Evolutionary lung function evaluated by impulse oscillometry in preschoolers with asthma

Función pulmonar evolutiva evaluada por oscilometría de impulso en prescolares con asma

Ramiro González Vera[a], Mónica Saavedra Bentjerodt[a], Alberto Vidal Grell[a], Jorge Mackenney Poblete[a]

[a]Centro de Enfermedades Respiratorias Pediátricas, Clínica Las Condes. Santiago, Chile

What do we know about the subject matter of this study?	**What does this study contribute to what is already known?**
Impulse Oscillometry (IOS) allows assessment of lung function in asthmatic preschoolers and measurement of bronchodilator response.	The evolution of IOS would allow a better characterization of the disease at this stage of life, to identify those whose pulmonary function does not improve, especially peripheral airway parameters to optimize its management.

Abstract

Impulse oscillometry (IOS) is useful for measuring lung function in preschool children. Our objective was to describe the alterations and evolutionary profile of IOS in asthmatic children under 6 years of age after one year of follow-up. **Patients and Method**: 62 preschoolers performed IOS at the beginning of the study and after one year. The proportion of altered IOS and bronchodilator response (BR +) at both times was compared, in addition to sub-analysis according to asthma control and presence of atopy. For the statistical analysis, we used McNemar's χ^2 and the Student's t-test with a 5% α error. **Results**: The initial IOS was altered in 80.6% and in 64.5%% after one year (p = 0.04). 77.4% of the children presented BR+ at the beginning of the study and 83.9% after one year. The uncontrolled asthma group presented a significant improvement in the X5 and D5-20 means, but the controlled asthma group did not. In atopic patients, only uncontrolled asthmatics improved X5, AX, and D5-20. **Conclusion**: IOS shows alterations in a high percentage of preschoolers with uncontrolled asthma, which decreases significantly at one year, but remains altered and with BR + in most children. Additional studies are required to identify different preschool asthma phenotypes and their evolution with treatment.

Correspondence:
Alberto Vidal
aevgmd@yahoo.es

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Introduction

Asthma in preschoolers is a common problem, with a prevalence ranging from 6 to 18%[1]. Many of these children will continue with symptoms at older ages, especially those with more severe asthma, and some will have decreased lung function in adolescence[2-4]. Evaluating lung function at this age is essential for proper diagnosis and follow-up of the disease.

Adapted spirometry has been recommended for preschoolers, however, a percentage of children fail to perform a test that meets quality criteria[5,6]. In this context, impulse oscillometry (IOS) appears as a good alternative, since it is a technique that does not require a forced expiratory maneuver and is performed during breathing at tidal volume, in a short period. It has been reported that it differentiates asthmatic preschool children from healthy ones, with higher sensitivity than spirometry[7].

In the IOS, R5 shows the total airway resistance, R20 the proximal airway resistance, and X5 the airway reactance, which measures air column motion forces (inertance) and elastic properties of the lung (capacitance). AX integrates the reactance at all frequencies and together with R5-20 are the most sensitive parameters to detect changes in the peripheral airway[8].

In recent times, the AX, R5-R20, and R5-20% parameters have become important, as they have proven to be useful for detecting alterations in lung function in preschool children and would reflect alterations in small airway function, with higher sensitivity than spirometric parameters[9,10]. Evaluation of the peripheral airway is especially important because its dysfunction has been linked to loss of asthma control[11].

IOS has been reported to be useful in predicting asthma exacerbations in young children and medium- and long-term disease follow-up[12-14]. IOS is a test that also allows the assessment of bronchodilator response, which can distinguish healthy children from asthmatic ones and would also be important for disease follow-up[15,16].

There is little evidence regarding the follow-up of treatment with IOS in preschoolers and we are not aware of any studies in this matter in our sphere. The objective of this study was to evaluate the usefulness of IOS in the follow-up of preschoolers with uncontrolled asthma, by measuring its variation over one year.

