Interrupter technique in young children
Applicability of interrupter resistance measurements using the MicroRint in daily practice

5.1

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Respir Med 2002, in press
Abstract

This study was performed to evaluate the applicability of a simple device (MicroRint®) for measuring airway resistance, to derive normal values and to compare values with maximal expiratory flow volume (MEFV) parameters in asthmatic and healthy children.

Repetitive Rint measurements were performed in 125 healthy children and 107 asthmatic children (age range 0.8-16.8 years). In 42 asthmatic patients Rint and MEFV values were compared and in 29 asthmatic children bronchodilator testing was performed.

Successful Rint measurements were possible in 91% of the children. The mean coefficient of variation of repeated measurements was 7.1(SD6.1)%. Rint values of healthy children showed a significant curvilinear correlation with age (r = -0.80, p<0.001) and height (r = -0.81, p<0.001). In asthmatic and healthy children Rint values were comparable. A significant inverse correlation was found between Rint and MEFV values (for FEV₁ and Rint r = -0.80, p<0.001). After bronchodilation there was a significant increase in FEV₁ and decrease in Rint, but changes between the two parameters did not correlate.

In conclusion, the interrupter technique is feasible and repeatable in children and has a significant correlation with other parameters of airway caliber. Baseline values do not discriminate healthy from asthmatic children.
Introduction

Medical history and physical examination are the most important parameters for diagnosis and treatment of recurrent respiratory problems in young children, because objective parameters of lung function can not always be obtained.

During the last decade several pulmonary function devices for young children have been developed, but most are only applicable in a research setting. Moreover, application of these devices often requires sedation of the child, special equipment and a laboratory setting.

One of the techniques, used for measuring resistance of the respiratory system is the interrupter technique, which was first described by Von Neergaard and Wirz in 19271.

The MicroRint® is a small portable data recording airway resistance meter, using the interrupter technique. It measures airway resistance during quiet breathing, requires minimal subject co-operation and can be used during spontaneous breathing and without sedation. Theoretically this makes it applicable even in very young children and in patients unable to co-operate with normal (forced) breathing techniques.

The basis of the interrupter technique is that, during transient interruption of the tidal airflow, alveolar pressure and mouth pressure equilibrate within a few milliseconds. The alveolar pressure can therefore be derived from the measurement at the mouth immediately after interruption. If the flow is measured immediately prior to interruption, the ratio of pressure to flow gives the interrupter resistance (Rint). It should be stated that pressure equilibration is incomplete in case of severe airway obstruction and that this is a limitation of the model on which Rint is based.

In adults, Rint shows a close correlation to airway resistance (Raw) measured by whole body plethysmography. In asthmatic subjects the methods were equally sensitive in detecting changes in airway resistance following bronchodilation2-3, but Rint tended to measure higher resistances, probably due to a contribution of chest wall rigidity, lung tissue resistance and the glottis to airway resistance4-5. Only recently studies have also evaluated the applicability of the Rint technique in children6-12.

The purpose of the present study was to evaluate the applicability of the MicroRint© in children with and without asthmatic symptoms in daily practice, to establish normal values and to compare Rint values with maxi-
mal expiratory flow volume (MEFV) parameters as measures of airway patency.

Subjects and methods

Subjects

Interrupter resistance was measured during spontaneous breathing in 232 children (112 male, 120 female). 107 children were known with doctor’s diagnosed asthma according to the British Thoracic Society (BTS) definition. These children were tested in a clinically stable situation. The other 125 children were recruited from two primary schools and two day care centers. For the latter group parents had completed a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Patients with a history of asthma, asthma treatment, dyspnoea, eczema, wheezing or recurrent coughing were not included into the study. Measurements in these children were performed during a visit to the schools. Informed consent was obtained from the parents of all children. Subject characteristics of 107 asthmatic and 125 healthy children are shown in Table 1. There were no significant differences between asthmatic and healthy children.

In 42 asthmatic children (mean age 8.7(3.4) years, FEV \textsubscript{1} 107.0(13.3) %pred.) MEFV curves were performed and MEFV parameters were compared with Rint values. In 35 of these children Rint and MEFV measurements were repeated, 15 minutes after inhalation of 800 micrograms salbutamol (pMDI through spacer). Because 6 children could not perform Rint measurements before bronchodilation, comparison of MEFV and Rint values could only be made in 29 children. Prior to pulmonary function testing no bronchodilators had been used for at least 6 hours.

