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Impulse Oscillometric Features and Respiratory System Models Track Small Airway Function in Children

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1. Introduction

Asthma is an inflammatory condition of the airways resulting in their hyper-reactivity, generating increased mucus, mucosal swelling and airway smooth muscle contraction all of which contribute to (partial) airway obstruction. The symptoms include chest tightness, coughing and wheezing, and in severe cases shortness of breath and low blood oxygen (1). According to Dorland's medical dictionary small airway impairment (SAI) is a chronic obstructive bronchitis with narrowing of the bronchioles and small bronchi. The term small airways refer to about 7th to 19th generation of airways with an inner diameter of about 2 to 0.5 mm. These airways are considered to be an important site of inflammation in asthma and chronic obstructive pulmonary disease (COPD). The atopic manifestation just prior to asthma could be early small airway disease (SAD) and then if inflammation persists, asthma would appear. SAD includes a spectrum of inflammatory and fibrotic pulmonary diseases centered on the small conducting airways.

According to the American Academy of Allergy Asthma & Immunology, Asthma and allergies stroke 1 out of 12 Americans and approximately 25 million Americans (8% of the U.S. population) had asthma in 2009. About 1 in 10 children (10%) had asthma and 1 in 12 adults (8%) had asthma in 2009. For the period 2008-2010, asthma prevalence was higher among children than adults. For the period 2008-2010, asthma prevalence was higher among multiple-race, black, and American Indian or Alaska Native persons than white persons. Asthma costs in the US grew from about \$53 billion in 2002 to about \$56 billion in 2007, about a 6% increase. Compared with adults, children had higher rates for asthma primary care and emergency department visits, similar hospitalization rates, and lower death rates. Asthma was linked to

3,447 deaths (about 9 per day) in 2007. Internationally asthma has a rising prevalence in low and middle income countries and it is reaching a steady level in high income countries. An estimated 300 million people worldwide suffer from asthma, with 250,000 annual deaths attributed to the disease; almost all of these deaths are avoidable (2).

In Mexico, 10% (approximately 10 million people), of the population suffer from asthma. It is the most common cause of chronic illnesses and emergency hospitalizations in children according to the Mexican College of Allergy, Asthma and Pediatric Pulmonology (3).

Assessment of respiratory function is important in diagnosis and monitoring of asthma and other respiratory diseases in children (4). The pulmonary function test most commonly used to detect asthma is spirometry, which measures the volume of air that can be moved in or out of the lungs as a function of time with rapid and maximal inspiratory and expiratory efforts. This requires a considerable degree of cooperation from the subject, which is difficult to achieve in older children and almost impossible to achieve by younger children. This makes the diagnosis of asthma difficult owing to the lack of objective measurements for younger children (5). Furthermore, it has been reported that some asthmatic patients do not improve spirometrically, despite clinical improvement with treatment (6). This is of concern because if asthma is not appropriately controlled, it can lead to permanent airway damage.

In contrast to forced spirometry, the Forced Oscillation Technique (FOT) superimposes small air pressure perturbations on the natural breathing of a subject to measure lungs mechanics (respiratory impedance). The Impulse Oscillometry System (IOS) measures respiratory impedance by using short pulses (impulses) of air pressure. It has been developed as a patient-friendly lung function test that minimizes demands on the patient and requires only passive cooperation of the patient wearing a nose clip, keeping lips tightly closed about a mouthpiece and breathing normally through the mouth. IOS has been used with success to assess lung function in healthy and asthmatic children and adolescents (4-32). In infants and children, reversible airway obstruction and bronchial hyperresponsiveness (BHR) are significant components contributing to the diagnosis of bronchial asthma (27). All this evidence, which will be described in detail, confirms that lung function in children and adolescents is sensitively and accurately assessed by the IOS, before and after bronchodilation. To build upon this evidence and demonstrate the potential enhancements in the clinical utility of IOS, here we present respiratory system Model Parameters and selected IOS features derived from Pre- and Post-bronchodilation data acquired from Anglo and Hispanic children, that offer significant improvements in quantitative evaluation of small airway impairments and assessment of asthma in this population.

In 1991, the American Thoracic Society published guidelines focusing on spirometry as the most widely used lung function test, where they presented Reference Values for spirometric parameters for Caucasian and Black men and women. They also mentioned that it is common practice to interpret the results of lung function tests in relation to Reference Values and in terms of whether or not they are considered to be within the “normal” range (33).

The European Respiratory Society in 1995 published a workshop report (34) about “Reference Values for Residual Volume (RV), Functional Residual Capacity (FRC) and Total

Lung Capacity (TLC)" in which it was mentioned that reference values play an important role in establishing whether the measured volumes fall within an expected range for healthy individuals of the same sex, similar stature, age, and other characteristics. They also point out that comparing reference with measured values is fraught with difficulties, as this may result in disease being undetected and as a consequence untreated. It is also mentioned that FRC is the only lung volume that can be measured routinely with accuracy and reliability, and in addition it is stated that attempts have been made to evaluate TLC and RV. In this report reference values (values for healthy subjects) and prediction equations for lung volumes for children and adults are obtained using different techniques like helium dilution and body plethysmography. These values are presented for different heights. However, this report does not include reference values and prediction equations based on the FOT or IOS.

Few studies have been developed to obtain Reference Values for healthy children using the FOT and IOS (35-42). It is essential to have IOS Reference Values for children, as this technique has been shown to be very effective in the detection of lung abnormalities. Therefore, here we intend to make an effort towards establishing normal IOS Reference Values in North American Anglo and Hispanic children 5 to 19 years old. We also aim to present baseline (pre-) and post-bronchodilation IOS parameters for Anglo and Hispanic children with Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI) and Asthma.

IOS data generate frequency-dependent curves of respiratory impedance (resistance and reactance) that are visually analyzed to recognize changes in their shape and magnitude and distinguish healthy respiratory function from dysfunction. The IOS data can be deployed to develop mechanical and equivalent electrical circuit models of the respiratory impedance to evaluate and quantify lung mechanics. In these equivalent models, electrical components analogous to mechanical resistance, compliance, and inertance inherent in the respiratory system are used. Therefore, estimates for these Model Parameters based on IOS measurements could be used as baseline measures for better detection, diagnosis, and treatment of different respiratory diseases (43).

Previous work by our research group for more than a decade has focused on development and analysis of different equivalent electrical circuit models for human respiratory impedance. This effort to date has demonstrated that the performance of extended Resistance Inductance Capacitance (eRIC) model and the augmented RIC (aRIC) model (an improvement of the eRIC model) ranked in the middle of a series of conventional models developed over the past several decades in terms of total cumulative error. However, they provide parameter estimates that are physiologically more realistic and in line with expected values in normal subjects and those suffering from pulmonary diseases (43-51), than previous models.

The IOS data collected from children for this study were partially analyzed and presented in several publications (52-61), the latest results of this research are presented in this chapter.

Here we determine the eRIC and aRIC model parameter estimates in addition to sensitive IOS measures of lung function in Normal (N) or Healthy (H), PSAI, SAI and Asthmatic (A), Anglo and Hispanic children. We further evaluate the performance of these models in

quantifying lung function in this population and analyze the correlation of these Model Parameters with sensitive IOS measures of lung function.

2. Pulmonary function tests and previous studies

Pulmonary function refers to how the lungs perform gas exchange. Pulmonary function testing is a practical application of Respiratory Physiology and is necessary for understanding abnormalities in lung function and the effects of treatments. Pulmonary function tests help to determine the severity of functional impairments or defects and the extent to which treatments restore normal function (62). In this section we first review two important pulmonary function tests: Spirometry and Impulse Oscillometry. We then perform a literature review of several studies that have been carried out in previous years to compare several Pulmonary Function Tests (PFTs) to assess the ability of FOT and IOS to measure pulmonary function and to discriminate between impaired and non-impaired conditions.

2.1. Spirometry

Spirometry is the most common PFT; it is a measurement of maximal airflow after deep inspiration to fill up the lungs. It can provide information about the size of the breathing tubes (mainly large airways) and about the presence of blockages to airflow (63). The measurements usually obtained from spirometry are (64):

- **FVC (Forced vital capacity):** Total volume of air that can be exhaled during a maximal forced expiration
- **FEV₁:** Forced expiratory volume in seconds. It is the volume of air expired in the first second of maximal expiration
- **FEV₁/ FVC:** Percentage of the FVC expired in one second
- **FEF_{25%-75%}:** Average expired flow over the middle half of FVC. It represents the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled
- **FEV₆:** Forced expiratory volume in six seconds
- **PE :** Peak expiratory flow represents the maximal expiratory flow rate achieved

The National Asthma Education and Prevention Program (NAEPP) Guidelines previously considered FEV₁ as the “gold standard” to assess asthma severity and control, but several studies have suggested that most children have normal or near normal FEV₁ even when they are symptomatic. Now the NAEPP has added FEV₁/ FVC ratio as an impairment criterion to classify asthma severity and control. The most important pulmonary function abnormalities seen in asthmatic children are decreases in the FEV₁/ FVC and the FEF_{25%-75%}, while FEV₁ remain in the normal range in spite of asthma severity (65).

2.2. Forced Oscillation Technique (FOT)

The fundamental principle of FOT is that respiratory mechanics can be measured from superimposition of external pressure oscillations on the respiratory system during resting

breathing (66). Therefore, FOT superimposes small external pressure signals on the natural breathing to determine a subject's breathing mechanics. FOT measures respiratory impedance to this applied forced pressure oscillations produced by a loud speaker (67). FOT is indicated as a reliable diagnostic tool to obtain tidal breathing analysis. One of the great advantages of FOT over other pulmonary function tests is that the results measured are independent of the subject respiratory pattern, therefore it is effort independent; it requires only passive cooperation from the subject breathing normally through a mouth piece, keeping lips airtight closed around it, while wearing a nose clips occluding the nares (68). FOT has been used in humans for more than 50 years; it has been used in children with three major clinical aims (69):

1. To characterize the lung function abnormalities of chronic respiratory diseases in children
2. As a diagnostic tool, especially to recognize asthma and bronchial responsiveness
3. To study the physiological mechanisms and pathophysiology of diverse conditions involving and/or threatening the respiratory system

FOT applied at oscillation frequencies between 3 and 35 Hz can provide helpful information to help distinguish between large and small airways. The use of multiple oscillation frequencies in FOT allows a separation of large airways from small airways. Frequencies below 15 Hz, low oscillation frequencies, have been shown to be transmitted more distally (peripherally) in the lungs, whilst frequencies higher than 20 Hz, high oscillation frequencies, can reach only the intermediate size airways. As a result low oscillation frequencies reflect small and large airways, while high oscillation frequencies merely reflect large airways. Therefore, changes in large airway resistance cause uniform changes in resistance at all oscillation frequencies (3-35 Hz), whereas changes in small airway resistance result in noticeable changes in low frequency (3-15 Hz) resistance with small or no change in high frequency resistance. Peripheral airways include all airways with a diameter less than 2mm, and large airways are those with diameters greater than 4 mm (66).

