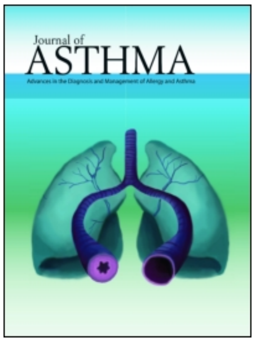

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"Reactance inversion" at low frequencies during lung function measurement by impulse oscillometry in children with persistent asthma[#]

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ABSTRACT

Background: Small airway dysfunction (SAD) in asthma can be measured by impulse oscillometry (IOS). Usually, the reactance should decrease with decreases in frequency oscillation. Sometimes an upward shift of the curve at low frequencies can be observed together with lower than expected reactance values. The actual value of the reactance at 5 Hz (X5) is calculated by the Sentry Suite application of the Jaeger Master screen iOS system™, providing the corrected X5 parameter (CX5). Our hypothesis is that correction of X5 is common in persistent asthma and it correlates better than X5 with the IOS parameters for evaluating SAD.

Methods: In this transversal study, we evaluated 507 children (3–18 years old) using IOS-spirometry (Sentry Suite, Vyntus®). Resistance of all airways (R5), reactance area (AX), resonant frequency (Fres), X5, CX5, difference between R5 and R20 (D5-20), and spirometry parameters were analyzed. Reactance inversion and CX5 prevalence by age range was determined. The mean IOS-Spyrometry values in children with and without CX5 were compared, and correlations with each IOS-spirometry parameter in the age groups were performed.

Results: CX5 was found in 83.5% of preschool children, 66.2% of schoolchildren, and 43.3% of adolescents ($p < 0.001$). The means of R5, AX, and D5-20 were significantly higher and FEV1 was significantly lower in children with CX5 ($p < 0.05$). In all ages, CX5 correlated better than X5 with IOS-spirometry parameters.

Conclusion: Reactance inversion and CX5 are frequent in asthmatic children, decrease with age, and correlate more closely than X5 with other IOS-spirometry parameters for evaluating SAD.

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Introduction

Asthma is one of the most prevalent chronic diseases in childhood (1), characterized by inflammation and obstruction in the small airways (2,3). The alteration in the small airways correlates with bronchial hyperreactivity, risk of exacerbations, incomplete response to corticosteroids, and persistent asthma symptoms (4–6). Small-airway dysfunction could also be present in asthmatic patients with apparently good control of the disease; however, it is more common in severe asthma. Therefore, identifying small-airway alterations allows better characterization and management of asthmatic patients (7,8).

Impulse oscillometry (IOS) has become relevant for lung function evaluation. IOS has been shown to be useful for detecting and evaluating small-airway dysfunction in patients even when spirometry is normal (9–12). IOS measures the impedance of the respiratory system (Z), which is the net force to be overcome to move the gas in and out of the respiratory system. Impedance involves the resistance (R) and the reactance (X). The R of the airway includes the resistance of the central and peripheral airway, which is the energy required to propagate the pressure wave through bronchi and bronchioles and distend the lung. R is measured when the pressure wave in phase with the air flow and does not have the opposition of the recoil of the airway and the lung. The X represents the reactive component of respiratory impedance and includes the inertial forces of the movement of the

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air column in the airways, called the inertance, with a positive sign, and the elastic properties of the lung, called capacitance, with a negative sign.

The resonant frequency (Fres) is where the reactance curve crosses the zero-impedance line. This is where the capacitive and inertive forces cancel out. Capacitance (C) is energy generated by the recoil of the lung after the pressure wave when there is no air flow out of phase oscillometry component. In the reactance curve, the low-frequency waves of 5 hz penetrate the lung with almost no resistance and reflect the lung's capacity to receive energy. Its value increases (becomes more negative) when there is hyperinflation or peripheral airway obstruction of pulmonary fibrosis.

