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Total specific airway resistance vs spirometry in asthma evaluation in children in a large real-life population

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ABSTRACT

Background: Total specific airway resistance (sRtot) has been introduced as an alternative technique to assess lung function with a particular application to younger children with asthma.

Objective: To establish a diagnostic value of the body plethysmographic parameter (sRtot) in asthma diagnosis in young children.

Methods: This was a prospective, noninterventional study. Children 4 to 18 year old with symptoms suggestive of asthma were included (n = 885). Subjects underwent body plethysmography and spirometry (when capable) with reversibility tests. Of 788 subjects who could perform spirometry in addition to body plethysmography, 578 were diagnosed with asthma. Subjects with asthma were treated for minimum of 6 months and then their asthma was confirmed or refuted.

Results: In 471 patients, asthma diagnosis was confirmed after 6 months of antiasthmatic treatment; 142 patients were 4 to 6 years old and 329 were 7 to 18 years old. Change in response to bronchodilator in children with asthma was significant for sRtot ($P = .02$) but not for forced expiration volume in 1 second ($P = .21$); sRtot was more sensitive and specific in identifying children with reversible obstruction than spirometry. There was a significant association between sRtot and asthma diagnosis in patients 4 to 6 years old (odds ratio 1.02, 95% confidence interval 1.01–1.03, $P = .001$); to differentiate subjects with asthma from those without asthma, the optimal cutoff point for sRtot was 174.5%. A sRtot value higher than 174.5% was associated with a positive prediction of an asthma diagnosis in patients 4 to 6 years old. A ratio of forced expiration volume in 1 second to forced vital capacity below 80% was not significantly associated with asthma.

Conclusion: These data support the recommendation of performing sRtot rather than spirometry in young children as a fairly sensitive marker of asthma.

Trial Registration: www.ClinicalTrials.gov (NCT01805635).

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Introduction

Asthma is a clinical diagnosis and there is no single diagnostic test for the disease.¹ The ability to objectively measure lung function in young children is critical for the diagnosis and assessment of asthma severity in this age group. According to current guidelines, spirometry is considered the primary method to detect the air flow limitation associated with asthma in children older than 5 years.² However, a recent study has indicated that

only 21% of physicians use spirometry in the diagnosis of asthma in children.³ This could be due to the difficulty in interpretation of results in a younger group and the fact that young children might be technically unable to perform spirometry, because it requires a deep inhalation (which can alter airway resistance).^{4,5} Air flow limitation is a result of many factors and increased airway resistance is one of them. Airway resistance is traditionally measured by relating air flow and driving pressure using body plethysmography, thus deriving total airway resistance (Rtot) and total specific airway resistance (sRtot). In this setting, sRtot has been introduced as an alternative technique to assess lung function with a particular application to younger children with asthma. This is because sRtot is noninvasive, easy to perform, and requires only minimal patient cooperation and could provide more sensitive measurements of airway resistance.

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The purpose of the present study was to prospectively compare the utility of sRtot and spirometry in the evaluation of young children with well-controlled asthma in a typical pediatric outpatient clinical allergy setting vs children without asthma. This was accomplished by assessing lung function by sRtot and comparing the findings with the measurement of lung function by spirometry. Response to bronchodilator was assessed using standard cutoff values for reversibility. The authors hypothesized that sRtot would be superior to spirometry in differentiating young children with asthma from those who did not have asthma. Thus, the authors determined the effectiveness of sRtot vs spirometry in children for sensitivity and specificity.

Methods

Study Design

This was a prospective, noninterventional study. All children 4 to 18 years old with symptoms suggestive of asthma, who were referred to the authors' allergy outpatient clinic from January 2010 through December 2012, and who could perform body plethysmography at their initial evaluation were entered into the study. Eight hundred eighty-five children met these criteria; children were divided into 2 age groups: 4 to 6 and 7 to 18 years old. Subjects who were evaluated underwent a history, physical examination, and whole-body plethysmography and spirometry (when capable). A diagnosis of asthma was established by physicians according to Global Initiative for Asthma (GINA) guidelines for asthma, which include symptoms of asthma, findings on physical examination of the respiratory system, improvement in pre-bronchodilator forced expiration volume in 1 second (FEV₁) of at least 12% (spirometry, when capable), improvement in the pre-bronchodilator specific airway resistance of at least 25% (body plethysmography) after administration of salbutamol (200 µg), and allergen sensitization.^{1,2} Of the 885 children entered into the study, 788 could perform spirometry in addition to body plethysmography and 517 of them were diagnosed with asthma. Eleven percent of children could not perform spirometry, and 95% of them were 4 to 5 years old. The data collected from the children unable to perform spirometry were omitted from the analysis.

