

EVALUATION OF PULMONARY FUNCTION PARAMETERS USING THE IMPULSE OSCILLOMETRY TECHNIQUE IN WHEEZY CHILDREN

By

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ABSTRACT

Background: Asthma is the most common chronic disease of childhood and the leading cause of morbidity from chronic illness. The challenge was the difficulty to make diagnosis of asthma in children 5 years and younger.

Objective: To evaluate the results of pulmonary function data by impulse oscillometry in young children with recurrent wheeze, its value to diagnose asthma, and to compare IOS data with result of asthma predictive index in young children.

Methods: A case control study was conducted on 60 children enrolled from the pediatric pulmonology and allergy outpatient clinic of Al-Hussein university hospital. Forty patients (group-1), were subdivided into group A: wheezy with positive Asthma predictive index and group B: wheezy with negative API, and 20 children (group-2): The patients were presented with recurrent attacks of wheeze suggestive clinically to be asthmatic (GINA,2018). All children were subjected to full history, physical examination, and pulmonary function by Impulse oscillometry (IOS). Absolute eosinophilic count (AEC) for patient group.

Results: This study revealed that the IOS parameters were significantly higher in patients compared to controls including pulmonary resistance (R5); respiratory reactance (X5); small airway resistance (R5-R20); Frequency (Fres) and reactance area (Ax). In patients there were a significant higher values pre than post bronchodilator as regard R5, R5-R20, Fres. and Ax. Also X5 parameter showed a significant change, being more negative pre- than post-bronchodilator, There were significant high values of IOS parameters in patients with positive API compared to those with negative API. There was positive correlation between AEC and IOS parameters post-bronchodilator. Also there was a significant association between asthma control score and asthma control using the reactance area (Ax) < 7 kPa/L.

Conclusion: Our study concluded that: IOS is helpful for diagnosis of asthma in children 5 years and younger, as it is sensitive and specific in identifying children with reversible obstruction. There was positive correlation with IOS parameter and AEC. This study showed usefulness of IOS and API to categorize the severity of the disease, and determination of asthma control using the reactance area (Ax) < 7 kPa/L. that reflects the degree of peripheral small airway obstruction.

Keywords: Children, Impulse Oscillometry, Pulmonary Function, wheeze, Asthma predictive index, absolute eosinophilic count.

Abbreviations used:

AX: Area under reactance curve between 5 Hz.

Fres.: resonant frequency.

R5: Resistance at 5 Hz, *R20* Resistance at 20 Hz and (*R5 – R20*) Difference between R5 and R20.

X Reactance, *X5* Reactance at 5 Hz and *Z* Impedance.

IOS: Impulse oscillometry.

AEC: Absolute eosinophilic count.

API: Asthma predictive Index.

INTRODUCTION

Asthma often begins in early childhood; in up to half of people with asthma, symptoms commence during childhood^[1].

It may be difficult to diagnose bronchial asthma in children 5 years and younger, because wheeze and cough are also common in children without asthma^[2]. A probability-based approach based on pattern of symptoms during and between viral respiratory infections may be helpful in making decisions about giving controller treatment^[3].

Accordingly, significant efforts have been made to develop noninvasive techniques that

accurately measure lung function in young children. Examples of such techniques include spirometry, infant body plethysmography, and Impulse oscillometry (IOS)^[4].

We choose Impulse Oscillometry (IOS) to work on in this study as it is noninvasive, rapid, safe and validated technique that measures respiratory impedance that is used as an indicator of lung function. It requires minimal cooperation from the subject and is therefore of great utility in young children, as well as in older children and adults^[5].

IOS can be performed easily in children aged more than 2 and up to any age, making it useful in children unable to perform traditional spirometry. It is more sensitive than spirometry at identifying pathology in the peripheral airways and may have better predictive value than spirometry in identifying patients with potential loss of asthma control^[6].

