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# Bronchodilator response in 3–6.5 years old healthy and stable asthmatic children

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*Bronchodilator response in 3–6.5 years old healthy and stable asthmatic children. J. Hellinckx, K. De Boeck, J. Bande-Knops, M. van der Poel, M. Demedts. ©ERS Journals Ltd 1998.*
**ABSTRACT: Few data are available on the bronchodilator response in preschool children. This study was set up to study baseline lung function and bronchodilator responses in healthy and asthmatic children younger than 7 yrs old.**

**In 281 preschool children attending kindergarten (age range 2.7–6.6 yrs old) respiratory system resistance ($R_{rs}$) and reactance ($X_{rs}$) by impulse oscillation system at 5, 10, 15, 20, 25 and 35 Hz as well as resonance frequency ($f_0$) were measured before and 20 min after 200 μg inhaled salbutamol by a metered-dose inhaler connected to a spacer device. Thirty-four of them were diagnosed as asthmatics based on a validated standardized questionnaire.**

**The mean $R_{rs}$ (±SD) at 5 Hz ($R_{rs,5}$) was 1.03 (±0.24) kPa·L$^{-1}$·s for healthy children and 1.09 (±0.26) kPa·L$^{-1}$·s for stable asthmatics. The mean change in $R_{rs,5}$ after salbutamol was -0.13 (±0.20) kPa·L$^{-1}$·s for the healthy children and -0.09 (±0.25) kPa·L$^{-1}$·s for the asthmatic group. The scatter for the measurements was striking.**

**Neither baseline values of impulse oscillation nor its changes after bronchodilator administration was significantly different between healthy and stable asthmatic children. A change in respiratory system resistance at 5 Hz of 40% is to be considered the cut-off for a "positive" bronchodilator response.**
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Reversibility of airway obstruction is considered one of the major criteria in the diagnosis of asthma in children, adolescents and adults [1, 2]. Different guidelines for the cut-off value have been proposed for forced expiratory volume in one second ($FEV_1$) and airway resistance ($R_{aw}$), expressed as either % baseline or as % predicted [3–10].

Spirometry is hard to perform in children younger than 6 yrs old. Normal values of $R_{aw}$ [11] and of total respiratory resistance ($R_{rs}$) measured with the forced oscillation technique (FOT) [12, 13] have been established in children [14–16]. Not many data are available on bronchodilation tests in asthmatic children younger than 6 yrs. In some of these studies the impulse oscillation system (IOS) was used [17, 18], a FOT involving the application of a rectangular pulse signal, whilst in the FOT a pseudorandom noise signal, containing harmonics up to 24 or 48 Hz, is generally used [13]. Both techniques give similar results (r=0.85) over wide ranges of resistance between 0.1 and 1.5 kPa·L$^{-1}$·s [19]. There are, however, no published data on bronchodilator response in healthy children younger than 6 yrs using oscillator techniques. Yet, as already stated, this research is essential [3] to establish the threshold for a significant response in asthmatic children.

The aims of the present study were to establish in children aged from 3–6 yrs: 1) normal reference values for the IOS; 2) the change in $R_{rs}$ and in respiratory reactance ($X_{rs}$) after inhalation of a $\beta_2$-agonist in healthy and in asthmatic children; and 3) to propose threshold values for a significant bronchodilator response.

The study protocol was approved by the ethical committee of the university hospital.

## Materials and methods

The study population consisted of 281 children with a mean age of 4.5 yrs (range 2.7–6.6), a mean height of 108 cm (range 93–131) and a mean weight of 18 kg (range 12–29); 129 males and 152 females. They were recruited from children attending kindergarten (95% of Belgian children between 3–6 yrs do so). During the first and the third year of kindergarten the children have a medical check-up. A standardized questionnaire on the diagnosis of asthma with a form for informed consent was sent to the parents of 480 of these children invited to the centre in the Leuven region (located in the central, most industrialized part of Belgium). Informed consent was obtained from the parents of 362 children; of these, 81 had to be excluded because of a lack of biometric information (10 children), unavailability at the time of the test (17 children) or failure to perform the test procedure (56 children). Therefore, 281 children, who were examined at the centre between 1 December, 1995 and 20 June, 1996 were included in the study. The relevant items and the scoring system of the standardized questionnaire on the presence of asthma are outlined in table 1. As the questions on wheezing and shortness of breath have proven to be most reproducible [20], these were given the most weight in the interpretation. A validation study of the questionnaire had