One of the most remarkable features of FOT in relation to spirometry is that it has a relatively greater sensitivity to peripheral airways disease; due to the fact that spirometry does not provide a clear indication of peripheral airway obstruction regardless of the information contained in the flow-volume curve and the values of mid-flow rates (FEF_{25%-75%}) (68).

2.3. Impulse Oscillometry System (IOS)

In 1956 Dubois presented the first study on FOT; in this study FOT was applied using sinusoidal oscillations with multiple single frequencies between 2 and 18 Hz. After this study several modifications of FOT were developed, until 1993 when the pulse technique was improved and commercially produced by the German company Jaeger. It was named Impulse Oscillometry System (IOS), as an easier to use method to measure respiratory resistance (R) and reactance (X). The advantages of IOS include good time resolution. It measures 5 pulses per second, with continuous resolution in the frequency domain using a

Fourier Integral (65-66) to calculate respiratory impedance. The IOS, as FOT, superimposes small air pressure perturbations on the natural breathing of a subject to measure the impedance of the respiratory system, offering an easy to use method as it does not require any effort from the subject being tested. An additional advantage is the simplicity of the hardware needed to generate the forced oscillations, allowing smaller, more efficient electronic and mechanical structures with minimal power loss (68).

Some disadvantages of the IOS have to be recognized. The fact that IOS measures spontaneous breathing from a subject allows biological variability, and to counteract this fact multiple tests are required to be performed in a subject in order to establish reliable mean values of IOS parameters. A special aspect of applying pulses of pressure is that they are applied within a very short time causing a higher impact on the respiratory system compared with other lung function tests, and this may be perceived as an unpleasant sensation during the measurements (68).

A Jaeger MasterScreen IOS (Viasys Healthcare, Inc. Yorba Linda, CA, USA) was used in this study. The system was calibrated every day using a 3-L syringe for volume calibrations and a reference resistance (0.2 KPa/L/s) for pressure calibrations. Children were asked to wear a nose clip, while breathing normally through a mouthpiece and were instructed to tightly close their lips around it to avoid air leakage. Three to five IOS test replicates were performed on each subject to ensure reproducible tests without artifacts caused by air leaks, swallowing, breath holding or vocalization (9). In each IOS test impulses were applied for a period of 30 to 45 seconds. IOS data were carefully reviewed off line and quality-assured by our expert clinician to reject segments affected by airflow leak or swallowing artifacts. Coherence was also used as a 'quality assurance index'; it is an index of causality between the input and the output of a linear system, therefore if the system is nonlinear or if it is contaminated by extraneous noise then the coherence is lower than expected. Therefore, measurements with low coherence were excluded in this research to avoid problems with artifacts. Coherence is considered by researchers as a useful guide to quality assurance (67).

2.3.1. IOS parameters

IOS is a multifrequency oscillation method; it provides measures of respiratory mechanics in terms of *respiratory impedance* as a function of frequency $Z(f)$.

Respiratory Impedance is the transfer function of pressure (P) and flow (Q), derived from the superimposed forced oscillation, after being separated from the respiratory pressure and flow.

$$Z(f) = P(f) / Q(f) \quad (1)$$

The respiratory *Impedance* (Z) measured by IOS is a complex quantity and consists of a real part called respiratory *Resistance* (R) and an imaginary part called respiratory *Reactance* (X).

$$Z(f) = R(f) + jX(f) \quad (2)$$

IOS also includes hallmarks such as *Resonant Frequency* (F_{res}) and *Reactance Area* (AX) also known as the “*Goldman Triangle*”. IOS yields these indices over a selected frequency range of 3 to 35 Hz (68).

A. Impedance Parameters: Respiratory Resistance (R) and Respiratory Reactance (X)

a. Respiratory Resistance (R)

The real part of the Impedance (Z) corresponds to the Resistance (R), which includes the resistance of the proximal (central) and distal (peripheral) airways as well as lung tissue and chest wall while these latter resistances are usually negligible. In healthy adult subjects, R is nearly independent of oscillation frequency. When an airway obstruction occurs, either central or peripheral, R5 (Resistance at 5 Hz) is increased above normal values. Central airway obstruction elevates R evenly independent of oscillation frequency. Peripheral airways obstruction is highest at low oscillation frequencies and falls with increasing frequency; this is called the negative frequency-dependence of Resistance (fdR). As peripheral resistance increases, R becomes more frequency dependent. Small children normally present frequency-dependence of resistance, and this may be greater than in adults in the presence of peripheral airflow obstruction. Resistance is measured in cmH₂O/L/s or KPa/L/s (68).

b. Respiratory Reactance (X)

The imaginary part of Z, the respiratory Reactance (X), includes the mass-inertive forces of the moving air column expressed in terms of Inertance (I) and the Elastic properties (compliance) of lung periphery expressed as capacitance (C) in electrical terms (68).

$$X(f) = \omega I - (1 / \omega C) \quad (3)$$

where

$$\omega = 2\pi f \{0 < f \leq f_{max}\}$$

C represents the ability of the respiratory system to store energy, primarily located in the lung periphery. The component of X associated with C is defined to be negative in sign. It means C is dominant at low oscillation frequencies, meanwhile the component of X related to I is positive in sign, meaning that I's property is more prominent at high oscillation frequencies (see figure 1). Reactance is measured in cmH₂O/L/s or KPa/L/s (68).

B. Other IOS parameters: Resonant Frequency (F_{res}), Reactance Area (AX) and Frequency dependence of resistance (R_5 - R_{25})

a. Resonant Frequency

The Resonant Frequency (F_{res}) is the point at which C and I are equal, therefore reactance is zero and is measured in Hertz (1/s) (68).

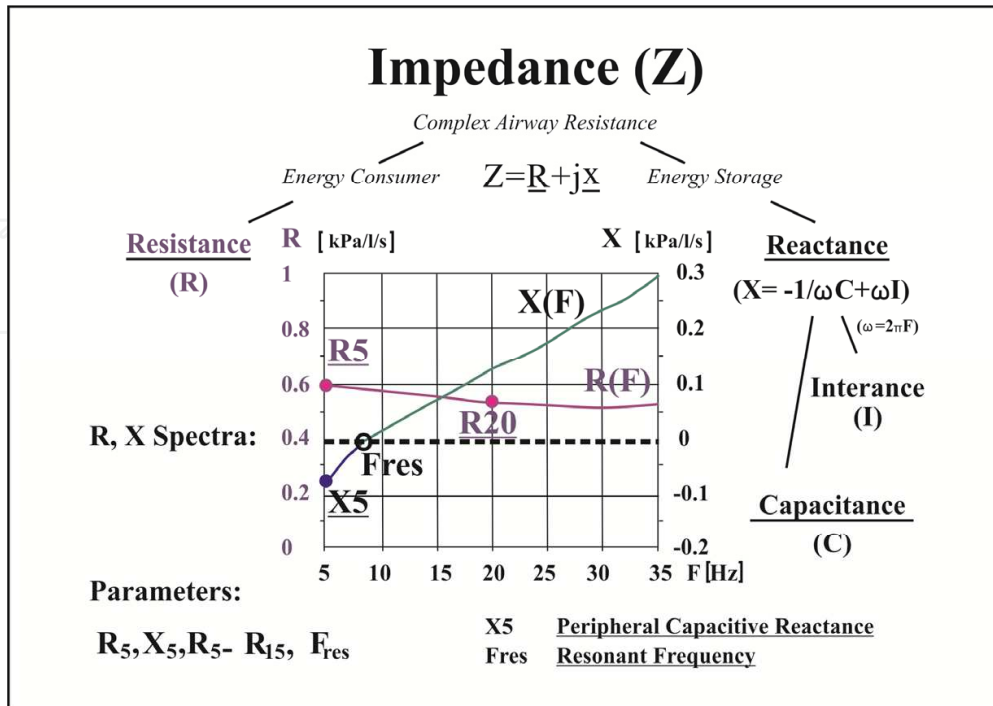


Figure 1. IOS parameters [76]

$$\omega_0 I = (1 / \omega_0 C) \quad (4)$$

This parameter should not be interpreted as a particular respiratory system mechanical property; instead it can be used as a suitable marker to separate low frequency from high frequency impedance. Respiratory system abnormalities cause F_{res} value to be increased [74].

b. Reactance Area (AX)

The Reactance Area (AX), – the “Goldman Triangle” – was introduced by Michael Goldman in his study on “Clinical applications of forced oscillations” (67); AX is the integrated low frequency respiratory reactance magnitude between 5 Hz and F_{res} , and is measured in cmH₂O/L or KPa/L. AX is a practical FO index related to respiratory compliance. AX is a single quantity that reflects changes in the degree of peripheral airway obstruction and closely correlates with fdR(68). *AX is a useful and sensitive index of peripheral airway function (66).*

Figure 2 shows data collected from a Normal (N) child and a child with Small Airway Impairment (SAI) for this research as an example. In this figure it can be observed that the **AX (the Goldman’s Triangle)** area is bigger for the child with SAI than for the normal child. It is interesting to notice that the values of F_{res} are very close for both children.

