

Pre/Postbronchodilator Interrupter Resistance Values in Healthy Young Children

Nicole Beydon, Francis Amsallem, Michèle Bellet, Michèle Boule, Michèle Chaussain, André Denjean, Régis Matran, Bernard Wuyam, Corinne Alberti, Claude Gaultier, and the French Pediatric Programme Hospitalier de Recherche Clinique Group

Physiology Departments of the Robert Debré Teaching Hospital, Saint-Vincent-de-Paul Teaching Hospital, and Trousseau Teaching Hospital, Paris; Public Health Department of the Robert Debré Teaching Hospital, Paris; Pediatric Department, Arnaud de Villeneuve Teaching Hospital, Montpellier; Physiology Departments, Morvan Teaching Hospital, Brest; Poitiers Teaching Hospital, Poitiers; Calmette Teaching Hospital, Lille; and Grenoble Teaching Hospital, Grenoble, France

The interrupter technique estimates flow resistance. It entails occlusion of the airways during tidal breathing while flow and mouth pressure are recorded. This noninvasive technique is easy to use in young children. The aim of the present study was to measure inspiratory and expiratory interrupter resistance ($R_{int_{insp}}$, $R_{int_{exp}}$) before and after bronchodilator administration in young healthy white children. We designed a multicenter study using a standardized procedure for Rint measurements. Centers in five French cities studied 91 children (48 boys and 43 girls; height, 92 to 129 cm; mean age 5.3 ± 1.4 years). Mean values were not significantly different for $R_{int_{insp}}$ and $R_{int_{exp}}$ (0.78 ± 0.21 versus 0.78 ± 0.20 $\text{KPa} \cdot \text{L}^{-1} \cdot \text{second}$). However, the difference between $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with age and being positive before 5 years and negative later on ($p < 0.02$). $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with height ($R_{int_{insp}}$ [$\text{KPa} \cdot \text{L}^{-1} \cdot \text{second}$] = $2.289 - 1.37 \cdot 10^{-2} \cdot H$ [cm], $R_{int_{exp}}$ [$\text{KPa} \cdot \text{L}^{-1} \cdot \text{second}$] = $2.021 - 1.12 \cdot 10^{-2} \cdot H$ [cm]; $p < 0.001$). Bronchodilator (salbutamol) administration significantly decreased $R_{int_{insp}}$ and $R_{int_{exp}}$ ($p < 0.001$). Bronchodilator-induced changes (% of predicted values) in mean $R_{int_{insp}}$ and mean $R_{int_{exp}}$ were -15% (95% confidence interval, -46 to $+15\%$) and -12% (95% confidence interval, -46 to $+22\%$), respectively. Sex did not affect pre- or postbronchodilator values. Data from the present study may prove useful for testing lung function in young children with respiratory disorders who failed to cooperate with forced expiratory maneuvers.

Keywords: inspiratory and expiratory interrupter resistance; reference values; preschool children

The interrupter technique is a noninvasive technique for estimating flow resistance, an important determinant of lung function, especially in children too young to accomplish forced respiratory maneuvers in a reproducible manner. The interrupter technique is easy to use in young children. Several recent studies used interrupter resistance (Rint) measurements in wheezy and/or asthmatic young children, particularly for testing bronchoreactivity (1–5).

The interrupter technique entails rapid and complete occlusion of the airways during a normal breathing cycle while flow and airway opening (or mouth) pressure (Pm) are recorded (6–9). The method is based on the assumption that al-

veolar pressure (PA) and Pm equilibrate at airway occlusion. Flow resistance is considered equal to Pm divided by the flow immediately before the interruption. Several methods have been suggested for estimating PA from the analysis of post-occlusion Pm curves, which comprise an initial, rapidly changing phase with rapid damped oscillations, followed by a second, slowly changing phase (6). Early studies using Pm measurement at the breakpoint between these two phases found that Rint overestimated plethysmographic airway resistance (Raw) in healthy human adults (6). Recent advances in equipment and computer analysis techniques have allowed a reappraisal of the interrupter method (8, 9). Curvilinear back-extrapolation of Pm back to the time of occlusion has been shown to improve PA estimates derived from the Pm curve and the correlation between Rint and Raw in healthy adults (8). Subsequent studies reported linear back-extrapolation methods (1–5, 9–15). Compliance of the upper airways may be responsible for lack of Pm-to-PA equilibration during airway occlusion, resulting in underestimation of flow resistance (9). However, studies performed using the Bates model suggest that as much as a 10-fold increase in airway resistance is measured correctly by the interrupter technique, provided upper airway compliance is not excessively high (16). This has been verified in adults with severe obstruction (9). Finally, Rint was higher during expiration than during inspiration in adults and school-age children (8, 10, 11), which can be explained by a diminished glottis opening during expiration (17).

Normative data for Rint measured during inspiration ($R_{int_{insp}}$) and/or expiration ($R_{int_{exp}}$) in young children have been published recently (4, 11, 14, 15). However, no previous studies determined both $R_{int_{insp}}$ and $R_{int_{exp}}$ before and after bronchodilator inhalation in healthy young children. The response to a bronchodilator in young children with respiratory disorders, however, has been examined in previous studies (1–5). Our aim was to measure $R_{int_{insp}}$ and $R_{int_{exp}}$ before and after bronchodilator administration in young, healthy white children. We designed a multicenter study using a standardized procedure for Rint measurements. Linear back-extrapolation of Pm was used to estimate PA for Rint calculation.

