Interrupter Resistance in Preschool Children
Measurement Characteristics and Reference Values

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There is a need for quick, reliable, and noninvasive lung function tests to assess airway obstruction in preschool children both for pediatric pulmonary care as well as for research purposes. We studied feasibility, reproducibility, and validity of measurements of the respiratory system using the interrupter technique (interrupter resistance [Rint]) and obtained reference values in children from a general population, 2 to 7 yr of age. Accuracy was studied by comparisons of Rint with plethysmographic airway resistance (Raw) in 20 patients (7 to 14 yr) with mild to severe chronic airway obstruction and was satisfactory in patients with FEV1 > 60% predicted. The technique proved sensitive enough to detect changes in airway caliber within a small group of 12 children who developed mild respiratory tract infections. Among children from a general population, subgroups with mild respiratory symptoms or mild respiratory disease had higher mean Rint values. Airway obstruction was better detected using expiratory rather than inspiratory interruptions, both programmed at peak tidal ventilatory flow. Reproducibility within subjects was satisfactory (intraclass correlation 0.82 and 0.79). The same applied to interobserver agreement (intraclass correlation 0.98). The interrupter technique proves to be a reliable and practical test of airway function, suitable for clinical and epidemiologic studies in preschool children.

Reliable lung function testing in preschool children is difficult because little cooperation and coordination can be expected at this age. Spirometric reference values for children have been obtained in children as young as 5 yr of age (1, 2) but reliable measurements are often not feasible. Several passive techniques have been developed (3–5), but have their limitations with respect to reliability, sensitivity, or interpretation (6). In the group between 2 and 7 yr there is a need for lung function techniques that require minimal cooperation and yet are reliable and sensitive enough to be valuable as a diagnostic tool (7, 8). The interrupter technique (9) requires only quiet breathing and is based on measurements of tidal airflow and mouth pressure before and directly after closure of a fast shutter near a pneumotachograph. The ratio between pressure difference and airflow equals the interrupter resistance (Rint). Thus, Rint reflects the resistance of the respiratory system. Only after equilibration of pressure within the airways, when mouth pressure equals alveolar pressure, Rint reflects airway resistance (Raw). Validation studies against Raw measured plethysmographically came up with satisfactory results (10–12). However, the within-subject variability may be higher than that of other techniques (6, 10, 13, 14), which has been attributed to factors such as the natural variability of inflation level and flow during quiet breathing, upper airway compliance, and position of the neck, glottis, and vocal cords (7, 13, 15). Large variability, and the lack of standardization and reference values (16) explain why the technique has not been widely used in clinical or epidemiologic lung function studies in the past. During the last decade, however, reference values have been published (17), modern applications of the technique have been evaluated (6, 10), and it has been demonstrated that within-subject variability of Rint measurements is sufficiently small to study the response to bronchoconstricting (6, 8, 10) and bronchodilating agents (6–8, 14) in young children. Together with the quick and noninvasive nature of the method, these data suggest that the technique is a potential diagnostic tool in pediatric pulmonology (6–8, 10, 11, 13, 14, 16, 18). More widespread acceptance and application of Rint measurements can only be expected when it is demonstrated that this technique is feasible, that its within-subject variability can be reduced further, and that the method can be used to identify groups of preschool children with minor respiratory symptoms or disease.

The aim of the present study was to investigate the feasibility and measurements characteristics of the interrupter method in preschool children. We explored ways to improve its precision, assessed within-subject and within-observer variability, characterized normal Rint values in healthy children, and investigated the biologic validity of the technique using a portable device.

METHODS

Subjects

Feasibility of the technique, reference values, and short-term reproducibility were investigated in children 2 to 4 yr of age from a daycare center and in children 4 to 7 yr of age from a kindergarten. Both institutions were located in suburban parts of the Rotterdam area, inhabited by middle-class income Dutch families. In this group we studied: (1) children with mild respiratory symptoms or mild respiratory disease to assess the sensitivity of the technique; (2) children without a history of any cardiopulmonary disease (such as prematurity with respiratory distress) and without current respiratory symptoms, to obtain reference values. We intended to obtain reference values from a normal population rather than from an ideal population (19). Therefore, respiratory infections in the past was not an exclusion criterion for this subgroup. Furthermore, children exposed to parental smoking but with a negative history of respiratory symptoms or disease were not analyzed separately but included in the normal population, unless it would appear that their mean Rint values would be significantly different from that of the reference group. Exclusion criteria were: anatomic abnormalities of the upper or lower airways, vocal cord disorders, chronic cardiopulmonary or other illnesses. In children attending the outpatient clinic of the Sophia Children’s Hospital because of asthma or cystic fibrosis, we investigated within-observer reproducibility of the technique and its validity by comparisons with Raw measured plethysmographically. The study was approved by the medical ethics committee of Erasmus University and University Hospital, and by the principals of the institutions involved. Written informed consent was given by the parents of the participating children. Measurements were carried out on a strictly voluntary basis.

