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# Normative Data and Predictive Equation of Interrupter Airway Resistance in Preschool Children in Japan

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Measurement of interrupter airway resistance ($R_{int}$) is a convenient alternative to standard spirometry for assessing respiratory function in uncooperative young children. The aim of the present prospective study was to establish the normative data and predictive equation of $R_{int}$ in Japanese preschool children. A total of 214 children were enrolled from a single kindergarten; however, 129 were excluded because they met at least 1 of the exclusion criteria, such as wheezing history or recent common cold. Expiratory $R_{int}$ values were assessed in 85 of the children, but technically unsatisfactory measurements were obtained in 5 of them. Thus, 80 healthy Japanese children (39 boys and 41 girls) without any history or symptoms of respiratory tract diseases were evaluated. Their age, body height, and body weight ranges (median) were 1.67 to 6.42 (4.38) years, 79.8 to 120.9 (102.5) cm, and 10.4 to 24.9 (15.8) kg, respectively. The mean $R_{int}$ was $0.93 \pm 0.25$ kPa/L/s (range=0.46−1.49 kPa/L/s). The $R_{int}$ tended to decrease with increasing age and body height ($r=-0.65$; $P<0.01$), but sex played no significant role ($P=0.71$). The predictive equation based on body height derived by linear regression was expiratory $R_{int}$ (kPa/L/s)=2.513−0.01567×body height (cm) (multiple correlation coefficient=0.653). Because 79 of the 80 measured $R_{int}$ values were within 140% of the predictive $R_{int}$ value, we calculated a 140% cut-off for predicting bronchoconstriction. Our results provide a reference value for evaluating the degree of airway obstruction in young Japanese children. (J Nippon Med Sch 2015; 82: 180−185)

**Key words:** respiratory function tests, airway resistance, logistic models, predictive equation

## Introduction

Respiratory function tests are essential for evaluating lung function in children with confirmed or suspected respiratory tract diseases[1]. The most commonly used method is standard spirometry, which provides information based on the forced expiratory flow-volume curve. Six conditions are needed to receive acceptable results from spirometry: instantaneous start of exhalation, rapid rise in flow to peak flow, sharp peak early in exhalation, smooth continuous fall in flow without interruptions, gradual fall in low flow area, and reproducible shape standard[2]. Therefore, standard spirometry cannot be performed in young children because little cooperation can be expected for this age[3].

For those children, an alternative technique is airway resistance measurement. Airway resistance enhances the degree of obstruction in the respiratory tract during spontaneous tidal breathing without cooperative effort. One method to measure airway resistance is the interrupter technique[4].

The purpose of the present prospective study was to establish the normative data and predictive equation of interrupter airway resistance ($R_{int}$) in Japanese preschool children.

## Subjects and Methods

### Subjects

The subjects were recruited from a single suburban kindergarten in Tokyo in October and November 2005. Children were excluded if they had had symptoms of respiratory tract diseases for at least 1 previous month. Also excluded were children with a history of significant respiratory tract disease (severe pneumonia or respiratory failure), chronic respiratory disease (bronchial

Table 1   Clinical Data (mean±SD, range) of the Subjects

| Variable | Total (n=80) | Boys (n=39) | Girls (n=41) | P |
|---|---|---|---|---|
| Age (years) | 4.22±1.37 (2.33−6.33) | 4.17±1.57 (1.57−6.42) | 4.28±1.17 (1.57−6.42) | 0.19 |
| Body height (cm) | 101.3±10.4 (83.4–118.8) | 100.8±11.3 (79.8–120.9) | 101.7±9.5 (79.8–120.9) | 0.27 |
| Body weight (kg) | 15.7±3.0 (10.4–21.8) | 15.8±3.2 (10.4–24.9) | 15.5±2.9 (10.4–24.9) | 0.40 |
| $R_{int}$ (kPa/L/s) | 0.93±0.25 (0.46−1.49) | 0.92±0.25 (0.46−1.48) | 0.94±0.25 (0.53−1.49) | 0.71 |

*P*<0.05 was considered significant according to the Student's *t*-test.
80 children, 39 boys and 41 girls, were analyzed. Their age range (median) was 1.67 to 6.42 (4.38) years. Their body height ranged from 79.8 to 120.9 cm (median=102.5 cm) and body weight ranged from 10.4 to 24.9 kg (median=15.8 kg). The mean $R_{int}$ was 0.93±0.25 kPa/L/s (range=0.46−1.49 kPa/L/s). No significant differences were detected between boys and girls.

asthma, 3 or more episodes of wheezing, or bronchopulmonary dysplasia), anatomical abnormalities of the respiratory tract, congenital or acquired cardiac illness, neuromuscular disease, or other significant systemic disease.