Patients were classified as having atopy based on history and skin prick testing. In patients unable to undergo skin testing, a serum specific IgE for a specific allergen was used.

All subjects with an asthma diagnosis were treated by their physicians according to GINA guidelines for minimum of 6 months and their asthma was confirmed or refuted.

The study was approved by the medical ethics committee of the Medical University of Lodz (Lodz, Poland). All parents or guardians of the patients gave their oral and written consent for the evaluation of data from medical documentation of their children. The study is registered at www.ClinicalTrials.gov (NCT01805635).

Allergen Sensitization

Skin prick testing to standard allergen extracts was performed using Allergopharma (Reinbek, Germany). A reaction wheal larger than 3 mm in diameter than the negative control recorded at 15 minutes was considered positive.

Measurement of serum specific IgE was used when necessary. Allergen sensitization was defined as a specific IgE level of at least 0.35 kU/L for at least 1 of the tested allergens (chemiluminescence method; Immulite 2000, XPI, Siemens, Berlin, Germany). For this study, allergy was defined as a serum IgE level of at least 0.35 kU/L specific for allergens (ie, dust mites, molds, cat and dog dander, grasses, wild grasses, and trees pollens).

Pulmonary Function Tests

Pulmonary function testing (body plethysmography and spirometry) was performed with a Master Screen unit (Erich Jaeger GmbH, Hochberg, Germany). Flow and volume were measured with a pressure-screen-type pneumotachograph that was calibrated daily. The sequence of measurements was whole-body plethysmography and then spirometry. Measurements were carried out in a familiar and quiet room. Standing height and weight were assessed: subjects were measured without shoes and wearing light summer clothing. During measurements, children were instructed to sit upright, and a nose clip and a non-compressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls provided by the lung function test equipment manufacturer. All pulmonary function tests were performed by 1 trained research technician according to American Thoracic Society and European Respiratory Society standards.^{6–8}

Total Specific Airway Resistance

Measurements were made during tidal breathing. The sRtot was measured in a constant-pressure body plethysmograph as the relation between simultaneous variations in respiratory flow and maximum changes in plethysmographic pressure during inspiration and expiration. The sRtot was calculated from the S-shaped resistance loops presented graphically by the computer connected to the plethysmograph. The relation between flow and pressure was displayed on line. The measurement was rejected if any alteration in the shape of the resistance loops was seen, because this could reflect face mask leakage, coughing, swallowing, or vocalization. Compensation for body temperature, barometric pressure, and water vapor-saturated conditions was performed electronically.⁹ The respiratory rate was 30 to 45 breaths/min. The mean value of 3 sequential measurements of sRtot was used as the result. When airway reversibility was being assessed, a bronchodilator was administered (200 µg of salbutamol) using a spacer. After 15 minutes, the sRtot measurement was repeated. Improvement in the pre-bronchodilator sRtot of at least 25% was used.

Spirometry

The highest of 3 successful measurements was taken and analyzed. The results were expressed as the percentage of a predicted value. Where applicable, a standard cutoff of 12% for reversibility was used.⁶

Statistical Methods

During the statistical analyses, stepwise binary logistic regression models were used to pinpoint which factor(s), taking into account the body plethysmographic and spirometric results, most significantly indicated the degree of asthma control in the examined patients 4 to 6 and 7 to 18 years old. In addition, Pearson product-moment correlation coefficients for the studied parameters were obtained separately for participants 4 to 6 and 7 to 18 years old. After selecting a factor that tended to influence the degree of asthma control, a receiver operating characteristic (ROC) curve was drawn, in addition to an area under the curve, sensitivity and specificity values, a cutoff point, and, hence, the clinical usefulness of assessing the degree of asthma control based on statistically meaningful factors, as described earlier.

All statistical computations were carried out using the STATA 12.1 Special Edition computer package (StataCorp LP, College Station, Texas). *P* values less than .05 were considered statistically significant.

