Respiratory Impedance and Bronchodilator Response in Healthy Italian Preschool Children

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Summary. Objective: To define normal values for respiratory resistance (R_{rs}) and reactance (X_{rs}) and bronchodilator response (BDR) in a population of healthy Italian preschool children using a commercially available forced oscillation device. Methods: R_{rs} and X_{rs} were measured in kindergartens in Viterbo, Italy. Regression analysis was performed taking into account height, weight, age, gender, and reference equations calculated. The coefficient of repeatability (CR) between two tests performed 15 min apart was calculated in a subset of children. BDR was assessed by repeating the measurements 15 min after the administration of 200 µg of inhaled salbutamol and calculated as an absolute change in R_{rs} and X_{rs} at 8 Hz, as a percent change in baseline, and as a change in Z-score calculated from the reference equations. Results: Lung function was attempted in 175 healthy children and successful in 163 (81 male, median age 4.8, range 2.9–6.1 years). R_{rs} and X_{rs} at 6, 8, and 10 Hz were related to height but not other variables. The CR was 1.53 hPa s L^{-1} for R_{rs8} and 0.91 hPa s L^{-1} for X_{rs8}. The 5th percentile for absolute R_{rs8} BDR was −3.16 hPa s L^{-1}, whereas the 95th percentile for absolute X_{rs8} BDR was 2.25 hPa s L^{-1}. These cut-off values corresponded to a change in the Z-score of −1.88 and 2.48, respectively. Conclusions: We have established reference equations for R_{rs} and X_{rs} in healthy Italian preschool children using forced oscillations. We recommend a change in Z-score of −1.88 for R_{rs8} and 2.48 for X_{rs8} as cut-off values for a positive BDR. **Pediatr Pulmonol. 2010; 45:1086–1094.** © 2010 Wiley-Liss, Inc.

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INTRODUCTION

Lung function testing is important in evaluating patients with respiratory diseases. Adults and cooperative older children, usually from school age, can perform tests that require specific respiratory maneuvres, such as spirometry, which requires maximal inspiration and maximal forced expiration, to measure lung function. In preschool children such maneuvres are frequently not possible. Respiratory impedance (Z_{rs}) can be measured with the forced oscillation technique (FOT). This is a useful tool in evaluating lung function in young children with limited ability to cooperate[1] and older children.[2−4] FOT has been shown to be applicable in the clinical evaluation of preschool children with cystic fibrosis[5] as well as older children with cystic fibrosis during a respiratory tract exacerbation.[6] Lung function measured with FOT has also been evaluated in children born prematurely with or without neonatal chronic lung disease.[7−9] FOT has also been shown to be a valid tool in the assessment of bronchodilator response (BDR) in different populations of patients, especially asthmatic or wheezing children.[4,10−14]

Before FOT can be introduced into clinical practice as a routine test, appropriate reference values from healthy

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populations are needed. Although, a number of data sets from children have been published these are likely to be specific to the equipment used and to the study population. Other reference data sets from large samples of children have been previously published using the pseudorandom noise as the forcing function.[2,15–18] Hall et al.[18] have previously reported Z_{rs} reference values in a population of Australian preschoolers using a commercially available FOT device that uses a pseudo-random noise as the forcing function. The Australian equation was compared to other equations previously published.[18] To date, no assessment of whether these data are applicable to other populations has been published.

For the clinical application of the technique, knowing the repeatability of the test and the BDR in healthy subjects is also necessary. The between-measurement coefficient of repeatability (CR, i.e., twice the standard deviation of the difference between two measurements) for FOT has been reported in healthy children to be between 1.1 and 2.6 $hPa\,s\,L^{-1}$ for respiratory resistance (R_{rs}) and between 1.2 and 1.7 $hPa\,s\,L^{-1}$ for respiratory reactance (X_{rs}).[18–20] Thamrin et al.[10] have shown BDR calculated as a percent change with respect to baseline of -37% for R_{rs8} and 67% for X_{rs8} in healthy Australian children. Oostveen et al.[14] have reported a decrease in resistance on average of 22% in wheezing children. In the present study, we measured lung function using FOT in 163 preschool aged Italian children to produce reference equations for R_{rs} and X_{rs} and to compare these with the Australian data. We also aimed to evaluate the repeatability of the test and to determine appropriate methods for assessing response to inhaled bronchodilator.