The research protocol was reviewed and approved by the institutional ethics committee. Written informed consent was obtained from the parents of the participating children.

**Measurement Protocol**

The $R_{int}$ during expiration was measured with MicroRint® device for pulmonary function testing (Micro Medical Ltd., Gillingham, UK). Mouth pressure ($P_{mo}$) was evaluated after a brief interruption in airflow (V'), and $R_{int}$ was calculated as $P_{mo}/V'$[5,6]. For standardized measurement, the subjects were seated upright by themselves or on an assistant's lap in a familiar and quiet room. They were instructed to breathe quietly through the mouth into a rubber facemask or mouthpiece while the neck was slightly extended and the cheeks and chin were supported. The median value of 5 sequential and technically satisfactory measurements was calculated. Measurements during irregular breathing, tachypnea, or mouthpiece leakage were rejected. Also rejected were tracings not showing the timing of airflow interruption and those with horizontal or declining pressure signals, suggesting mouthpiece leakage or altered breathing. Micro Medical became a brand of CareFusion Corporation, which was headquartered in San Diego, CA, USA. Recently, CareFusion Corporation merged with Becton, Dickinson and Company (Franklin Lakes, NJ, USA).

**Statistical Analysis**

Student's *t*-test was used to compare boys and girls.

Pearson correlation coefficients were calculated to assess the associations of $R_{int}$ with age, body height, and body weight. The reproducibility of measurements within subjects was estimated by the within-subject coefficient of variation (CVw), which was calculated from the standard deviation (SD) of 5 sequentially obtained $R_{int}$ values divided by the mean $R_{int}$ values in each subject. Linear regression was used to derive the predictive equation of $R_{int}$. Data are presented as the mean±SD or median and range. The *P*<0.05 was considered significant.

**Results**

**General Findings**

Of the 214 children examined, 129 met at least one exclusion criterion or did not have their parents' consent. Therefore, $R_{int}$ values were measured in 85 children; however, in 5 children with a facemask 5 sequential and technically satisfactory measurements failed to be completed. Thus, measurements were completed and data were analyzed in 80 children (39 boys and 41 girls). Among the 80 children the age range was 1.67 to 6.42 years (median= 4.38 years). the body height range was 79.8 to 120.9 cm (median=102.5 cm), and the body weight range was 10.4 to 24.9 kg (median=15.8 kg). The $R_{int}$ measurements were completed with a facemask in 69 children and with a mouthpiece in 11 children (age range=4.50−6.25 years; $R_{int}$ values=0.57 to 0.91 kPa/L/s). The $R_{int}$ values of age-matched children who underwent measurements with a mouthpiece or a facemask did not differ significantly (p= 0.76, data not shown). Thus, all 80 $R_{int}$ values were defined as a single group. The mean $R_{int}$ was 0.93±0.25 kPa/L/s (range=0.46−1.49 kPa/L/s). The $R_{int}$ values did not differ significantly between boys and girls (**Table 1**). The

$R_{int}$ (kPa/L/s)
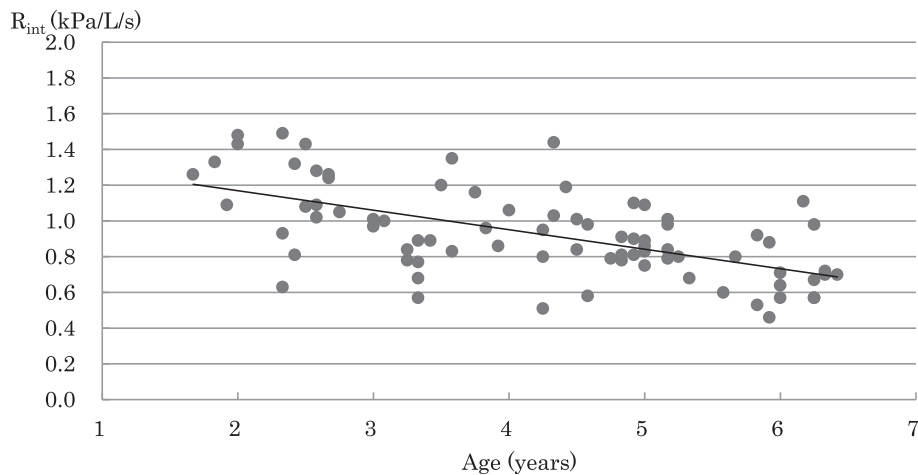


Fig. 1 $R_{int}$ distribution by age
Scatter plot illustrating the measured $R_{int}$ according to subject age. The solid line indicates the calculated regression line of the predicted $R_{int}$.

