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The sensitivity and specificity of the forced oscillation technique in the diagnosis of bronchoconstriction in children

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ABSTRACT

Objective: The forced oscillation technique (FOT) is a useful diagnostic respiratory system for children. However, the final value of the FOT in the diagnosis of bronchoconstriction is still open. The aim of the study was to evaluate the sensitivity and specificity of the FOT vs. body plethysmography tests in the measure of bronchoconstriction in asthmatic children.

Materials and methods: A total of 102 children aged 2 to 6 years diagnosed with early-onset asthma and 52 healthy controls were included in this prospective, randomized study. All asthmatic patients and healthy controls underwent a basic FOT as one measurement, according to the recommendation of the Resmon Pro FOT. Then, the reversibility test was performed 20 min after the administration of 200 mg salbutamol using the FOT and body plethysmography in all patients.

Results: The mean basic Rrs, Xrs and sRaw in asthmatic patients were, respectively, 11.13 ± 1.28 kPa sL⁻¹, -4.6 ± 1.18 kPa sL⁻¹ and 1.72 ± 0.58 kPa s. Similar parameters were significantly better in the control group ($p < 0.05$). A total of 73 (71.6%) asthmatic patients had a positive test using the FOT according to Calogero. In 4 (7.7%) patients in the control group, a positive test was obtained. In body plethysmography, similar results were reached, with a positive test in 76 (74.5%) study patients and 5 (9.6%) control patients.

Conclusions: A bronchial reversibility test with the use of the FOT is useful for the diagnosis of bronchial asthma, especially with the use of an Rrs parameter, such as the body plethysmography test.

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Introduction

The FOT is a noninvasive and easy-to-use method to investigate pulmonary system mechanics (1). This method is especially useful for patients who cooperate poorly during spirometry tests. The FOT uses small amplitude pressure oscillations superimposed on normal breathing without any respiratory maneuvers. Therefore, it has an advantage over other lung functional tests. This method is not new; however, it raises questions regarding usefulness. Many variants of the FOT have been developed in terms of measurement configuration, oscillation frequencies and final assessment (1). Despite observations that the FOT is useful for children in the diagnosis of bronchoconstriction, this method is still unappreciated in clinical practice (1–6).

The impedance (Zrs) is the relationship between pressure (P) and airflow (V). It is a form of total resistance, computed as a sum of the in-phase and

out-of-phase relationships between P and V. The in-phase component is the real part of Zrs and was named respiratory resistance (Rrs), and the out-of-phase is presented by reactance (Xrs) (1).

Therefore, Rrs and Xrs parameters have basic and real meaning in practice and are measured during the breathing cycle. Rrs is very sensitive to the degree of obstruction of the main central airways, thus rendering them small airways. Xrs is a parameter that enables clinicians to determine how effectively the lung is being ventilated in its distal areas or how well air reaches the peripheral areas. Xrs falls below predicted values at low oscillating frequencies in the following conditions: peripheral obstruction, the presence of tidal expiratory flow limitation, alveolar gas trapping and/or the closing of alveolar units. The FOT cannot completely separate underlying restrictive and obstructive changes (1).

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Asthma is characterized by reversible bronchoconstriction, and the FOT also allows for the performance of the reversibility bronchial test, which is frequently impossible to do in children (2). However, few studies have analyzed baseline airway obstruction in asthmatic patients using the FOT (1). Data has shown that Rrs measured by the FOT in the lower range of the frequency spectrum differentiate healthy and asthmatic children. The role of Xrs seems to be less important. On the other side, the differences in both value of Rrs and Xrs between baseline measurement and after salbutamol volume are evaluated for bronchial reversibility tests (1,4).

The aim of the study was to evaluate the sensitivity and specificity of FOT (Rrs, Xrs) in the as a tool to assess bronchoconstriction in asthmatic patients and to compare it with the body plethysmography test.

