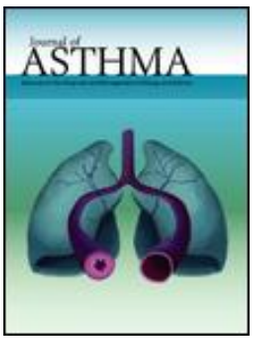

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DIAGNOSIS

Impulse oscillometry in acute and stable asthmatic children: a comparison with spirometry

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Abstract

Objective: Lung function tests have attracted interest for the diagnosis and follow-up of childhood asthma in recent years. For patients who cannot perform forced expiratory maneuvers, impulse oscillometry (IOS), performed during spontaneous breathing, may be an alternative tool. *Methods*: Thirty-five acute, 107 stable asthmatic and 103 healthy children who presented to our clinic performed IOS followed by spirometry before and after salbutamol inhalation. The mean baseline and reversibility of IOS and spirometry parameters were compared between the groups. Correlation analyses were undertaken within the asthmatics, and the healthy controls separately. To distinguish the three groups, the sensitivity and specificity of baseline and reversibility values of IOS and spirometry were computed. When spirometry was taken as the gold standard, the discriminating performance of IOS to detect the airway obstruction and reversibility was investigated. *Results*: The mean absolute values of Zrs, R5, R5−R20, X5, X10, X15, Fres, AX, and all spirometric parameters, and the mean reversibility values of R5, R10, Fres, AX and forced expiratory volume in one second were different between the groups and the highest area under curve values to discriminate the groups was obtained from area of reactance (AX) and ΔAX. Zrs, all resistance (including R5−R20) and reactance parameters, Fres and AX were correlated with at least one spirometric parameter. Spirometric reversibility was detected by ≤ -22.34 and ≤ -39.05 cut-off values of ΔR5 and ΔAX, respectively. *Conclusions*: IOS has shown a highly significant association with spirometric indices and reversibility testing. It may be a substitute for spirometry in children who fail to perform forced expiratory maneuvers.

Keywords

Childhood, impulse oscillometry, reversibility, spirometry

History

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Introduction

Asthma is the most common chronic respiratory disease in children [1]. Lung function tests can contribute to diagnosis, proper treatment and follow-up of asthmatic patients. Longitudinal monitoring of respiratory parameters allows early intervention, and improves prognosis [2,3].

Although there are a variety of tests, spirometry is the most commonly used lung function test, and it is also considered as the gold standard [4]. Unfortunately, some groups of patients, such as mentally retarded patients and young children, are not able to perform forced expiratory maneuvers. Moreover, during infancy, other lung function tests can be performed, but most of these are limited to the first 2 years of life, and have some high technical requirements [5].

Forced oscillation technique (FOT) is one of the several techniques, which has been used to obtain measures of respiratory function [5]. It was developed by Dubois et al. [6]. This method involves the application of pressure waves to the airway opening through a mouthpiece, and the measurement of respiratory system impedance from which resistance and reactance can be derived [7]. The impulse oscillometry system (IOS) is a type of FOT and was introduced by Jaeger Toennies GmbH (Hoechberg, Germany) in 1993. Rectangular waveform impulses are applied instead of pseudorandom noise signals, which have the advantage of generating a larger sample during measurements and emitting a continuous spectrum of frequencies that may provide more detailed characterization of respiratory function [8–10]. In this way, oscillometric techniques, which require only passive cooperation, have the potential to evaluate airflow limitation during tidal breathing. Therefore, it is an easily performed method for younger children and for those who cannot perform forced respiratory maneuvers.

Impulse oscillometry may be used to evaluate respiratory functions during an acute asthma attack as well as for the diagnosis and follow-up of asthma [8,11]. This technique has also been used to quantify the response to methacholine [12] and histamine [13] challenges in young asthmatic subjects.

The purpose of this study was to determine the relationship between IOS and conventional spirometry in acute and stable asthmatic, and healthy school-aged Turkish children. We also

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aimed to investigate if it was possible to use IOS as an alternative method to spirometry to diagnose and follow-up asthma.

