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ORIGINAL ARTICLE

Reference Values for Japanese Children's Respiratory Resistance Using the LMS Method

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ABSTRACT
Background: The forced oscillation technique (FOT) is useful for studying pulmonary function in children, as well as in school children with asthma. However, the standard values for respiratory resistance (Rrs) in Asian school children remain unknown. We evaluated the standard Rrs using a type of FOT, impulse oscillometry (IOS), in healthy Japanese children at elementary and junior high schools.
Methods: A total of 795 children (age range: 6-15 years; mean age ± SD: 11.1 ± 2.4 years; 404 boys, 391 girls) at elementary and junior high schools participated in the study. Of the 795 children, we evaluated the Rrs of 537 children aged 6-15 years (mean ± SD: 10.8 ± 2.4 years) using IOS.
Results: Regression analyses with three IOS parameters, Rrs at 5 Hz (R5), Rrs at 20 Hz (R20), and Rrs difference between 5 Hz and 20 Hz (R5-R20), for age, height, weight, and degree of obesity as independent variables demonstrated the strongest correlation between each parameter and children's height. All parameters decreased with increasing height. Using the lambda-mu-sigma (LMS) method, we created standard curves for the Rrs values based on height.
Conclusions: Our standard curves could be useful for diagnosis and control evaluation of childhood asthma.

KEY WORDS
children, forced oscillation technique, LMS method, reference value, respiratory resistance

ABBREVIATIONS
FOT, forced oscillation technique; IOS, impulse oscillometry; LMS, lambda-mu-sigma, R, resistance; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, Rrs difference between 5 Hz and 20 Hz.

INTRODUCTION

Impulse oscillometry (IOS) is a form of forced oscillation technique (FOT) that measures respiratory functions by applying mixed frequency rectangular pressure impulses to the airways.[1] While high frequency oscillations (>15-20 Hz) only reflect large-airway effects, low frequency oscillations (5-15 Hz) that are transmitted to the peripheral airways reflect both large-airway and small-airway effects.[2] IOS provides several parameters, including total airway resistance (resistance at 5 Hz: R5), proximal airway resistance (resistance at 20 Hz: R20), and peripheral capacitive reactance (reactance at 5 Hz: X5). These parameters individually indicate the condition of the small and large airways, and indirectly suggest the presence of airway inflammation. It has been agreed that the clinical diagnostic capacity of the FOT is comparable to that of spirometry.[3-5]

Reference values for pulmonary function tests are critical for the diagnosis of lung diseases. However, the establishment of reference values in pediatric co-

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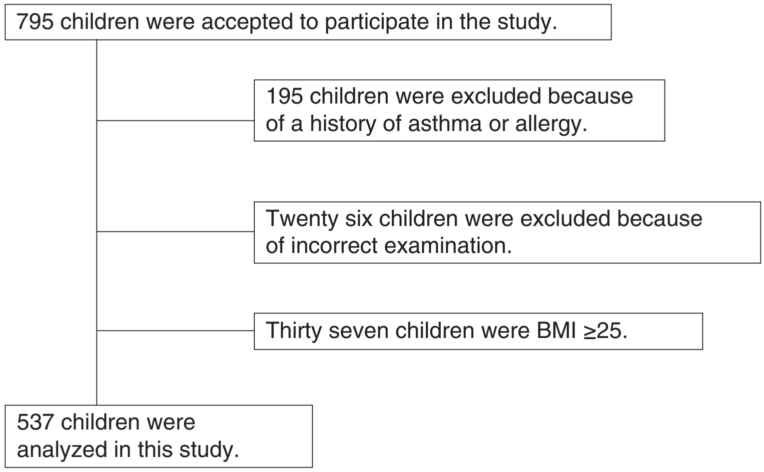

Fig. 1 Selection of candidates. A total of 795 children were accepted to participate, and 537 children were finally analyzed.

horts poses a great challenge because the reference values vary according to growth and development. Standard curves for breathing resistance in children have been reported.[6-8] Most of these are expressed as regression curves, in which it is assumed that the data show a normal distribution. However, since biological measurements do not usually fit into a normal distribution, the World Health Organization (WHO) does not recommend the use of regression curves to make predicted references for biological measurements. In this study, we determined the respiratory resistance (Rrs) of healthy children in Japan by IOS and created references using the lambda-mu-sigma (LMS) method, which is suitable for parameters with a non-normal distribution and strongly recommended by the WHO for references related to growth and development.[9]

