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# Impulse Oscillometric Features And Parsimonious Respiratory Models Track Small Airway Function In Hispanic And Anglo Children

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IMPULSE OSCILLOMETRIC FEATURES AND PARSIMONIOUS  
RESPIRATORY MODELS TRACK SMALL AIRWAY FUNCTION IN  
HISPANIC AND ANGLO CHILDREN

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Dean of the Graduate School

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Erika Guadalupe Meraz Tena

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To my beloved husband  
and sons Paul and Jose



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RESPIRATORY MODELS TRACK SMALL AIRWAY FUNCTION IN  
HISPANIC AND ANGLO CHILDREN

by

ERIKA GUADALUPE MERAZ TENA, MSc

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This work is also dedicated to the Memory of Dr. Michael Goldman; he made substantial contributions to the clinical application of the Forced Oscillation Technique over several decades. He was our role model. He inspired, guided, and educated us all by selflessly devoting his valuable time, spending his tremendous energy and sharing his vast expert knowledge in Pulmonary Physiology, FOT, and IOS testing and related areas. Tragically we lost him in March 2010. We will be eternally thankful for his teachings, collaboration and friendship. He will always be remembered, missed and present in our work and our hearts.

## Abstract

Asthma is an inflammatory condition of the peripheral (small) airways resulting in airway hyper-reactivity and, among other symptoms, airflow obstruction. It is the most prevalent chronic respiratory disease in children. Reliable and patient-friendly instruments and methods are required to help pulmonologists accurately detect asthma and Small Airway Impairment (SAI) with acceptable clinical accuracy, specificity and sensitivity. Impulse Oscillometry System (IOS) based on the Forced Oscillation Technique (FOT) has been successfully used to measure lung function in children with a high degree of sensitivity and specificity to SAI and Asthma. IOS is a patient-friendly lung function to measure the *mechanical impedance* of the respiratory system. Equivalent electrical circuit models of lung function have been developed that can be used to quantify severity of SAI. It has been shown that impulse oscillometric parameters as well as parameter estimates of these equivalent electrical circuit models provide useful indicators of lung function and therefore have the potential to be used as sensitive features for computer-aided classification of pulmonary function in health and disease. Previous work by our group has evaluated several known respiratory models and two parsimonious versions known as *extended RIC (eRIC)* and *augmented RIC (aRIC) models* have emerged which offer advantages over earlier models.

This doctoral research aims to analyze IOS data acquired from Anglo and Hispanic children during pre- and post-bronchodilation conditions, as well as use the eRIC and aRIC model estimated parameters to determine which ones are better to differentiate between constricted and non-constricted lung conditions. It is also the first attempt to establish reference values for North American Anglo and Hispanic children 5 to 19 years old, and find correlations between IOS and eRIC and aRIC model parameters. The overall objective is to develop a user-friendly tool to assist clinicians in the analysis and interpretation of IOS data to better detect, diagnose, and treat asthma conditions. In the near future, this approach offers the potential to be used for computer-aided classification of pulmonary diseases.

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# **Chapter 1: Introduction**

## **1.1 BACKGROUND AND SIGNIFICANCE OF THE PROJECT**

Asthma is an inflammatory condition of the airways resulting in airway function becoming hyper-reactive, and 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 the American Academy of Allergy and Asthma & Immunology, Asthma and allergies strike 1 out of 4 Americans and approximately 20 million Americans have asthma. Nine million U.S. children under 18 have been diagnosed with asthma. Every day in America 40,000 people miss school or work, 30,000 have an asthma attack, 5,000 visit the emergency room, and 1,000 are admitted to the hospital and, although asthma is rarely fatal, 11 persons die every day due to asthma. Direct health care costs for asthma in the U.S. total more than \$10 billion annually; and indirect costs (lost productivity) are \$8 billion giving a total of \$18 billion (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 for 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 lung mechanical parameters. The

Impulse Oscillometry System (IOS) measures respiratory impedance 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 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) (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (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 later in this dissertation, confirms that lung function in children and adolescents is sensitively and accurately assessed by IOS, before and after bronchodilation. However, it seems that there are different parameters that can offer significant information in assessment of asthma. For this reason, in this study it is proposed to evaluate IOS data acquired from Anglo and Hispanic children, pre- and post-bronchodilation, evaluating statistical significance between different IOS parameters.

The European Respiratory Society in 1995 published a workshop report (33) about “Reference Values for Residual Volume (RV), Functional Residual Capacity (FRC) and Total Lung Capacity” 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 Forced Oscillation Technique (FOT).

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 (34).

A few studies have been developed to obtain Reference values of healthy children using Forced Oscillation Technique (FOT) and IOS (35) (36) (37) (38) (39) (40) (41) (42). Those studies are also described in detail in another section of this research.

It is of vital importance to have IOS reference values for children, as this technique has been shown to be very useful in the detection of lung abnormalities. Therefore, this study is intended to make an effort towards establishing normal reference IOS values for North American Anglo and Hispanic children 5 to 19 years old. Also it aims 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 yields frequency-dependent curves of respiratory impedance that are visually analyzed to recognize changes in shape and magnitude of the curves and distinguish healthy respiratory function from disease. 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 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) (44) (45) (46) (47) (48) (49) (50) (51), than previous models.

The present study is proposed to determine eRIC and aRIC model parameter estimates of lung function in Normal (N) or Healthy (H), PSAI, SAI and Asthmatic (A) Anglo and Hispanic children, to evaluate the performance of these models in quantifying lung function in this population and to analyze the correlation of these models parameters with IOS measured and calculated parameters.

## **1.2 HYPOTHESIS AND GOALS OF THE PROJECT**

The hypotheses to be tested in this project are:

- Baseline IOS values of Resistance, Reactance, Fres or AX and IOS calculated values as frequency-dependence of Resistance (fdR) and AX, predict changes after bronchodilation in normal, PSAI, SAI, and Asthmatic children.
- eRIC and aRIC models of lung function based on IOS measurements yield estimates of lung resistance and compliance that can quantify respiratory mechanics to discriminate between N or H, PSAI, SAI and A children.
- The expected growth-related improvement in IOS and eRIC/aRIC parameter estimates will be greater in N/PSAI children than in SAI/A children.

Goals of the project are:

- ❖ Create a database of normal, PSAI, SAI, and Asthma IOS impedance and calculated values (judged by pulmonologist) and eRIC and aRIC model values for baseline and post-bronchodilation conditions.
- ❖ Determine statistical significance of differences between pre- and post-bronchodilation IOS data for all IOS parameters as well as eRIC and aRIC model parameters for Normal, PSAI, SAI and children with Asthma.
- ❖ Evaluate the performance of the IOS and eRIC/aRIC model parameters in evaluating lung changes over time (two years periods).
- ❖ Evaluate statistical correlation between different IOS and model parameters.

- ❖ Compare the performance of models derived parameters calculated with IOS data from 5 to 35 Hz and 3 to 25Hz.

### **1.3 PROPOSED WORK**

For this research, the following work to be performed is proposed:

- ✓ A database of Normal, PSAI, SAI, and Asthma IOS impedance and calculated values (judged by a pulmonologist) and eRIC and aRIC model values for baseline and post-bronchodilation conditions will be created for 112 children tested in pre-bronchodilation conditions and for 47 children tested with pre- and post-bronchodilation conditions.
- ✓ Statistical significance of differences between pre- and post-bronchodilation IOS data for all IOS parameters: Resistances and Reactances from 3 to 25 Hz, Fres, fdR (R3-R20, R5-R20), AX and eRIC and aRIC model parameters for Normal, PSAI, SAI and Asthmatic children will be determined.
- ✓ The performance of the IOS and parsimonious model parameters in evaluating lung changes over time (two years period) will be evaluated in 26 children tested in both years (2006 and 2008).
- ✓ Statistical correlation between different IOS and model parameters will be evaluated.
- ✓ A Comparison of the performance of model-derived parameters calculated with IOS data from 5 to 35 Hz and 3 to 25Hz will be performed.

## Chapter 2: Human Respiratory System Anatomy and Physiology

### 2.1 INTRODUCTION

In order to develop this research, an extensive knowledge of the Anatomy (structure), Physiology (function) and Pathophysiology (functional changes resulting from diseases or injury) of the Human Respiratory System is required. In this chapter, a review of these aspects is presented.

### 2.2 THE AIRWAYS AND ALVEOLI

The airways are the place where the atmospheric air and the gas-exchange membrane of the lungs are connected. The airways only provide a pathway to the inspired (inhaled) air to reach the gas exchange surface; they do not participate in gas exchange. Airways are divided into: Upper airways and lower airways. The inspired air is warmed, humidified and filtered by the upper airways in its transit to the gas exchange surface (52).

#### 2.2.1 The Upper Airways

The upper airways are composed of nose, oral cavity, pharynx and larynx, see Figure 2.1.

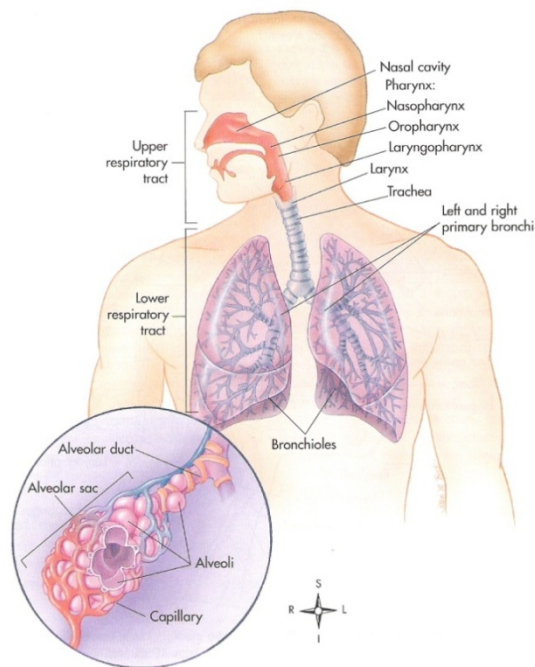


Figure 2.1 Respiratory System Structure (52).

The main functions of the nose are humidification, heating and filtering of the inspired air. The nose has a mucus-secreting epithelium called respiratory mucosa. Nasal secretions are the first defense against inspired agents; it contains immunoglobulins (antibodies) and inflammatory cells.

The pharynx is behind the nose and extends down to the larynx. The pharynx is subdivided into: nasopharynx, oropharynx, laryngopharynx (see Figure 2.1). A special type of tissue called lymphatic tissue in the nasopharynx and oropharynx provide an immunological defense. The oropharynx and laryngopharynx give way to food and air, and the laryngopharynx separates the digestive and respiratory tracts.

The larynx acts as a valve at the beginning of the trachea; it contains the vocal cords that control the size of the opening into the trachea (glottis). The larynx main functions are: speech and prevent the lower airway from aspirating solids and liquids during swallowing and breathing (52).

### **2.2.2 The Lower Airways**

Each lower airway subdivides in two different smaller airways. Each bifurcation creates a new generation of airways. The branches of the trachea and bronchi simulate an inverted tree called “tracheobronchial tree”, see Figure 2.2.

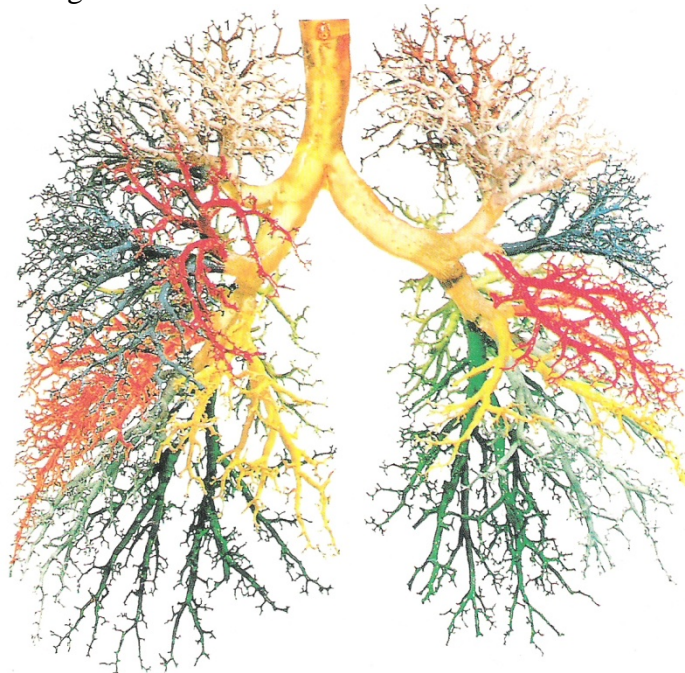


Figure 2.2 The Tracheobronchial Tree (52).



In an adult, the trachea measures around 11 cm, and then it divides into the right and left main stem bronchi, one for each lung. The left bronchus is smaller in diameter than the right one but two times bigger. Beginning in the trachea, each airway is divided (dichotomus branchi) until 23 to 27 subdivisions are formed (Figure 3). The divisions going from the trachea to division 16 are called conducting zone, and it is composed of trachea, bronchus (BR), bronchiole (BL), and terminal bronchiole (TBL). The zone going from division 17 to the terminal end (23 to 27 subdivisions) is called the transitional and respiratory zones, formed by respiratory bronchiole (RBL), alveolar duct (AD) and alveolar space (AS).

The alveoli (gas exchange zone) first appear in the respiratory bronchioles (divisions 17 to 19); it is the place where the gas exchange zone begins; this is illustrated in Figure 2.3.

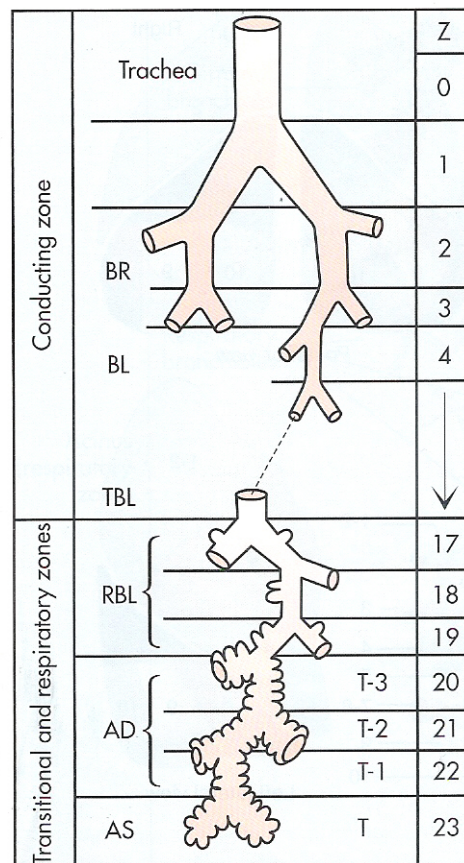


Figure 2.3 Branching of the airways (52).

From the third generation of airway divisions, the bronchi enter the parenchyma (essential supportive tissue composing the lung). The conducting airways give rise to around one million terminal

tubes at the level where the alveoli first appear. The adult lungs are composed of 300 million alveoli, representing a gas exchange area between 50 to 100 m<sup>2</sup>.

Bronchioles are less than 1mm in diameter surrounded by bronchial and bronchiolar smooth muscle. At the level of the 19<sup>th</sup> subdivision, the terminal bronchioles form the respiratory bronchioles, the place of gas exchange zone. The respiratory bronchioles are tubes containing in their walls small sacs called alveoli. Alveolar ducts subdivide into terminal units called alveolar sacs and alveoli. Alveoli (gas exchange membranes) separate air from pulmonary capillary blood. Each terminal bronchiole gives rise to an acinus (functional respiratory unit of the lung) as shown in Figure 2.4. Adjacent alveoli are connected by air channels called pores of Kohn (52).

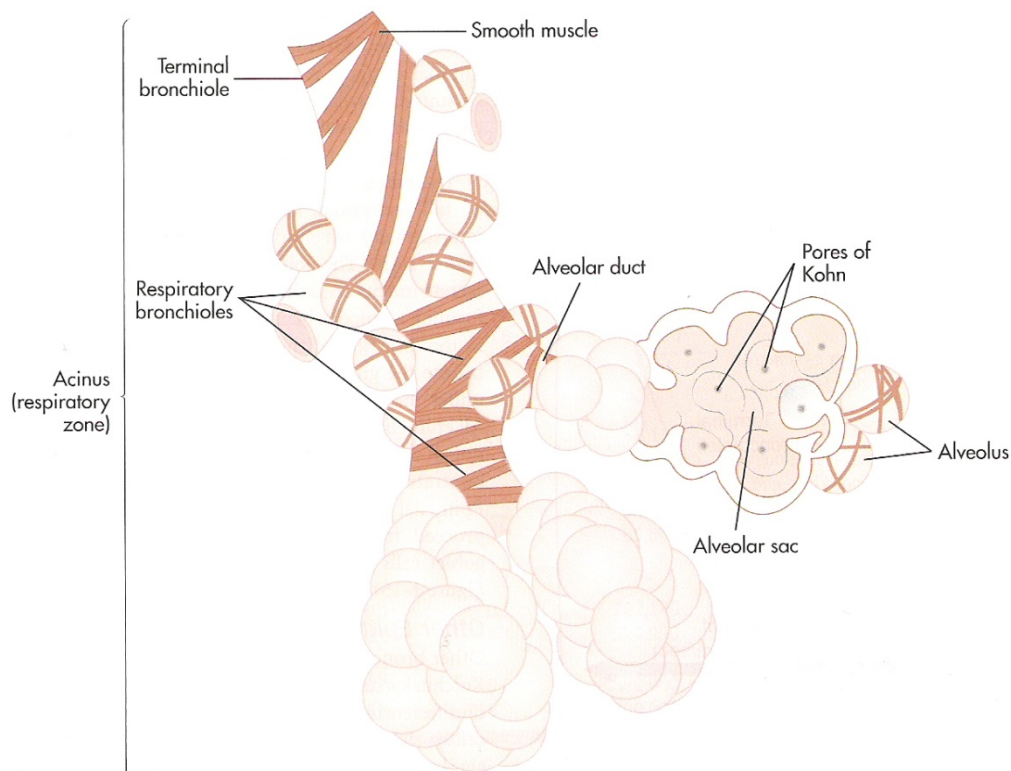


Figure 2.4 The acinus formed by terminal bronchiole subdivisions (52).

### 2.2.3 The Airways Resistance

The subdivisions of the airways generate a huge increase in the total airway cross sectional area, and the airflow velocity is abruptly reduced as inspired air reaches the alveoli. Airway less than 2 mm

represents only about 10% of the total resistance to airflow because of their huge cross sectional area. Consequently, upper airway resistance is usually much greater than lower airway resistance (52).

Small (lower or peripheral) airways refer to about 7 to 19<sup>th</sup> generation airways with an inner diameter of about 2 to 0.5 mm (53).

#### 2.2.4 The Microscopic Anatomy of Conducting Airways

A mucus secreting epithelium (tissue that line a cavity) called mucosa, lines the conducting airways. About 100 ml of mucus is secreted per day in healthy people; this volume is considerable increased in airway inflammation. Inflammation causes the mucosa to swell and smooth airway muscle to contract; this reaction is called **bronchospasm** (52).

### 2.3 THE LUNGS

The inflated lungs are conical, having a rounded apex upper part and a lower concave base (see Figure 2.5).

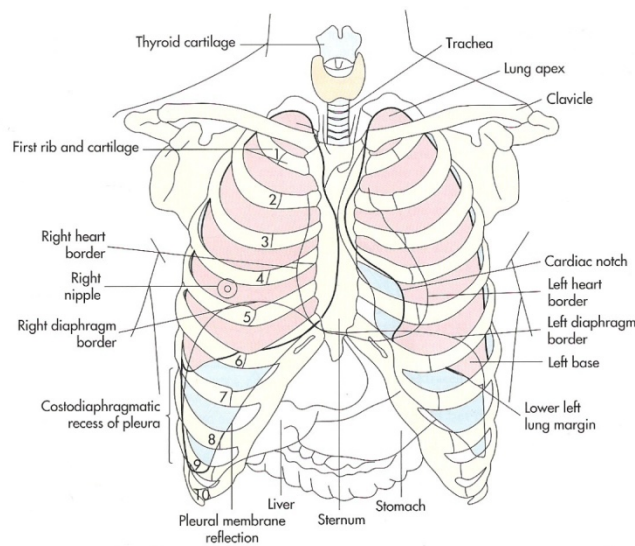


Figure 2.5 The Lungs (52).