IOS is used to diagnose, evaluate, and determine treatment response in those with asthma or other pulmonary disease states. IOS technique generates small pressured oscillations that are applied at the mouth and transmitted into the lungs, to help determine the Impedance (Z_{rs}) of the respiratory system which is defined as energy required to propagate the pressure wave through the airways^[7].

Pulmonary Resistance (R_{rs}) at different frequencies reflects total resistance, (resistance at 5 Hz [R_5]) or central airway resistance (resistance at 20 Hz [R_{20}]), the difference between R_5 and R_{20} ($R_5 - R_{20}$) reflects the resistance of small or peripheral airways^[8].

Respiratory reactance (X_{rs}) at 5 Hz (X_5), which is defined as amount of recoil, generated against that pressure wave; are the key component of Impedance and

are measured and graphically displayed. Reactance area (A_x) that reflects the degree of peripheral airways obstruction^[9].

Aims of the Work

The aim of this study was to evaluate the results of pulmonary function data by impulse oscillometry in young children with recurrent wheezy chest, and its capacity to diagnose Bronchial asthma in this age group (≤ 5 years). Also, to compare IOS data with the result of asthma predictive index and absolute eosinophilic count in patients 5 years and younger

PATIENTS AND METHODS

This case control study was conducted on 60 children from the pediatric pulmonology and allergy outpatient clinic of Al-Hussein hospital of Al Azhar University. It was done from August 2018 to December 2019. The children were divided into two groups:

1. Patient group: (Suggestive asthmatic group): They included 40 cases presenting with recurrent wheezy chest (at least 4 times/year) suggestive to be asthmatic based on clinical data and probability-based approach (GINA 2018). Their ages ranged from 2 to 5 years old. Our patients were subdivided into:

Group (A): wheezy children with positive Asthma predictive Index (API).

Group (B): wheezy children with negative API.

2. Control group: They included 20 children who are apparently normal without any pulmonary or chronic illness, and selected from pediatric relative of patients of the same age, sex and socioeconomic standard.

Inclusion criteria:

The inclusion criteria were: Ages ranged from 2 to 5 years old; Children presenting with recurrent attack of wheezy chest 4 times/year or more; Presence of other allergic disease will be included in the study.

Exclusion criteria:

Exclusion criteria were mentally impaired children. Any child aged below 2 years or above 5 years; chronic pulmonary, cardiac, renal and neuromuscular disorders.

Plan of the Study:

A. Full history taking.

B. Clinical examination.

C. Laboratory investigations: Estimation of absolute eosinophilic count for patients^[10].

- Chest x-ray to exclude chest infection or chronic pulmonary conditions.

- Prick skin testing^[11] to help in evaluation of Asthma Predictive Index (API).

Full history taking: including Age, sex, and residence refers to informal areas suffering from problems of accessibility, narrow streets, the absence of vacant land and open spaces, very high residential densities, insufficient infrastructure and services; Family history of asthma or atopy. Also apply the **asthma control score**^[12], and modified Asthma Predictive Index^[13].

Thorough general and chest examination.

Impulse oscillometry (IOS): JAEGER MS-IOS Digital is fully integrated with an IOS system^[14]. IOS requires the subject to breath normally (tidal breathing) into a mouthpiece, while a loudspeaker generates an impulse shaped pressure signal into the respiratory system. The IOS system was calibrated each day prior to the measurements using a 3-liter syringe. IOS measurements were performed in the sitting position with participants applying nose clips. Participants tidally breathed into the IOS mouthpiece for 30 seconds with the cheeks supported

by the hands of trained technicians. The technicians evaluated the efforts and made sure each observation consisted of at least 3 reproducible maneuvers which did not have artifacts caused by coughing, swallowing, vocalization or breathe holding. Administration of Salbutamol inhalation to evaluate results of IOS parameters post-bronchodilator.