Table 1

Descriptive statistics for parameters measured in the examined patients by age group and occurrence of asthma

Study group	Parameter	With asthma		Without asthma		Overall	
		Mean	SD	Mean	SD	Mean	SD
4–6 y old	Age (y)	4.98	0.96	5.21	0.80	5.07	0.90
	sRtot ^a	212.27	84.29	155.61	50.27	189.76	77.65
	RV ^b	171.31	99.24	187.48	108.58	177.77	102.97
	FVC ^c	96.96	18.06	84.22	20.16	95.88	17.87
	FEV ₁ ^d	101.00	19.83	100.52	20.90	100.81	20.19
	FEV ₁ /FVC ratio ^e	103.55	8.66	104.46	14.52	103.91	11.30
7–18 y old	Age (y)	11.08	2.77	12.29	2.44	11.45	2.73
	sRtot ^a	185.94	80.46	188.00	86.31	186.59	82.23
	RV ^b	134.82	94.41	154.23	91.33	140.91	93.73
	FVC ^c	96.29	12.74	96.29	12.71	96.29	12.71
	FEV ₁ ^d	97.35	13.64	97.55	15.44	97.41	14.21
	FEV ₁ /FVC ratio ^e	100.88	8.73	100.65	10.14	100.81	9.18

Abbreviations: FEV₁, forced expiration volume in 1 second; FVC, forced vital capacity; RV, residual volume; sRtot, total specific airway resistance.

^a*P* = .924, statistically significant between-group differences.

^b*P* < .001, statistically significant between-group differences.

^c*P* = .142, statistically significant between-group differences.

^d*P* < .001, statistically significant between-group differences.

^e*P* < .001, statistically significant between-group differences.

Results

Seven hundred sixty-eight children were included in the analysis: 517 with asthma and 251 without asthma (the absolute number of patients who performed whole-body plethysmography and spirometry); 20 patients were excluded because testing data were incomplete. Change in response to bronchodilator in children with asthma was significant for sRtot (*P* = .02) but not for FEV₁ (*P* = .21). In 471 patients, the asthma diagnosis was clinically confirmed after 6 months of antiasthmatic treatment; 142 patients were 4 to 6 years old (30%) and 329 were 7 to 18 years old (70%); 297 were considered to not have asthma. Perennial and seasonal allergies were diagnosed in 13 patients 4 to 6 years old (18.6%) vs 52 patients 7 to 18 years old (15.8%, *P* = .569). Clinical characteristics of the patients by age group and occurrence of asthma are presented in Table 1.

Association Analysis

Binary logistic regression analysis showed the following significant association with asthma: elevated sRtot levels in patients 4 to 6 years old (odds ratio 1.02, 95% confidence interval 1.01–1.03, *P* = .001). All other variables in the 2 age groups (listed in Tables 2 and 3) were not associated with an asthma diagnosis and they did not differentiate those with asthma from those without asthma. Descriptive statistics for whole-body plethysmographic and spirometric measurements in the examined patients by age group and occurrence of asthma are presented in Table 4.

Table 2

Computed Pearson product-moment correlation coefficients for investigated whole-body plethysmographic and spirometric measurements, with corresponding *P* values, in the examined patients 4 to 6 years old

	RV		FVC		FEV ₁		FEV ₁ /FVC		Age	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
sRtot	–0.078	.379	0.188	.025	0.091	.281	–0.166	.049	0.009	.909
RV		.069	0.435	.122	0.166	.002	0.977	–.038	0.666	
FVC			0.915	<.001	–0.148	.079	–0.081	.339		
FEV ₁				.126	0.134	.146	0.082			
FEV ₁ /FVC					–0.189	.024				

Abbreviations: FEV₁, forced expiration volume in 1 second; FEV₁%, percentage of predicted forced expiration volume in 1 second; FVC, forced vital capacity; RV, residual volume; sRtot, total specific airway resistance.

ROC Curve Analysis

The ROC curve illustrates the clinical usefulness of the identified determinant, which was extracted based on the empirical data (Fig 1). The other measurements did not differentiate those with asthma from those without asthma.

Because there was a significant association between sRtot and asthma diagnosis, the optimal cutoff point was established using sRtot curve analysis to differentiate those with from those without asthma. For sRtot, the area under the ROC curve was significantly higher than the reference (0.5) at 0.743.

The optimal cutoff point for sRtot was 174.5%. The sRtot was included in the next step of the analysis as a categorized variable, and a sRtot higher than 174.5% was defined as the asthma-predicting sRtot.

