Inversion of the reactance curve and X5 approx. are better parameters for measuring small-airway dysfunction in asthmatic children

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Abstract

Background: Small airway dysfunction in asthma can be measured by impulse oscillometry (IOS), where sometimes the reactance can exhibit an inversion of the curve, and its correction can determine a new value for X5: approximate X5 (X5 approx.). Our hypothesis is that X5 approx. exhibits a closer association with parameters of airway dysfunction in the IOS than X5. Methods: We analyzed 403 children (3-17 years old) who performed IOS (Sentry Suit, Vyntus®) and spirometry, recording R5, AX, X5, X5approx., Fres, D5-20 and FEF25-75. Groups X5 and X5 approx. were compared with respect to the percentage of abnormal IOS parameters, their averages, FEF25-75, and their correlation with each IOS parameter. Also, we explored the correlation between X5 and X5 approx. with each IOS parameter. Results: We found a significant decreasing prevalence of X5 approx. with age (84.6% in preschoolers, 67.2% in schoolchildren, and 36.5% in adolescents, p for trend <0.001). The preschoolers and schoolchildren with X5 approx. exhibited significant ($p<0.05$) alterations in many other IOS parameters (e.g. R5, Fes, AX, and D5-20) compared with those with X5. Adolescents exhibited a significant ($p<0.01$) alteration only for D5-20. The means of R5, AX, and D5-20 were significantly ($p<0.01$) higher in children with X5 approx. than with X5. Finally, in the all the age categories, compared with X5, X5 approx. correlated better with other IOS parameters and FEF25-75. Conclusion: The presence of X5 approx. decreases with age and correlates more closely than X5 with other IOS parameters for the evaluation of small airway dysfunction

Inversion of the reactance curve and X5 approx. are better parameters for measuring small-airway dysfunction in asthmatic children*

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Word count : 2033

Highlights box:

What is already known about this topic? Inversion of the reactance curve was anecdotally reported in cystic fibrosis (a disease characterized by small-airway dysfunction [SAD] and inhomogeneity ventilation). We speculate that this also can occur in asthma.

What does this article add to our knowledge? We describe, for first time, that 65.5% of persistent asthmatic children have inversion of the reactance curve and X5 approx. correction. The presence of X5 approx. decreases with age and correlates more closely than X5 with other IOS parameters for the evaluation of SAD.

How does this study impact current management guidelines?Inversion of the reactance curve and X5 approx. could be more useful parameters in the IOS to adjust the asthma treatment (especially the ultrafine inhaled corticosteroids).**Abstract:**

Background: Small airway dysfunction in asthma can be measured by impulse oscillometry (IOS), where sometimes the reactance can exhibit an inversion of the curve, and its correction can determine a new value for X5: approximate X5 (X5 approx.). Our hypothesis is that X5 approx. exhibits a closer association with parameters of airway dysfunction in the IOS than X5. **Methods** : We analyzed 403 children (3-17 years old) who performed IOS (Sentry Suit, Vyntus®) and spirometry, recording R5, AX, X5, X5approx., Fres, D5-20 and FEF_{25-75}. Groups X5 and X5 approx. were compared with respect to the percentage of abnormal IOS parameters, their averages, FEF_{25-75}, and their correlation with each IOS parameter. Also, we explored the correlation between X5 and X5 approx. with each IOS parameter. **Results:** We found a significant decreasing prevalence of X5 approx. with age (84.6% in preschoolers, 67.2% in schoolchildren, and 36.5% in adolescents, p for trend <0.001). The preschoolers and schoolchildren with X5 approx. exhibited significant ($p<0.05$) alterations in many other IOS parameters (e.g. R5, Fes, AX, and D5-20) compared with those with X5. Adolescents exhibited a significant ($p<0.01$) alteration only for D5-20. The means of R5, AX, and D5-20 were significantly ($p<0.01$) higher in children with X5 approx. than with X5. Finally, in the all the age categories, compared with X5, X5 approx. correlated better with other IOS parameters and FEF_{25-75}. **Conclusion** : The presence of X5 approx. decreases with age and correlates more closely than X5 with other IOS parameters for the evaluation of small airway dysfunction.