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Feasibility
When children refused to cooperate before the measurement, the attempt was classified as a refusal; when they began the measurement but stopped halfway, or if too few (< 5) reliable tracings were obtained, an attempt was classified as a failure. A measurement session was discontinued after 20 min or 10 attempts, whichever came first. The feasibility of the technique was rated on the basis of the proportion of failures and refusals relative to the total number of attempts. The success rate was defined as the percentage of approved tracings relative to the number of occlusions.

Data Analysis
Rint(i) and Rint(e) were expressed as median or mean values, depending on the individual data distribution of up to 10 measurements. The coefficient of variation was used to compare reproducibility with conventional lung function measurements. The minimal number of individual measurements needed to obtain a reliable estimate of Rint was assessed based on the improvement of the standard error of the estimate relative to the mean (SEM/mean) with increasing number of attempts. Reference values were described using linear regression, including standard independent variables such as standing height, weight, and age. When no effects of passive parental smoking or sex could be demonstrated, these subgroups were not analyzed separately. Z-scores [(measured Rint – predicted Rint)/(SD of the reference population)] were computed for each individual, to compare children or groups of children.

Biologic variability was studied in a group of 22 stable schoolchildren who were measured twice 10 to 21 d apart, while there was no change of respiratory symptoms. Within-observer variability was studied on Rint(e) in 20 outpatients by two investigators. Reproducibilities were studied according to Bland and Altman (22), and expressed as intraclass correlation (23). The existence of a learning effect was investigated in the reference population in whom Rint(e) and Rint(i) were studied in random order, using unpaired t tests of the Rint(e) – Rint(i) differences, according to measurement order. Validity of Rint measurements using plethysmographic Raw as the gold standard was studied in 20 young patients with asthma or cystic fibrosis according to Bland and Altman as well (22). The biologic validity of the technique in the preschool children was studied in two ways: First, in a group of 12 children who were asymptomatic during the first measurement and developed respiratory symptoms 10 to 21 d later, mean differences were analyzed using paired t tests. Second, we studied Z-scores for various subgroups classified according to respiratory symptoms or disease, and compared them with the reference population (unimpaired t tests).

RESULTS
Participants
Invitations to participate, including questionnaires, were sent to the parents of 298 children of the kindergarten and daycare center. Informed consent and answered questionnaires were returned for 169 (57%) children. Measurements were refused by 21 children, and failed in eight (Figure 1). Rint measurements were conducted in 139 (46%) children. In 128 of 139 children, disposable 22-mm-diameter cardboard mouthpieces were used. In 11 toddlers younger than 2 yr of age, a Laerdal face mask size 2 was used, whereas in three infants younger than 6 mo of age a Laerdal size 0 mask was used.

Feasibility
The feasibility of Rint(e) measurements was 12% in children 0 to 1 yr of age, 55% at age 1 to 2 yr, and 100% in children older than 6 yr of age. Feasibilities of the inspiratory maneuver were similar, being only slightly better in the youngest children (Figure 1). In 88% of children older than 2 yr of age feasible Rint measurements were obtained. The mean number of interruptions for Rint(e) varied from 9.2 for the 2- to 3-yr-olds to 9.8 for the 6- to 7-yr-olds; for Rint(i) these numbers were similar (9.7 to 9.9, respectively). Mean (± SD) success rates (percentage of acceptable tracings) in children with 9 to 10 in-
METHODS.

Compliance was assessed by interpreting the performance of subjects from the initial 10 Rint measurements. For the individual, the percentage of load interruptions (based on 10 interruptions) of Rint(e) or Rint(i) was calculated. The interobserver variability and reproducibility in 5 Rint measurements relative to the mean (SEM/mean) for 5 different patients was 5.1% and 3.7%, respectively; for Rint(i), these values were 4.7% and 3.5%. This implies that for 95% of subjects the precision of the single measurement is within 6–7% of the mean. The whole procedure of measuring height, weight, Rint(i), and Rint(e) in a child took between 20 min in some of the 2-yr-olds, and 7 min in children age 6 yr.