Table 1. – Relevant items and scoring system of the standardized questionnaire

1. Does your child wheeze?
   a) yes, daily
   b) yes, once a week
   c) yes, once a month
   d) yes, less than once a month
   e) yes, more than a year ago
   f) never
2. Does your child have shortness of breath?
   a) yes, daily
   b) yes, once a month
   c) yes, once a month
   d) yes, less than once a month
   e) never during the last year
3. Is there a provoking factor for this shortness of breath?
   a) pollen
   b) effort
   c) laughing or crying
   d) pets
   e) bedroom
   f) common cold
   g) unknown
4. Does your child cough?
   a) several times a day
   b) several times a week
   c) not every week
5. Does your child cough when he/she is not having a cold? Does your child cough after an effort?
6. Is your child suffering from asthma?
7. Does your child take any of the following drugs? (trade names are given)
   a) inhaled steroids
   b) cromoglycate, $\beta_2$-agonists, anticholinergics, aminophyllins.
8. Did your child take cromoglycate or inhaled steroids in the past?

Scoring system: three points were given for answer 1a, b or c, 2a, b or c and 7a; two points were given for answer 1d, 3a, b, c, d or e, 4a and 7b; and one and a half points were given extra if at least one of the next 4 was positive: 4b, 5, 6, 8. If the sum was Š4.5, the patient was considered asthmatic.

previously been set up at the hospital and at two private practices. The questionnaire was tested in a validation group (age range 3–7 yrs) of 34 asthmatics and 28 nonasthmatics, otherwise diagnosed by a qualified paediatrician. The sensitivity was 0.91, specificity 0.82 and Chi-square 47.6 ($p<0.000001$). Therefore, the questionnaire was considered valid.

The pulmonary function tool used was the IOS, developed by the Jaeger company (Würzburg, Germany). In short, rectangular mechanical impulses containing the whole frequency spectrum are applied to the respiratory system by a mouthpiece, while the patient is breathing quietly. The resulting pressure and volume signals are analysed for their amplitude and phase difference to determine the $R_{rs}$ and $X_{rs}$ of the total respiratory system [12, 13, 21, 22]. For each impulse 32 sample points were analysed. The FOT with pseudorandom noise has been evaluated in adults [22], and healthy children [15, 16, 23, 24] as well as in children with a variety of pathologies, but most of these latter studies were conducted in children older than 6 yrs. The most attractive features of this lung function tool are its effort-independence and its simplicity even in young children [25]. With IOS, as with FOT, mean values of $R_{rs}$ and $X_{rs}$ are measured, as well as $R_{rs}$ and $X_{rs}$ at specific frequencies (*e.g.* 5 Hz for IOS and 6 Hz for FOT) and resonant frequency for $X_{rs}$. As already stated, there was a good correlation (r=0.85) between $R_{rs}$ at 5 Hz with the IOS and $R_{rs}$ at 6 Hz with the FOT for wide ranges of resistance [19].

All pulmonary function tests were performed by J. Hellinckx. After a short explanation, the children perform-ed some practice trials. When the child was feeling comfortable, a measurement of 25–35 s was started. Patients were asked to breathe quietly through a round mouthpiece. A nose clip was used and the cheeks were supported by the hands of the investigator to minimize pressure loss through the upper airway shunt [26]. Measurements were discarded if the time-flow pattern showed apnoea, speaking, swallowing or air leak, as described by BISGAARD and KLUG [17]. The following parameters were recorded: $R_{rs}$ and $X_{rs}$ at 5, 10, 15, 20, 25 and 35 Hz and resonant frequency ($f_0$). Of the study population of 281 children, 253 were tested before and 20 min after administration of 200 µg salbutamol; the other 28 children were tested before and 20 min after placebo had been given to check for a possible learning effect. The spacer device used to administer the medication was a Babyhaler® (Glaxo Gmbh, Bad-Oldesloe, Germany) for children under the age of 4.7 yrs and a Volumatic® (Glaxo) above the age of 4.7 yrs. The dose was chosen according to BIBI *et al.* [2].