Graphic representation of these elements allows building the resistance line between R5 (resistance of all airways) and R20 (resistance of the central airway) and the reactance line from reactance at 5 Hz (X5) to the resonant frequency (Fres), where the reactance is equal to zero. IOS parameters such as X5, Fres, reactance area (AX), and the difference between R5 and R20 (D5-20) reflect changes in the obstruction of peripheral airways (13). Usually, the reactance line should decrease hyperbolically as the frequency decreases, from Fres to X5, but in some patients at low frequency the curve is inverted upward, tracing a curved trajectory. This is called "reactance inversion". The reactance becomes more negative as the frequency decreases. In this case, X5 should be more negative. To correctly represent the changes in the airway, it is necessary to calculate the value of X5 that corresponds to projecting that line without the reactance inversion, generating a new parameter, "corrected X5" (CX5), whose values are more negative than X5. This new parameter, CX5, is incorporated into some equipment, such as that of Jaeger-Carefusion, which provides X5 and CX5. These two values are equal when there is no inversion of the reactance curve.

We postulate that CX5 better represents small airway function than X5. Therefore, CX5 should correlate better than X5 with alterations in the other IOS and spirometry parameters (i.e. R5, Fres, AX, D5-20, and FEF_{25-75}) in evaluating the small airway's function. The aim of this study is to determine the prevalence of an inversion of the reactance curve in asthmatic children and whether CX5 correlates more closely than X5 with other IOS and spirometry parameters for small-airway evaluation.

Methods

This transversal study was done in the pediatric lung function laboratory at Clínica Las Condes, Santiago, Chile between September, 2018 and March, 2020. Data was collected from the IOS and spirometry of 507 asthmatic children (between 3 and 18 years of age) for which their pediatricians requested a lung function test. Children with other chronic respiratory diseases, cardiopathies, and immunodeficiencies were excluded. Patients had to be free of respiratory tract infection within 3 weeks prior to evaluation and had to discontinue short-acting beta-2 agonist for 4 h prior to testing. Written consent/assent was obtained from the parents/guardians and children who agreed to participate after receiving information about the study. The study was approved by the Ethics Committee of the institution.

The results of IOS, spirometry, asthma severity (according to GINA classification), and asthma control treatment were recorded in an encoded database. The IOS and the spirometry were performed according to ATS/ERS guidelines (14–17), using the Vyaire Vyntus model v-176430 (Mettawa, IL) with the Sentry Suite application. IOS measurements were performed in the sitting position with participants wearing nose clips and the method of cheek support at the hands of trained technicians. Participants tidally breathed into the IOS mouthpiece for at least 30 s for high-school aged children, and for children under 12 years of age, a minimum of 16 s was accepted. They were recorded until 3 sinusoidal readings were technically acceptable, with the coefficient of variability of resistance (Rrs) ≤15%. The equipment was calibrated daily, using a 3-L syringe, ruling out artifacts and leaks at different rates (flow) and with a reference resistance device (0.2 kPa/l/s) per manufacturer. The tests with the best coherence at frequencies of 5 to 30 Hz were chosen (it was 0.6 at 5 Hz and 0.9 at 10 Hz, with variability between measurements less than 10% at frequencies higher than 5 Hz). No leak was observed, the volume time plot did not drift, and there was appropriate inter-trial reproducibility of X and R. Children performed IOS and spirometry before and after 400 mcg salbutamol inhalation. IOS was performed first, followed by spirometry, to avoid force maneuvers causing changes in the IOS. In the IOS, the baseline values of R5 (Kpa/Ls), Fres (1/s), X5 (Kpa/Ls), CX5 (Kpa/Ls), AX (Kpa/Ls), and D5-20 (Kpa/Ls) were analyzed. In the spirometry, the baseline values of FEV_1 (L), $FEF_{0.75}$ (L), $FEV_{0.5}$ (L) and $FEF_{25-75\%}$ (L) were analyzed. The IOS predictive values used were Dencker (18), Malmberg (19), and Voegel (20). Spirometry was performed using Quanjer predictive values (21).

Statistical analysis

The patients were divided into three age categories: preschoolers (≥3 yrs and <6 yrs), schoolchildren (≥6 yrs and <12 yrs), and adolescents (≥12 yrs and <19 yrs). Differences in demographic characteristics were expressed in means and percentages, using the *t*-test or $\times^2$ according to each case. The global prevalence and by category and age of corrected reactance were measured.