Ethical Considerations:

1. Approval of ethical committee, Faculty of Medicine, Al-Azhar University.
2. Written consents from the parents of the patients.
3. The patients had their right to withdraw from the study at any time.
4. All the obtained data are confidential and the patients have the right to keep them.
5. The authors declare that there is no any financial conflict regarding the research and publication.

6. No conflict of interest regarding the study and publication.

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 and standard deviation, minimum, maximum, were compared by using student's t-test, and paired t-test. Pearson's correlation analysis was conducted to evaluate the association between continuous exposure and continuous covariates. 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.

RESULTS

Our results will demonstrate in the following tables.

Table (1): Demographic Data and Comparison between the two studied groups as regards Impulse oscillometry parameters

Variables		Group 1 (Patients)N=40	Group 2 (Control)N=20	t-test	P-Value
Male	N (%)	25(62.5%)	14 (70%)	0.330	0.566
Female	N (%)	15(37.5%)	6 (30%)		
Age (years)	Mean ± SD	3.67±0.82	3.9 ± 0.85	-0.728	0.469
IOS variables		Group 1 (Patients)N=40	Group 2 (Control)N=20	t- test	P-Value
R5 %	Mean ± SD	154 ±34.9	104.2 ± 18.6	5.951	0.000*
X5 [kPa/(L/s)]	Mean ± SD	-0.17±0.12	0.04 ± 0.26	-4.172	0.000*
R5-R20(%)	Mean ± SD	43.2±9.1	35.3 ± 6.5	3.452	0.001*
Fres (1/s)	Mean ± SD	25.9 ±2.02	24.4 ± 3.1	2.253	0.028*
Ax (kpa/l)	Mean ± SD	6.9 ±2.35	2.8 ±1.4	7.260	0.000*

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

This table showed that, There was no statistically significant difference between patients and control as regard gender, age and sex between the two studied groups with P>0.05.

There were significant differences in R5; X5; R5-R20; Fres and Ax respectively. IOS parameters increased in group 1 compared to group 2.

Table (2): Comparison between pre and post bronchodilator with impulse oscillometry parameters

IOS variables		pre bronchodilator	post bronchodilator	t- test	P-Value
R5 %	Mean ± SD	154 ± 34.91	113.8 ± 47.8	6.519	0.000*
X5 [kPa/(L/s)]	Mean ± SD	-0.17 ± 0.12	-0.1 ± 0.2	-2.37	0.023*
R5-R20(%)	Mean ± SD	43.2 ± 9.1	31.7 ± 7.6	9.32	0.000*
Fres (1/s)	Mean ± SD	25.9 ± 2.02	23.2 ± 3.3	6.716	0.000*
AX(KPa/L)	Mean ± SD	6.9 ± 2.4	3.7 ± 2.3	8.885	0.000*

* P-Value < 0.05 is significant; IOS= Impulse oscillometry

This table showed that, there were highly statistically significant differences in the response as regard R5, R5-R20,

Fres and Ax being higher pre than post bronchodilator with P-Value 0.000. In addition, X5 parameter showed highly

statistically significant difference between pre and post bronchodilator, being more negative pre than post bronchodilator with P-Value 0.023.

Table (3): Comparison between patients with positive asthma predictive index with patients with negative API regarding impulse oscillometry parameters

IOS variable		Group A Positive asthma predictive index	Group B Negative asthma predictive index	t- test	P-Value
R5 %	Mean ± SD	156.9 ± 34.4	108.5 ± 23.7	7.466	0.000*
X5 [KPa/(l/s)]	Mean ± SD	-0.17 ± 0.12	0.07 ± 0.27	-4.80	0.000*
R5-R20(%)	Mean ± SD	45.25±7.58	34.7 ± 6.7	6.56	0.000*
Fres (1/s)	Mean ± SD	25.9 ± 1.86	24.6 ± 3.03	2.43	0.017*
AX (KPa/L)	Mean ± SD	7.28 ± 2.24	3.48 ± 1.98	8.018	0.000*

