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To cite this article: Oscar Ramirez , Ivan Alvarez , Ricardo Aristizabal-Duque , Milena Villamil , Monica P. Sossa-Briceño & Carlos E. Rodriguez-Martinez (2020): A comparative analysis of the bronchodilatator response measured by impulse oscillometry and spirometry in asthmatic children living at high altitude, Journal of Asthma, DOI: [10.1080/02770903.2020.1801722](https://doi.org/10.1080/02770903.2020.1801722)

To link to this article: <https://doi.org/10.1080/02770903.2020.1801722>



Published online: 04 Aug 2020.



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A comparative analysis of the bronchodilator response measured by impulse oscillometry and spirometry in asthmatic children living at high altitude

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ABSTRACT

Objective: Although the assessment of a bronchodilator response (BDR) is a routine and important procedure when performing lung function tests, comparisons between spirometric and oscillometric BDRs in asthmatic children living at high altitude have not been previously reported. The aim of the present study was to compare spirometric and oscillometric BDRs in children living at high altitude, and to identify independent predictors of spirometric and oscillometric BDRs.

Methods: Between January and December, 2015, asthmatic children aged between 5 and 17 years old performed impulse oscillometry (IOS) and spirometry during the same visit before and after albuterol administration. The data were analyzed, and children were classified into those positive for oscillometric BDR only, those positive for spirometric BDR only, those positive for both BDRs, and those negative for both BDRs.

Results: Ninety-three asthmatic children (56 boys, 37 girls), with a median (IQR) age of 11 (8-13) years, made up the study population. Among the total of 93 participants, 13 (14.0%), 4 (4.3%), 0 (0%), and 76 (81.7%) were positive for spirometric BDR only, positive for oscillometric BDR only, positive for both BDRs, and negative for both BDRs, respectively. Age and baseline lung function were identified as significant predictors of positive spirometric BDR.

Conclusions: The present study shows poor concordance between positive spirometric and oscillometric BDRs, with a greater proportion of patients with a spirometric BDR when compared to those with positive oscillometric BDR. Additionally, age and baseline lung function are useful for predicting spirometric BDR results.

ARTICLE HISTORY

Received 5 March 2020
Revised 12 June 2020
Accepted 21 July 2020

KEYWORDS

Asthma; childhood; spirometry; reversibility; impulse oscillometry; bronchodilator response

Introduction

Spirometry is the most commonly used pulmonary function test for helping to assess the ventilatory function in children with suspected or manifested obstructive airway diseases, such as asthma, and for confirming a clinical diagnosis, assessing severity, determining prognosis, and determining the effect of therapeutic interventions (1). This is, among other factors, because spirometry is a highly standardized, relatively simple, noninvasive, inexpensive, and readily available test (2). When performing a spirometry test, assessment of a bronchodilator response (BDR) is a routine and important procedure both in clinical practice and in research settings (3). The results of BDR tests are commonly used as a basis for classification of

disease and choice of treatment by clinicians and as an inclusion criterion for studies by researchers (4). Additionally, BDR can identify a phenotype of pediatric asthma that is associated with worse health outcomes such as low lung function and poor asthma control (5). However, spirometry tests mainly measure central airway caliber, and are dependent on lung volumes, elastic recoil, strength of respiratory muscles, and expiratory breathing maneuvers, but are less helpful than other measures of respiratory function when assessing small airway function, respiratory muscle-independent lung function, and mechanical properties of the lung. Impulse oscillometry (IOS) is an effort-independent pulmonary function technique that requires minimal patient cooperation and allows

