Impulse oscillometry bronchodilator response in preschool children

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Abstract

Background: In preschoolers, performing an acceptable spirometry and measuring bronchodilator response (BDR) is challenging; impulse oscillometry (IOS) may be an alternative to spirometry. However, there is still no consensus in standardization of BDR for IOS in young children. **Objective**: The objective of the study was to identify optimal thresholds to define a positive BDR test with IOS. **Methods**: Young infants aged 3 to 6 years with suspected asthma were evaluated in a real life setting with both IOS and spirometry pre- and post-BDR. The BDR was defined as positive when the change of FEV1 was [?]12% and/or [?]200 mL. **Results**: Among 72 patients (age 4.98 ± 0.94 years; 64% boys), 36 (age 5.15 ± 0.99 years; 64% boys) were selected for the subsequent analysis according to ATS / ERS quality criteria of measurements. The spirometric BDR was found positive in seven subjects (19.4%). In IOS, the mean decrease in R5 and AX was 19.86% ± 10.04 and 44% ± 22.10, and the mean increase in X5 was 23.28% ± 17.82, respectively. A decrease in R5 of 25.7% (AUC 0.77, p = 0.03) and an increase in X5 of 25.7% (AUC 0.75, p = 0.04) showed the best combination of sensitivity and specificity to detect an increase of FEV1 [?]12% and/or [?]200 mL. **Conclusion**: The IOS may present a valid alternative to spirometry to measure BDR in preschool children. We are considering a decrease of 26% in R5 and an increase of 26% in X5 as diagnostic threshold for BDR.

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Keyword: oscillometry, spirometry, bronchodilator response, Preschool asthma

Introduction

Asthma is a common, chronic respiratory disease affecting an estimated 300 million individuals worldwide and all age groups. Global paediatric asthma prevalence has increased strikingly since the 1950s. Asthma is now the most common chronic respiratory condition affecting approximately 5.5 million subjects in the European Union, making it a leading cause of emergency department visits and 1 of the top 3 indications for hospitalization [1-4].

In preschool children, wheezing is one of the most common symptoms in clinical practice. Approximately one in three children has at least one episode of wheeze before their third birthday and a considerable minority of children will continue to experience wheezing in school years and beyond, diagnosed as asthmatic [5-7]. Moreover, preschoolers have the highest rate of unscheduled medical visits and more limitations of everyday activities for wheezing and asthma symptoms, compared with all other age groups [5,8,9]. However, there is considerable uncertainty in the diagnosis of asthma in preschool age, since lung function testing can rarely be performed in children below 3 years. In addition, there is no gold-standard to confirm the diagnosis of asthma and no single abnormal test by itself is sufficient to make the diagnosis [2]. Specifically, a recent European Respiratory Society (ERS) clinical practice guideline recommends using objective tests such as spirometry, bronchodilator reversibility test (BDR) and fractional exhaled nitric oxide (FeNO) as first line tests and bronchial challenge tests as second line tests [2,10].

Spirometry is the most common pulmonary function test, widely used in the non-invasive assessment of lung function to provide objective information for the diagnosis of lung diseases and monitoring lung health. In presence of an experienced operator, spirometry is achievable in the majority of children aged [?]5 years and major asthma guidelines recommend performing it as part of asthma diagnostic work-up [1,2,11-13]. It is important to note that spirometry as a one-off measurement has a low sensitivity and is therefore poor at excluding asthma. Due to the variable nature of the condition, it may result in normal values also in asthmatic patients and serial measurements may be required to confirm the diagnosis. Conversely, abnormal spirometry has good specificity for asthma [2,12].

In contrast with spirometry, which requires the active participation of the patient, the IOS represents an alternative technique to investigate lung function performing an effort-independent analysis of the mechanical properties of the lungs during tidal breathing. Several studies demonstrated that IOS may represent a key tool in studying respiratory function in preschool children (mainly over 3 years old) [14-21]. In this scenario, there is increasing research on IOS that, with or without bronchodilator reversibility, may represent a useful diagnostic tool in patients who cannot perform acceptable and reproducible spirometry manoeuvres [10,14,15-21]. Different studies have shown that a bronchodilator response (BDR) based on IOS is better than one based on spirometry. In children, several studies showed that a BDR based on IOS discriminates better asthmatic

from healthy subjects than one based on spirometry. However, in preschoolers, data are conflicting since in some studies IOS were not able to discriminate wheezy and non-wheezy patients [14,22-25].

Given the diversity of age ranges, equipment and protocols, there is still no consensus in the literature regarding standardization of the cut-off point for the bronchodilator response in preschoolers [14,22]. In past years, several authors suggested different cut-offs between 20-40% [14,23,26,27]. Nevertheless, a recent ERS technical standard suggests that a change of at least -40% in resistance at 5 Hz (R5), +50% in reactance at 5 Hz (X5) and -80% in area of reactance (AX) is required to consider as positive the response in either children or adults [14, 15]. The objective of the present study was to identify the optimal thresholds to define a positive BDR test with IOS in preschoolers with suspected asthma.