METHODS

Subjects

We conducted a multicenter study including children from eight pediatric lung function testing centers in hospitals in five French cities. One of the centers (Physiology Department, Robert Debré Teaching Hospital, Paris, France) coordinated the study, with the help of a local study coordinator in each of the other centers.

White children, 90 to 130 cm in height, were recruited. Criteria for healthiness were those recommended by international consensus (18). Children were eligible if they had none of the following exclusion criteria: premature birth, intrauterine growth retardation, chronic respi-

(Received in original form November 27, 2000; accepted in final form November 14, 2001)

Supported by a grant from the Programme Hospitalier de Recherche Clinique AOM 96.

Correspondence should be addressed to Claude Gaultier, Service de Physiologie, Hôpital Robert Debré, 48 Bd Serurier, 75019 Paris, France. E-mail: claude.gaultier@rdb.ap-hop-paris.fr

Requests for reprints to: Nicole Beydon, Service de Physiologie, Hôpital Robert Debré, 48 Boulevard Sérurier, 75019 Paris, France. E-mail: nicole.beydon@rdb.ap-hop-paris.fr

Am J Respir Crit Care Med Vol 165. pp 1388–1394, 2002

DOI: 10.1164/rccm.2011082

Internet address: www.atsjournals.org

ratory disease, cardiac disease, neurological disability, or a respiratory infection during the last 4 weeks. Children exposed to passive smoke were not excluded. Between April 1998 and December 1999, 101 children were recruited in the eight centers. The study coordinator performed a physical examination on each child on the day of the study, including height and weight measurements. All measurements were performed at the lung function testing laboratories of the study centers. The study was approved by the local ethics committee, and written informed consent was obtained from both parents of each child.

Equipment

All centers used a Spiroteq apparatus (Dyn'R Ltd, Toulouse, France) and the Programme Hospitalier de Recherche Clinique 2.55 computer program. The computer sent a digital signal to an analog converter, which controlled a motor-driven revolving disc that occluded the airways within 6 milliseconds and for 100 milliseconds. Each occlusion was triggered manually by the investigator and took place between 20% and 80% of the following tidal volume. Pm was sampled at 500 Hz. PA was estimated from the Pm pressure curve by performing linear back extrapolation of two mean points located at 30 and 70 milliseconds from a vertical line 15 milliseconds after occlusion onset (2, 3). The interrupter was connected to a heated pneumotachograph (Fleish 1, Lausanne, Switzerland). Flow calibration was performed once a day, with a precision of $\pm 1\%$. The flow signal used to calculate Rint was obtained just before the interruption.

Rint Measurement Procedure

A standardized procedure for Rint measurement and validation of Rint data was established and set up in all centers. Each child was first familiarized with the measuring equipment. He or she was seated comfortably, wore a noseclip, and breathed through a mouthpiece (dead space, 30 ml). An adult supported the child's jaw and cheeks, taking care to keep the child's neck straight. The child was asked to breathe as calmly as possible. The first occlusion was released after at least three respiratory cycles with a regular tidal volume and respiratory cycle duration.

As measurements proceeded, a computer displayed (1) the tidal volume, the volume at interruption, the preinterruption flow, the Pm curve, and the back-extrapolated Pm value for each interruption; and (2) an x/y graph of Pm values versus flow values for a series of interruption. The procedure for validating Rint measurements was the same in all eight centers and involved two steps performed by the investigators, based on a visual examination, and a third step performed by the computer, based on automated calculations. First, the investigators were asked to discard immediately all Rint values measured during breathing cycles disturbed by a respiratory pause, swallowing, speaking, moving, or coughing; or accompanied with a flagrant Pm curve error (blunted initial rapid changing phase, lack of oscillations, or aberrant second changing phase). Second, the investigators were asked to examine the x/y graph of Pm and flow and to delete Rint data for which the Pm values were aberrant relative to flow, i.e., too low, indicating a mouth leak, or too high either during inspiration, presumably because of inspiratory muscle activity, or during expiration, suggesting closure of the glottis. Third, the software automatically calculated the mean flow from the remaining Rint data and selected Rint values obtained within this mean flow ± 1 SD. At least seven validated Rint measurements with a coefficient of variation (CV) 20% or less were required for calculation of mean Rint values. The 20% limit for CV acceptance was chosen based on unpublished preliminary data showing that mean CV ± 2 SD was equal to 20%.

Measurements were performed between 9 A.M. and 3 P.M. Rint was measured in all children, first during expiration (Rint_{exp}), then during inspiration (Rint_{insp}), immediately before and 10 minutes after bronchodilator inhalation of 200 μ g of salbutamol, administered using a metered-dose inhaler and a spacer (Volumatic, Bad Oldesloe, Germany) in all children.

Data Collection

The following data were collected: coded patient identifiers (study center and subject number); anthropomorphic data; clinical history and physical examination findings; printed tidal volume; volume at interruption; flow; Pm values for each Rint measurement; and x/y Pm

versus flow graphs, saved on diskettes. All data were forwarded to the coordinating center, which performed detailed reviews of inclusion criteria. In addition, validity of the Rint measurements done in each study center were checked based on the following criteria: absence of aberrant pressure values on the x/y Pm versus flow graph, presence of at least seven measurements per series, and a CV of 20% or less at baseline.