measuring respiratory system resistance and reactance at different oscillation frequencies. Due to the fact that spirometry and IOS assess different aspects of lung function, IOS is now considered to be a useful supplement to spirometry, mainly in children with small airway hyperresponsiveness who may not be identified using spirometry (6). It has been shown that IOS parameters are more sensitive for identifying patients with asthma and for excluding those without asthma than conventional spirometric indices (7). In this regard, some studies aimed at comparing spirometric and oscillometric BDRs in asthmatic children have shown significantly greater BDR changes with IOS than observed with spirometry, suggesting that IOS might provide a useful diagnostic tool when monitoring the development of early asthma. However, to the best of our knowledge, none of these studies have been performed in children living at high altitude. Altitude above sea level could be a factor of central importance, because the decreased air density that obtains at higher elevations produces greater linear velocities of gases with the resultant increase in maximal flows, but only in large airways, with little or no effect on small-airway resistance (8). This is because small airways have fully developed laminar flow as opposed to large airways, where gas flow becomes more turbulent (8). Consequently, comparisons between spirometric and oscillometric BDRs in asthmatic children living at high altitudes could differ from those previously reported.

Accordingly, the aim of the present study was to compare spirometric and oscillometric BDRs in a population of asthmatic children living in Bogota, a Colombian city located at 2,640 m altitude. Additionally, the study was aimed at identifying independent predictors of spirometric and oscillometric BDRs.

Material and methods

Subjects

Children with a previous medical diagnosis of persistent asthma who were being regularly followed up in our respiratory unit, and were at least 5 years old, were invited to take part in this study between January and December, 2015, and only those who consented/assented were enrolled. Children with current or recent exacerbation of their asthmatic symptoms, and those with a significant chronic condition that was judged to interfere with the study aims, were excluded from the research.

Study design and procedures

After collecting sociodemographic information, the included children performed IOS and spirometry during the same visit, always performing spirometry immediately after IOS measurements, because of the impact that deep inhalation and forced expiratory maneuvers of spirometry have on IOS (i.e. resistance and reactance) values (9). The IOS parameters measured or calculated were resistance at 5 Hz (R5), resistance at 20 Hz (R20), the difference between R5 and R20 (R5-R20), reactance at 5 Hz (X5), resonant frequency (Fres), and reactance area (AX). The spirometric parameters obtained were forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), mean forced expiratory flow between 25% and 75% of FVC (FEF25-75%), and the ratio of FEV1 to FVC (FEV1/FVC).

Short-acting beta agonists were withdrawn at least 12 h before the IOS measurements. The IOS measurements were performed using a Jaeger MasterScreen Impulse Oscillometry system (Jaeger. Co, Wurzburg, Germany) between 8:00 a.m. and 12:00 p.m. by the same technician, who was previously trained to follow the procedures recommended in the official American Thoracic Society/European Respiratory Society (ATS/ERS) statement on pulmonary function testing in preschool children (10). Specifically, after a daily calibration using a 3-L syringe (for volume calibrations) and a reference resistance of 0.2 KPa/L/s (for pressure calibrations), three to five technically acceptable measurements were performed with the child seated with the neck slightly extended, breathing through a mouthpiece, and wearing a noseclip with the cheeks and mouth floor firmly supported. The quality control of the measurements was performed by visual inspection of the oscillometric traces, discarding measurements in which mouthpiece obstruction, cough, glottis closure, swallowing, breath holding, crying, vocalization, incomplete expiration, or leak around the mouthpiece were detected. Additionally, a coherence value ≥ 0.6 for R5 was considered to be an appropriate threshold for acceptability of the test. The reproducibility was assessed by means of the coefficient of variation, ensuring a value $< 10\%$ for both R5 and R20. As recommended, the acquisition time was 8 to 16 s, in order to include several breathing cycles. The spirometric procedure has been previously described in detail (11). Briefly, short-acting beta agonists were withdrawn for 12 h, and long-acting beta agonists were withdrawn for 24 h before the spirometric measurements. All the spirometric measurements were carried out with the same electronic spirometer (JAEGER