Patients and methods

Preschool children aged 3-6 years who attended between 01.05.2022 and 30.11.2022 the Division of Paediatric Allergy, Pulmonology and Cystic Fibrosis of the University Hospital in Frankfurt with suspected asthma were retrospectively analysed.

All children had a history of recurrent episodes of physician-documented wheezing, cough and/or respiratory distress with bronchodilator responsiveness of which at least one episode in the last 12 months. Furthermore, they were free from respiratory tract infections for [?]2 weeks prior to the measurements.

Atopy in children was defined as a positive skin prick test (SPT) $>$ 3 mm against common allergens (birch, grass, house dust mites, cat, milk and egg).

Patients receiving SABA and LABA, in the last 6 and 24 hours respectively, were excluded as well as those suffering from chronic disease or infections affecting the respiratory system (e.g., congenital heart disease, cystic fibrosis, bronchopulmonary dysplasia, tuberculosis, HIV).

Ethics approval was obtained from the ethics committee of the Goethe University in Frankfurt (Application Number 2022-1094). According to the German Federal Data Protection Act (BDSG) there is no right to information under article 15 of regulation (EU) 2016/679, as the data is required for scientific research purposes and providing the information would require a disproportionate effort.

Assessment of asthma control

The respiratory control of patients was assessed with the 5-item, caregiver-completed test for Respiratory and Asthma Control in Kids (TRACK). It includes frequency of respiratory symptoms (wheeze, cough, shortness of breath), activity limitation, and night-time awakenings in the past 4 weeks, rescue medication use in the past 3 months, and oral corticosteroid use in the previous year [28]. A total score of less than 80 suggests a suboptimal respiratory control status [29].

IOS measurements

IOS measurements were performed using a Vyntus(r) APS/IOS (Vyaire GmbH, Hochberg, Germany), calibrated daily with a 3 L syringe as directed by the manufacturer, and analysed using the SentrySuite(r) software package (version 3.10). According to current international recommendations, measurements were taken before spirometry to avoid the effect of forced spirometry manoeuvres on bronchial tone [15]. IOS measurements were performed in accordance with ERS guidelines [28]. Prior to testing, each child was familiarized with the procedure. During the measurement, the patient remained seated with the head in a neutral or slightly extended position, breathing through a mouthpiece and wearing a nose clip; moreover, the patient's cheeks were firmly maintained by the hands of the investigator or caregiver to minimize pressure losses. Only triplicate artefact-free IOS measurements lasting [?]20 s with a coherence value [?] 0.8 in R5 and [?] 0.9 in R20 and a coefficient of variation [?] 15% were selected.

Spirometry measurements

Spirometry measurements were conducted using a Vyntus(r) APS/IOS (Vyaire GmbH, Hochberg, Germany), calibrated daily with a 3 L syringe according to the manufacturer's instructions, and analysed using the Sen-

trySuite(r) software package (version 3.10). Spirometry was performed in accordance with ATS/ERS guidelines and after explanation and demonstration of the correct execution technique [57]. Among measurements fulfilling acceptability and usability criteria, three acceptable flow volume loops (FVL) were selected, with the second highest forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) within 0.1 L or 10% of the highest value.

Bronchodilator response (BDR)

One measurement according to the aforementioned criteria 15 min after administration of 400 µg of salbutamol via a metered-dose inhaler with spacer was selected for both IOS and spirometry. The spirometric BDR was defined as positive when change of forced expiratory volume in one second (FEV1) was [?]12% and/or [?] 200 mL.

Statistical analyses

Statistical analyses were conducted using GraphPad Prism 9.5.0 (GraphPad Software, LLC). Pulmonary function parameters and their respective z-scores were expressed as means and standard deviations (SDs). The correlations between IOS and spirometric parameters were evaluated using Spearman's rank correlation coefficient (ϱ). The correlation was considered minimal when ϱ was between 0 and 0.2, low when between 0.2 and 0.4; moderate between 0.4 and 0.6; good between 0.6 and 0.8; and very good between 0.8 and 1.

Pre- and post-BDR measures were compared using Wilcoxon signed-rank test, and differences between groups were evaluated using Mann-Whitney U-test.

To define the sensitivity and specificity of IOS parameters to detect an increase of 12% in FEV1, a receiver-operating characteristic (ROC) curve was plotted; cut-off levels were optimised using the Youden index (sensitivity + specificity - 1), and the accuracy was measured by the area under the ROC curve. A p-value of <0.05 was considered as statistically significant.

Results

Subjects

Among 72 patient records (mean age 4,98 ± 0,94 yrs; 64% boys) preliminarily identified as meeting the previously mentioned anamnestic inclusion criteria, 36 (mean age 5,15 ± 0,99 yrs; 64% boys) were associated with high-quality pulmonary function measurements for both IOS and spirometry and therefore selected for the subsequent statistical analysis. Their clinical characteristics are summarized in Table 1.