Methods

Airway resistance was measured using the MicroRint® (Micro Medical Limited, Kent, UK). Flow was measured with a pneumotachometer consisting of a steel resistive element and a high frequency solid-state pressure
transducer. The same pressure transducer was used to measure the mouth pressure post-occlusion. Measurements were performed in a sitting position. Children were entertained and attention was diverted to reduce their anxiety and to prevent abnormal breathing. Measurements were made using a cardboard mouthpiece (>10 years: 2.7 cm diameter, <10 years 2.0 cm) and the subjects were instructed to wear a nose clip, seal their lips around the mouthpiece and to lay their tongue on the floor of the mouth to prevent obstruction of airflow. Cheeks and mouth floor were supported by the hands of the investigator to prevent energy loss and to reduce the effect of mouth compliance. During spontaneous normal and quiet breathing the interrupter valve was operated manually twice to accustom the child to the shutter action. Thereafter, 10 airflow interruptions were made on the peak flow of an expiration; these occurred at random frequency and automatically so that they could not be anticipated, thus independent of the investigator’s timing. After 10 interruptions the median R_{int} value was displayed as were the flow and pressure curves. A single interruption resistance value was (automatically) rejected when an artifact on the pressure curve occurred. Manual rejection was performed in case of tachypnoea, usage of vocal cords, extreme neck flexion or extension or leakage of the mouth piece. Tracings not showing the timing of interruption on the flow tracing, or tracings with a horizontal or declining pressure signal suggesting leakage at the mouth, or with an altered ventilation pattern were discarded as well.

<table>
<thead>
<tr>
<th></th>
<th>asthma</th>
<th>healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of children</td>
<td>107</td>
<td>125</td>
</tr>
<tr>
<td>male/female</td>
<td>52/55</td>
<td>60/65</td>
</tr>
<tr>
<td>age (years (SD))</td>
<td>7.6 (3.3)</td>
<td>8.2 (2.8)</td>
</tr>
<tr>
<td>height (cm (SD))</td>
<td>125.8 (19.6)</td>
<td>132.2 (18.2)</td>
</tr>
<tr>
<td>weight (kg (SD))</td>
<td>27.4 (11.5)</td>
<td>29.8 (10.4)</td>
</tr>
<tr>
<td>no successful measures</td>
<td>10 (9%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>one successful measurement</td>
<td>17 (16%)</td>
<td>19 (15%)</td>
</tr>
<tr>
<td>two successful measurements</td>
<td>80 (75%)</td>
<td>96 (77%)</td>
</tr>
<tr>
<td>total successful measurements</td>
<td>97 (91%)</td>
<td>115 (92%)</td>
</tr>
</tbody>
</table>
Before a Rint measurement was considered successful, a median Rint value had to be obtained from a minimum of 5 out of 10 interruptions. Reasons for failure were recorded. The number of successful measurements and the number of acceptable interruptions per measurement were recorded. All Rint measurements were attempted twice in order to evaluate inter-measurement variability. Rint measurements always preceded MEFV maneuvers.

We evaluated the validity of Rint measurements by measuring the inter-measurement repeatability of two tests 30-60 seconds apart and the intra-measurement variability for every individual measurement consisting of 5-10 acceptable interruptions. Normal values were calculated for healthy subjects and these were compared with those for asthmatic children (according to age, height and gender).

MEFV curves were measured using a pneumotachometer system with a heated Lilly head (MasterScreen Pneumo or Jaeger Masterlab, Erich Jaeger, Würzburg, Germany). Equipment calibration conformed to ECSC (European Community for Steel and Coal) instructions. All measurements were BTPS corrected.

Values for the following parameters were obtained: FEV1, FVC, PEF, MEF75 and MEF50. All parameter values were described both as absolute values and as percentage of predicted values, described by the summary equations of Zapletal et al.

**Statistical analysis**

Data are reported as mean (SD), unless indicated otherwise.

The repeatability of Rint measurements was evaluated by inter-measurement and intra-measurement coefficients of variation (CV=SD/n). Bland Altman plots were constructed to find limits of agreement between two repeated measurements.

The reliability coefficient (RC), also called the intra class correlation coefficient, was used to describe the within-subject stability of average Rint values. In children with “n” successful interruptions the subject’s true Rint value was estimated by taking the average over n interruptions. The RC of this average calculated Rint was defined as:

\[
\text{RC} = \frac{\sum_{i=1}^{n} (Rint_i - \bar{Rint})^2}{n-1}
\]
\[ \text{RC} = \frac{\sigma^2_{\text{inter}}}{(\sigma^2_{\text{inter}} + \sigma^2_{\text{intra}}/n)} \]

in which \( \sigma^2_{\text{inter}} \) is the between-subject variance of true \( R_{\text{int}} \) mean, \( \sigma^2_{\text{intra}} \) is the within subject variance of single \( R_{\text{int}} \) values within one subject, and \( n \) is the number of interruptions used to calculate the average \( R_{\text{int}} \) within a subject. The nearer RC is to 1, the more stable the average ratio.

A student's t-test was used for comparison of data. Correlation between two parameters was evaluated by Pearson correlation coefficients. Correlation between age and number of successful measurements was analyzed using logistic regression with the number of successful measurements as the dependent variable.

Results

A. Feasibility

Results are shown in Table 1 and 2. At least one (out of two) acceptable baseline \( R_{\text{int}} \) measurement could be performed in 212 of the 232 children (91%) (Table 1); this percentage was similar in asthmatic (97/107 = 91%) and healthy children (115/125 = 92%). In 5 asthmatic children measurement was possible after, but not before bronchodilation (Table 2). Age distribution is shown in Figure 1.