The lung bases are placed over the major muscle of ventilation, the diaphragm; it divides the thoracic and abdominal cavities. The mediastinum is the central area of the chest cavity and it contains the heart, aorta, esophagus, great veins, trachea and mainstem bronchi. The mediastinal surface area is called hilum and it is the place where arteries, veins, and the main bronchus enter, this area can be

visualized as the root of the lungs. The pleural membranes, visceral and parietal, are membranes that form sealed envelopes surrounding each lung. The visceral pleura is attached to the surface of the lungs, and then it doubles back at the hilar area and forms the parietal pleura, which is attached to the inner chest wall surface (52).

### **2.3.1 Blood Supply to the Lungs**

The lungs have two main blood supplies: the pulmonary and the systemic circulation. The pulmonary circulation initiates in the right ventricle of the heart as the pulmonary artery, it carries deoxygenated blood to the lungs to be oxygenated. Pulmonary arterioles have many subdivisions that form the capillary beds that surround the alveoli forming a fine net. Beyond the alveoli, capillaries congregate to form venules and pulmonary veins, which carry oxygenated blood to the left atrium of the heart. Consequently, the entire cardiac output goes to the pulmonary circulation. The main function of the pulmonary circulation is to bring blood in contact with alveolar gas and make possible the oxygen and carbon dioxide exchange (52).

### **2.3.2 Nervous Control of the Lungs**

The skeletal muscles of the diaphragm and chest wall are innervated by the somatic nervous system (part of the peripheral nervous system associated with the voluntary control of body movements via skeletal muscles, and with sensory reception of external stimuli); meanwhile the airways are innervated by the autonomic nervous system (part of the peripheral nervous system that acts as a control system functioning largely below the level of consciousness, and controls visceral functions).

The lung is innervated completely by autonomic sensory and motor nerves (no voluntary control over airway smooth muscle exists). The autonomic nervous system is formed by sympathetic and parasympathetic divisions; these two differ in the place where its neurons are originated and in their function. The sympathetic division is involved in the stimulation of activities that prepare the body for action (e.g. increasing heart rate, activation of the release of sugar from the liver into the blood, etc.) called fight-or-flight response. The parasympathetic nervous system activates relaxation functions (e.g.

secretion of saliva or digestive enzymes into the stomach). For both divisions a neuron leaves the brainstem or spinal cord and forms a junction, called synapse, with cells of the innervated organ (effector organ). The union (synapse) between two neurons outside the spinal cord is called *ganglion*. The synapses between a neuron and an effector organ cell is called *neuromuscular junction*. The nerve impulses are transmitted across synapses by chemical substances called *neurotransmitters*; they are released in response to electrical impulses. The neurotransmitters travel across the synapse and stimulate the next neuron or effector organ. The two main neurotransmitters of the autonomic system are *acetylcholine* and *norepinephrine*. The fibers between the spinal cord and ganglia are *preganglionic fibers*; and those between the ganglia and the organ cell are *postganglionic fibers*. Sympathetic preganglionic fibers originate in the thoracic and lumbar regions of the spinal cord, parasympathetic fibers originate in the brain stem and sacral spinal cord (52).

### **2.3.2.1 Efferent (Motor) Responses: Sympathetic and Parasympathetic**

Efferent nerves (motor or effector neurons) carry nerve impulses away from the central nervous system to effectors such as muscles or glands. The opposite direction of flow is called afferent.

Sympathetic postganglionic fibers secrete norepinephrine; these neurons are called *adrenergic fibers*. Sympathetic stimulation causes relaxation in the smooth airway muscle, causing an increase in its diameter (*bronchodilation*) and decreasing airflow resistance. Drugs that stimulate the sympathetic system are called *adrenergic bronchodilators* and are used to reverse bronchoconstriction in asthma.

Parasympathetic postganglionic fibers innervate the smooth airway muscle of the lungs, mucous glands and the pulmonary blood vessels. They use *acetylcholine* as a neurotransmitter, and they are called *cholinergic fibers*. The major neural bronchoconstrictor mechanism and the major determinant of airway diameter are the parasympathetic impulses. The cholinergic impulses normally maintain a continuous smooth muscle contraction (baseline smooth muscle tone). Too much cholinergic stimulation can cause bronchospasm or airway muscle contraction. Drugs used to treat these conditions are called *anticholinergic bronchodilators*.

Parasympathetic stimulation increases the production of mucous and increments the viscosity of airway secretions. In contrast, sympathetic stimulation produces thin watery secretions only.

The large airways are mainly innervated by cholinergic fibers; these innervations diminish as airways become smaller. Sympathetic fibers are more uniformly distributed and adrenergic bronchodilators are equally effective in large and small airways. This is the reason why anticholinergic bronchodilator drugs are less useful than adrenergic bronchodilator drugs when bronchoconstriction involves small airways, such as in the case in Asthma (52).

### 2.3.2.2 Adrenergic and Cholinergic Receptors

A neurotransmitter has to bind very specific receptors on the cell membrane of a postganglionic fiber or an effector organ cell to stimulate it. Receptors are protein molecules placed on the surface of the cell and they can penetrate completely through the cell membrane; they can change their shapes when they bind with neurotransmitters, which cause excitatory or inhibitory reactions in the cell by changing its membrane permeability to specific ions or by inactivating or activating an intracellular enzyme.

Sympathetic and parasympathetic preganglionic fibers secrete *acetylcholine* (ACH) at ganglionic synapses (junctions) where they come in contact with postganglionic fibers (see figure 2.6). In these synapses the receptors of both divisions are cholinergic, they secrete both acetylcholine, and these receptors are called *nicotinic receptors*. When ACH binds with these nicotinic receptors postganglionic fibers spread the nerve impulse to the neuromuscular junction or effector organ. Once the impulse reaches the neuromuscular junction the sympathetic (adrenergic) fibers secrete *norepinephrine* (NE) and parasympathetic (cholinergic) fibers secrete acetylcholine again. Cholinergic receptors at the neuromuscular junction are called *muscarinic receptors*, they are different from those receptors on the ganglionic junctions; *when ACH binds them they produce bronchoconstriction and increased airway resistance*. On the contrary *when NE binds with adrenergic receptors on effector organ cells they produce bronchodilation and decreased airway resistance*. In summary, there are two types of cholinergic receptors: nicotinic and muscarinic. Similarly there are two major types of adrenergic



receptors: alpha ( $\alpha$ ) and beta ( $\beta$ ). Beta receptors subdivide into beta-1 ( $\beta_1$ ) and beta-2 ( $\beta_2$ ) receptors. Drugs that stimulate these receptors are called *agonists*, while substances that block or inhibit their responses are *antagonist*. Alpha and Beta agonists produce an opposite action, for example,  $\beta_2$  agonists cause vasodilation, while  $\alpha$  agonist cause vasoconstriction.

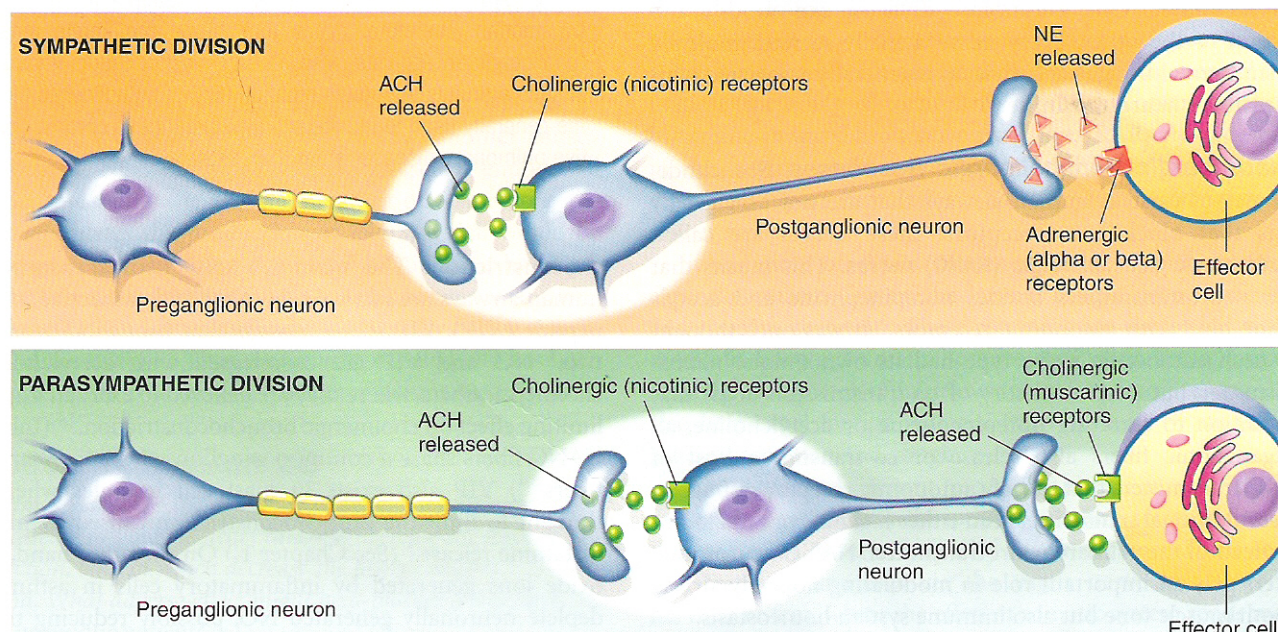


Figure 2.6. Autonomic Nervous System Neurotransmitters and Receptors (52).

Therefore cholinergic and  $\beta_2$  agonists drugs can cause bronchodilation.  *$\beta_2$  agonists and cholinergic antagonists are the two major drug types used to reverse bronchospasm in diseases such as asthma and chronic obstructive pulmonary disease (COPD).* In this research a  $\beta_2$ -agonist adrenergic drug called Xopenex (levalbutero HCl) was used to cause and measure bronchodilation (52).

## 2.4 THORACIC ANATOMY

The thorax is a cavity formed by the rib cage and its muscles, called intercostals muscles, the vertebrae, sternum, and diaphragm. It can be subdivided into three smaller cavities: the left and right pleural cavities and the mediastinum (52), see Figure 2.7.

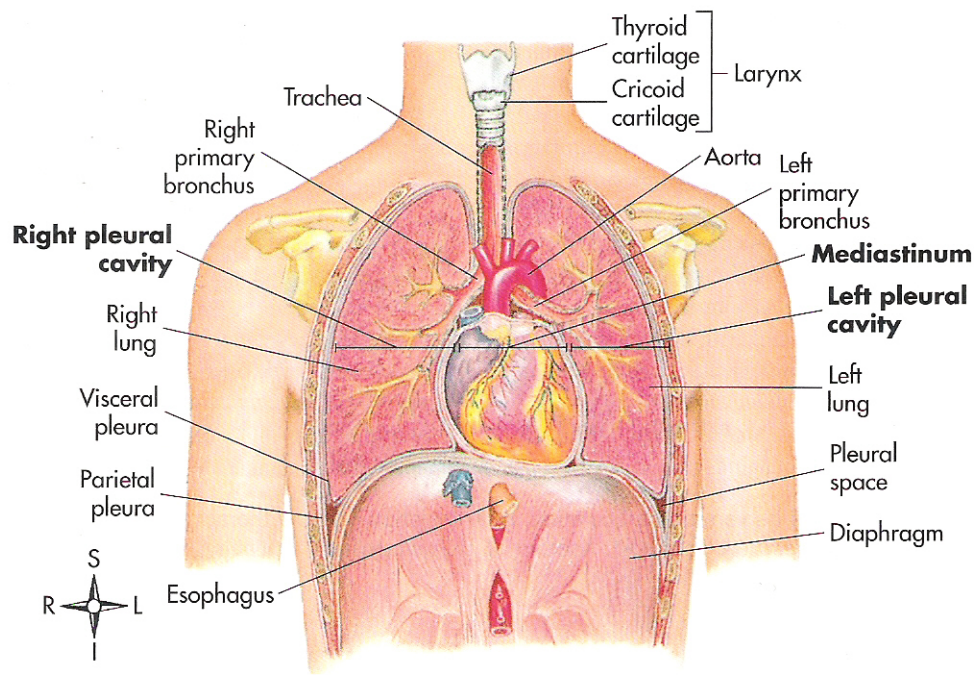


Figure 2.7 The Thoracic Cavity (52).

### 2.4.1 The Muscles of Ventilation

The muscles of ventilation are divided in two classifications: primary and accessory muscles. The major primary muscle is the diaphragm, and it is active in quiet breathing. Also the parasternal intercostals and scalene muscles are involved in quiet breathing but to a much smaller extent. Accessory muscles, only used when the ventilatory demand increases, comprise sternomastoids, pectoralis major, and abdominals.

Thoracic ribs and diaphragm work together to create three-dimensional changes in the thoracic volume. The diaphragm contracts and flattens to cause inspiration during normal quiet breathing; then it relaxes and returns to its resting shape during expiration due to elastic lung recoil.

Forceful exhalation below the resting level requires the contraction of abdominal muscles (52).

## 2.5 MECHANICS OF BREATHING

Respiration, the process of gas exchange in the body, takes places in three steps (54):

1. **Pulmonary Ventilation (breathing):** involves the mechanical flow of air into (inhalation) and out of (exhalation) the lungs.



2. **External Respiration:** exchange of gases between the respiratory zones of the lungs and the blood in pulmonary capillaries. Pulmonary capillaries blood loses carbon dioxide and obtains oxygen.
3. **Internal Respiration:** exchange of gases between the blood and tissue cells. The blood loses oxygen and obtains carbon dioxide. This process is also called cellular respiration.

### 2.5.1 Pressure Changes in Pulmonary Ventilation

Air flows from a region of a higher pressure to a region of a lower pressure; these pressure changes inside the lungs allow the process of breathing.

Pressure changes in pulmonary ventilation occur in two phases (54):

#### 1) **Inhalation:**

Inhalation (inspiration) is also called breathing in. Just before each inhalation the air pressure inside the lungs is equal to the pressure of the atmosphere (760 mmHg = 1 atmosphere at sea level). When the pressure inside the alveoli becomes lower than the atmospheric, air flows into the lungs. Air continues to flow into the lungs as long as a pressure difference exists (pressure gradient).

These pressure changes are accomplished by increasing the volume of the lungs. According to Boyle's law the volume of gas varies inversely with its pressure, this means that the pressure of gas in a closed container is inversely proportional to the volume of the container.

#### 2) **Exhalation:**

The process of breathing out is called exhalation (expiration). It is also possible due to a pressure gradient, but in opposite direction than inhalation, the pressure of the lungs becomes greater than the atmospheric pressure. Exhalation is a passive process because no muscular contraction is involved; exhalation is possible because of *elastic recoil* of the chest wall and lungs. Two forces contribute to elastic recoil: (1) the recoil of the elastic muscle fibers that were stretched during inhalation, and (2) the surface tension due to the of alveolar fluid.

### 2.5.2 Other Factors Affecting Pulmonary Ventilation

Three factors have an effect on the rate of airflow and the ease of pulmonary ventilation (54) :

#### a) Surface Tension:

A thin layer of alveolar fluid coats the alveoli's luminal surface and applies a force known as surface tension. Surface tension occurs in all air-water interfaces because water molecules are more attracted to each other than they are attracted to air (gas) molecules. Surface tension causes the alveoli to assume the smallest possible diameter. During respiration surface tension needs to be overcome enlarging the lungs during each inhalation.

#### b) Airway Resistance:

Friction encountered in the airways and alveoli is the major source of resistance to gas flow. Airflow (F, in L/sec) equals the pressure difference ( $\Delta P$ , in cmH<sub>2</sub>O) between the alveoli and the atmosphere divided by the resistance (R, cmH<sub>2</sub>O/L/s):

$$F = \Delta P/R \quad [1]$$

Airway resistance is inversely proportional to lung volume. Larger-diameter airways have decreased resistance. Airway resistance increases during exhalation as the bronchioles diameter decreases. The degree of contraction or relaxation of airways smooth muscles regulates air way diameter as well as resistance. Any condition that narrows or obstructs the airways increases its resistance.

#### c) Compliance of the Lungs:

Compliance refers to the amount of effort required to stretch the lungs and chest wall and its tendency to go back to its resting position once the stretching force is eliminated. High compliance means easy expansion of lungs and chest walls, and low compliance means that they offer resistance to expansion. Compliance is also known as elastic recoil of the lungs. For the purpose of this research the compliance measured with the Impulse Oscillometry System (IOS) is related to the volume increment caused by the IOS. An increment in volume is caused by the pressure impulses applied to the subjects mouth by the IOS. This volume is 16 ml/impulse. *After accounting for resistive pressure loss, the volume increment*

*divided by the mouth pressure pulse is compliance to be estimated by the IOS data and model analysis (55).*

## 2.6 LUNG VOLUMES AND CAPACITIES

Lung volumes and capacities refer to the volume of air associated with different phases of the respiratory cycle. Lung volumes are directly measured and lung capacities are calculated from lung volumes. The average total lung capacity of an adult is about 6 liters (6000 ml) of air, even though only a small amount of this capacity is used during normal breathing.

The Lung volumes are defined as follows (54):

- 1) **Tidal Volume (TV):** It is the volume of one breath and it is approximately 500 ml in an adult.
- 2) **Inspiratory Reserve Volume (IRV):** It represents the additional inhaled air that can be inspired after tidal volume, it is about 3100 ml.
- 3) **Expiratory Reserve Volume (ERV):** It is the additional exhaled air after a tidal volume, it is about 1200 ml.
- 4) **Residual Volume (RV):** It involves the remaining air after the exhalation of the expiratory reserve volume; this helps to maintain the alveoli always slightly inflated and it amounts to about 1200 ml.

There are four lung capacities, which are combinations of specific lung volumes [50]:

- 1) **Inspiratory Capacity (IC):** It represents the sum of tidal volume and inspiratory reserve volume.

$$IC = TV + IRV \quad [2]$$

$$IC = 500 \text{ ml} + 3100 \text{ ml} = 3600 \text{ ml}$$

- 2) **Functional Residual Capacity (FRC):** It is the sum of the residual volume and expiratory reserve volume.

$$FRC = RV + ERV \quad [3]$$

$$\text{FRC} = 1200 \text{ ml} + 1200 \text{ ml} = 2400 \text{ ml}$$

- 3) **Vital Capacity (VC):** Results from the sum of inspiratory reserve volume, tidal volume, and expiratory reserve volume.

$$\text{VC} = \text{IRV} + \text{TV} + \text{ERV} \quad [4]$$

$$\text{VC} = 3100 \text{ ml} + 500 \text{ ml} + 1200 \text{ ml} = 4800 \text{ ml}$$

- 4) **Total Lung Capacity (TLC):** Calculated from the sum of vital capacity and residual volume, it represents the sum of all lung volumes.

$$\text{TLC} = \text{VC} + \text{RV} \quad [5]$$

$$\text{TLC} = 4800 \text{ ml} + 1200 \text{ ml} = 6000 \text{ ml}$$

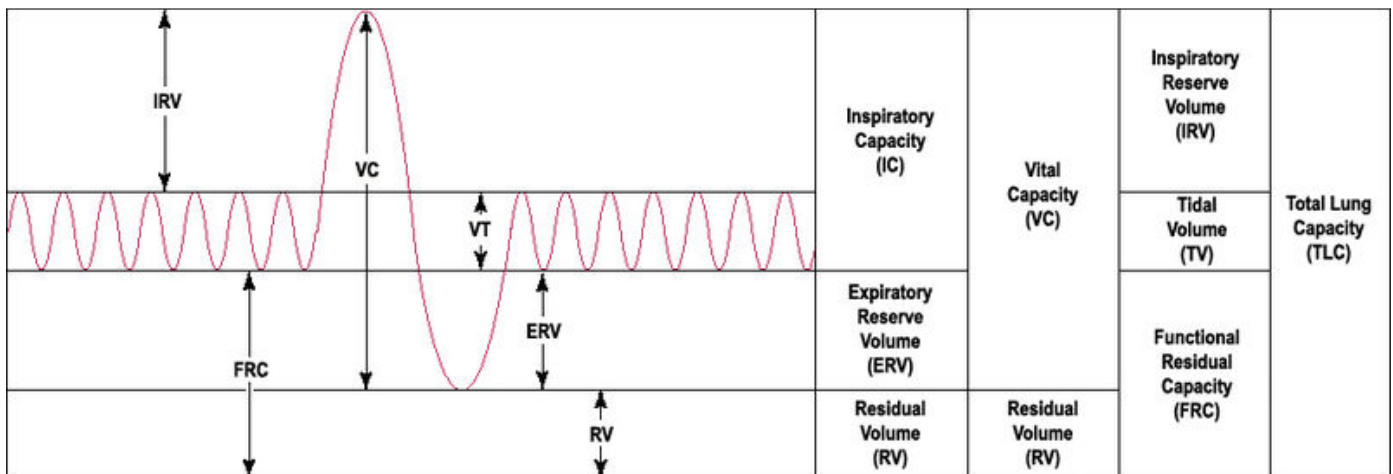


Figure 2.8 Lung Volumes and Capacities (55).