The selected patients were 23 male and 13 female with a mean age of 5,15 ± 0,99 years; 19 of 36 were atopic and 14 took control medications, specifically 1 LTRA (Montelukast), 5 ICS (Fluticasone) and 8 ICS + LABA (Fluticasone + Salmeterol).

Baseline lung function measurements

The baseline lung function measurements are presented in Table 2 and were characterized by a good correlation between FEV1 and the main IOS parameters. Specifically, the Spearman's rank correlation coefficient (ϱ) between FEV1 and R5, X5 and AX was of -0,67 ($p<0.0001$), 0,62 ($p<0.0001$) and 0,6 ($p=0.0001$), respectively.

Bronchodilator response

A positive spirometric BDR was detected in 7 patients (19.4% of total), who presented a mean increase in FEV1 on baseline of 18.71% ± 5.91.

Mean percentual changes on baseline of oscillometric parameters R5 and X5 differed significantly between patients with positive and negative spirometric BDR (Table 3). Patients with a positive BDR showed a decrease of 26.82% ± 6.58 in R5 whereas those with a negative BDR showed a decrease of 18.18% ± 10.08 for the same parameter ($p = 0.03$). Similarly, the increase in X5 resulted of 34.3% ± 9.83 and 20.59% ± 18.43 in subjects with a positive and a negative BDR, respectively ($p = 0.04$).

The Mann-Whitney U-test highlighted no significant differences in baseline IOS parameters between BDR-positive and BDR-negative patients (Table 4); furthermore, no significant differences emerged in clinical characteristics (age, atopy, TRACK score, taking of control medications). The modifications in all analyzed parameters for spirometry and IOS in all patients after BDR test are summarized in Table 5. All post-bronchodilation values were significantly different in relation to the respective pre-bronchodilation for all analysed indexes.

The mean modifications on baseline of main IOS parameters were -19.86% +- 10.04 ($p<0.0001$) in R5, 23.25% +- 17.85 ($p<0.0001$) in X5, and -44.63% +- 22.1 ($p<0.0001$) in AX.

After bronchodilator administration, the correlation between FEV1 and R5, X5 and AX was good only for R5 (ρ=-0.64; $p<0.0001$), whereas resulted moderate for X5 (ρ=0.42; p=0.01) and AX (ρ=-0.44; p=0.007). Finally, in assessing BDR, no significant correlation was found between FEV1 and all analyzed IOS parameters in terms of percentual change on baseline.

ROC curve analyses and optimal cut-off values

The performance of IOS parameters in predicting a positive BDR was assessed calculating the ROC curve for each analyzed parameter, that resulted significant only for R5 and X5 (figure 1).

A decrease in R5 of 25.7% on baseline exhibited the best combination of sensitivity and specificity (0.71 [95%CI 0.36-0.95] and 0,79 [95%CI 0.62-0.9], respectively) to detect an increase of FEV1 [?]12% and/or [?]200 mL with an area under the ROC (AUC) of 0.77 ($p = 0.03$).

Similarly, an increase in X5 of 25.7% on baseline resulted the optimal cut-off in terms of sensitivity and specificity (0.86 [95%CI 0.49-0.99] and 0.69 [95%CI 0.51-0.83], respectively) with an AUC of 0.75 ($p = 0.04$). Conversely, AX was not able to discriminate between a positive and negative BDR test (AUC 0.53; $p = 0.83$).

Discussion

In preschool age the diagnosis of asthma is particularly challenging due to both the heterogeneity of wheezing and to the difficulties of performing acceptable and reproducible spirometric manoeuvres. However, objectifying the lung function of these patients remains crucial to reduce the risk of misdiagnosis, over and under treatment of patients. In this context, the IOS represents a useful method for assessing lung function and BDR in young children. Several studies have demonstrated that IOS is capable of identifying airway obstruction and response to bronchodilators and bronchoconstrictors [17,19,23,24,26,27,30].

The presented study was aimed to identify the optimal oscillometric cut-offs of the BDR in preschool children with history and symptoms consistent with asthma. Regarding baseline measurements, we found a significant good correlation between FEV1 and IOS indices R5 (ρ=-0.67), X5 (ρ=0.62) and AX (ρ=0.6). Previously, Carvalho et al. found a significant weak to moderate associations only between FEV1 and IOS parameters that reflect small airway obstruction (Di5-20 and AX), whereas the correlation between FEV1 and R5 was minimal [31].

However, after BPD, a significant good correlation with FEV1 was demonstrated only for R5 (ρ=-0.64) whereas X5 and AX exhibited a significant moderate correlation (ρ=0.42 and ρ=-0.44, respectively). These data are consistent with those published by Olaguíbel et al., who demonstrated that R5 was correlated with FEV1 at both baseline and post-bronchodilator in 33 asthmatic preschoolers [32]. Moreover, among IOS parameters, R5 and X5 differed significantly between patients with positive and negative BDR. Specifically, the magnitude of this variation was of 26.82% ± 6.58 vs. 18.18% ± 10.08 for R5 and of 34.3% ± 9.83 vs. 20.59% ± 18.43 for X5 in patients with positive and negative BDR test, respectively. Considering that a positive BDR in patients with a symptom pattern consistent with asthma configures these patients as asthmatic and that in older children IOS is more sensitive than spirometry in assessing BDR, this finding is not surprising [10,22].