$R_{int}$ (kPa/L/sec)
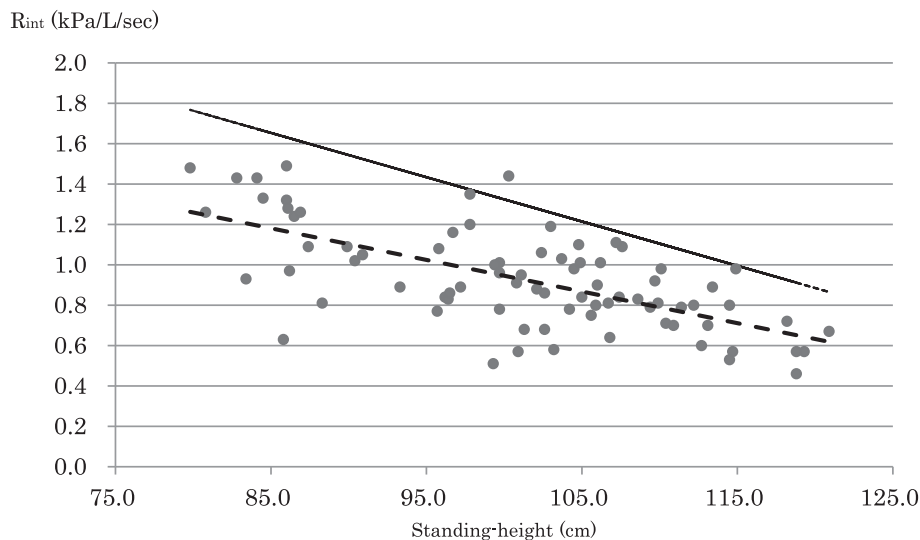


Fig. 2 $R_{int}$ distribution by height
Scatter plot illustrating the measured $R_{int}$ according to subject height. The dashed line indicates the predicted $R_{int}$ based on the standing height, and the solid line represents 140% of the predicted values.

5 children in whom the measurements failed to be completed ranged from 1.6 to 4.9 years, and 3 of the 5 children were boys. The major factor for incomplete measurement was unable to accept facemask.

The reproducibility of 5 sequential measurements in 80 children was calculated as 17.1%, which was the mean value of CVw (range=4.8% to 52.8%). The CVw showed significant but weak correlation with age (p<0.05, r= −0.3).

**Correlation between $R_{int}$ and Independent Variables**

The $R_{int}$ tended to decrease with increasing age (**Fig. 1**) and body height (**Fig. 2**). Significant linear relationships were noted between $R_{int}$ and age ($r=-0.599$), body height

($r=-0.653$), and body weight ($r=-0.608$, $P<0.01$).

**Predictive Equation of $R_{int}$**

Because body weight ($r=0.931$) and age ($r=0.920$) were highly correlated with body height, only body height was used as the explanatory variable in logistic regression. The derived first-degree polynomial equation was expiratory $R_{int}$ (kPa/L/s)=2.513−0.01567×body height (cm). The multiple correlation coefficient ($R^2$) was 0.653, indicating a significant but slightly weak correlation between the explanatory and the dependent variables. The second-degree polynomial equation was expiratory $R_{int}$= 3.2355−0.03028×body height (cm)+0.0000731×body height (cm). The $R^2$ of the second-degree polynomial equation

was 0.654 and similar to that of the first-degree polynomial equation. Therefore, the first-degree polynomial equation was adopted as the predictive equation of $R_{int}$ based on body height. To evaluate long-term repeatability, $R_{int}$ values were again measured in 64 children the following year. Comparing their measured $R_{int}$ value with the predictive value based on their body height, the correlation coefficient was 0.52 ($p < 0.01$).

## Discussion

The interrupter technique was developed as an alternative respiratory function test for patients in whom standard spirometry is difficult, such as awake young children. The $R_{int}$ measurement requires no effort, is minimally invasive, and requires minimal co-operation. Therefore, measuring $R_{int}$ it is a potential method for assessing airway obstruction in preschool children.

