

## Lung function and short-term outcome in young asthmatic children

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*Lung function and short-term outcome in young asthmatic children. B. Klug, H. Bisgaard.*  
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**ABSTRACT:** The aims of this study were to investigate lung function in 2–5-yr-old stable asthmatic children consecutively referred from general practitioners and to analyse the outcome on the basis of their requirement for antiasthmatic treatment and symptoms after 1.6–4.5 yrs.

Lung function was measured in 110 children with a mean±SD age of 3.8±1.0 yrs using the interruptor technique (resistance assessed using the interruptor technique ( $R_{int}$ )), whole body plethysmography (specific airway resistance ( $sR_{aw}$ ) and respiratory resistance ( $R_{rs,5}$ ) and reactance at 5 Hz ( $X_{rs,5}$ ) using the impulse oscillation technique.

$R_{int}$ ,  $sR_{aw}$ ,  $X_{rs,5}$  and  $R_{rs,5}$  were suggestive of impaired lung function in 44%, 14%, 11% and 7.5% of the children, respectively, with a predominance of children aged 2–3 yrs. Sixty-five per cent were treated with inhaled steroids, and 35% were treated only with  $\beta_2$ -agonists as needed; lung function was not significantly different between these two groups. Outcome after 2.9±0.7 yrs was not significantly different between children with  $R_{int}$  measurements above and those children with  $R_{int}$  measurements within the reference range at enrolment. Of these children, 58 and 59% were currently on antiasthmatic treatment, and 40% and 49% had current symptoms, respectively.

Impairment of lung function may be a common finding in stable young asthmatic children, but apparently this is not a risk factor for persistence of asthmatic symptoms.

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The diagnosis and monitoring of airway diseases involving wheeze in young children relies mainly on the history provided by the parents of the children and clinical observations. Reliable data on lung function can rarely be obtained in this age group using standard lung function tests [1]. A number of techniques applicable to lung function measurement in young children have recently been evaluated [2–4]. These techniques require passive cooperation only and measurements can be performed in un-sedated young children down to the age of 2 yrs.

The aim of the present study was to provide data on lung function in a sample of young asthmatic children, 2–5 yrs of age, consecutively referred from general practitioners. Subsequently, the clinical outcome in these children after 3 yrs was assessed in order to investigate the prognostic value of the lung function measurements.

### Methods

#### Patients

Asthmatic children aged 2–5 yrs referred to the paediatric asthma outpatient clinic from local general practitioners in the inner city of Copenhagen, Denmark were eligible for the study. The children were consecutively enrolled in the study over a period of 2 yrs. All children provided a history of three or more episodes of wheezing after the age of 1 yr. Children who had other

concurrent chronic lung disease were not included in the study nor were children who were referred from other hospitals. Whether or not the child had a history of eczema and the parents had a history of asthma or hay fever requiring medical treatment was recorded. The children were considered to be asymptomatic if they had no wheeze or rhonchi on auscultation and had been without symptoms of wheeze in the preceding 2 weeks. Treatment with  $\beta_2$ -agonists was stopped 6 hrs prior to the examination.

The parents were interviewed by telephone concerning their child's medical treatment and symptoms during the past year 1.5 yrs after enrolment of the last patient. During this interview a questionnaire was filled in to determine whether or not the child was currently being treated with an inhaled steroid or a  $\beta_2$ -agonist alone or whether treatment had been stopped. In children who had been taken off inhaled steroids, the duration of time since withdrawal of treatment was recorded. The parents were asked to estimate the number of episodes of cough with wheeze lasting >2 days in their child during the past year. The study was approved by the local ethics committee and written informed consent was obtained from the parents.

#### Measurements of lung function

Lung function measurements were obtained using three techniques: the interruptor technique (resistance assessed using the interruptor technique ( $R_{int}$ )), the impulse

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Table 1. – Demographic data of the study population

	Mean±SD	Range
Subjects n	110	
Males/females	67/43	
Age yrs	3.75±0.96	2.0–5.58
Height cm	101.1±8.1	84–120
Weight kg	16.6±2.9	11–24

oscillation technique (IOS), and a single-step method for measuring specific airway resistance ( $sR_{aw}$ ) by means of whole body plethysmography. The technical features of the equipment and measurement procedures have been described in detail previously [2, 3, 5]. All measurement procedures used in this study were identical to those employed in a recent study establishing reference values for lung function in young children [4].