MATERIALS AND METHODS

Study Subjects

Children attending kindergartens in Viterbo, Italy were approached. Parents were sent a consent form and questionnaire by the education authorities and asked to return these to the child's kindergarten. The Ethics Committee of the Local Health Authority in Viterbo approved the study and written consent was obtained from the parents.

Respiratory History

Respiratory history was assessed using a standardized questionnaire (ISAAC modified).[21] Subjects born at <36 weeks of gestational age or who had received oxygen after birth for more than 30 days were excluded. Subjects were defined as healthy, and thus included into the analysis, if they had never had a doctor diagnosis of asthma and had no more than three episodes of wheezing ever, with no episodes of wheezing during the previous 12 months. A personal history of atopy was defined as positive if the child had ever had allergic rhinitis and/or eczema. Also, parental history of atopy was considered to be positive if the parents had ever had allergic rhinitis or eczema or asthma and children were considered to be exposed to environmental tobacco smoke (ETS) if any family member smoked. All subjects were free of respiratory symptoms and signs at the time of testing.

Lung Function Assessment

Subjects underwent FOT measurements in the kindergartens in Viterbo. R_{rs} and X_{rs} were measured according to American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations,[1] using a commercial device (I2M; Chess Medical, Belgium, marketed by Cosmed, Rome, Italy), which uses a pseudo-random noise signal between 4 and 48 Hz. The device was calibrated every day before the testing using a calibration device of known impedance. The impedance of the mouthpiece and bacterial filter (Cosmed, Italy) was measured and subtracted by the equipment software automatically. During the test subjects sat in an upright position with a neutral position of the head and were connected to the oscillation device by the mouthpiece incorporating a bacterial filter. They wore a nose clip and they were instructed to breathe normally at tidal volume. The cheeks and the floor of the mouth of the subject were supported during all measurements by one of the investigators. Measurements were excluded if a sudden drift on the volume tracing (suggesting an incomplete seal around the mouth) or a reduction/interruption of the flow oscillations (suggesting movement of the mouth or tongue, swallowing, talking, or glottal closure) were detected by visual control on the screen.[1] The validity of the measurements at individual frequencies was assessed automatically by the software using the coherence function, which describes the statistical relationship between the input and output signals. A coherence function ≥ 0.95 is taken as an acceptable limit for Z_{rs} measurements.[1] Individual frequencies that had a coherence function of <0.95 were excluded and the entire measurement was discarded if three or more individual frequencies were unacceptable. Between three and five data epochs lasting 8 sec each were recorded to obtain at least three acceptable measurements.[1] R_{rs} and X_{rs} were calculated for each frequency and the mean of the obtained measurements reported for each child at the frequencies of 6, 8, and 10 Hz.

The short-term repeatability of the test was investigated in a subset of preschoolers. For this purpose, two sets of measurements were taken 15 min apart.

BDR was assessed by measuring again Z_{rs} 15 min after the administration of 200 µg of inhaled salbutamol administered at tidal breathing via MDI with a spacer (AeroChamber Plus, Trudell Medical International, London, ON, Canada).

Statistical Analysis

Data are reported as mean and standard deviation (SD) or median and range, according to the distribution of the variable. Individual within-test variations for Z_{rs} variables are expressed as coefficients of variation (CV), calculated as: $CV = (SD/mean) \times 100$, where SD is the standard deviation and the mean is the mean of all technically acceptable measurements. The coefficient of repeatability (CR) for two repeated sets of measurements was calculated as absolute value ($2 \times SD$ of the difference between the repeated measurements) and as relative value ($2 \times SD$ of the difference between repeated measurements as a percentage of the mean of the two measurements).

Stepwise multiple regression analysis was performed to take into account height, weight, age, and gender and potential effects of personal and parental history of atopy, and ETS exposure. Regression equations and the residual standard deviation (RSD) were determined for R_{rs} and X_{rs} at the frequencies of 6, 8, and 10 Hz. BDR was assessed using three indices: absolute change in R_{rs8} and X_{rs8}; percent change in R_{rs8} and X_{rs8} with respect to baseline; and as change in Z-score (post-salbutamol Z-score—baseline Z-score) for R_{rs8} and X_{rs8} calculated from the baseline data. SPSS for Windows (version 16.0) was used for the analysis. A two-tailed P-value of <0.05 was considered as statistically significant.