Table 1 Height, weight and body mass index of the children participating in the study

	Boys (n = 270)	Girls (n = 267)
Height (cm)		
median with range	138.7 (113.5-174.4)	140.0 (111.3-163.2)
mean ± SD	141.3 ± 16.0	139.0 ± 14.1
Weight (kg)		
median with range	34.3 (19.0-71.3)	33.8 (16.7-62.5)
mean ± SD	36.7 ± 12.5	35.3 ± 10.9
Body mass index		
median with range	17.1 (12.4-24.9)	17.62 (12.9-24.8)
mean ± SD	17.8 ± 2.7	17.8 ± 2.8

METHODS

STUDY PROTOCOL

In this study, 795 subjects (age range: 6-15 years; mean age ± SD: 11.1 ± 2.4 years; 404 boys, 391 girls) at elementary and junior high schools in a suburban area of Shibukawa City, Gunma Prefecture, Japan, were enrolled. Informed consent for the measurements was obtained from the guardians of each child by school authorities. The study was approved by the Ethics Committee of Gunma University Graduate School of Medicine.

Before taking measurements, the guardians completed an American Thoracic Society, Division of Lung Disease, respiratory questionnaire in Japanese to exclude asthma or allergic disorders.[10] Children with doctor-diagnosed asthma or a single history of wheezing were excluded from the study. Children with a history of upper respiratory tract infection during the 2 weeks before the investigation were also excluded. Measurements were performed under the supervision of three consistent experienced pediatricians, who judged whether the measurements were performed with correct maneuvers.

IOS SYSTEM

The Rrs and other IOS parameters were determined using an IOS system (MS-IOS; Jaeger) using techniques recommended by the manufacturer.[11] The measurements were made in the standing position with a nose-clip on. During the measurements, the cheeks were supported by the hands of investigators (for younger children) or by the children themselves. The pneumotachograph was calibrated each day prior to the measurements using a 3-L syringe, and the validity of the IOS calibration was tested every time against a reference impedance of 0.2 kPa/L/s supplied by the manufacturer.

Real-time recordings of mouth pressure and flow signals pulsed through a 5-20-Hz spectrum were su-

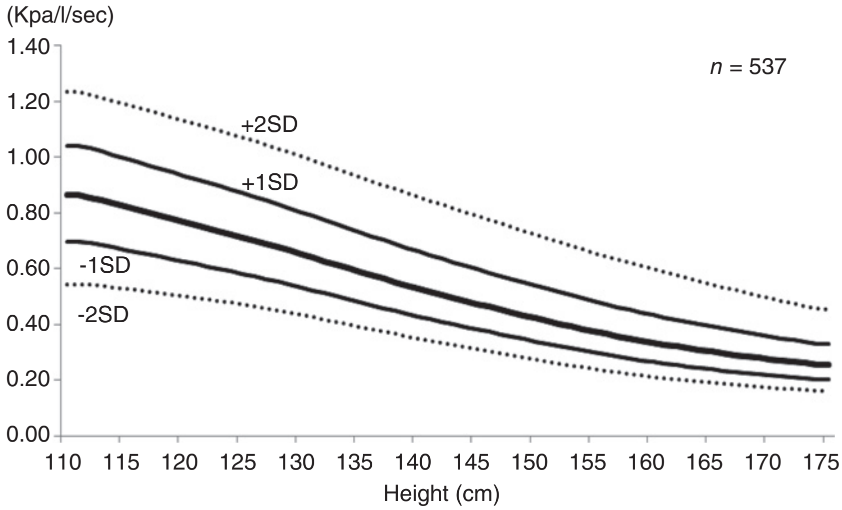

Fig. 2 Reference values of R5 according to height. As the child height increases, R20 decreases in a linear manner.