Contrary to findings by Malmberg et al., in our study the BDR was not related to baseline lung function since no significant difference in baseline spirometry and IOS parameters was found between patients with positive- and negative BDR [33].

Regarding to the optimal cut-offs for establishing a positive BDR with IOS in preschool children, we found that a decrease in R5 of 25.7% and an increase in X5 of 25.7% on baseline exhibited the best combination of sensitivity and specificity to detect an increase of FEV1 [?]12% and/or [?]200 mL with an AUC of 0,77 and 0,75, respectively. A recent ERS technical standard stated that recommended IOS thresholds that define BDR for both children and adults are -40% in R5, +50% in X5 and -80% in AX [34]. However, in preschoolers, there is still no consensus in the literature regarding standardization of oscillometric cut-offs for BDR.

Our findings are in close agreement with those obtained by Gleason et al. and Bisgaard and Nielsen, who suggested as cut-off a decrease in R5 of respectively 24% and 29% in children aged 2 to 6 years [35,36]. Similarly, Marotta et al. proposed to consider a decrease between 20 and 25% in R5 as a positive IOS BDR and this range was confirmed by Konstantinou et al. and Shin et al., who found a cut-off of 20.5% and 19% respectively [23,30,37]. In contrast, different results were obtained by other studies, that proposed a decrease in R5 between 37% and 43% as threshold to define a positive BDR [24-26].

In reference to X5 parameter, Shin et al. reported results comparable with those obtained in our work since they considered an increase of 24% as a positive BDR [30]. Nielsen et al. and Thamrin et al., on the other hand, fixed this threshold at 42 and 61%, respectively [25, 34, 35].

Finally, in our study, AX was not able to discriminate between a positive and negative BDR test (AUC 0,53; p = 0,83) although the work of Oostveen et al. suggested that a decrease on baseline of 81% is indicative for a positive BDR [24].

The large discrepancies detectable between the previously mentioned studies might be attributable to differences in IOS technique, populations, and study design. In fact, many of the reported thresholds for different oscillometric parameters are based on varying, heterogeneous criteria for the differentiation between asthmatic and non-asthmatic subjects (e.g., clinical diagnoses, questionnaire-based diagnoses). This fact, combined with the wide heterogeneity of preschool wheezing that complicates the diagnostic work-up of asthma in these patients, might explain the different results of various studies.

Our threshold values for oscillometric parameters were based on an objective criterion, such as a 12% increase in FEV1 and/or [?] 200 mL in patients able to perform acceptable and reproducible spirometry and high quality oscillometric measurements. This explains the small number of patients analyzed (n=36) despite the larger number of patients initially examined (n=72).

Nevertheless, the small number of evaluated patients and the retrospective nature of the study remain a limitation of the presented work. Furthermore, the approach to derive oscillometric thresholds from a less sensitive technique such as spirometry remains a limitation. However, BDR in spirometry still presents an objective consensus technique to diagnose asthma and might therefore be superior to discriminating thresholds by clinical parameters.

In conclusion, the IOS represents a useful technique since it requires only minimal collaboration of the patient and provides additional information to the spirometry; moreover, the BDR test is a further tool able to improve the sensitivity of IOS in detecting patients with small airway obstruction. Our data demonstrated a positive BDR at a 26% decrease in R5 and a 26% increase in X5 in preschoolers with symptoms consistent with asthma.

References

Global Strategy for Asthma Management and Prevention. 2022. Available online: https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf (accessed on 10 November 2022).

Gaillard EA, Kuehni CE, Turner S, Goutaki M, Holden KA, de Jong CCM, Lex C, Lo DKH, Lucas JS, Midulla F, Mozun R, Piacentini G, Rigau D, Rottier B, Thomas M, Tonia T, Usemann J, Yilmaz O, Zacharasiewicz A, Moeller A. European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years. Eur Respir J. 2021 Nov 4;58(5):2004173. doi: 10.1183/13993003.04173-2020. PMID: 33863747.

Patel SJ, Teach SJ. Asthma. Pediatr Rev. 2019 Nov;40(11):549-567. doi: 10.1542/pir.2018-0282. PMID: 31676529; PMCID: PMC6818355.

Achakulwisut P, Brauer M, Hystad P, Anenberg SC. Global, national, and urban burdens of paediatric asthma incidence attributable to ambient NO_2 pollution: estimates from global datasets. Lancet Planet Health. 2019 Apr;3(4):e166-e178. doi: 10.1016/S2542-5196(19)30046-4. Epub 2019 Apr 11. PMID: 30981709.

Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, Henderson J, Kuehni CE, Merkus PJ, Pedersen S, Valiulis A, Wennergren G, Bush A. Classification and pharmacological treatment of preschool wheezing: changes since 2008. Eur Respir J. 2014 Apr;43(4):1172-7. doi: 10.1183/09031936.00199913. Epub 2014 Feb 13. PMID: 24525447.

Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. Lancet. 2014 May 3;383(9928):1593-604. doi: 10.1016/S0140-6736(14)60615-2. PMID: 24792856.

Ruszczyński M, Ambrożej D, Adamiec A, Ryczaj K, Elenius V, Cavkaytar O, Maggina P, Makrinioti H, Papadopoulos N, Hedlin G, Konradsen JR, Schaub B, H Smits H, Jartti T, Feleszko W; EAACI Task Force on Clinical Practice Recommendations on Preschool Wheeze. Preschool wheezing and asthma in children: A systematic review of guidelines and quality appraisal with the AGREE II instrument. Pediatr Allergy Immunol. 2021 Jan;32(1):92-105. doi: 10.1111/pai.13334. Epub 2020 Oct 5. PMID: 32816386.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995 Jan 19;332(3):133-8. doi: 10.1056/NEJM199501193320301. PMID: 7800004.

Grigg J, Nibber A, Paton JY, Chisholm A, Guilbert TW, Kaplan A, Turner S, Roche N, Hillyer EV, Price DB; Respiratory Effectiveness Group. Matched cohort study of therapeutic strategies to prevent preschool wheezing/asthma attacks. J Asthma Allergy. 2018 Dec 11;11:309-321. doi: 10.2147/JAA.S178531. PMID: 30588038; PMCID: PMC6294169.

Chawes B, Elenius V. Pulmonary function testing for the diagnosis of asthma in preschool children. Curr Opin Allergy Clin Immunol. 2022 Apr 1;22(2):101-106. doi: 10.1097/ACI.0000000000000815. PMID: 35197431.

National Institute for Health and Care Excellence. Asthma: Diagnosis, Monitoring and Chronic Asthma Management. NICE Guideline [NG80]. Available from: www.nice.org.uk/guidance/ng80 Date last updated: 22 March 2021. Date last accessed: 18 November 2022.

Lo D, Beardsmore C, Roland D, Richardson M, Yang Y, Danvers L, Wilson A, Gaillard EA. Spirometry and FeNO testing for asthma in children in UK primary care: a prospective observational cohort study of feasibility and acceptability. Br J Gen Pract. 2020 Oct 29;70(700):e809-e816. doi: 10.3399/bjgp20X713033. PMID: 33077507; PMCID: PMC7575406.

Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, Cooper BG, Culver B, Derom E, Hall GL, Hallstrand TS, Leuppi JD, MacIntyre N, McCormack M, Rosenfeld M, Swenson ER. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J. 2022 Jul 13;60(1):2101499. doi: 10.1183/13993003.01499-2021. PMID: 34949706.

Medeiros D, Castro P, Bianca ACD, Sarinho E, Araújo JF, Correia Junior M, Rizzo JA. Impulse oscillometry: pulmonary function assessment in preschool children. Expert Rev Respir Med. 2020 Dec;14(12):1261-1266.

doi: 10.1080/17476348.2020.1813573. Epub 2020 Sep 20. PMID: 32852224.

Song TW, Kim KW, Kim ES, Park JW, Sohn MH, Kim KE. Utility of impulse oscillometry in young children with asthma. Pediatr Allergy Immunol. 2008 Dec;19(8):763-8. doi: 10.1111/j.1399-3038.2008.00734.x. Epub 2008 Mar 7. PMID: 18331417.

Knihtilä H, Kotaniemi-Syrjänen A, Pelkonen AS, Kalliola S, Mäkelä MJ, Malmberg LP. Small airway oscillometry indices: Repeatability and bronchodilator responsiveness in young children. Pediatr Pulmonol. 2017 Oct;52(10):1260-1267. doi: 10.1002/ppul.23794. Epub 2017 Aug 18. PMID: 28834381.

Schulze J, Smith HJ, Fuchs J, Herrmann E, Dressler M, Rose MA, Zielen S. Methacholine challenge in young children as evaluated by spirometry and impulse oscillometry. Respir Med. 2012 May;106(5):627-34. doi: 10.1016/j.rmed.2012.01.007. Epub 2012 Feb 10. PMID: 22326606.

Schulze J, Biedebach S, Christmann M, Herrmann E, Voss S, Zielen S. Impulse Oscillometry as a Predictor of Asthma Exacerbations in Young Children. Respiration. 2016;91(2):107-14. doi: 10.1159/000442448. Epub 2016 Jan 13. PMID: 26756585.

Bailly C, Crenesse D, Albertini M. Evaluation of impulse oscillometry during bronchial challenge testing in children. Pediatr Pulmonol. 2011 Dec;46(12):1209-14. doi: 10.1002/ppul.21492. Epub 2011 Jun 1. PMID: 21634033.

Burman J, Malmberg LP, Remes S, Jartti T, Pelkonen AS, Mäkelä MJ. Impulse oscillometry and free-running tests for diagnosing asthma and monitoring lung function in young children. Ann Allergy Asthma Immunol. 2021 Sep;127(3):326-333. doi: 10.1016/j.anai.2021.03.030. Epub 2021 Apr 2. PMID: 33819614.