Word count: 250

Introduction

Asthma is one of the most prevalent chronic diseases in childhood,[1] characterized by inflammation and obstruction in the small airways.[2,3] This alteration in the small airways correlates with bronchial hyperreactivity, risk of exacerbations, incomplete response to corticosteroids, and persist 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.[7] Therefore, identifying small-airway alterations allows better characterization and management of asthmatic patients.[8]

Impulse oscillometry (IOS) has become relevant for lung function evaluation, because several studies agree that it can assess small-airway dysfunction and detect abnormalities in patients even when spirometry is normal.[9-12] IOS measures the respiratory system resistance (R) and the reactance (X). 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 frequency of reactance [Fres], where the reactance is equal to cero. The following parameters, X5, Fres, reactance area (AX), and the difference between R5 and R20 (D5-D20) reflect changes in the obstruction of peripheral airways.

Usually, the reactance line should decrease hyperbolically as frequency decreases, from F Res to X5, but in some patients at low frequency the curve is inverted upward, tracing a curved trajectory. This is call "reactance inversion". The reactance becomes less negative as the frequency decreases. In this case, X5 should be more negative. The solution for correcting this problem is to calculate the value of X5 that corresponds by projecting that line without the reactance inversion, generating a new parameter, "approximate X5" (X5 approx.), whose values are more negative than X5. This new parameter, X5 approx., is incorporated into some equipment, such as that of Jaeger-Carefusion, which provides X5 and X5 approx. These two values are equal when there is no inversion of the reactance curve. We postulate that X5 approx. correctly represents changes in the respiratory tract. Therefore, it 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) that evaluate the function of small airways.

The aim of this study is to determine the prevalence of an inversion of the reactance curve in asthmatic children and whether X5 approx. more closely correlates with other IOS and spirometry parameters for small-airway evaluation than does X5.

Methods

This transversal study was done in the pediatric lung function laboratory at Clínica Las Condes, Santiago, Chile between September, 2018 and March, 2020. We included the IOS and spirometry of 445 asthmatic children (between 3 and 17 years of age) for which their pediatricians requested a lung function test. We excluded children with other chronic pulmonary diseases, cardiopathies, and immunodeficiencies. For the lung function tests, the patients had to be free of respiratory tract infection during the previous 3 weeks and having experienced no short beta-2 agonist use in the previous 24 hrs. 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.

We recorded the IOS and spirometry results, asthma severity (by GINA classification), and asthma controller therapy in a pre-codified database. The IOS and the spirometry were performed according to ATS/ERS guidelines[13,14] using the Vyaire Vyntus model v-176430 (Mettawa, IL) with the Sentry Suit application. IOS was performed first, followed by spirometry, in order to avoid force maneuvers' causing changes in the IOS. R5 (Kpa/Ls), Fres (1/s), X5 (Kpa/Ls), X5approx. (Kpa/Ls), AX (Kpa/Ls), and D5-20 (Kpa/Ls) basal values in the IOS and $FEF_{25-75\%}$ (L/s) in the spirometry were recorded. In accordance with several studies,[12,15-18] the following cutoffs for defining IOS abnormalities were used: R 5 [?]0.8, Fres [?]25 1/s, AX [?]2.5, and D5-20 [?]0.2 Kpa/Ls. These cutoffs were tested in a pilot study.

Also, the same day a skin prick test (SPTs) for twenty common inhalant and food allergens was performed on the forearms, as well as positive (histamine) and negative (solvent) controls. Atopy was defined as a positive reaction (wheal size diameter measuring 3 mm or more after subtraction of the control value) to one or more allergens.

Statistical analysis:

The patients were divided into three age categories: preschoolers ([?]3 yr and <6 yrs), schoolchildren ([?]6 yrs and <12 yrs), and adolescents ([?]12 yrs and [?]17 yrs). We identified the presence of the inversion of the reactance curve (Figure 1), and we measured the lineal tendency of the percentage of patients that required X5 approx. correction according to the age categories, using the Mantel-Haenszelx2 test. We analyzed the difference between patients with and without inversion of the reactance curve and X5 correction in the percentage of IOS alteration parameters. Then we measured the mean differences of IOS and $FEF_{25-75\%}$ between the groups of patients with and without X5 approx. correction. Also, the correlation of X5 and X5 approx. with the other IOS basal parameters in each age category was measured. The differences in % of basal parameters in IOS were calculated using the Fisherx2 test or the Pearson test with the Yates correction, where appropriate. For measuring the mean difference between patients with and without X5 approx. correction, the t-student test for an independent sample was used, and for the correlation of X5 and X5 approx. with the IOS and spirometry parameters, the Pearson correlation test was used. In both

analyses, normal distribution was verified.