Statistical Analysis

Continuous variables were expressed as medians (first quartile–third quartile) for each center, or means ($\pm$ SD) when all centers were combined. Categorical variables were expressed as numbers. Between-centers comparisons used the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Linear relationships linking the volume at interruption, expressed as the percent of tidal volume attributed to Rint_{insp} and Rint_{exp}, were tested using 120 Rint_{insp} and 120 Rint_{exp} measurements, obtained before and after bronchodilator administration (480 measurements in all). Comparisons between Rint values and CV measured at inspiration and at expiration before and after bronchodilator administration were performed using paired *t* tests.

Stepwise multiple linear regression was used to determine which of the following variables (standing height, weight, age, sex, and numbers of cigarettes smoked per day by mothers and the fathers) correlated significantly with prebronchodilator Rint_{insp} and Rint_{exp} and with the difference between Rint_{insp} and Rint_{exp}. To take a possible center effect into account, we performed a statistical adjustment assuming a random effect, i.e., using a mixed linear model (SAS MIXED procedure; SAS Institute, Cary, NC). The residual standard deviation of the best equation was calculated and used to compute the confidence interval of the study population. All tests were two-tailed and p-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 6.12 (SAS Institute).

RESULTS

Subjects

Of the 101 children recruited in the eight centers, 10 were excluded from the analysis. Six were excluded when the coordinating center found that they had noninclusion criteria: one had a history of asthma during infancy and another during childhood, one had a chronic cough, one had a history of intrauterine growth retardation, and two were taller than 130 cm. Baseline measurements were incomplete in two children. Finally, the coordinating center excluded two children because they had fewer than seven validated Rint measurements at baseline. The remaining 91 children had a mean age of 5.3 ± 1.4 years (2.9 to 7.9 years), a mean height of 112 ± 9.2 cm (92 to 129 cm), and a mean weight of 19.5 ± 3.6 kg (12 to 29 kg). Table 1 shows the anthropomorphic data in each age group. Thirty percent of the children were exposed to passive smoke by their parents (mean $\pm$ SD numbers of cigarettes smoked per day by the mothers and fathers were 6.7 ± 7.6 and 10.7 ± 11.9 , respectively). Table 2 shows the numbers, age and sex distributions, heights, and weights of the study children in each center. Ages, heights, and weights were significantly different among centers.

Prebronchodilator Rint Values

The mean number of measurements validated by the investigators was 11.1 ± 2.4 for Rint_{insp} and 11.7 ± 2.4 for Rint_{exp}. Of these measurements, 7.8 ± 1.2 for Rint_{insp} and 7.8 ± 1.2 for Rint_{exp} were selected by the computer within the mean flow ± 1 SD. Median volumes at interruption, expressed as percent of tidal volume, were 52% (25th–75th percentiles: 42–67%) for Rint_{insp} and 48% (25th–75th percentiles: 33–65%) for Rint_{exp}. No linear relationships were found between volumes at interruption and Rint_{insp} or Rint_{exp}. Median Rint_{insp} and Rint_{exp} val-

TABLE 1. ANTHROPOMETRIC CHARACTERISTICS BY AGE GROUP IN THE 91 STUDY CHILDREN

Age Range (years)	Sex* (boys/girls)	Age† (years)	Height (cm)	Weight (kg)
2.9–3.9	11/12	3.6 (3.3–3.7)	101 (98–103)	15 (14–17)
4–4.9	6/8	4.5 (4.3–4.7)	108.5 (104–111)	17.3 (16–19)
5–5.9	13/9	5.3 (5.2–5.7)	113 (109–118.5)	20.5 (18–22)
6–6.9	10/10	6.5 (6.2–6.7)	119 (117–121)	21.8 (21–24)
7–7.9	8/4	7.3 (7.2–7.6)	124 (122–128.5)	23 (22.5–25)

* Number of boys and girls.

† Median (25th–75th percentiles).

ues were significantly different across centers ($p < 0.01$, $p < 0.03$, respectively) (Table 2). The intrasubject CV of $R_{int_{insp}}$ was slightly but significantly lower than that of $R_{int_{exp}}$ ($p < 0.02$) (Table 3). $R_{int_{insp}}$ and $R_{int_{exp}}$ CV did not change significantly with age or across centers (Table 2).

Mean values for the 91 study children were not significantly different for $R_{int_{insp}}$ and $R_{int_{exp}}$ (Table 3). However, the difference between $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with age, being positive in children younger than 5 years and negative in those older than 5 years ($p < 0.02$) (Figure 1).

$R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with height ($p < 0.001$) (Table 4, Figure 2). The regression coefficients did not differ significantly when age, weight, sex, and/or parental smoking (total number of cigarettes smoked per day by both parents) were taken into account.

Postbronchodilator Rint Values

Median volumes at interruption expressed as percent of tidal volume were not significantly different before and after bronchodilator for $R_{int_{insp}}$ and for $R_{int_{exp}}$ (median [25th–75th percentiles]: 52% [42–67%] versus 50% [42–65%] and 48% [33–65%] versus 50% [35–65%], respectively). No linear relationships were found between volumes at interruption and $R_{int_{insp}}$ or $R_{int_{exp}}$ after bronchodilator administration. The CV of $R_{int_{exp}}$ was significantly larger after than before bronchodilator administration ($p < 0.03$) and significantly greater than CV $R_{int_{insp}}$ ($p < 0.02$) (Table 3).

