Original Article

Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children

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Summary. *Background:* Asthma is common among young children. The assessment of respiratory resistance by the impulse oscillometry system (IOS), based on the superimposition of respiratory flow by short-time impulses, requires no patient active collaboration.
Aim: We evaluated the baseline repeatability and bronchodilator response of IOS indices in preschool children, their correlation with spirometry and whole body plethysmography, and differences between atopic and non-atopic children.
Patients and methods: Thirty-three asthmatic children (3-6 yrs.) underwent IOS measurement (R5rs, R20rs and X5rs) by triplicate at the baseline, after placebo and after salbutamol inhalation. Spirometry (FEV_1) and whole body plethysmography (sRaw) were made at the baseline and after salbutamol. Baseline within-test (coefficient of variation: CV%) and between-test repeatability (baseline-placebo) were addressed. Bronchodilator response was evaluated by the SD index (change in multiples of the between-test repeatability).
Results: Baseline repeatability for R5rs was 4.1%. Its values decreased by 2SD after salbutamol inhalation, and correlated with FEV_1 and sRaw at both, baseline (r=-0.51 and r=0.49) and post-salbutamol (r=-0.63 and r=0.54). A trend towards correlation between salbutamol-induced changes in R5rs and in sRaw (r=0.33) was observed. Atopic and non-atopic children showed no differences in lung function.
Conclusion: IOS was well accepted by young asthmatic children and provided reproducible and sensitive indices of lung function. Resistance values obtained by IOS at low frequency (R5rs) were reproducible and correlated with spirometry and plethysmographic values.

Key Words: childhood asthma, impulse oscillometry, plethysmography, airway resistance, repeatability, bronchodilator response.

Introduction

Asthma is a chronic inflammatory disease of the airways characterized by lung function variability and bronchial hyperresponsiveness [1]. It usually starts at the early stages of life [2] and is considered one of the most common chronic diseases in childhood with an estimated prevalence of about 15% [3]. The benefits of the early onset of anti-inflammatory treatment in asthma have been widely reported [4, 5]. A number of non-atopic children are presented with a clinical pattern different to allergic asthma since symptoms develop during respiratory viral infections [6] and possibly they exhibit decreased responses to regular anti-inflammatory treatment [7].

In children under 6 yrs of age both forced expiratory manoeuvres and non-invasive techniques of exploring airway inflammation are seldom feasible and

reproducible [8]. This lack of objective parameters hampers asthma diagnosis [9] and limits our knowledge of its treatment. Airway resistance, a direct reflection of bronchial caliber, can be measured by whole body plethysmography (specific airway resistance [sRaw]). Although simple, this technique requires costly and sophisticated equipment and further, some young children refuse to stay in the cabin [10]. In turn, the impulse oscillometry system (IOS) is a small and portable device that measures the properties of the respiratory system by estimating the response to short-time impulses applied via a loudspeaker [11]. The measurement of the flow signal created by the impulse and the resulting pressure response of the thoracic systems yields the respiratory impedance (Zrs) that is subdivided into respiratory resistance (Rrs) and respiratory reactance (Xrs) [11,12]. This technique requires little collaboration from patients since only tidal volume breaths are required and children up to 2 yrs old can be examined [12]. The capacity of IOS to detect airway caliber changes secondary to the inhalation of either bronchodilating [13,14] or bronchoconstricting [14,15] agents in young children has been reported.

In this study we have studied 36 asthmatic children aged 3 to 6 yrs and we evaluated: 1) baseline within-test and between-test repeatability of IOS measurements; 2) response to salbutamol inhalation assessed by IOS, plethysmography and when possible, forced spirometry; 3) correlation among the three methods, and 4) differences in lung function indices between atopic and non-atopic children.

Patients and methods

Study design

We evaluated 36 children younger than 6 yrs old (69.7% male), representing all the asthmatic children that had consecutively visited our Allergy office for 4 months and whose parents agreed that they enter the study. Bronchial asthma diagnosis was made according to international guidelines [16]. All drugs were withdrawn for 12 hours before the tests. Skin prick tests were performed with a panel of standard airborne (mites, pollens, molds, danders) and food (egg, milk, wheat, cod, peanut and peach) allergens (ALK-Abelló, Madrid, Spain) [17]. All the tests were performed on the same day, according to the schedule (Figure 1). Placebo and salbutamol (4 puffs, 400 μg) metered-dose inhalers and plastic spacer devices (Volumatic®, Glaxo Wellcome, Burgos, Spain) were used.