Of all children, 76% were able to produce two successive measurements. A significant although weak correlation was found between age and number of successful measurements (\( r = 0.18, p < 0.01 \)). Of 20 preschool children (15 in kindergarten, 5 in outpatient clinic) in whom two repetitive efforts were made at least one successful measurement was possible in 15 (75%) of children. Results for pre school children are presented in Table 3. The main reasons for failure were blowing into or sucking on the device, or refusal to take the device into the mouth.

The mean number of successful interruptions per measurement was not significantly different between healthy (7.6 (2.2)) and asthmatic (8.0 (2.1)) children. There was a significant correlation between age and the number of successful interruptions (i.e. during 1 measurement), (\( r = 0.17, p = 0.012 \)).
Table 2. Feasibility of Rint measurements in the different subject groups (n = number, meas = measurements). * Because 5 children in the bronchodilator group were only able to produce values after B2, only 212 usable baseline measurements were evaluated.

<table>
<thead>
<tr>
<th></th>
<th>n meas.</th>
<th>Number of successful measurements</th>
<th>≥1 good test</th>
<th>All good tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>158</td>
<td>2</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>C (no B2)</td>
<td>24</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>(-/+ B2)</td>
<td>35</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>total</td>
<td>232</td>
<td>15*</td>
<td>33</td>
<td>156</td>
</tr>
</tbody>
</table>

A = kindergarten, B = schoolchildren, C = outpatient clinic patients

Figure 1. Age distribution of children able to perform Rint measurement
Table 3. Feasibility of Rint measurements in pre school children (n = number).

<table>
<thead>
<tr>
<th></th>
<th>No successful measurement</th>
<th>One successful measurement</th>
<th>Two successful measurements</th>
<th>At least one successful measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1-2 years</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-3 years</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>4 (78%)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>5</td>
<td>8 (35%)</td>
<td>7 (40%)</td>
</tr>
</tbody>
</table>

B. Validity

Rint measurements of 212 children were evaluated before or without bronchodilation. The mean inter-measurement coefficient of variation (CV) was 7.1(6.1). CV correlated significantly with both age ($r = -0.214$, $p=0.004$) and height ($r = -0.215$, $p =0.004$). There were no significant differences between girls and boys, or between asthmatic and healthy children.
The mean difference between 2 consecutive measurements was -0.005 (+0.11) kPa.L^{-1}.s, indicating that 95% of the values of Rint in the second measurement fell between -0.23 and +0.21 kPa.L^{-1}.s (lower and upper limits of agreement, Figure 2). There was a significant inverse correlation between the absolute difference between two measurements and both age \((r = -0.283, p<0.001)\) and height \((r = -0.256, p<0.001)\).

The mean intra-measurement CV was 12.2 (5.5)%. There was a significant correlation between CV and both age \((r = -0.277, p<0.001)\) and height \((r = -0.317, p<0.001)\). No significant differences were found between girls and boys or between asthmatic and healthy children. Reliability coefficients of 1-10 interruptions are shown in Figure 3. The use of one single interruption \((n=1)\) would result in a Rint value with a reliability coefficient of 0.90. An increase in the number of interruptions would increase the reliability coefficient of the subsequently measured Rint value.

Figure 3. Reliability coefficients of the Rint value calculated as an average of n sequential interruptions.

C. Normal values

The mean Rint of healthy children was 0.64 (0.26) kPa.L^{-1}.s. There was a significant correlation between age and Rint \((r = -0.80, p<0.001)\) and between height and Rint \((r = -0.81, p<0.001)\). Figure 4 shows the Rint values for healthy children in relation to their height. This curvilinear relation was best represented by the regression formula:
Rint (kPa.L\(^{-1}\).s) = 0.0001x(height)\(^2\) - 0.0399x(height) + 4.0288, with height expressed in cm. (R\(^2 = 0.65\)). Addition of age to this model did not improve R\(^2\). There were no differences between boys and girls.

For asthmatic children the mean Rint value was 0.70 (+0.27) kPa.L\(^{-1}\).s,

\[ y = 0.0001x^2 - 0.0399x + 4.0288 \]

**Figure 4.** Rint values in healthy children versus height.

**Figure 5.** Rint values in asthmatic children versus FEV\(_1\).
which was not significantly different from normal values and was also significantly correlated with age and height. There was a large overlap between the Rint values of healthy and asthmatic children, irrespective of a doctor’s diagnosis or a questionnaire based diagnosis of asthma.

Table 4. Correlation between Rint and MEFV parameters in 42 asthmatic children (r = correlation coefficient)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>-0.775</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁</td>
<td>-0.797</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEF</td>
<td>-0.754</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF50</td>
<td>-0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF75</td>
<td>-0.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 6. Rint values before (baseline) and after bronchodilation in 29 asthma patients (dashed line is mean value).
D. Comparison with MEFV measurements

Rint correlated significantly with FEV$_1$ in asthmatic children ($r = -0.800$, $p<0.001$, Figure 5). Significant inverse correlations were observed between Rint and absolute values of FVC, PEF, MEF$_{25}$, MEF$_{50}$ and MEF$_{75}$ (Table 4), but not between Rint and MEFV parameters presented as percentage of predicted.

