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Impulse Oscillometry in Assessment of Asthma Control in Egyptian Children

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ABSTRACT

Background: Assessing asthma control and early detection of children at risk is challenging due to discrepancy in symptom perception. Traditional spirometry requires children to perform forced expiratory maneuvers while IOS require minimal cooperation. The aim of this study was to determine sensitivity and specificity of IOS compared to clinical asthma control parameters among asthmatic children. **Methods:** 80 children were enrolled, Group 1 (patients) according to clinical manifestations in GINA (2019), Group 2 (Control), 40 healthy children with matched age, sex, and socioeconomic standard, subjected to history taking, general and chest examination. Family history of atopy and wheezing followed by SPT, IOS was performed in compliance with the ERS/ATS guidelines by Master Screen IOS system. **Results:** More than one third of group1 were positive to inhaled allergen.R5, R5-R20, Fres and Ax were significantly higher among asthmatics. Bronchodilator response was significant in both controlled and uncontrolled children. There was a significant association between asthma control clinically and IOS parameter AX < 7 (kPa/L). Assessing asthma control using IOS parameter AX < 7 kPa/L showed 68.18 % sensitivity and 88.89 % specificity. **Conclusions:** Impulse Oscillometry is a noninvasive, rapid, validated technique that helps in identification of asthma control among asthmatic children using R5, X5, AX as sensitive and specific indicators.

Keywords: Oscillometry, Asthma, discrepancy, symptom perception, Egyptian Children

1. Introduction

Asthma is the most common childhood chronic disease characterized by airway obstruction. Asthma control with early diagnosis are the milestones in asthma treatment guidelines to decrease asthma morbidity among children represented by school absences, emergency department visits and frequent hospitalizations (Martinez *et al.,*1995; Carroll *et al.,* 2011).

Assessing asthma control and early detection of children at risk is challenging due to discrepancy in symptom perception among children, parents, and available subjective asthma control tests. Level of asthma control is the extent to which features of asthma are observed on children and reduced by treatment. Examples of numerical asthma control tools for children are Children Asthma Control Test (c-ACT) and Asthma Control Questionnaire (ACQ) (Liu *et al.,* 2007).

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Few objective methods had been validated to assess asthma control among children younger than 4 years. The Test for Respiratory and Asthma Control in Kids questionnaire (TRACK) is the only instrument validated to evaluate control of respiratory symptoms in children less than 5 years using recurrent respiratory symptoms, nocturnal awakenings, limitation of daily activities the last 4 weeks and using bronchodilators the last 3 months as indicator of asthma control (Murphy *et al.,* 2009; Gustavo *et al.,* 2018). An available objective test as traditional spirometry requires the child to perform forced expiratory maneuvers, which is difficult for young children and in turn affects its accuracy (Liu *et al.,* 2007).

Accordingly, validated techniques as Tidal breathing measurements, and Impulse oscillometry (IOS) appeared as noninvasive, rapid, safe objective methods that measure respiratory impedance as an indicator of lung function (Spahn *et al.,* 2004). They require minimal cooperation making them beneficial among young children aged more than 2 years, unable to perform traditional spirometry (Bisgaard *et al.,* 2012).

IOS identify peripheral airways pathology and may have better predictive value in identifying patients with potential loss of asthma control and in the clinical diagnosis of patients with airway hyper-reactivity than spirometry (Bickel *et al.,* 2014). IOS can diagnose and determine treatment response in those with asthma or other pulmonary diseases. IOS generates small, pressured oscillations at the mouth and transmitted into the lungs, to help determine Impedance (Zrs) of the respiratory system; energy required to propagate the pressure wave through the airways (Galant *et al.,* 2017).

IOS measures Pulmonary Resistance (Rrs) at 5 Hz (R5) and (R20); a measure of central and peripheral airway caliber; including resistance of oropharynx, larynx, trachea, large and small airways (Lee *et al.,* 2012). Additionally, Respiratory reactance (Xrs) at 5 Hz (X5); amount of recoil generated against that pressure wave and the Reactance Area (Ax) that reflects the degree of peripheral airways obstruction (Brashier and Salvi, 2015).

