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.[13] 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%pred and ΔXrs5%pred) independent of these factors.

Baseline lung function, bronchodilator responses, and FE_{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_{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_{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.

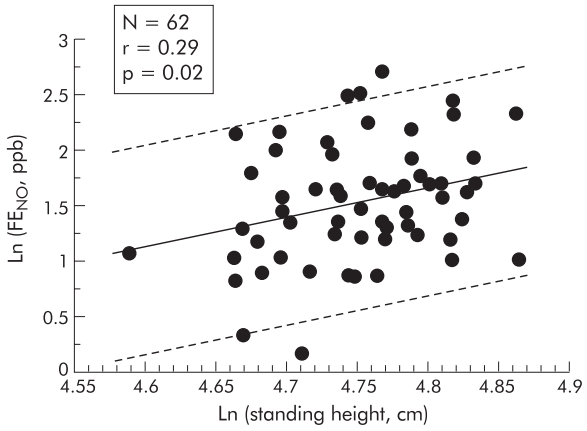

Figure 1 Exhaled nitric oxide concentration (FE_{NO}) as a function of standing height in healthy non-atopic children. The solid line represents the line of regression (mean (SE) Ln (FE_{NO}, ppb) = 2.67 (1.15) × Ln (Standing height, cm) – 11.15 (5.48); r^2 = 0.08) and the dashed lines show the 95% prediction interval (RSD=0.504).

In the chronic cough group the mean (SE) concentration of FE_{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_{NO} was not significantly associated with atopy. Compared with atopic children with probable asthma with mean (SE) FE_{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_{NO}.

Boxplot presentations of Rrs5, Xrs5, ΔRrs5%pred, and FE_{NO} in the study groups are shown in fig 2. In the combined clinical series of patients (n=96) the concentration of FE_{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 ΔRrs5%pred (r=0.29, p=0.004) but not significantly to Rrs5, ΔXrs5, or ΔXrs5%pred. Within the separate patient groups the correlations were not significant.

Based on the distribution of the healthy controls, the 5th (for Xrs5, ΔRs5%pred and ΔXrs5%pred) and 95th (for FE_{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_{NO} concentrations but Rrs5 and Xrs5 were abnormal in only five (24%) and 11 (52%), respectively. Abnormal reversibility (ΔRrs5%pred or ΔXrs5%pred) was present in six children (29%) with probable asthma. The results of the discriminative properties of FE_{NO} and IOS variables are shown by ROC analysis in fig 3. FE_{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 ΔRrs5%pred (AUC 0.76, 95% CI 0.64 to 0.85; fig 3). The optimal cut off level for FE_{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_{NO} had a high negative predictive value (95%).

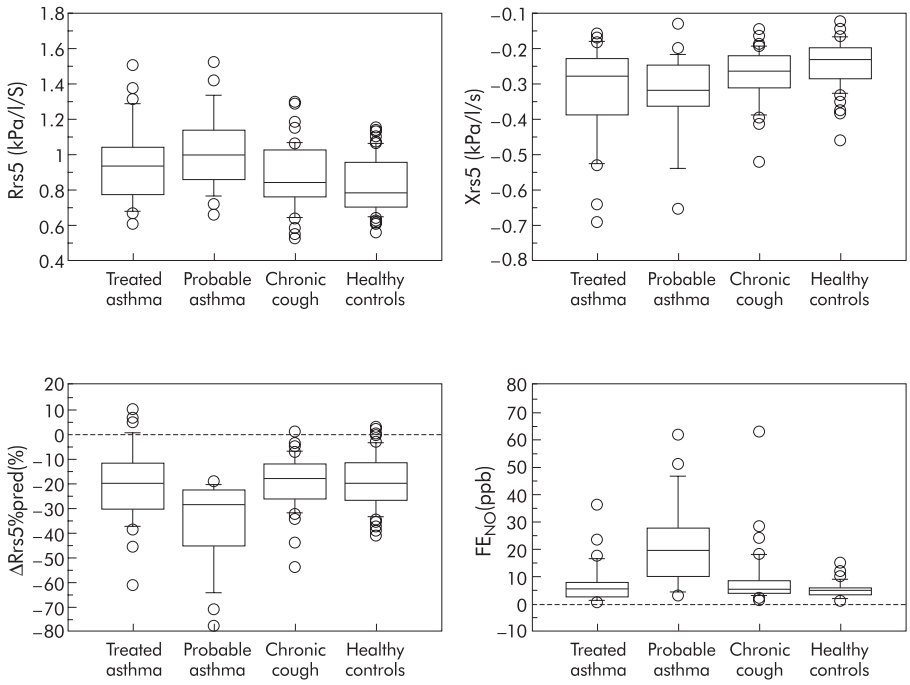

Figure 2 Boxplot presentation of the distribution of respiratory resistance and reactance at 5 Hz (Rrs5 and Xrs5), bronchodilator responsiveness (ΔRrs5%pred), and exhaled nitric oxide (FE_{NO}) in the study groups.