E. Reversibility

After bronchodilation a significant increase in mean FEV$_1$ from 1.59 (+0.60) L to 1.69 (+0.69) L (mean increase +0.10 (+0.13) L, $p < 0.001$) coincided with a significant decrease in mean Rint from 0.71 (+0.21) kPa.L$^{-1}$.s to 0.54 (+0.18) kPa.L$^{-1}$.s (mean decrease -0.15 (+0.11) kPa.L$^{-1}$.s, $p < 0.001$) (Figure 6). In only 8 children an increase of more than 8% of FEV$_1$%pred. was observed. 21 pairs were concordant (increase in FEV$_1$ and decrease in Rint). However, the linear correlation between changes in Rint and FEV$_1$ was not significant ($r=0.12$, $p=0.59$).

Discussion

We evaluated the feasibility and repeatability of the MicroRint© in a group of asthmatic and healthy children. The majority of children of all ages was able to perform Rint measurements and repeatability was good. Rint values showed a significant correlation with absolute MEFV parameters. Although in most asthmatic patients a decrease in Rint was found after bronchodilation, there was no linear correlation between changes in Rint and changes in FEV$_1$.

A. Feasibility

The setting for measuring Rint was either a simple office setting in schools (and day care centers) or the outpatient department. Measurements were performed by rather inexperienced medical students, formerly unknown
with the method, who received only minimal instructions about use of the device before starting Rint measurements. All children were inexperienced with MicroRint measurements. We tried to distract the children from “conscious breathing” by playing games, parental presence or observer attendance. Parents were encouraged to attend the measurements in order to reassure their children and encourage the correct use of the device; ideally there should be a quiet testing area with sufficient “quiet” distraction. The use of a facemask (without nose clips) might enable measurements in smaller children but may also introduce problems such as leakage, increase of dead space, intranasal obstructions and nasal breathing. Klug and Bisgaard used a facemask with a built-in non compressible mouthpiece in order to prevent nasal breathing and to support the cheeks. In a recent study Child et al found higher values of Rint using a mouth piece compared to face mask. They were equally reproducible, but values were not interchangeable.

In our study, children 4 years and older were generally quite able to cooperate in MicroRint measurements, which led to reliable results. In younger children co-operation was less easily achieved. In the present study only 40% of 1-3 year old children were able to perform two measurements; similar data were reported by Bridge and co-workers, who performed successful reversibility testing in 53%, 71% and 91% of 2, 3 and 4 year old children, respectively.

B. Validity

Inter-measurement variability of two tests, 30-60 seconds apart, was small. The mean difference between two Rint measurements was comparable with data found by Bridge et al. These differences decreased with increasing age (and height) as could be expected. In our study the variability is low compared to earlier reports, especially when we take into account that measurements were performed in inexperienced children and by relatively inexperienced medical students. Intra-measurement variability for individual measurements consisting of 5-10 interruptions was also small, especially in the older children. Both intra- and inter-measurement variability were independent of gender, diagnosis and bronchodilation, which augments the applicability.

The small inter-measurement variability allows for the application of this technique in bronchial challenge testing, using the “variance based” provo-
cation dose (giving a change in $R_{int}$ to “baseline $R_{int} + 2$ SD”). This method proved to be a very good discriminator between healthy and asthmatic19.

Reliability coefficients for statistical evaluation of the stability of $R_{int}$ after 1-10 interruptions showed that even after one or two interruptions a reliable $R_{int}$ value can be found, which indicates that the premise to use a minimum of 5 acceptable interruptions to measure $R_{int}$ is acceptable. In the present study after 5 interruptions the reliability coefficient rose to 0.98. In an earlier study we evaluated the reliability coefficients of tidal breathing flow pattern analysis in quietly breathing children; reliability coefficients were much lower20, indicating that Micro$R_{int}$ measurements can be performed in a much shorter time span.

C. Reference values

We found a significant correlation between height (and age) and $R_{int}$, reflecting a decrease in airway resistance during growth. The data were not log-transformed to achieve normal distribution prior to the fit. In this study only a general impression of height-$R_{int}$ correlation was presented. In a recent study we presented reference values for children 3-13 years of age, using log-transformed data21.

The range was wide and no differences were found between healthy and asthmatic children.