RESULTS

Questionnaires were distributed to families of 690 children and 324 were returned. Two children with neurological problems were excluded and consent for lung function testing was not obtained from 47 children. Eighty-four children had a diagnosis of asthma or had recurrent respiratory symptoms and were excluded from the current analysis. Measurements could not be attempted in 16 children due to equipment failure. Lung function measurements were attempted in 175 healthy children and data successfully obtained from 163 children aged 2.9–6.1 years. Demographic characteristics of the population are shown in Table 1. The success rate of FOT increased with age: being 66% (2/3) for children <3 years

TABLE 1— Characteristics of the Population of Children

	n = 163
Age, years	4.8 (2.9–6.1)
Male, n	81 (49.7)
Height, cm	107.8 (6.5)
Weight, kg	19.9 (3.5)
Personal history of atopy, n	59 (37.1)
Parental history of atopy, n	37 (24.7)
ETS exposure, n	86 (54.1)

Data are expressed as median (range) for age, mean (SD) for height and weight, and n (%) for gender, personal history of atopy, parental history of atopy, and environmental tobacco smoke (ETS) exposure.

TABLE 2— Group MEAN and SD of R_{rs} and X_{rs} and the Within-Test Variability in the Study Population

	Mean	SD	CV (%)	n
R_{rs6} hPa s L^{-1}	8.40	0.74	8.8	143
R_{rs8} hPa s L^{-1}	8.49	0.49	5.9	163
R_{rs10} hPa s L^{-1}	8.16	0.51	6.3	163
X_{rs6} hPa s L^{-1}	−3.24	0.55	17.2	143
X_{rs8} hPa s L^{-1}	−2.45	0.43	18.8	163
X_{rs10} hPa s L^{-1}	−2.23	0.38	18.6	163

SD, standard deviation; CV, coefficient of variation.

old; 90.6% (29/32) for children from 3 to <4 years; 94.4% (67/71) for children from 4 to <5 years; 93.8% (61/65) for children aged 5 to <6 years, and 100% (4/4) for children older than 6 years of age.

Group mean data for R_{rs} and X_{rs} at 6, 8, and 10 Hz as well as the within-test variability are reported in Table 2. A smaller number of acceptable measurements for R_{rs6} were obtained due to coherence <0.95 (n = 143). There were no significant sex differences in any variable. The prediction equations for the relationship between height (Ht) and respiratory impedance were determined and the standard deviation of residuals (RSD) calculated. The result for the frequencies of 6, 8, and 10 Hz is shown in Table 3. Weight, age, personal and parental history of atopy, as well as ETS exposure did not significantly affect Z_{rs} after taking height into account. The relationship between height and R_{rs} and X_{rs} at 8 Hz for study population is shown in Figure 1.

Short-term repeatability of the test was assessed in 44 children. A smaller number of acceptable measurements for R_{rs6} were obtained due to coherence <0.95 (n = 37). CR for R_{rs} and X_{rs} at 6, 8, and 10 Hz is shown in Table 4. The difference between the two repeated measurements was not correlated to the mean values of the two measurements (data not shown).

BDR was assessed in 154 children. R_{rs8} and X_{rs8} changed significantly after salbutamol (baseline R_{rs8} 8.49 hPa s L^{-1} <u>versus</u> post-salbutamol R_{rs8} 7.40 hPa s L^{-1}, $P < 0.001$; baseline X_{rs8} −2.44 hPa s L^{-1} versus post-salbutamol X_{rs8} −1.73 hPa s L^{-1}, $P < 0.001$). The 5th percentile for the absolute R_{rs8} BDR was −3.16 hPa s L^{-1},

TABLE 3— Regression Relationship Between Respiratory Impedance and Height in the Study Population

	Equation	RSD	R-square	P-value
R_{rs6}	$23.452 - (0.139 \times Ht)$	1.79	0.204	<0.001
R_{rs8}	$22.692 - (0.132 \times Ht)$	1.70	0.202	<0.001
R_{rs10}	$21.453 - (0.123 \times Ht)$	1.52	0.216	<0.001
X_{rs6}	$-11.990 + (0.081 \times Ht)$	0.84	0.280	<0.001
X_{rs8}	$-9.584 + (0.066 \times Ht)$	0.91	0.182	<0.001
X_{rs10}	$-9.001 + (0.063 \times Ht)$	0.94	0.158	<0.001