IOS measurements

The Jaeger MasterScreen Impulse Oscillometry System (Jaeger, Med Point Technologies, Inc., Milbury, OH) [12] provided with reference values in preschool age was used [18]. Impedance was defined as the spectral ratio between the amplitude of the pressure wave signal and the resulting flow signal. From its values, airway resistance at 5 and 20 Hz (R5rs and R20rs) and reactance at 5 Hz (X5rs) were automatically calculated. The system was regularly calibrated against reference impedance of 0.2 $kPa \cdot L^{-1} \cdot s^{-1}$. During testing, children wore nose-clips; they were sat with the neck slightly extended and the lips sealed around the mouthpiece. A technician supported his/her cheeks with both hands. Records took about 30 seconds of undisturbed tidal breathing. Disturbance from coughing or vocalization resulted in a new measurement. Three correct measurements were averaged at each time point. Variability of both, R5rs and X5rs lower than 5% was required for acceptance of each IOS manoeuvre.

Spirometry and Plethysmography

FEV_1 and specific airway resistance (sRaw) were measured with a constant-volume whole-body plethysmograph (Jaeger, Würzburg, Germany) [19,20] provided with reference values for young children [21]. This equipment has a computer-animated system that was used to improve children performance with manoeuvres. Three valid manoeuvres with a forced expiratory period longer than 1 second and at least two out of them with FEV_1 variability lower than 5% were required for acceptance spirometry [22].

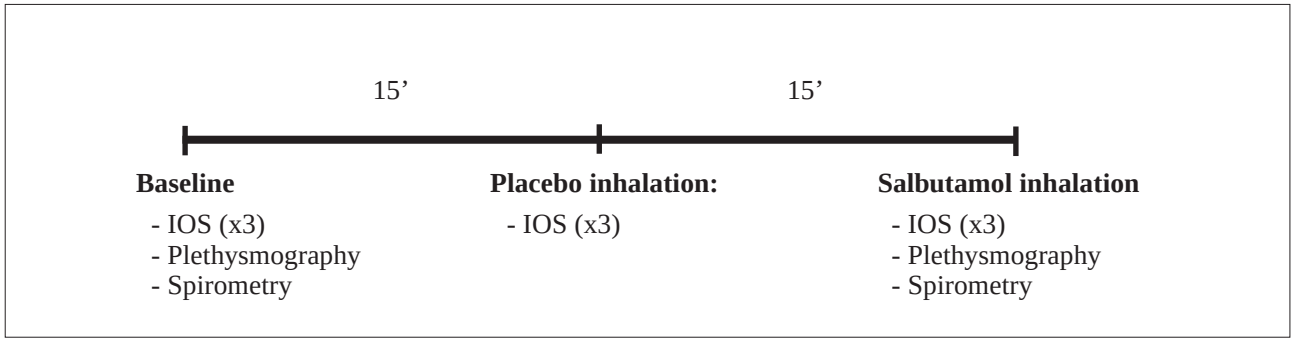

Figure 1. Study design.

Table 1. Mean and standard deviation of the lung function measurements performed at baseline, post-placebo and post-salbutamol (values given as percentage of the predicted values). Differences between baseline and post-salbutamol measurements (t-test for paired data).

	Baseline	Post-placebo	Post-salbutamol	p
R5Rs (%)	86.0 ± 17,6	84.6 ± 17.8	69.1 ± 17.2	< 0.001
R20Rs (%)	89.5 ± 18.4	87.3 ± 16.0	78.7 ± 12.7	0.001
X5Rs (%)	84.8 ± 31.1	77.4 ± 22.5	59.7 ± 17.9	< 0.001
sRaw (%)	176 ± 64.7	Not done	131.4 ± 46.6	0.001
FEV_1 (%)	108.9 ± 21.0	Not done	116.5 ±22.6	< 0.001

Raw was defined as the ratio between the change in inspiratory and expiratory pressures and associated respiratory flow rates. BTPS compensation (body temperature, barometric pressure and water vapour saturation) was electronic. Measurements were performed during tidal breathing without attempts to make patients pant. The mean value of five sequential specific resistance loops, that appeared similar as judged by slope and shape, was retained as outcome.