The sample size for establishing the difference between groups without X5 and with X5 correction was calculated in accordance with the pilot study, and 380 patients were needed with 80% of power and 0.05 alfa. For the statistical analysis, SPSS$^{(r)}$ v17.0 (IBM, Armonk, NY) software was used.

Results

Of the 445 asthmatic children initially included, 42 were excluded (9 preschoolers and 2 schoolchildren did not perform properly the IOS, and 41 patients did not sign the consent); therefore, 403 (88.6%) asthmatic were included, the mean age was 8.9 years, 57.1% were males, and 22.6% were preschoolers, 59% schoolchildren, and 18.4% adolescents. The severity of asthma according to GINA was 28.3% mildly persistent, 63.8% moderately persistent, and 7.9% severely persistent, and 32.5% were atopic according to the SPT.

Among the demographic characteristics by age category, the presence of an inversion of the reactance curve and the X5 approx. correction is shown in Table 1. The schoolchildren and adolescents with X5 approx. were older, and schoolchildren with X5 approx. were shorter than those without X5 approx. The prevalence of atopy, asthma severity, and use of controller therapy were similar between children with and without X5 approx. correction, by age category. A total of 264 children (65.5%) presented an inversion of the reactance curve and correction of X5 to X5 approx. Patients that required an X5 correction showed a significant lineal tendency by age category (Figure 2).

The percentage of abnormal values in R5, Fes, AX, and D5-20 was significantly higher among preschoolers and schoolchildren who exhibited an inversion of the reactance curve. However, only abnormal values of D5-20 were found among adolescents with an inversion of the reactance curve (Table 2). The mean of all the IOS parameters was significantly higher in children with X5 approx. for all age categories, while the mean of the spirometry parameter ($FEF_{25-75\%}$) was significantly higher in children with X5 approx. for schoolchildren and adolescents (Table 3).

The correlation of X5 approx. with all the IOS parameters and the $FEF_{25-75\%}$ was higher than the correlation of X5. The correlation of X5 approx. with AX and D5-20 was strongly negative in adolescents and with D5-20 in preschoolers. The correlation of X5 approx. was considerably negative with R5 and Fres in adolescents, with R5, AX, and D5-20 in schoolchildren, and with R5 and AX in preschoolers (Table 4).

Discussion

We described, for first time, the prevalence of an inversion of the reactance curve and the X5 approx. correction in asthmatic children. We found that these phenomena occurred in 65.5% of the cases, and this high prevalence is perhaps because the majority of our population had moderately or severely persistent asthma, so even in an asymptomatic period they could persist in showing a small-airway obstruction with IOS but with normal spirometry. Other studies have shown the presence of a small-airway obstruction in the IOS but with normal spirometry.[19,20]

In our study, the X5 approx. correction was needed in more than 80% of preschoolers, 67% of schoolchildren, and 36.5% of adolescents (p for trend < 0.001), indicating that this phenomenon is related to age. Several factors could explain why the reversal of reactance is more frequent in preschoolers, e.g. the smaller caliber of the airway, which makes the parallel resonance more visible, and the fact that the site of obstruction is predominantly the small airway, which makes it more severe. In addition, the lung function deficits that these children can carry even from birth and changes in the structure of the lung such as hypertrophy of the bronchial smooth muscle that has been found in biopsies are factors that could also have an influence.[21-25]

The adolescents that needed X5 approx. correction had significantly higher abnormal values of D5-20 in the IOS. There was clear evidence suggesting that the higher abnormal D5-20 values were associated with peripheral airway dysfunction in children and adolescents.[26,27] This phenomenon was not found for other IOS parameters, maybe due to the cutoff used for adolescents' being too high; therefore, it would perhaps be better to use an adult cutoff for determining peripheral airway obstruction.[28,29]