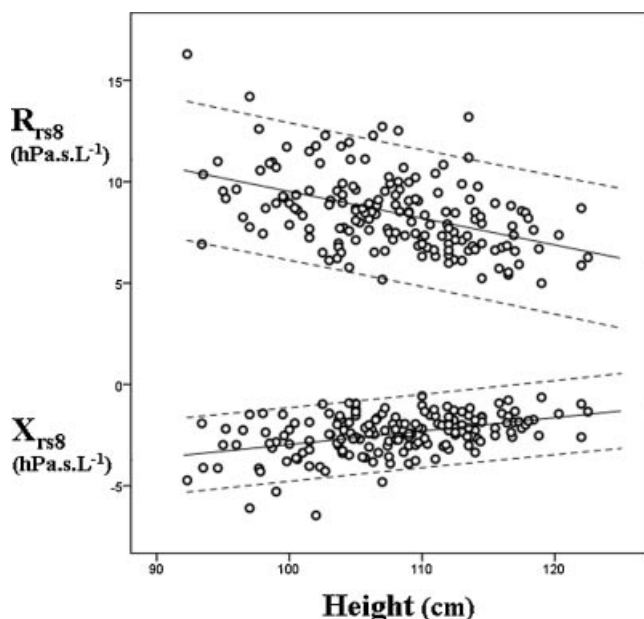RSD, standard deviation of residuals; Ht, height in centimetres.

Fig. 1. Relationship between height and respiratory impedance Z_{rs} at 8 Hz in preschool children. The single values are expressed as circles, the regression line and the 95% confidence intervals are shown as solid lines. Respiratory resistance at 8 Hz (R_{rs8}). Respiratory reactance at 8 Hz (X_{rs8}).

whereas the 95th percentile for the absolute X_{rs8} BDR was $2.25 \, hPa\, s\, L^{-1}$. These cut-off values corresponded to a percent change with respect to baseline of -34% and 61%, respectively, and a change in the Z-score of -1.88 and 2.48, respectively. The changes in all three indices of bronchodilation were related to the magnitude of the baseline measurement for both R_{rs8} and X_{rs8} (Table 5, Fig. 2). BDR, expressed as a percent of baseline, was correlated with height for R_{rs8} ($r = 0.18$, $b = -0.386$, $P = 0.029$), but not for X_{rs8} ($r = 0.13$, $b = 0.712$, $P = 0.112$). No significant correlations were found between height and absolute BDR ($r = 0.09$, $b = -0.017$, $P = 0.287$ for R_{rs8}; $r = 0.20$, $b = -0.002$, $P = 0.805$ for X_{rs8}) or change in Z-score ($r = 0.09$, $b = -0,010$, $P = 0.287$ for R_{rs8}; $r = 0.02$, $b = -0.003$, $P = 0.805$ for X_{rs8}).

Using the Australian equations[18] to calculate Z-scores for Italian children and comparing then with Z-scores

TABLE 4— Mean Absolute and Relative Coefficient of Repeatability (CR) for R_{rs} and X_{rs} at 6, 8, and 10 Hz.

	Absolute CR ($hPa\, s\, L^{-1}$)	Relative CR (%)	n
R_{rs6}	2.18	26.90	37
R_{rs8}	1.53	18.78	44
R_{rs10}	1.29	16.45	44
X_{rs6}	1.17	40.85	37
X_{rs8}	0.91	39.22	44
X_{rs10}	0.89	43.37	44