Statistical analysis

The SPSS Windows 8.0 (SPSS; Chicago, IL, USA) was used. The averaged indices from the three IOS manoeuvres recorded at each stage (baseline, post-placebo and post-salbutamol) were used for analysis. Repeatability of IOS measurements was investigated by within and between-test variability. The first was stated in terms of coefficient of variation (CV%) defined as the residual "mean square" of the 3 baseline recordings, expressed as percentage of the mean (ANOVA) [12, 23]. The averaged values of the baseline and placebo recordings were used to calculate between-test variability (standard deviation of the differences divided by the square root of 2) [23]. The SD index was defined by the rate between the change in lung function measurements and between-test variability [12].

Paired t-test was used to compare recordings at the different stages. Response to both placebo and salbutamol was calculated: 1) SD index; 2) percentage of the baseline values (Δ% baseline) and 3) percentage of the predicted values (Δ% predicted). Pearson´s correlation rank coefficient was used to evaluate correlation. Statistical significance was established at $p<0.05$.

Results

The study was well accepted by all but 3 children (younger than 4 yrs old). Reproducible forced spirometry was obtained in 28 patients (85%). The median of age of children who completed the study was 5 yrs. (interquartile range: 3-6). Duration of asthma was lower than 1 yr in 45.5% of patients. All children were stable at the time of the study and taking regular treatment with inhaled corticosteroids (39.4%), leukotriene modifiers (12.1%) or short-acting ß agonist drugs used "as needed" (48.5%). According to clinical history and skin prick tests, 48.5% had non-allergic asthma whereas the remaining (51.5%) were allergic to mites (70.6%), molds (17.6%) and animal dander (11.8%).

Baseline, placebo and post-salbutamol study

The mean values and the standard deviation (SD) of the 3 IOS measurements recorded at the baseline, post-placebo and post-salbutamol are listed in Table 1. Baseline within-test repeatability of IOS measurements was 4.1% for R5rs, 4.0 for R20rs and 5.6% for X5rs. Between-test variability (baseline-placebo) was 0.92 for R5rs, 0.74 for R20rs and 0.70 for X5rs. No difference was observed between averaged baseline and placebo recordings. Differences between baseline and post-salbutamol recordings are shown in Table 1. Indices of bronchodilator response are given in Table 2.

Table 2. Mean changes in lung function indices expressed as within subject standard deviation (wsSD) units, change as percent of the baseline values (Δ% baseline) and change as percent of the predicted values (Δ% predicted).

	wsSD units	Δ% baseline	Δ% predicted
R5Rs	-1.97 ± 1.51	-19.0 ± 12.7	-16.5 ± 12.6
R20Rs	-1.026 ± 1.61	-10.1 ± 16	-11.5 ± 16.1
X5Rs	1.27 ± 1.23	23.5 ± 21.3	22.0 ± 21.2
sRaw	Not done	-22.2 ± 16.4	-45.7 ± 42.2
FEV_1	Not done	7.5 ± 12.7	7.6 ± 11.8

Correlation

At the baseline we observed a degree of correlation between IOS measurements and both sRaw (p=0.006, r=0.49 for R5rs) and FEV_1 (p=0.006, r=-0.51 for R5rs and p=0.015, r=-0.46 for R20rs). Following salbutamol inhalation, IOS measurements correlated with sRaw (p=0.002, r=0.54 for R5rs and p=0.045, r=0.37 for R20rs) and FEV_1 (p<0.001, r=-0.63 for R5rs, p<0.001, r=-0.66 for R20rs and, p=0.004, r=0.54 for X5rs) values. Salbutamol-induced R5rs changes (Δ% baseline) showed a trend towards correlation with sRaw changes (p=0.07, r=0.33).

Comparative study between groups

When children were compared according to asthma aetiology, no differences in either baseline values or bronchodilator response were observed (Table 3).

Table 3. Mean values (given as percentage of the predicted values) of the lung function indices at the baseline.