The repeatability of the tests was acceptable; indeed, the mean difference (±SD) between the two measurements in the control group (n=28) was 0.099±0.073 kPa·L$^{-1}$·s or 8.5% of baseline for $R_{rs}$ at 5 Hz ($R_{rs,5}$) and 0.109±0.092 kPa·L$^{-1}$·s or 25.5% of baseline for $X_{rs}$ at 5 Hz ($X_{rs,5}$).

Statistics were analysed using Epi Info (CDCP, Atlanta, GA, USA) and SAS (SAS Institute, Cary, NC, USA) and consisted in analyses of means±1SD, 95% confidence intervals, analysis of variance (ANOVA), student t-tests for unpaired samples, and linear and multiple regression analyses.

## Results

Of the 281 studied children, 34 were diagnosed as asthmatic by the questionnaire. This is 12% of the tested population. Two hundred and fifty three children were given 200 µg salbutamol for the bronchodilation test and 28 received placebo; in these groups, 25 and 9 children, respectively, were asthmatic. Of the 34 asthmatics, 16 were receiving treatment (seven were taking cromoglycate and six inhaled steroids; 14 were taking a bronchodilator *p.r.n.*).

In the 247 nonasthmatic children the mean (±SD) $R_{rs,5}$ was 1.06 kPa·L$^{-1}$·s for the males and 1.02 (±0.22) kPa·L$^{-1}$·s for the females. The differences between the sexes at higher frequencies were even smaller. These differences were not statistically significant (at 95% confidence interval). Of the reactances, only the $X_{rs}$ at 15 Hz ($X_{rs,15}$) was significantly different (p=0.03) between males and females; but the difference was small, as the mean $X_{rs,15}$ was -0.16 (±0.09) kPa·L$^{-1}$·s for males and -0.14 (±0.09) kPa·L$^{-1}$·s for females. Therefore, it was decided to calculate mean values for both sexes combined. Means (±SD) were 1.03 (±0.24) kPa·L$^{-1}$·s for $R_{rs,5}$ and -0.35 (±0.13) kPa·L$^{-1}$·s for $X_{rs,5}$. Linear regression analysis was applied to describe values for $R_{rs}$ and $X_{rs}$ in function of height, at different frequencies, for both sexes together. The correlation coefficient (r) for height and $R_{rs,5}$ was 0.33 ($p<0.001$) and for height and $X_{rs,5}$ 0.19 ($p<0.01$). Inclusion of weight and

age in a multiple regression model did not narrow the confidence interval, so only height was used. A summary of all parameters is given in table 2. In figure 1 the regression line of $R_{rs,5}$ as a function of height is plotted, with the individual data for asthmatics and nonasthmatics. In the asthmatic population, means (±SD) were 1.09 (±0.26) kPa·L$^{-1}$·s for $R_{rs,5}$, -0.38 (±0.18) kPa·L$^{-1}$·s for $X_{rs,5}$ and 27.7 (±3.0) Hz for $f_0$, which were not significantly different from the values for nonasthmatics. No significant differences could be found at higher frequencies. Figure 2 shows the 95% confidence intervals for $R_{rs}$ and $X_{rs}$ in healthy children with a height of 105.5 cm, corresponding to the mean height of the asthmatics; the mean (±SD) values for $R_{rs}$ and $X_{rs}$ in the asthmatics are also presented and appear to be situated within the normal ranges.