In this study we used GINA guidelines together with validated questionnaire and performed IOS. This study aimed at determining sensitivity and specificity of IOS compared to clinical asthma control parameters among asthmatic children.

2. Methods

This case control study was conducted on 80 Egyptian children enrolled from pediatric pulmonology and allergy outpatient clinic of Al-Hussein hospital of Al Azhar University from August 2018 to December 2019. IOS procedure was performed at the Pediatric Pulmonary Functions Unit, Medical Research Centre of Excellence, National Research Centre.

Inclusion criteria: asthmatic children aged from 2 to 5 years, ability to perform impulse oscillometry according to ATS/ ERS recommendations (Mochizuki, 2012).

Exclusion criteria: pulmonary diseases as cystic fibrosis, bronchopulmonary dysplasia; chronic systemic conditions as heart diseases, neurologic disorders; congenital malformations and mental impairment

The children were divided into two groups:

Group 1: (asthmatics) 40 children assessed according to clinical manifestations described in GINA (2019) and diagnosed with asthma. Asthma control was assessed clinically using asthma control index and grouped accordingly to controlled and uncontrolled groups.

Group 2: (Control), 40 apparently healthy children with matched age, sex and socioeconomic standard.

All children were subjected to full history taking, general and chest examination. Family history of atopy and wheezing followed by Skin prick test to identify allergies toward common allergens as pet dander, dust, pollen, dust mites and some food allergens, such as wheat, milk, whole egg, egg white, beef and shrimp.

To perform the Skin prick test (SPT) few drops of the purified allergen were gently pricked on the skin surface, the forearm. Histamine (10 mg/mL) was used as the positive control, and normal

saline was used as the negative control. A mean wheal size of more than 3 mm and wheals caused by histamine were considered positive when measured after 15 minutes. Atopy was defined as at least one positive sensitization on SPT with the CAP FEIA technology (Phadiatop©, Pharmacia, Uppsala, Sweden), (Heinzerling *et al.,* 2013).

Impulse oscillometry (IOS):

Impulse oscillometry (IOS) was performed in compliance with the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines by MasterScreen IOS system (Jaeger Co., Germany), (Beydon *et al.,* 2007).

The IOS system was calibrated each day prior to measurements using a 3-liter syringe. Children with their guardians had the IOS technique explained by the physician before the procedures.

In sitting position and with an applied nasal clip, each child was asked to breath normally (tidal breathing) into a mouthpiece correctly placed between his teeth and held with lips for 30 seconds with cheeks supported by hands of the child's guardian, while a loudspeaker generates an impulse shaped pressure signal into the respiratory system. The physician evaluated the efforts and made sure each observation consisted of at least 3 reproducible maneuvers without artifacts caused by coughing, swallowing, vocalization or breath- holding. Impulse Oscillometry was performed before and after administration of salbutamol from a metered-dose inhaler with a spacer to assess bronchodilator responsiveness.

IOS parameters obtained at the end of the application were resistances (R5, 20) at 5---20 Hz, R5-R20 (resistance at 5 Hz minus resistance at 20 Hz), reactance at 5 Hz (X5), 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).

Statistical Analysis

Statistical analysis was performed using statistical package for social sciences (SPSS) version 21 for windows (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation, minimum, maximum, were compared by using student's t-test, Categorical data were expressed as frequencies and percentages, and were analyzed with the two-tailed chi square test to find the association between them. Sensitivity and specificity were calculated to find the possibility of using R5 and X5 to diagnose bronchial asthma and the possibility of AX to detect asthma control. $P < 0.05$ was accepted as statistically significant.

3. Results

Eighty children were enrolled at this study, Group 1 (patients), 40 asthmatic children 25(62.5%) males and 15(37.5%) females aged 3.67±0.82 years, weight (Kg), height (cm) BMI (kg/m2) were 16.01±2.34, 99.30±7.47, 16.19±1.18 respectively.