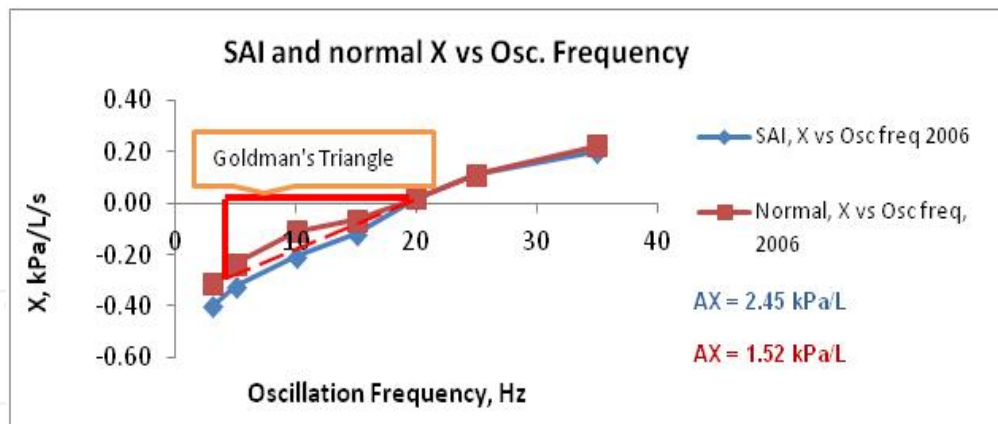


Figure 2. Reactance measurements in a Normal and a SAI child as a function of oscillation frequency.

a) Frequency-dependence of resistance (fdR or R5-R20)

It is simply the subtraction of the measured resistance at 20 Hz from the resistance at 5 Hz or 3 Hz. Frequency-dependence of resistance is a characteristic of peripheral airway dysfunction (66).

$$R5 - R20 = R5 - R20 \quad (5)$$

Changes in AX with treatment interventions parallel changes in frequency-dependence of R. It has been suggested by Goldman et al. (66) that the magnitudes of frequency dependence of R and AX appear to reflect a similarly predominant influence of peripheral airway mechanical function.

Frequency-dependence of resistance occurs in healthy children, and to a better extent in children with respiratory system distresses (67). There is now plenty of evidence that peripheral airway inflammation is present in asthma patients, and frequency-dependence of resistance occurs significantly in asthma (68).

2.4. Bronchodilation phenotype

The bronchodilation response as a physiological response to short-acting beta agonist medicines has been recommended to demonstrate reversibility of airflow obstruction consistent with the definition of asthma (65).

Bronchoconstriction is defined as increased tone of airway smooth muscles due to inflammation; and bronchodilation is defined as decrease in smooth muscle tone, and as a result a decrease in inflammation. When an increase of airways smooth muscle tone occurs, R increases due to a corresponding decrease in airway lumen. R also increases due to inflammation or edema. In asthmatics, high and low frequency R decreases after bronchodilation, showing a larger decrease in low-frequency R and a resultant decrease in frequency-dependence of resistance. In addition FOT has been reported to demonstrate larger sensitivity to inhaled corticosteroid or to β -agonist inhalation than spirometry (68).

According to a study on PFT in preschool children in 2007, FOT has been successfully performed in different settings, and a number of studies have demonstrated that FOT was capable of identifying airway obstruction and reactions to bronchodilators and bronchoconstrictors (71). Several studies have been developed to assess bronchodilator responses using FOT. Marotta et al. (7) performed a study in 4-year old children concluding that IOS bronchodilator responses are remarkably abnormal in this population (children presented a significant bronchodilator response), and that IOS is a useful diagnostic tool in detection of early asthma development. Oostveen et al. (72) performed a comprehensive review on methodology, recommendations and future developments of FOT in clinical practice stating that FOT is a reliable method to assess bronchial hyper-responsiveness in adults and children. Ortiz et al. (8) performed an IOS study in children 2 to 5 years old in El Paso, Texas, finding that IOS is an acceptable method of assessing airway responses to bronchoactive drugs in this age group. In a more recent study related to the use of FOT to detect bronchodilation in children, Bar-Yishay et al. (73) concluded that FOT could reliably measure response to bronchodilator therapy. Recently Song et al (13) researched the utility of impulse oscillometry in young children with asthma finding that asthmatic children differed from control subjects in IOS-assessed bronchodilator response and that there were some significant correlations between bronchodilator responses of spirometric and IOS parameters. Galant et al. (65) stated that bronchodilator response (BDR) would appear to give important additional information about airway inflammation and found that IOS is a promising test to identify asthmatic preschoolers.

All this evidence confirms that lung function in children and adolescents is sensitively and accurately assessed by IOS, before and after bronchodilation. Nevertheless few longitudinal Forced Oscillation (FO) data exist in healthy subjects or in those with airflow obstruction. Oostveen et al. (72) noted the need for a practical FO index to define airway obstruction.

2.5. IOS studies

2.5.1. IOS vs. Spirometry

Table 1 provides a summary of several IOS vs Spirometry studies, with their descriptions, different IOS parameters analyzed and conclusions.

Table 1 summarizes the utility of different IOS indexes of lung function in relation to spirometric parameters in different subpopulations studied between 2002 and 2009. The conclusions emphasize the necessity to analyze these parameters to determine their efficacy to differentiate between Healthy and Impaired respiratory systems. In our study we focused on the most significant IOS indexes of lung function and pushed the boundary by further analyzing the respiratory impedance Model Parameters to differentiate between Healthy and Impaired respiratory conditions in children.

Researchers	Evaluated Population	Evaluated Parameters	Conclusions
Marota et al. [7] 2003	asthmatic and non-asthmatic 4 years	R5, X5, F _{res}	IOS bronchodilator responses are remarkably abnormal in this population. IOS is a useful tool for asthma assessment
Goldman et al. [9] 2002	asthmatics 10-17 years	R5, R5-R15, AX	Significant differences between R5, R5-R15 and AX were seen. Spirometric indices showed no change. IOS parameters are sensitive measures of bronchomotor tone changes in these adolescents.
Saadeh et al. [11] 2003	asthma symptoms 4-62 years	R5, R5-R15, AX	Some asthmatic patients manifest normal spirometry despite continuing symptoms, these patients may be more sensitively managed using IOS
Gaylor et al. [6] 2003	asthmatics 5-80 years	R5, R5-R15, AX	IOS shows systematic improvements after inhaled levalbuterol, IO is more sensitive than spirometry and IOS should be considered before changing therapy in asthmatic patients whose FEV ₁ fails to improve
Vink et al. [12] 2003	asthmatics 5-17 years	R and X at 5-35 Hz	Resistance values measured at 5Hz showed to be superior to PEF measurements, IOS parameters can be easily used as an indirect measure of airflow obstruction.
Song et al. [13] 2008	asthmatics and controls 3-6 years	R5, R10, R20, R35	Spirometry did not present statistically significant differences between groups. There were some significant correlations between bronchodilator responses of spirometry and IOS parameters. IOS is a useful diagnostic tool and might be a helpful objective outcome measure.
Song et al. [14] 2008	asthmatics and controls 7-15 years	R and X at 5-35 Hz R5-R20	FEV ₁ and PEF _R showed significant correlation with impedance and resistance at 5,10,20 and 35 Hz in both groups,

Researchers	Evaluated Population	Evaluated Parameters	Conclusions
			FVC correlated with Z and R at 10, 20 and 35 Hz in both groups. IOS is an appropriate measure of lung function when spirometry and PEF can not be performed.
Antonova et al. [15] 2006	mild and moderate asthmatics 6 years	Z, R5, X5, F _{res}	No significant differences for spirometry were found, IOS presented significant increase in total impedance (Z), R5 and F _{res} , and significant decrease in X5. IOS may be more sensitive than spirometry for assessment of inflammatory process and degree of asthma severity.
Linares et al. [16] 2002	asthmatics 6-15 years	R5, X5, F _{res}	There were good correlation between spirometry and IOS, best correlation: R5 and FEV ₁ , and R5 and FEF25.
Lewis-Brown et al. [17] 2005	asthmatics 5-18 years	R5	Spirometry and IOS should be used together in asthma evaluation.
Nieto et al. [24] 2006	mild asthma	Z5, R5, R20, X5, F _{res}	Z5, R5, R20, X5, and F _{res} showed improvements, no changes were found in the control group. IOS is more sensitive than conventional spirometry.
Hur et al. [25] 2008	children	X5 and R5	IOS parameters were more discriminative than FEV₁ for detecting decreased lung function and showed a good correlation with FEV ₁ .
Larsen et al. [26] 2009	mild to moderate asthma 6-14 years	AX	AX was unique in reflecting ongoing improvement in contrast to spirometric values, AX might detect alterations in airway mechanics not reflected by spirometry.
Hellinckx et al. [28] 1998	healthy and asthmatic kindergarten children 2.7 - 6.6 years old	R and X at 5-35 Hz, F _{res}	No significant differences between groups for IOS parameters A change in R5 of 40% is to be considered as the cut-off for a "positive" bronchodilator response.

Researchers	Evaluated Population	Evaluated Parameters	Conclusions
Graw-Panzer et al. [29] 2009	46 inner-city children with asthma 4-20 years	R5 and R20	There is increased airway resistance as measured by IOS when there is airway obstruction measured by spirometry. A mean drop of R5 by -24 was found to be significant

Table 1. IOS vs Spirometry Studies

2.5.2. IOS vs Other techniques

Other researchers have compared IOS with spirometry and other techniques. Table 2 presents a summary of several such studies, with their descriptions, different IOS parameters analyzed and conclusions.

IOS, Spirometry and Whole body Plethysmography			
Researchers	Evaluated Population	Evaluated Parameters	General Conclusions
Olaguibel et al. [18] 2005	asthmatics 3-6 year old	R5, R20, X5	IOS was well accepted for young asthmatic children and produced reproducible and sensitive indices of lung function, R5 correlated with spirometry and plethysmographic values.
IOS and Whole body Plethysmography			
Tomalak et al. [19] 2006	chronic respiratory diseases (asthma, allergic diseases, cystic fibrosis, bronchiectasis and lung fibrosis) 5-18 years	R5, R20, R35	All three resistances correlated significantly with plethysmographic Raw and the strongest correlation was observed for R5. IOS may be useful in diagnosing children with obstructive respiratory diseases.

IOS, Interrupter Technique Resistance (Rint), Transcutaneous Measurement of Oxygen Tension (Ptc, O2) and Whole Body Plethysmography			
Bisgaard et al. [20]	suspected asthma	R and X at 5-35 Hz	IOS total respiratory impedance (Z), Rint, and Ptc,O2 changed
1995	4-6 years		in parallel with sRaw and FEV1, these three parameters provide convenient indices of changes in lung function.
Klug et al. [10]	asthmatics	R and X at 5-35 Hz	All the evaluated techniques reliably reflect short-term
1996	2-4 years		changes in lung function.
IOS, Interrupter Technique Resistance (Rint) and Whole Body Plethysmography			
Klug et al. [4]	Caucasian, no chronic diseases	R5,R10,X5,X10, Z5,Fres	Techniques require minimal cooperation and allowed
1998	2-7 years		measurement of lung function in 80% of the tested children.
Nielsen et al. [21]	asthmatics and controls	R5, X5	Whole body plethysmography (sRaw) was superior
2000	2-5 years		in separating both groups.
Nielsen et al. [23]	asthmatics and controls	R5, X5	Whole body plethysmography (sRaw) was superior
2001	2-5 years		in separating both groups.
IOS, Spirometry and exhaled nitric oxide (eNO)			
Todaki et al [30]	62 asthmatics, 13 wheezy and	R20 and R5-R20	A significant decrease occurred in the eNO level
2009	17 healthy children		and it correlated with maximal expiratory flow at 50% vital capacity R5-R20

Table 2. IOS vs other Techniques Studies

Table 2 summarizes the utility of different IOS indexes of lung function in relation to parameters acquired from a variety of other pulmonary function test in different

subpopulations studied between 1995 and 2009. The conclusions emphasize the necessity to analyze these IOS parameters to determine their efficacy to differentiate between Healthy and Impaired respiratory systems.