Patients and Method

Prospective study conducted at *Clinica Las Condes* in Santiago, Chile, between August 2016 and September 2018, corresponding to a cohort of children with persistent asthma aged 3 to 5 years, who attended non-randomly for a pulmonary function test in the Pediatric Pulmonology department.

The inclusion criteria were a confirmed diagnosis of asthma by a pediatric pulmonologist, according to the recommendations of the Global Initiative for Asthma (GINA) 2016[17], requiring permanent pharmacological treatment and presenting clinical features of uncontrolled asthma. Uncontrolled asthma was defined when patients recorded three or more episodes of physician-confirmed wheezing in the last 6 months and having received oral corticosteroid treatment for 3 to 5 days in any of these episodes. Patients with other chronic respiratory, heart, or neuromuscular disease and those with diseases that prevented the performance of pulmonary function tests were excluded.

At the beginning of the study, the IOS was performed, named initial IOS, and the patients were scheduled for a skin allergy test. The participants were monitored by their treating physician, who indicated and/or adjusted the treatment. After one year, the IOS was repeated, named the final IOS. At the second visit, respiratory symptoms, bronchodilator use, oral corticosteroids, emergency visits, asthma-related hospitalizations Eliminar punto final and permanent pharmacological treatment used in the last 3 months were recorded.

Based on these parameters, patients were classified into controlled and uncontrolled. Patients were classified as uncontrolled asthmatics if in the last quarter of follow-up they had presented an episode of wheezing and/or received oral corticosteroids for 3 to 5 days and/or required an unscheduled emergency or outpatient visit, and/or received oral salbutamol for more than 7 days, and controlled asthmatics were those who did not present any of the aforementioned characteristics.

Pulmonary function was evaluated using a spirometer associated with IOS with a computerized pneumotachograph (Jaeger Viasys D-97204 model MasterScreen IOS 732595, Germany 2009), previously calibrated according to the manufacturer's recommendations. The tests were performed with the patient seated, with a nose clip, holding her/his cheeks and breathing calmly through the mouthpiece connected to the equipment, assisted by a trained technician.

Measurements were made for at least 30 seconds, until 3 technically acceptable sinusoidal readings were obtained, without artifacts or leaks. The tests with the best coherence at frequencies from 5 to 30 Hz were chosen. Coherence was 0.6 to 5 Hz and 0.9 to 10 Hz, with a variability lower than 10% between measurements at frequencies higher than 5 Hz[18].

Patients were required to be free of respiratory symptoms in the last 2 weeks before the IOS and to discontinue the use of short-acting bronchodilators the night before the test and long-acting bronchodila-

tors 48 hours before. For the bronchodilator test, 400 µg of salbutamol was administered in four puffs with a pressurized metered-dose inhaler, spaced at least 60 seconds apart through a valved holding chamber.

Measurements of resistance R5 and R20, reactance at 5 Hz (X5), and Reactance area (AX) were recorded, and values were expressed in KPa/Ls. The absolute difference between R5 and R20 (D5-20) was calculated. Baseline IOS was considered abnormal if at least one of the following alterations was found: R5 ≥ 140% of predicted and/or X5 ≥ 140% of predicted and/or AX ≥ 3 KPa/Ls and/or D5-20 ≥ 0.2 Kpa/Ls. The reference values used were those published by Duiverman provided by the team and applicable to children aged 2.3 to 12.5 years[19].

Bronchodilator response (BR+) was considered when at least one of the following changes was found: 40% decrease in AX, 20% decrease in R5 and/or R20 and/or D5-20, and/or 30% increase in X5 after administering 400 mg of salbutamol[7,10,20,21].

The allergy skin test (AST) was performed according to the laboratory's technique of the allergy center of *Clínica Las Condes* with indication of not having received treatment with antihistamines or oral corticosteroids in the 7 days before the test. This test included the measurement of 20 common aeroallergens certified by the laboratory by skin prick method (6 intradomiciliary and 14 extradomiciliary) and was considered positive if the diameter of the papule was 3 mm or more, for at least one of them.