Group 2 (control) 40 children 24 male and 16 female aged 3.9 ± 0.85 years, 16.6 ± 2.7kg weight, 102.8 ± 8.6 cm height, 15.8 ± 1.1 (kg/m2) BMI. No statistical difference regarding this demographic data

According to skin prick test more than one third of the group1 were positive to inhaled allergen, while inhaled food allergen positive patients represented 27.5% of group 1 (Figure 1). History of parental asthma was negative in 65% of asthmatic children (group1).

Impulse Oscillometry parameters (R5, R5-R20, Fres and Ax) were all higher among group 1 compared with control, with significant statistical difference as shown in Table 1. Airway ability to recoil represented by X5 parameter was more negative among group1 compared with control p=0.000.

On comparing response to bronchodilator administration in patient group there was highly statistically significant difference regarding R5, R5-R20, Fres and Ax being higher pre than post bronchodilator P-Value=0.000. Also, X5 parameter showed highly statistically significant differences between the two groups being more negative pre than post bronchodilator P-Value = 0.023.Group 1 was then regrouped according to the asthma control and IOS parameters were then compared, controlled patients had lower readings as regards X5 and R5-R20 (%) but statistical significance was found inR5 and AX variables considering that X5 was more negative among uncontrolled asthmatic children while Fres was the same in both groups Table 2 & 2A .

As shown in table 3, R5-R20 and AX values were statistically higher among asthmatics who had positive skin prick test (SPT) compared with negative skin prick test asthmatic children. Meanwhile R5 and Fres were higher in positive SPT children but didn't reach statistically significant difference same as X5 that was more negative among positive SPT children insignificantly.

There was a significant association between asthma control clinically and by using the IOS parameter AX < 7 (kPa/L) Figure (2). Sensitivity and specificity of IOS variables to detect asthma control is shown in table 4.

Table 1: Comparison between the two studied groups as regards Impulse oscillometry parameters

IOS variables	Group1 (asthmatic) n=40 Mean ± SD	Group2 (Control) n=40 Mean ± SD	t- test	P-Value
R5 [kPa/(L/s)]	154 ±34.9	104.2 ± 18.6	5.951	0.000*
X5 [kPa/(L/s)]	-0.17±0.12	0.04 ± 0.26	-4.172	0.000*
R5-R20(%)	43.2±9.1	35.3 ± 6.5	3.452	0.001*
Fres (1\s)	25.9 ±2.02	24.4 ± 3.1	2.253	0.028*
Ax (kpa\l)	6.9 ±2.35	2.8 ±1.4	7.260	0.000*

*SD= Standard deviation; p<0.05 is Significant; IOS= Impulse oscillometry;

Table 2: Comparison between controlled and uncontrolled asthmatic children as regards impulse oscillometry parameters pre and post bronchodilator

IOS variable		Controlled n=22 Mean ± SD	Uncontrolled n=18 Mean ± SD	t-test	P-Value
R5 kPa/(L/s)	**Pre-BD**	144.04±40.00	166.21±23.08	-2.082	0.044*
	Post-BD	122.71±63.63	102.82±4.32	1.320	0.195
X5 kPa/(L/s)	**Pre-BD**	-0.18±0.11	-0.16±0.13	-0.475	0.637
	Post-BD	-0.077±0.18	-0.11±0.15	0.631	0.532
R5-R20(%)	**Pre-BD**	40.80±11.51	46.03±2.89	-1.877	0.068
	Post-BD	31.50±10.03	32.04±3.06	-0.221	0.826
Fres (1/s)	**Pre-BD**	25.93±2.47	25.91±1.38	0.029	0.977
	Post-BD	22.72±4.37	23.76±1.09	-0.984	0.331
AX (kPa/L)	**Pre-BD**	5.84±2.40	8.30±1.45	-3.804	0.001*
	Post-BD	4.05±3.02	3.35±0.77	0.952	0.347

*p < 0.05 is significant

Table 2A: Comparison of IOS pre and post bronchodilator according to asthma control