2.5.3. IOS studies

Table 3 presents a summary of several IOS studies, with their descriptions, different IOS parameters analyzed and conclusions.

Researchers	Evaluated Population	Evaluated Parameters	General Conclusions
Ortiz et al. [8] 2002	asthmatics 2-5 years	X5	IOS is an acceptable method to assess airway response to bronchoactive drugs in this age group.
Goldman et al. [22] 2008	asthmatics 2-5 years	R5, R5-R20, AX	IOS indices are sensitive measures of lung mechanical responses to bronchodilators in this group of children.
Menendez et al. [31] 2008	asthmatics 2-5 years	R5,R5-R20, AX	IOS R5, R5-R20, AX are sensitive measures of lung mechanics responses to SABA and LABA in pre-school children with asthma
Jee et al. [32] 2010	asthmatics and chronic cough (controls) children	R, X, Fres and AX	IOS parameters were significantly different between groups in the methacholine challenge

Table 3. IOS studies

The outcomes of most recent studies carried out between 2002 and 2010 presented in table 3 show the utility of different IOS parameters including the AX, “the Godlman’s Triangle”, as sensitive measures to assess lung function.

As mentioned before, a number of previous IOS studies, summarized in tables 1, 2 and 3, demonstrate that IOS is able to sensitively and accurately evaluate lung function in children and adolescents, using Pre- and Post-bronchodilation conditions and bronchial challenge. These studies further show that that different IOS parameters at different frequencies serve as quantitative indicators to evaluate the Pre- and Post-bronchodilation response and bronchial challenge results. It is also remarkable that very few studies, only the most recent ones, reported the analysis of the AX parameter, which could offer critical information about lung function in children and adolescents as stated by Goldman et al. (9, 22), Nieto et al. (24), Larsen et al. (26) and Menendez et al. (31). Therefore, here we aim to statistically evaluate the performance of all IOS measured and calculated parameters (Resistances and Reactances, Fres, AX, frequency-dependence of resistance R3-R20 and R5-R20) over 3-35 Hz

during pre-post- bronchodilation conditions. We place special emphasis on the previously observed most significant IOS and Model Parameters and will determine which one of these parameters is more effective in differentiating between Pre- and Post-bronchodilation conditions.

2.5.4. IOS reference values - Previous studies

Table 4 below presents a summary of several studies performed to determine Reference FOT and IOS values in children.

Researchers	Method Used	Evaluated Population	Conclusions
Clement et al. [35] 1987	FOT	Belgian 403 healthy children 4 to 20 years	R and X vs frequency data depended on age or height, on sex, and slightly on weight. With growth R and the frequency-dependence of R decrease while X increases. Adult values of R and X can be observed at 15 years of age in girls and at 18 years in boys.
Ducharme et al. [36] 1998	FOT	North American children (white,black,asian,others) 206 healthy children 3 to 17 years	Height is the best predictor for total respiratory resistance at 8,12 and 16 Hz in children.
Frei et al. [37] 2005	IOS	North American 222 white children 3 to 10 years old 100 to 150 cm in height	Standing height was the only significant predictor for all variables Resistance and Fres decreased by height, but also by age, and reactance increased.
Dencker et al. [38] 2006	IOS	Swedish 2 to 10 years 360 children 90-160 cm	All variables were related to body height, and most of them were weakly related to weight.
Nowowiejska et al. [39] 2008	IOS	Polish 626 healthy children aged 3-18	Body height was the best predictor and resistances were best predicted with exponential models while reactances with linear ones. R decreased with height while X increased.
Amra et al. [40] 2008	IOS	Iranian 509 healthy children	These measurements can be used clinically to help diagnose and monitor respiratory disorders, independent of effort.
Wee et al. [41] 2007	IOS	Korean 92 children	IOS is a feasible method to measure the respiratory resistance in children. The reference values using IOS

Researchers	Method Used	Evaluated Population	Conclusions
		7 to 12 years old	seems to be useful to diagnose a variety of respiratory diseases.
Jee et al. [42] 2010	IOS	Korean children 143 3-6 years	Healthy young children had better results in IOS parameters than main reference values reported before.

Table 4. IOS Reference Values

Table 4 shows that only few studies have been developed in order to determine Reference IOS Values for children.

In 1991, the American Thoracic Society published guidelines focusing on spirometry as the most widely used lung function test. This document states that it is common practice to interpret the results of lung function tests in relation to Reference Values and in terms of whether or not they are considered to be within the “normal” range (33).

The European Respiratory Society published a workshop report in 1995 (34) about some commonly measured spirometry parameters such as RV, FRC and TLC. In this document it is stated that reference values play an important role in establishing whether the measured respiratory volumes fall within an expected range for healthy individuals of the same sex, similar stature, age, and other characteristics. In this report reference values (values for healthy subjects) and prediction equations for lung volumes for children and adults are obtained using different techniques like helium dilution and body plethysmography. These values are presented for different heights. However, this report does not include reference values and prediction equations based on the FOT or IOS.

From table 4 we observe that it is crucial to have IOS Reference Values for children. These have been very effective in the detection of lung abnormalities, as demonstrated in table 1, 2, and 3. Therefore, in our research here we attempt to take the first steps towards establishing IOS Reference Values in Healthy North American Anglo and Hispanic children 5 to 19 years old. We also aim to present baseline (pre-) and post-bronchodilation IOS parameter values for this subpopulation of children with Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI) and Asthma (A).

3. Respiratory system models

The IOS and FOT impedance curves can be represented by equivalent electrical circuit models of the human respiratory system with components analogous to the resistances, compliances and inertances inherent in the characterization of this system. Respiratory system component values could be estimated using well-established parameter estimation methods. These could then be used to assist physicians in the diagnosis and treatment of different respiratory diseases (43).

In our research we have special interest in the small airways disease (SAD) or small airway impairment (SAI) and asthma. An effective means to characterize small airway dysfunction is by integrating realistic models of lung mechanics based on physiological measurements made by FOT or IOS and other techniques (74).

Different equivalent electrical circuit models with lumped parameter components representing the resistances, inertances, and compliances of the respiratory system have been developed and analyzed over the years by different research groups (44).

Previous work by our research team has focused on development and analysis of six different equivalent electrical circuit models of human respiratory impedance. Our efforts to date, have demonstrated that the performance of the extended RIC (eRIC) and augmented RIC (aRIC) models rank in the middle of a series of conventional models developed over the past several decades in terms of total cumulative error. However, they provide parameter estimates that are physiologically more realistic and in line with expected values in healthy subjects and those suffering from pulmonary diseases than previous models (43-51).

In the following paragraphs we will introduce the two respiratory system models analyzed in this study: the Extended Resistance-Inertance-Compliance (eRIC) and the Augmented Resistance-Inertance-Compliance (aRIC) models.

a. Extended RIC (eRIC) Model

This model is proposed as an improvement of the RIC model, with an additional Peripheral resistance (R_p) connected in parallel with the capacitance. Therefore, the eRIC model is composed of central (large airway) Resistance (R_c), large airway Inertance (I), peripheral (small airway) Compliance (C_p) and peripheral (small airway) Resistance (R_p). This added R_p allows for the frequency-dependence of resistance observed in impedance data, which is not possible for the RIC model. R_p models the small airways resistance. On the other hand the eRIC model can be also considered as a simplification of either DuBois' (with I_i equal to zero and C_t equal to infinity) or the Mead's model (with C_l , C_w equal to infinity and C_e equal to zero) (43). The electrical equivalent circuit for the eRIC model is shown in Figure 3:

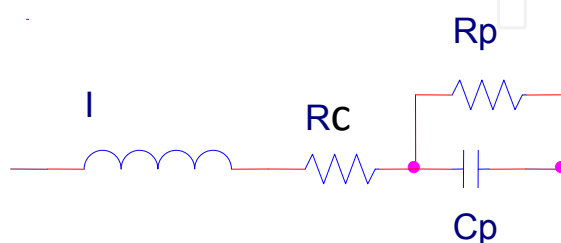


Figure 3. eRIC model (47).

The eRIC model impedance is calculated as follows:

$$Z = R_c + \frac{R_p}{1 + (\omega R_p C_p)^2} + j \left(\omega I - \frac{\omega R_p^2 C_p}{1 + (\omega R_p C_p)^2} \right) \quad (6)$$

b. Augmented RIC Model

This model was proposed as an improvement to the eRIC model and it can be considered as a simplification of the Mead's model. aRIC is composed of central (large airway) Resistance (R_c), large airway Inertance (I), peripheral (small airway) Compliance (C_p), peripheral (small airway) Resistance (R_p) and an additional compliance C_e (see figure 4), representing extrathoracic compliance. Its additional capacitance C_e , representing extrathoracic compliance, is thought to increase the real part of the respiratory system's impedance at the higher frequencies due to upper airways shunt effects as observed in IOS data (44).

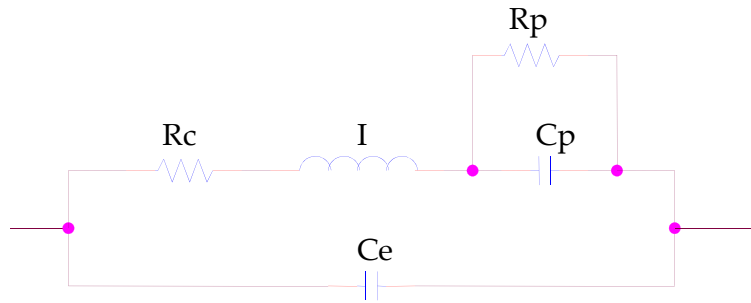


Figure 4. aRIC Model (47).