TABLE 5— Different Indices of Bronchodilation for R_{rs} and X_{rs} at 8 Hz and Their Relationship With the Magnitude of the Baseline Measurement Expressed As r (Correlation Coefficient) and b (Regression Coefficient)

	r	b	P
R_{rs8} absolute change	0.49	-0.317	<0.001
X_{rs8} absolute change	0.67	-0.523	<0.001
R_{rs8} change in percent baseline	0.30	-2.249	<0.001
X_{rs8} change in percent baseline	0.33	-11.525	<0.001
R_{rs8} change in Z-score	0.49	-0.189	<0.001
X_{rs8} change in Z-score	0.67	-0.574	<0.001

calculated using the Italian equations from the present study showed minor differences for R_{rs10} (0.23, $P = 0.036$), X_{rs8} (0.32, $P = 0.012$), and X_{rs10} (0.65, $P < 0.001$). No significant differences were found for R_{rs6} (-0.02, $P = 0.82$), R_{rs8} (0.10, $P = 0.43$), and X_{rs6} (-0.02, $P = 0.68$). The equations for R_{rs8} and X_{rs8} for both the Australian and the Italian populations are shown in Figure 3.

DISCUSSION

The results of the present study confirm that the FOT is feasible and is a potentially useful tool for evaluating lung function in preschool children. With this study, we provide reference data for Italian children. In addition, we have shown that the technique is repeatable and appropriate for assessing bronchodilation as change in R_{rs} or X_{rs} Z-score.

According to the most recent ATS/ERS recommendations[1] the measurements should be considered acceptable primarily based on the coefficient of variability (CV) of the individual frequencies. In the present study, measurements in which three or more individual frequencies had a coherence of <0.95 were excluded. Rejecting data at a single frequency where the coherence is <0.95 is important as this provides a recognized standard for quality control and is built into the software of the I2M FOT device. Data with lower coherence suggests low signal to noise ratio and a violation of the underlying assumption of a linear relationship between the input and output signals. We recommend reporting R_{rs} and X_{rs} at 8 Hz as these data can be obtained from most children and are reproducible in the short term (Table 2).

From a clinical point of view it is very important to have appropriate reference data for a given population. FOT can be used in young or older children not able to perform spirometry. Knowing the reference equation it is possible to detect abnormal lung function and, as previously mentioned, FOT can then be used in the follow-up of children with lung diseases such as asthma, neonatal chronic lung disease, or cystic fibrosis or asthma.[5,7–9,13–14] The reference equations calculated from the healthy Italian children in the present study are very similar to those published by Hall et al.[18] from Australian children
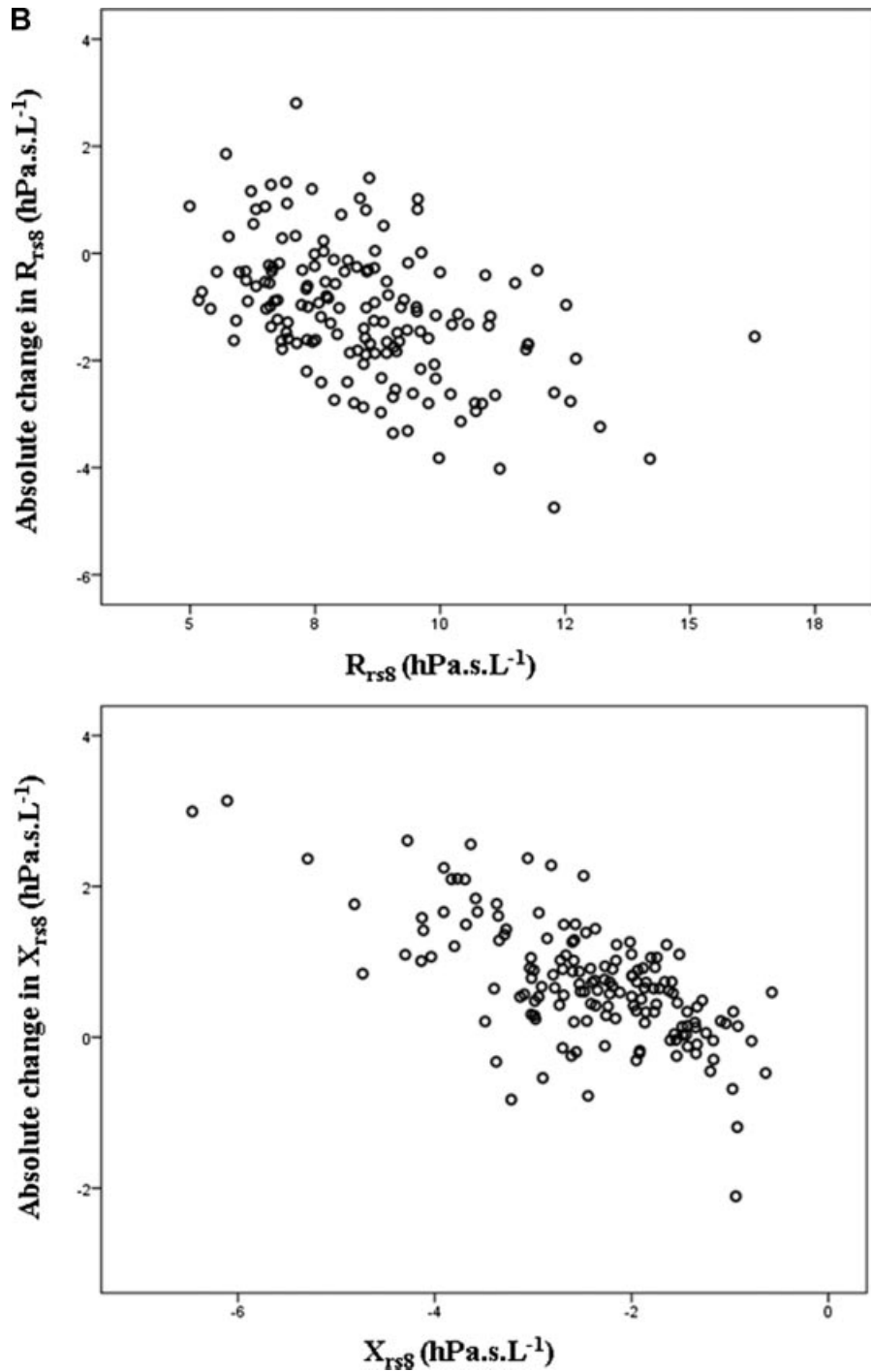
Fig. 2. (*Continued*)