IOS	Asthma control	Prebrochodilator Mean ± SD	Postbronchodilator Mean ± SD	t-test	p
R5 kPa/(L/s)]	**Controlled**	144.04±40.00	122.71±63.63	2.503	0.021*
	Uncontrolled	166.21±23.08	102.82±4.32	12.882	0.000*
X5 [kPa/(L/s)]	**Controlled**	-0.18±0.11	-0.077±0.18	-2.311	0.031*
	Uncontrolled	-0.16±0.13	-0.11±0.15	-0.978	0.342
R5-R20 (%)	**Controlled**	40.80±11.51	31.50±10.03	5.075	0.000*
	Uncontrolled	46.03±2.89	32.04±3.06	10.281	0.000*
Fres (1/s)	**Controlled**	25.93±2.47	22.72±4.37	4.440	0.000*
	Uncontrolled	25.91±1.38	23.76±1.09	15.650	0.000*
AX (kPa/L)	**Controlled**	5.84±2.40	4.05±3.02	4.919	0.000*
	Uncontrolled	8.30±1.45	3.35±0.77	13.052	0.000*

*p < 0.05 is significant

Table 3: Comparison between patients with skin prick test positive\ negative as regards impulse oscillometry

IOS Variables	Positive SPT- n=33 Mean ± SD	Negative SPT- n=7 Mean ± SD	t- test	P-Value
R5 [kPa/(L/s)]	158.75±33.33	131.67±35.89	1.928	0.061
X5 [KPa/(L/s)]	-0.172±0.120	-0.138±0.122	-0.678	0.502
R5-R20 (%)	45.46±7.60	32.27±7.58	4.171	0.000*
Fres (1/s)	26.08±1.82	25.15±2.866	1.112	0.273
AX (KPa/L)	7.39±2.197	4.84±2.04	2.817	0.008*

* P-Value < 0.05 is significant; IOS= Impulse oscillometry,SPT=skin prick test

Table 4: Sensitivity and specificity of IOS variables to detect asthma control

IOS variables	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
R5 [kPa/(L/s)]	65.00%	100.00%	100.00%	74.07%	82.50%
X5 [kPa/(L/s)]	67.50%	80.00%	77.14%	71.11%	73.75%
AX(KPa/L)	68.18%	88.89%	88.24%	69.57%	77.50%

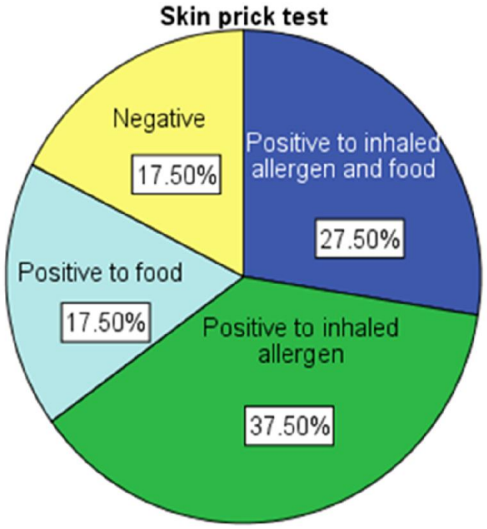

Fig. 1: Pie chart showing distribution of skin prick test results among patient group