$R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly after bronchodilator administration ($p < 0.001$) (Table 3). Mean $R_{int_{insp}}$ was significantly lower than mean $R_{int_{exp}}$ after bronchodilator ad-

ministration ($p < 0.01$) (Table 3). The mean bronchodilator-induced change expressed as the percentage of the predicted value was -15% for $R_{int_{insp}}$ (95% confidence interval, -46 to $+15\%$) and -12% for $R_{int_{exp}}$ (95% confidence interval, -46 to $+22\%$). Height, age, sex, and/or passive smoking had no effect on bronchodilator-induced changes in $R_{int_{insp}}$ or $R_{int_{exp}}$ expressed as the absolute value or as the percentage of the prebronchodilator value or predicted value.

DISCUSSION

The present multicenter study in healthy young white children confirms that (1) R_{int} could be measured easily in young children; and (2) $R_{int_{insp}}$ and $R_{int_{exp}}$ decreases linearly with height and is independent of sex. The new finding of this study is that the difference between $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with age, being positive in children younger than 5 years and negative in older children. Furthermore, changes in $R_{int_{insp}}$ and $R_{int_{exp}}$ after bronchodilator administration are reported here for the first time in healthy young children. No differences in $R_{int_{insp}}$ and $R_{int_{exp}}$ decreases after bronchodilator administration were observed between boys and girls.

Subjects

Only white children were studied because of the differences in airway growth reported between black and white children (19). Abnormalities in airway growth and dynamics have been found in children with a history of premature birth and/or intrauterine growth retardation (20), and children with either or both characteristics were consequently excluded. Exposure to passive smoke by the parents was not selected as an exclusion criteria because as many as 38% of French adults smoke (21). Thirty percent of our children were exposed to passive smoke by their parents. However, the number of cigarettes smoked by the parents included as an independent variable in the stepwise multiple regression analysis did not significantly modify the equations between $R_{int_{insp}}$ and $R_{int_{exp}}$ and height. Our study did not include air quality controls in the five cities. Therefore, we cannot rule out the possibility that differences in exposure to air pollutants across the five cities may have resulted in differences in airway growth (22).

Acceptability of the interrupter technique was excellent: complete measurement sets were obtained in all but two children.

TABLE 2. ANTHROPOMETRIC CHARACTERISTICS BY STUDY CENTER IN THE 91 STUDY CHILDREN

Centers	1	2	3	4	5	6	7	8
Number of children	21	8	13	14	12	13	7	2
Boys/Girls	10/11	5/3	10/4	9/5	2/9	7/6	3/4	1/1
Age, years*	3.9 (3.5–5.3)	5.2 (4–6.6)	6.5 (5.6–6.7)	5.75 (5–6.7)	4.6 (4.1–5.8)	5.3 (3.9–6.7)	6.1 (4.3–7.2)	5.8 3.5
Height, cm†	103 (100–113)	108 (103.5–119.2)	118.5 (113–123)	117.7 (108–120)	111.5 (104.7–118.7)	113 (108–118)	115 (111–121)	108.5 95
Weight, kg†	17 (15–20.4)	16 (14.7–20.7)	21 (19–24)	22.3 (19–24)	19 (17.7–21.2)	19 (17–20)	21 (16.5–23)	18 15
$R_{int_{insp}}$, $KPa \cdot L^{-1} \cdot second^{\dagger}$	0.84 (0.76–0.98)	0.58 (0.55–0.74)	0.70 (0.67–0.78)	0.83 (0.67–0.90)	0.86 (0.70–0.97)	0.74 (0.54–0.87)	0.54 (0.45–0.58)	0.82 0.89
CV, $R_{int_{insp}}$, %	12.1 (10.1–14.2)	11.4 (7.7–12)	9.7 (8.8–11.8)	9.1 (8.2–10.4)	10.4 (8.2–13.4)	12.2 (9.1–15.8)	11.8 (8.8–14.7)	5.7 11.8
$R_{int_{exp}}$, $KPa \cdot L^{-1} \cdot second^*$	0.80 (0.60–0.91)	0.65 (0.53–0.74)	0.71 (0.68–0.87)	0.80 (0.73–0.90)	0.90 (0.71–0.93)	0.81 (0.72–0.91)	0.54 (0.47–0.70)	0.85 0.87
CV $R_{int_{exp}}$, %	14 (11.8–15.3)	12.5 (11.5–13.7)	10.7 (9.7–13.6)	11.3 (9.3–11.6)	10.5 (8–13.8)	12.3 (11.2–13.9)	13.3 (10–15.1)	15 12

Definition of abbreviations: CV = coefficient of variation; $R_{int_{exp}}$ = expiratory interrupter resistance; $R_{int_{insp}}$ = inspiratory interrupter resistance.

Continuous variables are expressed as medians (25th–75th percentiles) for each center except center 8, for which absolute values are shown.

p Value for between-center comparisons.

* $p < 0.03$.

† $p < 0.01$.

TABLE 3. PRE- AND POSTBRONCHODILATOR INSPIRATORY AND EXPIRATORY INTERRUPTER RESISTANCE VALUES

	$R_{int_{insp}}$ ($KPa \cdot L^{-1} \cdot second$)	CV $R_{int_{insp}}$ (%)	$R_{int_{exp}}$ ($KPa \cdot L^{-1} \cdot second$)	CV $R_{int_{exp}}$ (%)
Prebronchodilator	0.78 ± 0.21	11.1 ± 3.4	0.78 ± 0.20	$12.1 \pm 3.2^*$
Postbronchodilator	$0.66 \pm 0.18^\dagger$	12 ± 3.8	$0.69 \pm 0.19^{\ddagger\S}$	$13.8 \pm 4.8^{*\S}$

For definition of abbreviations, see Table 2.