Direct measurement of airway resistance ($R_{aw}$) is traditionally performed with whole-body plethysmography. The $R_{aw}$ is calculated from the ratio of change in alveolar pressure ($P_{alv}$) and oral airflow. In contrast, the interrupter technique is based on the assumption that during transient occlusion of the airway at the mouth, $P_{alv}$ will equilibrate rapidly with $P_{mo}$. Therefore, $R_{int}$ can be calculated from the ratio of $P_{mo}$ (measured immediately after occlusion) to airflow (measured just before occlusion). To measure $R_{int}$ with MicroRint® device for pulmonary function testing, adequate cheek support and acceptance of a facemask or mouthpiece with a noseclip are essential. The measurement of $R_{int}$ fails mainly because of nonacceptance of the facemask, especially by younger children[7].

The present study is, to our knowledge, the first to measure expiratory $R_{int}$ in healthy Japanese preschool children. Since 2005, the physiques of Japanese children have not altered; thus, our data are applicable to the present day, and the measurement devices now used are similar to those used in 2005. In the present study, $R_{int}$ measurements were able to be completed in most children, as reported previously[8]. As in another previous study, no significant sex differences were detected with the measured $R_{int}$ values[9].

The $R_{int}$ of preschool children has been reported in several Japanese studies[10,11]. Kazuma[10] measured $R_{int}$ in 62 preschool children without asthma (aged 5 months to 5 years), in 71 children with asthma (aged 7 months to 5 years) 10 to 15 minutes after salbutamol inhalation (0.01 mg/kg/dose) during symptom exacerbation, and in 57 children with asthma (aged 10 months to 5 years) who

were asymptomatic for at least 2 weeks. The mean $R_{int}$ of these groups was $0.85 \pm 0.45$, $1.47 \pm 0.8$, and $0.81 \pm 0.28$ kPa/L/s, respectively. The mean $R_{int}$ in the present study ($0.93 \pm 0.25$ kPa/L/s) was similar to the control values in the study by Kazuma.

Watanabe[11] derived the predictive equation of $R_{int}$ from the body height of 72 healthy preschool children. The equation in these children was $R_{int} = 2.6147 - 0.0152 \times$ body height (cm) and yielded consistently higher values than the present predictive equation. The predictive equation derived by Saito[12] for children with asymptomatic bronchial asthma for at least 2 weeks is $R_{int} = 1.8525 - 0.0109 \times$ body height (cm). The regression coefficient ($R^2 = 0.2242$) was poorer than that of the present study ($R^2 = 0.653$)[12]. The $R_{int}$ showed inverse relationships with body height, age, and body weight, in the present study. Therefore, the predictive equation also showed an inverse relationship, similar to previous reports[8,13]. The relationship can be explained by increasing airway dimensions and is consistent with the reported reference equations of airway resistance measured by plethysmography[14].

Respiratory resistance usually increases in the presence of lower respiratory infection or asthmatic symptoms. Thus, to validate our predictive equation, the number of outliers was evaluated. The ratio between the measured and predicted $R_{int}$ was plotted according to body height (**Fig. 3**). The standard deviation of the ratio was 0.20 (20.0%), and +2 SD was 140%, which was designated as the cut-off value for outliers. Based on this cut-off, 1 of 80 subjects was an outlier. If the measured $R_{int}$ value exceeded 140% of the predicted $R_{int}$ according to body height, then the respiratory resistance was considered to have significantly increased (**Fig. 2**). On the other hand, 2 of the 80 subjects had less than 60% of the predicted $R_{int}$. These perhaps indicated poor measurement of pressure change in the mouth at the shutter closing (brief interruption in airflow) because of inadequate cheek support (**Fig. 3**).