The sample size was calculated through a pilot study with 50 patients for each age category. This allowed defining the number of patients to calculate the prevalence of corrected reactance in each age group: 122 preschool children, 209 schoolchildren, and 127 adolescents.

The linear trend of the prevalence of reactance corrected according to age categories was calculated using the Mantel–Haenszel $\times^2$ test. The mean difference between patients with and without corrected reactance was measured using the *t*-test. A mean difference of 0.15 Kpa/Ls was estimated for R5, AX, and D5-20 in IOS and 0.1 L of FEV_1 in spirometry, requiring a minimum of 68 preschoolers, 68 schoolchildren and 42 adolescents to establish significant differences. Finally, Pearson's correlation test between X5 and CX5 was measured with each IOS-spirometry parameter in each age category. For this test, the number of patients greatly exceeded the required minimum sample size. For the analyses, the normal distribution was verified, alpha errors of 0.05 and beta of 0.20 for each group was used, and probability (*p*) values ≤0.05 were considered statistically significant. For the statistical analysis, SPSS® v17.0 (IBM, Armonk, NY) software was used.

Results

Of the 576 asthmatic children initially included, 69 were excluded (23 preschoolers and 5 schoolchildren did not properly perform the IOS, and 41 patients did not sign the consent form). Therefore, 507 (88%) asthmatic children were included in the study, the mean age was 9.3 years, age range between 3 to 18 years, and 57.9% were males. By age category, they were distributed into 27.4% preschoolers, 46.2% schoolchildren, and 26.4% adolescents. The severity of asthma according to GINA was 31.2% mildly persistent, 60.9% moderately persistent, and 7.9% severely persistent.

No significant demographic differences were found by age category between patients with and without corrected X5 (Table 1). A total of 329 children (64.8%) presented an inversion of the reactance curve and CX5. Patients that required an X5 correction showed a significant linear tendency by age category, where preschoolers had the highest prevalence (Table 2).

In the IOS parameters, it was found that the mean value of R5, AX, and D5-20 was significantly higher in children with correction of X5 for all age categories. In the spirometry parameters, FEV_1 was significantly lower in children with CX5 for all age categories. $FEV_{0.5}$ and $FEV_{0.75}$ was found to be significantly lower in preschoolers with CX5, while $FEF_{25-75\%}$ was significantly lower in school children and adolescents with CX5 (Table 3).

The correlation of CX5 with R5, AX, D5-20, and the $FEF_{25-75\%}$ was higher than the correlation of X5 in all age categories. In preschool children, a better correlation was also found between CX5 and $FEV_{0.5}$ and $FEV_{0.75}$ than with X5. In preschoolers, the low negative correlation of X5 with D5-20 improved to highly negative with CX5. In schoolchildren, the moderately negative correlation of X5 with R5 and D5-20 improved to highly negative with CX5. Finally, in adolescents the moderately negative correlation of X5 with AX and D5-20 improved to a very highly negative with CX5 (Table 4).

Table 1. Demographic characteristics of persistent asthmatic children, by age categories ($n = 507$).

	Preschoolers (≥ 3yr and < 6yr) ($N = 139$)			Schoolchildren (≥ 6yr and < 12yr) ($N = 234$)			Adolescents (≥ 12yr and < 19yr) ($N = 134$)		
	X5 ($n = 23$)	CX5 ($n = 116$)	p*	X5 ($n = 79$)	CX5 ($n = 155$)	p*	X5 ($n = 76$)	CX5 ($n = 58$)	p*
Age (years)	5.1	4.8	0.08	9.2	8.9	0.08	14.8	14.4	0.5
Weight (K)	20.2	20.2	0.9	33	33.3	0.8	56.5	54.6	0.4
Height (cm)	111.7	110.1	0.3	135.6	133.3	0.1	162.7	160	0.08
Sex (%male)	50	55.2	0.9	55.7	60	0.6	59.2	62.1	0.9
Moderate to severe asthma (%) Controller	47.8	61.2	0.3	75.9	75.5	0.9	64.5	62.1	0.9
Therapy:									
ICS (%)	43.5	45.7	0.8	27.8	25.8	0.9	11.8	8.6	0.7
ICS + LABA (%)	21.7	17.2	0.9	43.3	35.5	0.2	56.6	58.6	0.9
LTRA (%)	8.7	9.5	0.8	5.1	12.9	0.1	5.3	1.7	0.5

Numbers are expressed in % and mean, *p values for *t*-student *o* $\times^2$ test, X5 = uncorrected reactance at 5 Hz, CX5 = corrected reactance at 5 Hz, ICS = Inhaled corticosteroids, LABA = Long-acting beta-agonist, LTRA = leukotriene receptor antagonists.