Measurement Characteristics

The mean (95% CI) difference between individual mean and median values of Rint(e) was 0.007 (0.002, 0.012) kPa/Ls. Rint(i) measurements showed a similar trend (p = 0.16). Because of the skewed distribution for individual measurements, all further analyses were based on the median value of up to 10 individual measurements.

The mean (± SD) coefficients of variation for Rint(e) and Rint(i) were 11.6 ± 5.6% and 10.6 ± 5.4%, respectively. Average individual SEM relative to the mean (SEM/mean) for 5 and 10 Rint(e) measurements were 5.1% and 3.7%, respectively; for Rint(i) these values were 4.7% and 3.5%. This implies that for 95% of subjects the precision of the single measurement (based on 10 interruptions) of Rint(e) or Rint(i) is better than 7.4% or 7.0%, respectively.

Reference Values

Reference equations were based on children 2 yr of age and older because below that age, measurements could only be conducted using a face mask with unknown (compliance) characteristics, unlikely to be comparable with a cardboard mouthpiece. Reference values were obtained from those children with a negative history of asthma, recurrent rhinitis, or eczema, without cardiorespiratory or other chronic disease, and with no respiratory symptoms in the past month. Significant differences of Rint values owing to sex or parental smoking could not be demonstrated in asymptomatic nor in symptomatic children (p > 0.37). Therefore, 54 children of either sex, and with different passive smoking history were pooled in the reference equations. The number of children age 2–3, 3–4, 4–5, 5–6, and 6–7 yr of age were 3, 5, 12, 18, and 16, respectively. The best predictor for Rint was standing height in a linear model. The addition of other variables (age, weight, or sex) did not contribute significantly to the model (p > 0.07). Least squares regression equations related to height (expressed in cm) were:

\[
\text{Rint}(e) = 2.61 - 0.016 \cdot \text{height} \quad \text{RSD: 0.13}
\]

\[
\text{Rint}(i) = 2.59 - 0.017 \cdot \text{height} \quad \text{RSD: 0.12}
\]

Reference curves are shown in Figure 2. Rint(e) was systematically higher than Rint(i) in all children and the difference between the two did not correlate with sex or age: mean (95% CI) difference was 0.051 (0.17, 0.85) kPa/Ls. No learning effect could be demonstrated (p = 0.17).

Biologic Validity

In 12 healthy children who developed mild respiratory tract infections 10 to 21 d after their first measurement, Rint was increased the second time. Mean (95% CI) difference between two consecutive measurements for Rint(e) was 0.08 (0.03, 0.13) kPa/Ls, p = 0.002 (Figure 3). For Rint(i) this difference was 0.04 (0.002, 0.07) kPa/Ls, p = 0.04.

The 128 children were classified according to their history of respiratory symptoms or disease (Table 1). Mean Z-scores of Rint values of subgroups of children are listed in Table 2. Asymptomatic children with asthma or eczema or both (n = 32) had significantly elevated Z-scores for Rint(e) (p < 0.02) as well as for Rint (i) (p = 0.005). In 20 children with asthma or eczema or both, with current respiratory symptoms, Rint(e) Z-scores were increased (p = 0.006) and Rint(i) showed a similar trend. In a subgroup of nine children with eczema without asthma who had no current respiratory symptoms, Rint(e) was elevated (p = 0.002), and Rint(i) tended to be higher too (p = 0.06). In children with recurrent rhinitis, Rint(e) and Rint(i) were of similar magnitude as the reference group.

Validity, Interobserver Variability, and Reproducibility

The validity of Rint measurements was assessed by comparisons with plethysmographic Raw in 20 outpatients (13 boys) with asthma or cystic fibrosis [mean (± SD) age 12.9 ± 2.7 yr,
and mean (range) FEV$_1$ 87 (37 to 113%) predicted. The mean (95% CI) differences between Raw – Rint(e), and Raw – Rint(i) were 0.05 (–0.1, 0.2) kPa/L/s and 0.09 (–0.08, 0.28) kPa/L/s, respectively. The difference became greater with decreasing FEV$_1$ (percent predicted): r = −0.55 (p = 0.05). This was mainly affected by measurements in three cystic fibrosis patients with severe airways obstruction (FEV$_1$ < 60% predicted): When these were excluded, no significant correlation was found (r = 0.31, p = 0.39) and the mean (95% CI) differences between Raw – Rint(e) and Raw – Rint(i) were −0.05 (−0.16, 0.11) and −0.02 (−0.48, 0.088) kPa/L/s, respectively.