There were no relevant gender differences. Few data on reference $R_{int}$ values were available until recently. Van Altena et al. evaluated $R_{int}$ values in adults and reported a mean $R_{int}$ of 0.38 (+0.17) kPa.L$^{-1}$.s and a significant relationship between $R_{int}$ and both age and height22. For a more extensive use of the interrupter technique in children reference values are needed for the (whole) pediatric age group. Until now no reference values are available for children over 7 years of age. In young children reference data were presented in two recent studies23,24. In 1998 Klug and Bisgaard published reference values of $R_{int}$ for 2-7 year old children, related to height8; they also found a wide range and that a single measurement could not demonstrate airway obstruction. In preschool children Mckenzie et al found significant differences between children with recurrent wheezing and both healthy controls and recurrent coughers24. The present study failed to distinguish healthy from asthmatic subjects using only baseline values. This might be due to the fact that these patients were symptom free during examination and were probably only mildly affected (normal FEV$_1$ %pred).
Recently we found in a study on ICS efficacy that baseline FEV\textsubscript{1} in mildly asthmatic children is often in the normal range\textsuperscript{25}. Probably also R\textsubscript{int} in mild asthmatics can be in the normal range. This may explain the inability of a single R\textsubscript{int} measurement to discriminate between healthy and asthmatics. Recent studies showed comparable results for airway resistance measured by impulse oscillometry, e.g. Hellinckx et al. found no difference in respiratory system resistance at 5 Hz (R\textsubscript{rs5}) between healthy and asthmatic children, nor in changes after bronchodilation\textsuperscript{26}.

D. Comparison between R\textsubscript{int} and MEFV parameters

We found a significant curvilinear relation between maximal expiratory flow volume parameters and R\textsubscript{int}. The R\textsubscript{int} values correlated well with FEV\textsubscript{1}, FVC and PEF, but only when absolute values were concerned. The latter is caused by the fact that during growth there is an absolute gradual decrease of airway resistance and increase of air flows, but of course not of pulmonary function parameters, expressed as percentage of predicted. Comparable results were reported by Mijnsbergen et al. who found a correlation coefficient of -0.74 in asthmatic patients and -0.58 in CF patients\textsuperscript{27}. Two other studies compared FEV\textsubscript{1} and interrupter conductance (G\textsubscript{int}), the reciprocal of R\textsubscript{int}; both reported highly significant correlations between G\textsubscript{int} and absolute FEV\textsubscript{1} and PEF values\textsuperscript{3,28}.

E. Reversibility testing

As with FEV\textsubscript{1} and many other pulmonary function test parameters baseline R\textsubscript{int} measurements could not differentiate between asthmatic and healthy children. There was a significant decrease of airway resistance after bronchodilation, coinciding with a small increase in FEV\textsubscript{1} and PEF. In our group of asthma patients with rather mild airway obstruction only small changes in airway resistance and patency could be expected. Mean percentual improvement of R\textsubscript{int} values after bronchodilation was higher than that of FEV\textsubscript{1} (22.5% versus 6.3%). In this study reversibility testing was not performed in healthy children. The latter has been performed in a recent study by Beydon et al. In a group of 5.3 (1.4) year old children they found a change (% of predicted values) in expiratory R\textsubscript{int} of -12% (95% CI -46% to +22%)\textsuperscript{29}.
In our very young children, the repeatability was relatively poor, which restricts reversibility testing. If we consider a decrease in Rint greater than two SD of variance (i.e. 0.22 kPa.L⁻¹.s⁻¹) to reflect reversibility, this reversibility was found in only a small percentage of children with proven reversibility, shown by FEV₁ measurements. Bridge and co-workers studied reversibility in wheezy pre-school children and found a significant decrease in most children; however, because no MEFV measurements were performed in these children the correlation with FEV₁ was unknown. McKenzie et al compared Rint reversibility in healthy, coughing and wheezing preschool children and showed that percentual Rint decrease is less in healthy preschool children compared to wheezing children.

We found a poor and non-significant correlation between changes of FEV₁ and Rint after bronchodilation. Morrison et al reported comparable results in young CF patients. To our knowledge no studies have evaluated this correlation in adults (MEDLINE search 1965-2001). In our opinion the poor correlation between changes in FEV₁ and Rint is probably due to the fact that measures of lung function obtained from a forced expiratory maneuver may have different physiologic implications than those measured during tidal breathing, as was also mentioned by other investigators. This and the fact that these children were probably only mildly asthmatic may explain the lack of correlation between FEV₁ and Rint changes.

We conclude that MicroRint® measurement provides a feasible and repeatable method for measuring airway resistance in children of all ages. Normal values show a highly significant correlations with age and height. The correlation with MEFV measurements is good. A single measurement cannot identify airway obstruction and reversibility testing shows a significant decrease in many asthmatic children, although not significantly correlating with changes in FEV₁.


Measurements of interrupter resistance.
Reference values for children 3-13 years of age
Abstract

The interrupter technique is a convenient and sensitive technique to study airway function in subjects who cannot actively participate in (forced) ventilatory function tests. Reference values for pre-school children exist but are lacking for children over the age of 7. We obtained reference values for expiratory interrupter resistance (Rinte) in 208 healthy Dutch Caucasian children 3-13 years of age. A curvilinear relationship between Rint and height was observed, similar to published airways resistance data measured plethysmographically. No significant differences in cross-sectional trend or level of Rint were observed according to gender. Based on the reference equation: 10log (Rinte) = 0.645 - 0.00668 x standing height(cm) kPa/L/s and residual standard deviation (0.093 kPa/L/s), Z-scores can be used to express individual Rint values and to describe intra- and interindividual differences. Rint provides a tool for clinical and epidemiological assessment of airway function in a large age range.
Introduction