For the analysis of the results, frequencies were calculated for qualitative variables (proportions) and summary measures for the quantitative ones (means). Through McNemar's test, we measured the effective variation of discordant cases (positive to negative or negative to positive), between the initial and the final IOS, considering each of the 62 patients as their own control.

To measure the variation in mean baseline and bronchodilator response values between the initial and final IOS, Student's t-test for dependent or paired samples was used. This test was also used in two subanalyses with a smaller group of patients. The first one was to measure the variation of baseline mean values between initial and final IOS in the two asthma control categories. The second one was the variation of baseline mean values between initial and final IOS according to asthma control and allergic sensitization degree. Normal distribution was checked for quantitative variables.

The sample size was calculated based on a pilot sample. In this sample, a minimum of 59 patients was considered necessary to obtain a difference of at least 15% in the discordant cases of altered IOS between both studies and a minimum of 62 patients to obtain a difference of at least 0.08 Kpa/Ls between the average of the R5 parameter of the final IOS and the initial one, considering a percentage of losses not exceeding 10% for both calculations. In both comparisons, the power was 80% and 5% of error.

The research was approved by the institution's ethics committee and parents signed informed consent.

Results

Out of the 83 patients invited to participate in the study, 11 did not accept, and 10 presented exclusion criteria; therefore, 62 patients were included. Table 1 shows the demographic data of the patients.

At the beginning of the study, all patients were under permanent pharmacological treatment for their asthma. In the last 3 months of follow-up, 61 of the 62 patients (98.3%) maintained some type of controller therapy, 46 (74.2%) received inhaled corticosteroids, 6 (9.7%) montelukast, 5 (8.1%) inhaled corticosteroids plus montelukast, and 4 (6.5%) long-acting beta-2 agonist plus inhaled corticosteroid.

There were no losses since all included patients were able to perform the final IOS and complete follow-up after a year. In the last 3 months of follow-up, 28 patients (45.2%) were classified as controlled and 34 patients (54.8%) as uncontrolled, 16 patients (25.8%) required use of oral corticosteroid, 7 patients (11.3%) made emergency visits due to exacerbations, and there were no hospitalizations due to asthma. At 1-year follow-up, the proportion of patients with altered IOS decreased and the one of patients with BR+ increased (Figure 1).

25.8% (16 patients) of those with altered initial IOS changed to normal IOS in the second study, and only 9.8% (6 patients) who had normal IOS in the first study changed to altered IOS in the second one, which was a significant difference (p = 0.04). 12.9% (8 patients) who had BR+ in the first study switched to BR- in the second one and 19.4% (12 patients) with BR- in the first study switched to BR+ in the second one, which difference was not significant (p = 0.43).

The averages of the baseline values of R5 Kpa/Ls, R20 Kpa/Ls, X5 Kpa/Ls, AX Kpa/Ls, and D5-20 Kpa/Ls improved significantly in the final IOS compared with the initial one (Table 2). The variation of BR averages in these same parameters was measured, showing no significant differences between the initial and final IOS (data not included). Table 3 shows the variation of baseline mean of the final IOS compared with the initial one, between controlled and uncontrolled asthmatics at the end of follow-up. The controlled group presented a statistically significant improvement in baseline means of R5, R20, AX, and the uncontrolled group,

showed a statistically significant improvement in all baseline parameters analyzed (R5, R20, X5, AX, and D5-20). The variation of BR+ was measured in controlled and uncontrolled patients, with no significant differences (data not included).

Out of the 62 patients, 47 underwent the AST, and in this subgroup, we measured the variation of baseline means and BR between initial and final IOS. In this group, we found four categories of oscillometric response at 1-year follow-up: 6 (12.7%) controlled with negative AST, 13 (27.7%) uncontrolled with negative AST, 13 (27.7%) controlled with positive AST, and 15 (31.9%) uncontrolled with positive AST (Table 4). In none of these four categories analyzed was there a statistically significant variation in bronchodilator response means (data not included).

Discussion

Our results show that IOS detects alterations in lung function in asthmatic preschoolers, which is in line with what has been published by different authors, who indicate that it is an important test to evaluate lung function and diagnose asthma at a young age[8,9,20,21].