Interrater reliability was assessed from Rint(e) measurements in 20 patients with asthma or cystic fibrosis, by two investigators. One observer had conducted several hundreds of tests (J.M.); the other was new to the procedure. Intraclass correlation coefficient was 0.98. Within-subject variability was studied in 22 stable children from the reference population with an interval of 2 wk. Mean (95% CI) differences between duplicate measurements of Rint(e) and Rint(i) were −0.05

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**Biologic Validity**

We observed that mean Rint values were elevated in children with minor respiratory symptoms or disease compared with the reference population. We consider this remarkable as these differences only reflected minor disease. Both Rint(e) and Rint(i) were elevated in 32 children who had asthma or eczema, or both, and no current respiratory symptoms according to the questionnaires. The latter may indicate that these children had respiratory symptoms that were not recognized by their parents nor perceived by the children themselves.

Rint(e) seemed slightly more sensitive in detecting subclinical differences in airway caliber within and between subjects than Rint(i) because: (1) in healthy children with current mild respiratory tract infections, Rint(e) was elevated compared with control subjects, unlike Rint(i); (2) Rint(e) increased somewhat more than Rint(i) within subjects who developed respiratory symptoms (productive cough without dyspnea or wheeze); (3) in the subgroup of nine children with eczema only

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**Table 2. Mean (95% CI) Differences Between Z-Scores of Different Subgroups and the Reference Population**

<table>
<thead>
<tr>
<th>Category (n)</th>
<th>Rint(e)</th>
<th>Rint(i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals, symptoms (10)</td>
<td>0.87 (0.09, 1.65)*</td>
<td>0.43 (−0.28, 1.14)</td>
</tr>
<tr>
<td>Recurrent rhinitis (7)</td>
<td>−0.19 (−1.07, 0.69)</td>
<td>−0.36 (−1.18, 0.46)</td>
</tr>
<tr>
<td>Recurrent rhinitis, symptoms (5)</td>
<td>0.15 (−0.77, 1.06)</td>
<td>−0.09 (−2.11, 1.94)</td>
</tr>
<tr>
<td>Asthma and/or eczema (32)</td>
<td>0.73 (0.12, 1.33)*</td>
<td>1.0 (0.32, 1.69)</td>
</tr>
<tr>
<td>Asthma and/or eczema, symptoms (20)</td>
<td>0.72 (0.22, 1.23)</td>
<td>0.4 (−0.1, 0.9)</td>
</tr>
</tbody>
</table>

* p ≤ 0.03; † p ≤ 0.006, unpaired t tests.
(and no asthma or current respiratory symptoms), Rint(e) was elevated whereas Rint(i) only showed a trend to be higher; (4) in 20 symptomatic children with asthma or eczema, or both, mean Rint(e), but not Rint(i) was increased compared with the reference group. From the present study it cannot be inferred why mean Rint(i) in 32 asymptomatic children with asthma or allergy was elevated compared with control subjects, whereas mean Rint(i) in 20 symptomatic children with asthma or allergy showed more overlap with the reference group. There may be differences between the groups accounting for this: sample size, asthma severity, treatment, biologic variability, and misclassification based on the questionnaires may all affect mean Rint(i) values of these two subgroups.

The greater sensitivity of Rint(e) in detecting abnormal airway patency compared with Rint(i) remains to be explained. Factors such as dynamic airway compression, and airway hysteresis patterns may partly explain this phenomenon. It is conceivable that peripheral airway obstruction, resulting in a larger pressure drop in the airways during tidal expiration, leads to more dynamic airway compression and larger Rint values than in unobstructed children. Likewise, if airway hysteresis occurs during tidal breathing, and results in different airway behavior in asthmatic children compared with normals as occurs in adults (24, 25), then this may add to less airway patency during expiration and not during inspiration in the asthmatic group. To our knowledge, such studies on airway hysteresis in children are lacking, and both hypothesized mechanisms need further studies to be verified. Obviously, we were not able to standardize level of inflation, as volume is not registered during Rint procedures (and difficult to assess with conventional technique in preschool children). However, airway obstruction would normally be compensated for by increased levels of inflation. This would rather lower Rint values than increase them (15), resulting in an underestimation of the differences between subgroups or within children. However, in spite of all this, the technique still appeared sensitive enough to detect the differences caused by mild respiratory symptoms within subjects and between subgroups. The increase of Rint within subjects who developed mild respiratory infections cannot be explained by rhinitis because of the nose clip, but oropharyngeal inflammation may have contributed to increased Rint values, in addition to lower airway obstruction.