Vyntus™ SPIRO) between 8:00 a.m. and 12:00 p.m. by the same technician, who was previously trained to follow the procedures recommended by the American Thoracic Society-ATS/European Respiratory Society-ERS Task Force (12). Volume calibration was performed every day before data collection with a 3-l syringe. Spirometry parameter values were automatically corrected for body temperature, barometric pressure, and water vapor saturation (BTPS). The measurements were performed with the children in the sitting position, using a disposable mouthpiece and a nose clip. Children were first asked to take in a deep breath, to the maximum extent possible, and subsequently to exhale as hard and as fast as possible and keep going until there was no air left. A minimum of three and a maximum of eight spirometric maneuvers were performed, terminating the attempts when at least three maneuvers achieved the acceptability criteria and the best two of these measurements fulfilled the reproducibility criteria according to the ATS/ERS Task Force criteria for spirometry of acceptable quality. The best flow volume curve was selected for each participant based on the acceptable flow volume curve with the largest sum of FVC and FEV1.

Both the spirometric and the IOS measurements were repeated as described above 15 min after administration of 200 mcg of albuterol (Ventilan, GlaxoSmithKline) via a pressurized metered dose inhaler and a valved-holding chamber with a mouthpiece (Aero-chamber Plus®).

The study protocol was approved by the Research and Ethics Committee of the Santa Clara Hospital in Bogota. All parents and children gave consent/assent before study participation.

Lung function variable definitions

Following the recommendations given in the latest version of the European Respiratory Society (ERS) task force document on technical standards for respiratory oscillometry, a positive oscillometric BDR is defined as a decrease of at least 40% in R5, an increase of at least 50% in X5, or a decrease of at least 80% in AX after bronchodilator administration (13). A positive spirometric BDR was defined as the difference between pre and post-bronchodilator FEV1 percent predicted value equal to or greater than 12% (14). Subsequently, similarly to what was done by Sheen Y.H., et al., participants were classified into those positive for oscillometric BDR only, those positive for spirometric BDR only, those positive for both BDRs, and those negative for both BDRs (6).

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR), whichever is appropriate. Categorical variables are presented as numbers (percentage). Differences in continuous variables between the four above-mentioned categories of BDR (positive for oscillometric BDR only, positive for spirometric BDR only, positive for both BDRs, and negative for both BDRs) were analyzed using a one-way analysis of variance (ANOVA) with the post-hoc Tukey test or the non-parametric ANOVA (Kruskal-Wallis) test, as appropriate. Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test, whichever was appropriate.

The correlations between IOS and spirometric parameters were evaluated using Pearson's correlation coefficient (r) or Spearman's rank correlation coefficient (ρ), whichever was appropriate. The concordance between oscillometric and spirometric BDRs was evaluated using Cohen's kappa coefficient (k), considering $k > 0.75$ as excellent concordance, k between 0.40 and 0.75 as fair to good concordance, and $k < 0.40$ as poor concordance. Multinomial logistic regression models were adjusted in order to identify independent predictors of categories of BDR. Age, gender, and spirometric and oscillometric parameters measured by baseline (FEV1, R5 and X5) were included as control variables in the regression analyses.

Regression results are reported as relative risk ratios (RRRs) and their respective 95% confidence intervals (CI). All statistical tests were two-tailed, and the significance level used was $p < 0.05$. The data were analyzed with the Statistical Package Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study population

We included data from 93 stable asthmatic children in our analysis, with 56 male (60.2%) and 37 (39.8%) female subjects. The median (IQR) of the age was 11 (8–13) years, with the following age group distribution: 65 (69.9%) $\leq$ 12 years, and 28 (30.1%) $>$ 12 years. The categories did not differ from each other with respect to median age, weight, height, and gender (Table 1).

Baseline lung function measurements

Spirometric and IOS absolute (and percent of predicted) measurements at baseline, according to the

Table 1. Sociodemographic and lung function parameters, differentiated by categories of bronchodilator response (BDR)*.