The IOS parameters used were the resistance at 5 Hz ( $R_{rs,5}$ ) and the reactance at 5 Hz ( $X_{rs,5}$ ), for which the coherence function was calculated.  $sR_{aw}$  was calculated from the specific resistance loops using the line connecting the maximum change in plethysmographic volume during inspiration and expiration [4]. Children who were unable to perform the plethysmographic procedures alone were accompanied by an adult [5].

#### Procedures

The measurements of lung function were performed after clinical evaluation of the children. The response to an inhaled bronchodilator was studied in a subset of children. Terbutaline 0.5 mg (Bricanyl; Astra, Copenhagen, Denmark) was inhaled from a low volume metal spacer (NebuChamber, Astra) and measurements of lung function were obtained 20 min later.

#### Analysis of data

The reproducibility of the measurements was estimated by means of the within subject SD ( $s_{DW}$ ), calculated as the SD of the differences between paired measurements from all subjects divided by  $\sqrt{2}$ . Measurements in individual patients were calculated as the mean of paired measurements. Lung function data were expressed as a percentage of the predicted value according to height [4]. Measurements were considered suggestive of impaired respiratory function if above the 97.5% prediction limit of the reference value (values below the 2.5% prediction limit for  $X_{rs,5}$ ). The percentage of children with measurements outside the reference range was compared in children aged above and below the mean age of the study population (3.75 yrs). The difference between pre- and post-bronchodilator measurements was expressed as a multiple of the  $s_{DW}$  of the individual method. An unpaired t-test was used for comparing mean values of continuous variables. Differences in proportions were assessed using the Chi-squared test. The Mann-Whitney rank sum test for unmatched data was used for comparing data that were not normally distributed. A p-value <0.05 was considered statistically significant.

## Results

#### Study population

One hundred and forty five children entered the study. Six children had clinical signs of airway obstruction and were excluded from the study. No measurements could be obtained in 29 children (mean age 2.9±0.54 yrs) of whom 21 were receiving regular treatment with inhaled steroids and eight were treated with inhaled  $\beta_2$ -agonists as required. Lung function measurements were obtained in 110 asymptomatic children. The demographic data of the children who completed measurements are given in table 1. Thirty four per cent of the children had a history of eczema. Current or past asthma or hayfever requiring medical treatment was reported by either parent in 31% of children.

#### Antiasthmatic treatment

Seventy two (65%) children were treated with inhaled steroids on a regular basis and had been on this treatment for  $\geq 1$  month prior to testing of lung function; 38 (35%) were treated only with inhaled  $\beta_2$ -agonists as required. Of the children treated with inhaled steroids, budesonide was used by 93%, with a mean dose of 431  $\mu\text{g}\cdot\text{day}^{-1}$  (range 100–800  $\mu\text{g}\cdot\text{day}^{-1}$ ). Most children were studied during the initial high-dose induction phase of this treatment [6]. The medication was administered by metered-dose inhaler with a plastic spacer device in all children except one who used a dry powder inhaler.

#### Lung function measurements

Lung function measurement data are given in table 2. The  $s_{DW}$  of  $sR_{aw}$ ,  $R_{int}$ ,  $R_{rs,5}$  and  $X_{rs,5}$  were 0.12, 0.10, 0.13 and 0.11 respectively. Measurements suggestive of impaired respiratory function were found in 14, 44, 7.5 and 11% of the children for  $sR_{aw}$ ,  $R_{int}$ ,  $R_{rs,5}$  and  $X_{rs,5}$ , respectively (fig. 1). The coherence function of IOS measurements at 5 Hz was 0.71±0.11. Measurements above the reference range were particularly prevalent among the youngest children.  $R_{int}$  were above the reference range in 59% of the children aged 2–3.75 yrs in comparison with 29% in children aged 3.8–5.75 yrs ( $p<0.05$ ). The

Table 2. – Lung function data from 110 asymptomatic young asthmatic children

	$sR_{aw}$ kPa·s	$R_{int}$ kPa·L <sup>-1</sup> ·s	$R_{rs,5}$ kPa·L <sup>-1</sup> ·s	$X_{rs,5}$ kPa·L <sup>-1</sup> ·s
Subjects n	102	109	106	106
Mean	1.45±0.29	1.35±0.31	1.44±0.27	-0.54±0.22
% pred*	109±22	129±28	104±20	109±40
Subjects outside normal range n	14 <sup>#</sup>	48 <sup>#</sup>	8 <sup>#</sup>	12 <sup>+</sup>

Data are presented as mean±SD. \*: values >100% pred indicate reduced lung function; #: number of subjects with measurements >97.5% limit of predicted normal value; +: number of subjects with measurements <2.5% limit of predicted normal value.  $sR_{aw}$ : specific airway resistance;  $R_{int}$ : resistance assessed using the interruptor technique;  $R_{rs,5}$ : respiratory resistance at 5 Hz;  $X_{rs,5}$ : respiratory reactance at 5 Hz.