The interrupter technique is one of the few lung function tests which can be used for assessment of airway calibre in young children. With this technique, measurements of the resistance of the respiratory system (Rint) can be carried out quickly, with minimal co-operation of the child. Rint measurements have been shown to be reproducible, sufficiently sensitive to detect (sub)clinical airway obstruction, and correlate satisfactorily with measurements of airway resistance. The technique can not only be used as a tool to screen for airway obstruction, but also to assess the responses to bronchodilating and bronchoconstricting agents. It is especially suitable for pre-school children because it only requires passive co-operation. However, passive measurements of airway function may also be required for clinical research in older children, or in older children who are unable to perform forced expiratory manoeuvres because of developmental disorders or neuromuscular disease. Till now, reference data are available for young children and adults, but not for children over 7 years of age. The aim of the present study was to expand the previous data set in order to better describe relationships between expiratory resistance and body size. We obtained normal Rint values during expiration (Rinte) in 208 healthy Caucasian children aged 3-13 years, from a general population. Measurements were preferably made during expiration rather than during inspiration because Rinte appears to be more sensitive to detect changes in resistance within children due to respiratory infections, and to discriminate better between children with and without respiratory symptoms or disease as compared to Rinti.

Methods

Dataset

Rint measurements were carried out using identical equipment and the same measurement protocol in 2 sets of healthy Dutch Caucasian children aged 1-13 years, recruited from 2 day-care centres, 2 kindergartens, and 2
elementary schools. Information on respiratory symptoms, eczema, allergy, parental smoking, doctors diagnosis of asthma, and asthma medication was obtained using modified ISAAC questionnaires. Children were included in the reference population when they had no respiratory symptoms in the month prior to or during the measurements. Exclusion criteria were: history of asthma, recurrent rhinitis, eczema, cardiorespiratory or other chronic disease, known anatomical abnormalities of the upper or lower airways, and vocal cord disorders. We intended to obtain reference values from a normal population rather than from an ideal population. Therefore, mild respiratory symptoms not requiring medical care in the past, and involuntary exposure to parental smoking without a history of respiratory symptoms or disease were no exclusion criteria. The study and its protocol were approved by the medical ethics committees of the medical centres and by the principals and boards of the institutes involved. Informed consent was given by the parents of all participating children. When children refused co-operation, no Rint measurements were attempted.

Equipment

Interrupter resistance was assessed using the MicroRint (Micro Medical Ltd, Rochester, UK), as described previously. Rint was calculated using the back extrapolation technique to t=0 ms after shutter closure during 100 ms. Daily calibrations of pressure and flow (volume) were carried out using a manometer and a 2 litre precision pump. All measurements were carried out with a filter (Micro Medical Ltd, Rochester, UK) in place to prevent contamination and dysfunctioning.

Measurement protocol

The protocol has been described previously. After the supervisor of the children explained the purpose of the measurements, a measurement was demonstrated on the supervisor and subsequent measurements were carried out in groups of 2-4 children at a time, in a familiar and quiet room. Children were seated and no physical exercise was allowed during 10 minutes prior to the measurements. During measurements, children were instructed to breathe quietly, sitting upright while the cheeks and chin were
supported from behind by the investigator. The head was positioned in slight extension and a nose clip was used. The position of the MicroRint was adjusted on a support arm to facilitate unobstructed breathing. A minimal number of 5 correct tracings (maximal 10) was obtained at the peak of expiratory tidal flow, because expiratory interruptions seem more sensitive in detecting airways obstruction than those during inspiration. Tracings were rejected in the cases of: tachypnoea, usage of the vocal cords, extreme neck flexion or extension, or leakage of the mouth piece. Tracings not showing the timing of interruption on the flow tracing, or tracings with a horizontal or declining pressure signal suggesting leakage at the mouth, or altered ventilation pattern were discarded as well (illustrated in Figure 2).

Data analysis

The individual Rinte data were expressed as median values because individual data are not normally distributed. Reference values for Rinte were described based on a model assuming a linear or curvilinear relationship with the standard independent variables standing height, weight, and age. Because of physiological similarities between Rint and plethysmographically obtained $R_{aw}$, we hypothesised that an exponential model with standing height would make the best fit for the Rinte data, similarly as published reference equations for $R_{aw}$. Trends of residuals with height or age were assessed from linear regression analyses. The threshold for statistical significance was set at $p=0.05$.