Materials and methods

Study subjects

Patients diagnosed with asthma and a healthy control group were included in the study in three allergy outpatient centers in Poland. A screening of patients who met the inclusion criteria was conducted, as well as a randomization procedure, and 102 children from 2 to 6 years of age diagnosed with early-onset asthma were selected among all 194 prescreened participants. The screening was performed by pulmonologists and allergologists. A diagnosis of bronchial asthma was based on the Martinez criteria and clinical history (including an assessment with the Asthma Predictive Index), physical examination, differential diagnosis of bronchial obstruction and response to the included anti-inflammatory treatment (7). The number of included patients was based on a power calculation that took into account the expected effect size. The randomization procedure with random selection relied on the use of computer-generated numbers (Excel, version 14.3.0, 2015, Microsoft corporation, Poland). The control group included 52 healthy children in the same age range from families in which relatives presented with asthma (parents or grandparents). The children took part in preventive examination, including the FOT and body plethysmography reversibility tests, despite a lack of asthma symptoms. It was a voluntary program for children whose parents agreed and signed a separate consent form, including salbutamol use. There was also separate agreement of the Bioethical Committee (Warsaw, No 87921/18).

For the study group, the following inclusion criteria were used: 1) children aged 2 to 6 years were diagnosed

with chronic bronchial asthma, with a minimum of a 3-month history of the diagnosis, which was to be based on the Martinez criteria and clinical history (including an assessment with the Asthma Predictive Index (API); physical examination; differential diagnosis of bronchial obstruction; and response to the included anti-inflammatory treatment; 2) bronchial asthma during anti-inflammatory treatment (inhaled glucocorticosteroids or inhaled glucocorticosteroids + montelukast + short beta agonist) had to be present for a minimum of 3 months; and 3) informed consents by parents or legal guardians and patients (above 5 years of age) were signed and dated. For the control group, the following inclusion criteria were used: 1) no medical history or clinical evidence of bronchial asthma; and 2) informed consents by parents or legal guardians and patients (above 5 years of age) were also signed and dated. Patients were excluded from the study for the following reasons: a current active infection of the respiratory system, an infection of the lower respiratory tract 4 weeks prior to the study, chronic diseases other than bronchial asthma, pulmonary inflammation, or bronchiolitis that passed in the first year of life.

Study design

The study design was a prospective, randomized study. The study was approved by the Local Bioethical Committee in Poland.

Protocol

Physical examination

History of atopic diseases. Medical history and diagnosis of asthma (see criterion no. 1) were checked before lung function assessments.

Atopy was defined as the presence of allergic rhinitis and/or atopic dermatitis in participants. The results of skin prick tests on common allergens and serum concentrations of allergen-specific and total IgE were analyzed. A similar criterion was used to recognize atopy in the parents.

During the visit, a general physical examination was conducted, including a rhinoscopy examination and assessments of height and weight.

FOT

The study was performed using the Resmon Pro device (Restech SRL, Italy marketed by MGCD Diagnostic USA), in accordance with the guidelines and recommendations of the American Thoracic

Society/European Respiratory Society (ATS/ERS) (2,7). The device was calibrated every day. On the day of the study, patients were asked not to use bronchodilators. The study was performed using a single wave frequency of 8 Hz, which is suggested for children. The standards were adopted for the Caucasian race (4). The test was carried out in a sitting position with the head in a neutral position or with a slightly raised chin. The software analyzed the data recorded during a minimum of 10 calm breathing cycles. For data analysis, the parameters of the total Rrs value and inspiratory and expiratory components, as well as total Xrs and its inspiratory and expiratory components, were used. The validity of the measurement at 8 Hz was assessed automatically by the Resmon Pro software using the coherence function. At least three acceptable measurements were analyzed.

Reversibility of the bronchial obstruction test. After performing the initial FOT study, all participants inhaled the short-acting beta 2-agonist salbutamol MDI 200 mcg through an inhalation chamber (Aerochamber Plus, Trudell Medical International, London, ON, Canada). After 15 min of taking the drug, the FOT examination was performed again. The values of Rrs and Xrs were evaluated, including their inspiratory and expiratory components, before and after the administration of the bronchodilator.