Values presented are mean $\pm$ SD.

* Significantly greater than CV $R_{int_{insp}}$, $p < 0.02$.

† Significantly smaller than prebronchodilator R_{int} , $p < 0.001$.

‡ Significantly greater than postbronchodilator $R_{int_{insp}}$, $p < 0.01$.

§ Significantly greater than prebronchodilator CV $R_{int_{exp}}$, $p < 0.03$.

Rint Measurements

Similar interrupter and software were used for R_{int} measurements in all eight centers. The closing speed of the interrupter device was within the range recommended by Bates and colleagues (23). PA was estimated from Pm curves using linear back extrapolation (1–5, 9–15), a procedure that shares similarities with that described by Jackson and colleagues (8). Phagoo and coworkers compared R_{int} values using curvilinear and linear back-extrapolation methods and found less variability with linear back-extrapolation (12, 13). The R_{int} measurement procedure included careful support of the cheeks and floor of the mouth, aimed at reducing the compliance of this section of the extrathoracic airways. Such support has been shown to improve R_{int} measurement significantly in healthy school-aged children (11), but not in healthy younger children (15) or in healthy adults (9).

Previous studies of R_{int} measurement in children did not provide a detailed description of the criteria used to validate R_{int} measurements (1–4, 10, 11, 14, 15). We carefully standardized the R_{int} measurement validation. The interruptions were performed between 20 and 80% of tidal volumes. No linear relationships were found between the volume at interruption and R_{int} , confirming previous data in children (11). Our device was not preprogrammed to activate occlusion at a particular flow (1–4, 10, 12–15). However, R_{int} data were selected by the computer within a narrow range of flows. Mean R_{int} was the average of seven validated measurements. Previous data (unpublished) from our laboratory showed that the CV of R_{int} in young children was not changed by using more than seven validated R_{int} measurements. The CV of $R_{int_{exp}}$ was slightly but significantly higher than that of $R_{int_{insp}}$, a difference possibly ascribable to changes in glottal opening during expiration (17). Neither age nor center influenced the CV of $R_{int_{insp}}$ or $R_{int_{exp}}$.

Prebronchodilator Rint Values

Normative data for $R_{int_{insp}}$ and/or $R_{int_{exp}}$ in young children have been collected recently in single-center studies (4, 11, 14, 15, 24). This study provides the first multicenter normative

data for $R_{int_{insp}}$ and $R_{int_{exp}}$ obtained using a statistical model that integrates center-to-center variability, thus allowing extrapolation of our findings to the general population of children of similar age. We found that height was the most significant predictor of R_{int} , in keeping with all earlier studies but one (4). One study reported R_{int} values according to height in a group of children, from early childhood to adolescence (11); few young children were included, however, so that the results cannot be compared with our data. Lombardi and colleagues recently reported the regression equations of $R_{int_{insp}}$ and $R_{int_{exp}}$ on height determined from a single-center study of 284 healthy young children (15). Our regression equations for $R_{int_{insp}}$ and $R_{int_{exp}}$ on height (Table 4) are not significantly different from theirs (Student's test on regression coefficients) (15), indicating that our multicenter study encountered similar variability in $R_{int_{insp}}$ and $R_{int_{exp}}$ measurements as the large, single-center study of Lombardi and coworkers (15). Merkus and colleagues reported $R_{int_{insp}}$ and $R_{int_{exp}}$ data in 59 healthy young children from a single center. They did not report the variability of the regression coefficients and, consequently, statistical comparisons with our model cannot be made (14). Nevertheless, the intercept and the slope of the relationship linking $R_{int_{insp}}$ and $R_{int_{exp}}$ to height were apparently higher than in the present study (14). These differences may be ascribable to the smaller number of study children shorter than 110 cm in height as compared with our study (16 versus 39) (18). $R_{int_{exp}}$ values presented according to subject age have been reported in 2- to 5-year-old children with no history of respiratory symptoms (4). These values were within the range of those obtained in the 4-year-olds in our study, i.e., 0.85 kPa/L/second and 0.86 kPa/L/second. Finally, Klug and Bisgaard (24) reported $R_{int_{insp}}$ values in a large group of young children, but used the opening interrupter method, in which the pressure used for R_{int} calculation was measured at the end of an 80-millisecond occlusion and the flow shortly after airway reopening. R_{int} measured by this method is thought to represent flow resistance plus the tissue viscoelastic component of the respiratory system (7). Lanteri and Sly reported an increase in the tissue viscoelastic component beyond 2 years of age (25). Consistent with this finding, $R_{int_{insp}}$ values measured using the opening interrupter method were higher than those obtained in the present study (24).

In previous studies of either R_{int} or resistance measured using the oscillation technique, values were slightly but significantly higher during expiration than during inspiration in both school-age children and adults (8, 10, 11, 26). This difference can be explained by diminished glottal opening during expiration (17). No significant differences between mean $R_{int_{insp}}$ and $R_{int_{exp}}$ were observed in this study of young children, as reported by Lombardi and colleagues (15). However, we found that the difference between $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly with age, being positive in children under 5 years of

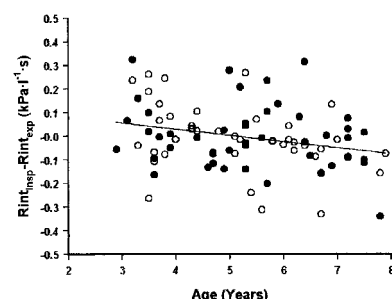


Figure 1. Relationship between age (years) and the difference between prebronchodilator $R_{int_{insp}}$ and $R_{int_{exp}}$ ($KPa \cdot L^{-1} \cdot second$). The solid circles indicate boys and the open circles girls. The solid line is the regression line. $y = -0.025x + 0.123$; $p < 0.02$.