significant difference for R_{rs8} and only a minor difference for X_{rs8} was found. Both study populations were largely Caucasian and of similar age and height range. The Italian data were collected in the field whereas the Australian data were largely collected in a specialized pulmonary function laboratory. The similarity in the equations, as shown in Figure 3, encourages an effort to combine data sets from different parts of the world to provide an international

reference data set, as has been done for other techniques. Such a data set would also allow appropriate examination of potential influences on lung function, such as sex, atopy, family history of asthma, and atopy that are rarely significant in individual data sets due to limited sample size.

For the clinical interpretation of the measurements it is necessary to consider the repeatability of the test. In the
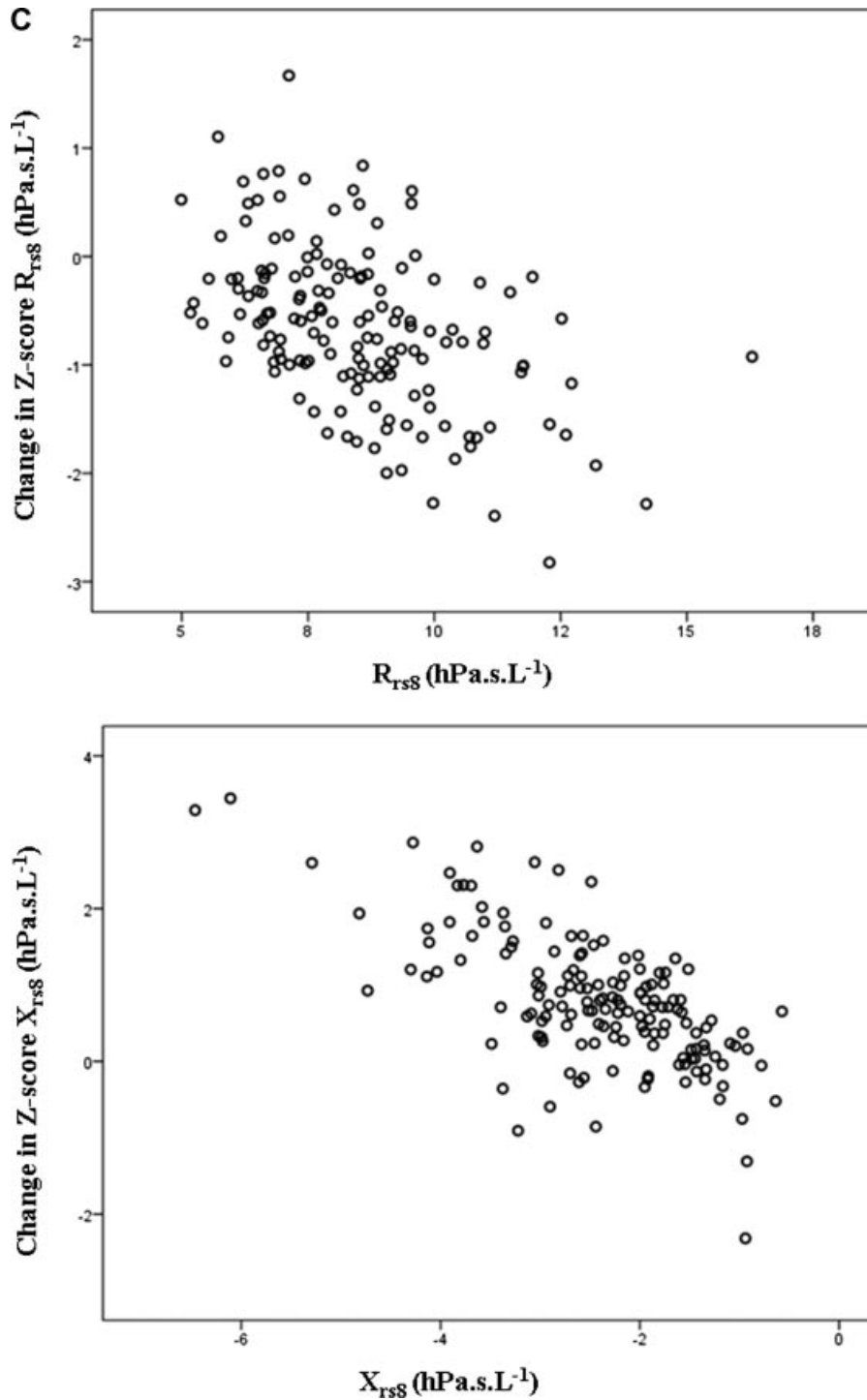
Fig. 2. (*Continued*)