Variable	Positive for spirometric BDR only (n = 13)	Positive for oscillometric BDR only (n = 4)	Negative for both BDRs (n = 76)	p value
Age (years), median (IQR)	11,0 (8,0-13,5)	11,0 (11,0-11,7)	11,0 (8,0-13,0)	0,975
Gender (M/F)	9/4	3/1	44/32	0,614
Weight, Kg	39,0 (30,0-47,5)	39,0 (32,5-45,5)	39,0 (29,0-49,5)	0,997
Height, cm	149,0 (127,5-152,0)	146,5 (134,7-156,0)	142,0 (127,5-155,0)	0,878
FEV1 pre-B2 / % predicted	1,85 (1,09-2,17)/ 83,4	2,32 (1,97-2,49)/ 99,5	2,25 (1,64-2,83)/ 107,0	0,028**
FEV1 post-B2 / % predicted	2,17 (1,29-2,56)/ 99,2	2,47 (2,11-2,62)/ 106,0	2,26 (1,69-2,86)/ 113,4	0,317
FVC pre-B2 / % predicted	2,78 (1,66-3,11)/ 104,0	2,79 (2,60-3,18)/ 111,5	2,57 (1,88-3,25)/ 106,1	0,740
FVC post-B2 / % predicted	2,92 (1,73-3,33)/ 108,7	2,78 (2,55-3,29)/ 112,2	2,58 (1,95-3,22)/ 107,9	0,804
R5 pre-B2 / % predicted	8,53 (4,55-9,40)/ 111,5	5,70 (5,28-8,49)/ 80,1	5,70 (4,43-6,95)/ 88,6	0,075
R5 post-B2 / % predicted	6,29 (3,83-7,13)/ 80,7	4,99 (3,70-6,42)/ 78,5	4,81 (3,41-5,99)/ 75,1	0,244
R20 pre-B2 / % predicted	5,54 (3,43-6,01)/ 93,5	4,67 (4,24-5,93)/ 92,3	4,34 (3,57-5,28)/ 91,6	0,272
R20 post-B2 / % predicted	4,67 (3,21-5,15)/ 82,2	4,77 (3,11-5,16)/ 91,1	3,72 (2,92-4,54)/ 74,8	0,156
X5 pre-B2 / % predicted	-2,44 (-2,74 - 2,01)/ 102,8	-1,79 (-1,92 - 1,00)/ 87,7	-1,84 (-2,19 - 1,28)/ 88,4	0,003**
X5 post-B2 / % predicted	-1,65 (-1,83 - 1,36)/ 72,7	-1,22 (-1,63 - 0,50)/ 67,2	-1,43 (-1,80 - 1,08)/ 75,5	0,238
Fres pre-B2	27,62 (21,05-53,45)	21,38 (15,12-47,84)	20,82 (16,89-27,19)	0,132
Fres post-B2	20,27 (15,12-24,63)	16,72 (9,03-49,76)	18,37 (13,26-20,82)	0,249
AX pre-B2	22,68 (10,49-42,62)	14,00 (6,05-58,16)	12,65 (6,06-21,54)	0,117
AX post-B2	12,36 (6,27-18,93)	4,09 (1,06-7,00)	8,05 (3,74-14,81)	0,054

*BDR: bronchodilator response, IQR: interquartile range, FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, R5: resistance at 5 Hz, R20: resistance at 20 Hz, X5: reactance at 5 Hz, Fres: resonant frequency, AX: reactance area.

** $p < 0.05$.

categories of BDR, are presented in Table 1. The majority of these associations are self-explanatory. However, some deserve special attention: FEV1 and X5 measured at baseline were significantly different among the categories analyzed.

Bronchodilator response

Spirometric and IOS absolute (and percent of predicted) post-bronchodilator measurements, according to the categories of BDR, are presented in Table 1. A significantly greater proportion of patients were positive for spirometric BDR as compared to oscillometric BDR. (14.0% vs. 4.3%, $p < 0.001$).