Ling Y, Si M, Niu Y, Han Y, Xu Y. The predictive value of impulse oscillometry for asthma exacerbations in childhood: A systematic review and meta-analyses. Pediatr Pulmonol. 2021 Jul;56(7):1850-1856. doi: 10.1002/ppul.25374. Epub 2021 Mar 23. PMID: 33756052; PMCID: PMC8251639.

Kaminsky DA, Simpson SJ, Berger KI, Calverley P, de Melo PL, Dandurand R, Dellacà RL, Farah CS, Farré R, Hall GL, Ioan I, Irvin CG, Kaczka DW, King GG, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oostveen E, Oppenheimer BW, Robinson PD, van den Berge M, Thamrin C. Clinical significance and applications of oscillometry. Eur Respir Rev. 2022 Feb 9;31(163):210208. doi: 10.1183/16000617.0208-2021. PMID: 35140105; PMCID: PMC9488764.

Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. J Allergy Clin Immunol. 2003 Aug;112(2):317-22. doi: 10.1067/mai.2003.1627. PMID: 12897737.

Oostveen E, Dom S, Desager K, Hagendorens M, De Backer W, Weyler J. Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes. Eur Respir J. 2010 Apr;35(4):865-72. doi: 10.1183/09031936.00023409. Epub 2009 Nov 19. PMID: 19926751.

Thamrin C, Gangell CL, Udomittipong K, Kusel MM, Patterson H, Fukushima T, Schultz A, Hall GL, Stick SM, Sly PD. Assessment of bronchodilator responsiveness in preschool children using forced oscillations. Thorax. 2007 Sep;62(9):814-9. doi: 10.1136/thx.2006.071290. Epub 2007 Apr 5. PMID: 17412777; PMCID: PMC2117298.

Hellinckx J, De Boeck K, Bande-Knops J, van der Poel M, Demedts M. Bronchodilator response in 3-6.5 years old healthy and stable asthmatic children. Eur Respir J. 1998 Aug;12(2):438-43. doi: 10.1183/09031936.98.12020438. PMID: 9727798.

Jee HM, Kwak JH, Jung DW, Han MY. Useful parameters of bronchial hyperresponsiveness measured with an impulse oscillation technique in preschool children. J Asthma. 2010 Apr;47(3):227-32. doi: 10.3109/02770901003624259. PMID: 20394507.

Murphy KR, Zeiger RS, Kosinski M, Chipps B, Mellon M, Schatz M, Lampl K, Hanlon JT, Ramachandran S. Test for respiratory and asthma control in kids (TRACK): a caregiver-completed questionnaire for preschool-aged children. J Allergy Clin Immunol. 2009 Apr;123(4):833-9.e9. doi: 10.1016/j.jaci.2009.01.058. PMID: 19348922.

Chipps B, Zeiger RS, Murphy K, Mellon M, Schatz M, Kosinski M, Lampl K, Ramachandran S. Longitudinal validation of the Test for Respiratory and Asthma Control in Kids in pediatric practices. Pediatrics. 2011 Mar;127(3):e737-47. doi: 10.1542/peds.2010-1465. Epub 2011 Feb 21. Erratum in: Pediatrics. 2012 Mar;129(3):595-6. PMID: 21339276.

Shin YH, Jang SJ, Yoon JW, Jee HM, Choi SH, Yum HY, Han MY. Oscillometric and spirometric bronchodilator response in preschool children with and without asthma. Can Respir J. 2012 Jul-Aug;19(4):273-7. doi: 10.1155/2012/560323. PMID: 22891189; PMCID: PMC3411394.

Carvalho Vidal Reis Leiria Pinto PC, Martins P, Peralta I, Neuparth N. Is there any association between spirometry and impulse oscillometry in asthmatic preschool children? European Respiratory Journal Sep 2018, 52 (suppl 62) PA1312; DOI: 10.1183/13993003.congress-2018.PA1312.

Olaguíbel JM, Alvarez-Puebla MJ, Anda M, Gómez B, García BE, Tabar AI, Arroabarren E. Comparative analysis of the bronchodilator response measured by impulse oscillometry (IOS), spirometry and body plethysmography in asthmatic children. J Investig Allergol Clin Immunol. 2005;15(2):102-6. PMID: 16047709.

Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax. 2003 Jun;58(6):494-9. doi: 10.1136/thorax.58.6.494. PMID: 12775859; PMCID: PMC1746693.

King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, Farré R, Hall GL, Ioan I, Irvin CG, Kaczka DW, Kaminsky DA, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oppenheimer BW, Simpson SJ, Thamrin C, van den Berge M, Oostveen E. Technical standards for respiratory oscillometry. Eur Respir J. 2020 Feb 27;55(2):1900753. doi: 10.1183/13993003.00753-2019. PMID: 31772002.