For children, a bronchial reversibility test can be considered positive if the pre-post reduction in the total Rrs values measured at 8 Hz is $>32\%$ or $2.79 \text{ cm H}_2\text{O}/(\text{L/s})$ (8).

Body plethysmography

After 1 day, body plethysmography was performed with the reversibility test, as mentioned above, in the same period of time as the FOT. Whole-body plethysmography is a single-step method for measuring specific airway resistance (sRaw). The technical features and measurement procedures were based on Bisgaard (9). A bronchial reversibility test can be considered positive if the pre-post reduction in the total sRaw is 25%.

Statistical analysis

The Statistica 8.2 computer program (SaftPol, Kraków) was used for the statistical analysis of the results. The descriptive analysis of the results is presented as the mean and standard deviation. The analysis used Student's t-tests for related and unrelated samples, as well as chi-square tests for parameters that did have normal distributions. A receiver operating characteristic (ROC) curve was generated to determine the cutoff value corresponding to the best compromise between sensitivity and specificity, defined as the point of the curve closest to the upper left-hand corner. Statistical significance was assumed for $p < 0.05$.

Results

The characteristics of the groups are presented in Table 1. Basic Rrs had significantly higher mean values in patients with asthma than in participants in the control group (healthy): $12.16 \pm 2.17 \text{ (kPa sL}^{-1}\text{)}$ vs. 8.54 ± 1.88 ($p < 0.05$). There were no significant differences between groups for sRaw and Xrs.

There were no relationships among BMI, sex and FOT parameters ($p > 0.05$). The presence of atopic features in the patient or in his or her family did not affect the Rsr and Xrs values for $p > 0.05$.

A total of 76 (74.5%) asthmatic patients had a positive test using the FOT according to Calogero (8). In 5 (9.6%) patients in the control group, a positive test was obtained. With body plethysmography, similar results were found: 74 (72.5%) and 4 (7.7%) for study and control patients, respectively.

Values for analysis of resistance (R_{rs}), reactance (X_{rs}) and specific airway resistance (sRaw) at baseline in the studied groups are presented in Tables 2 and 3.

Sensitivity and specificity of FOT parameters to recognize asthma

The ROC curves shown in Figure 1 correspond to the sensitivity and specificity of possible cutoff points for changes between pre- and post-salbutamol values for

Table 1. Characteristics of the studied groups.

	Asthma (n = 102)	Control (n = 52)	p*
Age	4.9 ± 1.6	4.3 ± 1.9	NS
Women (%)	48.1	51.9	NS
Height (cm)	117.8 ± 8.9	112.8 ± 6.12	NS
BMI	12.63	13.11	NS
Atopy (%)	76 (74.5)	19 (36.5)	<0.05
Time from the diagnosis of asthma in months (%)	15.9 ± 4.8	—	NS
Atopy in family (%)	54 (52.9)	21 (40.4)	<0.05
R (%)	77 (75.5)	30 (57.6)	NS
AD (%)	17 (16.7)	6 (11.5)	<0.05

Legend: R – chronic rhinitis; AD – dermatitis allergica; * Student's t-tests for related samples or chi-square tests were used.

Table 2. The values of Rrs, Xrs and sRaw in the asthmatic groups.