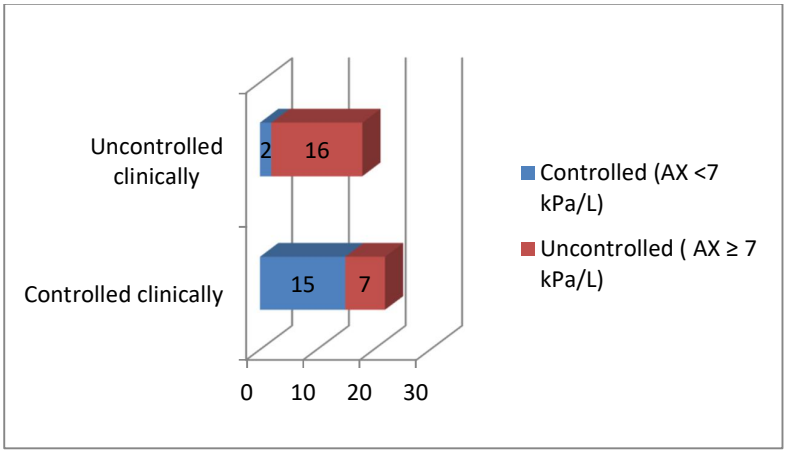

Fig. 2: Association between asthma control clinically and control using AX < 7 (kPa/L)

Discussion

Asthma is the most common chronic lung disorders characterized by airway obstruction. Early diagnosis and control of asthma in children is very important as appropriate treatment has great impact on the disease course (Holtzman 2012). This study aimed to assess IOS parameters of airway resistance and reactance among asthmatic children and compare them in relation to asthma control.

In this study asthma was reported to be more common among boys than girls (62.5% and 37.5%, respectively). These results were in concordance with the finding of El-Nemr and Al-Ghndour, (2013) who stated that asthma was more common in boys than girls (67.4% and 32.6%, respectively). Similarly, an analysis of the Isle of Wight (IOW) birth cohort identified males as being at higher risk of asthma and wheeze up until 10 years of age, with a switch in prevalence occurring by 18 years old, (Soto-Ramírez *et al.,* 2013).

In our study, more than half (65%) of asthmatic children had negative family history of parental asthma which contradicts what El-Nemr and Al-Ghndour, (2013) reported that parental assessment of asthma correctly identified 76.1% of patients with asthma, as well as Komarow *et al.,* (2012) who stated on the basis of a questionnaire, that parental assessment of asthma correctly identified 78% of patients with asthma. This contradiction may be due to our small size sample and the presence of many risk factors, which increase the incidence of wheeze and asthma as the use of fast foods and food additives. Also, Cairo (our study governorate) is mainly an urban district with heavy traffic surrounded by multiple industrialized areas where air pollution by Sulphur dioxide, nitrogen dioxide, carbon monoxide, ozone and particulate matter is one of the highest levels worldwide.

Regarding IOS parameters, this study showed significant difference in R5; X5; R5-R20; Fres and Ax between asthmatics and control group in concordance with the finding of El-Nemr and Al-Ghndour,2013 who stated that there were highly statistically significant differences between both groups regarding R5, X5, and R5–R20%, being higher in patients compared with controls. Thus, impulse oscillometry measurements (R5%, X5pred.-X5, and R5–R20%) were able to accurately discriminate asthmatic patients from controls. However, R20% was indistinguishable between the two groups.

In this study, comparing response pre and post bronchodilator administration among asthmatic controlled children regarding Impulse Oscillometry parameters there was a highly statistically significant difference regarding R5, R5-R20, Fres and Ax being higher pre than post bronchodilator. Previous studies suggested that asthma can be reliably diagnosed with IOS bronchodilator response values: a 20% to 40% decrease in R5, (Marotta *et al.,* 2003). These results are in concordance with those of Chavasse *et al.* (2002) in their study of 29 asthmatic patients and 24 healthy individuals to evaluate bronchodilator response by impulse oscillometry.

Also, X5 parameter showed highly statistically significant differences between the two subgroups being more negative pre than post bronchodilator. These results are in concordance with those of El-Nemr and Al-Ghndour,2013, who stated that there was a highly statistically significant difference regarding degree of reversibility, represented by R5, X5, and R5–R20%; however, R20% showed a non-significant statistical difference. Also, Meraz *et al.* (2008) compared impulse oscillometry parameters pre and post bronchodilator administration and showed that there was a larger decrease, with significant differences in R5, R5–R20%, and X5, indicating improved lung function and small airway function.