Methods

Thirty-five children with acute asthma exacerbation, 107 children with stable asthma and 103 healthy children were recruited. Children who were diagnosed with asthma and who were being followed up in our department were all invited to take part in this study, and only those who consented were enrolled. Asthma was diagnosed according the National Heart, Lung and Blood Institute (NHLBI) asthma guideline [2]. None of the asthmatic children were on any medication at the time of their presentation. Asthma exacerbations were defined as an acute or subacute episode of progressively worsening shortness of breath, cough, chest tightness, tachypnea and wheezing, or some combination of these symptoms and physical examination findings [2]. Children presenting with these symptoms were assigned to the acute asthmatic group. Children were assigned to the stable asthma group if they met the criteria for well-controlled asthma as defined in the NHLBI asthma guideline for the last three months [2]. All asthmatic patients were of mild intermittant type. The healthy control group consisted of children who presented to other departments, and they were selected according to the following criteria: (1) No personal/family history of wheezing, asthma, allergic rhinitis or eczema; (2) No history of low birth weight, premature birth, neonatal mechanical ventilation or bronchopulmonary dysplasia; (3) No passive smoking in the house; (4) No upper respiratory tract infection in the previous two weeks; (5) Normal physical findings; (6) No facial/oral abnormality; (7) No obesity [10]. All children and their parents gave written informed constent prior to the study, and the study design was approved by the local ethics committee.

Children performed IOS and spirometry before and after 200 mcg salbutamol inhalation. Because of the possible effects of forced expiratory maneuvers on the bronchial motor tonus, first IOS, and then spirometry was performed [14].

IOS was performed in compliance with the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines [15] by MasterScreen Impulse Oscillometry system (JaegerCO, Wurzburg, Germany). The system was calibrated through a single volume of air (3 L) at different rates (flow) and also with a reference resistance device ($0.2\,kPa\,L^{-1}\,s^{-1}$) supplied by the manufacturer. Any short acting beta agonists were stopped 12 h prior to the application of IOS. Acute asthmatic children who had not taken any drugs before the presentation to our department performed lung function tests. Any children who had previously taken any medication were excluded from the study. IOS was performed during spontaneous breathing (see Supplementary material for details about the IOS procedure). The output pressure and flow signals were analyzed for 30 s in the frequency range of 5–20 Hz for their amplitude and phase differences to determine the resistance (R) and reactance (X), which are the components of impedance (Zrs). The IOS parameters obtained at the end of the application were resistances (R5, 10, 15, 20), and reactances (X5, 10, 15, 20) at 5–20 Hz, R5−R20 (resistance at 5 Hz minus resistance at 20 Hz), resonant frequency (Fres, the frequency where the X value is zero) and area of the reactance curve (AX, integral of X values from 5 Hz to Fres).

Spirometric measurements were performed by Master Screen Spirometry System (JaegerCO) according to the ATS guideline [10]. Calibration of the spirometer was done with volume, and corrected for body temperature and pressure. Age, sex and race were used for comparison with reference populations.

The children used nose clips and performed forced expiratory maneuvers. The best three technically acceptable blows were recorded and the best values were retained. Flow-volume curves were obtained. Spirometry results for forced expiratory volume in one second (FEV1), FEV1/forced vital capacity (FVC), maximum mid-expiratory flow (MMEF) were recorded. The software of spirometry automatically calculates the output for the predicted values and the percent predicted values of these parameters according to the participants' age, gender, weight and height.

To calculate the reversibility, difference between the absolute values of parameters obtained before and after salbutamol inhalation were divided by the absolute values before salbutamol, and the result was multiplied by 100.

If the values of FEV1 and/or FEV1/FVC were less than 80% of the percent predicted values and/or if the percent predicted value of MMEF was less than 60%, then it was accepted as spirometric airway obstruction. Spirometric reversibility is defined either by an increase in FEV1 of $\geq$12% and >200 mL from baseline after short-acting bronchodilator inhalation [2].

Statistics

For interval variables that follow the normal distribution, the three groups' mean values and standard deviations were compared by analysis of variance test, and for interval variables that do not follow the normal distribution by Kruskal–Wallis test. Post hoc analyses were performed by Bonferroni test. The correlations between IOS and spirometry parameters were analyzed by Pearson and Spearman analyses. The discriminating performance, sensitivity, and specificity values of IOS and spirometry to discriminate the three groups were investigated by receiver-operating characteristic (ROC) curves. When spirometry was taken as the gold standard, the discriminating performance of IOS to detect spirometric airway obstruction and reversibility according to predefined standardized spirometric criteria were investigated [16]. Statistical significance was set at $p<0.05$ (two-tailed). Data were analyzed using SPSS for Windows 16.0 and Med Calc.

Results

All children were aged 6–17 years. The mean age was 10.82 ± 2.53 (6–16) years for acute asthmatic, 10.57 ± 2.5 (7–17) years for stable asthmatic and 11.35 ± 2.54 (7–17) years for healthy children. Seventeen (48.5 %) of acute asthmatic children, 58 (54.2%) of stable asthmatic children and 55 (53.3%) of the healthy children were male. The groups did not differ from each other on mean age, height, weight and gender (Table 1).