At the end of follow-up, there was a significant improvement of previously altered IOS, however, a high percentage remained altered. This would indicate that in asthmatic preschoolers, with the clinical characteristics of the group studied, improvement is slow, which could be explained by the treatment used or the disease's severity, evidenced by a frequent impairment of small airway function. Shi et al, indeed, demonstrated that small airway function parameters such as D5-20 and AX were useful in distinguishing controlled and uncontrolled patients and predicting the risk of loss of asthma control in a 3-month follow-up of asthmatic children[13].

The improvement in IOS observed over 1 year is consistent with that reported by Saadeh, who found that asthmatic children on permanent asthma treatment show improvement in R5 and AX over time[14]. The mean value of all IOS parameters significantly improves after one year of treatment, suggesting that a significant group achieves improved lung function. However, about 50% maintained uncontrolled asthma, and most continued with controller treatment. This could be explained by poor adherence to treatment, suboptimal treatment, or that this is a group of more severe asthmatics, which in our opinion is the most likely explanation. The latter could be deduced due to the type of alterations found in IOS and because it agrees with a previous study of asthmatic preschoolers, which showed that some of the IOS parameters are useful to measure the disease's severity[22].

The uncontrolled group showed significant improvement in all variables, However, in the controlled group, there was no improvement in X5 or D5-20. We believe that this is because the uncontrolled group

Table 1. Demographic variables and allergy skin test results in preschool children with asthma

Variable	n (%) o $\overline{X}$ ± DS
Males	32 (51.6)
Age	
3 years	10 (16.1)
4 years	27 (43.6)
5 years	25 (40.3)
Average weigth (kg)	19.1 ± 3.2
Average weight (kg)	110 ± 5.9
Positive AST	28 (59.6)

AST: allergy skin test; $\overline{X}$: means; SD: standard deviation.
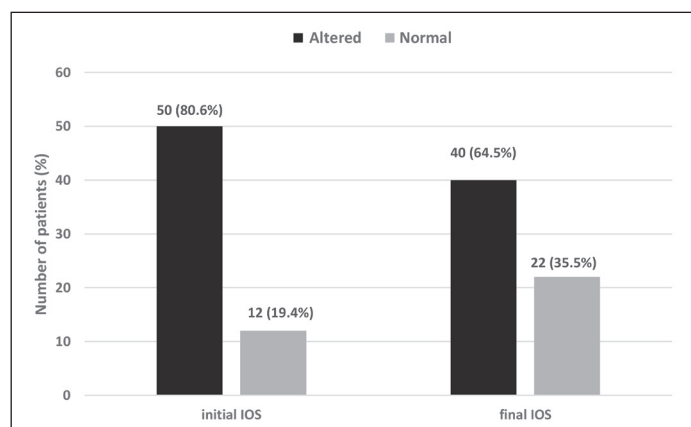
Figure 1. Number of patients and percentage with altered impulse oscillometry (IOS) in the initial study and after one year of follow-up.

Table 2. Comparative analysis of initial impulse oscillometry parameters after one year of follow-up in asthmatic preschool children

IOS parameter	Initial IOS $\overline{X}$ ± DS	Final IOS $\overline{X}$ ± DS	p
R5 (Kpa/Ls)	1.01 ± 0.19	0.82 ± 0.2	0.00001
R20 (Kpa/Ls)	0.71 ± 0.12	0.56 ± 0.12	0.00001
X5 (Kpa/Ls)	-0.35 ± 0.14	-0.29 ± 0.09	0.0003
AX (Kpa/Ls)	3.22 ± 1.5	2.48 ± 1.32	0.00004
D5-20 (Kpa/Ls)	0.31 ± 0.13	0.26 ± 0.13	0.02

R5: Resistance at 5 Hertz; R20: Resistance at 20 Hertz; X5: Reactance at 5 Hertz; AX: reactance area; D5-20: resistance difference at 5 and 20 Hertz; Kpa/Ls: Kilopascal/liter per second; IOS: Impulse oscillometry; $\overline{X}$: means; SD: standard deviation.