Table 2. Prevalence of corrected reactance in relation to age ($n = 507$).

	Preschoolers (≥ 3yr and < 6yr) $N = 139$	Schoolchildren (≥ 6yr and < 12yr) $N = 234$	Adolescents (≥ 12yr and < 19yr) $N = 134$	*p
CX5 n (%)	116 (83.5)	155 (66.2)	58 (43.3)	<0.0000001

CX5 = corrected reactance at 5 Hz, *p values for extended Mantel–Haenszel chi square linear trend.

Table 3. Comparison of IOS-Spirometry parameters and X5 differences, by age categories ($n = 507$).

	Preschoolers (≥ 3yr and < 6yr)			Schoolchildren (≥ 6yr and < 12yr)			Adolescents (≥ 12yr and < 19yr)		
	X5	CX5	*p	X5	CX5	*p	X5	CX5	*p
R5 Kpa/Ls	0.84 ± 0.1	1.07 ± 0.2	<0.001	0.62 ± 0.1	0.83 ± 0.2	<0.001	0.43 ± 0.1	0.58 ± 0.1	<0.001
Fres 1/S	24.8 ± 6.3	26.6 ± 5.7	NS	20.8 ± 3.5	24.4 ± 4.8	<0.001	16.5 ± 5.1	20.2 ± 5.2	<0.001
AX Kpa/Ls	2.7 ± 1.1	4.4 ± 2	<0.001	1.7 ± 0.9	3.1 ± 1.9	<0.001	0.7 ± 0.5	1.4 ± 1.3	<0.001
D5-20 Kpa/Ls	0.24 ± 0.13	0.42 ± 0.15	<0.001	0.17 ± 0.08	0.32 ± 0.1	<0.001	0.08 ± 0.05	0.2 ± 0.1	<0.001
FEV1 L	1.28 ± 0.2	1.17 ± 0.2	<0.05	2.02 ± 0.4	1.8 ± 0.4	< 0.01	3.4 ± 0.7	3 ± 0.5	<0.001
FEF 25-75% L	1.49 ± 0.3	1.34 ± 0.4	NS	2.07 ± 0.6	1.78 ± 0.5	<0.001	3.5 ± 1	2.9 ± 0.8	<0.001
FEV 0.75 L	1.16 ± 0.2	1.06 ± 0.2	<0.05	N/A	N/A	N/A	N/A	N/A	N/A
FEV 0.5 L	0.97 ± 0.1	0.88 ± 0.1	<0.05	N/A	N/A	N/A	N/A	N/A	N/A

Numbers are expressed in mean ± DS, X5 = uncorrected reactance at 5 Hz, CX5 = corrected reactance at 5 Hz, *p values for t-Student test (< 0.05,< 0.01 < 0.001), NS = non-significant, N/A = not applicable, R5= Resistance at 5 Hz, Fres: resonant frequency, AX: reactance area, D5-20: resistance at 5 Hz minus resistance at 20 Hz, FEV1 = forced expiratory volume in 1 s, FEV 0.75 = forced expiratory volume in 0.75 s, FEV 0.5 = forced expiratory volume in 0.5 s, FEF25-75% = forced expiratory flow at 25–75%, L = Liter, Kpa/Ls = Kilopascal divided into liters.

Table 4. Correlation between X5 and X5a with other IOS-Spirometry parameters, by age categories ($n = 507$).