The correlation between absolute IOS and absolute spirometry values before salbutamol inhalation was analyzed for healthy and asthmatic children separately. All IOS parameters were correlated with at least one spirometric parameter in both asthmatics and healthy controls (see Supplementary Tables 1 and 2).

The comparison of the mean baseline absolute IOS values, percent predicted spirometric values, and comparison of the mean reversibility values between acute asthmatic, stable asthmatic and healthy children groups are shown Table 2.

The discriminating power of baseline absolute IOS values and percent predicted spirometry values to discriminate the three groups was analyzed (Table 3). Baseline AX had the highest area under curve (AUC) for all comparisons between the three groups. For the AX parameter, the >6.12 kPa/L cut-off value distinguished acute and stable asthmatics with 85% sensitivity and 79.2% specificity, and the >6.32 kPa/L cut-off value distinguished stable asthmatics and healthy controls with 79.3% sensitivity and 83.1% specificity.

The discriminating power of reversibility values for IOS and spirometric indices was analyzed, and sensitivity and specificity according to different cut-off values were calculated (Table 4). The significant parameters that

Table 1. Age, gender, height and weight of children in this study.

	Acute asthma ($n = 35$)	Stable asthma ($n = 107$)	Healthy control ($n = 103$)	p Value
Age (years)	10.82 ± 2.53	10.57 ± 2.50	11.35 ± 2.54	0.08
Mean ± SD	(6–16)	(7–17)	(7–17)	
Male sex, n (%)	17 (48.5)	58 (54.2)	67 (65)	<0.001*
Height (cm)	144.68 ± 13.88	143.94 ± 14.04	146.78 ± 14.63	0.344
Mean ± SD	(109–175)	(120–182)	(119–175)	
Weight (kg)	40.37 ± 12.65	40.64 ± 16.11	(21–77)	0.948
Mean ± SD	(15–68)	(21–110)		

*Statistically significant between acute asthmatic and healthy control groups.

Table 2. Comparison of mean baseline and mean bronchodilator response values of acute asthmatic, stable asthmatic and healthy control children.

	Mean ± SD			p Value		
Parameter	Acute asthma ($n = 35$)	Stable asthma ($n = 107$)	Healthy control ($n = 103$)	Acute vs. stable	Acute vs. healthy	Stable vs. healthy
Baseline measurements						
Zrs (kPa L^{-1} s)	0.92 ± 0.27	0.78 ± 0.23	0.69 ± 0.22	0.008	<0.001	<0.001
R5 (kPa L^{-1} s)	0.86 ± 0.24	0.74 ± 0.22	0.67 ± 0.19	0.013	<0.001	0.012
R10 (kPa L^{-1} s)	0.68 ± 0.27	0.61 ± 0.17	0.55 ± 0.16	0.154	0.001	0.013
R15 (kPa L^{-1} s)	0.56 ± 0.15	0.57 ± 0.15	0.49 ± 0.14	0.808	0.015	0.001
R20 (kPa L^{-1} s)	0.51 ± 0.15	0.56 ± 0.15	0.46 ± 0.12	0.178	0.014	<0.001
R5−R20 (kPa L^{-1} s)	0.35 ± 0.18	0.24 ± 0.10	0.18 ± 0.11	<0.001	<0.001	0.009
X5(kPa L^{-1} s)	−0.29 ± 0.15	−0.22 ± 0.09	−0.19 ± 0.1	0.002	<0.001	0.011
X10 (kPa L^{-1} s)	−0.2 ± 0.12	−0.11 ± 0.07	−0.08 ± 0.18	0.001	<0.001	0.008
X15 (kPa L^{-1} s)	−0.15 ± 0.09	−0.09 ± 0.07	−0.06 ± 0.07	<0.001	<0.001	0.009
X20 (kPa L^{-1} s)	0.01 ± 0.07	−0.01 ± 0.6	−0.2 ± 0.6	0.06	0.004	0.864
Fres (Hz)	23.94 ± 6.14	18.87 ± 5.88	15.13 ± 5.72	0.014	0.003	0.015
AX (kPa/L)	2.16 ± 2.02	1.79 ± 1.25	1.23 ± 1.02	<0.001	<0.001	<0.001
FEV1 (%)	83.5 ± 19.5	95.7 ± 13.2	105.9 ± 13.9	0.012	<0.001	0.001
FEV1/FVC	72.51 ± 10.45	80.53 ± 7.99	87.58 ± 8.75	<0.001	<0.001	<0.001
MMEF (%)	52.3 ± 28.4	70.6 ± 24.5	100.7 ± 27.9	0.007	<0.001	<0.001
Bronchodilator response						
ΔZrs%	−12.34 ± 2.14	−14.31 ± 1.13	−16.13 ± 3.14	0.64	0.09	0.14
ΔR5%	−19.66 ± 14.31	−17.45 ± 10.77	−15.40 ± 12.28	0.011	0.013	0.015
ΔR10%	−16.55 ± 17.94	−13.68 ± 11.67	−9.12 ± 19.55	0.015	0.010	0.010
ΔR15%	−11.92 ± 17.84	−8.02 ± 36.25	−11.6 ± 12.93	0.230	0.072	0.123
ΔR20%	−14.55 ± 28.82	−11.16 ± 10.7	−9.07 ± 13.16	0.082	0.123	0.092
ΔR5−R20%	−31.00 ± 25.54	−35.86 ± 52.13	−29.12 ± 56.7	0.086	0.342	0.128
ΔX5%	−20.66 ± 30.65	−18.05 ± 36.45	−25.86 ± 47.88	0.213	0.096	0.423
ΔX10%	−23.39 ± 57.55	−43.67 ± 55.38	−34.97 ± 70.47	0.412	0.521	0.132
ΔX15%	−46.3 ± 47.68	−32.2 ± 24.87	−18.85 ± 134.2	0.276	0.089	0.091
ΔX20%	−46.91 ± 31.65	−77.06 ± 44.9	25.68 ± 43.61	0.097	0.063	0.119
ΔFres	−18.91 ± 21.49	−13.10 ± 31.64	−11.64 ± 15.64	0.010	0.014	0.015
ΔAX%	−47.32 ± 26.01	−42.82 ± 24.81	−37.87 ± 45.81	0.002	0.004	0.005
ΔFEV1%	13.20 ± 7.96	7.15 ± 7.17	5.21 ± 6.04	0.008	0.009	0.007
ΔFEV1/FVC	8.38 ± 9.9	5.79 ± 5.55	4.53 ± 8.51	0.354	0.414	0.086
ΔMMEF%	33.49 ± 24.36	27.49 ± 26.89	24.69 ± 31.35	0.059	0.076	0.110