Subgroup Association Analysis

According to the results of binary logistic regression analysis, the association of the 2 subgroups (subjects 4–6 and 7–18 years old with and without asthma) was analyzed. The asthma-predicting sRtot increased the risk of asthma in patients. The asthma-predicting sRtot increased the risk of asthma in subjects 4 to 6 years old regardless of sensitization to allergens. A ratio of FEV₁ to forced vital capacity (FVC) below 80% was not significantly associated with asthma in patients 4 to 6 and 7 to 18 years old.

Diagnostic Value

Sensitivity, specificity, positive predictive value, and negative predictive value of the asthma-predicting sRtot in patients 4 to 6 years old are presented in Figure 1.

Sensitivity, specificity, positive predictive value, and negative predictive value of the asthma-predicting sRtot in patients 7 to 18 years were 62.3%, 40.8%, 69.2%, and 32.8%, respectively. These values did not identify subjects with asthma in this subgroup.

Discussion

This study was performed to establish a diagnostic value of body plethysmographic parameters for diagnosing asthma in young children. The sRtot was associated with asthma diagnosis in patients 4 to 6 years old. In addition, sRtot was more sensitive and specific in identifying children with reversible obstruction than spirometry. Moreover, there was an increased risk of asthma diagnosis with a higher sRtot; the optimal value of sRtot for the clinical diagnosis of asthma was 174.5%. Furthermore, this parameter, categorized at the optimal cutoff point, was associated with a positive prediction of an asthma diagnosis (sRtot >174.5%) in patients 4 to 6 years old and was defined as the asthma-predicting sRtot. Moreover, when a sRtot lower than 174.5% was observed, the probability of an asthma diagnosis decreased. For a FEV₁/FVC ratio below 80%, FEV₁ reversibility was not significantly associated with asthma in patients 4 to 6 and 7 to 18 years old. When

Table 3
Computed Pearson product-moment correlation coefficients for investigated whole-body plethysmographic and spirometric measurements, with corresponding *P* values, in the examined patients 7 to 18 years old

	RV		FVC		FEV ₁		FEV ₁ %/FVC		Age	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
sRtot	0.217	<.001	−0.042	.455	−0.310	<.001	−0.467	<.001	−0.006	.919
RV		.002	0.969	−.133	0.025	−.214	<0.001	−.018	0.761	
FVC			0.807	<.001	−0.109	.052	0.139	.013		
FEV ₁				.461	<0.001	.120	0.032			
FEV ₁ %/FVC					0.004	.719				

Abbreviations: FEV₁, forced expiration volume in 1 second; FEV₁%, percentage of predicted forced expiration volume in 1 second; FVC, forced vital capacity; RV, residual volume; sRtot, total specific airway resistance.

spirometry and body plethysmography are performed, the present data support the recommendation of performing sRtot rather than spirometry in young children. The sRtot was a fairly sensitive marker of asthma, particularly to confirm asthma in very young children who have difficulty performing spirometry.

There are limited studies directly comparing body plethysmographic with spirometric parameters in a large population of young children. One study found that Rtot was more sensitive than FEV₁, forced oscillation technique, and resistance by the interrupter technique in detecting bronchoconstriction in normal subjects.¹⁰ As described by Child,¹¹ sRtot is an easy, cheap, noninvasive, and effort-independent measurement that is reproducible in children as young as 2 to 3 years old and is helpful in assessing bronchodilator responsiveness. Most recently, Beydon et al¹² found that interrupter resistance had poor sensitivity to detect baseline obstruction but fairly good sensitivity and specificity to detect reversibility in schoolchildren with asthma. Unfortunately, bronchial obstruction appears episodically in children with asthma and is rarely detected, which decreases the clinical value of such findings. Based on the bronchodilator response in the present patients who could perform spirometry and sRtot, sRtot was better than spirometry for identifying children with asthma and ROC curve analyses suggest it is a more sensitive and specific tool for distinguishing between these groups of children. The present data are consistent with other reports that have shown that significant differences in sRtot bronchodilator responses distinguish those with asthma from those without asthma, which is not detected by spirometry.¹³ Other limitations of spirometry include effort dependency, which affects testing in young children; the failure rate in the 4- to 6-year-old children in the present study was 10%. In these young children, a significant association between sRtot measurement and asthma diagnosis was found; moreover, this

association was significant only in preschoolers. The lack of importance of sRtot in other studies might be explained by its too high variability in schoolchildren or weak relation between baseline FEV₁ and sRtot, which has been reported.^{14,15} Beydon et al¹² found that the baseline relation between FEV₁ and sRtot was weak in large group of schoolchildren. The same could be true for other spirometric indices in the present study, based on previous results.^{16–21} This discrepancy also could be explained by an unspecific bias of sRtot measurement in preschoolers, such as cooperation, tonsil enlargement, or recurrent upper respiratory tract infections.