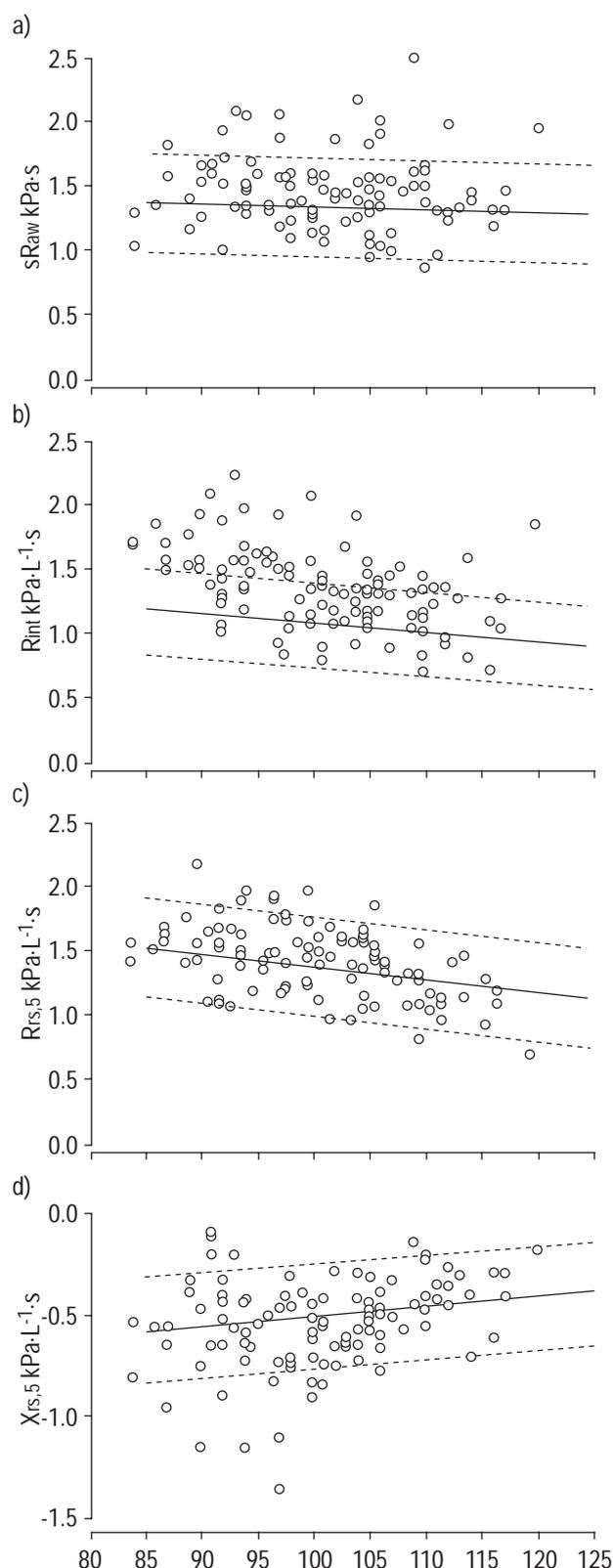


Fig. 1. — Lung function measurements in 109 asymptomatic young asthmatic children obtained by means of four different methods: a) specific airway resistance ( $sRaw$ ); b) resistance assessed using the interruptor technique ( $R_{int}$ ); c) respiratory resistance at 5 Hz ( $R_{rs,5}$ ); and d) respiratory reactance at 5 Hz ( $X_{rs,5}$ ). — : predicted normal value according to height; - - - : 95% limits of the predicted value.

percentage of boys and girls with  $R_{int}$  above the reference range was not significantly different, 42 and 46%, respectively. Measurements were completed with all of the applied methods in 95 children. Among these children the number of subjects with measurements suggestive of impaired lung function were 13, 41, eight and 11 children for  $sRaw$ ,  $R_{int}$ ,  $R_{rs,5}$  and  $X_{rs,5}$ , respectively. Among the 41 children with  $R_{int}$  above the reference range, concordant findings with  $sRaw$ ,  $R_{rs,5}$  and  $X_{rs,5}$  were found in seven, five and six children, respectively, and in two children only were the measurements above the reference range of all four methods.