Mean ± SD reversibility values are given. FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; MMEF, maximum mid-expiratory flow; Fres, resonant frequency; AX, area of the reactance curve. Bonferroni correction was applied.
Δ: The difference between the absolute values obtained before and after salbutamol inhalation were divided by the absolute values before salbutamol and the result was multiplied by 100.

Table 3. ROC curve analyses of baseline values to discriminate acute asthmatic, stable asthmatic and healthy children.

	Acute asthmatic vs. stable asthmatic					Acute asthmatic vs. healthy					Stable asthmatic vs. healthy				
	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value
Z5 (kPa L^{-1} s)	0.641	51.4	74.8	>0.92	0.01	0.724	62.9	74.8	>0.77	<0.0001	0.601	73.8	45.6	>0.61	0.0097
R5 (kPa L^{-1} s)	0.639	85.7	39.3	>0.66	0.01	0.616	74.3	48.5	>0.42	0.031	0.596	42.1	74.8	>0.77	0.0136
R10 (kPa L^{-1} s)	0.563	91.4	23.4	>0.48	0.26	0.649	94.3	26.2	>0.38	0.0309	0.614	80.4	43.7	>0.47	0.0033
R15 (kPa L^{-1} s)	0.535	57.1	54.2	>0.54	0.55	0.656	88.6	51.5	>0.42	0.0002	0.649	84.1	42.7	>0.43	0.0001
R20 (kPa L^{-1} s)	0.575	51.4	64.5	>0.48	0.17	0.560	68.6	74.8	>0.26	<0.0001	0.681	79.4	50.5	>0.43	<0.0001
R5−R20 (kPa L^{-1} s)	0.780	74.3	74.8	>0.25	<0.0001	0.756	68.6	74.8	>0.26	<0.0001	0.544	71	42.7	>0.23	0.02
X5 (kPa L^{-1} s)	0.628	37.1	88.8	≤0.33	0.02	0.747	71.4	70.9	≤0.14	<0.0001	0.602	58.9	63.1	≤0.02	0.0097
X10 (kPa L^{-1} s)	0.724	71.4	68.2	≤0.14	<0.0001	0.726	80	53.4	≤0.09	<0.0001	0.542	68.2	47.6	≤0.078	0.03
X15 (kPa L^{-1} s)	0.758	54.3	88.8	≤0.16	<0.0001	0.697	62.9	75.7	>0.02	0.0007	0.548	87.9	25.2	≤0.15	0.021
X20 (kPa L^{-1} s)	0.688	57.1	80.4	>0.03	0.21	0.769	68.6	79.6	>0.09	<0.0001	0.524	59.8	50.5	>−0.03	0.06
Fres (Hz)	0.638	94.3	34.6	>18.06	0.0059	0.664	88.6	48.5	>19.6	0.0012	0.524	21.5	90.3	>25.78	0.018
AX (kPa/L)	0.840	85	79.2	>6.12	<0.001	0.830	86.2	81.2	>7.01	<0.001	0.678	79.3	83.1	>6.32	<0.001
FEV1%	0.692	60	74.8	<88.5	0.0006	0.828	82.9	72.8	<100	<0.0001	0.694	72	67	<102.7	<0.0001
FEV1/FVC	0.712	57.1	79.4	<86.9	0.0001	0.827	77.1	82.5	<93.4	<0.0001	0.711	86.9	53.4	<104.2	<0.0001
MMEF%	0.727	62.9	79.4	<52	<0.0001	0.893	85.7	84.5	<72.7	<0.0001	0.792	76.6	76.7	<86.5	<0.0001

FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; MMEF, maximum mid-expiratory flow; Fres, resonant frequency; AX, area of the reactance curve.

Table 4. ROC curve analysis of reversibility values to discriminate acute asthmatic, stable asthmatic and healthy children.

	Acute asthmatic vs. stable asthmatic					Acute asthmatic vs. healthy					Stable asthmatic vs. healthy				
	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value	AUC	Sensitivity (%)	Specificity (%)	Cut-off (%)	*p* Value
ΔZ5	0.572	40	80.4	≤25.5	0.24	0.440	65.4	56.1	≤19.9	0.06	0.587	62.6	58.3	≤−14.9	0.028
ΔR5	0.720	71.3	88.8	≤29.7	0.002	0.715	68	81	≤31.4	0.004	0.580	85	31.4	≤−21.2	0.021
ΔR10	0.685	82.9	65.2	≤25.3	0.004	0.700	73.2	69.0	≤36.4	0.015	0.568	56.7	83.5	≤−22.9	0.002
ΔR15	0.517	28.9	76	≤38	0.72	0.514	56.1	18.9	≤65.7	0.56	0.503	75.7	2.9	≤8.8	0.87
ΔR20	0.505	77.1	9.3	≤19.0	0.93	0.345	61.9	45.3	≤34.1	0.12	0.562	81.3	38.8	≤−1.28	0.123
ΔR5−R20	0.530	97.1	22.6	≤41.3	0.57	0.531	64.1	70.0	≤43.2	0.08	0.403	50.2	76.1	≤−13.6	0.09
ΔX5	0.610	66.3	56.7	>32.4	0.3	0.505	78	16.5	>61.5	0.92	0.483	56.7	66.6	>12.7	0.08
ΔX10	0.599	45.3	66.2	>24.5	0.070	0.535	91.2	32.7	>66.6	0.50	0.390	59.2	61.5	>13.2	0.13
ΔX15	0.341	53.4	65.3	>70	0.081	0.504	74.3	46	>60	0.94	0.451	61.3	80.0	>21.2	0.21
ΔX20	0.435	65.3	65.4	≤31.4	0.7237	0.643	47.1	77.7	≤72	0.008	0.390	67.9	67.2	≤20.8	0.41
ΔFres	0.637	85.7	43	≤26.1	0.008	0.544	94.3	23.3	>−34.9	0.023	0.577	44.9	75.7	≤25.2	0.05
ΔAX	0.780	77.1	85.4	≤32.4	<0.0001	0.840	77.1	67.8	≤40.2	0.001	0.712	88.7	74.2	≤39.4	0.006
ΔFEV1	0.725	62.9	78.5	>11.7	<0.0001	0.790	62.9	88.3	>11.3	<0.0001	0.603	56.1	68	>4.8	0.009
ΔFEV1/FVC	0.589	40	88.8	>11	0.15	0.647	60	71.8	>4.8	0.01	0.601	50.5	71.8	>4.8	0.01
ΔMMEF	0.431	43.5	66.7	>30.3	0.06	0.467	67.8	63.4	>12.3	0.24	0.508	52.3	58.3	>28	0.83

FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; MMEF, maximum mid-expiratory flow; Fres, resonant frequency; AX, area of the reactance curve.

Table 5. Discriminant properties of IOS parameters to discriminate predefined FEV1 and/or FEV1/FVC (FEV1 <80%, FEV1/FVC <80%) and MMEF (MMEF <60%) cut-off values.