Gleason M, Covar R, Gelfand E, Szefler SJ, Larsen G. Lung function measurements using forced oscillation in young children. In: Proc. of the World Asthma Meeting; 2001.

Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. Am J Respir Crit Care Med. 2001 Aug 15;164(4):554-9. doi: 10.1164/ajrccm.164.4.2006119. PMID: 11520714.

Konstantinou GN, Papadopoulos NG, Manousakis E, Xepapadaki P. Virus-Induced Asthma/Wheeze in Preschool Children: Longitudinal Assessment of Airflow Limitation Using Impulse Oscillometry. J Clin Med. 2019 Sep 16;8(9):1475. doi: 10.3390/jcm8091475. PMID: 31527510; PMCID: PMC6780792.

Tables and figures

Table 1. Clinical and anamnestic characteristics of patients.

	Total
Patients [n]	36
Male / Female [n]	23 / 13
Age [years, mean ± SD]	5.15 ± 0.99
Height [cm, mean ± SD]	113.14 ± 8.9
Weight [kg, mean ± SD]	19.83 ± 4.32
BMI [kg/m2, mean ± SD]	15,.3 ± 1.51
Atopy [n/%]	19 (52.8)
TRACK score [mean ± SD]	68,33 ± 20,84
Control medications:	Control medications:

	Total
Total [n/%]	14 (38.9)
LTRA [n/%]	1 (2.8)
ICS [n/%]	5 (13.8)
ICS + LABA [n/%]	8 (22,2)

Abbreviations: LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

Table 2: Baseline lung function measurements of patients .

Parameter	**Mean ± SD**
FVC [L]	1.21 ± 0.32
FVC % predicted [%]	93.06 ± 15.18
FVC z-score	-0.52 ± 1.13
FEV1 [L]	1.12 ± 0.28
FEV1% predicted [%]	95.11 ± 14.19
FEV1 z-score	-0.37 ± 1.1
R5 [KPa/(L/s)]	0.92 ± 0.19
R5 % predicted [%]	104.32 ± 17.71
R5 z-score	0.19 ± 0.89
X5 [KPa/(L/s)]	-0.35 ± 0.12
X5 z-score	-0.74 ± 1.24
Fres [1/s]	25.01 ± 4.11
Fres z-score	2.11 ± 1.04
Di5-20 [KPa/(L/s)]	0.32 ± 0.14
AX [KPa/L]	3.63 ± 1.67

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; R5, resistance at 5 Hz; X5, reactance at 5 Hz; Fres, resonant frequency; Di5-20, difference of resistance at 5 Hz and 20 Hz; AX, area of reactance.

Table 3: Change on baseline in IOS parameters in BDR-positive and BDR-negative patients.

Parameter	**Positive-BDR** % Change on baseline [Mean ± SD]	**Negative-BDR** % Change on baseline [Mean ± SD]	**P**
R5 [KPa/(L/s)]	-2.82 ± 6.58	-18.18 ± 10.08	0.03
X5 [KPa/(L/s)]	34.3 ± 9.83	20.59 ± 18.43	0.04
Fres [1/s]	-13.28 ± 4.87	-17.39 ± 14.21	0.5
Di5-20 [KPa/(L/s)]	-35.19 ± 23.15	-38.58 ± 28.9	0.6
AX [KPa/L]	-48.27 ± 14.48	-43.75 ± 23.7	0.85

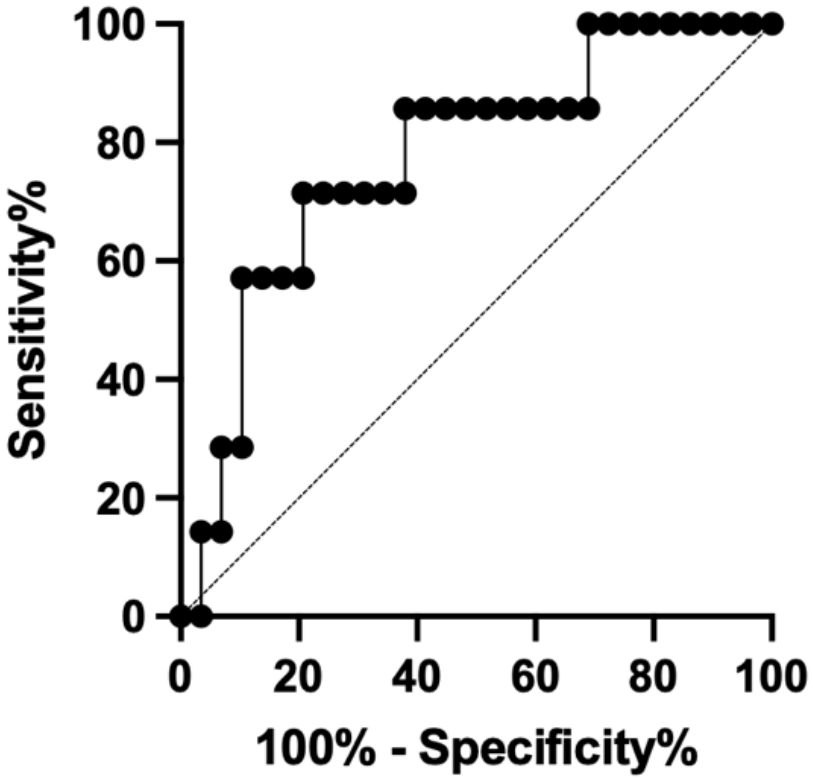
Table 4: Baseline IOS parameters in BDR-positive and BDR-negative patients.