A study by Nakade et al.[15] included 1,536 healthy Japanese adults aged 21 to 80 years and 33 patients with newly diagnosed asthmatic aged 18 to 80 years and found that the measured $R_{int}$ value was inversely correlated with body height (141−180 cm). The measured $R_{int}$ value is minimally invasive, requires minimal patient co-operation, and is simple to perform, but the significant difference in the measured and predicted $R_{int}$ values between adults and children reflects the reproducibility of the results. Thus, in the study of adults conducted by Nakade et al., a 120% cut-off appeared to be a useful in-
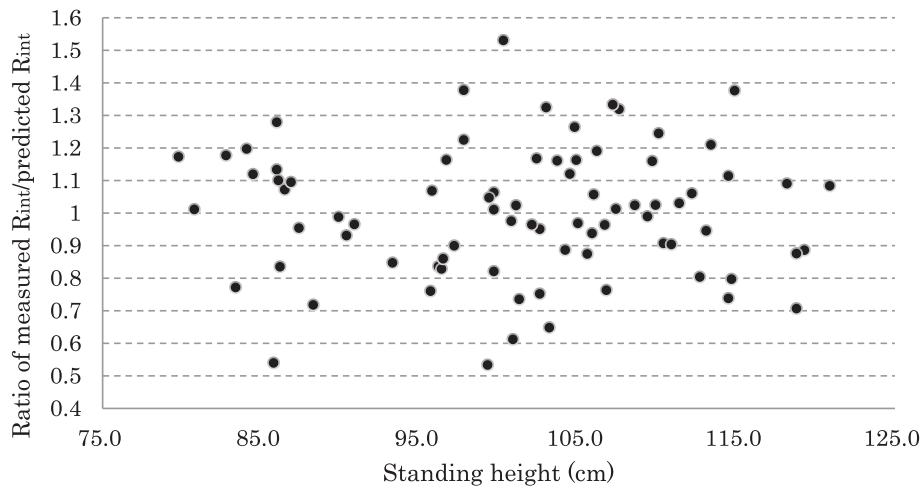
Fig. 3   Ratio of measured $R_{int}$/predicted $R_{int}$ by height
Scatter plot illustrating the ratio of the measured $R_{int}$/predicted $R_{int}$ according to subject height. The standard deviation (SD) of the ratio was 0.20 (20.0%); thus, +2 SD was calculated as 140%. The cut-off for outliers was designated as >140%, and with this standard, 1 of 80 total subjects was an outlier.

dicator for screening for asthma. However, in preschool children, we calculated a 140% cut-off for predicting bronchoconstriction.

Predictive equations of $R_{int}$ based on body height have also been reported in other countries. The equation derived by Lombardi et al.[8] from 284 healthy Italian white children aged 3.0 to 6.4 years is 2.126878−0.012538×body height (cm). Merkus et al.[16] examined 208 healthy Dutch white children aged 3 to 13 years and arrived at $R_{int}$= 1.927−0.00992×body height (cm). The present predictive equation is similar to those reported in the Italian and Dutch studies.

With regard to ethnic groups, McKenzie et al.[17] found no significant differences in $R_{int}$ among white, African-Caribbean, and Bangladeshi people in east London. Son et al.[18] reported a mean $R_{int}$ of 1.78±0.71 and 1.72±0.73 kPa/L/s in 3-year-old Korean boys and girls, respectively. For boys and girls with a body height of 96 to 100 cm, the mean $R_{int}$ was 1.54±0.49 and 1.71±0.77 kPa/L/s, respectively. Based on our predictive equation, the predicted $R_{int}$ at a body height of 100 cm was 0.946 kPa/L/s, indicating −1.21 SD for boys and −0.99 SD for girls for the Korean result. These differences despite the same race can be explained by differences in the measuring device (Microlab 4000) or the size of the trunk[19].

Respiratory resistance can also be measured with impulse oscillometry (IOS), in which a forced oscillation technique is used to apply mixed frequency, rectangular pressure impulses to the airways. Total airway resistance increases at 5 Hz (R5) because these low-frequency oscil-

lations (5−15 Hz) are transmitted to the peripheral airway. The measured $R_{int}$ also increases the total airway resistance. Klug et al.[7] found that in 120 subjects aged 2 to 7 years the R5 was 1.29±0.22 kPa/L/s (mean±SD) and the $R_{int}$ was 0.99±0.19 kPa/L/s.

**Study Limitations**

The examined children of the present study were recruited from a single kindergarten and sample size was small. To validate our predictive equation for universal use, the favorable number of subjects would be estimated approximately 260[20], and additional investigations in preschool children of other Japanese cities are needed. In addition, passive smoking exposure was not evaluated during the study period. Passive smoking can decrease pulmonary function; therefore, to eliminate this factor, more detailed subject recruitment is recommended in future studies.

**Conclusions**

Healthy Japanese preschool children show no significant difference in $R_{int}$ between sexes. Body height is the best predictor of $R_{int}$. Notably, $R_{int}$ may not differ significantly among children of different races. The study confirms the feasibility of $R_{int}$ measurement in young Japanese children, especially those with lower respiratory tract infection or asthma. Futhermore, $R_{int}$ would also enable comparisons with exhaled nitric oxide concentration and lung sound analysis.

dren, parents, and personnel who participated and contributed in this study.

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