	FEV1 and/or FEV1/FVC <80%					MMEF <60%				
	AUC	*p* Value	Cut-off (%)	Sensitivity (%)	Specificity (%)	AUC	*p* Value	Cut-off (%)	Sensitivity (%)	Specificity (%)
Zrs	0.703	<0.001	>0.775	75	59.3	0.708	<0.001	>0.595	95.6	37.5
R5	0.696	<0.001	>0.685	86.1	49.3	0.700	<0.001	>0.585	95.6	38.1
R10	0.632	0.011	>0.542	74	56	0.665	<0.001	>0.485	95.6	39.8
R15	0.566	0.204	>0.240	56	53	0.617	0.004	>0.425	88.4	33.5
R20	0.565	0.211	>0.211	64	42.7	0.609	0.008	>0.395	94.2	29.5
R5 − R20	0.747	<0.001	>0.245	88.9	67	0.722	<0.001	>0.165	85.5	51.1
X5	0.766	<0.001	≤0.245	75	68.9	0.724	<0.001	≤0.245	63.8	72.7
X10	0.731	<0.001	≤0.165	66.7	76.5	0.746	<0.001	≤0.079	91.3	47.2
X15	0.726	<0.001	≤0.125	63.9	75.6	0.721	<0.001	≤0.085	76.8	63.1
X20	0.538	0.471	>0.11	48.8	77.4	0.542	0.52	>0.12	64.3	61.8
Fres	0.632	0.011	>19.77	88.9	43.5	0.686	<0.001	>20.125	88.4	52.3
AX	0.697	<0.001	>2.62	55.6	78.5	0.733	<0.001	>1.275	89.8	53.4

FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; MMEF, maximum mid-expiratory flow; Fres, resonant frequency; AX, area of the reactance curve.

Table 6. ROC curve analyses of IOS reversibility to detect spirometric reversibility.

	AUC	*p* Value	Cut-off (%)	Sensitivity (%)	Specificity (%)
ΔZrs %	0.646	0.0005	≤−22.33	49.2	76.7
ΔR5 %	0.599	0.0283	≤−22.34	47.7	75.6
ΔR10 %	0.564	0.1505	≤−22.81	47.7	73.9
ΔR15 %	0.517	0.7038	≤6.38	73.8	13.9
ΔR20 %	0.507	0.8770	>−2.7	35.4	72.8
ΔR5 − R20 %	0.509	0.81	≤16.9	56.7	66.6
ΔX5 %	0.658	0.06	≤−33.85	50	79.1
ΔX10 %	0.567	0.07	≤18.7	65.8	84.2
ΔX15 %	0.502	0.96	≤−23.1	77.1	70.7
ΔX20 %	0.578	0.51	≤11.81	78.0	45.6
ΔFres %	0.599	0.025	≤−21.77	52.3	68.9
ΔAX %	0.649	0.0003	≤−39.05	72.3	56.7

Fres, resonant frequency; AX, area of the reactance curve.

discriminated all three groups were ΔR5, ΔR10, ΔAX, ΔFres, ΔFEV1% according to the highest AUC values.

Airway obstruction detected by FEV1 (FEV1 <80%) and/or FEV1/FVC (FEV1/FVC <80%) could as well be detected by Zrs, R5, R10, R5–R20, X5, X10, X15, Fres and AX of IOS, and airway obstruction detected by MMEF (MMEF <60%) could as well be detected by Zrs, R5, R10, R15, R20, R5–R20, X5, X10, X15, Fres, AX of IOS (Table 5).

The discriminating performance of reversibility testing with IOS to determine the spirometric reversibility (either an increase in FEV1 of ≥12%, or >200 mL from baseline after inhalation of a short-acting bronchodilator) was investigated. Postbronchodilator changes of IOS parameters, Zrs, R5, AX, Fres were found to significantly detect the reversibility revealed by spirometry (Table 6). The most significant IOS parameter to determine reversibility was ΔAX. For ΔAX, the ≤−39.05 cut-off value had 72.3% sensitivity and 56.7% specificity.

Discussion

It has previously been shown that IOS can be performed in children as young as 2 years old, and it has been documented to provide reliable results for these children [17]. It has been reported that only 26% of preschool children were able to succeed three good attempts by spirometry [18]. This percentage clearly indicates that spirometry is not a feasible assessment instrument for young children. In this study, we hypothesized that IOS might be an alternative method to spirometry for children by investigating the relationship between IOS and spirometry, and by evaluating the discriminating performance of IOS and spirometry in detecting acute and stable asthmatic children.