## 2.7 HUMAN RESPIRATORY SYSTEM DISEASES

Respiratory system diseases are the third highest leading cause of death in America (56).

Common respiratory diseases are the following:

### a) Asthma:

Asthma is a chronic respiratory disease but it is still a manageable condition. In the United States, asthma affects 14 to 15 million people (56). Asthma is one of the most common chronic disorders in children, currently affecting approximately 7.1 million children under 18 years. Asthma is the third leading cause of hospitalization among children under the

age of 15. Asthma is the third leading cause of school absenteeism; in 2008, asthma caused an estimated 14.4 million lost school days in children with an asthma attack (57).

Asthma is a disorder characterized by chronic airway inflammation, airway hypersensitivity to a variety of stimuli, and airway obstruction that is at least partially reversible. Asthma is more common in children than in adults. Symptoms include difficult breathing, coughing, wheezing, chest tightness, tachycardia, fatigue, moist skin, and anxiety (54).

Inflammation of the airways lining is the most common characteristic of asthma. Certain cells lining the airways, when stimulated release chemical substances that lead to inflammation; this causes the lining of the airways to swell and narrow. The inflammation can last a long time, even for weeks. Most people with asthma have always some degree of inflammation all of the time. With airways inflammation, increased sensitivity of the airways occurs and the airways become more irritable. Airway obstruction is caused by tightening of the muscles surrounding them; this condition is called bronchospasm and it causes further narrowing of the inflamed airways. In some patients with asthma, the airways mucus glands produce excessive, thick mucus, which also cause airway obstruction (56).

There are different types of medicines used to treat asthma, they include:

1. **Long-term control medications:** In most cases, these medications need to be taken every day. They are four different types (58):
  - **Inhaled corticosteroids** are the most commonly prescribed type of long-term asthma medication. Long-term use of these medications has been related with slightly slowed growth in children, but the effect is minor.
  - **Leukotriene modifiers** are oral medications that avoid asthma symptoms for up to 24 hours. In rare cases, these medications have been associated to psychological reactions, such as agitation, aggression, hallucinations, depression and suicidal thinking.

- **Combination inhalers** contain an inhaled corticosteroid in addition to a long-acting beta agonist (LABA). In some situations, long-acting beta agonists have been linked to severe asthma attacks. For this reason LABA medications should always be given to a patient with an inhaler that also contains a corticosteroid.
  - **Theophylline** is a daily pill that helps keep the airways open, it relaxes the airways muscles.
2. **Quick-relief medications:** Also called rescue medications, they include (58):
- **Short acting- beta agonists** are inhaled bronchodilator medications that can very quickly ease the symptoms during an asthma attack. As stated before the medicine Xopenex (levalbuterol), used in this research, belongs to this classification of medicines. Its effects last several hours.
  - **Ipratropium (Atrovent)** is sometimes prescribed to treat an asthma attack because it causes an immediate relief of symptoms.
  - **Oral and intravenous corticosteroids** relieve airway inflammation caused by severe asthma. They can possibly cause serious side effects when they are used for long periods of time.

**b) Small Airways Diseases (SAD) or Small Airways Impairments (SAI):**

The term small airways refer to about 7<sup>th</sup> to 19<sup>th</sup> 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. The atopic manifestation just prior to asthma could be early SAD and then if inflammation persists, asthma would appear (53).

Small airways disease includes a spectrum of inflammatory and fibrotic pulmonary diseases centered on the small conducting airways (59). Small airways inflammation with structural remodeling may be responsible for recurrent attacks in bronchial asthma. SAD always presents inflammation of small bronchi and bronchioles with minimal emphysema

(destruction of alveolar walls). Exposure to tobacco smoke, air bone pollutants, mineral dusts, and viral respiratory infections may result in SAD (60).

**c) Chronic Obstructive Respiratory Disease (COPD):**

COPD is a respiratory disorder characterized by chronic and recurrent airflow obstruction, which increases airway resistance (54). COPD is a leading cause of death and illness worldwide. Most COPD is caused by long-term smoking (61). The main types of COPD are emphysema and chronic bronchitis (54):

- 1. Emphysema:** Is a disorder where the walls of the alveoli are destroyed, producing abnormally large air spaces that remain filled with air during exhalation. Oxygen diffusion across the damaged respiratory membrane is reduced due to the narrowed surface area for gas exchange. Blood oxygen level is to some extent lowered. As the number of damaged alveolar walls increases, lung elastic recoil decreases due to loss of elastic fibers, and an increasing amount of air is trapped in the lungs at the end of expiration. Treatment consists of cessation of smoking and removing other environmental irritants, breathing exercises, use of bronchodilators, and oxygen therapy.
- 2. Chronic Bronchitis:** Is an illness characterized by excessive secretion of bronchial mucus and accompanied by a productive cough that lasts for at least three months of the year for two successive years. Other symptoms are shortness of breath, wheezing, cyanosis, and pulmonary hypertension. Treatment is similar to emphysema treatment.

**d) Lung Cancer:**

Lung cancer is the second most diagnosed cancer in men and women, and it is the number one cause of death from cancer each year in both men and women (62). Most people with lung cancer die within a year after diagnosis. Cigarette smoke is the most common cause of lung cancer. Other causes are ionizing radiation and inhaled irritants (like asbestos and radon gas). Emphysema normally is a precursor of lung cancer. The most common type

of lung cancer is bronchogenic carcinoma which begins in the epithelium of the bronchial tubes. The tumors begin as epithelial lesions that grow to form bigger masses that obstruct the bronchial tubes or invade adjacent lung tissue. Symptoms are related to the location of the tumor. Treatment consists of partial or complete surgical removal of a diseased lung, radiation therapy, and chemotherapy (54).

**e) Pneumonia:**

It is an acute infection or inflammation of the alveoli. It is the most common infectious cause of death in the United States (54). Pneumonia is caused by bacteria, a virus or fungi; its symptoms can vary from mild to severe (63). The most common cause of pneumonia is the pneumococcal bacterium *Streptococcus pneumoniae*. Elderly, infants and immunocompromised individuals, cigarette smokers and individuals with obstructive lung disease are the most susceptible to pneumonia. Symptoms are fever, chills, productive or dry cough, malaise (feeling of discomfort or illness), chest pain, and in some cases dyspnea (difficult breathing) and hemoptysis (spitting blood). Treatment may involve antibiotics, bronchodilators, oxygen therapy, increased fluid intake, and chest physiotherapy (percussion, vibration and postural drainage) (54).

**f) Tuberculosis:**

It is caused by the bacterium *Mycobacterium tuberculosis* producing an infectious contagious disease; it mainly affects the lungs and the pleurae but can affect other body parts. The bacterium can remain dormant for life, but an impaired immune system can enable the bacterium become active (54). In the recent years there have been advances in its treatment, but tuberculosis still remains a major cause of illness and death worldwide, especially in Africa and Asia. Tuberculosis is the cause of death of 2 million people every year (64). Symptoms that do not develop until disease is advanced are: fatigue, weight loss, lethargy, anorexia, a low fever, night sweats, cough, dyspnea, chest pain and hemoptysis (54). Treatments for tuberculosis take longer than treating other types of bacterial infections; antibiotics for this illness have to be taken for at least six to nine months. The prescribed



drugs and length of treatment depend on age, overall health, drug resistance, form of tuberculosis (active or latent) and its location (64).

#### **g) Coryza and Influenza**

Coryza or common cold is an upper respiratory tract viral infection (65). It can be caused by hundreds of viruses. Symptoms include sneezing, excessive nasal secretion, dry cough, and congestion. The simple cold does not include fever. Complications comprise sinusitis, asthma, bronchitis, ear infections and laryngitis. Preschool children are at greatest risk of recurrent colds, but even healthy adults can expect to have few colds each year. It has been suggested in recent investigations a relation between level of stress and frequent colds. Treatments include pain relievers, decongestant nasal sprays and cough syrups (54).

Influenza is also a viral infection; its symptoms consist of chills, high fever, headache and muscular aches and cold like symptoms (54). Influenza can be deadly, approximately tens of thousands of people in the United States die each year of complications of influenza. Complications include pneumonia, bronchitis, sinus infection and ear infections. Frequently the only treatments are bed rest and plenty of fluids, but sometimes an antiviral medication needs to be prescribed (66).

#### **h) Pulmonary Edema**

Is an abnormal accumulation of fluid in the interstitial spaces and alveoli of the lungs (54). Heart problems are the main cause of pulmonary edema, but fluid accumulation can happen for other reasons like pneumonia, exposure to certain toxins and medications and exercising or living at high elevations (67). The most recurrent symptom is dyspnea. Other symptoms include: wheezing, tachypnea (rapid breathing rate), restlessness, a feeling of suffocation, cyanosis, paleness and diaphoresis (excessive perspiration). Treatments are: oxygen administration, drugs that dilate the bronchioles and lower blood pressure, diuretics and drugs that correct acid-base imbalance, suctioning of airways and mechanical ventilation (54).

**i) Cystic Fibrosis (CF)**

Is an inherited disease of secretory epithelia that affects the airways, liver, pancreas, small intestine and sweat glands. Its cause is a genetic mutation (54). CF affects the cells that produce mucus, sweat and digestive juices. Usually these secretions are thin and slippery, but in CF, the secretions are thick and sticky. Instead of acting as lubricant, the secretions plug up tubes, ducts and passageways, mainly in the pancreas and lungs. CF is most common in white people of northern European ancestry. One of the first symptoms is an excessively salty taste to the skin; other symptoms include: persistent cough, wheezing, repeated lung infections, repeated sinus infections, foul-smelling, greasy stools, poor weight gain and growth, distended abdomen from constipation and intestine blockage. There is no cure for CF, but some medications like antibiotics, mucus-thinning drugs and bronchodilators, can improve symptoms and reduce complications. Some mechanical devices to help loosen lung mucus are used (chest clapper, inflatable vest and breathing devices). Other treatments include feeding tubes, lung transplant and bowel surgery (68).

## Chapter 3: Pulmonary Function Tests and Previous Studies

### 3.1 INTRODUCTION

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 treatment restores a normal function (52). In this chapter we focus on the review of two important pulmonary function tests: Spirometry and Impulse Oscillometry using the Impulse Oscillation System (IOS); and a literature review of several studies that have been performed in the previous years to compare several Pulmonary Function Tests (PFTs) to assess the ability of Forced Oscillation Technique (FOT) and IOS to measure pulmonary function and to discriminate between impaired and non-impaired lung function.

### 3.2 SPIROMETRY

Spirometry is the most common pulmonary system test; it is a measurement of maximal airflow after deep breath 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 (69). The measurements usually obtained from spirometry are (70) :

- **FVC (Forced vital capacity) :** Total volume of air that can be exhaled during a maximal forced expiration
- **FEV<sub>1</sub> :** Forced expiratory volume in seconds is the volume expired in the first second of maximal expiration
- **FEV<sub>1</sub>/ FVC:** Percentage of the FVC expired in one second
- **FEF<sub>25%-75%</sub>:** 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
- **FEV<sub>6</sub>:** Forced expiratory volume in six seconds.

- **PEF** : Peak expiratory flow represents the maximal expiratory flow rate achieved

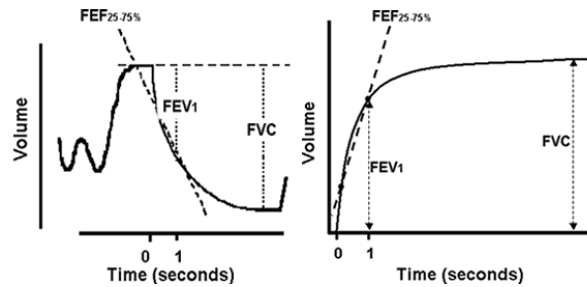


Figure 3.1 Spirometry parameters (70).

Spirometry parameters are shown in Figure 3.1.

The National Asthma Education and Prevention Program (NAEPP) Guidelines previously considered  $FEV_1$  as the “gold standard” to assess asthma severity and control, but several studies have suggested that most children have normal or near normal  $FEV_1$  even when they are symptomatic. Now the NAEPP has added  $FEV_1/FVC$  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  $FEV_1/FVC$  and the  $FEF_{25\%-75\%}$ , while  $FEV_1$  remain in the normal range in spite of asthma severity (71).

### 3.3 FORCED OSCILLATION TECHNIQUE AND IMPULSE OSCILLOMETRY SYSTEM (IOS)

The fundamental principle of Forced Oscillation Technique (FOT) is that respiratory mechanics can be measured from superimposition of external pressure oscillations on the respiratory system during resting breathing (72). Therefore, FOT superimposes small external pressure signals on the natural breathing of a subject to determine its breathing mechanics. FOT measures respiratory impedance to this applied forced pressure oscillations produced by a loud speaker (73). FOT is indicated as a reliable diagnostic tool to obtain tidal breathing analysis. One of the great advantages of FOT over other pulmonary systems 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, wearing a nose clips occluding the nares (74).

FOT has been used in humans for more than 50 years; it has been used in children with three major clinical aims (75):

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 situations 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 a 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 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 (72).

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 ( $FEF_{25\%-75\%}$ ) (74).

### **3.3.1 Impulse Oscillation Technique**

In 1956 Dubois presented the first study about FOT; in this study FOT was applied using sinusoidal oscillations with multiple single frequencies between 2 and 18 cycles per second. 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, and continuous resolution in the frequency domain using a Fourier Integral (71) (72). 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 because 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 (74).

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 (74).

### **3.3.2 IOS Aperiodic Waveforms**

The IOS produces aperiodic waveforms through an impulse generator that applies pulses of limited magnitude with 30-40 ms duration. The feature of an aperiodic waveform is the continuous spectrum after its time transformation into the frequency domain, using Fourier integral and its efficient implementation using in the Fast Fourier Transform (FFT). A continuous spectrum is especially important in impaired respiratory systems with regional nonhomogenities (see Figure 3.2) where resistance, reactance and coherence spectra may manifest deviations from its normally smooth and uniform continuous spectra.

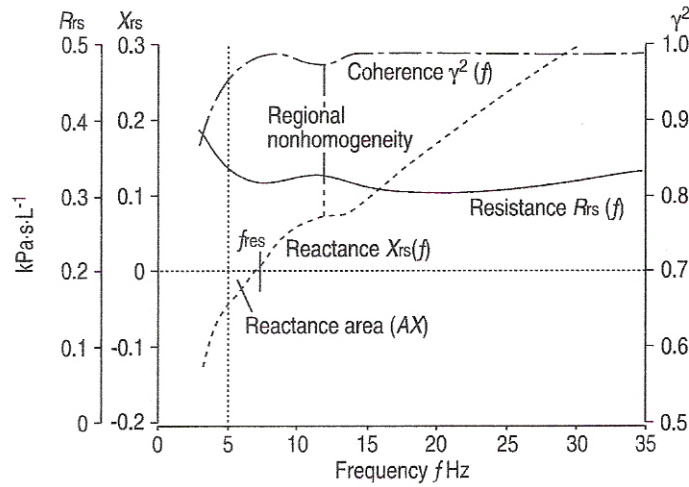


Figure 3.2 Data for spectra of Respiratory Resistance, Reactance and Coherence from 3 to 35 Hz (74)

Impulse power spectra for pressure and flow generated by the IOS are illustrated in Figure 3.3.

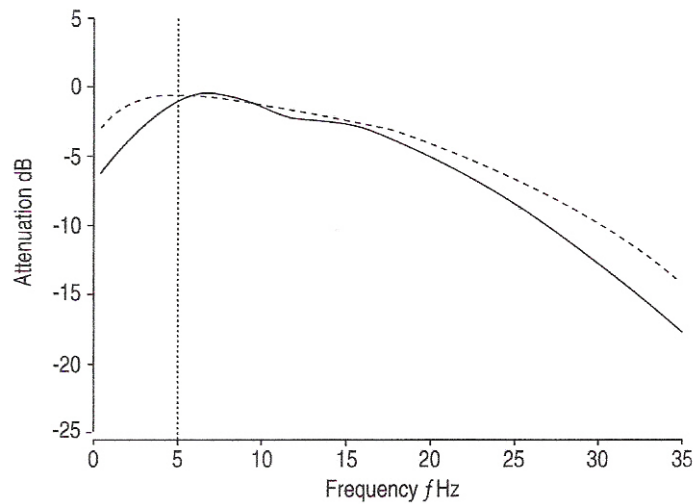


Figure 3.3 Power spectra for flow ( — ) and pressure (-----) (74).

### 3.3.3 IOS Technical Features

In Figure 3.4 a schematic diagram of the IOS and its measuring-head and connectors is shown. The pneumotachograph, with a resistance of  $36 \text{ Pa.s.L}^{-1}$  measures the flow. The proximal side of the pneumotachograph is connected to flow and pressure transducers. To avoid phase differences, matched transducers are used for both pressure and flow channels. Pressure and flow signals are sampled with a sampling frequency of 200 Hz frequency and are converted to numbers by a 12-bit analog-to-digital

converter. The terminal resistor provides a low-impedance pathway for respiratory flow; it allows that sufficient impulse pressure is transmitted into the respiratory system (74).

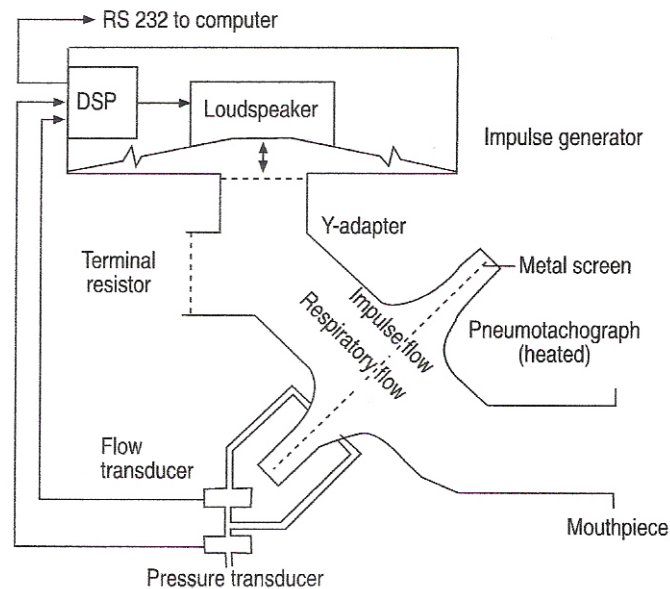


Figure 3.4 Schematic diagram of the IOS with its measuring-head and connectors (74)

The IOS performs measurements as follows: when the subject breaths ambient air using the tubing between mouthpiece and terminating resistor, the loudspeaker generates and transmits pressure impulses by the Y-adaptor, pneumotachograph and mouthpiece into the respiratory tract, then the last two register the breathing activities signals and the applied forcing impulses for further processing (74).

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 (73). Figure 3.5 shows a typical IOS screen, and in Figure 3.6 we observe a child undergoing the IOS test.