	Preschoolers (≥ 3yr and < 6yr)		Schoolchildren (≥ 6yr and < 12yr)		Adolescents (≥ 12yr and < 19yr)	
	X5 r	**CX5 r**	**X5 r**	**CX5 r**	**X5 r**	**CX5 r**
R5 Kpa/Ls	−0.33**	−0.58**	−0.6**	−0.83**	−0.68**	−0.83**
Fres 1/S	−0.34**	−0.34**	−0.42**	−0.62**	−0.68**	−0.69**
AX Kpa/Ls	−0.46**	−0.61**	−0.76**	−0.82**	−0.85**	−0.92**
D5-20 Kpa/Ls	−0.39**	−0.73**	−0.64**	−0.88**	−0.7**	−0.9**
FEV1 L	0.33**	0.4**	0.49**	0.51**	0.43**	0.40**
FEF 25-75 L	0.32**	0.44**	0.45**	0.49**	0.4**	0.42**
FEV 0.75 L	0.33**	0.39**	N/A	N/A	N/A	N/A
FEV 0.5 L	0.37**	0.42**	N/A	N/A	N/A	N/A

Numbers express the r Pearson correlation Coefficient, X5 = uncorrected reactance at 5 Hz, CX5 = corrected reactance at 5 Hz, **$p < 0.001$ for Pearson Correlation Coefficient, N/A = not applicable, R5= Resistance at 5 Hz, Fres: resonant frequency, AX: reactance area, D5-20: resistance at 5 Hz minus resistance at 20 Hz, FEV1 = forced expiratory volume in 1 s, FEV 0.75 = forced expiratory volume in 0.75 s, FEV 0.5 = forced expiratory volume in 0.5 s, FEF25–75% = forced expiratory flow at 25–75%, L = Liter, Kpa/Ls = Kilopascal divided into liters per second, 1/S = 1 divided per second.

Discussion

We described, for the first time, the presence of a reactance inversion and CX5 in asthmatic children. In this study, almost two thirds of the patients exhibited a reactance inversion with the respective X5 correction. This high prevalence could be explained by the fact that most of our population had moderate to severe persistent asthma, in which the presence of SAD has been demonstrated in IOS even with normal spirometry.

In the present study, the X5 correction was necessary in more than 80% of preschoolers, 66% of schoolchildren, and 43% of adolescents (p for trend <0.001), indicating that this phenomenon is related to age. R5, AX, and D5-20 mean values were higher in the CX5 group, Fres was higher in preschoolers with CX5, with no statistical significance, and in schoolchildren and adolescents it was higher in the CX5 group, with a highly significant difference.

With respect to the comparison of spirometry values, FEV_1 was significantly lower in the three age groups and $FEF_{25–75}$ was lower in schoolchildren and adolescents. Furthermore, when using spirometric parameters recommended for preschool children such as $FEV_{0.5}$ and $FEV_{0.75}$, the group with CX5 also showed lower means. These results show that children with CX5 have poorer lung function with both methods. It is also noteworthy that the mean of R5 and AX in preschool and schoolchildren with CX5 exceeded the cutoff points for uncontrolled asthma reported by Tirakitsoontorn et al. at those ages (22). Likewise, in adolescents with CX5, the means of AX and D5-20 were found to be above the cutoff points reported by Shi et al. for uncontrolled asthma (9).

The correlation of CX5 (negative with IOS and positive with spirometry) was better than X5 for most of the lung function parameters used, especially AX, D5-20, and $FEF_{25–75.}$ These findings suggest that CX5 is a more sensitive parameter than X5 for demonstrating small airway dysfunction in IOS and spirometry. Alteration of IOS parameters such as D5-20 and AX is associated with dysfunction of the peripheral airways (23), being found to be higher in children with severe exercise-induced bronchoconstriction (6), uncontrolled asthma (9,10), greater number of exacerbations (12,24), and moderate to severe asthma with normal FEV_1 (25). For these patients, the use of ultrafine inhaled corticosteroids (ICS) that can reach small airways <2 mm in diameter has been suggested (26,27). Previous studies (28,29) have shown the association between lower values of $FEF_{25–75\%}$ and asthma severity, ICS use, exacerbations, and bronchodilator response in children with normal FEV_1; therefore, the presence of CX5 may have similar implications. It could be hypothesized that the inversion of the reactance curve and the corrected X5 could be useful for identifying this asthma phenotype.