The range of the changes after administration of 200 µg salbutamol was large. In the nonasthmatic group (table 3) the mean change (±SD) was -0.13 (±0.20) kPa·L$^{-1}$·s for $R_{rs,5}$ and +0.052 (±0.132) kPa·L$^{-1}$·s for $X_{rs,5}$. The change was not significantly different between males and fem-ales. There was a correlation between baseline and change (r=-0.50, p<0.001 for $R_{rs}$; r=-0.63, p<0.001 for $X_{rs}$). When the 25 asthmatics were considered, mean change (±SD) was -0.09 (±0.25) kPa·L$^{-1}$·s for $R_{rs,5}$, +0.08 (±0.15) kPa·L$^{-1}$·s for $X_{rs}$ and -2.6 (±4.2) Hz for $f_0$. These values were not significantly different from those in the nonasthmatics. The change provoked by salbutamol, expressed as % of baseline, was for the whole group -11.9 (±18)% for $R_{rs,5}$, -10.2 (±15.9)% for $R_{rs}$ at 10 Hz ($R_{rs,10}$), -6.5 (±44.1)% for $X_{rs,5}$, -20.7 (±54.7)% for $X_{rs}$ at 10 Hz ($X_{rs,10}$) and -11.4 (±17.5)% for $f_0$. These changes were all significantly different from zero (p<0.03 for $X_{rs}$; p<0.0001 for $R_{rs,5}$, $R_{rs,10}$, $X_{rs,10}$, $f_0$). In figure 3 the change in $R_{rs,5}$ after administration of salbutamol (in % of baseline) is shown as a function of $R_{rs,5}$ expressed as % predicted.

When placebo was given the mean change (±SD) for $R_{rs,5}$ was +0.004 (±0.14) kPa·L$^{-1}$·s and for $X_{rs,5}$ -0.05 (±0.13) kPa·L$^{-1}$·s, which is significantly different from the change when salbutamol is given (p<0.001). In figure 4 the mean changes (±SD) of $R_{rs}$ are shown for the 25 asthmatics and 228 healthy children, compared with the placebo group. The changes of $X_{rs}$ in the three groups are shown in figure 5.

Table 2. – Baseline respiratory resistance ($R_{rs}$) and reactance ($X_{rs}$) and regression equations in function of height in 247 nonasthmatic children

| | *y* | *a* | *b* | *r* |
|---|---|---|---|---|
| $R_{rs,5}$ | 1.03±0.23 | -0.0095280 | 2.0643065 | -0.33 |
| $R_{rs,10}$ | 0.89±0.18 | -0.0075718 | 1.7075376 | -0.33 |
| $R_{rs,15}$ | 0.81±0.16 | -0.0070199 | 1.5709699 | -0.35 |
| $R_{rs,20}$ | 0.74±0.15 | -0.0063355 | 1.4279232 | -0.34 |
| $R_{rs,25}$ | 0.70±0.14 | -0.0055574 | 1.2980854 | -0.32 |
| $R_{rs,35}$ | 0.69±0.12 | -0.0050031 | 1.2296459 | -0.33 |
| $X_{rs,5}$ | -0.35±0.13 | 0.0030634 | -0.6812083 | 0.19 |
| $X_{rs,10}$ | -0.20±0.10 | 0.0024795 | -0.4641258 | 0.20 |
| $X_{rs,15}$ | -0.15±0.09 | 0.0019946 | -0.3656876 | 0.17 |
| $X_{rs,20}$ | -0.09±0.08 | 0.0018283 | -0.2847529 | 0.19 |
| $X_{rs,25}$ | -0.01±0.07 | 0.0013528 | -0.1534239 | 0.16 |
| $X_{rs,35}$ | 0.17±0.06 | -0.0002245 | 0.1944854 | -0.03 |
| $f_0$ | 25.0±4.3 | -0.0921224 | 34.9207112 | -0.17 |

Values are shown as means±SD. *y*: a×height + b; height in cm, *y* in kPa·L$^{-1}$·s$^{-1}$ for $R_{rs}$ and $X_{rs}$ and in Hz for resonance frequency ($f_0$). *r*: correlation coefficient of height and *y*.