Our study has revealed the following results: All IOS parameters were correlated with spirometry parameters. Except for the X20 parameter of IOS, all IOS parameters were able to distinguish asthmatic children (both acute and stable) from healthy controls. Although R5, R10, Fres and AX values of reversibility were significantly different across all three groups, the most statistically significant results were obtained by ΔAX. This was also the most significant differentiator of spirometric reversibility.

There are many studies about the correlation of IOS parameters with those of spirometry. In the study by Vink et al., in 19 asthmatic children, the correlation of FEV1 with IOS parameters was investigated, and a high correlation, especially in low frequencies, was reported [19]. In the study by Nair et al., in asthmatics and healthy subjects aged 18–65, the IOS R5 parameter was found to be correlated with FEV1 [20]. In the study by Moreau et al., FEV1, MMEF, FVC were positively correlated with R5, R20, Fres, Zrs, and negatively correlated with X5 in children with cystic fibrosis. These studies, therefore, have been able to show that many

spirometry and IOS parameters are correlated with each other in asthma and other obstructive lung diseases. Aside from spirometry, it has been shown that resistance calculated by plethismography (Raw) is strongly correlated with the R5 [21]. In our study, we found higher number of correlations between spirometry and IOS at low and high resistance and reactance values both in asthmatic and healthy children than previously reported. In line with the previous studies, we also found that baseline IOS parameters at low frequencies had higher correlational coefficients.

There are studies that compared the mean prebronchodilator and reversibility values of IOS parameters in healthy children and children with obstructive airway disease to assess whether IOS might be an alternative or complementary method to spirometry [8,22–24]. The evaluation of the effect of bronchodilators is especially important for preschool children in determining the phenotype of wheezing, especially for nonatopics [25]. In some studies comparing the mean prebronchodilator values of IOS and spirometry between asthmatic and healthy children, no difference was found except for the baseline R5 parameter in the study by Song et al., whereas after the inhalation of salbutamol, the reversibility mean scores of ΔR5, ΔR10, ΔR20, ΔR35, ΔX5, ΔAX were found to be different between groups but the spirometric reversibility values showed no difference. These studies concluded that IOS was superior to spirometry in detecting the response to bronchodilatator agents, and that the most reliable parameter to detect the bronchodilatator response was R5 [8,22,24]. In these studies, the spirometric values may not have been able to detect any difference because it is technically difficult to implement spirometry in preschool children. Also there are limited number of studies on the sensitivity and specificity of prebronchodilator values of IOS and spirometry for asthma diagnosis. In a study conducted with 87 asthmatic patients, 87 patients with chronic obstructive pulmonary disease and 56 healthy individuals, the most sensitive parameter to differentiate the asthmatic patients from the healthy control subjects was found to be R20 [26]. In another study, it was found that R5 was more sensitive than FEV1/FVC in differentiating asthmatic patients from control subjects [27]. It was also noted that the R5−R20 and AX parameters were valuable in differentiating uncontrolled and stable asthmatics. Moreover, it was claimed that there is a relationship between small airway obstruction and these parameters in uncontrolled asthmatics [28]. In our study, we both compared the mean values of IOS and spirometry and analyzed for sensitivity and specificity to discriminate the three groups. The results, we obtained from the comparisons of mean scores as well as the ROC analyses suggested that especially the parameters related to the small airways are more significantly able to discriminate all three groups. Besides being able to make the distinction between stable asthmatics and healthy controls as previously demonstrated [8,29], the present study revealed that IOS is also helpful for the differentiation of acute asthmatic children. To the best of our knowledge, this is the first study in English to differentiate acute asthmatic patients from stable asthmatics and healthy controls. In the only other study, which is in Chinese, acute asthmatic children were found to be higher and significantly different from stable asthmatics and healthy controls on the mean values of the following IOS parameters: R5, R20, R5−R20, X5, Fres and Zrs [30]. However, as clinically observed, children in the acute asthmatic period may fail to perform the forced expiratory maneuvers, and IOS may be an easier method. In our study, low-frequency IOS parameters, which especially reflect peripheral airways, differantiated acute asthmatics from stable asthmatics, and this points out to the importance of assessment of the relationship between peripheral airways and asthma exacerbations. The results also indicated that asthmatic children, both acute and stable, can be distinguished from the healthy children by all the resistance parameters of the IOS. This finding reflects the possibility that asthmatic children can be identified according to the resistance parameters.