Table 2 R5 reference values according to height

Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD	Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD
110	0.55	0.70	0.86	1.04	1.23	146	0.30	0.37	0.46	0.59	0.77
113	0.54	0.68	0.84	1.02	1.21	149	0.28	0.35	0.43	0.55	0.73
116	0.52	0.66	0.81	0.98	1.18	152	0.26	0.32	0.40	0.51	0.70
119	0.51	0.63	0.78	0.95	1.14	155	0.24	0.30	0.38	0.48	0.66
122	0.49	0.61	0.75	0.91	1.11	158	0.22	0.28	0.35	0.45	0.62
125	0.47	0.58	0.71	0.87	1.07	161	0.21	0.26	0.33	0.42	0.59
128	0.45	0.55	0.68	0.83	1.03	164	0.19	0.24	0.31	0.40	0.55
131	0.43	0.52	0.64	0.79	0.99	167	0.18	0.23	0.29	0.38	0.52
134	0.40	0.49	0.60	0.74	0.94	170	0.17	0.22	0.28	0.36	0.49
137	0.37	0.46	0.56	0.70	0.90	173	0.17	0.21	0.26	0.34	0.47
140	0.35	0.43	0.53	0.66	0.86	175	0.16	0.20	0.25	0.33	0.45
143	0.33	0.40	0.49	0.62	0.82						

n = 537.

perimposed over tracings of the tidal breathing and displayed on a computer screen. Measurements of resistance at 5 and 20 Hz and their difference (R5, R20, and R5-R20) and respiratory impedance at 5 Hz were recorded. It was agreed that the value of R20 mainly demonstrated the central Rrs, and that the value of R5-R20, as the Rrs difference between 5 Hz and 20 Hz, demonstrated the peripheral airway.[11,12]

STATISTICAL ANALYSIS

Reference values of R5, R20 and R5-R20 were computed by the LMS method using LMS ChartMaker Light 2.1 software (Medical Research Council, London, UK).[13-15] Briefly, this method describes the distribution of the target parameter at a given height by normal approximation after a Box-Cox transformation. The height-dependent estimates of L, M, and S for the three parameters of lambda (Box-Cox power), mu, and sigma (mean and coefficient of variation after transformation), respectively, provide the name for this method. The estimation of these parameters as a function of the height uses a penalized maximum likelihood approach where the penalty term is composed of integrals over the squared second derivatives expressing the smoothness of the curves. The final curves were restricted to cover the height range of 110-175 cm, for which the data of R5, R20 and R5-R20 could be corrected.

RESULTS

Informed consent from their guardians was obtained for 795 children to participate in the study (Fig. 1). The age range was 6-15 years (mean ± SD: 11.1 ± 2.4 years), and the children comprised 404 boys and 391

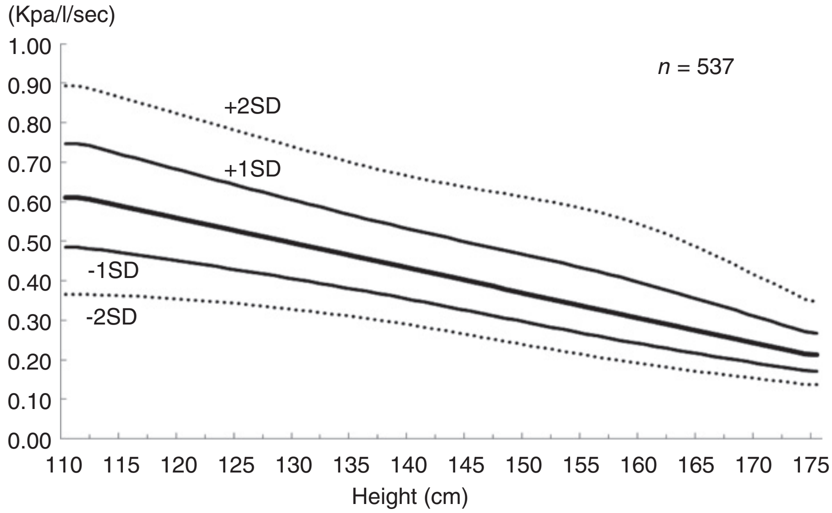

Fig. 3 Reference values of R20 according to height. As the child height increases, R20 decreases in a linear manner.

Table 3 R20 reference values according to height

Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD	Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD
110	0.37	0.48	0.61	0.75	0.89	146	0.26	0.32	0.39	0.49	0.63
113	0.36	0.48	0.60	0.73	0.88	149	0.24	0.30	0.37	0.47	0.62
116	0.36	0.47	0.58	0.71	0.85	152	0.23	0.28	0.35	0.45	0.60
119	0.36	0.45	0.56	0.69	0.83	155	0.21	0.27	0.33	0.43	0.58
122	0.35	0.44	0.54	0.66	0.80	158	0.20	0.25	0.32	0.41	0.56
125	0.34	0.43	0.52	0.64	0.78	161	0.18	0.23	0.30	0.39	0.53
128	0.33	0.41	0.51	0.62	0.75	164	0.17	0.22	0.28	0.36	0.49
131	0.32	0.40	0.49	0.59	0.73	167	0.16	0.20	0.26	0.33	0.45
134	0.31	0.38	0.47	0.57	0.70	170	0.15	0.19	0.24	0.31	0.41
137	0.30	0.37	0.45	0.55	0.68	173	0.14	0.18	0.22	0.28	0.37
140	0.29	0.35	0.43	0.53	0.66	175	0.14	0.17	0.21	0.27	0.35
143	0.27	0.33	0.41	0.51	0.65						