The aRIC impedance is given by:

$$Z = \frac{A(R_c A + R_p)}{\left[A(1 - \omega^2 I C_e) + (\omega^2 R_p^2 C_p C_e) \right]^2 + \left[\omega C_e (R_c A + R_p) \right]^2} + j \frac{\omega (I A - R_p^2 C_p) \left[A - \omega^2 C_e (I A - R_p^2 C_p) \right] - \omega C_e (R_c A + R_p)^2}{\left[A(1 - \omega^2 I C_e) + (\omega^2 R_p^2 C_p C_e) \right]^2 + \left[\omega C_e (R_c A + R_p) \right]^2} \quad (7)$$

3.1. Parameter estimation technique

Lung properties of a subject can be characterized by determination of the parameters of a respiratory system model that best fits its behavior. This information can then be used, with comparison to Reference Values, to determine underdeveloped features or existence of pathological conditions (55).

For this research the eRIC (R_c , I , R_p and C_p) and aRIC (R_c , I , R_p , C_p and C_e) model parameters were estimated using the average values of Resistances (R values) and Reactances (X values) from 5 to 25 Hz (R_5 , R_{10} , R_{15} , R_{20} , R_{25} , X_5 , X_{10} , X_{15} , X_{20} and X_{25}) for each child tested.

In Table 5 an example of respiratory system's IOS-based Resistance and Reactance values for a healthy male child (15 years old, 181.6 cm height and 84.1 kg weight) are presented. These IOS data were recorded before and after the use of a bronchodilator (Pre-B and post-B). In Table 6 an example of the Model Parameters calculated for the same child is given.

Pre-B	R5	R10	R15	R20	R25	X3	X5	X10	X15	X20	X25
	0.32	0.27	0.27	0.28	0.3	-0.11	-0.08	-0.01	0.03	0.06	0.08
Post-B	R5	R10	R15	R20	R25	X3	X5	X10	X15	X20	X25
	0.3	0.26	0.26	0.28	0.3	-0.12	-0.08	0	0.04	0.08	0.11

Table 5. Respiratory system's Resistance (kPa/l/s) and Reactance (kPa/l/s) values for a healthy male child.

pre-B	aRIC	Rc (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s ²)	Cp (l/kPa)	Ce (l/kPa)	eRIC	Rc (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s ²)	Cp (l/kPa)
		0.256	0.209	0.001	0.233	0.004		0.277	0.314	0.0007	0.282
post-B	aRIC	Rc (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s ²)	Cp (l/kPa)	Ce (l/kPa)	eRIC	Rc (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s ²)	Cp (l/kPa)
		0.245	0.239	0.001	0.241	0.004		0.274	0.58	0.0008	0.289

Table 6. Model Parameters calculated for a healthy male child.

Estimating Model Parameters is comparable to curve-fitting. Consequently a suitable error criterion E has to be selected and minimized. For this research the least square (LS) criterion was selected as follows:

$$E = \sum \left[ZR(f) - ZR_{est}(f) \right]^2 + \left[Zx(f) - Zx_{est}(f) \right]^2 \quad (8)$$

where

$$f = 5, 10, 15, 20, 25 \text{ Hz}$$

This LS criterion was used to minimize the sum of the squared errors between the measured IOS ZR and Zx and the estimated resistive ZR_{est} and the estimated reactance Zx_{est} at frequencies between 5 to 25 Hz (at 5 Hz intervals). The LS criterion was selected due to its commonplace use, its relation with other system identification algorithms and its availability in different software packages (44).

Due to the nonlinear dependence of the aRIC and eRIC impedance functions on the model parameters, the Matlab lsq-nonlin (nonlinear LS) was used in both algorithms, which are based on Newton's Method. Each estimation run began with an initial random guess, a parameter estimate vector produced by a random number generator appropriately weighted. Random initial guesses ranging consistently from 0 to 5, 0 to 0.5, and 0 to 0.05 were used to estimate the values of resistances, capacitances and inductances, respectively.

For each child's averaged IOS data a total of 50 iterations were used to find parameter estimates minimizing the error function, with the Matlab program stopping each time when E (error value) changed by less than a factor of 10^{-9} from one iteration to the next one. Therefore, the LS error value at the end provided a measure of the goodness of fit to the given test data for each model (44).

4. Research method design and statistical analysis

This study was developed as part of a NIH-funded research to perform IOS evaluation of lung function in Anglo and Hispanic children 5-19 years old living in the El Paso, Texas area. The data were collected at Western Sky Medical Research clinic and in a Health Fair held in a Socorro District school over a 3 years period (2006-2008). The IOS data collected for this research were quality-assured by our expert clinician and pulmonologist, the late Professor Michael Goldman and were then classified by him into four categories: Normal, Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI) and Asthma (A).

The data presented in this study were collected in 2008. The data collected were Pre- and Post-bronchodilation data. The data collected analyzed in this study were acquired from 47 children in 2008. Three to five IOS test replicates were performed on each subject to ensure reproducible tests without artifacts caused by air leaks, swallowing, breath holding or vocalization. IOS data were carefully reviewed off line and quality-assured to reject segments affected by airflow leak or swallowing artifacts. A Jaeger MasterScreen IOS (Viasys Healthcare, Inc. Yorba Linda, CA, and USA) was used in this study. The system was calibrated every day before data collection using a 3-L syringe for volume calibrations and a reference resistance (0.2 KPa/L/s) for pressure calibrations. Children were asked to wear a nose clip, while breathing normally through a mouthpiece and were instructed to tightly close their lips around it to avoid air leakage. Children tested using a bronchodilation medicine, called Levalbuterol (Xopenex), were tested (pre-bronchodilation), performing 3 to 5 IOS tests. Then the medicine (Xopenex) was given to the children using a nebulizer for 6 minutes and after that the children were asked to rest for 10 minutes; and finally after this waiting period the children were again tested recording 3 to 5 IOS tests (post-bronchodilation).

This research study was supported in part by NIH grant #1 S11 ES013339-01 A1: UTEP-UNM HSC ARCH Program on Border Asthma. The research protocol was approved by the Institutional Review Board of the University of Texas at El Paso. Informed consents were obtained from children over 18 years and the parents or care givers of children under 18 years. A questionnaire on asthma or allergy symptoms provided by the ARCH Program was then completed by the participants or their parents.

Statistical analyses of IOS measured and calculated parameters as well as the eRIC and aRIC model parameters between Pre- and Post-bronchodilation data were made using t-distribution (differences of the means) test and statistical significance was established at a $p < 0.05$ level.

5. Results and discussions

The IOS data collected from 47 children in 2008 and Model Parameters calculated from them, under pre-bronchodilation and post-bronchodilation conditions were analyzed. The eRIC and aRIC Model Parameters were calculated over the frequency range of 5 to 25 Hz.

The IOS and Model Parameters selected for analysis were selected from our previous publications as they produced significant results to differentiate between Healthy and Impaired as well as, between Pre- and Post- bronchodilation conditions. These parameters were chosen due to their ability to evaluate respiratory system's properties and impairments. The IOS, eRIC and aRIC Model Parameters analyzed were: R3, R5, R3-R20, R5-R20, X3, X5, AX, Fres, eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp. In addition to our previous published results, we included IOS parameters at 3 Hz (R3, X3, R3-R20) to our analysis here to evaluate their performance.

After quality assurance by our expert clinician, the collected IOS data from all 47 children were classified into four groups: 6 Healthy (or Normal), 4 PSAI, 11 definite SAI and 24 Asthmatics. Children in these four groups were either Anglo or Hispanic based upon their parent's declarations in the questionnaires.

Mean \pm standard deviation and range values (Pre- and Post-B data collected in 2008) for each IOS and Model Parameters analyzed are presented in Table 7 for Healthy children, in Table 8 for PSAI children, in Table 9 for children with SAI, and in Table 10 for those with Asthma.

IOS Measurements and Model Parameters					
Healthy Group N=6					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean \pm SD		Range	Mean \pm SD
R3 (kPa/l/s)	0.34-0.59	0.41 \pm 0.09	R3 (kPa/l/s)	0.30-0.54	0.38 \pm 0.08
R5 (kPa/l/s)	0.29-0.51	0.35 \pm 0.08	R5 (kPa/l/s)	0.25-0.48	0.33 \pm 0.08
R3-R20 (kPa/l/s)	0.05-0.12	0.09 \pm 0.02	R3-R20 (kPa/l/s)	0.03-0.13	0.08 \pm 0.04
R5-R20 (kPa/l/s)	-0.08	0.03 \pm 0.03	R5-R20 (kPa/l/s)	-0.1	0.03 \pm 0.04
X3 (kPa/l/s)	-0.12	-0.16 \pm 0.05	X3 (kPa/l/s)	-0.13	-0.15 \pm 0.05
X5 (kPa/l/s)	-0.06	-0.10 \pm 0.02	X5 (kPa/l/s)	-0.05	-0.10 \pm 0.02
AX (kPa/l)	0.18-0.36	0.26 \pm 0.06	AX (kPa/l)	0.16-0.36	0.24 \pm 0.07
Fres (1/s)	10.26-13.46	11.18 \pm 1.15	Fres (1/s)	9.6-13.74	10.99 \pm 1.76
eRIC Cp (l/kPa)	0.2073-0.2816	0.2346 \pm 0.0284	eRIC Cp (l/kPa)	0.1894-0.2892	0.2297 \pm 0.0362
Rp (kPa/l/s)	0.2163-0.8016	0.5665 \pm 0.2788	Rp (kPa/l/s)	0.2227-0.5801	0.3501 \pm 0.1630
aRIC Cp (l/kPa)	0.1851-0.2331	0.2091 \pm 0.0169	aRIC Cp (l/kPa)	0.1436-0.2411	0.2087 \pm 0.0366
Rp (kPa/l/s)	0.1891-0.7206	0.3922 \pm 0.2057	Rp (kPa/l/s)	0.1992-0.6173	0.3151 \pm 0.1710

Table 7. Healthy children IOS and Model Parameters Pre- and Post-B (N=6)