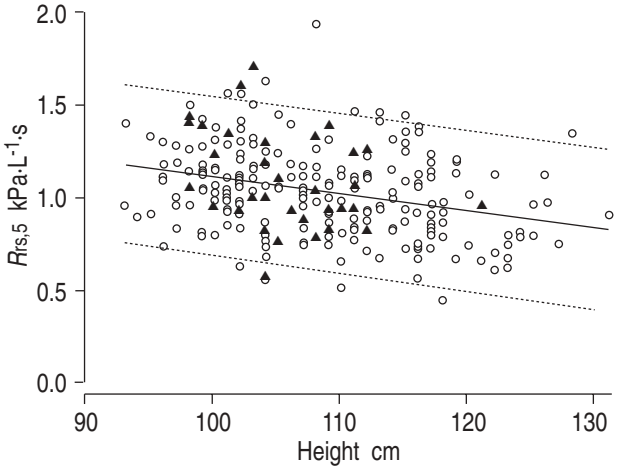


Fig. 1. – Linear regression of respiratory resistance at 5 Hz ($R_{rs,5}$) in function of height in 247 nonasthmatic children, with 95% confidence intervals (·····). ○: individual data of the nonasthmatics; ▲: data of 34 asthmatics.

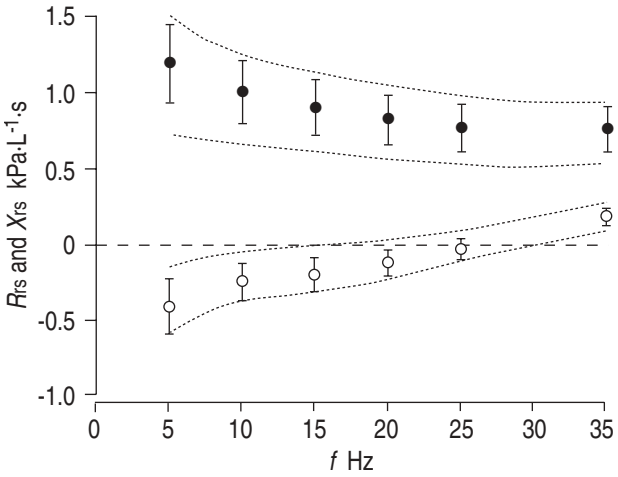


Fig. 2. – ·····: 95% confidence intervals for respiratory resistance ($R_{rs}$, ●) and reactance ($X_{rs}$, ○) at different frequencies for the nonasthmatic children of height 105.5 cm, which is the average height of the asthmatic. The values of the asthmatics are shown by the circles (±1 SD) and are situated within the normal ranges.

Table 3. – Absolute change in respiratory resistance ($R_{rs}$) and reactance ($X_{rs}$) after 200 µg salbutamol in 228 nonasthmatic children

| | |
|---|---|
| $R_{rs,5}$ | -0.134±0.203 |
| $R_{rs,10}$ | -0.099±0.147 |
| $R_{rs,15}$ | -0.067±0.126 |
| $R_{rs,20}$ | -0.047±0.122 |
| $R_{rs,25}$ | -0.039±0.177 |
| $R_{rs,35}$ | -0.035±0.104 |
| $X_{rs,5}$ | 0.052±0.132 |
| $X_{rs,10}$ | 0.061±0.089 |
| $X_{rs,15}$ | 0.063±0.079 |
| $X_{rs,20}$ | 0.051±0.060 |
| $X_{rs,25}$ | 0.040±0.056 |
| $X_{rs,35}$ | 0.025±0.055 |
| $f_0$ | -3.1±4.2 |

Values are shown as mean±SD. $R_{rs}$ and $X_{rs}$ in kPa·L$^{-1}$·s at indicated Hz. $f_0$: resonance frequency (Hz).