Table 3. Variation of impulse oscillometry parameters after one year of follow-up in preschool children with controlled and uncontrolled asthma

IOS Parameter	Controlled Asthma (n = 28)			Uncontrolled Asthma (n = 34)		
	Initial IOS $\overline{X} \pm DS$	Fnal IOS $\overline{X} \pm DS$	p	Initial IOS $\overline{X} \pm DS$	Final IOS $\overline{X} \pm DS$	p
R5 (Kpa/Ls)	0.99 ± 0.16	0.82 ± 0.17	0.00001	1.04 ± 0.21	0.83 ± 0.16	0.00001
R20 (Kpa/Ls)	0.7 ± 0.11	0.57 ± 0.13	0.00001	0.71 ± 0.13	0.56 ± 0.12	0.00001
X5 (Kpa/Ls)	-0.34 ± 0.19	-0.28 ± 0.08	NS	-0.37 ± 0.08	-0.3 ± 0.1	0.001
AX (Kpa/Ls)	2.9 ± 1.6	2.3 ± 1.2	0.02	3.5 ± 1.37	2.7 ± 1.38	0.0007
D5-20 (Kpa/Ls)	0.28 ± 0.12	0.25 ± 0.13	NS	0.33 ± 0.14	0.26 ± 0.13	0.04

R5: Resistance at 5 Hertz; R20: Resistance at 20 Hertz; X5: reactance at 5 Hertz; AX: reactance area; D5-20: difference in resistance at 5 and 20 Hertz; Kpa/Ls: Kilopascal/liter per second; IOS: Impulse oscillometry; $\overline{X}$: means; SD: standard deviation; NS: not significant.

Table 4. Variation of impulse oscillometry parameters after one year of follow-up in preschool children according to the results of the allergy skin test and asthma control

IOS Parameter	Negative AST				Positive AST			
	Controlled asthma		Uncontrolled asthma		Controlled asthma		Uncontrolled asthma	
	Initial IOS $\overline{X} \pm DS$	Final IOS $\overline{X} \pm DS$	Initial IOS $\overline{X} \pm DS$	Final IOS $\overline{X} \pm DS$	Initial IOS $\overline{X} \pm DS$	Final IOS $\overline{X} \pm DS$	Initial IOS $\overline{X} \pm DS$	Final IOS $\overline{X} \pm DS$
R5 (Kpa/Ls)	1.02 ± 0.2	0.8 ± 0.2*	1.08 ± 0.2	0.8 ± 0.2*	0.98 ± 0.1	0.81 ± 0.1*	1.07 ± 0.1	0.85 ± 0.1*
R20 (Kpa/Ls)	0.7 ± 0.1	0.53 ± 0.1	0.72 ± 0.1	0.51 ± 0.1*	0.73 ± 0.1	0.57 ± 0.1*	0.73 ± 0.1	0.59 ± 0.1*
X5 (Kpa/Ls)	-0.46 ± 0.4	-0.29 ± 0.1	-0.4 ± 0.1	-0.34 ± 0.1	-0.3 ± 0.08	-0.28 ± 0.07	-0.37 ± 0.06	-0.28 ± 0.06*
AX (Kpa/Ls)	3.5 ± 3.3	2.6 ± 1.8	4 ± 1.4	3 ± 1.4*	2.5 ± 0.6	2.2 ± 1.1	3.4 ± 1.3	2.5 ± 1.4 *
D5-20 (Kpa/Ls)	0.3 ± 0.2	0.3 ± 0.1	0.35 ± 0.1	0.33 ± 0.1	0.25 ± 0.1	0.24 ± 0.1	0.34 ± 0.1	0.25 ± 0.1*

AST: Allergy skin test; R5: Resistance at 5 Hertz; R20: Resistance at 20 Hertz; X5: reactance at 5 Hertz; AX: reactance area, D5-20: difference in resistance at 5 and 20 Hertz; Kpa/Ls: Kilopascal/liter per second; IOS: Impulse oscillometry; $\overline{X}$: means; SD: standard deviation; *p < 0.05.

started the follow-up with higher averages in AX and D5-20 and lower in X5, in other words, with greater involvement of the small airway than the controlled group. This is in line with some studies where these parameters have been reported as good predictors of control or exacerbations in the medium term[11,13,23].