TABLE 4. REGRESSION OF INSPIRATORY AND EXPIRATORY INTERRUPTER RESISTANCE ON HEIGHT

	$R_{int_{insp}}$ ($KPa \cdot L^{-1} \cdot second$)	$R_{int_{exp}}$ ($KPa \cdot L^{-1} \cdot second$)
Equation		
Intercept	2,289 (CI: 1.783; 2.796 SEM = 0.2142)	2,021 (CI: 1.488; 2.555 SEM = 0.2255)
Height, cm	$-1.37 \cdot 10^{-2}$ * (CI: $-1.74 \cdot 10^{-2}$; $-0.99 \cdot 10^{-2}$ SEM = 0.00189)	$-1.12 \cdot 10^{-2}$ * (CI: $-1.51 \cdot 10^{-2}$; $-0.72 \cdot 10^{-2}$ SEM = 0.001989)
Residuals		
SD	0.17	0.18
95% CI, $KPa \cdot L^{-1} \cdot second$	$\pm 0.33^{\dagger}$	$\pm 0.35^{\dagger}$
Predicted values		
95% CI, %	59–146 [‡]	56–147 [‡]

Definition of abbreviations: CI = 95% confidence interval; $R_{int_{exp}}$ = expiratory interrupter resistance; $R_{int_{insp}}$ = inspiratory interrupter resistance; SEM = standard error of the mean.

Number of subjects: 91.

* $p < 0.001$.

[†] Residual standard deviation with upper and lower 2.5 and 97.5 percentiles of predicted value.

[‡] 95% confidence interval for the percentage of the predicted value.

age and negative in older children. Jeans and colleagues (27) reported that the size of the nasopharyngeal airway decreased between 3 and 5 years of age because the surface area of the soft tissues grew faster than that of the nasopharyngeal airway. At the oropharyngeal level, a faster increase in the surface area of soft tissues as compared with that of the pharyngeal airway may result in an increase in upper airway resistance. If this is the case, the reduction in glottal opening during expiration may not exceed that of the pharyngeal lumen, explaining the lower $R_{int_{exp}}$ than $R_{int_{insp}}$ in very young children. Flow resistance may become higher during expiration than during

inspiration when the surface area of the oropharyngeal soft tissues remains relatively constant, while the area of the oropharyngeal airway increases. Our data, demonstrating that the difference between $R_{int_{insp}}$ and $R_{int_{exp}}$ changes with age and are relevant to clinical practice: $R_{int_{insp}}$ data and $R_{int_{exp}}$ data should be reported separately in young children.

Measurements of maximal expiratory flows at low lung volumes (28) suggest that sex may influence airway growth and dynamics. Girls have been reported to have higher flows than boys during early and late childhood (28, 29). Since maximal expiratory flows at low lung volumes are believed to reflect small airway geometry, girls may have larger peripheral airways than boys. The central airways contribute most of the resistance to airflow. Conflicting data have been reported on the effect of sex on resistance to airflow. An early study found higher values in boys than in girls (30). However, in a recent study, sex had no effect on R_{int} in paralyzed, mechanically ventilated children of whom the youngest were a few weeks old and the oldest were adolescents (25). Our data are in agreement with these results and with reports of resistance measured in young children using the interrupter techniques and forced oscillations (14, 15, 31).

Postbronchodilator R_{int} Values

Early studies found a significant increase in airway conductance or a significant decrease in total pulmonary resistance after β -adrenoceptor agonist inhalation in healthy adults and older children (32, 33). No previous studies have provided data for both $R_{int_{insp}}$ and $R_{int_{exp}}$ before and after bronchodilator administration in healthy young children. However, the response to a bronchodilator has been tested using the interrupter technique: $R_{int_{insp}}$ (1, 5) or $R_{int_{exp}}$ (2–4) decreased after bronchodilator administration in young children with respiratory disorders. In our study of healthy young children, both $R_{int_{insp}}$ and $R_{int_{exp}}$ decreased significantly after salbutamol administration. The mean R_{int} decrease expressed as the percent of predicted values was within the range reported for resistance measured in young children using the forced oscillations technique (34). Salbutamol had a slightly but significantly larger effect on $R_{int_{insp}}$ than on $R_{int_{exp}}$. To the best of our knowledge, no previous studies have examined the effects of β -adrenoceptor agonist inhalation on both upper and lower airway resistance during inspiration and expiration in healthy adults or children.