IOS Measurements and Model Parameters					
PSAI Group N=4					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean±SD		Range	Mean±SD
R3 (kPa/l/s)	0.47-0.99	0.67±0.25	R3 (kPa/l/s)	0.37-0.96	0.60±0.27
R5 (kPa/l/s)	0.39-0.84	0.57±0.21	R5 (kPa/l/s)	0.30-0.87	0.50±0.26
R3-R20 (kPa/l/s)	0.14-0.44	0.30±0.15	R3-R20 (kPa/l/s)	0.14-0.39	0.26±0.12
R5-R20 (kPa/l/s)	0.07-0.29	0.19±0.11	R5-R20 (kPa/l/s)	0.07-0.30	0.17±0.10
X3 (kPa/l/s)	-0.43	-0.28±0.11	X3 (kPa/l/s)	-0.12	-0.24±0.06
X5 (kPa/l/s)	-0.18	-0.22±0.09	X5 (kPa/l/s)	-0.11	-0.17±0.05
AX (kPa/l)	0.57-2.57	1.31±0.95	AX (kPa/l)	0.43-2.20	1.11±0.82
Fres (1/s)	15.53-17.36	16.44±0.92	Fres (1/s)	12.47-17.19	15.37±2.54
eRIC Cp (l/kPa)	0.0445-0.1616	0.0963±0.0556	eRIC Cp (l/kPa)	0.0243-0.1636	0.0978±0.0621
Rp (kPa/l/s)	0.4398-0.6730	0.5443±0.1211	Rp (kPa/l/s)	0.3539-0.6174	0.4886±0.1180
aRIC Cp (l/kPa)	0.0389-0.1616	0.0858±0.0572	aRIC Cp (l/kPa)	0.0077-0.1636	0.0861±0.0690
Rp (kPa/l/s)	0.3561-0.6730	0.5116±0.1403	Rp (kPa/l/s)	0.3539-0.8784	0.5339±0.2423

Table 8. PSAI children IOS and Model Parameters Pre- and Post-B (N=4)

IOS Measurements and Model Parameters					
SAI Group N=11					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean±SD		Range	Mean±SD
R3 (kPa/l/s)	0.55-0.91	0.73±0.12	R3 (kPa/l/s)	0.50-0.92	0.67±0.14
R5 (kPa/l/s)	0.46-0.72	0.61±0.09	R5 (kPa/l/s)	0.43-0.78	0.57±0.12
R3-R20 (kPa/l/s)	0.25-0.57	0.38±0.10	R3-R20 (kPa/l/s)	0.16-0.51	0.30±0.10
R5-R20 (kPa/l/s)	0.17-0.38	0.26±0.06	R5-R20 (kPa/l/s)	0.07-0.37	0.20±0.08
X3 (kPa/l/s)	-0.32	-0.32±0.11	X3 (kPa/l/s)	-0.27	-0.26±0.08
X5 (kPa/l/s)	-0.27	-0.25±0.09	X5 (kPa/l/s)	-0.2	-0.20±0.07
AX (kPa/l)	1.10-2.73	1.87±0.52	AX (kPa/l)	0.54-2.61	1.36±0.59
Fres (1/s)	17.37-23.15	19.47±1.95	Fres (1/s)	16.8-23.41	19.44±2.26
eRIC Cp (l/kPa)	0.0356-0.0710	0.0533±0.0105	eRIC Cp (l/kPa)	0.0358-0.1485	0.0733±0.0291
Rp (kPa/l/s)	0.3126-0.9167	0.5885±0.1990	Rp (kPa/l/s)	0.3082-0.8075	0.5023±0.1651
aRIC Cp (l/kPa)	0.0150-0.1007	0.0409±0.0230	aRIC Cp (l/kPa)	0.0185-0.1485	0.0485±0.0404
Rp (kPa/l/s)	0.3486-0.7291	0.4992±0.1100	Rp (kPa/l/s)	0.3243-0.5810	0.4359±0.0982

Table 9. SAI children IOS and Models Parameter Pre- and Post-B (N=11)

IOS Measurements and Model Parameters					
Asthma Group N=24					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean±SD		Range	Mean±SD
R3 (kPa/l/s)	0.45-1.77	0.82±0.26	R3 (kPa/l/s)	0.37-1.31	0.62±0.20
R5 (kPa/l/s)	0.39-1.28	0.68±0.19	R5 (kPa/l/s)	0.32-1.04	0.52±0.16
R3-R20 (kPa/l/s)	0.14-1.24	0.44±0.22	R3-R20 (kPa/l/s)	0.10-0.78	0.30±0.14
R5-R20 (kPa/l/s)	0.07-0.75	0.30±0.14	R5-R20 (kPa/l/s)	0.05-0.52	0.20±0.10
X3 (kPa/l/s)	-0.74	-0.34±0.15	X3 (kPa/l/s)	-0.55	-0.27±0.13
X5 (kPa/l/s)	-0.69	-0.29±0.14	X5 (kPa/l/s)	-0.47	-0.21±0.11
AX (kPa/l)	0.45-6.61	2.24±1.23	AX (kPa/l)	0.28-4.35	1.38±0.90
Fres (1/s)	14.44-24.19	19.48±2.64	Fres (1/s)	12.76-20.86	17.68±2.35
eRIC Cp (l/kPa)	0.0200-0.1782	0.0593±0.0347	eRIC Cp (l/kPa)	0.0047-0.2466	0.0848±0.0527
Rp (kPa/l/s)	0.2925-1.8113	0.6749±0.2949	Rp (kPa/l/s)	0.2318-1.2561	0.5050±0.2148
aRIC Cp (l/kPa)	0.0148-0.1522	0.0570±0.0390	aRIC Cp (l/kPa)	0.0047-0.2087	0.0776±0.0519
Rp (kPa/l/s)	0.2250-1.6536	0.5840±0.2848	Rp (kPa/l/s)	0.1604-1.1443	0.4288±0.2033

Table 10. Asthmatic children IOS and Model Parameters Pre- and Post-B (N=24)

With the tabulation of IOS and Model Parameters we achieved one of the goals of this research, to present baseline (Pre-) and Post-bronchodilation IOS parameters in Anglo and Hispanic children, classified in four groups: Healthy (table 7), Probable Small Airway Impairment (PSAI) (table 8), Small Airway Impairment (SAI) (table 9) and Asthma (table 10).

As expected, in the Healthy group (table 7), comparing Pre- and Post-bronchodilation IOS and Model Parameters mean values, there are almost no differences between Pre- and Post-bronchodilation measurements. In table 8, for the PSAI group we observe a modest difference between the mean IOS and Model Parameters during the Pre and Post-bronchodilation conditions. In contrast, in tables 9 and 10 we observe a noticeably bigger difference between the IOS and Model Parameters mean values, comparing Pre and Post-bronchodilation conditions. Also as expected, the biggest difference between Pre- and Post-bronchodilation conditions exists (table 10), in the Asthmatic children group, for all the IOS and Model Parameters mean values.

Our expert clinician confirmed that the range of values of all analyzed features: R3, R5, R3-R20, R5-R20, X3, X5, AX, Fres, eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp obtained for the SAD and Asthmatic groups were comparable to those values he has observed over many years in other asthmatic children of the same age range. Going to increasingly abnormal levels of "diagnostic classification," R3, R5, R5-R20, AX, Fres and Rp continue to increase from Normal to PSAI to SAI to Asthma, while X3, X5 and Cp decreased in this progression.

Figures 5, 6, 7, 8, 9, 10 and 11 show in a more graphical fashion the changes in the most significant IOS and Model Parameters mean values for each of the four groups.