Results

Subjects

The first dataset consisted of 135 healthy Dutch children (60 boys) studied in Rotterdam, the Netherlands, who were selected from a survey in which the parents of 698 children were asked for participation. Permission was given for 341 (49%) children: 36 refused participation, and 12 failed to complete the measurements. Of the remaining 293 children 135 (39%) met the inclusion criteria and completed the measurements. This included 54...
healthy children described previously\textsuperscript{6}. The second dataset consisted of 79 Dutch children (41 boys) studied in Utrecht, the Netherlands. These were selected from a study in which parents of 445 children were asked for participation. For 212 (48\%) of these children such permission was obtained. In 200 children reliable Rint measurements were carried out of whom 79 (40\%) met the inclusion criteria listed above. Both studies were carried out in suburban parts of the cities, inhabited with middle-class income Dutch families. Only 2 out of the 24 children who failed to complete the measurements were older than 4 years of age. Anthropometric data of all 214 children are summarised in Table 1. The children from dataset 1 were slightly younger than those from dataset 2 (Table 2). The coefficients of variation from dataset 1 showed a trend to be larger than that from dataset 2 (Table 2). This seemed to be explained by the differences in age between centres: Especially below the age of 6 yrs, there was a negative correlation between coefficient of variation and age ($r=-0.21$, $p=0.004$). Because reliable measurements could only be obtained in 6 children younger than 3 years of age the reference equation was based on the 208 children 3-13 years.

### Table 1. Anthropometric data of the reference population.

<table>
<thead>
<tr>
<th>Age range (n)</th>
<th>Gender M/F</th>
<th>Mean (SD) height</th>
<th>Mean (SD) weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 yrs (6)</td>
<td>4/2</td>
<td>88.2 (6.8)</td>
<td>12.9 (2.5)</td>
</tr>
<tr>
<td>3-4 yrs (8)</td>
<td>3/6</td>
<td>104.9 (6.2)</td>
<td>17.2 (2.0)</td>
</tr>
<tr>
<td>4-5 yrs (17)</td>
<td>7/10</td>
<td>109.5 (3.7)</td>
<td>18.6 (2.1)</td>
</tr>
<tr>
<td>5-6 yrs (28)</td>
<td>12/16</td>
<td>116.4 (4.3)</td>
<td>21.1 (2.0)</td>
</tr>
<tr>
<td>6-7 yrs (29)</td>
<td>12/17</td>
<td>119.8 (4.9)</td>
<td>22.8 (3.0)</td>
</tr>
<tr>
<td>7-8 yrs (25)</td>
<td>13/12</td>
<td>129.9 (4.6)</td>
<td>26.5 (3.5)</td>
</tr>
<tr>
<td>8-9 yrs (29)</td>
<td>8/21</td>
<td>133.1 (7.5)</td>
<td>29.1 (6.2)</td>
</tr>
<tr>
<td>9-10 yrs (21)</td>
<td>15/6</td>
<td>142.3 (5.0)</td>
<td>35.1 (5.2)</td>
</tr>
<tr>
<td>10-11 yrs (17)</td>
<td>10/8</td>
<td>149.1 (4.3)</td>
<td>39.1 (6.7)</td>
</tr>
<tr>
<td>11-12 yrs (24)</td>
<td>11/13</td>
<td>154.7 (6.7)</td>
<td>41.1 (6.7)</td>
</tr>
<tr>
<td>12-13 yrs (8)</td>
<td>6/2</td>
<td>156.7 (10.6)</td>
<td>47.8 (12.9)</td>
</tr>
</tbody>
</table>
Reference equation for Rint

An inverse, curvilinear relationship was found between Rinte, and the independent variables standing height, age and weight. When standing height was used in an exponential model instead of a linear model with Rinte, the explained variance increased from 59 to 63 % and the residual standard deviation (RSD) decreased from 0.150 to 0.093 kPa/L/s. Residuals of the exponential model were homoscedastically distributed, demonstrating no trend with standing height (Figure 1). When age was added next to

Table 2. Differences between 2 data sets. *: p<0.03, unpaired t-tests.

<table>
<thead>
<tr>
<th></th>
<th>Dataset 1 (Rotterdam)</th>
<th>Dataset 2 (Utrecht)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean(SD))</td>
<td>7.4 (2.6)</td>
<td>8.4 (2.9)*</td>
</tr>
<tr>
<td>Standing Height (cm, mean(SD))</td>
<td>128 (18)</td>
<td>133 (20)*</td>
</tr>
<tr>
<td>Weight (kg, mean (SD))</td>
<td>27.2 (9.3)</td>
<td>30.7 (11.5)*</td>
</tr>
<tr>
<td>Boys/Girls</td>
<td>62/76</td>
<td>41/38</td>
</tr>
<tr>
<td>Coefficient of Variance (% median(range))</td>
<td>11.7 (1.2 - 21.4)</td>
<td>6.9 (0 - 35)</td>
</tr>
</tbody>
</table>

Figure 1. Relationship between $10^{\log(Rint)}$ and standing height for 208 children. The solid and dotted lines illustrate the exponential model (mean and 95% confidence bands).
Figure 2a-c. Examples of Rinte recordings. Fig 2a: correct manoeuvre, clearly visible timing of interruption on the flow tracing and approved interpolation and extrapolation of pressure signal. Fig 2b: Visible leakage at the mouth, and a horizontal pressure signal following interruption. Fig 2c: Flow signal affected by the usage of the vocal cords, and horizontal pressure signal.
standing height in an exponential model, the explained variance increased with less than 3%, and the improvement of RSD was less than 0.0003 kPa/L/s. When age was used as the only independent variable in an exponential model with Rinte, the explained variance was 64% (RSD = 0.091 kPa/L/s), but the distribution of the residuals became heteroscedastic for subjects older than 10 years. In the age range >10 years, the variability of standing height for age was larger than in the younger subjects. Using weight as the only independent variable, explained variance was 49%, (RSD=0.108 kPa/L/s).