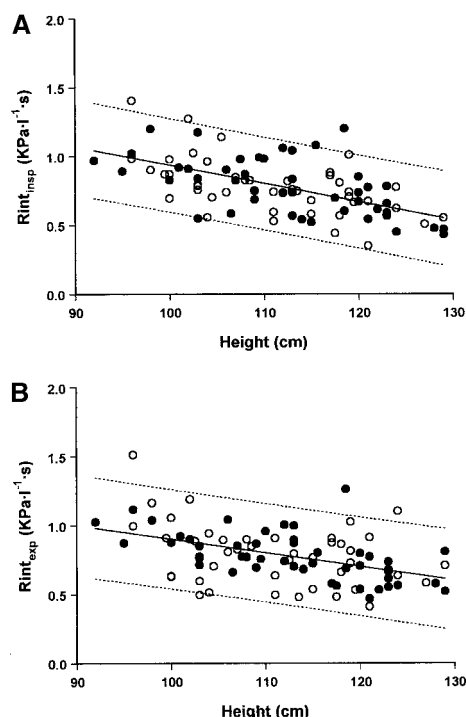


Figure 2. Relationships between height (cm) and prebronchodilator $R_{int_{insp}}$ ($KPa \cdot L^{-1} \cdot second$) (top panel) and between height and prebronchodilator $R_{int_{exp}}$ ($KPa \cdot L^{-1} \cdot second$) (bottom panel). The solid lines are regression lines and the dotted lines 95% confidence interval limits. The solid circles indicate boys and the open circles girls. (See regression equations in Table 4.)

The Rint decrease after salbutamol inhalation was neither significantly different between the boys and girls in our study nor between those in a previous study of resistances, measured using the forced oscillations technique (34). In contrast, a study involving expiratory maneuvers found evidence of sex-related differences in airway muscle tone (35), suggesting that the muscle tone of the peripheral airway at rest may be less responsive to β -adrenoceptor agonists in boys than in girls.

In line with a previous report on the effect of bronchodilator administration on resistance, measured using the forced oscillations technique (34), the salbutamol-induced Rint decrease varied widely across individuals in our study. This variability in the response to a bronchodilator across healthy children may be due to differences in environmental conditions and genetic makeup (36).

Conclusion

The present multicenter study of Rint measurements obtained using a standardized procedure provides Rint values according to height during both inspiration and expiration in healthy young white children, before and after bronchodilator. Acceptability of the technique was excellent, confirming previous reports of ease of use in young children. We show that the difference between $R_{int,insp}$ and $R_{int,exp}$ decreased with age, being positive in children younger than 5 years and negative in older children. This indicates that $R_{int,insp}$ data and $R_{int,exp}$ data should be reported separately in young children. The present Rint values may prove useful for testing lung function in young children with respiratory disorders who fail to cooperate with forced expiratory maneuvers. However, the large interindividual variability in the postbronchodilator Rint decrease in healthy children complicates determination of the optimal cut-off for defining a positive bronchodilator response in children with respiratory disorders.

Acknowledgment: The authors are grateful to the physicians who participated in the study: H. Trang and A. Bernard (Robert Debré Teaching Hospital, Paris); M. Voisin and F. Couwil (Arnaud de Villeneuve Teaching Hospital, Montpellier); Y. Grossi and D. Sarni (Morvan Teaching Hospital, Brest); J.L. Iniguez (Saint-Vincent-de-Paul Teaching Hospital, Paris); V. Diaz (Poitiers Teaching Hospital, Poitiers); E. Cixous (Calmette Teaching Hospital, Lille); and I. Pin, C. Pilenko-Mc Guigan, and H. Bensaidane (Grenoble Teaching Hospital, Grenoble). For their technical assistance, the authors thank S. Benjamaa, C. Foucard, M. Pisca, F. Dubois, and J.C. Sismeiro (Robert Debré Teaching Hospital, Paris); V. Alibert (Arnaud de Villeneuve Teaching Hospital, Montpellier); MN. Guiffaut (Morvan Teaching Hospital, Brest); C. Lebeau and A. Roche (Saint-Vincent-de-Paul Teaching Hospital, Paris); MC. Mathlin (Calmette Teaching Hospital, Lille); M. Guyard, B. Julien, and M. Trochu (Grenoble Teaching Hospital, Grenoble). The authors are thankful to P. Le Corre (Dyn'R Ltd, Toulouse) for assistance with the computer program, to F. Zerah and A. Harf (Henri Mondor Teaching Hospital, Créteil) for their advice during the preparation of the grant, and to S. England (New Brunswick University, Piscataway, New Jersey) for her helpful comments. The authors are especially indebted to the parents and the children who participated in the study.