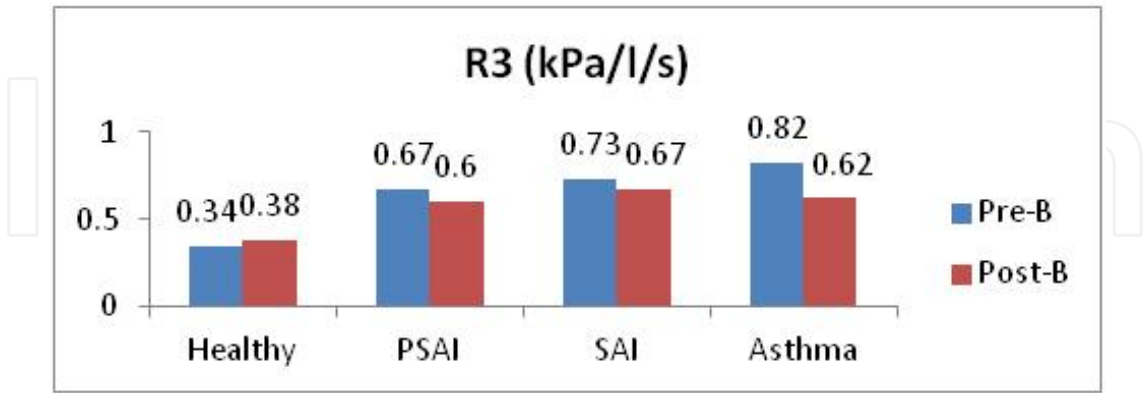


Figure 5. R3 mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

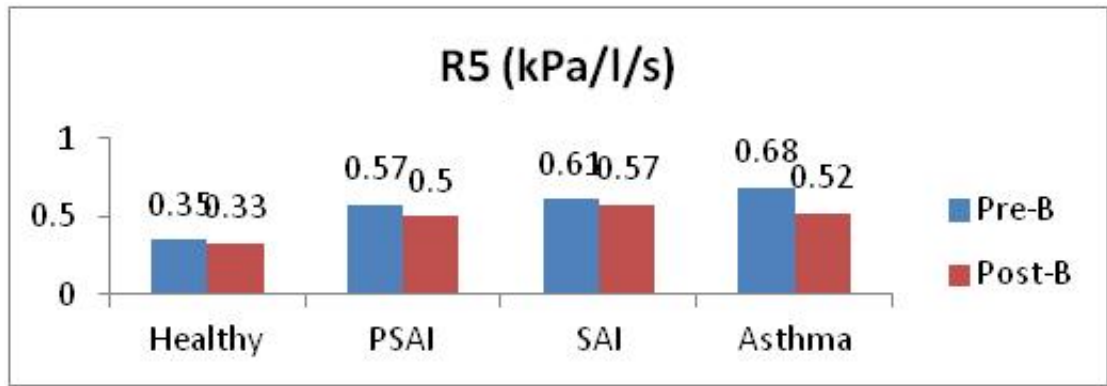


Figure 6. R5 mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

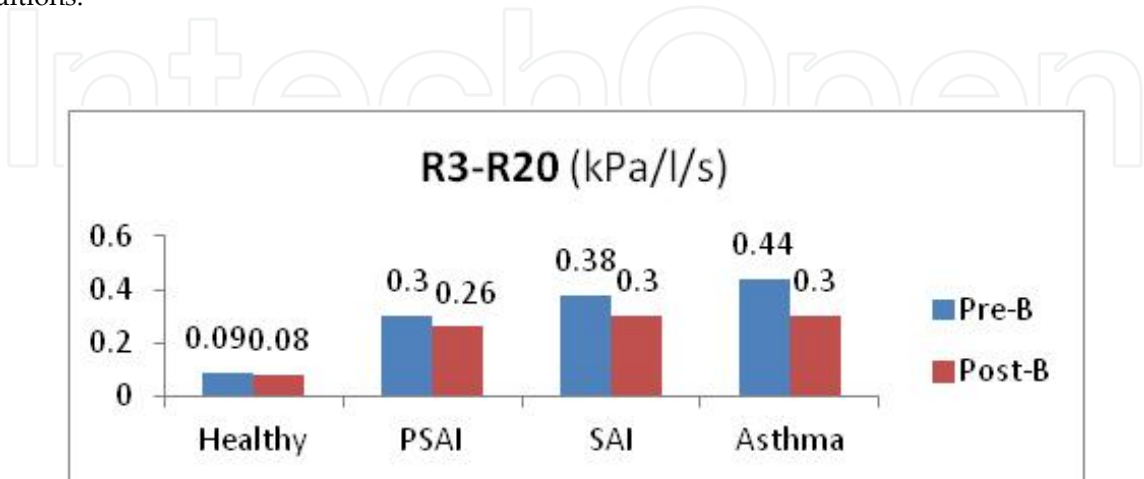


Figure 7. R3-R20 mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

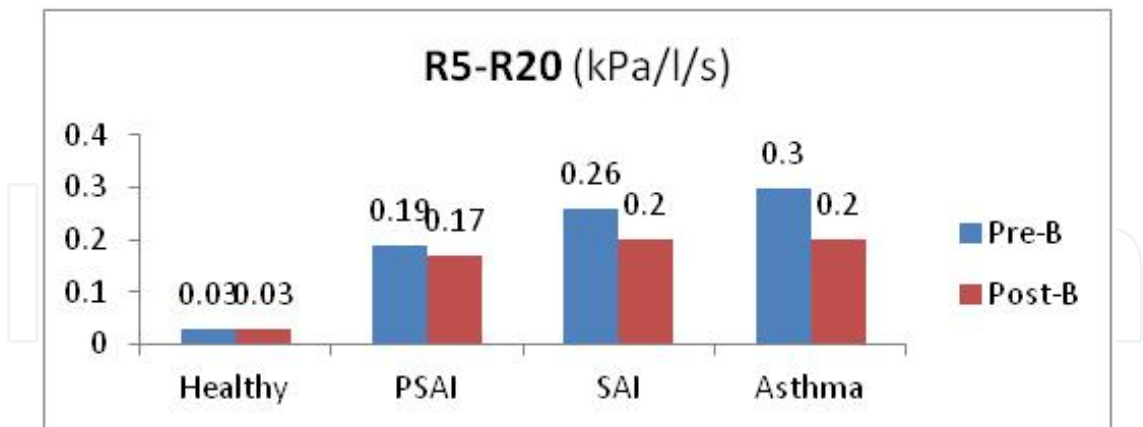


Figure 8. R5-R20 mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

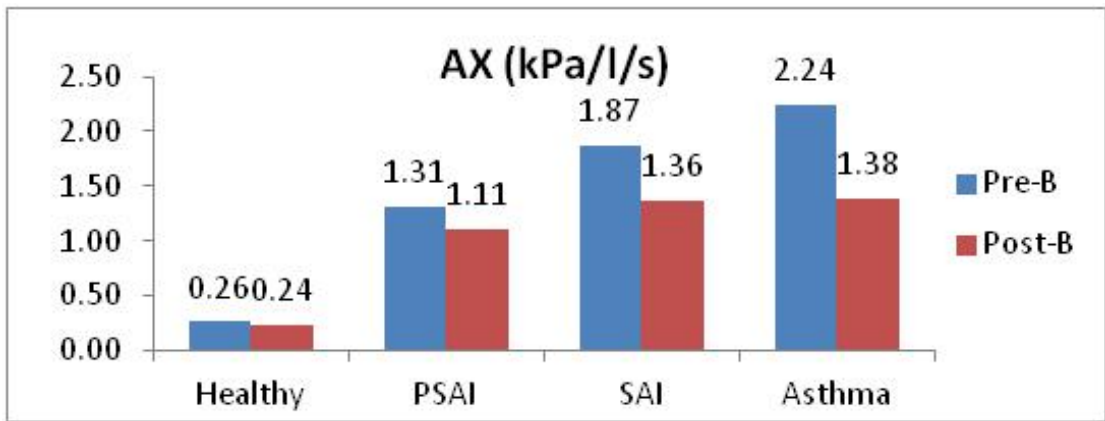


Figure 9. AX mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

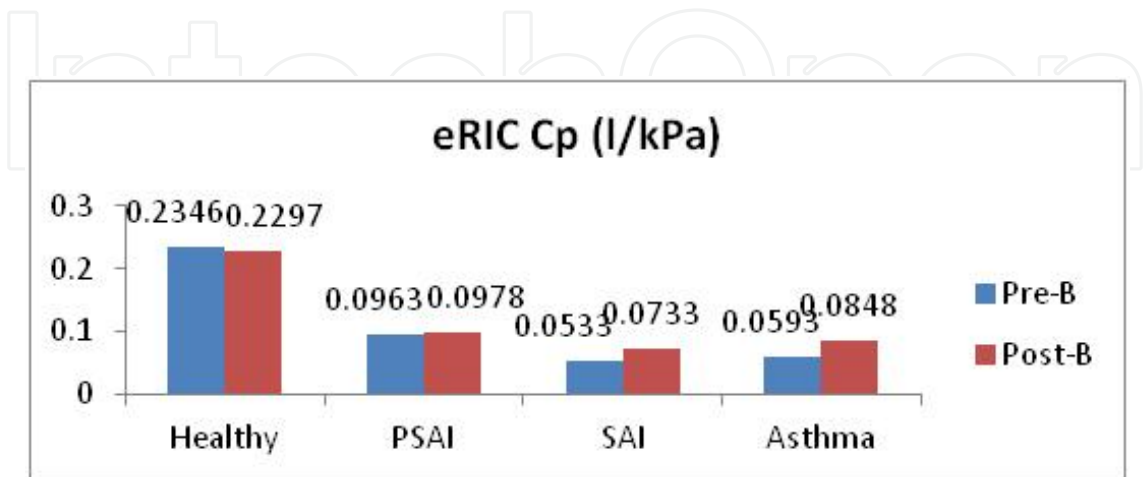


Figure 10. eRIC Cp mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

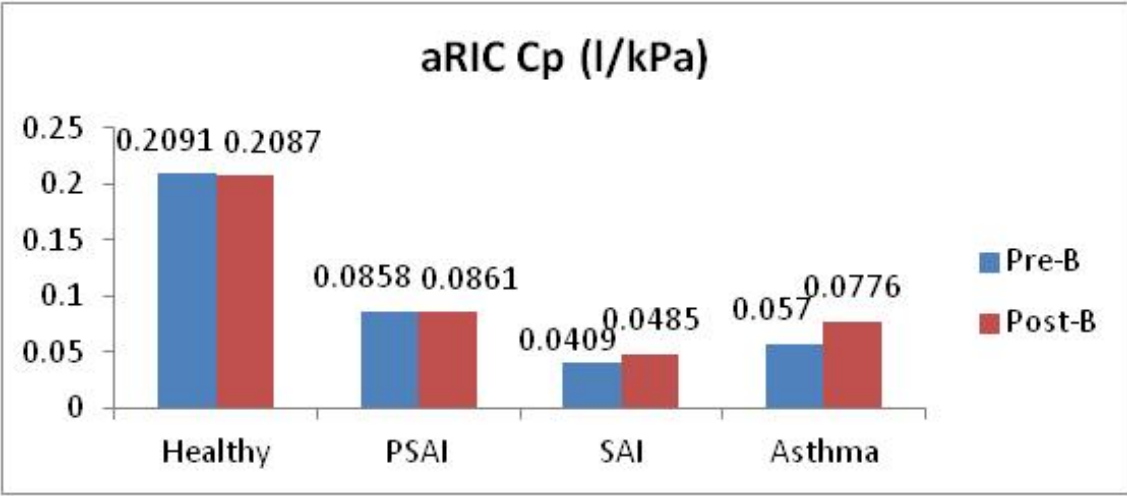


Figure 11. aRIC Cp mean values for the H, PSAI, SAI and Asthmatic children under Pre- and Post-B conditions.

Similarities between Normal and PSAI groups and between SAI and Asthmatic groups were also observed.

From tables 7,8,9, and10 and figures 7,8,9, 10 and 11 we can observe that the most significant IOS and Model Parameters for children classified as Healthy or PSAI were comparable, as these parameters showed a modest difference between these groups. However, these same parameters exhibited clear increases in R3, R5, R3-R20, R5-R20, AX, Fres, and Rp, and a clear decrease in X3, X5 and Cp going from Normal to PSAI. Going to increasingly abnormal levels of "diagnostic classification," R5, R5-R20, AX, Fres and Rp continue to increase from Healthy to PSAI to SAI to Asthmatic conditions, while X5 and Cp decrease in this progression. Differences between SAI and Asthmatic children were also modest.

In the statistical analysis performed for this research comparing Pre- and Post-B IOS and eRIC and aRIC Model Parameters in the Normal or Healthy group, no significant differences were observed (see Table 11).

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Healthy (Normal) Group	
	Pre-B vs Post-B p values
All IOS and Model Parameters	>0.05

Table 11. Healthy group p values.

Comparing Pre- and Post-B IOS and eRIC and aRIC Model Parameters for the PSAI group only R3, R35 and eRIC Rc showed significant differences (see Table 12.)

Comparing Pre- and Post-B IOS and eRIC and aRIC Model Parameters for the SAI group the following parameters showed significant differences: R3,R5,X3,X5,X10,X15,R3-R20,R5-R20,AX,aRIC Rp, eRIC Rp, eRIC I and eRIC Cp (see Table 13).

PSAI Group	
	Pre-B vs Post-B p values
R3 (kPa/l/s)	<0.05
R35 (kPa/l/s)	<0.03
eRIC Rc (kPa/l/s)	<0.04

Table 12. PSAI group p values.

SAI Group	
	Pre-B vs Post-B p value
R3 (kPa/l/s)	<0.02
R5 (kPa/l/s)	<0.05
X3 (kPa/l/s)	<0.02
X5 (kPa/l/s)	<0.005
X10 (kPa/l/s)	<0.001
X15 (kPa/l/s)	<0.005
R3-R20 (kPa/l/s)	<0.001
R5-R20 (kPa/l/s)	<0.005
AX (kPa/l/s)	<0.0002
aRIC Rp (kPa/l/s)	<0.01
eRIC Rp (kPa/l/s)	<0.02
I(kPa/l/s ²)	<0.05
Cp (l/kPa)	<0.03

Table 13. SAI group p values

Comparing Pre- and Post-B IOS, eRIC and aRIC Model Parameters for the Asthmatic group all of the parameters showed significant differences with the exception of aRIC Ce and eRIC I (see Table 14).