	Atopic asthma	**Non-atopic asthma**
R5rs (%)	83.5 ± 15.3	88.6 ± 20.0
R20rs (%)	91.8 ± 18.9	87.0 ± 18.0
X5rs (%)	81.9 ± 20.8	87.8 ± 29.7
FEV_1(%)	112.9 ± 20.9	104.6 ± 21.2

Discussion

Lung function exploration is often difficult in young children [10]. Airway resistance is a direct reflection of bronchial caliber and can be used to evaluate airway narrowing. Impulse oscillometry is a non-invasive and effort-independent technique, that only requires breathing at tidal volume for 30 seconds [12]. We examined the repeatability and validity of IOS in 36 asthmatic children (3 to 6 yrs old) whose diagnosis was based upon recurrent episodes of wheezing, cough and dyspnea during the last year, with asthma as the most probable diagnosis [16]. The technique was well accepted by children (92%) and exhibited good within-test repeatability, with coefficients (4.1% for R5rs and 5.6% for X5rs) lower than both the 10% proposed as acceptable limit for R5rs in pre-school children [24] and those (10% for R5rs and 16% for X5rs) previously reported [12, 25].

Secondly, we evaluated the bronchodilator response to salbutamol and compared the results obtained with the three techniques. The t-test for paired data exhibited statistically significant changes between baseline and post-salbutamol recordings but not between baseline and post-placebo. Bronchodilator response was evaluated by the SD index, calculated from variability between baseline and post-placebo recordings. This index transforms the absolute changes experienced by one individual variable into multiples of its baseline repeatability allowing comparison with different measurements [12]. Changes from baseline ≥ 2-fold the baseline variability have been suggested as evidence of a significant bronchodilator effect [13]. In our study, R5rs was the index showing the greatest sensitivity to salbutamol inhalation, increasing nearly 2-fold the SD value.

Even in healthy children, salbutamol inhalation reduces the values of both R5rs and sRaw [26, 27], suggesting that these techniques (IOS and plethysmography) can detect minimal changes in airway caliber [24]. Consequently, drops in R5rs values of 29% [26] or even of 40% for other authors [27] have been proposed necessary to consider a bronchodilator response positive. The change in R5rs values observed in our study did not reach that limit which could be attributed to two facts: clinical stability of children at the time of the study and that half of them were on regular treatment with antiasthmatic drugs. In turn, airway reactance (X5rs), which is not modified by salbutamol in healthy children [28], changed in our study by 22% suggesting a real though small bronchodilator response.

Changes in IOS indices occurred in parallel with those observed in sRaw and FEV_1. Correlation observed at the baseline and following salbutamol inhalation between R5rs and, sRaw and FEV_1, gives coherence to IOS recordings in lung function exploration. The lack of higher degrees of correlation between salbutamol-induced changes recorded with the 3 techniques could be ascribed to the fact that they are measuring different aspects of lung dynamics: while sRaw exclusively measures airway resistance, FEV_1 is a flow-volume index that only indirectly reflects it. IOS impedance is subdivided into respiratory resistance, mainly determined by central airways caliber and respiratory reactance that depends upon the compliant properties of the chest-lung system (airways, lung tissue and chest wall) [11].

In some non-atopic children, asthma is presented as a benign and transient disease that probably reflects a congenitally narrow airway, predisposing to asthma symptoms in the context of viral respiratory infections [6]. In this group, regular prophylactic treatment is controversial [7]. We grouped patients into atopic and non-atopic asthma based on their responses to skin tests with common airborne and food allergens that were performed at the time of the study. The absence of differences between groups could be attributed to either small size of samples, short duration of asthma symptoms or clinical stability of children. It is also possible that, at the early stages of life, our criterion of grouping patients based upon skin test results is fictitious.

In conclusion, IOS is a simple and non- invasive technique that provides repeatable and valid indices to explore lung function in young children. Airway resistance at low frequencies (R5rs) is, according to our results, the index that shows the highest repeatability and validity. In clinical practice, IOS measurement could contribute to both, obtain additional information to forced spirometry manoeuvres and evaluate lung function among subjects in whom spirometry is no feasible. Further studies are needed to provide standardized guidelines on its usage and criteria for technical reliability of results.

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