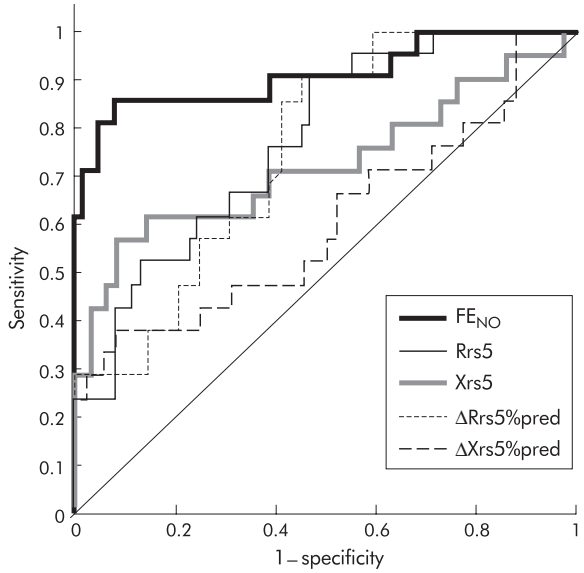

Figure 3 ROC characteristics of FE_{NO}, baseline lung function (Rrs5, Xrs5), and bronchodilator responsiveness (ΔRrs5%pred and ΔXrs5%pred) in discriminating between children with probable asthma (n=21) and healthy controls (n=62).

DISCUSSION

Exhaled nitric oxide as an inflammatory marker of asthma was superior to measures of lung function assessed by the oscillometric technique in distinguishing preschool children with probable asthma. The diagnostic value of FE_{NO} [17–19] and the oscillometric method [5 8] have been previously studied in preschool children with asthma. We compared the usefulness of these new techniques in our series of children at the age where the diagnosis of asthma has traditionally been largely based on clinical history. With the assumption that FE_{NO} reflects airway eosinophilia in asthma, the results emphasise the presence of airway inflammation at the early stages of asthma, even in preschool children.

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,[20] while the role of FE_{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.[21] 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 FE_{NO} in non-atopic asthma. Atopy alone does not seem to explain the variation in FE_{NO} since the atopic children with chronic cough had significantly lower values than atopic children with probable asthma.

In children with asthma FE_{NO} has been found to correlate with sputum eosinophilia[9] as well as eosinophilia in biopsy specimens,[22] and it is also associated with other clinical characteristics of asthma such as airway hyperresponsiveness,[23] bronchodilator responses,[24] and exercise induced bronchoconstriction.[25] In our patients FE_{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 FE_{NO} in preschool asthmatic or healthy children are available.[17 19 26] In particular, studies based on the single exhalation technique recently recommended by the American Thoracic Society are lacking.[10 14] In these guidelines children are expected to exhale against a resistor for at least 6 seconds with a constant flow of approximately 50 ml/s. Although a slightly larger variation in exhaled flow (40–60 ml/s) was allowed in the present study than is recommended, the applicability of this standard

Table 3 Sensitivity, specificity, and predictive values of baseline lung function, bronchodilator responses, and exhaled nitric oxide at optimal cut off level in discriminating between children with probable asthma and healthy children

Test parameter (cut off)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
FE_{NO} (>1.5SD)	86	92	78	95
Rrs5 (>0.3SD)	90	53	40	94
Xrs5 (<–1.5SD)	57	91	70	86
ΔRrs5%pred (<–21.2%)	90	55	46	93
ΔXrs5%pred (<–55.3%)	38	91	67	77

Rrs5=resistance at 5 Hz; Xrs5=reactance at 5 Hz; FE_{NO}=exhaled nitric oxide.

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_{NO} observed in the healthy children studied (5.3 ppb) was slightly less than that reported by Baraldi *et al*[18] 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[19] 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_{NO} in the present study is in agreement with the findings of Franklin *et al*.[27]

The oscillometric technique has been found to be a useful method for assessing lung function and bronchodilator responsiveness in young children.[5 6 8 28] 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 *et al*[4] 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[8] 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 β_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.[12] 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.[29] In preschool children wheeze is also associated with signs of airway inflammation expressed as high concentrations of NO in exhaled air.[17]

Our study is the first to combine lung function data with FE_{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_{NO}) were more constantly present than changes in lung function, and FE_{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_{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.[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.[30] 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.[29] No reports on FE_{NO} in preschool children with persistent cough have previously been published. We found significantly raised FE_{NO} values in some of these children, suggesting airway inflammation. FE_{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_{NO} may be a promising tool in identifying subjects with asthma.[31]