Significant differences between these groups in the aforementioned IOS and Model Parameters were found. Comparing Normal Pre-B to PSAI Pre-B, all of the IOS and Model Parameters showed significant differences, with the exception of aRIC Rp and eRIC Rp. Comparing Normal (Healthy) Post-B and PSAI Post-B, the majority of the parameters showed significant differences with the exception of R3, R5, eRIC Rp and aRIC Rp. Comparing PSAI Pre-B and SAI Pre-B data, only three parameters showed significant differences between these groups: Fres, eRIC Cp and aRIC Cp. For PSAI Post-B and SAI

Post-B, only Fres showed a significant difference. Finally comparing SAI Pre-B vs Asthma Pre-B, and SAI Post-B vs Asthma Post-B, no significant differences were found.

Asthmatic Group	
	Pre-B vs Post-B p value
R3 (kPa/l/s)	<1.5E-9
R5 (kPa/l/s)	<1.6E-10
R10 (kPa/l/s)	<9.7E-08
R15 (kPa/l/s)	<0.0002
R20 (kPa/l/s)	<0.0002
R25 (kPa/l/s)	<3.9E-07
R35 (kPa/l/s)	<1.7E-06
X3 (kPa/l/s)	<0.005
X5 (kPa/l/s)	<0.002
X10 (kPa/l/s)	<0.0003
X15 (kPa/l/s)	<1.4E-6
X20 (kPa/l/s)	<0.0002
X25 (kPa/l/s)	<0.01
X35 (kPa/l/s)	<0.003
R3-R20 (kPa/l/s)	<5.6E-06
R5-R20 (kPa/l/s)	<2.5E-06
AX (kPa/l/s)	<3.1E-08
Fres (1/s)	<0.0002
aRIC Rc (kPa/l/s)	<0.006
Rp (kPa/l/s)	<4.5E-07
I (kPa/l/s ²)	<0.002
Cp (l/kPa)	<0.0003
eRIC Rc (kPa/l/s)	<0.002
Rp (kPa/l/s)	<4.5E-06
Cp (l/kPa)	<0.0003

Table 14. Asthmatic group p values

These selected parameters seem to be sensitive and reliable indices of lung function for respiratory disease classification using Impulse Oscillometric data, eRIC and aRIC Model Parameters.

The correlation coefficient (r) between children Heights and these IOS and Model Parameters was also analyzed. The parameters showed a good correlation, the best correlation was observed for R5 with R = 0.764, and the lowest r value (0.542) was observed for X5. In Table 15 the values for these correlations are presented.

Correlation with Height	
Parameters	r
R3 (kPa/l/s)	0.762
R5 (kPa/l/s)	0.764
X3 (kPa/l/s)	0.557
X5 (kPa/l/s)	0.542
R3-R20 (kPa/l/s)	0.688
R5-R20 (kPa/l/s)	0.62
AX (kPa/l/s)	0.741
Fres (1/s)	0.666
eRIC Cp (l/kPa)	0.762
Rp (kPa/l/s)	0.513
aRIC Cp (l/kPa)	0.717
Rp (kPa/l/s)	0.643

Table 15. Correlation coefficients (r) between Height and IOS and respiratory system Model Parameters for 2008 data.

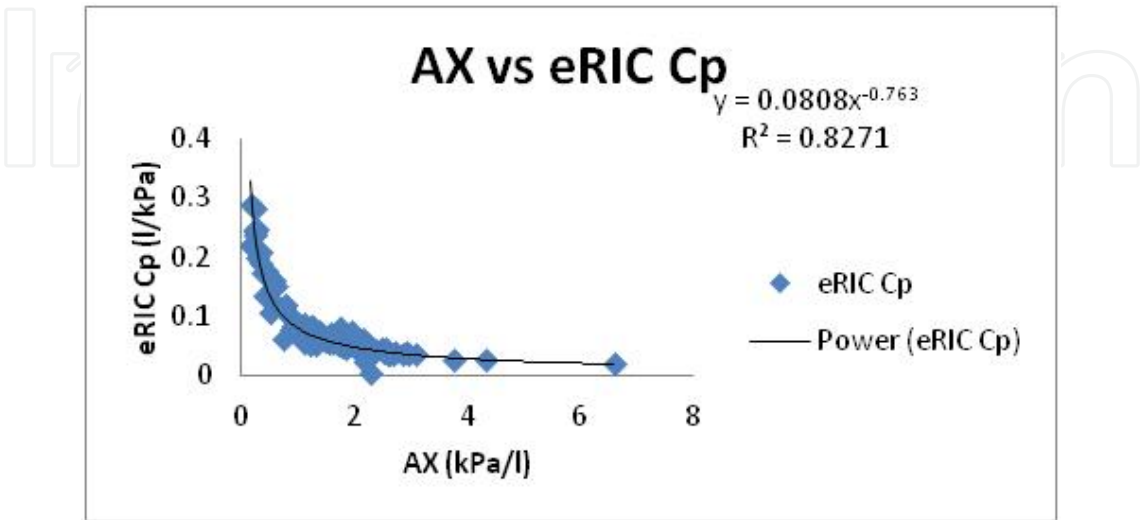


Figure 12. Correlation between AX and eRIC Cp for Pre- and Post-B data.

The statistical correlation between AX and both models' Cps, and R3-R20 and R5-R20 with both models' Rps were also evaluated. The best correlation observed was between AX and eRIC Cp with a value of $r = 0.909$. The correlation between AX and aRIC Cp had a lower r value equal to 0.760. For the correlation between R3-R20 and eRIC Rp, r was equal to 0.589. The correlation between R5-R20 and eRIC Rp was $r = 0.516$. For R3-R20 and aRIC Rp, $r = 0.787$. And finally the correlation between R5-R20 and aRIC Rp was $r = 0.731$. Figure 12 illustrates the best correlation observed. This was between AX and eRIC Cp.

6. Conclusions

While expert clinician diagnostic classification distinguished between children based on 4 levels of perceived normality or absence thereof of the visual patterns of IOS data, with the essential features characterizing the differences being associated with abnormalities group mean IOS and the aRIC model data appear to fall into two distinctly different groups: either Normal or Asthmatic, with the essential features characterizing the differences being associated with abnormalities of peripheral airways.

Our present and previous studies (52-61, 75), have demonstrated that equivalent electrical circuit Model Parameters of the human respiratory system are able to track changes in the respiratory system function after bronchodilation. Both the eRIC and aRIC models clearly distinguished between children who were Normal (Healthy) or possibly had mild SAI, who showed no significant changes with bronchodilation-BD), and those who were Asthmatic with SAI, both at baseline and at Pre- to Post-BD conditions. The eRIC model showed an apparently larger peripheral airway compliance (Cp) than the aRIC model, probably because it might include some of the "extrathoracic airway compliance" (Ce). On the other hand, the eRIC model is more parsimonious, and the parameter, Ce, that may be difficult for physicians to understand, appears to show no significant change Post-BD in the Asthmatic group.

It can be observed that children classified as Normal (Healthy) or possible SAI were relatively similar in both IOS and the aRIC model parameters. However, they showed clear increases in R3, R5, R3-R20, R5-R20, AX, Fres, and Rp, and a clear decrease in X3, X5 and Cp going from Normal to PSAI.

Going to increasingly abnormal levels of "diagnostic classification," R3, R5, R5-R20, AX, Fres and Rp continue to increase from Healthy to PSAI to SAI to Asthma, while X3, X5 and Cp decrease in this progression. Differences between SAI and Asthmatic children were modest.

The features used in this work seem to be sensitive and reliable indices for automatic respiratory disease classification using Impulse Oscillometry data. The correlation between AX and the eRIC Cp was the best correlation in both Pre-B and Post-B work.

Our expert clinician confirmed that the range of values of all analyzed features: R3, R5, R3-R20, R5-R20, X3, X5, AX, Fres, eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp obtained for the

SAD and Asthmatic groups were comparable to those values he has observed over many years in other asthmatic children of the same age range.

Comparing all the IOS parameters for Pre- and Post-B data and the eRIC and aRIC Model Parameters in the Normal group, no significant differences were observed. Also comparing Pre- and Post-B parameters for the PSAI group only R3, R5 and the eRIC Rc showed significant differences. Similarly evaluating Pre- and Post-B values for the SAI group, the following parameters showed significant differences: R3, R5, X3, X5, X10, X15, R3-R20, R5-R20, AX, the aRIC Rp, eRIC Rp, eRIC I and eRIC Cp. Finally evaluating Pre- and Post-B values for the Asthmatic group all of the parameters showed significant differences with the exception of the aRIC Ce and eRIC I.

The selected IOS and model derived parameters (R3, R5, R3-R20, R5-R20, X3, X5, AX, Fres, the eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp) showed a good correlation with children Heights.

In this research study focusing on children with and without SAI (Healthy), the eRIC Model Parameters showed to be consistent and to some extent more closely correlated with IOS measures compared to the aRIC model parameters. As eRIC is more intuitive, less complex and a more parsimonious model (75), it may be considered a more suitable diagnostic tool for clinical applications than the aRIC model.

IOS lung function data are similarly well-modeled by the eRIC (without upper airway shunt compliance) and aRIC models (with upper airway shunt compliance), which are reduced versions of the popular Mead's model developed at Harvard several decades ago, based on the close correlations of their corresponding parameters excluding Ce. The eRIC model is a more parsimonious and equally powerful model in capturing the differences between SAI and H children, therefore it is recommended as a clinically-preferred model of lung function based on IOS data.

In summary, we conclude that the IOS parameters AX and the eRIC model-derived parameter Cp are the most reliable parameters to track small airway function in children before and after bronchodilation. AX (the "Goldman Triangle"), representing the integrated low frequency respiratory reactance magnitude between 5 Hz and F_{res} , and the eRIC Cp corresponding to the peripheral (small airway) compliance demonstrated superior diagnostic discrimination compared to all other parameters analyzed and emerged as useful and reliable indices of small airway function in children.

Further work in a larger number of H and SAI children is required to establish normal values for these sensitive indices and enable researchers in this field to perform more effective and timely evaluation, detection, diagnosis, and treatment of different respiratory diseases. Also future work should be performed in order to collect data from a larger sample of children and perform a statistical analysis in order to evaluate IOS parameters and both models (eRIC and aRIC) performances to evaluate these changes in lung function. A definitive choice between the eRIC and aRIC models will require further assessments in a larger sample of children.

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