Parameter	**Positive-BDR** [Mean ± SD]	**Negative-BDR** [Mean ± SD]	**P**
R5 [KPa/(L/s)]	1,04 ± 0,20	0,9 ± 0,18	0,09

Parameter	**Positive-BDR** [Mean ± SD]	**Negative-BDR** [Mean ± SD]	**P**
R5 % predicted [%]	116,43 ± 13,39	101,4 ± 17,56	
R5 z-score	0,80 ± 0,70	0,04 ± 0,88	
X5 [KPa/(L/s)]	-0,45 ± 0,2	-0,33 ± 0,09	0,07
X5 z-score	-1,78 ± 1,96	-0,49 ± 0,87	
Fres [1/s]	25,5 ± 4,38	24,89 ± 4,12	0,61
Fres z-score	2,26 ± 1,08	2,08 ± 1,04	
Di5-20 [KPa/(L/s)]	0,44 ± 0,11	0,29 ± 0,13	0,06
AX [KPa/L]	4,91 ± 2,2	3,32 ± 1,39	0,07

Table 5: Post-bronchodilator lung function measurements of all patients.

Parameter	**Post-BDR** [Mean ± SD]	**Post-BDR** % Change on baseline [Mean ± SD]	**P**
FVC [L]	1.24 ± 0.35	2.67 ± 7.6	0.02
FVC % predicted [%]	95.06 ± 15.20	-	
FVC z-score	-0.37 ± 1.14	-	
FEV1 [L]	1.18 ± 0.30	5.44 ± 9.16	0.0002
FEV1% predicted [%]	99.78 ± 14.54	-	
FEV1 z-score	0 ± 1.11	-	
R5 [KPa/(L/s)]	0.74 ± 0.15	-19.86 ± 10.04	<0.0001
R5 % predicted [%]	83.19 ± 14.07	-	
R5 z-score	-0.81 ± 0.74	-	
X5 [KPa/(L/s)]	-0.26 ± 0.09	23.25 ± 1.,85	<0.0001
X5 z-score	2.91 ± 15.99	-	
Fres [1/s]	20.64 ± 3.56	-16.59 ± 12.97	<0,0001
Fres z-score	0.97 ± 0.91	-	
Di5-20 [KPa/(L/s)]	0.19 ± 0.10	-37.92 ± 27.6	<0.0001
AX [KPa/L]	1.92 ± 1	-44.63 ± 2.,1	<0.0001



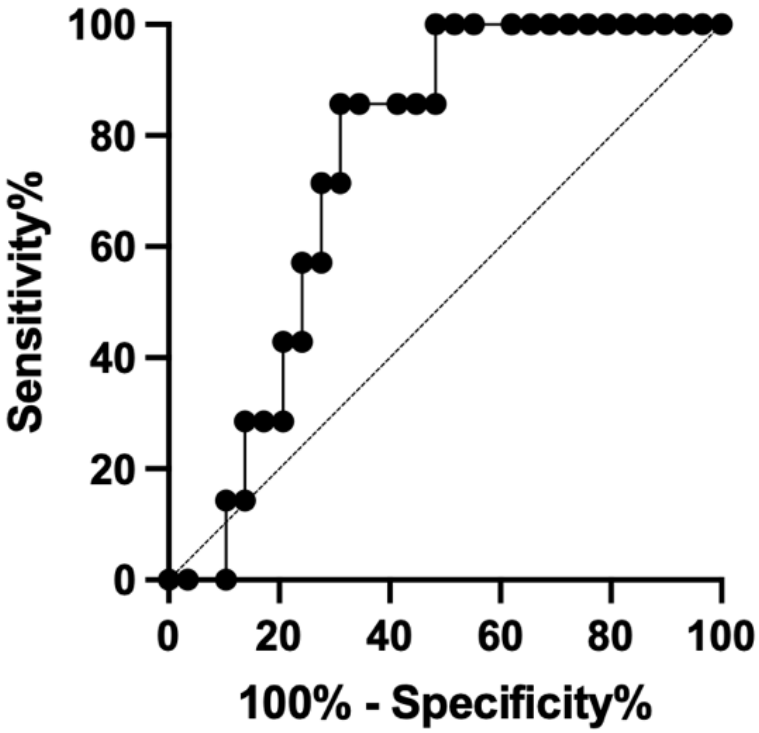


Figure 1 : **Receiver-operating characteristic (ROC) curves**

Changes in R5 (left, AUC 0.77; p = 0.03) and in X5 (right, AUC 0.75; p = 0.04) from baseline to detect a 12% increase in FEV1.