The factors that could explain why reactance inversion is more frequent in preschoolers are the smaller caliber of the airway and the fact that the site of obstruction is predominantly the small airway, which makes the obstruction more severe, so the accessed pulmonary chamber becomes so small-sized that the superimposed parallel resonance is visible and prevents seeing the normal course of the reactance lined (30). Also, the lung function deficits that these children may have from birth and the changes in the lung structure such as the hypertrophy of the bronchial smooth muscle that has been found in the biopsies may be the cause of peripheral airway obstruction (31–35).

It important to mention that this inversion of the reactance curve was anecdotally reported in cystic fibrosis (36), a disease characterized by small-airway dysfunction, the presence of different time constant units, and inhomogeneity ventilation, which can also occur in asthma. Also, expiratory reactance abnormalities have been reported in adults with COPD and expiratory dynamic airway collapse (37).

In school-age children and adolescents, reactance inversion may occur through different mechanisms than in preschoolers and seems to be related to the difference between expiratory and inspiratory reactance, suggesting that excessive expiratory airway narrowing in children with heterogeneous lung disease leads to more lung units participating in oscillatory flow during inspiration than during expiration. It was recently reported that the changes in R5, X5, and AX between inspiration and expiration can be a useful index for diagnosis of asthma in children without assessment of the response to a bronchodilator, which could increase the chances of early diagnosis and appropriate management of asthma in children (38). How this in turn could lead to higher inertance, lower elastance, or both at low frequencies is unclear, but could result in reactance inversion. Reactance inversion is a poorly understood phenomenon that may affect the variability and interpretation of Xrs at 5 Hz if reactance correction is not applied to obtain CX5.

Our study has some limitations. First, we did not know the asthma control level of each patient, and it would be ideal to know if this new parameter CX5 is associated with uncontrolled asthma. Second, we were not able to follow up with these patients, and it would be of interest to know if patients who required X5 correction had worse asthma evolution or more persistent symptoms than those who did not require X5 correction. Therefore, future studies that take these considerations into account are needed.

In conclusion, this study showed that inversion of the reactance curve is exhibited in a high percentage of asthmatic children and that it significantly decreases with age. Compared to X5, CX5 correlated better with other IOS parameters and with $FEF_{25–75}$, suggesting that it is a good indicator of SAD and is useful for asthma management in children.