We conclude that FE_{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_{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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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.
2 **Faniran A**, Peat J, Woolcock A. Persistent cough: is it asthma ? *Arch Dis Child* 1998;**79**:411–4.
3 **Klug B**, Bisgaard H. Measurement of lung function in awake 2–4-year old asthmatic children during methacholine challenge and acute asthma. *Pediatr Pulmonol* 1996;**21**:290–300.
4 **Hellinckx J**, De Boeck K, Bande-Knops J, *et al*. Bronchodilator response in 3–6.5 year old healthy and stable asthmatic children. *Eur Respir J* 1998;**12**:438–43.
5 **Delacourt C**, Lorino H, Herve-Guillot M, *et al*. Use of the forced oscillation technique to assess airway obstruction and reversibility in children. *Am J Respir Crit Care Med* 2000;**161**:730–6.
6 **Malmberg L**, Mieskonen S, Pelkonen A, *et al*. Lung function measured by the oscillometric method in prematurely born children with chronic lung disease. *Eur Respir J* 2000;**16**:598–603.
7 **Merkus P**, Mijnsbergen J, Hop W, *et al*. Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001;**163**:1350–5.
8 **Nielsen K**, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med* 2001;**164**:554–9.
9 **Gibson P**, Henry R, Thomas P. Noninvasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. *Eur Respir J* 2000;**16**:1008–15.
10 **Baraldi E**, de Jongste J. ERS/ATS statement. Measurement of exhaled nitric oxide in children, 2001. *Eur Respir J* 2002;**20**:223–37.
11 **Rytilä P**, Metso T, Heikkinen K, *et al*. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. *Eur Respir J* 2000;**16**:824–30.
12 **Warner J**, Naspitz C. Third international pediatric consensus statement of childhood asthma. *Pediatr Pulmonol* 1998;**25**:1–17.
13 **Malmberg L**, Pelkonen A, Poussa T, *et al*. Determinants of respiratory system input impedance and bronchodilator response in healthy Finnish preschool children. *Clin Physiol* 2002;**22**:71–8.
14 **American Thoracic Society**. Recommendations for standardized procedures for online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children. *Am J Respir Crit Care Med* 1999;**160**:2104–17.
15 **Miller M**, Pincock A. Predicted values: how should we use them? *Thorax* 1988;**43**:265–7.
16 **Zweig M**, Campbell G. Receiver operating characteristic (ROC) plots: a fundamental evaluation in clinical medicine. *Clin Chem* 1993;**39**:561–77.
17 **Baraldi E**, Dario C, Ongaro R, *et al*. Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children. *Am J Respir Crit Care Med* 1999;**159**:1284–8.
18 **Baraldi E**, Scollo M, Zaramella C, *et al*. A simple flow-driven method for online measurement of exhaled NO starting at the age of 4 to 5 years. *Am J Respir Crit Care Med* 2000;**162**:1828–32.
19 **Buchvald F**, Bisgaard H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. *Am J Respir Crit Care Med* 2001;**163**:699–704.
20 **Frank T**, Adisesh A, Pickering A, *et al*. Relationship between exhaled nitric oxide and childhood asthma. *Am J Respir Crit Care Med* 1998;**158**:1032–6.
21 **Martinez F**. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;**109**:362–7.
22 **Payne D**, Adcock I, Wilson N, *et al*. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001;**164**:1376–81.
23 **Piacentini G**, Bodini A, Costella S, *et al*. Exhaled nitric oxide, serum ECP and airway hyperresponsiveness in mild asthmatic children. *Eur Respir J* 2000;**15**:839–43.
24 **Colon-Semidey A**, Marshik P, Crowley M, *et al*. Correlation between reversibility of airway obstruction and exhaled nitric oxide levels in children with stable bronchial asthma. *Pediatr Pulmonol* 2000;**30**:385–92.
25 **Scollo M**, Zanconato S, Ongaro R, *et al*. Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. *Am J Respir Crit Care Med* 2000;**161**:1047–50.
26 **Visser M**, Wit M-C, van Aalderen W, *et al*. Exhaled nitric oxide in children measured by tidal breathing method: differences between asthmatics and nonasthmatic controls. *Pediatr Pulmonol* 2000;**29**:434–7.
27 **Franklin P**, Taplin R, Stick S. A community study of exhaled nitric oxide in healthy children. *Am J Respir Crit Care Med* 1999;**159**:69–73.
28 **Bisgaard H**, Klug B. Lung function measurement in awake young children. *Eur Respir J* 1995;**8**:2067–75.
29 **McKenzie S**, Bridge P, Healy M. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;**15**:833–8.
30 **Chang A**. Isolated cough: probably not asthma. *Arch Dis Child* 1999;**80**:211–3.
31 **Chatkin J**, Ansarin K, Silkoff P, *et al*. Exhaled nitric oxide as a noninvasive assessement of chronic cough. *Am J Respir Crit Care Med* 1999;**159**:1810–3.