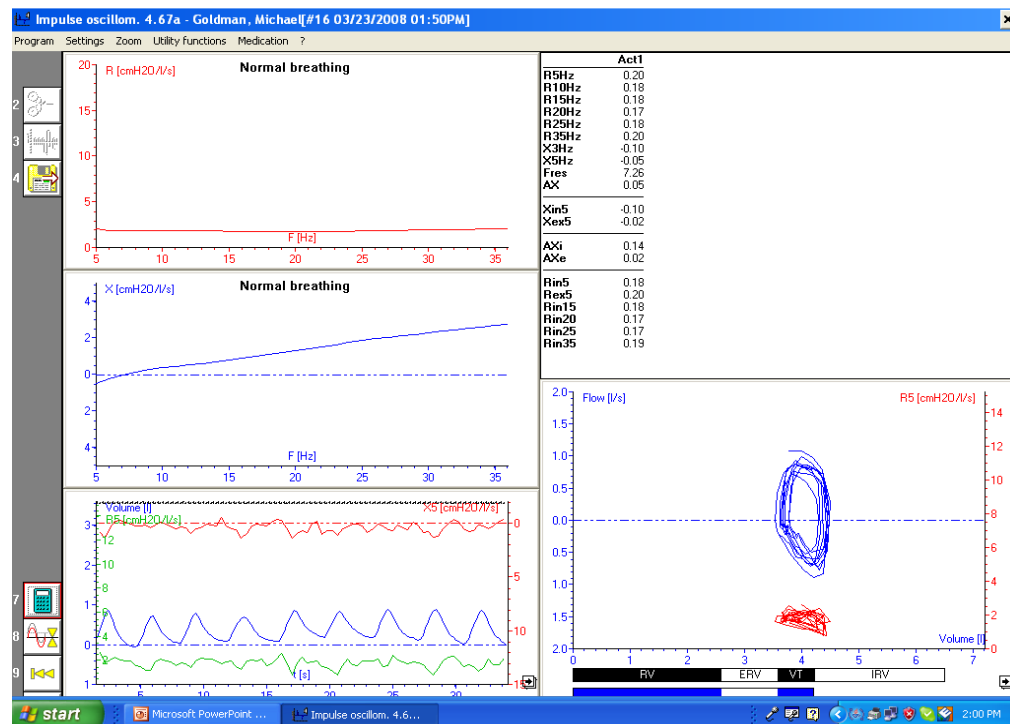


Figure 3.5 IOS main screen



Figure 3.6 A child undergoing pulmonary function testing by the IOS.

### 3.3.4 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 (V), derived from the superimposed forced oscillation, after being separated from the respiratory pressure and flow.

$$Z(f) = P(f) / V(f) \quad [6]$$

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).

$$Z(f) = R(f) + jX(f) \quad [7]$$

IOS also includes hallmarks such as *Resonant Frequency* ( $F_{res}$ ) and *Reactance Area* (AX) also known as the “*Goldman Triangle*”. IOS offers all this indices over a selected frequency range of 3 to 35 Hz (74).

#### 3.3.4.1 Impedance Parameters: Respiratory Resistance (R) and Respiratory Reactance (X)

##### a) Respiratory Resistance:

The real part of the Impedance 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 cmH<sub>2</sub>O/L/s or KPa/L/s (74).

### 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 in terms of capacitance (C) (74).

$$X(f) = \omega I - (1/\omega C) \quad [8]$$

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

It is important to notice that C is not equivalent to compliance, in medical terms. 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 property is more prominent at high oscillation frequencies (see figure 3.7). Reactance is measured in cmH<sub>2</sub>O/L/s or KPa/L/s (74).

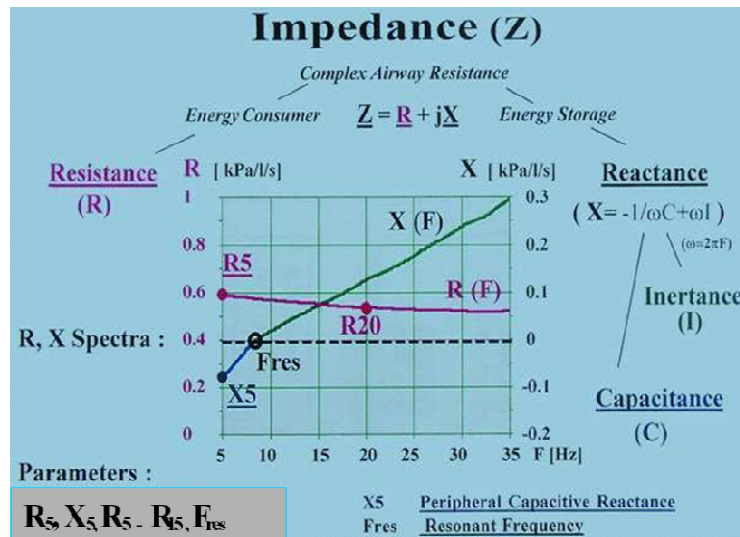


Figure 3.7 IOS parameters (76)

### 3.3.4.2 Other IOS parameters: Resonant Frequency (F<sub>res</sub>), Reactance Area (AX) and Frequency dependence of resistance (R<sub>5</sub>-R<sub>25</sub>)

#### a) Resonant Frequency:

The Resonant Frequency (f<sub>res</sub>) is the point at which C and I are equal, therefore reactance is zero and is measured in Hertz (1/s) (74).

$$\omega_0.I = (1/\omega_0.C) \quad [9]$$

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 – “Goldman Triangle”) was introduced by Goldman in his study about “Clinical applications of forced oscillations” (73); AX is the integrated low frequency respiratory reactance magnitude between 5 Hz and  $F_{res}$ , and it is measured in cmH<sub>2</sub>O/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 (74). *AX is a useful and sensitive index of peripheral airway function* (72).

Figure 3.8 shows data collected in 2006 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 (Goldman’s Triangle)** triangular 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.

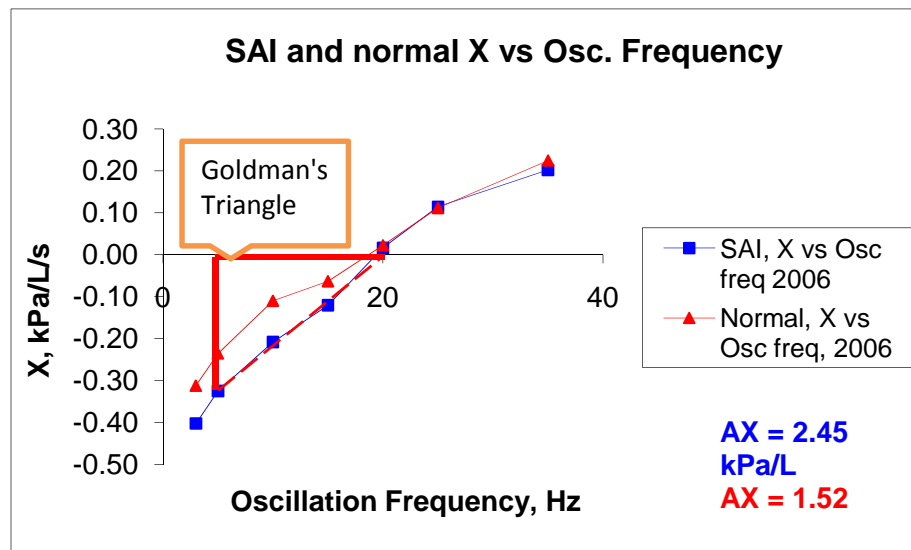


Figure 3.8: Reactance measurements in a Normal and a SAI child as a function of oscillation frequency

### c) Frequency dependence of resistance (fdR or R5-R20):

It is simply the subtraction of the measured resistance at 20 Hz and the resistance at 5 Hz or 3 Hz. Frequency dependence of resistance is a characteristic for peripheral airway dysfunction (72).

$$R5-R20 = R5 - R20 \quad [10]$$

Changes in AX with treatment interventions parallel changes in frequency dependence of R. It has been suggested by Goldman et al. (72) 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 (73). There is now plenty of evidence that peripheral airway inflammation is present in asthma patients, and frequency dependence of resistance occurs significantly in asthma (74).

### **3.4 BRONCHODILATION PHENOTYPE**

The bronchodilation response as a physiological response to short-acting beta agonist has been recommended to demonstrate reversibility of airflow obstruction consistent with the definition of asthma (71).

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 happens R also increases, due to a correspondent decrease in airway lumen. R 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  $\beta$ -agonist inhalation than spirometry (74).

According to a recently developed document on Pulmonary Function Testing in Preschool Children (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 broncho-constrictors (77). 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. (78) 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. (79) 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. (71) 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. (78) noted the need for a practical FO index to define airway obstruction.

### **3.5 IOS PREVIOUS STUDIES**

#### **3.5.1 IOS vs Spirometry Studies**

Several research groups have developed studies to compare IOS vs Spirometry performance to assess respiratory function in children. Marotta et al. (7) in 2003 evaluated bronchodilator responses measured by IOS and spirometry in 4-year old asthmatic and nonasthmatic children. The children performed IOS and spirometry before and after albuterol administration. In this study they assessed IOS Resistance and Reactance at 5 Hz ( $R_5$  and  $X_5$ ) and Resonant Frequency ( $F_{res}$ ). Asthmatic vs non-asthmatic children presented significant differences in IOS parameters. Therefore, they suggested that IOS bronchodilator responses are remarkably abnormal in this population (children presented a

significant bronchodilator response) and IOS is a useful tool for the early detection of asthma development. Goldman et al. (9) in 2002 performed a study to assess spirometric indices and respiratory impedance measured with the IOS in stable asthmatic adolescents over three consecutive days. They found significant differences between R5, frequency dependence of Resistance (R5-R15) and low frequency reactance area (AX). However, spirometric indices showed no change. They concluded that these IOS parameters are sensitive measures that can be used to detect changes in bronchomotor tone in asthmatic adolescents. It has also been reported by Saadeh et al. (11) in 2003 that some asthmatic patients manifest normal spirometry after initiation of treatment, despite continuing symptoms, and abnormal IOS test results. They analyzed spirometry and IOS data pre- and post-levolbuterol from patients with asthma symptoms. These patients had follow up visits and spirometry and IOS tests at 3, 6 and 12 weeks. They concluded that these patients may be more sensitively managed using IOS. Gaylor, et al. (6) in 2003, conducted a research analyzing IOS data from 21 asthmatic subjects 5-80 years old comparing IOS data and spirometry pre- and post-levolbuterol. They stated that Force Oscillation (FO) is more sensitive than spirometry for detecting early small airway disease and in detecting responses to therapeutic or bronchial challenge in children and adults. They concluded that the use of IOS should be considered before changing therapy in asthmatic patients whose FEV<sub>1</sub> fails to improve, if the treatments have improved symptoms. Vink et al. (12) in 2003, performed a study in 19 asthmatic children to evaluate the sensitivity and specificity of IOS parameters, R and X at frequencies of 5-35 Hz, to quantify changes in airflow obstruction in comparison with forced expiratory volume in the first second (FEV<sub>1</sub>) using a pneumotachometer system, and peak expiratory flow (PEF) using a spirometer. They concluded that IOS parameters can be easily used as an indirect measure of airflow obstruction and that Resistance values measured at a frequency of 5 Hz showed to be superior to PEF measurements. In a more recent study by Song et al. (13) in 2008, the correlation between IOS, spirometry and peak expiratory flow rate (PEFR) was assessed in 77 asthmatic and 55 control Korean children aged 3 to 6 years. The IOS parameters analyzed were the IOS Resistance at 5, 10, 20 and 35 Hz (R5, R10, R20 and R35). IOS and spirometry were performed in these groups of children, before and after bronchodilation. Their results showed that conventional spirometry parameters did not present statistically significant differences, and

there were some significant correlations between bronchodilator responses of spirometric parameters and IOS parameters. They concluded that IOS is a useful diagnostic tool in detection of early asthma development and might be a helpful objective outcome measure of early interventions. The same group of researchers (14) conducted another study, also in 2008, in 48 children with asthma and 66 control children aged 7-15 years of age in order to evaluate the correlation between spirometry values and IOS in children with asthma. Their findings were that FEV<sub>1</sub> and peak expiratory flow rate (PEFR) showed significant correlation with impedance and resistance at 5, 10, 20 and 35 Hz, both in asthmatic and control children. Also FVC showed correlation with impedance and resistance at 10, 20 and 35 Hz in both groups of children. Therefore, they concluded that FEV<sub>1</sub>, FVC and PEFR were significantly correlated with IOS parameters, in both asthmatic and control subjects and they affirmed that IOS is an appropriate measure of lung function when spirometry and PEF cannot be performed. Antonova et al. (15) in 2006 performed another study in preschool children 6 years old with mild and moderate bronchial asthma (BA). The sensitivity of impulse oscilometry and spirometry for assessment of the degree of severity of bronchial asthma were evaluated. The studied parameters were: FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub> from spirometry and IOS total Impedance (Zrs), Rrs5 (R5), Xrs5 (X5) and F<sub>res</sub>; they compared mild BA vs moderate BA. No significant differences for spirometry parameters were obtained between both groups, whereas IOS parameters demonstrated significant increase in total Impedance (Z), R5 and F<sub>res</sub> and significant decrease in X5. Therefore, they suggested that Impulse Oscillometry may be a more sensitive method than spirometry for assessment of the inflammatory process and degree of severity of bronchial asthma in children. Linares et al. (16) in 2002 tested 98 asthmatic children, 6 to 15 years old, with the purpose of evaluating the correlation between spirometry and IOS. In this study IOS R5, X5 and F<sub>res</sub> were correlated with FEV<sub>1</sub>, FEF<sub>25</sub>, FEF<sub>50</sub>, FEF<sub>75</sub>, and FEF<sub>25-75</sub>. Their findings showed that there were a good correlation between spirometry and IOS in this group of children, having the best correlations between R5 and FEV<sub>1</sub>, and between R5 and FEF<sub>25</sub>. In other studies, like the study conducted by Lewis-Brown et al. (17) in 2005, children with asthma from 5 to 18 years were assessed to evaluate the association between FEV<sub>1</sub>, and FVC with IOS R5. FEV<sub>1</sub> and FVC were not associated with IOS R5. The researchers concluded that spirometry and IOS should be used together along with clinical



history in evaluating patients for asthma, and they also stated that IOS should not be used in assessing asthma until further studies have been performed.

In a different type of study developed to assess a specific oral drug called montelukast, that improves pulmonary function and can reach lower airways, Nieto et al. (24) in 2006 evaluated 23 children with mild asthma using spirometry and IOS. They stated that this drug showed improvements in all IOS parameters tested: Z5, R5, R20, X5 and  $F_{res}$ . No changes were found in the control group. Expiratory flows remained unchanged except for a small but significant worsening of  $FEF_{25-75}$ . Therefore, they concluded that IOS is more sensitive than conventional spirometry.

In two more recent studies performed by Hur et al. (25) in 2008 and Larsen et al. (26) in 2009, other comparisons between IOS and spirometry were made. Hur et al (25) tested 174 children in a methacholine challenge evaluating correlation between  $FEV_1$ , X5 and R5. They concluded that IOS parameters were more discriminative than  $FEV_1$  for detecting decreased lung function and showed a good correlation with  $FEV_1$ . Larsen et al. (26) tested children from 6 to 14 years with mild to moderate persistent asthma using IOS and spirometry in a long term pediatric trial using different therapies. They specifically evaluated  $FEV_1$ ,  $FEV_1/FVC$  ratio,  $FEF_{25-75}$ , as well as AX and concluded that AX was unique in reflecting ongoing improvement during the latter part of the trial in contrast to spirometric values, emphasizing that the pattern of improvement observed in AX suggest that this test might detect alterations in airway mechanics not reflected by spirometry.

Hellinckx et al. [28] in 1998 studied 281 healthy and asthmatic children, 2.7 to 6.6 years old, looking at IOS parameters (R and X at 5, 10, 15, 20, 25 and 35Hz) before and after bronchodilation using salbutamol. Their results showed that neither baseline values of impulse oscillation nor its changes after bronchodilation was significantly different between healthy and stable asthmatic children. They recommended that a change in R5 of 40% is to be considered as the cut-off for a “positive” bronchodilator response. In another more recent study performed by Graw-Panzer et al. (29) in 2009 compared IOS vs spirometry performance using a bronchodilator; they tested 46 inner-city (4-20 years old) children with asthma before and after bronchodilation, using the IOS parameters R5 and R20, and the spirometry parameters FVC,  $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$ . They found that reversible

bronchoconstriction is consistent with a drop in mean resistance at R5. They also observed a correlation of the degree of BD response measured by IOS and spirometry. These researchers finally concluded that there is increased airway resistance as measured by IOS when there is airway obstruction measured by spirometry and further studies are needed to establish normative data values for IOS airway resistance. Table 1 provides summaries of all these IOS vs Spirometry studies.

Table 3.1 IOS vs Spirometry Studies

Researchers	Evaluated Population	Evaluated Parameters	Conclusions
Marota et al. [7] 2003	asthmatic and non-asthmatic 4 years	R5,X5, F <sub>res</sub>	IOS bronchodilator responses are remarkably abnormal in this population. <b>IOS is a useful tool for asthma assessment</b>
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. <b>IOS parameters are sensitive measures of bronchomotor tone changes in these adolescents.</b>
Saadeh et al. [11] 2003	asthma symptoms 4-62 years	R5, R5-R15,AX	Some asthmatic patients manifest normal spirometry despite continuing symptoms, <b>these patients may be more sensitively managed using IOS</b>
Gaylor et al. [6] 2003	asthmatics 5-80 years	R5, R5-R15,AX	IOS shows systematic improvements after inhaled levabulterol, <b>FO is more sensitive than spirometry</b> and IOS should be considered before changing therapy in asthmatic patients whose FEV <sub>1</sub> 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, <b>IOS parameters can be easily used as an indirect measure of airflow obstruction.</b>
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. <b>IOS is a useful diagnostic tool and might be a helpful objective outcome measure.</b>
Song et al. [14] 2008	asthmatics and controls 7-15 years	R and X at 5-35 Hz R5-R20	FEV <sub>1</sub> and PEFR showed significant correlation with impedance and resistance at 5,10,20 and 35 Hz in both groups, FVC correlated with Z and R at 10, 20 and 35 Hz in both groups. <b>IOS is an appropriate measure of lung function when spirometry and PEF can not be performed.</b>

Antonova et al. [15] 2006	mild and moderate asthmatics 6 years	Z, R5,X5,F <sub>res</sub>	No significant differences for spirometry were found, IOS presented significant increase in total impedance (Z), R5 and Fres, and significant decrease in X5. <b>IOS may be more sensitive than spirometry for assessment of inflammatory process and degree of asthma severity.</b>
Linares et al. [16] 2002	asthmatics 6-15 years	R5,X5,F <sub>res</sub>	<b>There were good correlation between spirometry and IOS,</b> best correlation: R5 and FEV <sub>1</sub> , 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 <sub>res</sub>	Z5, R5, R20, X5, and F <sub>res</sub> showed improvements, no changes were found in the control group. <b>IOS is more sensitive than conventional spirometry.</b>
Hur et al. [25] 2008	children	X5 and R5	<b>IOS parameters were more discriminative than FEV<sub>1</sub></b> for detecting decreased lung function and showed a good correlation with FEV <sub>1</sub> .
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, <b>AX might detect</b> alterations in airway mechanics not reflected by <b>spirometry.</b>
Hellinckx et al. [28] 1998	healthy and asthmatic kindergarten children 2.7 - 6.6 years old	R and X at 5-35 Hz,F <sub>res</sub>	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.
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

### 3.5.2 IOS vs Other Techniques

Other researchers have compared IOS with spirometry and other techniques. Olaguibel et al. (18) in 2005 evaluated repeatability and bronchodilator response of IOS indices in 33 preschool children (3-6 years old), and their correlation with spirometry and whole body plethysmography. They evaluated R5, R20 and X5 IOS parameters, at base line, after placebo and salbutamol inhalation, and FEV<sub>1</sub>, whole body plethysmography (sRaw) at baseline and after salbutamol. They concluded that IOS was positively accepted by young asthmatic children, IOS provided reproducible and sensitive indices of lung function, and IOS resistance values obtained at low frequencies (R5) were reproducible and correlated with

spirometry and plethysmographic values. Similarly Tomalak et al. (19) in 2006 tested 334 children ages 5-18 years comparing the results of plethysmographic measurements of airway resistance ( $R_{aw}$ ) with IOS data ( $R_5$ ,  $R_{20}$  and  $R_{35}$ ). They observed that all three resistances correlated significantly with plethysmographic  $R_{aw}$ , and the strongest correlation was observed for  $R_5$ .  $R_5$ ,  $R_{20}$  and  $R_{35}$  were significantly greater than  $R_{aw}$ . They finally suggested that IOS may be useful in diagnosis of children with obstructive respiratory diseases. Bisgaard et al. (20) in 1995 and Klug et al. (10) in 1996 performed studies comparing IOS, interrupter technique resistance ( $R_{int}$ ) and transcutaneous measurements of oxygen tension ( $P_{tc}O_2$ ), specific airway resistance  $sR_{aw}$  (whole body plethysmography) and FEV1 (spirometry). They assessed lung changes after a methacholine challenge in small children 4-6 years (20) and 2-4 years old children (10) with suspected asthma and asthma, respectively. Bisgaard et al. observed that IOS' total respiratory impedance ( $Z$ ),  $R_{int}$ , and  $P_{tc}O_2$  changed in parallel with  $sR_{aw}$  and FEV1, and stated that these three parameters ( $Z$ ,  $R_{int}$ , and  $P_{tc}O_2$ ) provided convenient indices of changes in lung function. Similarly, Klug et al. reported that all the evaluated techniques reliably reflect short-term changes in lung function and can offer helpful estimates of airway function.