Reference Values
The reference equations in the present study showed an inverse relationship between standing height and Rint with low biologic variability. This contrast with reference equations of Rint in preschool children as published by Klug and Bisgaard (17) may be due to a difference in measurement procedure rather than to differences in the equipment or population size. We assessed Rint using interruptions at the peak tidal inspiratory and expiratory flow, whereas Klug and Bisgaard standardized interruptions to occur during inspiration, at 50 ml above FRC (17). The latter implies that with increasing age, interruptions occurred at relatively lower inflation levels, which may explain less decline of Rint with increasing standing height. Interruptions in our study were programmed at peaks of expiratory or inspiratory flow (7, 10, 13) with no standardization of inflation level. However, when the two studies are compared, the explained variance of our equations (40%) and standard deviation (0.12 kPa/L/s) compare favorably with 21% explained variance and standard deviation of 0.16 kPa/L/s (17). This suggests that because of a different measurement procedure, a volume correction was introduced which has improved the sensitivity of the technique. The inverse relationship between Rint values and standing height can very well be explained by increasing airway dimensions during growth and is consistent with the reported reference equations for Raw (26).

This study demonstrates that within a group of preschool children from a general population, the interrupter technique is sensitive enough to detect alterations in Raw within children, and differences between subgroups of children. It shows that short-term changes in Raw within children resulting from minor respiratory infections could be documented, and that Rint(e) seems more sensitive than Rint(i). Furthermore, it was possible to discriminate between subgroups with respiratory symptoms or disease. As is the case for more conventional lung function parameters, there was a considerable overlap of Rint with normals, but mild symptoms did not go undetected, and children with reported eczema or asthma had significantly higher Rint values than the reference population. It should be stressed that this was a group of children with only mild asthma, that used little or no medication (only 13 of 52 used medication on a regular basis). We did not observe a negative relationship between parental smoking and Rint values. From this it can not be concluded that airway function is not affected by passive smoking. It may also reflect a bias of selective smoking, or may indicate that the effects of smoke exposure are too small to detect with Rint in a population of this size. The validity of the technique using plethysmographic Raw as the gold standard seems acceptable as long as airways obstruction is not severe, as was published previously (12). This is partly explained by the fact that body plethysmography measures Raw only, whereas the interrupter technique determines resistance of the respiratory system. In the presence of significant airway obstruction, however, measurements of both techniques will be affected by time constants of the upper airways and incomplete equilibration of airway pressures. Moreover, tracings of Raw measurements become more difficult to interpret (open loops) and there is no consensus on how to approach this issue (26). The excellent interobserver reliability is a reflection of both the simplicity of handling the equipment and interpreting the tracings and the relatively large natural variability of the signal.

In conclusion, this study supports the statement that the interrupter technique is one of the few valuable and feasible diagnostic tools to assess airway function in preschool children (6–8, 10, 11, 13, 14, 16, 18). Furthermore, it also addresses several issues that have not received much attention so far in the literature. Other investigators have studied the use of Rint in a laboratory setting in patients but did not study ways to improve precision, and did not compare the clinical usefulness of Rint(e) versus Rint(i). We found that the natural variability of the data can be reduced using median values and 10 interruptions during each measurement and that Rint(e) measurements were more sensitive than Rint(i) measurements in detecting increased Raw. The biologic validity of the interrupter technique has not been assessed before. This study indicates that the technique is sensitive enough to detect small changes in airway function within children from a general population, and to distinguish groups of children with minor respiratory symptoms or mild respiratory disease from normals. Reference values of Rint(e) and Rint(i) related to standing height, based on interruptions at peak expiratory and inspiratory tidal flow, improved the explained variance considerably. These aspects make strong arguments to use this technique for assessment of airway function in preschool children. This holds for pediatric pulmonary care, pediatric clinical research, but also for epidemiologic studies, because measurements can be carried out quickly, and with a portable device. For these applications, the interrupter technique is a welcome diagnostic tool.
for a category of children in whom respiratory function testing was often needed, but not feasible.

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