n = 537.

girls. All 795 children with informed consent were subjected to IOS measurements. Of these 795 children, 195 children were excluded from further analysis because of a history of bronchial asthma or wheezing. Another 26 children were excluded because of incorrect examination, as judged by the examiners, and 37 children were excluded because of obesity with a body mass index (BMI) of 25 or higher, which is thought to have influences on lung function.[16,17] Consequently, the data for 537 children were analyzed in this study. The distributions of age and height in the final population are shown in Table 1.

We studied the associations of three IOS parameters, R5, R20, and R5-R20, with age, height, weight, and degree of obesity. Of these parameters, we found the strongest correlation between the Rrs and height. All of the IOS parameters, R5, R20, and R5-R20, decreased with increasing height. Based on these observations, we used the LMS method to create standard curves for the total airway Rrs (R5; Fig. 2, Table 2), the proximal Rrs (R20; Fig. 3, Table 3) and peripheral Rrs (R5-R20; Fig. 4, Table 4) with the children's heights.

DISCUSSION

In this study, we used the LMS method to construct standard curves for Rrs obtained by IOS. The standard curves were based on height, because we found the strongest correlations between the Rrs values and height. This is consistent with a previous report, in which height was also used to make a reference for IOS.[6] The standard curve for R5-R20 in the present study showed a characteristic feature of an increasing

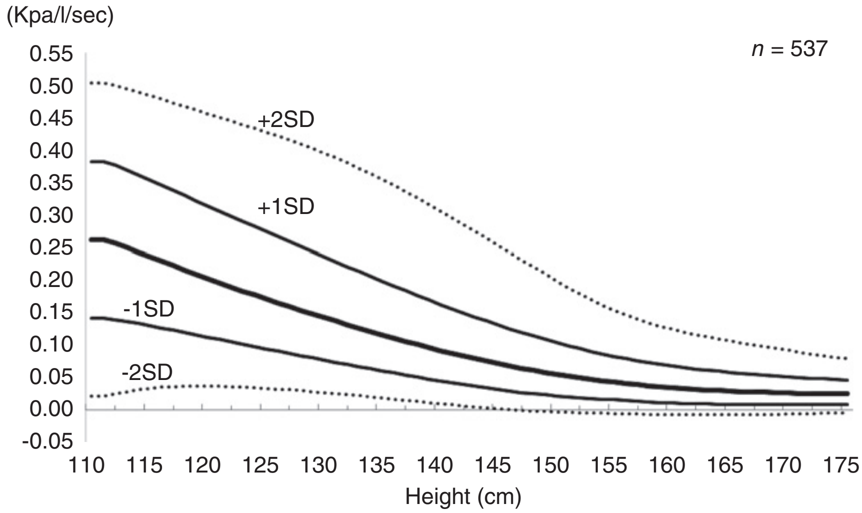

Fig. 4 Reference values of R5-R20 according to height. As the child height increases, R5-R20 gradually decreases. At heights above 150 cm, the range of SD becomes small.

Table 4 R5-R20 reference values according to height

Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD	Height (cm)	-2SD	-1SD	0SD	+1SD	+2SD
110	0.02	0.14	0.26	0.38	0.50	146	0.00	0.03	0.07	0.13	0.24
113	0.03	0.14	0.25	0.37	0.50	149	0.00	0.02	0.06	0.11	0.21
116	0.03	0.13	0.23	0.35	0.48	152	0.00	0.02	0.05	0.09	0.18
119	0.04	0.12	0.21	0.32	0.46	155	-0.01	0.02	0.04	0.08	0.15
122	0.04	0.10	0.19	0.30	0.45	158	-0.01	0.01	0.04	0.07	0.13
125	0.03	0.09	0.17	0.27	0.43	161	-0.01	0.01	0.03	0.07	0.12
128	0.03	0.08	0.15	0.25	0.41	164	-0.01	0.01	0.03	0.06	0.11
131	0.03	0.07	0.14	0.23	0.39	167	-0.01	0.01	0.03	0.06	0.10
134	0.02	0.06	0.12	0.21	0.36	170	-0.01	0.01	0.03	0.05	0.09
137	0.01	0.05	0.11	0.18	0.34	173	-0.01	0.01	0.02	0.05	0.08
140	0.01	0.04	0.09	0.16	0.31	175	0.00	0.01	0.02	0.05	0.08
143	0.00	0.04	0.08	0.14	0.27						