The percentage of children in whom  $R_{int}$  were above the reference range was not significantly different between children treated with inhaled steroids (44%) and children treated only with  $\beta_2$ -agonists as required (43%). In 19 children with a history of eczema and at least one parent with asthma or rhinitis and in 50 children with no history of eczema and no parental asthma or rhinitis, the percentage of children with  $R_{int}$  above the reference range was not significantly different, 58 and 40%, respectively.

#### Bronchodilator response

The response to inhalation of terbutaline was investigated in 31 children with an age of  $3.9 \pm 0.9$  yrs. All indices of lung function changed significantly after bronchodilation. The change after bronchodilator was greatest for  $R_{int}$ , whereas  $X_{rs,5}$  showed the smallest change (table 3).

#### Follow-up

Follow-up data were obtained in 103 (94%) (age  $3.7 \pm 0.9$  yrs) of the 110 children. Data were not available in seven children, who at the time of the initial lung function test had a mean age of 4.2 yrs. The observation period was  $2.9 \pm 0.7$  yrs (range 1.6–3.9 yrs) and age of the children at follow-up  $6.6 \pm 1.2$  yrs. At follow-up, 84% of the children were no longer affiliated to the paediatric asthma outpatient department. Of the children, 58% were still receiving anti-asthmatic medication; 55% of males and 63% of females. Data on treatment at enrolment and at follow-up are given in table 4. The percentage of subjects receiving antiasthmatic medication at follow-up was nearly identical in children with  $R_{int}$  above and in children with  $R_{int}$  within the reference range at enrolment, 58% and 59%, respectively. Of the children, 46% had current symptoms defined as one or more episodes of cough with wheeze lasting  $>2$  days in the past year (table 4). In children with  $R_{int}$  above and in children with  $R_{int}$  within the reference range at enrolment, the percentage with current symptoms was not significantly different, 40% and 49%, respectively.

Treatment with inhaled steroids had been withdrawn in 29 (78%) of the 37 children who were younger than 4 yrs at enrolment, in comparison with 10 (36%) of the 28 children aged  $\geq 4$  yrs at enrolment ( $p < 0.001$ ). Among children currently treated with inhaled steroids, a significantly higher percentage (54%) had suffered three or more episodes of cough with wheeze in the past year in comparison with 20% of children treated with  $\beta_2$ -agonist alone and 2% of children who received no treatment. At follow-up, 17 (89%) of 19 children with a history of eczema and at least one parent

Table 3. – Response to bronchodilator in asymptomatic children with recurrent wheeze

	$sR_{aw}$ kPa·s	$R_{int}$ kPa·L <sup>-1</sup> ·s	$R_{rs,5}$ kPa·L <sup>-1</sup> ·s	$X_{rs,5}$ kPa·L <sup>-1</sup> ·s
Subjects n	29	31	31	31
Before bronchodilator				
Mean	1.47±0.28	1.21±0.20	1.48±0.25	-0.59±0.22
% pred	110±21	128±29	107±17	117±39
After bronchodilator*				
Mean	1.33±0.31	1.07±0.26	1.25±0.22	-0.43±0.14
% pred	91±15	103±24	90±15	85±26
Difference <sup>+</sup>				
$\Delta_{SDW}$	2.1	2.7	2.1	1.5
(95% CI)	(1.4–2.9)	(2.0–3.3)	(1.3–2.9)	(1.0–2.0)

Data are presented as mean±SD. \*: terbutaline 0.5 mg inhaled from a low-volume metal spacer; <sup>+</sup>: between pre- and post-bronchodilator measurements expressed as a multiple of the within subject SD ( $\Delta_{SDW}$ ).  $sR_{aw}$ : specific airway resistance;  $R_{int}$ : resistance assessed using the interruptor technique;  $R_{rs,5}$ : respiratory resistance at 5 Hz;  $X_{rs,5}$ : respiratory reactance at 5 Hz.

with asthma or rhinitis were still on antiasthmatic treatment in comparison with 22 (39%) of 51 children with no history of eczema and no parental asthma or rhinitis ( $p<0.05$ ), and the percentage of children who had suffered three or more episodes of cough with wheeze in the past year in the two groups was 47% and 14%, respectively ( $p<0.05$ ).