Also other studies have been presented where they assessed respiratory resistance by the interrupter technique ( $R_{int}$ ),  $Z$ , and IOS resistance ( $R$ ) and reactance ( $X$ ) and whole body plethysmography. Klug et al. (4) tested 121 children 2-7 years, Nielsen et al. (21) tested 38 asthmatic and 29 control children 2-5 years, and Nielsen et al. (23) tested 37 healthy controls and 55 asthmatic children 2-5 years using these three techniques to evaluate their performance in assessing lung function in children. Klug et al. (4) found that the techniques require minimal cooperation and allow measurement of lung function in 80% of the tested children, although Nielsen (21) and (23) concluded that whole body plethysmography ( $sR_{aw}$ ) was superior in separating both groups, asthmatic from healthy control subjects in these children.

One of the most recent studies was the study performed by Todaki et al. (30) in 2009 where this research team compared IOS, spirometry and exhaled nitric oxide (eNO). They used a protocol consisting of bronchoconstriction phase and a bronchodilation phase in 92 children (62 with asthma, 13 wheezy children and 17 healthy children). They analyzed  $R_{20}$  and  $R_5$ - $R_{20}$ . They observed that a

significant decrease occurred in the eNO level after methacholine inhalation challenge, and this decrease did not correlate with FEV1 and R20, but it correlated with the percentage decline observed in maximal expiratory flow at 50% vital capacity and with the change in small airway resistance (R5-R20).

Table 3.2 IOS vs other Techniques Studies

<b>IOS, Spirometry and Whole body Plethysmography</b>			
<b>Researchers</b>	<b>Evaluated Population</b>	<b>Evaluated Parameters</b>	<b>General Conclusions</b>
Olaguibel et al. [18]  2005	asthmatics  3-6 year old	R5,R20,X5	<b>IOS was well accepted for young asthmatic children and produced reproducible and sensitive indices of lung function,</b>  R5 correlated with spirometry and plethysmographic values.
<b>IOS and Whole body Plethysmography</b>			
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.  <b>IOS may be useful in diagnosing children with obstructive respiratory diseases.</b>
<b>IOS, Interrupter Technique Resistance (Rint), Transcutaneous Measurement of Oxygen Tension (Ptc, O2) and Whole Body Plethysmography</b>			
Bisgaard et al. [20] 1995	suspected asthma 4-6 years	R and X at 5-35 Hz	IOS total respiratory impedance (Z), Rint, and Ptc,O2 changed in parallel with sRaw and FEV1, <b>these three parameters provide convenient indices of changes in lung function.</b>
Klug et al. [10] 1996	asthmatics 2-4 years	R and X at 5-35 Hz	<b>All the evaluated techniques reliably reflect short-term changes in lung function.</b>
<b>IOS, Interrupter Technique Resistance (Rint) and Whole Body Plethysmography</b>			
Klug et al. [4]  1998	Caucasian, no chronic diseases 2-7 years	R5,R10,X5,X10,Z5,Fres	<b>Techniques require minimal cooperation and allowed measurement of lung function in 80% of the tested children.</b>
Nielsen et al. [21] 2000	asthmatics and controls 2-5 years	R5,X5	<b>Whole body plethysmography (sRaw) was superior in separating both groups.</b>
Nielsen et al. [23] 2001	asthmatics and controls 2-5 years	R5, X5	<b>Whole body plethysmography (sRaw) was superior in separating both groups.</b>
<b>IOS, Spirometry and exhaled nitric oxide (eNO)</b>			
Todaki et al [30] 2009	62 asthmatics, 13 wheezy and 17 healthy children	R20 and R5-R20	<b>A significant decrease occurred in the eNO level and it correlated with maximal expiratory flow at 50% vital capacity R5-R20</b>

### 3.5.3 IOS Studies

Ortiz et al. (8) in 2002 assessed the bronchodilator response in 10 children 2-5 years using IOS, analyzing X5 as primary efficacy variable. They confirmed that IOS is an acceptable method to assess airway response to bronchoactive drugs in this age group. Similarly, Goldman et al. (22) in 2008 analyzed the same group of children as Ortiz et al. (8), they evaluated R5, R5-R20, and AX. They concluded that IOS indices are sensitive measures of lung mechanical responses to bronchodilators in this group of children. Also in 2008 Menendez et al. (31) performed a study about IOS parameters measuring the effects of short and long acting Beta-agonist in the same children as Ortiz et al. (8). They analyzed R5, R5-R20, AX and respiratory model parameters for peripheral resistance (Rp) and compliance (Cp). They concluded that IOS parameters reflecting airway mechanics respond 5 min after albuterol and salmeterol in young children; Rp decreased and Cp increased after albuterol and salmeterol at 5 minutes; IOS R5, R5-R20, AX are sensitive measures of lung mechanics responses to SABA and LABA in pre-school children with asthma. Other study realized by Jee et al. (32) in 2010 also evaluated IOS parameters R, X, Fres and AX, with the aim of exploring which level of provocative concentration (PC) is appropriate for bronchial challenge in asthmatic children. They tested 51 children with asthma and 41 children with chronic cough, used as controls. The IOS parameters were significantly different between groups in the methacholine challenge. The authors finally suggested that PC(80)\_X5 might be a useful parameter to assess bronchial challenge in preschool children.

Table 3.3 IOS studies

Researchers	Evaluated Population	Evaluated Parameters	General Conclusions
Ortiz et al. [8] 2002	asthmatics 2-5 years	X5	<b>IOS is an acceptable method to assess airway response</b> to bronchoactive drugs in this age group.
Goldman et al. [22] 2008	asthmatics 2-5 years	R5, R5-R20, AX	<b>IOS indices are sensitive measures of lung mechanical responses</b> to bronchodilators in this group of children.
Menendez et al. [31] 2008	asthmatics 2-5 years	R5,R5-R20, AX	<b>IOS R5, R5-R20, AX are sensitive measures of lung mechanics responses</b> 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	<b>IOS parameters were significantly different between groups</b> in the methacholine challenge

As mentioned before these previous IOS studies sensitively and accurately evaluated lung function in children and adolescents, using pre and post bronchodilation conditions and bronchial challenge. However, it is observed that different parameters at different frequencies have been used during the years 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 these 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, this study aims 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) from 3-35 Hz before and after bronchodilation, to determine which one of these parameters better differentiates between pre and post bronchodilation conditions. It is also worthwhile to investigate whether impedance measures at 3 Hz could offer more significant information compared to impedance values measured at 5Hz.

### **3.6 IOS REFERENCE VALUES - PREVIOUS STUDIES**

Clement et al. (35) in 1987 obtained reference values using FOT for 403 healthy Belgian children 4 to 20 years of age measuring R and X between 4 and 26 Hz. They found that R and X vs frequency data depended on age or height, on sex, and slightly on weight. They mentioned that with growth R and the frequency dependence of R decrease while X increases. They also highlighted that 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) in 1998 did a study to determine Reference values in North American children (206 healthy children aged 3 to 17 years) assessing respiratory resistance measurements using FOT at 8, 12 and 16 Hz. They found that Height is the best predictor for total respiratory resistance at 8, 12 and 16 Hz in children. In 2005, Frei et al. (37) did a study aimed to obtain reference equations also in North American children to be used for assessing respiratory function by using IOS. They analyzed values of R and X at 5, 10, 15, 20, 25 and 35 Hz and Fres in 222 white children 3 to 10 years old (100 to 150 cm in height). They found that standing height was the only significant predictor for all variables, and concluded that

Resistance and  $F_{res}$  decreased by height, but also by age, and reactance increased. In 2006, in a study performed in Sweden, Dencker et al. (38) used IOS to obtain reference values for respiratory system impedance in children 2 to 10 years old. Their aim was to extend the reference values for IOS variables and to study their correlation with height, weight and age in healthy children. They tested 360 children assessing R and X at 5, 10, 15 and 20 Hz, total respiratory impedance (Z) and  $F_{res}$ , and concluded that all variables were related to body height, and most of them were weakly related to weight. They presented reference equations for children (height: 90-160 cm). Two more recent studies performed in 2008 presented reference values for IOS in healthy Polish (39) and healthy Iranian children (40) aged 3-18 and 5-19 years old, respectively. Nowowiejska et al. (39) evaluated 626 healthy Polish children in order to construct equations describing normal values of oscillatory parameters using IOS (R and X at 5, 10, 15, 20, 25, 35 Hz and  $F_{res}$ ). They also found that 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. On the other hand, Amra et al. (40) presented IOS data from 509 healthy Iranian children measuring R and X at 5, 15 and 20 Hz, and their prediction equations. In 2007, Wee et al (41) also presented a study about IOS Reference values for respiratory system Impedance for 92 children (7 to 12 years old). They obtained reference values for R and X, finding that height was the most significant predictor of R and X. They concluded that IOS is a feasible method to measure the respiratory resistance in children, and that they obtained reference IOS values that seemed to be useful to diagnose a variety of respiratory diseases. Finally in 2010 Jee et al. (42) presented a study about Reference values for healthy Korean children 3-6 years old, a total of 607 children were tested but only 143 children were successful in performing IOS. They used the following IOS parameters: R5, R10, X5, X10 and AX. They stated that their study suggested reference values for healthy Asian children aged 3-6 years, and that healthy young children had better results in IOS parameters than main reference values reported before.

Others studies have also been performed in adults to obtain reference values and elaborate predictive equations using the IOS.

Therefore, as stated before, this study is the first attempt to provide IOS reference values for healthy Anglo and Hispanic children 5 to 19 years old, and also presents baseline and post-



bronchodilation IOS values for Anglo and Hispanic children with Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI) and Asthma.

Table 3.4 IOS Reference Values

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. <b>Adult values of R and X can be observed at 15 years of age in girls and at 18 years in boys.</b>
Ducharme et al. [36]  1998	FOT	North American children (white,black,asian,others) 206 healthy children 3 to 17 years	<b>Height is the best predictor for total respiratory resistance at 8,12 and 16 Hz in children.</b>
Frei et al. [37] 2005	IOS	North American 222 white children 3 to 10 years old 100 to 150 cm in height	<b>Standing height was the only significant predictor for all variables</b> 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	<b>All variables were related to body height,</b> and most of them were weakly related to weight.
Nowowiejska et al. [39] 2008	IOS	Polish 626 healthy children aged 3-18	<b>Body height was the best predictor</b> 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	<b>These measurements can be used clinically to help diagnose and monitor respiratory disorders, independent of effort</b>
Wee et al. [41] 2007	IOS	Korean 92 children 7 to 12 years old	IOS is a feasible method to measure the respiratory resistance in children. <b>This reference values using IOS seems to be useful to diagnose a variety of respiratory diseases.</b>
Jee et al. [42] 2010	IOS	Korean children 143 3-6 years	<b>Healthy young children had better results in IOS parameters than main reference values reported before.</b>

## **Chapter 4: Respiratory System Models**

### **4.1 INTRODUCTION**

The IOS and FOT impedance curves can be correlated with respiratory system's electrical models with components analogous to the resistances, compliances and inertances inherent of the respiratory system. With specially designed algorithms, respiratory system component values can be estimated, and these estimated parameters could be used to assist physicians in the diagnosis and treatment of different respiratory diseases (43).

In this research we have special interest in the small airways diseases and asthma; an effective means to evaluate small airways performance could be achieved by integrating realistic models of lung function based on physiological measurements made by FOT or IOS and other techniques (80).

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 group 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) (44) (45) (46) (47) (48) (49) (50) (51).

This chapter is intended to give a brief summary of different respiratory system electrical circuit models, with special focus on the six models evaluated in our research efforts and to also to present a succinct review of the results obtained.

### **4.2 RESPIRATORY SYSTEM MODELS**

As stated before, several respiratory systems electrical circuit models have been developed and analyzed over the years. The simplest of these models are the Resistance-Capacitance (RC) and the

Resistance-Inductance-Capacitance (RIC), which have been studied by several researchers (81) (82). Other more sophisticated six-element model was presented by DuBois et al in 1956 (83) and has also been studied by other research groups like Eyles et al (84), Lutchen et al (85), and Lutchen (86). Mead suggested a seven-element model in 1961 (87) and a number of studies have also been developed to validate it (81) . Mead also presented a simplified model, a 5 element model, in 1969 (88), this model is referred by Diong et al as Mead 1969 model, and has been studied by different research groups as well (82) (84) .

Our research group developed two new models: extended RIC (eRIC) and augmented RIC (aRIC) model. The first one was conceived as an improvement of the RIC model, and the second one as an improvement of the eRIC model or as a simplification of the Mead seven-element or DuBois model. Also our research group has developed several studies to test and validate these new models against the previously mentioned models (RC, RIC, DuBois and Mead).

A summary of these mentioned models is given below:

**a) Resistance-Capacitance (RC) model:**

This is the simplest model to illustrate the respiratory mechanics; it consists of one alveolus with compliance ( $C$ ) and resistance ( $R$ ). In this model  $C$  comprises the elastic properties of the lungs and chest walls and  $R$  describes the airways flow resistance and the viscous properties of the tissue. According to Schmidt et al. (81) this model is typically used to determine lung mechanics from the measured signals, but is not appropriate for dynamic applications with higher frequencies, because the inertance of air and tissue are not included.  $R$  is typically given in  $\text{cmH}_2\text{O}/\text{L}/\text{s}$  or  $\text{kPa}/\text{L}/\text{s}$ , and  $C$  in  $\text{L}/\text{cmH}_2\text{O}$  or  $\text{L}/\text{kPa}$ .

The electrical circuit is shown in figure 4.1.



Figure 4.1 RC Model (47)

The impedance of this model can be calculated by the following equation:

$$Z = R - j/(\omega C) \quad [11]$$

where  $\omega=2\pi f$  and  $j = \sqrt{-1}$

**b) Resistance-Inductance-Capacitance (RIC) Model:**

This model differs from the RC model because of the addition of the inertance of air and tissue component represented by an electrical coil required for oscillatory studies (81). With  $R$  typically given in cmH<sub>2</sub>O/L/s or kPa/L/s,  $I$  in cmH<sub>2</sub>O/L/s<sup>2</sup> or kPa/L/s<sup>2</sup>, and  $C$  in L/cmH<sub>2</sub>O or L/kPa).

The electrical circuit representing this model is shown in figure 4.2.

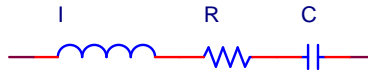


Figure 4.2 RIC Model (47)

The impedance of this model is calculated using the formula:

$$Z = R + j\left(\omega I - \frac{1}{\omega C}\right) \quad [12]$$

where  $\omega=2\pi f$  and  $j = \sqrt{-1}$

Schmidt et al. (81) developed a study using this RIC model about and presented a computer simulation of measured respiratory impedance in newborns using FOT data, concluding that FOT offers a deeper insight into the structure of the respiratory system.

Also in a previous study, in 1982, Eyles et al. (82) compared the performance of the RIC model with Mead's 1969 five-element model, concluding that the five-element model provided a better fit than the RIC model.

**c) DuBois' model:**

This model was presented by DuBois et al. in 1956; in the same study he developed to present for first time the basic principles of FOT (83). In this model the resistance, inductance and compliance is divided into different compartments. The model is composed of airway resistance ( $R_{aw}$ ), tissue resistance ( $R_t$ ), airway inductance ( $I_{aw}$ ), tissue inductance ( $I_t$ ), tissue compliance ( $C_t$ ) and alveolar compliance ( $C_g$ ). This model is illustrated in Figure 4.3.

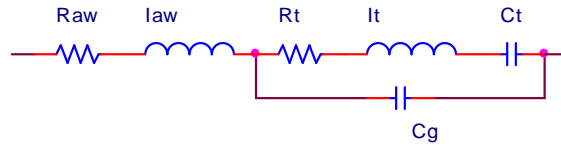


Figure 4.3 Dubois Model (47)

This model impedance is calculated as follows:

$$Z = R_{aw} + j\omega I_{aw} + \frac{R_t C_t^2 \omega^2}{(C_g C_t I_t)^2 \omega^6 + [C_g C_t (C_g C_t R_t^2 - 2I_t (C_g + C_t))] \omega^4 + (C_g + C_t)^2 \omega^2} - \frac{j\omega [C_g C_t^2 I_t^2 \omega^4 - C_t (2C_g I_t + C_t I_t - C_g C_t R_t^2) \omega^2 + (C_g + C_t)]}{(C_g C_t I_t)^2 \omega^6 + [C_g C_t (C_g C_t R_t^2 - 2I_t (C_g + C_t))] \omega^4 + (C_g + C_t)^2 \omega^2} \quad [13]$$

Eyles et al. (84) did a comparison between three different parallel compartment models of respiratory mechanics, with model 1 equivalent to Mead 1969, and model 2 to DuBois' model. This study ended with the conclusion that Model 1 (Mead 1969) presented the best interpretation of the forced random noise impedance data analyzed.

Lutchen et al. (85) and Lutchen et al. (86) also performed an analysis of different respiratory system's models, including DuBois' model. In the first study, they focused on the physiological interpretations based on lumped element models to fit respiratory impedance data, and in the second one the objective was to determine optimal frequencies for estimating parameters for respiratory impedance data.

**d) Mead's Model:**

Mead suggested a seven-element model in his study on mechanical oscillations of the lungs (87). According to Schmidt (81) this model allows the simulation of different factors affecting the respiratory system mechanics like extrathoracic compliance ( $C_e$ ) by the mouth and face mask, chest wall properties, air leaks generated around the face mask or endotracheal influences. Mead's model parameters are: inertance ( $I$ ), central and peripheral resistances ( $R_c$  and  $R_p$ ), lung, chest wall, bronchial tube, and extrathoracic compliances ( $C_l$ ,  $C_w$ ,  $C_b$ ,  $C_e$ ), as shown in figure 4.4.

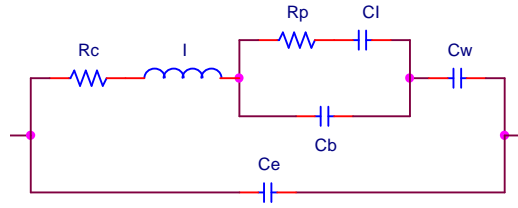


Figure 4.4 Mead's Model (47)

Mead's model impedance is calculated using the formula:

$$Z = \frac{-j}{\omega C_e} \parallel Z_m \quad [14]$$

where

$$Z_m = \frac{R_p C_l^2}{\omega^2 R_p^2 C_b^2 C_l^2 + (C_b + C_l)^2} + R_c + j \left( -\frac{\omega^2 R_p^2 C_b C_l^2 + C_b + C_l}{\omega [\omega^2 R_p^2 C_b^2 C_l^2 + (C_b + C_l)^2]} + \omega I - \frac{1}{\omega C_w} \right) \quad [15]$$

so

$$Z_R = \text{Re}(Z) = \frac{R_m}{1 - 2\omega C_e X_m + \omega^2 C_e^2 (R_m^2 + X_m^2)}$$

$$Z_X = \text{Im}(Z) = \frac{X_m - \omega C_e (R_m^2 + X_m^2)}{1 - 2\omega C_e X_m + \omega^2 C_e^2 (R_m^2 + X_m^2)} \quad [16]$$

A simplification of this model was named “Mead 1969” model (44) where the model has only five components,  $C_w$  and  $C_e$  are discarded from the previous model.

**e) 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  $I_t$  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 eRIC model is shown in Figure 4.5:

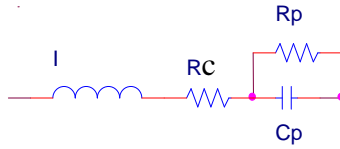


Figure 4.5 eRIC model (47)

The eRIC model impedance is calculated as follows:

$$Z = R_c + \frac{R_p}{1 + (\omega R_p C_p)^2} + j \left( \omega I - \frac{\omega R_p^2 C_p}{1 + (\omega R_p C_p)^2} \right) \quad [17]$$

**f) 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 4.6),

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).