Reference equations for Rinte are:

linear model:
\[
\text{Rinte} = 1.927 - 0.00992 \times \text{standing height (cm)} \text{ kPa/L/s}
\]

\[
r = -0.77, \ RSD = 0.150 \text{ kPa/L/s} \ (p<0.001).
\]

exponential model:
\[
10 \log (\text{Rinte}) = 0.645 - 0.00668 \times \text{standing height (cm)} \text{ kPa/L/s}
\]

\[
r = -0.79, \ RSD = 0.093 \text{ kPa/L/s} \ (p<0.001).
\]

Based on the exponential model, the mean (SEM) of standardised residuals for 97 boys and 111 girls were -0.079 (0.096) kPa/L/s and 0.071 (0.097) kPa/L/s, respectively, with a mean (95% CI) difference between boys and girls of 0.15 (-0.12, 0.42) kPa/L/s. No trend was observed between standing height and standardised residuals for boys or girls. The separate regression equations from the 2 datasets did not differ significantly in a multiple regression model that included centre (p=0.33) and interaction between standing height and centre (p=0.59).

Discussion

Few studies have reported reference equations for the interrupter technique in young school children\textsuperscript{6,7,11,12}, but for older children these are lacking. Because of the possible applications for this technique in a larger age range (epidemiological and clinical research, children unable to participate in active lung function measurements), we obtained normal values for Rinte in 208 healthy Caucasian children between the ages 3 and 13 years. In our
previous study a linear model to describe the relationship between height and Rinte was considered satisfactory but in the present study, due to the larger range for height, an exponential model appeared more appropriate because of a curvilinear relationship. This pattern is consistent with reports of data of R_{aw} in healthy children. This is the largest study of Rinte in healthy pre-school and school children studied so far. Despite the large number of observations, we could not demonstrate a significant sex-related difference in airway patency. This suggests that a possible small difference of airways resistance between sexes is not clinically relevant, or that it can not be detected measuring resistance of the respiratory system with this technique.

We used height and not age as independent variable because of physiological arguments, and not because the relationship between height and Rinte was statistically superior. It is conceivable that body size can function as a proxy for airway calibre, whereas age may indirectly reflect airway size in children below the age of 13 years as well, but not in adolescents or adults. Age may be equally valid and a more convenient independent variable in reference equations for Rinte, but this is probably limited to young children only. Indeed, the variability of the residuals in the children over 10 years of age from the present study was considerably increased compared to that in children below that age, which is explained by a larger variation of height for age.

Because the residuals of the exponential model were normally distributed (with RSD=0.093 kPa/L/s), individual measurements can be expressed as Z-scores: 
\[ Z = \frac{10 \log(\text{measured Rinte}) - 10 \log(\text{predicted Rinte})}{\text{RSD}} \]

which facilitate comparisons within and between individuals. As long as there is no international standardisation for Rinte measurements, reference equations are likely to differ according to the equipment and protocol of shutter timing and back-extrapolation, as well. In the protocol of the present study, interruptions were programmed at peak tidal expiratory flow which appears to standardise inflation level. The linear model of the present study fits remarkably well with the reference equation (Rint = 1.993 - 0.0092 x height(cm) - 0.0009 x age(ys)) kPa/L/s of van Altena et al. who studied Rint in 172 adults and teenagers, although the exact measurement procedure was not described and the population and equipment differed markedly. Our results are not comparable with those of Klug et al. who programmed inspiratory interruptions at 50 ml above FRC. The effect of this procedure might have been that with increasing body size, interrupt-
tions occurred at progressively lower inflation levels. This could very well explain the lesser slope with height and lower explained variance of their reference equations.

It is difficult to compare R_{int} values with those of measurements of R_{aw} or \( R_L \) from healthy populations because of differences in technique, and population characteristics, but our reference equation compares favourably with those of Dab et al.\(^\text{17} \) (\( \log R_{aw} = 0.712 - 0.0064 \times \text{height(cm)} \)), and those of Helliessen et al.\(^\text{18} \) (\( \log R_L = 0.627 - 0.0068 \times \text{height(cm)} \)).

We were able to measure R_{inte} reliably in only 6 children younger than 3 years of age and do not recommend routine assessment of R_{int} below 3 years of age because of low feasibility in that age range\(^6 \). The use of face masks in those children may enhance the feasibility of the test, but R_{int} measurements obtained using face masks can differ from those obtained with mouthpieces\(^21 \). This will depend on compliance and resistance of the mask, and on the degree of airways obstruction. R_{int} measurements using face masks may require specific reference equations. For young children over 3 years of age, the interrupter technique remains probably one of the most convenient and sensitive tests for airway function available, with the possibility to use the same technique over a wide age range.
References