Declaration of interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Foliaki S, Annesi-Maesano I, Daniel R, Fakakovikaetau M, Magatongia M, Tuuau-Potoi N, Waqatakirewa L, Cheng SK, Pearce N. Prevalence of symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: the International Study of Asthma and Allergies in Childhood (ISAAC). Allergy. 2007;62(3):259–264. doi:10.1111/j.1398-9995.2007.01343.x.
2. Tulic MK, Christodoulopoulos P, Hamid Q. Small airway inflammation in asthma. Respir Res. 2001;2(6):333–339. doi:10.1186/rr83.
3. van der Wiel E, Postma DS, van der Molen T, Schiphof-Godart L, Ten Hacken NH, van den Berge M. Effects of small airway dysfunction on the clinical expression of asthma: a focus on asthma symptoms and bronchial hyperresponsiveness. Allergy. 2014;69(12):1681–1688. doi:10.1111/all.12510.
4. van der Wiel E, ten Hacken NH, Postma DS, van den Berge M . Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. J Allergy Clin Immunol. 2013;131(3):646–657. doi:10.1016/j.jaci.2012.12.1567.
5. Alfieri V, Aiello M, Pisi R, Tzani P, Mariani E, Marangio E, Olivieri D, Nicolini G, Chetta A. Small airway dysfunction is associated to excessive bronchoconstriction in asthmatic patients. Respir Res. 2014;15(1):86. doi:10.1186/s12931-014-0086-1.
6. Kalliola S, Malmberg LP, Pelkonen AS, Mäkelä MJ. Aberrant small airway's function relates to asthma severity in young children. Respir Med. 2016; 111:16–20. doi:10.1016/j.rmed.2015.12.006.
7. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, Papi A, Van der Molen T, Rabe KF, Siddiqui S, ATLANTIS Study Group, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med. 2019;7(5):402–416. doi:10.1016/S2213-2600(19)30049-9.
8. Carpagnano GE, Scioscia G, Lacedonia D, Stornelli SR, Irene Quarato CM, Soccio P, Resta O, Foschino Barbaro MP. Treatment response according to small airways disease status: The effects of high strength extrafine pMDI beclomethasone dipropionate/formoterol fumarate in fixed dose combination in moderate uncontrolled asthmatic patients. Pulm Pharmacol Ther. 2020; 60:101879. doi:10.1016/j.pupt.2019.101879.
9. Shi Y, Aledia AS, Tatavoosian AV, Vijayalakshmi S, Galant SP, George SC. Relating small airways to asthma control by using impulse oscillometry in children. J Allergy Clin Immunol. 2012;129(3):671–678. doi:10.1016/j.jaci.2011.11.002.
10. Shi Y, Aledia AS, Galant SP, George SC. Peripheral airway impairment measured by oscillometry predicts loss of asthma control in children. J Allergy Clin Immunol. 2013;131(3):718–723. doi:10.1016/j.jaci.2012.09.022.
11. Shin YH, Yoon JW, Choi SH, Baek JH, Kim HY, Jee HM, Yum HY, Han MY. Use of impulse oscillometry system in assessment of asthma severity for preschool children. J Asthma. 2013;50(2):198–203. doi:10.3109/02770903.2012.751996.
12. Batmaz SB, Kuyucu S, Arıkoglu T, Tezol O, Aydogdu A. Impulse oscillometry in acute and stable asthmatic children: a comparison with spirometry. J Asthma. 2016;53(2):179–186. doi:10.3109/02770903.2015.1081699.
13. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. Chest. 2014;146(3):841–847. doi:10.1378/chest.13-1875.
14. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304–1345. doi:10.1164/rccm.200605-642ST.
15. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, Farré R, Hall GL, Ioan I, Irvin CG, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55(2):1900753. doi:10.1183/13993003.00753-2019.
16. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, Hallstrand TS, Hankinson JL, Kaminsky DA, MacIntyre NR, ATS Committee on Proficiency Standards for Pulmonary Function Laboratories, et al. ATS committee on proficiency standards for pulmonary function laboratories. Recommendations for a standardized pulmonary function report. An official American thoracic society technical statement. Am J Respir Crit Care Med. 2017;196(11):1463–1472. doi:10.1164/rccm.201710-1981ST.
17. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi:10.1164/rccm.201908-1590ST.
18. Dencker M, Malmberg LP, Valind S, Thorsson O, Karlsson MK, Pelkonen A, Pohjanpalo A, Haahtela T, Turpeinen M, Wollmer P . Reference values for respiratory system impedance by using impulse oscillometry in children aged 2–11 years. Clin Physiol Funct Imaging. 2006;26(4):247–250. doi:10.1111/j.1475-097X.2006.00682.x.
19. Malmberg LP, Pelkonen A, Poussa T, Pohianpalo A, Haahtela T, Turpeinen M. Determinants of respiratory system input impedance and bronchodilator response in healthy Finnish preschool children. Clin Physiol Funct Imaging. 2002; 22(1):64–71.
20. Vogel J, Smidt U. Impulse oscillometry: analysis of lung mechanics in general practice and the clinic, epidemiology and experimental research. Frankfurt am Main: Pmi-Verlagsgruppe, 1994.
21. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, ERS Global Lung Function Initiative, et al. ERS Global Lung Function Initiative. Multi-ethnic reference