### Discussion

In this study, subclinical impairment of lung function was found in a considerable proportion of stable young asthmatic children considered to be appropriately treated. After a mean follow-up period of 3 yrs, the outcome was similar, in terms of treatment and symptoms, in children who had impairment of lung function and in children who had normal lung function at enrolment in the study. Hence, lung function measurements were not helpful in identifying children with a poor prognosis.

#### Lung function measurements

The present results show that the sensitivity of clinical assessment of respiratory function in young children is poor. Lung function measurements are therefore likely to be a useful tool in the early identification of young children with significant though not clinically apparent impairment of lung function, and as a means of objective assessment of the response to medical treatment.  $R_{int}$  identified impair-

ment of lung function in more children than did  $sR_{aw}$  and IOS measurements, although the sensitivity of the methods to changes after bronchodilation was almost the same. The fact that the methods reflect different mechanical properties of the respiratory system is probably the most important factor in explaining the poor agreement between the methods. The reference values employed in this study were collected in healthy children concurrently with the measurements in asthmatic children. Therefore, it is unlikely that the present findings could be caused by a systematic error.

The majority of the children in the present cohort (65%) were treated with inhaled steroids likely to have improved lung function [7–10]. The high prevalence of lung function impairment despite treatment may be due to airway inflammation or sequelae thereof, although some children may have congenital diminishment of airway function [11–14].

#### Follow-up

The children included in this study were referred from general practitioners and the vast majority of the children had mild or moderate symptoms. They were initially treated according to the treatment strategy currently employed in Denmark, using inhaled steroids as first-line therapy not only in children with severe or persistent symptoms but also in children who have recurrent mild wheezing apart from respiratory tract infections. Inhaled steroids are initially given in high doses and subsequently tapered of, and, in the absence of symptoms, treatment is stopped to ascertain the need for continuous treatment [6, 15]. Cromoglycates are not used and treatment with  $\beta_2$ -agonists as needed as monotherapy is confined to children with infrequent mild symptoms.

The outcome after a mean period of time of almost 3 yrs was assessed using the requirement for antiasthmatic therapy and symptoms during the past year as outcome measures. The requirement for antiasthmatic therapy and symptoms at follow-up were not different between children with impairment of lung function at enrolment in the study and children who had normal lung function. However, at the time of follow-up, the majority of the children were treated by their general practitioner and therefore probably not treated uniformly according to the guidelines. Furthermore, the number of episodes of cough with wheeze in the children as reported by their parents provided only a crude estimate of the presence and severity of asthmatic symptoms [16]. This may restrict, but not invalidate, the present assessment of outcome, which supported by the fact that that, in keeping with findings

Table 4. – Relation between antiasthmatic inhalation therapy at enrolment and therapy and asthmatic symptoms at follow-up in 103 children

Therapy at follow-up	Therapy at enrolment		Asthmatic symptoms at follow-up*	
	Steroid n (%)	$\beta_2$ -agonist n (%)	No current symptoms n	Current symptoms n (median, range)
Steroid	26 (40)	9 (24)	5	30 (3.5, 1–10)
$\beta_2$ -agonist	16 (25)	9 (24)	16	9 (3.0, 1–4)
No medication	23 (35)	20 (52)	35	8 (1.5, 1–4)

\*: one or more episodes of cough with wheeze lasting >2 days during the past year.

in other studies [13, 17–19], among children with an atopic predisposition a significantly higher percentage was found that had current symptoms and were currently on anti-asthmatic therapy in comparison with children without an atopic predisposition. Treatment with inhaled steroids had been withdrawn in 78% of the children who were younger than 4 yrs at enrolment in comparison with 36% of children aged  $\geq 4$  yrs at enrolment, indicating that 2–3 yrs-old children with asthmatic symptoms have a more favourable prognosis than 4–5 yr-olds with asthmatic symptoms.

To the authors' knowledge this is the first report on lung function status in a large group of young children with asthmatic symptoms after the second year of life treated according to current guidelines. In this group of clinically stable asthmatic children, it was found that impairment of lung function was common in 2–5 yr-olds, but not associated with an unfavourable outcome as judged by symptoms and requirement for treatment 3 yrs later. The clinical implications of demonstrating airway obstruction by means of lung function measurement in young asthmatic children deserves further study.

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