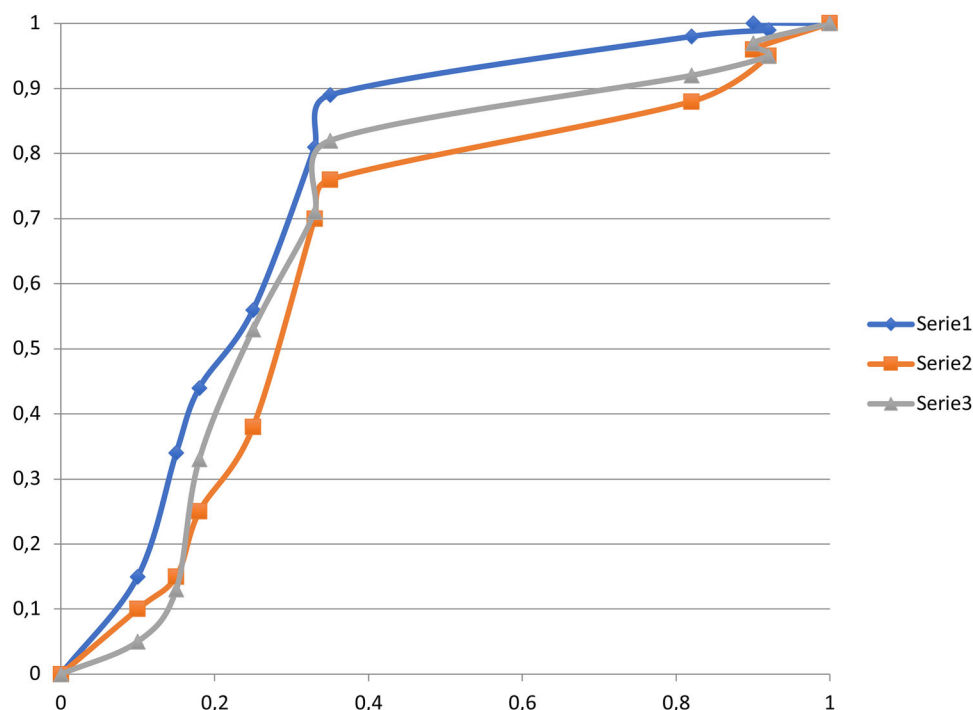
	R _{rs} kPa sL ⁻¹ R _{rs} (% of norm)	X _{rs} kPa sL ⁻¹ X _{rs} (% of norm)	sRaw kPa s (% of norm)
Mean ± SD % pred before bronchodilator	12.16 ± 2.17 (123 ± 19)	-4.32 ± 1.42 (127 ± 23)	1.42 ± 0.28 (129.7 ± 26)
Mean ± SD %pred after bronchodilator	6.88 ± 1.74 (89 ± 12)	-4.01 ± 1.23 (89 ± 7)	1.55 ± 0.83 (93 ± 6)
Δ (95%CI)	3.89(1.89-4.59)	2.21 (1.77-2.94)	1.7 (1.32-2.59)

Legend: Δ – differences between before and after bronchodilator; Rrs – resistance; Xrs –reactance; sRaw – specific airway resistance.

Table 3. The values of Rrs, Xrs and sRaw in the control groups.

	R _{rs} kPa sL ⁻¹ R _{rs} (% of norm)	X _{rs} kPa sL ⁻¹ X _{rs} (% of norm)	sRaw kPa s
Mean % pred before bronchodilator	8.54 ± 1.88 (92 ± 9)	-3.42 ± 1.27 (98 ± 6)	1.28 ± 0.6 (93.2 ± 7)
Mean %pred after bronchodilator	8.02 ± 2.43 (111 ± 15)	-2.72 ± 0.79 (94 ± 7)	1.15 ± 0.55 (92 ± 7)
Δ (95%CI)	0.81 (0.47-1.98)	0.69 (0.88-1.27)	0.1 (0.03-0.29)

Legend: Δ – differences between before and after bronchodilator; Rrs – resistance; Xrs –reactance; sRaw – specific airway resistance.

**Figure 1.** ROC curves corresponding to the sensitivity and specificity of possible cutoff points for changes in Rrs (diamonds), Xrs (squares) and sRaw (triangles) pre- and post-salbutamol for discriminating children with and without asthma.

Rrs, Xrs and sRaw to discriminate children with asthma from those without asthma.

The point of the ROC curve closest to the upper left-hand corner corresponded to a 35% decrease in Rrs after bronchodilator use and yielded 84% sensitivity and 75% specificity. For sRaw, a similar relationship was observed: a 32% decrease after bronchodilator use yielded 77% sensitivity and 79% specificity. A 23% change in Xrs after bronchodilator use yielded 56% sensitivity and 63% specificity.