n = 537.

decline at around 150 cm. This is one of the different points from previously reported references.

Many previous reports have concluded that the FOT is reliable for assessing pulmonary function in children with asthma.[18,19] It has also been suggested that the clinical diagnostic capability of respiratory impedance measurements with the FOT is comparable to that of spirometry.[20] One of the advantages of the FOT is that minimal cooperation by the patient is needed and no respiratory maneuvers are required, since the impulses are superimposed on the resting breathing of the subject.[21] Use of the FOT should be taken into consideration for patients in whom spirometry or other pulmonary function tests cannot be performed or for cases where the results of other tests appear to be unreliable.[22] In addition, the FOT was demonstrated to be able to efficiently assess bronchial hyperresponsiveness.[8] Another advantage of the FOT over interrupter techniques or body plethysmography is that the FOT partitions the respiratory system mechanics into Rrs and reactance (Xrs),[23] and an abnormal R5-R20 and/or Xrs might provide important information about reductions in small-airway conductance and increased lung elastance. Considering these characteristic features, the FOT is a useful and powerful method for studying pulmonary functions in children with asthma.[24]

Well-defined and precise references for Rrs in different ages or statures are vital for the diagnosis of respiratory diseases in children. Various reference values for IOS have been reported using pediatric cohorts in North America, Poland, and Korea.[6-8] However, these reference values adjusted for body height estimated by linear or non-linear regression analyses are statistically incorrect, because the variability of lung function measurements around the median is not uniform across different ages and heights, and there is skewness in the distributions. Thus, conventional regression analysis is not adequate to model the complex relationships between body height and IOS variables. The LMS method is a longstanding and highly cited technique for constructing age- or body size-related reference ranges for skewed data.[25,26] The Box-Cox power (lambda) to transform the data to near-normality, the median (mu), and the generalized coefficient of variation (sigma) together define the moments as functions of age or body size, hence the name LMS (lambda-mu-sigma). The method has been used to construct national growth references in many countries. The WHO chose to use the LMS method for the analysis of its recently published growth standard.[9] Recently, reference values for pulmonary function tests using the LMS method were reported.[25,26] However, reference values for IOS using the LMS method have not yet been estimated. Our present data provide the first IOS references for children based on the LMS method.

One of the caveats of this study was to make a diagnosis of asthma, allergy, and wheezing only using questionnaires. Therefore, it remains possible that some patients with "silent asthma", i.e. those who suffer from asthma but showed no symptoms of bronchial asthma at the time, were included in the study. In addition, the presence of allergic or chronic rhinitis was not clearly determined, since we excluded asthma and all allergic disorders from the study based on the questionnaires. It is too difficult to use the criteria for physician-diagnosed asthma in a school-based study like this.

We excluded obese children with their BMI above 25 from the analysis because it has been shown that obesity affects lung resistance and is associated with severity of asthma.[16,17] Indeed previous studies on respiratory resistance have excluded obese subjects.[3,6,7] Our preliminary analysis showed that -57% of obese children have higher R5-R20 (over +1 SD) compared to the reference values, supporting that obesity affects respiratory resistance.

In the present study, we did not take sex into account when constructing the standard curves. One of the reasons for this is that no significant differences between boys and girls were found in this study (data not shown). However, we cannot completely exclude the possibility that such differences might arise when the number of children, especially of adolescents, is increased. We are planning a study on a much larger population to create more precise standard curves in the near future.

In conclusion, we have measured the Rrs of students at elementary and junior high schools in Japan using IOS, and created standard curves by the LMS method. Our results could be useful for the diagnosis and control evaluation of childhood asthma. In the future, we would like to push forward a study of the relevance of obesity and sex to the Rrs in asthmatic children using our new references.

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