The authors previously sought to find the initial sRtot cutoff value that could confirm an asthma diagnosis.²² Surprisingly, this cutoff was higher than the border reference range and, in consequence, should be used in clinical practice to confirm a diagnosis of asthma in young children. Those results are supplemented with a new, probably optimal, value of sRtot for the confirmation of the clinical diagnosis of asthma in children younger than those in the previous cohort.²²

The role and significant value of a FEV₁/FVC ratio below 80% as a significant predictor of asthma in children are well known.² However, in the present study, a FEV₁/FVC ratio below 80% was not significantly associated with asthma in patients 4 to 6 and 7 to 18 years old.

The major strength of this study is the large sample, which overcomes the natural variability of lung function parameters and makes the present results more reliable. All patients participating in this study were under the regular care of allergy specialists from the authors' clinic, including physical examination, lung function measurements, and other necessary tests, which excludes any

Table 4
Odds ratios with 95% confidence intervals for age and investigated whole-body plethysmographic and spirometric measurements by occurrence of asthma in the examined patients by age group

Study group	Parameter	Occurrence of asthma		
		Odds ratio	95% CI	<i>P</i> value
4–6 y old	Age (y)	0.69	0.45–1.05	.084
	sRtot	1.02	1.01–1.03	.001
	RV	1.00	0.99–1.00	.551
	FVC	1.03	0.98–1.09	.219
	FEV ₁	0.97	0.93–1.02	.250
	FEV ₁ /FVC ratio	1.02	0.99–1.05	.150
7–18 y old	Age (y)	0.81	0.73–0.90	<.001
	sRtot	1.00	1.00–1.00	.699
	RV	1.00	0.99–1.00	.122
	FVC	1.07	0.97–1.17	.173
	FEV ₁	0.94	0.86–1.04	.236
	FEV ₁ /FVC ratio	1.06	0.97–1.16	.185

Abbreviations: CI, confidence interval; FEV₁, forced expiration volume in 1 second; FVC, forced vital capacity; RV, residual volume; sRtot, total specific airway resistance.

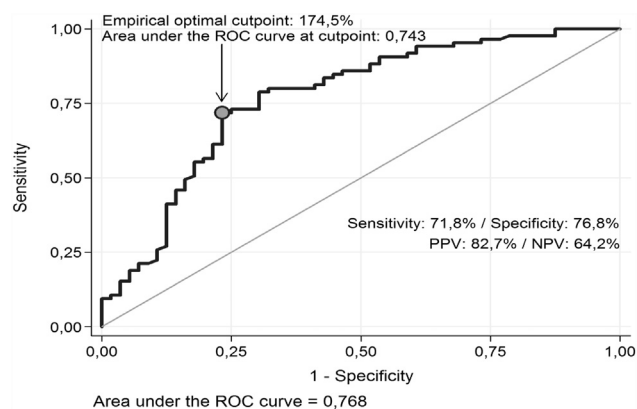


Figure 1. Receiver operating characteristic (ROC) curve illustrating the clinical usefulness of total specific airway resistance measurements in subjects 4 to 6 years old. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of asthma-predicting total specific airway resistance in patients aged 4 to 6 years old are presented.

doubts concerning the heterogeneity of diagnostic and therapeutic procedures. Therefore, all lung function tests were performed according to guidelines.^{6,7}

There has been a recent trend toward predicting asthma at school age in preschool children.²³ Guidelines define asthma by the presence of reversible airway obstruction, which requires the performance of spirometric tests and then bronchial provocation tests if the spirometric results are normal. To confirm asthma in young children who cannot perform spirometry, it would have been preferable if an additional test of bronchial hyperresponsiveness, such as reversibility of sRtot, had been included in the diagnostic procedure. According to the present results, all children with suspected asthma should be screened by sRtot as opposed to just analyzing histories. Such an approach helps confirm asthma in children with asthma-like symptoms. It is reasonable to treat symptomatic children with a high sRtot with an obligatory assessment of efficacy. The present results suggest that asthma-predicting sRtot, as defined in the present study, could serve as a reliable tool to in the evaluation of preschool children with asthma. The greater sensitivity and specificity of sRtot shown in this study in addition to its wider application in young children suggest incorporating body plethysmography into the standard guidelines for the management of asthma in children.

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