* P-Value < 0.05 is significant; IOS= Impulse oscillometry

This table showed that, there was positive correlation between IOS parameters and AEC values especially post-bronchodilator and on Comparison between patients in group A “with

positive asthma predictive index” and patients in group B with “negative API, we found significant higher values in R5, X5, R5-R20, Fres, and AX with P-Value < 0.05

Table (4): Association between clinical asthma control score and control using Ax < 7 (kPa/L)

		Asthma control score		Total	
		Controlled	Non- controlled		
AX parameter	Controlled (< 7 kPa/L)	Count	15	2	17
		% within AX group 2	88.2%	11.8%	100.0%
	Uncontrolled (≥ 7 kPa/L)	Count	7	16	23
		% within AX group 2	30.4%	69.6%	100.0%

Pearson Chi-Square = 13.195, p = 0.000*

This table revealed a significant association between asthma control score and asthma control using the reactance area

that reflects the degree of peripheral small airway obstruction (Ax) < 7 kPa/L.

Table (5): Correlation between Absolute eosinophilic count and IOS parameters in patients with Normal and elevated Absolute eosinophils

IOS variable	Normal Absolute eosinophils patients (≤ 400), n=15		Elevated Absolute eosinophils patients (> 400), n=25	
	R	P value	R	P value
Pre R5 %	-0.224	0.423	0.402	0.047*
Post R5 %	0.242	0.385	0.342	0.094
Pre X5 [KPa/(l/s)]	0.305	0.268	-0.088	0.675
Post X5 [KPa/(l/s)]	0.067	0.814	0.421	0.036*
Pre R5-R20(%)	-0.230	0.409	0.166	0.429
Post R5-R20(%)	0.051	0.858	0.480	0.015*
Pre Fres (1/s)	0.267	0.336	0.046	0.827
Post Fres (1/s)	0.303	0.272	0.288	0.163
Pre AX (KPa/L)	0.065	0.818	0.194	0.352
Post AX (KPa/L)	0.320	0.244	0.481	0.015*

R Pearson's correlation coefficient, *p < 0.05 is significant

This table showed that, Ax could be used to diagnose asthma control using cutoff 7 (kpa/L) with 68.18% sensitivity and 88.89% specificity. In addition

to, there was positive significant correlation between Absolute eosinophil count and pre R5, post X5, post R5-R20 and post AX.

DISCUSSION

Asthma is the most common chronic inflammatory disease in childhood. Worldwide, the prevalence of asthma among children has increased steadily during the last two decades **Holtzman et al.**,^[15]. Recurrent wheeze is estimated in one third of children of preschool age and can cause significant morbidity **Mallol et al.**,^[16]. It may be difficult to make confident diagnosis of asthma in children 5 years and

younger **Jee et al.**,^[2]. Impulse oscillometry (IOS) is a much simpler technique that has been increasingly used as a noninvasive method to assess airway resistance and reactance in children **shi et al.**,^[17].

In our study, forty wheezy children were enrolled with Male to female ratio was 5:3. The mean age was 3.67 ± 0.82 . Distribution of age, sex showing no significant difference between the studied groups. In the same aspect **shi et**

al.,^[17] with analysis of variance showed that R5-20 or Ax had no correlation with gender, but did correlate with age **shi et al.**,^[18].

This result was in concordance with the finding of **El-Nemr and Al-Ghndour**,^[19] who stated that asthma more common in boys than girls (67.4% and 32.6%, respectively).