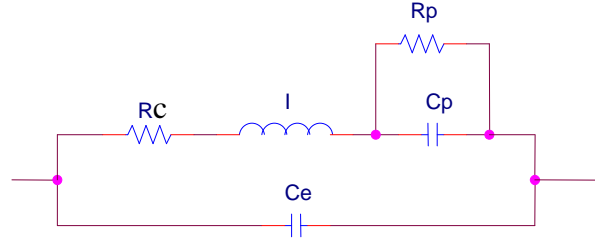


Figure 4.6 aRIC Model (47)

The aRIC impedance is given by:

$$Z = \frac{A(R_c A + R_p)}{\left[ A(1 - \omega^2 I C_e) + (\omega^2 R_p^2 C_p C_e) \right]^2 + \left[ \omega C_e (R_c A + R_p) \right]^2} + j \frac{\omega(I A - R_p^2 C_p) \left[ A - \omega^2 C_e (I A - R_p^2 C_p) \right] - \omega C_e (R_c A + R_p)^2}{\left[ A(1 - \omega^2 I C_e) + (\omega^2 R_p^2 C_p C_e) \right]^2 + \left[ \omega C_e (R_c A + R_p) \right]^2} \quad [18]$$

### 4.3 PREVIOUS STUDIES ABOUT eRIC AND aRIC MODELS

Several studies have been conducted by our research group to validate eRIC and aRIC models comparing their performance, in terms of total cumulative error, with other well-known models of the human respiratory system (RIC, Viscoelastic, Mead 1969, DuBois, and Mead) (43) (44) (45) (46) (47) (48) (49) (50) (51).

Diong et al. (43) conducted a study to compare RIC, Viscoelastic, DuBois, Mead with the eRIC respiratory model. Parameter estimates for these models were obtained with the objective of comparing their performance. Parameter estimates were obtained from IOS data in two groups of subjects, (1) five



adults with mild obstructive lung disease (bronchiectasis) and 5 healthy adults, and (2) Three asthmatic children and one healthy child. The eRIC model ranked in the middle in terms of magnitude of modeling error in the four groups of subjects, even though it offered more realistic values than Mead's model which presented the least estimation errors for this data.

Diong et al. (44) presented a new model called aRIC model, comparing its performance with the RIC, Mead 1969, DuBois', Mead's and the eRIC models. They analyzed data from 37 asthmatic children (2-5 years old), pre- and post-bronchodilation data, 10 adults diagnosed with chronic obstructive pulmonary disease (COPD) and 10 adults with no identifiable respiratory disease. The aRIC model was 13.77-66.6% more accurate than the eRIC model at fitting the analyzed data, while its parameter estimates ranked again in the middle in terms of modeling error, and it offered the advantage, similarly to the eRIC model in the previous study, of producing more realistic values than Mead 1969, DuBois' and Mead's models. This research group also presented a parameter, the peripheral airway compliance ( $C_p$ ), as statistically significant discriminator between unconstructed and constricted conditions in asthma and COPD.

Woo et al. (51) performed a similar study comparing RC, RIC, the eRIC, Mead's, Dubois' and Viscoelastic models. Their dataset was comprised of 106 subjects with various respiratory diseases like asthma and COPD. They concluded that the DuBois' and the eRIC models seemed to provide the most robust parameter estimates for this data.

Baswa et al (48) analyzed the same six models as Woo et al [46], in 5 subjects with airflow obstruction including asthma or COPD and 5 normal subjects. They stated that Mead's model seemed to provide the most robust and accurate parameter estimates for this population, but this model's parameter estimates for both groups of subjects were not realistic, while those for the eRIC model were more so.

Rajagiri et al. (46) analyzed data from 5 adults with bronchiectasis and 5 adults with no known respiratory diseases, and 105 patients (13 to 85 years old) diagnosed with a respiratory disease like asthma, COPD and sarcoidosis, comparing the performance of the RIC, eRIC, DuBois', Mead's and the aRIC models. They similarly observed that Mead's model yielded the best fit, however it again produced unrealistically large values for lung compliance and chest wall compliance. On the contrary

aRIC produced more in line parameter estimates with what is physiologically expected, even though this model presented a little larger estimation error than the Mead's Model.

Rajagiri et al. (47) presented a similar study but analyzed the performance of the same models in Australian children data, 168 children 2 to 8 years old diagnosed with asthma, and 193 children with the same age range with no known respiratory disease. DuBois' model produced the least estimation error, and the aRIC model ranked in the middle in terms of magnitude of modeling error for this data. However, similarly to previous studies, DuBois' and Mead's models produced unrealistically large values for lung compliance ( $C_l$ ), chest wall compliance ( $C_w$ ), and tissue compliance ( $C_t$ ).

Rajagiri et al. (45) did a similar study analyzing 156 tests of children with asthma and 173 tests of healthy children, comparing the same models as their previous study [42]. The aRIC model again ranked in the middle of the other analyzed models, while DuBois' model showed the best fit, but Mead's and DuBois' models again produced unrealistic values for  $C_l$  and  $C_w$  and  $C_t$ . Their results suggested that the capacitance parameter ( $C_p$ ) of the aRIC model provides good discrimination between these two groups, and they affirmed that this finding corresponded well with asthma physiology.

Nguyen T-U et al. (49) (50) presented two new respiratory system models: the Mead- $C_w$  and the Mead- $C_l$ , which are intermediate in complexity between the Mead's model and the aRIC model. These two models were compared with the RIC, eRIC, aRIC and Mead's models. IOS data from 5 adults diagnosed with COPD and 8 normal adults were used. They showed that these two new models produced lower errors than all other models, except for the Mead's model. However, these two models also showed unrealistic values for  $C_w$  and  $C_l$ . Therefore, this study concluded that the aRIC model seems to be the most useful respiratory model for IOS-based computer aided detection and diagnosis of lung pathologies.

All these research studies (summarized in Table 4.1) confirm that the eRIC and aRIC models are two respiratory models that offer advantages over other well-known respiratory models to be used in assessment and treatment of asthma or other respiratory diseases. Consequently, this research aims to quantitatively evaluate the performance of the eRIC and aRIC models in Normal, PSAI, SAI and Asthmatic Anglo and Hispanic children 5 to 19 years old.

Table 4.1 summarizes the previous studies on the aRIC and eRIC models performance.

Table 4.1 Previous studies about the aRIC and eRIC performance

Researchers	Evaluated Population	Model Evaluated	Conclusions
Diong et al. [38]	5 adults with bronchiectasis 5 healthy adults 3 asthmatic and one healthy child	<b>eRIC</b> RIC Viscoelastic DuBois Mead	<b>eRIC ranked in the middle</b> in terms of magnitude of modeling error in the four groups of subjects, but it offered more realistic values than Mead's model which offered the least estimation errors.
Diong et al. [39]	37 asthmatic children (2-5 years old) pre- and post- data 10 adults with COPD 10 healthy adults	<b>aRIC</b> <b>eRIC</b> RIC Mead 1969 DuBois Mead	<b>aRIC was 13.77-66.6% more accurate than eRIC model at fitting the data.</b> <b>aRIC parameter estimates ranked in the middle</b> in terms of modeling error, aRIC produced more realistic values than Mead 1969, DuBois' and Mead's models
Woo et al. [46]	106 subjects various respiratory diseases like asthma and COPD	<b>eRIC</b> RC RIC Viscoelastic DuBois Mead	<b>DuBois' and the eRIC models</b> provided the <b>most robust parameter estimates</b> for this data
Baswa et al [43]	5 subjects with airflow obstruction like asthma or COPD and 5 normal subjects	<b>eRIC</b> RC RIC Viscoelastic DuBois Mead	Mead's model provided the most robust and accurate parameter estimates, but some of these parameters were not realistic, while <b>eRIC parameters were more reasonable</b>
Rajagiri et al. [41]	5 adults with bronchiectasis and 5 healthy adults 105 patients with respiratory diseases	<b>aRIC</b> <b>eRIC</b> RIC DuBois Mead	Mead's model yielded the best fit however it again produced unrealistically large values for lung compliance (CI) and chest wall compliance (Cw). <b>aRIC produced more in line parameter estimates,</b> and <b>a little larger estimation error than the Mead's Model</b>
Rajagiri et al. [42]	168 children with asthma 193 normal children	<b>aRIC</b> <b>eRIC</b> RIC DuBois	DuBois' model produced the least estimation error the <b>aRIC model ranked in the middle</b> . DuBois' and Mead's models produced unrealistically large values CI and Cw and

		Mead	and tissue compliance (Ct).
Rajagiri et al. [40]	156 tests of children with asthma and 173 tests of normal children	aRIC	<b>aRIC again ranked in the middle</b>
		eRIC	DuBois' model showed the best fit
		RIC	Mead's and DuBois' models again produced
		DuBois	unrealistic values for Cl, Cw and Ct.
		Mead	<b>C<sub>p</sub> of the aRIC model provides good discrimination</b>
Nguyen T-U et al. [44, 45]	5 adults diagnosed with COPD and 8 normal adults	aRIC	Mead-Cw and Mead-Cl produced lower errors
		eRIC	than all other models, except for the Mead's model
		Mead-C <sub>w</sub>	however they showed unrealistic values for C <sub>w</sub> and C <sub>i</sub>
		Mead-Cl	<b>aRIC model seems to be the most useful</b>
		RIC	<b>respiratory model</b>
		Mead	

#### 4.4 PARAMETER ESTIMATION TECHNIQUE

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

For this research the eRIC (R<sub>c</sub>, I, R<sub>p</sub> and C<sub>p</sub>) and aRIC (R<sub>c</sub>, I, R<sub>p</sub>, C<sub>p</sub> and C<sub>e</sub>) respiratory models parameters were estimated using the average values of Resistances and Reactances from 5 to 25 Hz (R5, R10, R15, R20, R25, X5, X10, X15, X20 and X25) for each child tested.

In Table 4.2 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. This IOS data was recorded before and after the use of a bronchodilator (pre-B and post-B). In Table 4.3 an example of the model parameters calculated for the same child is given.

Table 4.2 Respiratory system's resistance and reactance values for a healthy male child.

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 4.3 Model parameters calculated for a healthy male child

<b>pre-B</b>	<b>aRIC</b>	<b>Rc</b>	<b>Rp</b>	<b>I</b>	<b>Cp</b>	<b>Ce</b>	<b>eRIC</b>	<b>Rc</b>	<b>Rp</b>	<b>I</b>	<b>Cp</b>
		0.256	0.209	0.001	0.233	0.004		0.277	0.314	0.0007	0.282
<b>post-B</b>	<b>aRIC</b>	<b>Rc</b>	<b>Rp</b>	<b>I</b>	<b>Cp</b>	<b>Ce</b>	<b>eRIC</b>	<b>Rc</b>	<b>Rp</b>	<b>I</b>	<b>Cp</b>
		0.245	0.239	0.001	0.241	0.004		0.274	0.58	0.0008	0.289

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 criterion (LS) was selected as follows:

$$E = \sum [Z_R(f) - Z_{R,est}(f)]^2 + [Z_x(f) - Z_{x,est}(f)]^2 \quad [19]$$

where  $f = 5, 10, 15, 20, 25$

This LS criterion was used to minimize the sum of the squared errors between the measured IOS  $Z_R$  and  $Z_x$  and the estimated resistive  $Z_{R,est}$  and the estimated reactance  $Z_{x,est}$ . 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).

Because of the nonlinear dependence of the aRIC and eRIC impedance functions on the parameters, the Matlab lsq-nonlin (nonlinear LS) was used in both models algorithms, which are based upon 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 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 provides at the end a measure of the goodness of fit to the given test data for each model (44).

## **Chapter 5: Methods**

### **5.1 INTRODUCTION**

This chapter provides an explanation of the methodology of this research project was designed, the statistical analysis used, the selection of subjects (children) recruited for this research, as well as how every IOS was used to acquire high quality respiratory impedance data.

### **5.2 RESEARCH METHOD DESIGN AND STATISTICAL ANALYSIS**

This study was developed to perform IOS pulmonary function testing 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. The IOS data collected for this research were analyzed by our expert clinician and classified into four categories: Normal, Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI) and Asthma.

The data were collected in 2006 and 2008. The data collected in 2006 were pre-bronchodilation data, and the data collected in 2008 were pre- and post-bronchodilation data. 112 children were tested in 2006 and 47 children in 2008, 26 of these children were tested in both years. 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 by our expert clinician 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 like previously described for 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 it 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 tests).

This research study was supported in part by NIH grant #1 S11 ES013339-01 A1: UTEP-UNM HSC ARCH Program on Border Asthma. The ARCH program provided a questionnaire about asthma or allergy symptoms to be filled out and signed by participating children 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 Means) test and statistical significance will be established at  $p < 0.05$  level.

### **5.3 HUMAN SUBJECT INTERACTIONS**

#### **1. Sources of Participants**

Medical staff of the Western Sky Medical Research clinic were in charge of contacting the children' participating children's parents and making appointments for lung function testing IOS and data collection. Some of the 2006 IOS data were collected from children attending the Socorro High School Health Fair who wished to participate in our research study.

#### **2. Procedure for Obtaining Informed Consent**

An informed consent form was given to every parent and child providing them with a detailed description of the study. The parents or children over 18 were asked to sign the consent form if they agreed to participate in this study.

### **5.4 IOS TESTS PROCEDURE**

The following is a detailed explanation about how IOS testing was performed for this research:

- a. Turn on the computer and double-click the LAB Jaeger Lab Manager Icon and you will be placed in the initial (start up) IOS screen. Wait 5 minutes to allow the system to warm up. You will automatically be placed into the main screen.
- b. Look at the bottom of the main screen and you will find several tabs: Main group, Data Base, Calibrations, Generation, and Utilities.

- c. The first thing you need to do is the Calibration of the equipment, double click the Calibration tab and do the required Volume and Pressure Calibrations, these calibrations have to be done every day before using the IOS equipment. A detailed explanation of how to perform these calibrations is presented in appendix A.
- d. Then go back to the main screen and go to Patient data screen and enter the personal data of the subject you want to test: first and last name, identification number, date of birth, sex, height and weight. If you are testing a child already tested, just enter the patient's last name and tap the enter key three times to find his/her information.
- e. Click F10 to go back to the main IOS screen. Check that the first and last names of the patient you are testing are on the top of the main IOS screen.
- f. Tell the subject that you are going to test his/her normal breathing through his/her mouth, and in order to do this you need them to wear a nose clip to close their nostrils. Emphasize that it is extremely important that all his/her breathing air goes through his/her mouth and the nose must be completely occluded with the nose clip to avoid air leakage and mistakes in the measurement.
- g. For the purpose of this project the children tested were from 5-19 years old. There are two different mouthpieces sizes. Use the appropriate according to the age and mouth size of the child.
- h. If you are using the small mouth piece, ask the child to put his/her tongue underneath the mouthpiece to keep it out of the air flow. After this, ask them to tightly close his/her mouth around the mouthpiece, double-check that their mouths be sealed around the mouthpieces (no air leakage). It is a big help if you put a mouthpiece in your mouth and show the children how to place it.
- i. If the child is using the big mouthpiece, ask the child to put the tip of his/her tongue under the tongue depressor to keep it out of the way. Ask the child to bite the two bite blocks of the mouthpiece and ask them to place the flange between his/her gums and lips, the flange should be inside his/her lips but outside teeth. Double-check that their mouths



be sealed around the mouthpieces (no air leakage). It is a big help if you put a mouthpiece in your mouth and show the children how to place it.

- j. Ask the child to sit comfortably, but ask them to have a straight back and neck, hands and arms under his/her thighs (uncrossed), straight legs (uncrossed), feet on the floor (if they can reach the floor) and ask them not to move during the test. Verify the correct position of the children.
- k. Tell the child you are going to do around 4 or 5 tests that last around 20 seconds each. This way you ensure you will have at least 3 good tests and the child knows what to expect. For a small child, it helps if you actually count the seconds out loud during the test, to help them to be calm and wait until you reach the number 20.
- l. If you are doing the test in a house ask the mother or father to allow you to place the equipment in front of the television. The television will occupy the attention of the children and help them to relax and focus on the television program they choose; this way they will breathe normally without paying attention to it; which is the way we normally breathe.
- m. If you are doing a test in a clinic or set environment without television, ask the child to close his/her eyes and think about something they really like during the test (20 or 30 seconds).
- n. Place a new filter to the 45 degrees angle tube and connect the mouthpiece chosen for the child at the end of the filter using a plastic glove and ensure the attachments be airtight. Put the mouthpiece in front of the child and support arm of the equipment (with the filter and mouthpiece on it).
- o. Ask the child to place the mouthpiece in her/his mouth and check his/her correct position (back and neck straight). Do the appropriate movements to obtain the position required. Once you finish placing the child in the optimal position, ask him/her to get the mouthpiece out of his/her mouth.

- p. Move the support arm of the equipment away from the child face prior to the first 5 seconds to allow the equipment to realize the zero adjustment.
- q. It is convenient to hide the IOS screen from the child to avoid distractions or intentional changes in children breathing to obtain good tests results.
- r. Double click on Impulse Oscillometry Icon to begin the IOS test, and you will see a dialog box asking you not to approach the mouthpiece to do the zero adjustment.
- s. Ask the child to feel the popping through the mouth piece with his/her hand for few seconds, and let him/her know he/she will feel this popping while he/she breathes during the test but it will not cause any harm or pain.
- t. Ask the child to place the mouthpiece and nose clip in his/her mouth and nose to begin the test.
- u. Through the test duration look at the child's face and verify tight closure of the lips around the mouthpiece and correct position of the nose clip. Ask the child to focus on the TV program or in thinking about something they really like with closed eyes (in case you do not have a TV in front of the children). This way, they will forget about breathing and begin to breathe normally.
- v. Wait a few seconds until you see repeatable breathing cycles on the IOS screen (breathing stabilization). After this, click icon 2 to begin test recording.
- w. Record the test for 20 seconds for small children and for 30 to 40 seconds for older children and then terminate the test by clicking icon 7.
- x. In the volume tracing you should see breaths of comparable size. If you see an abrupt increase in Z5 during the test it may indicate a swallow. Ask the children to avoid swallowing if possible during the test, and before each test ask them to swallow several times to avoid swallowing during the test.
- y. Verify the Coherence graph in the left bottom window for quality assurance, coherence should be 0.7 to 0.8 at 5 Hz and rise to 0.9 on 10Hz, and then progressively increase to

- 1.0 at higher frequencies. If you forget to ask the child to use the nose clip or if there is an air leakage from the children mouths, you will see an artificial increase in Coherence.
- z. In the top left window you will see a Resistance graph (R vs. frequency), “for healthy adults or older children R line should remain nearly constant during all oscillation frequencies”.
  - aa. In the middle left window, Reactance graph (X), you will observe a diagram of X vs. frequency. “The X tracing for healthy adults or older children ought to start slightly below zero at the left of the graph, and increase crossing zero at 7-12 Hz”.
  - bb. You can visualize the values measured (numbers) for R, X, AX,  $F_{res}$  and Coherence at the top right window.
  - cc. Check the test for airflow leak pressing icon 4; this will bring you up a “save measurement” dialog box. **Ensure that new test have a black dot on the left, and save primary data and check default small boxes (this is extremely important to save the data).** Click on Yes to save the test data. This will show you the test directory which tells you how many tests you have done on the child you are testing. Highlight the last test and click ok. This will bring you up the raw data; amplify a small portion (containing at least one inhalation and one expiration) of the volume blue trace by placing the mouse in a point, holding the left mouse and moving the cursor to a second point, and check for corrugations. **Airflow leak is manifest when the corrugations appear during inspiration, near end-inspiration and during early expiration.**
  - dd. Repeat the IOS test 4 or 5 more times, to make sure you get at least three good tests, and save each test as a “new test”.

A detailed explanation about archiving IOS data, how to define where the data is being saved in the computer, how to back up the IOS data recorded to be transfer to another computer, or to simply do a back up on a USB, can be found in appendix A.

## Chapter 6: Results and Discussions





### 6.1 INTRODUCTION

In this chapter the obtained results in this research will be presented and discussed on detail. Every result will be related to its specific hypothesis. First the results obtained from the analysis of the Pre-B data recorded in 2006 will be presented in relation to hypothesis 1: “Base line IOS values of Resistance, Reactance, Fres or AX and IOS calculated values as R3-R20 and R5-R20 predict changes after bronchodilation in Normal, PSAI, SAI, and Asthmatic children”; and then results of analysis of the Pre- and Post-B data recorded in 2008 related to hypothesis 2 will be presented: “The eRIC and aRIC models of lung function based on IOS measurements yield estimates of lung resistance and compliance that can quantify respiratory mechanics to discriminate between normal, PSAI, SAI and asthmatic children”.