In a study of diagnostic value of IOS according to the bronchodilator response, the most sensitive and specific values were found to be ΔR10 and ΔAX (cut-off −8.58 and −29.11, respectively) [8]. Also, a bronchodilator response of 20–40% in R5, and 15–30% in R10 was suggestive of reversible obstruction [15,22]. In our study, the discriminating performance to differentiate acute asthmatic patients, stable asthmatic patients, and healthy children, ΔR5, ΔR10, ΔFres and ΔAX parameters was highly significant akin to the results obtained from the mean reversibility comparisons. This is compatible with previous studies [8,15,22]. The best parameter to discriminate the three groups was ΔAX, for which moderate to high AUC values were obtained. For AX, a 32.4% or greater decrease after salbutamol inhalation discriminates acute asthmatics from stable asthmatics, a 40.2% or greater decrease discriminates acute asthmatics from healthy controls and a 39.4% or greater decrease in AX distinguishes stable asthmatics from healthy controls. The baseline and bronchodilator response of AX value had significant sensitivity and specificity to differentiate acute and stable asthmatic patients from the healthy controls. AX is an integrative index of low frequency reactance that is sensitive to change in degree of airflow obstruction [9]. If there is an obstruction in small airways, the magnitude of X values increases. It is advantageous to determine the obstruction because the AX value is the reflection of more than one X value at different frequencies. As previously reported in the literature, AX is the most reliable parameter to track lung function in children before and after bronchodilator, and to evaluate the response to asthma treatment in the long term [28,31]. In our study the reason why we did not obtain any significant results with the reversibility of reactance values at low frequencies may be due to the unrealistic percentage changes of reactance parameters from negative to positive values at low frequencies.

Spirometry is a lung function test which is standardized and its reliability has been proven [15]. If the reversibility and obstruction detected by spirometry, which is generally accepted as the gold standard method, can also be detected by IOS, then it would seem reasonable to use IOS in clinical practice as an alternative method to spirometry. Not many studies have focused on this. In a study of 30 children with cystic fibrosis, none of the R5, X5, Fres and Zrs values was significantly able to differentiate the children whose FEV1% predicted values were below 80%. The authors proposed that

this was due to the low number of children with expected FEV1% values lower than 80% [32,33]. Since children with acute asthma attack were also enrolled in our study, patients with low spirometeric values were sufficient in number. Significant IOS cut-off values were detected for predefined spirometric obstruction criteria. As the AX parameter, the R5−R20 parameter is also helpful in evaluating small airways by IOS. R5 demonstrates the total airway, and R20 demonstrates the proximal airway resistance. So, small airway resistance may be demonstrated by R5−R20 (frequency dependence of resistance) [9,27]. In spirometry, the MMEF value is thought to represent the small airway obstruction. In our study, patients who were found to have obstruction by MMEF were also detected by the AX and R5−R20 values and the AUCs for both of these parameters were >0.7. For patients who had demonstrated reversibility by spirometry, the best corresponding performance in IOS was that of AX's.

Because there are no reference values of IOS specific for children in our community, we used the raw values of IOS instead of the percentage of predicted values. There are studies that have shown IOS parameters may be affected by height, age and gender [34–36]. Therefore, the reliability of our calculated cut-off values may be vulnerable to demographic factors, which is one of the limitations of our study. Although the conversion of raw values of IOS parameters to percent predicted values has been proposed to be a more reliable way to compare the results between IOS and spirometry, some previous studies in the literature have used the exact method of our study to compare the results of IOS parameters and spirometry due to differences of reference values between populations [19,22,28,37]. Therefore, we chose not to convert our raw values in line with these reports. Also reference values for AX have rarely been reported for school aged children and adolescents in the literature, so it is difficult to draw any conclusions in relation to reference values. However, since reversibility testing is not affected by the demographic factors, the reversibility cut-off values for some IOS parameters can be used to diagnose asthma in clinically eligible children.

The number of participants in the acute asthmatic group is relatively smaller than the other groups. This is a limitation of our study, however, the sample size was adequate for power analysis. Another limitation of our study is related to the inclusion of children aged 7–17 years. IOS is predominantly used for preschool children.

Conclusions

IOS is a lung function test, which is correlated with spirometry. Especially, the AX parameter is useful for the discrimination of acute asthmatic, stable asthmatic and healthy children, and the detection of spirometric obstruction and reversibility. A cut-off score of ≤ -39.4 for ΔAX identifies acute asthmatic children, a score of ≤ -32.4 identifies stable asthmatic children, whereas a score of ≤ -39.05 can detect spirometric reversibility.

Declaration of interest

The authors declare that they have no conflict of interest. S.B.B., S.K. designed the study and wrote the manuscript. T.A., Ö.T., A.A. contributed to data collection. S.B.B. and S.K. performed the statistical analysis and interpretation of the results. All authors read and approved the final manuscript. This study received no funds from any agency.

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