Comparison between the two studied groups as regards IOS parameters there were significant higher values in patients compared to controls in R5; X5; R5-R20; Fres and Ax with P-value 0.000; 0.000; 0.001; 0.028; 0.000 respectively. These results were in concordance with the finding of **El-Nemr and Al-Ghndour**,^[19] who stated that there were highly statistically significant differences as regards R5%, X5pred.-X5, and R5-R20%, being higher in patients compared with controls. Thus, IOS parameters (R5%, X5pred.-X5, and R5-R20%) were able to accurately discriminate asthmatic patients from controls. However, R20% was indistinguishable between the two groups. These results agree with that described by **Chavasse et al.**,^[20] who in their study of 29 asthmatic patients and 24 healthy individuals to evaluate bronchodilator response by impulse oscillometry in healthy

individuals compared with asthmatic patients found that resistance and reactance were higher in asthmatic patients than in controls. In same aspect **shi et al.**,^[17] results suggest that elevated indices representing both resistance R5-R20 and reactance Ax were the best indicators of uncontrolled asthma. Comparing response to bronchodilator administration in patient group there was highly statistically significant difference in response as regard R5, R5-R20, Fres and Ax being higher pre than post bronchodilator with P-Value=0.000. Also, X5 parameter showing highly statistically significant differences, being more negative pre than post bronchodilator P-Value 0.023. **Marotta et al.**,^[21] suggested that asthma can be reliably diagnosed with the IOS bronchodilator response values: a 20% to 40% decrease in R5. Also, X5 parameter showing highly statistically significant differences, being more negative pre than post bronchodilator. These results are in concordance with those of **El-Nemr and Al-Ghndour**,^[19] who stated that there was a highly statistically significant difference in response to bronchodilator as regards the degree of reversibility, represented by R5%, X5pred.-X5, and R5-R20%; however, R20%

showed a non-significant statistical difference. Also, in concordance with **Meraz et al.**,^[22] who compared IOS parameters pre and post bronchodilator administration and showed that there was a significant decrease, in R5%, R5–R20%, and X5, indicating improved lung function and small airway function. **Marotta et al.**,^[21] also reported that significant differences in the percentage change of resistance at 5 Hz were observed after bronchodilator use.

This study revealed a significant association between asthma control score and asthma control using the reactance area that reflects the degree of peripheral small airway obstruction (Ax) < 7 kPa/L. There was a significant association between asthma control score and asthma control using Ax < 7 kPa/L. Ax could be used to diagnose asthma control using cutoff 7 (kpa/L) with 68.18% sensitivity and 88.89% specificity.

In this study there was positive correlation between IOS parameter and API values. The presence of 1 major criterion or 2 minor criteria is associated with asthma. Although the API has been used clinically, it has a relatively low positive predictive value.⁽¹⁰⁾ These data agree with

that described by **Albuquerque et al.**,^[23] they mention that 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.

This study revealed that there was positive significant correlation between elevated eosinophil count patient group, and IOS parameters in pre R5, post X5, post R5-R20 and post Ax. **Nadif et al.**^[20] reported that Blood eosinophil counts correlate with the degree of airway inflammation and asthmatic activity. They found that blood eosinophilia ($\geq 250/\text{mm}^3$) was related to frequent asthma attacks and nocturnal symptoms. Elevated blood eosinophil counts in infants with wheezing correlated with persistent wheezing at the school age **Gaillard et al.**,^[25] In another study **Just et al.**,^[26] followed up 219 infants with recurrent wheezing until they were 6 years old and found that 27% of them had persistent wheezing at 6 years of age, and the most important risk factor for persistent wheezing was blood eosinophilia ($\geq 470/\text{mm}^3$). They suggested that the absence of eosinophilia could predict future remission of wheezing.

CONCLUSION

- We can conclude that IOS is helpful for diagnosis of asthma in children 5 years and younger as it is sensitive and specific in identifying children with reversible obstruction. There was positive correlation with IOS parameter and AEC post-bronchodilator.
- This study showed usefulness of IOS with API to categorize the severity of the disease, and determination of asthma control using the reactance area (AX) < 7 kPa/L. that reflects the degree of peripheral airway obstruction. Both resistance R5-R20 and reactance Ax were the best indicators of uncontrolled asthma.
- IOS was more sensitive and specific in identifying children with reversible obstruction and requires minimal cooperation from young children and is therefore of great utility in preschool children.