References

- Chowienzyk PJ, Lawson CP, Lane S, Johnson R, Wilson N, Silverman M, Cochrane GM. A flow interruption device for measurement of airway resistance. *Eur Respir J* 1991;4:623–628.
- Phagoo SB, Wilson NM, Silverman M. Evaluation of the interrupter technique for measuring change in airway resistance in 5-year-old asthmatic children. *Pediatr Pulmonol* 1995;20:387–395.
- Phagoo SB, Wilson NM, Silverman M. Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3-year-old children. *Eur Respir J* 1996;9:1374–1380.
- McKenzie SA, Bridge PD, Healy MJR. Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J* 2000;15:833–838.
- Beydon N, Trang-Pham H, Bernard A, Gaultier C. Measurements of resistance by the interrupter technique and of transcutaneous partial pressure of oxygen in young children during methacholine challenge. *Pediatr Pulmonol* 2001;31:238–246.
- Mead J, Whittenberger L. Evaluation of airway interruption technique as a method for measuring pulmonary air-flow resistance. *J Appl Physiol* 1954;6:408–416.
- Bates JHT, Baconnier P, Milic-Emili J. A theoretical analysis of interrupter technique for measuring respiratory mechanics. *J Appl Physiol* 1988;64:2204–2214.
- Jackson AC, Milhorn HT, Norman JR. A reevaluation of the interrupter technique for airway resistance measurement. *J Appl Physiol* 1974;36:264–268.
- Liistro G, Stanescu D, Rodenstein D, Veriter C. Reassessment of the interruption technique for measuring flow resistance in humans. *J Appl Physiol* 1989;67:933–937.
- Carter ER, Stecenko AA, Pollock BH, Jaeger MJ. Evaluation of the interrupter technique for the use of assessing airway obstruction in children. *Pediatr Pulmonol* 1994;17:211–217.
- Oswald-Mammoser M, Llerena C, Speich JP, Donato L, Lonsdorfer J. Measurements of respiratory system resistance by the interrupter technique in healthy and asthmatic children. *Pediatr Pulmonol* 1997;24:78–85.
- Phagoo SB, Watson RA, Pride NB, Silverman M. Accuracy and sensitivity of the interrupter technique for measuring the response to bronchial challenge in normal subjects. *Eur Respir J* 1993;6:996–1003.
- Phagoo SB, Watson RA, Silverman M, Pride NB. Comparison of four methods of assessing airflow resistance before and after induced airway narrowing in normal subjects. *J Appl Physiol* 1995;79:518–525.
- Merkus PJF, Mijnsbergen JY, Hop WCJ, de Jongste JC. Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001;163:1350–1355.
- Lombardi E, Sly PD, Concutelli C, November E, Veneruso G, Frongia G, Bernardini R, Vicrucci A. Reference values of interrupter respiratory resistance in healthy preschool white children. *Thorax* 2001;56:691–695.
- Bates JHT, Sly PD, Kochi T, Martin JG. The effect of proximal compliance on interrupter measurements of resistance. *Respir Physiol* 1987;70:301–312.
- England SJ, Bartlett D Jr, Daubenspeck JA. Influence of human vocal cord movements on airflow and resistance during eupnea. *J Appl Physiol* 1982;59:773–779.
- Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS workshop on lung volume measurements official statement of the European Respiratory Society. *Eur Respir J* 1995;8:492–506.
- Wall A, Olson D, Bonn A, Creelman T, Buist AS. Lung function in North American Indian children: reference standards for spirometry maximal expiratory flow volume curves, and peak expiratory flow. *Am Rev Respir Dis* 1982;125:158–162.
- Nikolajev K, Heinonen K, Hakulinen A, Lämsimies E. Effects of intra-uterine growth retardation and prematurity on spirometric flow values and lung volumes at school age in twin pairs. *Pediatr Pulmonol* 1998;25:367–370.
- French Committee for Health Education. Baromètre Santé Vanves. Vol. 2. 2000-CFES
- Frischer T, Studnicka M, Gartner C, Tauber E, Horak F, Veiter A, Spengler J, Kühn J, Urbanek R. Lung function growth and ambient ozone. A three-year population study in school children. *Am J Respir Crit Care Med* 1999;160:390–396.
- Bates JHT, Hunter IW, Sly PD, Okubo S, Filiatrault S, Milic-Emili J. Effect of valve closure time on the determination of respiratory resistance by flow interruption. *Med Biol Eng Comput* 1987;25:136–140.
- Klug B, Bisgaard H. Specific airway resistance, interrupter resistance, and respiratory impedance in healthy children aged 2–7 years. *Pediatr Pulmonol* 1998;25:322–331.
- Lanteri J, Sly PD. Changes in respiratory mechanics with age. *J Appl Physiol* 1993;74:369–378.
- Solymar L, Aronsson PH, Bake B, Bjure J. Respiratory resistance and impedance magnitude in healthy children aged 2–18 years. *Pediatr Pulmonol* 1985;1:134–140.
- Jeans WD, Fernando DCJ, Maw AR, Leighton BC. A longitudinal study of the growth of the nasopharynx and its contents in normal children. *Br J Radiol* 1981;54:117–121.
- Pagtakhan RD, Bjelland JC, Landau LI, Loughlin G, Kaltenborn W, Seeley G, Taussig LM. Sex differences in growth patterns of the airways and lung parenchyma in children. *J Appl Physiol* 1984;56:1204–1210.
- Taussig LM. Maximal expiratory flows at functional residual capacity: a test of lung function for young children. *Am Rev Respir Dis* 1977;116:1031–1038.
- Doershuk CF, Fisher BJ, Matthews LW. Specific airway resistance from the perinatal period into adulthood. *Am Rev Respir Dis* 1974;109:452–457.

31. Mazurek H, Willim G, Marchal F, Haluszka J, Tomalak W. Input respiratory impedance measured by head generator in preschool children. *Pediatr Pulmonol* 2000;30:47–55.
32. Hensley MJ, O'Cain CF, McFadden ER, Ingram RH. Distribution of bronchodilatation in normal subjects: beta-agonist versus atropine. *J Appl Physiol* 1978;45:778–782.
33. Gaultier CL, Reinberg A, Girard F. Circadian rhythms in lung resistance and dynamic compliance in healthy children: effects of two bronchodilators. *Respir Physiol* 1977;31:169–182.
34. Hellinckx J, De Boeck K, Bande-Knops J, Van der Poel M, Demedts M. Bronchodilator response in 3-6.5 year-old healthy and stable asthmatic children. *Eur Respir J* 1998;12:438–443.
35. Landau LI, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. *Pediatr Pulmonol* 1993;16:31–35.
36. Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R. Association between genetic polymorphisms of the β 2-adrenoceptor and response to albuterol in children with and without a history of wheezing. *J Clin Invest* 1997;100:3184–3188.