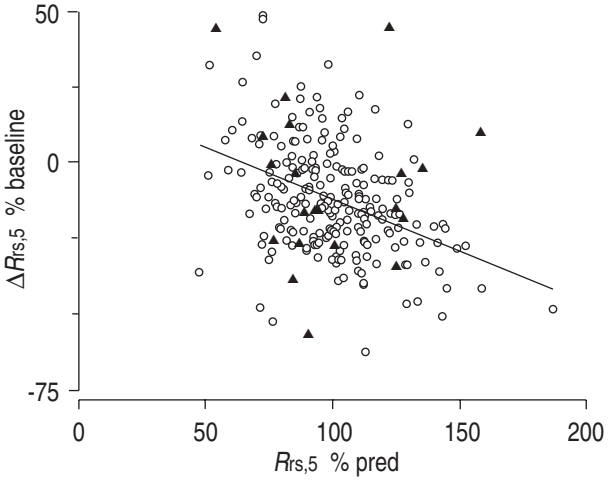


Fig. 3. – Regression line for the change in respiratory resistance at 5 Hz ($R_{rs,5}$) after administration of 200 µg salbutamol as a function of the baseline value of $R_{rs}$ in 228 healthy children (○). The data of 25 asthmatics are drawn on the same graph (▲).

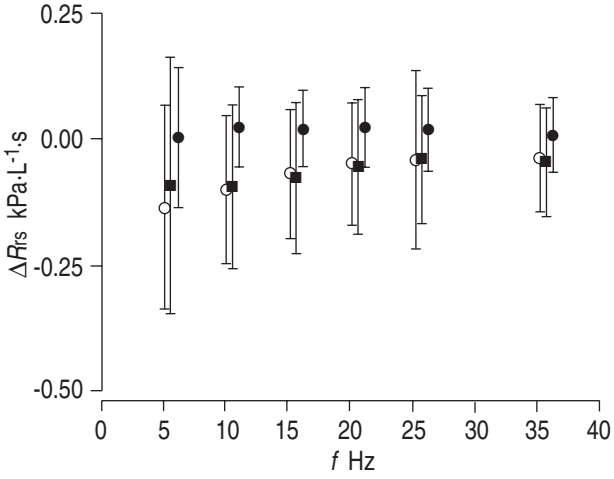


Fig. 4. – Mean changes (±SD) in respiratory resistance ($R_{rs}$) after 200 µg salbutamol plotted for the 228 healthy children ( ) and 25 asthmatics (■), compared with the changes in 28 children who received placebo (●).

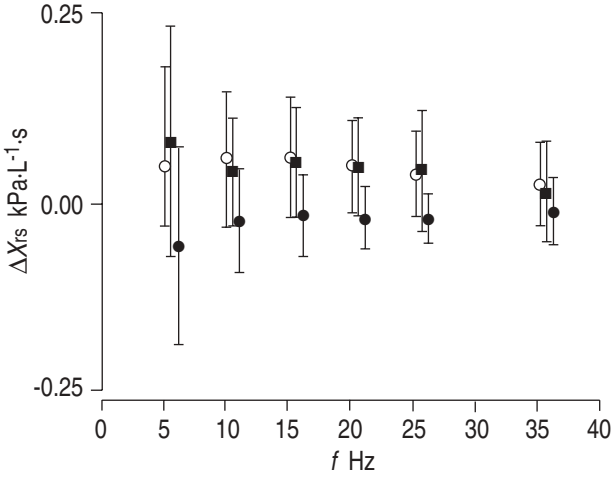


Fig. 5. – Mean changes (±SD) in respiratory reactance ($X_{rs}$) plotted for the 228 healthy children (○) and 25 asthmatics (■), compared with the changes in 28 children who received placebo (●).

## Discussion

The baseline values for $R_{rs}$ with the IOS in children are slightly higher than those of Duiverman [23] and Clement *et al*. [27] with FOT, but in those studies most of the collected data were obtained in somewhat older children and $R_{rs}$ at 6 Hz ($R_{rs,6}$) was measured. The changes after salbutamol are similar in healthy children and in stable asthmatics with normal baseline values. In both groups the change in $R_{rs,5}$ is about 12% of baseline value.

The study population was representative for Belgium, as most children in this country attend kindergarten. The rate of participation in the study was very good. A standardized questionnaire was used to detect children with asthma. As the reliability and reproducibility of questionnaires have been subject to discussion [28] this questionnaire was validated in a separate group of children and it appeared to have high sensitivity and specificity based on the clinical asthma diagnosis by qualified paediatricians. Although the gold standard for the diagnosis of asthma in children is not clearly established [29], the diagnosis by physicians has indeed been shown to be the most specific for validation of questionnaires [30].