There is also recent evidence that shows that up to 20% of asthmatics under 12 years of age with good control of the disease could present alteration of peripheral airway parameters in IOS, which could determine a new asthma phenotype, with clinical and prognostic implications still unknown[24].

In preschoolers with asthma, it has been suggested that BR+ in IOS could identify bronchial hyperresponsiveness of the small airway more accurately than spirometry, contributing to a better pathophysiological and clinical characterization of the disease[25].

An unexpected finding in this study was the increase in BR+ in the final IOS compared with the initial one and the absence of a significant decrease in the means of the individual parameters of BR+ between the two studies. This could be explained by the severity of asthma in the included children, who maintain airway hyperresponsiveness, which has been reported in long-term follow-up studies with asthmatic preschoolers where the persistence of BR+ is associated with greater bronchodilator response in adolescence, which would justify its follow-up[26].

We found four different types of evolution in oscillometric parameters according to asthma control and allergic sensitization, which could represent different phenotypes of preschool asthma. The group of non-atopic and uncontrolled patients showed significant variations in the means R20 and AX, which did not occur in the controlled patients. In the uncontrolled atopic group, significant mean variations occurred in X5, AX, and D5-20, which were not observed in the controlled group. We suggest that the non-atopic controlled group could consists of less severe children, who will no longer wheeze, while the non-controlled

atopics would have more severe pathology and greater peripheral airway dysfunction.

In the latter group, a higher risk of persistent asthma and better response to inhaled steroid therapy have been reported, which, in our opinion, could explain the statistically significant improvement found in all IOS parameter means after one year of treatment[27,28]. This is consistent with that reported by Reddy et al. who could distinguish different phenotypes of preschoolers wheezing using IOS, including severe atopic and non-atopic wheezers. In both groups, there was airway dysfunction evaluated by IOS and they were characterized by emergency visits, exacerbations, and steroid use despite being on controller treatment[29].

The authors emphasize the importance of early identification of these phenotypes, and suggest that their findings could be in line with another study that identified two groups of school asthmatics with high requirements for controller therapy; one group atopic with moderately decreased lung function and frequent exacerbations, and the other one non-atopic with slightly decreased lung function, fewer exacerbations, but highly symptomatic[30].

In any case, we believe that the finding of altered IOS in preschool asthma justifies long-term follow-up in all groups, regardless of their phenotype, since there is evidence that alterations in lung function at a young age are associated with a greater need for treatment, symptoms persistence, and alterations in lung function in adolescence[26,31,32].

Our results allow us to affirm that IOS is a useful study in follow-up and monitoring of asthma in preschoolers, its use detects small airway dysfunction and could help to better evaluate the effect of different treatments (e.g., preferring ultrafine-particle inhaled corticosteroids that act in the peripheral airways) and distinguish possible different phenotypes of asthma at this age.

The most important limitation of the study is the low number of patients included, which reduced the power of the comparisons between atopic and non-atopic patients. A larger number of patients could al-low establishing a predictive value for some IOS parameters, better characterizing small airway function, its relationship with having poor or persistent asthma control, and the role of atopy. Further studies of lung function in asthma are needed that include longer-term patients with mild to moderate episodic and intermittent asthma and that also allow evaluation of the impact of different therapies on their evolution.

In conclusion, our findings confirm that the IOS of preschool children improves significantly at one year of follow-up, however, these children maintain a high percentage of altered IOS and BR+ that could reflect the severity of the disease. The variation of parameters reflecting small airway obstruction could be useful in identifying and characterizing some recently reported asthma phenotypes, which have been associated with greater severity and persistence of symptoms until adolescence.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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