Correlation and concordance between spirometric and oscillometric measurements

There were statistically significant correlations between FEV1 and all IOS parameters measured at baseline. Likewise, at baseline, FVC correlated significantly with all IOS measurements (Table 2). The strongest correlation was between FEV1 and R5 ($\rho = -0.753$, $p < 0.001$) (Table 2). Among the total of 93 participants, 13 (14.0%), 4 (4.3%), 0 (0%), and 76 (81.7%) were positive for spirometric BDR only, positive for oscillometric BDR only, positive for both BDRs, and negative for both BDRs, respectively.

The concordance between oscillometric and spirometric BDRs yielded poor and non-significant concordance ($k = 0.006$, $p = 0.410$).

Clinical characteristics of children with different spirometric and oscillometric BDR results

As was mentioned above, multinomial logistic regression models were adjusted in order to identify independent predictors of categories of BDR. By default, Stata chose the most frequently occurring category (patients negative for both BDRs) to be the control group. Therefore, in the multinomial logistic regression analyses, we found that age and baseline FEV1 were independent predictors of a positive spirometric BDR only (relative to patients negative for both BDRs). Likewise, relative to patients negative for both BDRs, R5 and X5 measured at baseline tended to be independent predictors of a positive oscillometric BDR only, although they did not reach statistical significance (Table 3).

Discussion

The present study shows a poor concordance between positive spirometric and oscillometric BDR in a population of pediatric patients with stable asthma living in a city located at high altitude, with a significantly greater proportion of patients with a spirometric BDR when compared to those with positive oscillometric BDR. Additionally, the findings of the present study suggest that age and baseline lung function are relevant predictors of a positive spirometric BDR.

The most striking result to emerge from the present study is that we have provided additional information on the comparison of the BDR measured by

Table 2. Correlations between oscillometric and spirometric parameters measured at baseline*.

	R5	R20	X5	Fres	AX
FEV1	−0,753**	−0,646**	0,616**	−0,613**	−0,684**
FVC	−0,671**	−0,586**	0,537**	−0,516**	−0,595**

*The correlations between IOS and spirometric parameters were evaluated using the Spearman's rank correlation coefficient (ρ). FEV1: forced expiratory volume in the first second, FVC: forced vital capacity, R5: resistance at 5 Hz, R20: resistance at 20 Hz, X5: reactance at 5 Hz, Fres: resonant frequency, AX: reactance area.

**Correlation is significant at the 0,01 level (2-tailed).

spirometry and by IOS in stable asthmatic patients, but on this occasion, in children living in a city located at 2,640 m altitude. Due to the fact that the decreased air density that occurs at higher elevations produces an increase in maximal flows in large airways (with little or no effect on small-airway resistance) (8), it is plausible to consider that BDR measurements performed at high altitudes could influence spirometric more than oscillometric results. This is mainly because spirometry and IOS evaluate different portions of the respiratory system: while spirometric parameters evaluate mainly central airway caliber, the difference between the resistance measured at low-frequency and high-frequency signals (R5-R20) in IOS represents the resistance of the distal airways (15). In this respect, in contrast with what was previously reported in other studies performed at lower altitudes (7,16,17), in our study spirometry was superior to IOS for detecting BDR, supporting the concept that in childhood asthma the flow-limiting segments are in larger airways, where flow is density-dependent (18), because of the decreased air density that occurs at higher elevations (8), as is the case for the present study. Nevertheless, an alternative explanation is worth considering: although there is a recent consensus stating that a positive oscillometric BDR is defined as a decrease of at least 40% in R5, an increase of at least 50% in X5, or an decrease of at least 80% in AX after bronchodilator administration (13), the results may vary if earlier definitions are taken into account. Specifically, when using the same definition of positive oscillometric BDR used in other published studies ($\geq 20\%$ and $\geq 40\%$ decline from baseline in R5 and AX, respectively) (17,19), 28 (30.1%) children would be considered to have a positive oscillometric BDR (data not shown), which would indicate a greater proportion of patients with a positive oscillometric BDR when compared to those with positive spirometric BDR.