The present study shows that IOS can be used routinely in young children. Considering the baseline values, no difference between males and females was found. No agreement exists in the literature on this point: Duiverman *et al.* [14] reported a higher resistance in males up to 8 yrs, whereas Clement *et al*. [27] reported a higher resistance in females up to 7.5 yrs, both measured with FOT. The range of normal values for a given height is large. This is not a consequence of the variability of the test, as the repeatability of the test is acceptable. The reason for the range is that, similarly to FOT, other factors unrelated to age, height, weight and sex have an important influence on the values. Not only the overall airway diameter is im-portant, but the circumference at specific "choke points" and the compliance of the airway [31], especially of the upper airway [26], also have an influence.

The regression formulae in the present paper provide an alternative to the equations of Duiverman *et al.* [14] which were obtained on FOT, at the age when IOS is most useful, namely before spirometry can be routinely perfor-med. The equations are easy to use and frequency charact-eristics are well described. Ninety-five per cent confidence intervals can be easily calculated, which makes interpretation easier.

A main issue of this study was to find out how much $R_{rs}$ changes after $\beta_2$-agonists in healthy children and if the change is larger in asthmatics and thus find the cut-off level that can be used in the diagnosis of asthma. To the best of our knowledge, this has never been evaluated in children of this age. The mean change in $R_{rs,5}$ in healthy children was 12% (relative to baseline, which is also the predicted value) and the change should be more than -41.4% before it is outside the 95% confidence interval. The effect of salbutamol was, however, not significantly different for the asthmatic children with a normal baseline. The risk of overinterpretation of a change after bronchodilation should thus be stressed and the availability of the present reference values with 95% confidence intervals can be an important tool against overinterpretation. From these data we suggest that the cut-off level for a "significant" or "positive" bronchodilator response in asthmatic children

should be situated at -40% pred. As the asthmatic children had normal baseline values and were stable, changes in $R_{rs,5}$ of 40% should not be expected. As far as we know no data are available on the bronchodilator response in asthmatic children of younger than 7 yrs old with increased baseline values. In adult asthmatics with increased baseline values we found [10] a bronchodilator response in $R_{aw}$ of -88±77% pred (or -35±21% baseline), while the response was only -26% pred in healthy subjects. The bronchodilator response in $R_{aw}$ is very similar to that in $R_{rs,6}$ at least in adults, indeed VAN NOORD *et al*. [9] found in pa-tients with obstructive lung disease (asthma or chronic obstructive pulmonary disease (COPD)) a bronchodilator response in $R_{aw}$ of -0.11±0.10 kPa·L$^{-1}$·s and in $R_{rs,6}$ of -0.12±0.12 kPa·L$^{-1}$·s.

It should also be noted that worsening of $R_{rs}$ and/or $X_{rs}$ after salbutamol was found in some of the healthy and asthmatic children. This finding is not unusual in children but has mainly been described after forced respiratory manoeuvres such as $FEV_1$ in cystic fibrosis patients [32, 33].

The absence of difference in baseline function and in bronchodilator response between these asthmatics and healthy children may be obscured by the wide scatter of the response but may also be attributed to the fact that these young patients were stable as they were attending kindergarten, and also to the fact that half of them were treated (16/34). Additionally, in this study the severity of asthma was not assessed. Most probably, the majority of the asthmatics had mild asthma. In mild asthmatics the bronchial epithelium has been shown to be normal during stable intervals [34]. Dividing the asthma group into subgroups of severity would have made the sample too small for a correct interpretation. These results demonstrate that lung function tests may be normal during stable intervals in young asthmatic children. The results of this study are suggestive of a normal airway patency between asthmatic episodes.

In conclusion, normal values for children between 3 and 6.5 yrs old were given for baseline impulse oscillation tests and after 200 µg of salbutamol. Baseline predictions were expressed as a function of height and predictions of the effect of salbutamol were expressed as a function of baseline values. The range of the predicted values was large. A relative change up to 40% after salbutamol should be regarded as within the normal range. With the impulse oscillation technique airway resistance and reactance mea-surements were similar in stable asthmatics under treatment and in healthy children.

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