Finally the results associated with hypothesis 3 will be presented: “The expected growth-related improvement in IOS and the eRIC/aRIC parameter estimates will be greater in Normal/PSAI children than in SAI/Asthmatic children”.

Also in this section a detailed explanation will be given on how the goals and proposed work of this research were addressed.

Goals of the project are:

-  Create a database of Normal, PSAI, SAI, and Asthma IOS impedance values (judged by physiologist) and the eRIC and aRIC model values for baseline and post-bronchodilation conditions.
-  Determine statistical significance of differences between pre- and post- bronchodilation IOS data for all IOS parameters as well as the eRIC and aRIC model parameters for Normal, PSAI, SAI and children with asthma.
-  Evaluate the performance of the IOS and the eRIC/aRIC model parameters in evaluating lung function over time (two years periods).
-  Evaluate statistical correlation between different IOS and model parameters.

- ✚ Compare the performance of the eRIC/aRIC model-derived parameters calculated from IOS data over 5 - 35 Hz and 3 – 25 Hz.

For this research the following work was proposed (Proposed Work):

- ✚ A database of Normal, PSAI, SAI, and Asthma IOS impedance values (judged by physiologist) and the eRIC and aRIC model values for baseline and post-bronchodilation conditions will be created for the 112 children tested under pre-bronchodilation conditions and for the 47 children tested under pre and post bronchodilation conditions.
- ✚ Statistical significance of differences between pre- and post- bronchodilation IOS data for all IOS parameters Resistances and Reactances from 3 to 25 Hz,  $F_{res}$ , AX and the eRIC and aRIC model parameters for Normal, PSAI, SAI and Asthmatic children will be determined.
- ✚ The performance of the IOS and models parameters in evaluating lung function over time (two years period) will be evaluated in 26 children tested in both years (2006 and 2008).
- ✚ Statistical correlation between different IOS and model parameters will be evaluated.
- ✚ A comparison of the performance of model-derived parameters calculated from IOS data over 5 - 35 Hz and 3 – 25 Hz will be performed.

## 6.2 RESULTS AND DISCUSSIONS FROM HYPOTHESES 1, 2

### Hypothesis 1

- ✚ **“Baseline IOS values of Resistance, Reactance,  $F_{res}$  or AX and IOS calculated values as R3-R20 and R5-R20 predict changes after bronchodilation in normal, PSAI, SAI, and Asthmatic children”.**

### Hypothesis 2

- ✚ **“The eRIC and aRIC models of lung function based on IOS measurements yield estimates of lung resistance and compliance that can quantify respiratory mechanics to discriminate between Normal, PSAI, SAI and asthmatic children”.**

### 6.2.1 Previous Prebronchodilation work

The IOS data collected in 2006 from children for this PhD study were analyzed and presented in several publications (89) (90) (91) (92) (93) (94).

In the following paragraphs a description of the analyses and publications, performed for this research, with the IOS data, calculated parameters, and the eRIC and aRIC model parameters collected in 2006 will be presented.

The publications are:

#### 1. “Modeling Human Respiratory Impedance in Anglo Asthmatic Children” (89).

In the first published study in 2007 (89) the IOS data collected from 19 Anglo asthmatic children 5 to 15 years old were analyzed and presented. The IOS parameters analyzed were  $R_5$ ,  $R_5-R_{15}$ ,  $AX_{\text{measured}}$ ,  $AX_{\text{calculated}}$ ,  $F_{\text{res}}$  and the eRIC/aRIC model parameter estimates were obtained for this children group. The  $AX_{\text{calculated}}$  formula and analysis were previously presented by Diong et al. (43).

All IOS data acquired from males and females were *analyzed in order to determine any gender differences* between the two groups. Mean  $\pm$  SD of measured and calculated values for males and females are presented in Table 6.1. Although most values were numerically larger in males than females, only  $R_5-R_{15}$  showed a *significant difference* between these groups.

Table 6.1 IOS Measurements and Calculated Values

IOS Measurements and Calculated Values				
Parameter	Males		Females	
	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD
$R_5$ (cmH <sub>2</sub> O/L/s)	5.15 - 9.53	7.37 $\pm$ 1.49	4.83 - 8.09	6.59 $\pm$ 1.23
$R_5-R_{15}$ (cmH <sub>2</sub> O/L/s)	1.50 - 4.92	2.94 $\pm$ 1.00	1.02 - 3.30	2.07 $\pm$ 0.74
$AX_{\text{measured}}$ (cmH <sub>2</sub> O/L)	13.00 - 44.23	25.99 $\pm$ 10.2	8.82 - 28.59	18.1 $\pm$ 7.75
$AX_{\text{calculated}}$ (cmH <sub>2</sub> O/L)	11.64 - 45.02	24.16 $\pm$ 10.33	9.42 - 26.24	17.3 $\pm$ 6.73
$F_{\text{res}}$ (1/s)	17.68 - 23.3	20.24 $\pm$ 1.50	16.94 - 21.48	19.81 $\pm$ 1.55

The parameters for the aRIC ( $R$ ,  $R_p$ ,  $I$ ,  $C_p$ , and  $C_e$ ) and the eRIC ( $R$ ,  $R_p$ ,  $I$ , and  $C_p$ ) models were estimated using average resistance and reactance values of the IOS parameters at different frequencies (5, 10, 15, 20, 25, and 35 Hz) for 19 Anglo/asthmatic children. These parameter estimation calculations were carried out by using number of algorithms developed by our group. **Model parameters of both the aRIC model ( $R$ ,  $R_p$ ,  $I$ ,  $C_p$  and  $C_e$ ) and the eRIC model ( $R$ ,  $R_p$ ,  $I$ ,  $C_p$ ) showed no significant**

**differences between males and females**, hence they were combined to represent the Anglo/asthmatic children. Mean values for estimated parameters for respiratory models, t-value and the outcome of statistical t-tests between models parameters are presented in Table 6.2. The correlation coefficient between  $AX_{\text{measured}}$  and  $AX_{\text{calculated}}$  was equal to 0.988.

Table 6.2 Estimated Parameters for Anglo/Asthmatic children

Estimated parameters for Anglo/asthmatic children				
	R	$R_p$	I	C
aRIC	0.34733	0.60581	0.00202	0.04042
eRIC	0.43715	0.70941	0.00118	0.06287
t-value	-3.9	-1.18	7.3	-3.84
Significance	Yes	No	Yes	Yes

The **conclusions** were that **R5-R15 (frequency-dependence of resistance)** seemed to be a **sensitive index to gender differences in lung function between asthmatic males and females in Anglo subjects**. A high correlation between  $AX_{\text{measured}}$  and  $AX_{\text{calculated}}$  values was observed, indicating that  $AX_{\text{calculated}}$  is a good approximation to the measured AX value. **As significant differences were found between the eRIC and aRIC model parameters**, future work is necessary to compare these data with data from normal Anglo/non-asthmatic children (or using data from the same group, as their own control, after bronchodilation) to determine which model performs better in discriminating between Anglo/asthmatic and Anglo/non-asthmatic children.

## 2. “Modeling Human Respiratory Impedance in Hispanic Asthmatic children 5 to 17 Years Old” (90).

IOS data from 6 Hispanic children diagnosed with asthma were analyzed for this research. The following IOS parameters were used in this investigation: R5 (Resistance at 5 Hz), R5-R15 (index of frequency- dependence of resistance), AX (Reactance Area), Fres (Resonant Frequency). The average values of the IOS parameters (Resistance and Reactance at frequencies 5, 10, 15, 20, 25 and 35 Hz) were used to estimate the model parameters for the eRIC and aRIC models. Mean, standard deviation and range values of measured and calculated values obtained from the IOS are presented in Table 6.3.

Table 6.3 IOS Measurements

IOS Measurements N=6		
Parameter	Range	Mean $\pm$ SD
<b>R5</b> (cmH <sub>2</sub> O/L/s)	7.92-10.45	8.9 $\pm$ 0.9
<b>R5-R15</b> (cmH <sub>2</sub> O/L/s)	2.14-4.33	3.3 $\pm$ 0.8
<b>AX</b> (cmH <sub>2</sub> O/L)	22.77-41.15	32.3 $\pm$ 5.7
<b>Fres</b> (1/s)	20.15-22.17	21.0 $\pm$ 0.7

The calculated parameters for eRIC and aRIC respiratory models, are shown in Table 6.4.

Table 6.4 Model parameters

Estimated parameters					
	R (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s <sup>2</sup> )	Cp (l/kPa)	Ce (l/kPa)
<b>aRIC</b>	0.43118	0.79303	0.00242	0.03006	0.00276
<b>eRIC</b>	0.53150	0.94306	0.00140	0.04344	

The **conclusions** of this paper were that the range of values of the **measured and estimated IOS parameters**: R5, R5-R15, AX and Fres, and parameters for aRIC and eRIC models obtained for this group **were comparable to those values observed in other asthmatic children of the same age range.**

### 3. “Modeling Human Respiratory Impedance in Normal Children 5 to 17 Years Old” (91).

For this research we used IOS parameters that have been previously reported to be sensitive measures for detection of changes in bronchomotor tone and peripheral airway obstruction in asthmatic children. These parameters were: R5 (Resistance at 5 Hz), R5-R15 (index of frequency-dependence of resistance), AX (Reactance Area) and resonant Frequency (Fres).

The aRIC model parameters (R, Rp, I, Cp, and Ce) were calculated using IOS data from each child (averaged values of Resistance and Reactance at 5, 10, 15, 20, 25 and 35 Hz).

Using previously collected data from asthmatic Anglo and Hispanic children, we compared the present model parameter data from non-asthmatic (“normal”) Anglo and Hispanic children with those from asthmatic Anglo and Hispanic children. **Our aim was to determine whether normal parameters were statistically significantly different from asthmatic parameters.** IOS data from 5 Anglo (one female and 4 males) and 6 Hispanic (2 females and 4 males) non-asthmatic children were collected for



this research. The IOS measurements for the normal group are shown in Table 6.5. The IOS parameters selected for this study, and model parameters calculated were chosen to correspond to previously published asthmatic IOS and model parameters. Student t-distribution test and a statistical significance at  $p < 0.05$  were used.

Using the aRIC model **statistically significant differences between Anglo nonasthmatic (normal) and Anglo asthmatic children** (see Table 6.6) were found for **R, Rp, I, and Cp** parameters. Similarly, **statistically significant differences in the same model parameters between normal Hispanic and asthmatic Hispanic children were found** (see Table 6.7). The differences between normal and asthmatic small airway parameters (Rp, Cp) were greater than a factor of 2, and were relatively larger than differences between normal and asthmatic large airway parameters (R, I) in both Anglo and Hispanic groups. **It was concluded that the aRIC model allows clear discrimination between normal and asthmatic Anglo and Hispanic children.**

Table 6.5 IOS Measurements for the Normal Children

IOS Measurements				
Parameter	Anglo N=5		Hispanic N=6	
	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD
<b>R5</b> (cmH <sub>2</sub> O/L/s)	2.80-5.74	4.02 $\pm$ 1.07	3.11-5.10	4.13 $\pm$ 0.69
<b>R5-R15</b> (cmH <sub>2</sub> O/L/s)	0.36-0.78	0.59 $\pm$ 0.15	0.31-0.76	0.60 $\pm$ 0.16
<b>AX</b> (cmH <sub>2</sub> O/L)	1.94-5.61	3.56 $\pm$ 1.44	3.16-5.61	3.88 $\pm$ 0.85
Fres (1/s)	9.55-16.82	12.79 $\pm$ 2.58	11.39-14.11	13.44 $\pm$ 2.13

Table 6.6 Estimated Parameters for the Anglo Group Using aRIC Model

Estimated Parameters for Anglo Group using aRIC model						
		R (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s <sup>2</sup> )	Cp (l/kPa)	Ce (l/kPa)
<b>Non-Asthmatic N=5</b>	mean	0.28124	0.24128	0.00136	0.14342	0.00313
<b>Asthmatic N=19</b>	mean	0.34733	0.60581	0.00202	0.04042	0.00353
	<b>t</b>	-1.86328	-3.35880	-3.15879	6.77500	-1.24789
	<b>Significance</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>

Table 6.7 Estimated Parameters for the Hispanic group using aRIC Model

Estimated Parameters for Hispanic Group using aRIC model						
		R (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s <sup>2</sup> )	Cp (l/kPa)	Ce (l/kPa)
<b>Non-Asthmatic N=6</b>	mean	0.31107	0.38278	0.00130	0.14208	0.00291
<b>Asthmatic N=6</b>	mean	0.43118	0.79303	0.00242	0.03006	0.00276
	t	-3.81489	-3.85550	-5.36106	5.64820	0.50732
	<b>Significance</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>No</b>

#### 4. “Impulse Oscillometric Features of Lung Function: Towards Computer-Aided Classification of Respiratory Diseases in Children” (92)

IOS data from 76 children were used for this investigation. Mean  $\pm$  SD and range values are presented in Table 6.8 for the Studied Population.

Table 6.8 Study Population

Study Population		
	Range	Mean $\pm$ SD
<b>Age</b> (years)	5-17	10.6 $\pm$ 3.7
<b>Height</b> (cm)	106.4-183.4	145.2 $\pm$ 20.7
<b>Weight</b> (kg)	16.8-93.8	43.6 $\pm$ 19.2

For automatic classification of IOS respiratory patterns those IOS parameters that have been previously reported to be sensitive measures for detection of peripheral airway obstruction: R5, R5-R15, and AX (8), Fres and the aRIC model parameters were selected.

After detailed re-analysis of all IOS test data, 11 children were considered to be "normal", 17 to possibly have Mild Small Airway Disease (PSAD), 29 to manifest definite SAD and 19 to manifest IOS data characteristic of asthma. Children in the SAD and Asthmatic groups were all of Anglo ethnic background, while those in the normal and possible SAD groups included those with either Anglo or Hispanic ethnic background.

A total of 9 features was considered to be used for computer-assisted classification of asthmatic data in children based on IOS measurements. Mean  $\pm$  standard deviation and range values for each feature, obtained from IOS data and model parameters, are shown in Table 6.9 for normal children, in

Table 6.10 for those with possible SAD (PSAD), in Table 6.11 for children with SAD, and in Table 6.12 for those with Asthma.

Table 6.9 IOS Measurements and Model Parameters for the Normal Children

IOS Measurements and Model Parameters		
Normal Group N=11		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.28-0.56	0.40 ± 0.09
<b>R5-R15</b> (kPa/l/s)	0.03-0.08	0.06 ± 0.01
<b>AX</b> (kPa/l)	0.19-0.55	0.37 ± 0.11
<b>Fres</b> (1/s)	9.55-17.39	13.14 ± 2.36
<b>Rc</b> (kPa/l/s)	0.1917-0.4029	0.2975 ± 0.0610
<b>Rp</b> (kPa/l/s)	0.0881-0.7953	0.3185 ± 0.1682
<b>I</b> (kPa/l/s <sup>2</sup> )	0.0008-0.0019	0.0013 ± 0.0003
<b>Cp</b> (l/kPa)	0.0481-0.2272	0.1427 ± 0.0510
<b>Ce</b> (l/kPa)	0.0024-0.0043	0.0030 ± 0.0006
<b>Cp/Rp</b> (l <sup>2</sup> /kPa <sup>2</sup> s)	0.1549-1.9620	0.5856 ± 0.4758

Table 6.10 IOS Measurements and Model Parameters for the PSAD Children

IOS Measurements and Model Parameters		
Possible SAD group N=17		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.35-0.70	0.49 ± 0.11
<b>R5-R15</b> (kPa/l/s)	0.07-0.28	0.12 ± 0.06
<b>AX</b> (kPa/l)	0.42-2.01	0.87 ± 0.49
<b>Fres</b> (1/s)	13.35-19.02	16.70 ± 1.89
<b>Rc</b> (kPa/l/s)	0.2223-0.5578	0.3175 ± 0.0793
<b>Rp</b> (kPa/l/s)	0.2284-0.8014	0.3884 ± 0.1561
<b>I</b> (kPa/l/s <sup>2</sup> )	0.0010-0.0020	0.0015 ± 0.0003
<b>Cp</b> (l/kPa)	0.0393-0.1411	0.0858 ± 0.0307
<b>Ce</b> (l/kPa)	0.0020-0.0038	0.0030 ± 0.0006
<b>Cp/Rp</b> (l <sup>2</sup> /kPa <sup>2</sup> s)	0.0697-0.4857	0.2666 ± 0.1438

Table 6.11 IOS Measurements and Model Parameters for the SAD Children.

IOS Measurements and Model Parameters		
SAD group N=29		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.38-0.85	0.62 ± 0.13
<b>R5-R15</b> (kPa/l/s)	0.05-0.41	0.22 ± 0.09
<b>AX</b> (kPa/l)	0.46-3.15	1.76 ± 0.71
<b>Fres</b> (1/s)	15.78-23.23	18.55 ± 1.74
<b>Rc</b> (kPa/l/s)	0.2404-0.4813	0.3384 ± 0.0659

<b>Rp</b> (kPa/l/s)	0.2964-1.1517	0.5659 ± 0.1998
<b>I</b> (kPa/l/s <sup>2</sup> )	0.0010-0.0025	0.0018 ± 0.0004
<b>Cp</b> (l/kPa)	0.0279-0.1560	0.0543 ± 0.0247
<b>Ce</b> (l/kPa)	0.0017-0.0044	0.0032 ± 0.0006
<b>Cp/Rp</b> (l <sup>2</sup> /kPa <sup>2</sup> s)	0.0354-0.4620	0.1169 ± 0.0905

Table 6.12 IOS Measurements and Model Parameters for the Asthmatic Children

<b>IOS Measurements and Model Parameters</b>		
<b>Asthma group N=19</b>		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.47-0.94	0.70 ± 0.14
<b>R5-R15</b> (kPa/l/s)	0.10-0.48	0.26 ± 0.10
<b>AX</b> (kPa/l)	0.87-4.34	2.30 ± 1.00
<b>Fres</b> (1/s)	16.94-23.30	20.10 ± 1.53
<b>Rc</b> (kPa/l/s)	0.2637-0.5295	0.3473 ± 0.0665
<b>Rp</b> (kPa/l/s)	0.3109-1.1963	0.6058 ± 0.2280
<b>I</b> (kPa/l/s <sup>2</sup> )	0.0014-0.0029	0.0020 ± 0.0004
<b>Cp</b> (l/kPa)	0.0209-0.0695	0.0404 ± 0.0124
<b>Ce</b> (l/kPa)	0.0024-0.0044	0.0035 ± 0.0006
<b>Cp/Rp</b> (l <sup>2</sup> /kPa <sup>2</sup> s)	0.0204-0.1740	0.081 ± 0.0448

The range of values of each feature, measured and estimated IOS parameters: R5, R5-R15, AX and Fres, and the aRIC model parameters: R, Rp, I, Cp, Cp/Rp and Ce, obtained for the SAD and Asthmatic groups were comparable to those values observed in other asthmatic children of the same age range.

**It can be observed that children classified as normal or possible SAD were relatively similar in both IOS and aRIC model parameters,** with however, clear increases in R5-R15, AX, Fres, and Rp, and a clear decrease in Cp going from normal to possible SAD. For Cp/Rp a decrease from normal to asthmatic groups was observed.

Going to increasingly abnormal levels of "diagnostic classification," R5, R5-R15, AX, Fres and Rp continue to increase from possible SAD to SAD to asthma, while Cp decreases in this progression.

**Differences between SAD and asthmatic children are again modest.**

While expert clinician diagnostic classification distinguished between children based on 4 levels of perceived normality of 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.

The features used in this work seem to be sensitive and reliable indices for automatic respiratory disease classification using Impulse Oscillometry data. In our other publications we reported on the performance of a neuro-fuzzy classifier using these indices as powerful features for computer-aided classification of asthmatic and normal children.

5. **“Normal Impulse Oscillometry (IOS) Lung Function Parameters in Adolescents Residing in El Paso, TX” (93).**

Documented prevalence and severity of asthma in Hispanic (H) children are greater than those in Anglo (A) children. This has been attributed to either socio-economic factors (access to medical care) or urban living, which increases the risk of developing asthma, with more H than A children living in urban environments. To address these issues, we recruited, by random selection, both H and A children in the same urban environment known to have poor air quality in El Paso, Texas, to assess severity and prevalence of lung dysfunction in children.

Data from 5 Anglo (1 female) and 6 Hispanic (2 females) normal, non-asthmatic adolescents, 11 to 17 years old, were used for this purpose, and **R5, R5-R15 and AX were analyzed and were not significantly different between these groups.** It was concluded that despite a slightly greater BMI in Hispanic adolescents, **there were no differences in lung function parameters reflective of peripheral airway dysfunction in this group of normal adolescents** that might suggest genetic differences in adolescents living in similar urban environments.