In this study uncontrolled asthmatics differed from controlled patients only in R5 and AX variables prebronchodilator while Shi *et al*. (2012) study found all IOS variables in uncontrolled asthma significantly different from those of controlled asthma prior to bronchodilator. In the same aspect, Dawman *et al*. (2020) found a significant difference in R5-20 and AX in controlled and uncontrolled states.

Many studies found that IOS parameters are important in determining the status of smaller airways and highlighted the role of AX parameter representing the smaller airways as an indicator of long-term control and treatment response in childhood asthma (Larsen *et al.,* 2009; Meraz *et al.,* 2011). This was observed in this study by the difference between controlled and uncontrolled asthmatic children even if these results didn't reach the statistically significant level that may be a result of small sample and\or young age of the participants. Also, Jabbal *et al.* (2016) mentioned that (R5-R20) difference and AX variable are more closely related to asthma control.

There was a significant association between asthma control score and asthma control using the IOS parameter AX < 7 kPa/L. Thus, it can be used to assess asthma control using cutoff 7 (kPa/L) with 68.18 % sensitivity and 88.89 % specificity. In this study 85% of asthmatic patient had positive API but no significant association between patients response to bronchodilator (by R5 parameter) and patient with positive API, which is more than what Albuquerque *et al*. (2015) mentioned; among the 48 children evaluated at school age, 20 (41.7%) were diagnosed with asthma; 13 of them (65%) had a positive API at 2-4 years.

Our study showed that mean Ax value was significantly more in positive skin prick test patients compared to negative skin prick test patients P-Value =0.008, while R5-R20 had high significant difference comparing patients with positive\negative skin prick test P=0.000. At the same aspect Shi *et al*. (2013) found that 77%of the studied asthmatic children had positive skin prick test and were categorized in their study as atopic asthmatic group. This result contradicts what Song *et al*. (2008) mentioned that no significant baseline reading in the IOS R5 between non atopic asthmatic and non-atopic healthy groups.

In this study positive and negative predictive values in impulse oscillometry parameters were (77.1% and 71.1%) for X5 with accuracy (73.7%) and (100% and 74%) for R5 with accuracy (82.5%) in diagnosis of asthma using cutoff 0.15 kpa\l\s and 150 kpa\l\s respectively. These results are in accordance with Komarow *et al*. (2012) who stated that IOS to correctly diagnose those with asthma versus those without asthma was 77% and 76%, respectively. However, these results are not in line with Al-Mutairi *et al*. (2007) who stated that the sensitivity of IOS was only 31.3% and the specificity was 80.5%. However, it can, discriminate between diseased and non- diseased subjects.

4. Conclusions

The results obtained in this study concluded that: Impulse Oscillometry (IOS) is a noninvasive, rapid, safe, sensitive, and specific tool to diagnose asthma. It can be used as an objective tool to identify asthma control among asthmatic children. R5, X5, AX may act as good indicator of asthma control. Further studies using larger sample size are needed to confirm our findings.

List of Abbreviations:
c-ACT: Children Asthma Control Test
ACQ: Asthma Control Questionnaire
TRACK: The Test for Respiratory and Asthma Control in Kids
IOS: Impulse Oscillometry
Zrs: Impedance of the Respiratory System
Rrs: Pulmonary Resistance
Xrs: Respiratory Reactance
Ax: Reactance Area
GINA: Global Initiative for Asthma
ATS: American Thoracic Society
ERS: European Respiratory Society
SPT: Skin Prick Test
SPSS: Statistical Package for Social Sciences
BMI: Body Mass Index
IOW: Isle of Wight
API: Asthma Predictive Index

Declarations
Ethics approval and consent to participate:

A written consent was taken from each enrolled child's parent, after approval of ethical committee, Faculty of Medicine, Al-Azhar University.

Consent for publication
Not applicable

Availability of data and material

Patients' data are stored in the spirometry system in Pediatric Pulmonary Function Unit in National Research Centre.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' Contribution

HG was responsible for the study conception and design.SM and SA were responsible for selection of patients and collection of medical data. DA performed IOS on patients and collected their test results. SF had a major contribution in interpreting data and writing the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the study.

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