Among schoolchildren and preschoolers needing X5 approx. correction, the mean values of R5, Fres, AX, and D5-20 were significantly higher. The alterations of these IOS parameters were associated with peripheral airway dysfunction and with an asthma phenotype characterized by inadequate control, normal FEV1, alteration in $FEF_{25-75\%}$, air trapping, and higher AX and D5-20. For these patients, the use of ultrafine inhaled corticosteroids (ICS) that can reach small airways <2 mm in diameter was suggested.[6,8,26,29,30] Therefore, it could be hypothesized that the inversion of the reactance curve and the X5 approx. correction could be useful for identifying this asthma phenotype.

Among schoolchildren and adolescents, the mean $FEF_{25-75\%}$ value was significantly lower in the group that required X5 approx. correction, and this confirmed that these patients had alterations in the small airways manifested by spirometry. Previous studies[31,32] 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 X5 approx. may have similar implications.

Compared to X5, X5 approx. exhibited closer correlation with other IOS parameters and $FEF_{25-75\%}$. This finding, together with the abnormal results and means in the IOS, suggests that X5 approx. is a better parameter for measuring small airway alteration than X5. This is especially important in preschoolers, since this is the age where morbidity and hospitalizations for asthma occur more frequently than in other childhood ages.[33,34] Therefore, having an objective parameter (X5 approx.) could be useful for improving their asthma management.

Is important to mention that this inversion of the reactance curve was anecdotally reported in cystic fibrosis, [35] a disease characterized by small-airway dysfunction, the presence of different time constant units, and inhomogeneity ventilation, which can also occur in asthma, as was shown in the present study.

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 (X5 approx.) is associated with uncontrolled asthma. Second, we were not be 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, that it significantly decreases with age, and that it has a close association with IOS parameter alterations that measure small-airway dysfunction. Compared to X5, X5 approx. correlated better with other IOS parameters and with FEF2575, suggesting that it is a good indicator for asthma management in children.

Figure Legends:

Figure 1. IOS with inversion of the reactance curve.

On the left, female pre-school, 5 years and 1 month old, weight 20k, size 117 cm, with inversion of the reactance curve in the IOS (red arrow). Value of X5 (black dashed line) Value of X5 approx. (green dashed line). On the right are the pre-bronchodilator values of X5 (X5Hz) and X5 approx. (X5Hz c) recorded by IOS on the same patient. Mejor= best, Tiempo medic= measuring time.

Figure 2. Proportion of patients who required correction with X5 approx. lineal by age categories.

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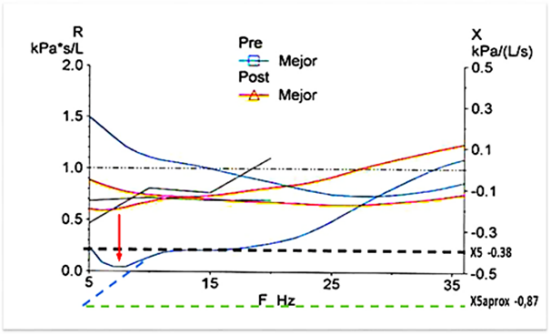
Tables 1,2,3,4 final 15082020.docx available at https://authorea.com/users/352160/articles/476518-inversion-of-the-reactance-curve-and-x5-approx-are-better-parameters-for-measuring-small-airway-dysfunction-in-asthmatic-children

Figure 1. IOS with inversion of the reactance curve.



		Teór.	PRE	%Pre/T
VT	L	0.29	0.42	146
Z5Hz	kPa/(L/s)	0.73	1.55	211
R5Hz	kPa/(L/s)	0.68	1.50	219
R20Hz	kPa/(L/s)	0.70	0.87	125
R35Hz	kPa/(L/s)		0.85	
X5Hz	kPa/(L/s)	-0.27	-0.38	142
X5Hz c	kPa/(L/s)	-0.27	-0.87	326
Fres.	1/s	16.58	22.96	138
AX	kPa/L		9.22	
Di5-20	kPa/(L/s)		0.63	
D5-20%	%		41.61	
Tiempo medic.			15:48	

Figure 2. Proportion of patients who required correction with X5 approx. lineal by age categories.