Discussion

The FOT is a valuable method in the assessment of bronchoconstriction; however, it is difficult to

balance this method with other bronchial function tests (1,2,8–11).

The obtained results show that the measurement of the FOT can discriminate patients with asthma from healthy controls. These results could be used to confirm that the FOT is a useful tool in the diagnosis of asthma with the use of a reversibility test in children. However, it should be noted that asthma in children is diagnosed based on medical history and clinical symptoms (12). There are many different opinions regarding the role of Rrs and Xrs in the diagnosis of asthma. Some trials do not result in abnormal resistance and reactance in asthmatic children (2,10,11). Large discrepancies in the results are explained by various criteria for including children

with asthma, their different ages and different starting values.

The basic Rrs and Xrs values in healthy subjects were comparable to those of patients in the study by Calogero et al., who examined healthy Italian pre-school children (4,9).

The differences between Rrs and Xrs could be dependent on the frequencies that were used. In our studies, 8 Hz was used only because it was recommended by other authors (4,5,8) and also according to the ATS/ERS criteria (2). This restriction improves the quality of results and makes them more reliable. It was confirmed that Rrs measured by the FOT in the lower range of the frequency is significantly different between children with asthma and healthy children (1,2). The advantages of the low frequency range are more relevant to the mechanical properties manifested during spontaneous breathing (1,2). Therefore, many methods, including Resmon Pro devices, have been used. This method was also in accordance with the ATS/ERS recommendation. The low- and high-frequency FOT reveals different mechanical properties of the respiratory system, and it is still being studied (1,2).

Several studies compared the FOT with spirometry and/or whole body plethysmography in the assessment of airflow obstruction. Rrs measured by the FOT and body plethysmography (sRaw) showed good correlation, but relationships between the FOT and FEV₁. Hellincke et al. confirmed that FOT yields a body plethysmography test and that the FOT yields similar values but is not identical (8).

Some authors suggest that resistance measured by the FOT, especially at low frequency, is a highly reproducible index and is compatible with FEV₁; moreover, Rrs is a more sensitive parameter than FEV₁ for detecting airway obstruction (13,14). A similar observation with a good correlation between Rrs and sRaw was confirmed in this study.

Xrs has a weak value for the immediate diagnosis of airway obstruction, and it is difficult to compare it with FEV₁ and FVC (1). Therefore, it seems that Xrs has a lower value in asthma diagnosis. On the other hand, there are data that Xrs may be more sensitive than Rrs in detecting the response to bronchial challenge in small children (1).

The bronchodilator response using the FOT is also valuable for assessing patients with asthma and monitoring the effectiveness of therapy (15). Only 2% of healthy controls had positive results; this outcome is a positive predictor of the specificity of this method.

There are data that the best cutoff value to establish significant reversibility in response to salbutamol with

reference to an increase in FEV₁ > 10% predicted was a decrease in Rrs > -1 SD score equivalent or a 27.8 decrease in Rrs (16). This is significantly in line with the results obtained.

It is worth remembering that a reversibility test using spirometry is frequently impossible to perform for children, and the final results also have limited specificity and sensitivity. Our data are consistent with those based on an Italian population (9).

We also agree with Vu et al. that Rrs after salbutamol appears to be the most relevant parameter in asthma diagnostics, but the improvement in Xrs after salbutamol might indicate a reversal of airflow limitation during tidal breathing (3).

Our study has some limitations, including the low number of patients, which does not allow us to draw conclusions about standards and to better discriminate patients with asthma from control patients. We only focused on the FOT, and there were no accompanying spirometry tests that could be compared. Such attempts were made, but as a result of weak cooperation, it was not possible to use this method in further analysis. However, the results are proof that the FOT has an advantage in such diagnostics.

Conclusion

The FOT appears to be an important tool in asthma assessment in children. A bronchial reversibility test with the use of the FOT is valuable for the diagnosis of asthma, and this method is comparable with body plethysmography in such situations. Further studies are needed.

Conflict of interest

The authors report no conflict of interest

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