current study, between-measurement repeatability was defined as absolute CR (2 ×SD of the difference between the repeated measurements made 15 min apart), according to the international recommendations,[1] and relative CR (2× SD of the difference between repeated measurements as a percentage of the mean of the two measurements). We have reported an absolute and a relative CR for R_{rs8} and for X_{rs8} (as shown in Table 4) that are similar to other previously published between-measurement repeatability values.[18–20] This short-term CR describes the variability introduced by having the child make two sets of measurements 15 min apart. Sources of variability that may contribute to this CR include: different breathing pattern; different level of engagement and co-operation by
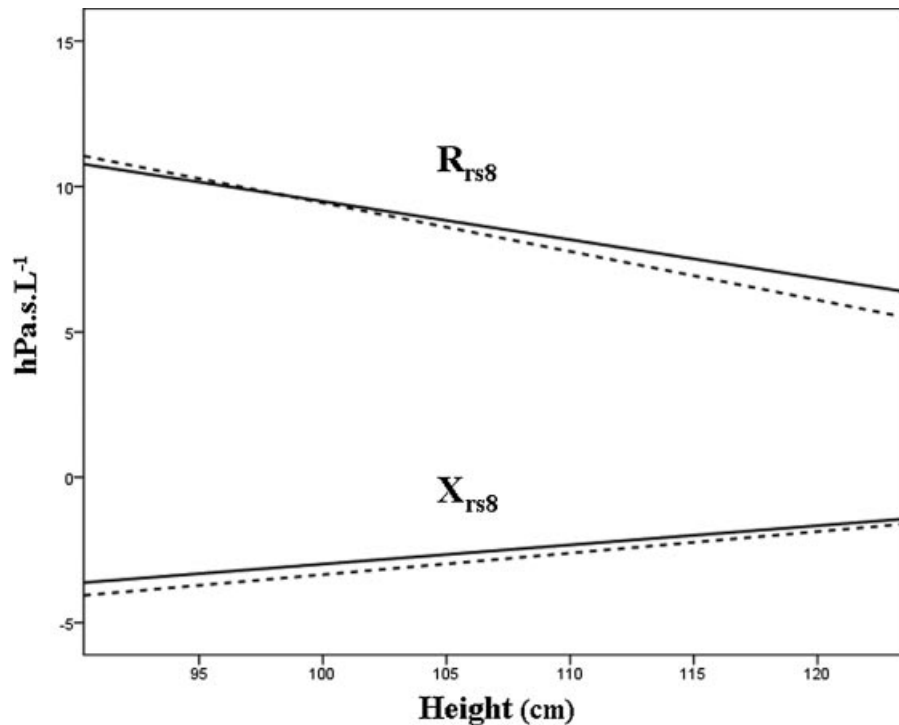
Fig. 3. Predicted values for respiratory resistance (R_{rs8}) and reactance (X_{rs8}) at 8 Hz using the equations by Hall et al.[18] (dashed lines) and the equations reported in the present study (full lines).