With respect to the differences between spirometric and oscillometric BDRs, it is worth considering the effect of the deep breath, which is necessary for performing the spirometric maneuvers, but not the IOS

Table 3. Predictors of spirometric and oscillometric bronchodilator response in pediatric asthmatic patients, in multivariate analysis*.

Category/ variable	Relative risk ratios (RRRs) (CI 95%)	p-value
Positive for spirometric BDR only		
Age	2,95 (1,52-5,73)	0,001
Gender	0,26 (0,04-1,57)	0,144
FEV1	0,005 (0,0002-0,11)	0,001
R5	1,26 (0,73-2,17)	0,404
X5	1,48 (0,49-4,43)	0,480
Positive for oscillometric BDR only		
Age	1,64 (0,73-3,71)	0,228
Gender	0,48 (0,03-6,40)	0,580
FEV1	0,45 (0,01-14,84)	0,655
R5	2,46 (0,87-6,93)	0,088
X5	10,05 (0,72-139,51)	0,085

*Patients negative for both BDRs was the control group. BDR: bronchodilator response, FEV1: forced expiratory volume in the first second, R5: resistance at 5 Hz, X5: reactance at 5 Hz.

measurements. Mildly asthmatic patients tend to bronchodilate after a deep inhalation, so mild bronchoconstriction could be masked by the bronchodilating effects of performing spirometric maneuvers, but should still be evident when performing IOS measurements (20). Additionally, while specific airway resistance is sensitive to changes in resistance anywhere along the airway, FEV1 is sensitive to only those changes occurring upstream from the choke point, therefore making it possible that depending on the location of the airway dilation in response to a bronchodilator, the airway resistance may change without significant change in FEV1 (20). Finally, due to the fact that spirometric maneuvers may be difficult to achieve, because they are effort dependent and require more cooperation and motivation than IOS maneuvers, it is possible that spirometric maneuvers may have been affected by undercooperation of some children, especially some post-bronchodilator measurements (6).

With regard to the prediction of differential BDR, baseline lung function was a relevant predictor of different spirometric and oscillometric BDRs. These findings are in complete agreement with previous reports in the literature showing that low FEV1 baseline values predict a positive spirometric BDR (6,12), and low baseline IOS values predict a positive oscillometric BDR (6,21–23).

Our results regarding a significant and positive relationship between age and spirometric BDR in the multivariable analysis is consistent with previous observations that have reported that the level of response to bronchodilators increases significantly with increasing age in asthmatic children (24). Moreover, the greater strength of association observed between age and spirometric BDR when compared to

age and oscillometric BDR is consistent with previous studies suggesting that the advantages that IOS has with regard to the lung physiology (the possibility of measuring the small airway “quiet zone”, enabling respiratory system distensibility and identification of nonuniformities in airflow distribution) may result in a better differentiation of airway hyperreactivity in young children when using IOS compared with the spirometry (6).

We are aware that our study may have at least two limitations. The first is the small sample size, which may have reduced the power of the regression analyses. The second is that we could have missed important relevant predictors in the regression analyses, so interpretation of our findings needs to be cautious. However, we are confident that we have provided further evidence for comparative analyses on spirometric and oscillometric BDRs, in this case in children living at high altitude.

Conclusion/key findings

In conclusion, the present study shows a poor concordance between positive spirometric and oscillometric BDR in a population of pediatric patients with stable asthma living in a city located at high altitude, with a significantly greater proportion of patients with a spirometric BDR when compared to those with positive oscillometric BDR. Additionally, certain clinical characteristics such as age and baseline lung function, are useful for predicting spirometric results. Future studies must determine if these clinical characteristics could also be useful for identifying subsets of patients with worse asthma health outcomes.

Acknowledgements

The authors thank Mr. Charlie Barret for his editorial assistance.

Declarations of interest

None.

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