RECOMMENDATIONS

From this study, we recommended the following:

- Impulse oscillometry is useful in diagnoses, evaluation and determination of treatment response in preschool children,

as well as in older children with asthma.

- Incorporate IOS into future standard guidelines for the management of children with asthma.
- Further studies are needed with increased number of patients and different age groups to support widespread use of IOS in diagnoses and evaluation of childhood asthma.

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تقييم وظائف التنفس باستخدام جهاز التذبذب الوميضي في الأطفال الذين يعانون من صفير بالصدر

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الهدف: تقييم نتائج وظائف التنفس عن طريق قياس التذبذب الوميضي لدى الأطفال الصغار الذين يعانون من صفير متكرر، وقيمته لتشخيص الربو الشعبي، واستخدامه كمؤشر تنبؤي للربو لدى الأطفال الصغار.

المقدمة: الربو هو أكثر الأمراض المزمنة شيوعاً في مرحلة الطفولة والسبب الرئيسي لمرضاة الأطفال من الأمراض المزمنة. كان التحدي هو صعوبة إجراء تشخيص الربو الشعبي لدى الأطفال من سن 5 سنوات وأقل.

طرق البحث: تم إجراء دراسة حالة على 40 طفلاً مسجلاً في وحدة أمراض الرئة سواء بقسم الأطفال او العيادة الخارجية في مستشفى الحسين الجامعي. تم تقسيم 40 طفلاً (مجموعة المرضى) إلى مجموعة ذات مؤشر تنبؤي للربو إيجابي ومجموعة ذات مؤشر تنبؤي سلبي، و 20 طفلاً (تعتبر مجموعة تحكم).

خضع جميع الأطفال لأخذ التاريخ الكامل، والفحص الطبي الكامل، وتحديد اذا كان الطفل المصاب بالربو الشعبي متحكماً في عدد الازمات من عدمه، كما تم عمل وظائف تنفس للأطفال باستخدام التذبذب الومضي.

النتائج:

● كشفت هذه الدراسة أن معايير التذبذب الومضي المختلفة كانت أعلى بشكل ملحوظ في المرضى مقارنة بمجموعة الكنترول بما في ذلك المقاومة الرئوية (R5)، مفاعلة تنفسية (X5)، مقاومة مجرى الهواء الصغيرة (R5-20)؛ التردد (Fres) ومنطقة المفاعلة (Ax). حيث سجلت المعايير الاتية R5، AX، Fres، R5-R20 قيم اعلى بكثير مقارنة باستخدام موسعات الشعب الهوائية.

● كما أظهر X5 تغيراً كبيراً، حيث كان أكثر سلبية من ما بعد موسع القصبات مع. و كانت هناك قيم عالية كبيرة من معايير التذبذب الومضي في المرضى الذين يعانون مجموعة ذات مؤشر تنبؤي للربو إيجابي مقارنة مع أولئك الذين مجموعة ذات مؤشر تنبؤي للربو سلبي. كان هناك ارتباط إيجابي بين معايير التذبذب الومضي و معايير تحديد التحكم بالازما بعد استخدام موسعات الشعب الهوائية.

خلصت دراستنا إلى أن:

- التذبذب الوميضي مفيد لتشخيص الربو عند الأطفال من سن 5 سنوات وأقل لأنه حساس ومحدد في تحديد الأطفال الذين يعانون من الربو الشعبي.
- كان هناك ارتباط إيجابي مع معايير التذبذب الوميضي ومعايير التحكم بالربو وكذلك تصنيف لشدة المرض.
- تحديد السيطرة على الربو باستخدام منطقة التفاعل $AX < 7$ كيلو باسكال / لتر. التي تعكس درجة انسداد القصيبات الهوائية صغيرة الحجم.
- كانت كل من المقاومة R5-R20 و AX المفاعلات أفضل مؤشرات الربو غير المنضبط.