the child; and any minute to minute fluctuations in airway calibre due to changes in airway tone. It is reasonable to expect that true changes in the physiological state of the lungs will be minimal in healthy children over this time interval. Knowledge of these short-term changes in measured lung function without any therapeutic intervention are vital to interpreting true changes due to salbutamol inhalation. However, in the present study, we have found that the change in lung function in healthy preschool children after salbutamol was higher than the short-term variability of the test, reflecting a true BDR and highlighting the importance of cut-off for BDR based on measurements in healthy preschoolers.

In the present study, we assessed BDR using R_{rs} and X_{rs} at 8 Hz as these were previously recommended by Thamrin et al.[10] Our data onfirm their earlier data that the change in both R_{rs} and X_{rs} following bronchodilator was related to the magnitude of the baseline values. In our study, we have found a correlation between BDR expressed as a percent of baseline and height for R_{rs8}. BDR, as measured by FOT, is an expression of the change in airway caliber following inhalation of a bronchodilator. The change in R_{rs} is directly related to the increase in airway caliber of conducting airways, that is, those airways in which gas movement occurs by bulk flow. Although, X_{rs} primarily reflects the elastic and inertive properties of the respiratory system, the mechanical properties of small airways, that is those in which gas

movement occurs by facilitated diffusion, are also included. Thus, the change in X_{rs} with bronchodilator is more complex. The airways become larger and the respiratory system becomes less stiff with growth and development, reflected here by both baseline lung function and height. Thus, it is not surprising that we found a relationship between the magnitude of the BDR and both baseline lung function and height. Oostveen et al.[14] have recently argued that using absolute change in lung function to express BDR avoids hiding differences in baseline bronchomotor tone, which they implied underlies the difference in baseline lung function in children with different wheeze phenotypes. However, as argued by Thamrin et al.[22] correcting for differences in airway caliber due to size rather than underlying bronchomotor tone is critical to getting the clinical interpretation correct. Normalizing lung function to the child's height, as occurs by using Z-score or expressing lung function as a percent of the predicted value, should remove height-dependence of the BDR. Indeed, in the present study by using Z-scores to represent R_{rs8} and X_{rs8} the change in lung function following bronchodilator was no longer related to the child's height. This finding is similar to that reported by the Australian group.[18]

The major difference between our study and the one from Thamrin et al.[10] is the use of 600 µg of salbutamol to assess BDR whereas 200 µg was used in the present study. Despite this difference, the change in both R_{rs8} and X_{rs8}

with salbutamol was similar, being 40% and 35%, respectively, for R_{rs8} and 65% and 61%, respectively, for X_{rs8}. The similarities in BDR despite the substantial difference in salbutamol dose show that 200 µg is sufficient for healthy children and likely reflects a relatively flat dose–response curve in such children. Other studies have reported similar changes in lung function following bronchodilatation measured with FOT in asthmatic children[13] or with different wheezing phenotypes.[14]

In conclusion, the data from the present study give the reference equation for R_{rs} and X_{rs} for Italian children between 2 and 6 years of age. The data also demonstrate that healthy Italian preschool children have similar lung function, as assessed by the FOT using the similar commercially available equipment, to healthy Australian preschool children. In addition, we have demonstrated that the most appropriate index for determine BDR is a decrease in R_{rs8} Z-score of ≥ 1.88 or an increase in X_{rs8} Z-score of ≥ 2.48 in preschool children.

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