values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–1343. doi:10.1183/09031936.00080312.
22. Tirakitsoontorn P, Crookes M, Fregeau W, Pabelonio N, Morphew T, Shin HW, Galant SP. Recognition of the peripheral airway impairment phenotype in children with well-controlled asthma. Ann Allergy Asthma Immunol. 2018;121(6):692–698. doi:10.1016/j.anai.2018.08.023.
23. Meraz EG, Nazeran H, Ramos CD, Nava P, Diong B, Goldman MD, Goldman CA. Analysis of impulse oscillometric measures of lung function and respiratory system model parameters in small airway-impaired and healthy children over a 2-year period. BioMed Eng Online. 2011;10(1):21. https://doi.org:10.1186/1475-925X-10-21. doi:10.1186/1475-925X-10-21.
24. 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):107–114. doi:10.1159/000442448.
25. Azaldegi G, Korta J, Sardón O, Corcuera P, Pérez-Yarza EG. Small airway dysfunction in children with controlled asthma. Arch Bronconeumol. 2019;55(4):208–213. doi:10.1016/j.arbres.2018.08.005.
26. Amirav I, Newhouse MT, Minocchieri S, Castro-Rodriguez JA, Schüepp KG. Factors that affect the efficacy of inhaled corticosteroids for infants and young children. J Allergy Clin Immunol. 2010;125(6):1206–1211. doi:10.1016/j.jaci.2010.01.034.
27. van Aalderen WM, Grigg J, Guilbert TW, Roche N, Israel E, Martin RJ, Colice G, Postma DS, Hillyer EV, Burden A, et al. Small-particle inhaled corticosteroid as first-line or step-up controller therapy in childhood asthma. J Allergy Clin Immunol Pract. 2015;3(5):721–731.e16. doi:10.1016/j.jaip.2015.04.012.
28. Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF, Jr, Szefler SJ, Taussig L, Bacharier LB, Morgan W, Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Forced expiratory flow between 25% and 75% of vital capacity and FEV1/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV1 values. J Allergy Clin Immunol. 2010;126(3):527–534.e8. doi:10.1016/j.jaci.2010.05.016.
29. Rao DR, Gaffin JM, Baxi SN, Sheehan WJ, Hoffman EB, Phipatanakul W. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. J Asthma. 2012;49(6):586–592. doi:10.3109/02770903.2012.690481.
30. Smith HJ, Reinhold P, Goldman MD. Forced oscillation technique and impulse oscillometry. European Respiratory Monograph. Ch. 5. In: Gosselink R, Stam H, ed. Lung function testing. Sheffield: European Respiratory Society Publications; 2005:72–105.
31. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A, NAC Manchester Asthma and Allergy Study Group. Wheeze phenotypes and lung function in preschool children. Am J Respir Crit Care Med. 2005;171(3):231–237. doi:10.1164/rccm.200406-695OC.
32. Belgrave DC, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. Am J Respir Crit Care Med. 2014;189(9):1101–1109. doi:10.1164/rccm.201309-1700OC.
33. McKay KO, Hogg JC. The contribution of airway structure to early childhood asthma. Med J Aust. 2002;177(S6):S45–S47. doi:10.5694/j.1326-5377.2002.tb04852.x.
34. Bonato M, Tiné M, Bazzan E, Biondini D, Saetta M, Baraldo S. Early airway pathological changes in children: new insights into the natural history of wheezing. JCM. 2019;8(8):1180. doi:10.3390/jcm8081180.
35. O'Reilly R, Ullmann N, Irving S, Bossley CJ, Sonnappa S, Zhu J, Oates T, Banya W, Jeffery PK, Bush A, et al. Increased airway smooth muscle in preschool wheezers who have asthma at school age. J Allergy Clin Immunol. 2013;131(4):1024–1032. doi:10.1016/j.jaci.2012.08.044.
36. Allen JL, Ren CL, McDonough J, Clem CC. "Reactance inversion" at low frequencies in a child undergoing treatment of a cystic fibrosis exacerbation. Pediatr Investig. 2019;3(4):257–260. doi:10.1002/ped4.12169.
37. Fielding DI, Travers J, Nguyen P, Brown MG, Hartel G, Morrison S. Expiratory reactance abnormalities in patients with expiratory dynamic airway collapse: a new application of impulse oscillometry. ERJ Open Res. 2018; 4(4):00080-2018–2018. doi:10.1183/23120541.00080-2018.
38. Sol IS, Kim YH, Kim S, Kim JD, Choi SH, Kim KW, Sohn MH. Assessment of within-breath impulse oscillometry parameters in children with asthma. Pediatr Pulmonol. 2019;54(2):117–124.