6. **“Abnormality of Oscillometric Resistances and Reactances is Greater in Hispanic than Anglo Children in El Paso, TX” (94)**

Also in the same year a study was performed where children, ages 5–17 years, underwent oscillometry (IOS) tests, to assess their respiratory impedance. R and X values were compared with historical normal data in children of similar age to aid diagnostic assignment by an observer blinded to

ethnicity/diagnosis of asthma/allergies. Diagnoses were: Normal (N), Probable Small Airway Impairment (PSAI), Small Airway Impairment (SAI), or Asthmatic groups, based on IOS R and X values. Equivalent electrical circuit model analysis utilized the aRIC model, yielding estimates of central and peripheral airway resistances. The results suggested that children classified N or PSAI did not differ in IOS/model analyses between Hispanics and Anglos. Children classified as SAI or Asthmatic were significantly different, (unpaired t-test) independent of age/height: Rrs, Xrs and central airway resistance were greater in Hispanics with PSAI; R and X were greater in Hispanics for the Asthmatic group. The conclusion was that in an urban environment with diminished air quality, **Hispanic and Anglo children whose R and X are normal for age and size do not differ. Among children whose IOS R and X are consistent with significant SAI, Hispanic children are more severely affected than Anglos, with increased calculated large and small airway resistances**

A summary of this pre-bronchodilation research work is presented in table 6.13.

Table 6.13 Prebronchodilation work

Researchers	Evaluated Population	Evaluated Parameters	Place of Publication	Conclusions
Meraz et al. (89)	19 Anglos Asthmatics 5 to 15 years old	R5, R5-R15, AX <sub>measured</sub> , AX <sub>calculated</sub> , Fres and the eRIC and aRIC	<b>23rd Southern Biomedical Engineering Conference (SBEC) 2007</b>	<b>R5-R15</b> seemed to be a <b>sensitive</b> index to <b>gender differences</b> , high correlation between AX <sub>measured</sub> and AX <sub>calculated</sub> values was observed, and <b>significant differences were found between the eRIC and aRIC models</b>
Meraz et al. (90)	6 Asthmatic Hispanics 5-10 years old	R5, R5-R15, AX and Fres and eRIC and aRIC	<b>24rd SBEC 2008</b>	eRIC and aRIC calculated values were presented for this group of asthmatic children
Meraz et al. (91)	5 Anglos and 6 Hispanics normals, 11 - 17 years, 19 Anglo Asthmatics , 5 to 15 years old, 6 Hispanic asthmatic, 5-10 years	R5, R5-R15, AX and Fres and eRIC and aRIC	<b>24rd SBEC 2008</b>	Statistical significances were found between normals and asthmatics, in both ethnic groups, in all aRIC parameters, except for Ce.
Meraz et al. (92)	76 children	R5, R5-R15, AX, Fres,	Proceedings of the 30 <sup>th</sup> AIC	<b>The mean, standard deviation and range</b>

	5-17 years Normals, PSAI, SAI and Asthmatics	aRIC and Cp/Rp	of the <b>IEEE EMBS</b> , Vancouver, Canada <b>2008</b>	<b>of these parameters (features) were presented for each group of children.</b> For Cp/Rp, a decrease from normal to asthmatic groups was observed. <b>IOS and aRIC data appeared to fall into two distinctly different groups: either normal or asthmatic</b>
Meraz et al. (93)	5 Anglos and 6 Hispanics, normals, 11 to 17	R5, R5-R15 and AX	2008 Annual Meeting of the <b>American College of Epidemiology</b> , Tuxon, Arizona <b>2008</b>	No differences in normal adolescents that might suggest genetic differences in adolescents living in similar urban environments, were found
Goldman et al. (94)	Children 5 to 17 years Normals, PSAI, SAI and Asthmatics		<b>CHEST Conference 2008</b>	Hispanic and Anglo children whose R and X are normal for age and size do not differ. Among children with significant SAI Hispanic children are more severely affected than Anglos

## 6.2.2 Previous Pre- and Post-bronchodilation Work

The IOS data collected from children for this PhD study in 2008, before and after bronchodilation (pre-B and post-B) were analyzed and presented in several publications.

In the following paragraphs a description of these analyses and publications, using IOS data, calculated parameters, and the eRIC/aRIC model parameters (using first Model's codes) collected in 2008 (pre-B and post-B) will be presented.

### 1. “Modeling Human Respiratory Impedance in Hispanic Asthmatic Children” (95).

IOS data collected from 40 Asthmatic Hispanic children 2-5 years old by Ortiz and Menendez (8) were analyzed for this research. This study included IOS parameters: R5, R5-R15, AX and Fres for this group. The aRIC model parameters: R, Rp, I, Cp and Ce, were statistically analyzed. The average values of each IOS parameter (Resistance and Reactance at 5, 10, 15, 20, 25, and 35 Hz) were used to estimate the model parameters for the aRIC model. Mean  $\pm$  SD of measured and calculated values for both pre- and post-bronchodilation are presented in Table 6.14.

Table 6.14 IOS measurements and calculated values for pre-B and post-B data

IOS Measurements and Calculated Values				
Parameter	Pre-Bronchodilation		Post-Bronchodilation	
	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD
<b>R<sub>5</sub></b> (Kpa/L/s)	0.67-1.47	1.09 $\pm$ 0.24	0.39-1.38	0.80 $\pm$ 0.22
<b>R<sub>5</sub>-R<sub>15</sub></b> (Kpa/L/s)	0.10-0.65	0.30 $\pm$ 0.13	0.02-0.30	0.14 $\pm$ 0.07
<b>AX</b> (Kpa/L)	1.98-13.20	5.53 $\pm$ 2.78	0.41-7.48	2.82 $\pm$ 1.61
<b>F<sub>res</sub></b> (1/s)	17.61-33.38	23.77 $\pm$ 3.23	15.15-28.87	19.80 $\pm$ 3.49

Values of R<sub>5</sub>, R<sub>5</sub>-R<sub>15</sub>, AX and F<sub>res</sub> were numerically larger in pre-bronchodilation than in post-bronchodilation and showed *significant differences*. All model parameters of the aRIC model (R, R<sub>p</sub>, I, and C<sub>p</sub>, C<sub>e</sub>) showed *significant differences* between pre- and post-bronchodilation tests. Mean values for estimated parameters for the aRIC respiratory model, t-value and the outcome of statistical t-tests comparing pre- and post-bronchodilation parameters are presented in Table 6.15.

Table 6.15 Estimated parameters for the aRIC model

Estimated parameters						
		R	R <sub>p</sub>	I	C	C <sub>e</sub>
Pre-B	<b>aRIC</b>	0.66482	1.31345	0.00176	0.03385	0.00048
Post-B	<b>aRIC</b>	0.58499	0.97275	0.00143	0.05982	0.00019
	<b>t-value</b>	2.16	3.27	3.22	-7.13	2.71
<b>Significance</b>		<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>

It is worthy of note that the parameters estimated by the eRIC model (not shown here) and the aRIC model were quite similar in general; and that C<sub>e</sub> estimated by the aRIC was two orders of magnitude smaller than C<sub>p</sub>, and decreased very significantly from pre- to post-bronchodilation, while C<sub>p</sub> increased significantly from pre- to post-bronchodilation. The very small magnitude of C<sub>e</sub> is consistent with small “shunt compliance” and is observed in association with manual compression of the cheeks by either the larger children or the parent during IOS testing. As expected, when peripheral airway impedance decreased after bronchodilation, calculated shunt compliance decreased even more.

The study suggested the following conclusions: The range of values of R<sub>5</sub>, R<sub>5</sub>-R<sub>15</sub>, AX and F<sub>res</sub> obtained for pre-bronchodilation and post-bronchodilation tests for Hispanic/Asthmatic subjects 2-5 years of age were comparable to those values observed in other Asthmatic children in the same age



range. The IOS parameters representing *frequency-dependence of resistance*,  $R_5$ ,  $R_5 - R_{15}$ , and the parameters AX and  $F_{res}$  seem to be sensitive indices for pre- and post-bronchodilation differences in lung function (sensitive indices of *peripheral airway obstruction*). The significant differences in  $R_5-R_{15}$  and AX have potential application toward use of simpler airflow perturbation devices that use two perturbation frequencies at 5 Hz and  $F_{res}$ . As significant differences were found between all model parameters of the aRIC model, these indicate that the aRIC model is sensitive to differentiate between constricted (Asthmatic condition) and non-constricted (non-asthmatic condition) airways.

## **2. “Respiratory System Model Parameters Track Changes in Lung Function After Bronchodilation” (96).**

Twenty six Anglo children 6 to 19 years old were tested for this paper; their data was analyzed and classified into four categories: Normal, PSAI, SAI, and Asthma, and also eRIC and aRIC model parameters were calculated and analyzed for this four groups of children. Model derived parameters were compared between pre- and post-bronchodilator tests. The IOS parameters analyzed were:  $R_3$ ,  $R_5$ ,  $R_{10}$ ,  $R_3-R_{20}$ ,  $R_5-R_{20}$ ,  $X_3$ ,  $X_5$ ,  $X_{10}$  and AX.

All 26 children provided IOS data which was analyzed by our expert clinician and finally classified into two groups: a) A Normal or Possible Small Airway Impairments (Normal/PSAI) group and b) An Asthma or Small Airway Impairment (Asthma/SAI) group. A total of 9 children were classified in the first group (Normal or PSAI) and the remaining 17 were classified in the second group (Asthma or SAI).

It was previously demonstrated that 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, group mean IOS and electrical equivalent 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 (92).

Pre- and Post-bronchodilation mean IOS data, t-values and significance information for the Normal/PSAI group and for the Asthma/SAI group are shown in Tables 6.16 and 6.17 respectively.

Table 6.16 IOS Parameters for the Normal/PSAI group

IOS Parameters for the Normal/PSAI group				
IOS parameters	Pre-BD Mean	Post-BD Mean	t-value	Significance
R3 (kPa/l/s)	0.57	0.52	0.5	No
R5 (kPa/l/s)	0.48	0.43	0.56	No
R10 (kPa/l/s)	0.4	0.37	0.37	No
R3-R20 (kPa/l/s)	0.24	0.18	0.99	No
R5-R20 (kPa/l/s)	0.15	0.1	1.27	No
X3 (kPa/l/s)	-0.24	-0.23	-0.09	No
X5 (kPa/l/s)	-0.18	-0.16	-0.37	No
X10 (kPa/l/s)	-0.08	-0.05	-0.82	No
AX (kPa/L)	1.09	0.79	0.84	No

Table 6.17 IOS Parameters for the Asthma/SAI group

IOS Parameters for the Asthma/SAI group				
IOS parameters	Pre-BD Mean	Post-BD Mean	t-value	Significance
R3 (kPa/l/s)	0.75	0.61	2.87	Yes
R5 (kPa/l/s)	0.63	0.52	2.74	Yes
R10 (kPa/l/s)	0.49	0.42	2.15	Yes
R3-R20 (kPa/l/s)	0.4	0.3	2.52	Yes
R5-R20 (kPa/l/s)	0.27	0.2	2.39	Yes
X3 (kPa/l/s)	-0.31	-0.23	-2.44	Yes
X5 (kPa/l/s)	-0.25	-0.19	-2.81	Yes
X10 (kPa/l/s)	-0.16	-0.11	-2.65	Yes
AX (kPa/l)	1.99	1.32	2.71	Yes

Table 6.18 shows mean values for the aRIC model parameters in the Normal/PSAI group for pre- and post-BD data, their calculated t-values and significance.

Table 6.18 aRIC Model Parameters for the Normal/PSAI group

aRIC model Parameters for the Normal/PSAI group					
aRIC	R (kPa/l/s)	Rp (kPa/l/s)	I (kPa/l/s <sup>2</sup> )	Cp (l/kPa)	Ce (l/kPa)
Pre-BD mean	0.28615	0.43204	0.00147	0.11373	0.00299
Post-BD mean	0.30955	0.40147	0.00125	0.13378	0.00276
t-value	-0.5	0.38	1.1	-0.52	0.51
Significance	No	No	No	No	No

Table 6.19 shows mean values for the aRIC model parameters in the Asthma/SAI group for pre- and post-bronchodilation data, their calculated t-values and significance.

Table 6.19 aRIC model Parameters for the Asthma/SAI group

<b>aRIC model Parameters for the Asthma/SAI group</b>					
<b>aRIC</b>	<b>R (kPa/l/s)</b>	<b>Rp (kPa/l/s)</b>	<b>I (kPa/l/s<sup>2</sup>)</b>	<b>Cp (l/kPa)</b>	<b>Ce (l/kPa)</b>
Pre-BD mean	0.31388	0.54952	0.00181	0.04578	0.00343
Post-B mean	0.27529	0.42296	0.00158	0.06224	0.0035
t-value	1.83	2.67	2.19	-2.24	-0.27
Significance	No	Yes	Yes	Yes	No

Table 6.20 shows mean values for the eRIC model parameters in the Normal/PSAI group for pre- and post-BD data, their calculated t-value and significance.

Table 6.20 eRIC model Parameters for the Normal/PSAI group

<b>eRIC model Parameters for the Normal/PSAI group</b>				
<b>eRIC</b>	<b>R (kPa/l/s)</b>	<b>Rp (kPa/l/s)</b>	<b>I (kPa/l/s<sup>2</sup>)</b>	<b>Cp (l/kPa)</b>
Pre-BD mean	0.34652	0.63213	0.00104	0.14317
Post-BD mean	0.3486	0.57084	0.00096	0.15983
t-value	-0.04	0.55	0.59	-0.41
Significance	No	No	No	No

Table 6.21 shows mean values for the eRIC model parameters in the Asthma/SAI group for pre- and post-BD data, their calculated t-value and significance

Table 6.21 eRIC model parameters for the Asthma/SAI group

<b>eRIC model Parameters for the Asthma/SAI group</b>				
<b>eRIC</b>	<b>R (kPa/l/s)</b>	<b>Rp (kPa/l/s)</b>	<b>I (kPa/l/s<sup>2</sup>)</b>	<b>Cp (l/kPa)</b>
Pre-BD mean	0.3879	0.63778	0.00118	0.06731
Post-BD mean	0.34046	0.49469	0.0011	0.09014
t-value	2.1	2.52	1.35	-2.33
Significance	Yes	Yes	No	Yes

*The present study has shown that electrical equivalent model parameters track changes in lung function after bronchodilation.* Both the eRIC and aRIC models clearly distinguish between children who are normal (or possibly have mild small airway impairment (SAI), who show no significant changes with bronchodilator (BD)), and those who are asthmatic with SAI, both at baseline and regarding the pre- to post-BD changes in lung function. The eRIC model shows an apparently larger peripheral airway compliance (Cp) than the aRIC model, probably because it may include some of the “extrathoracic airway compliance” (Ce). eRIC also fails to show significant change in inertance (I) post-BD in the asthma group, while aRIC does. On the other hand, *eRIC 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 asthma group.*

*Cp values derived from both the eRIC and aRIC models were closely correlated with AX.* The range of values for normal subjects and those with small airway impairment, before and after inhaling bronchodilator appear to fall along a unique power regression trend line, such that intervention with bronchodilator moves the data points along this single regression toward the more normal data range.

A definitive choice between eRIC and aRIC models will require further assessments.

### **3. “Forced Oscillation (IOS) measures in airway-impaired and normal children over 2 years (97)”**

Few longitudinal Forced Oscillation (FO) data exist in normal subjects or in those with airflow obstruction. Oostveen et al (78) noted need for a *practical FO index to define airway obstruction*. This study documents Impulse Oscillation (IOS) data in children and adolescents (7-15 yrs of age) in El Paso Texas, USA over a two-year time period between 2006-2008. Children were randomly selected to participate in a lung function study related to contaminated environmental air conditions using IOS in 2006, in El Paso TX. We classified subjects as either “normal” or having small airway impairment (SAI) on initial baseline IOS studies in 2006 using data of Clément et al (35) as a guide to normality. We requested subjects studied in 2006 to return in 2008 for more complete IOS testing pre- and post-

bronchodilator (BD). 26 subjects returned for re-evaluation in 2008. The majority (17/26) were classified in 2006 as manifesting SAI, while 9 were ‘normal’ in 2006.

We tabulated IOS R3, R5, X3, X5, R3-R20, R5-R20 and AX to assess expected growth-related, and BD-mediated decreases in R and X magnitudes; and analyzed a respiratory system electrical model for large and small airway resistance and compliance.

Table 6.22 shows statistical significance of differences between normal and SAI subjects at baseline in 2006 and pre- and post-BD in 2008.

Table 6.23 shows significant differences from baseline to 2008 pre-BD and from pre- to post-BD, in 2008.

Table 6.22 Statistical significance of differences between normal and SAI subjects

	R5(kPa/l/s)		R5-R20(kPa/l/s)		AX(kPa/l)		Rp(kPa/l/s)		Cp(l/kPa)	
	SAI	NL	SAI	NL	SAI	NL	SAI	NL	SAI	NL
<b>2006</b>	0.72	0.59	0.31	<b>0.20**</b>	2.45	<b>1.52*</b>	0.71	0.51	0.04	<b>0.08*</b>
<b>2008 pre</b>	0.63	<b>0.48**</b>	0.27	<b>0.15***</b>	1.99	<b>1.09*</b>	0.55	0.43	0.05	<b>0.13***</b>
<b>2008 post</b>	0.52	0.43	0.2	<b>0.10***</b>	1.32	0.79	0.42	0.4	0.06	<b>0.15****</b>

\* = p < 0.02 compared to SAI

\*\* = p < 0.03 compared to SAI

\*\*\* = p < 0.01 compared to SAI

\*\*\*\* = p < 0.001 compared to SAI

Table 6.23 Significant differences from baseline (2006) to 2008 pre-BD and from pre- to post-BD in 2008

	R5		R5-R20		AX		Rp		Cp	
	SAI	NL	SAI	NL	SAI	NL	SAI	NL	SAI	NL
<b>2006-2008</b>	< 0.001	< 0.003	NS	NS	< 0.01	< 0.01	< 0.003	NS	< 0.04	< 0.04
<b>2008 PRE/POST</b>	< 0.0001	NS	< 0.003	< 0.03	< 0.00001	< 0.03	< 0.0002	NS	< 0.002	< 0.04

In children with SAI, R3 and R5 decreased (13%, p < 0.001 for both), R3-R20 and R5-R20 (11% and 13%, p < 0.003 for both) and AX (19%, p < 0.002) from 2006 to 2008 pre-BD. Post-BD decreases in all IOS parameters were larger (19-34%, all p < 0.003). R and X variability were larger at 3 than 5 Hz; but mean changes were comparable. In children without SAI, growth-related R and X magnitude

decreases from 2006-2008 were larger (20-28%  $p < 0.003$  for all) than post-BD decreases in 2008 (4-27%,  $p < 0.03$  for AX only); mean changes at 3 and 5 Hz were comparable. Electrical equivalent model analyses manifested comparable magnitudes of change to those of primary IOS data.

Children with SAI manifested small growth-related decreases in R and X magnitudes compared to BD responses; normal children showed the opposite pattern. In this study, mean changes were similar at 3 and 5 Hz. IOS parameters at 3 and 5 Hz were closely related in this small sample. IOS parameters differed consistently between normal and SAI children over 2 years.

Model-derived Cp and Rp tracked IOS indices of small airway function (derived from Rrs and Xrs over 5 to 35 Hz as inputs). Electrical model parameters appeared to be as sensitive as primary IOS data. Peripheral airway compliance (Cp) was more sensitive than peripheral airway resistance (Rp). Cp was significantly larger in normal than SAI children, consistently over time. A larger sample population is required to confirm the trends observed in the present work.

In Table 6.24 a summary of these Pre- and Post- Bronchodilation work is presented.

Table 6.24 Summary of Pre- and Post- Bronchodilation Work

Researchers	Evaluated Population	Evaluated Parameters	Place of Publication	Conclusions
Meraz et al. (95)	40 Asthmatic Hispanic 2-5 years	R5, R5-R15, AX ,Fres and aRIC	Proceedings of the 29 <sup>th</sup> Annual International Conference (AIC) of the <b>IEEE EMBS</b> , Lyon, France <b>2007</b>	<b>All IOS</b> parameters seemed to be <b>sensitive indices</b> for pre and post bronchodilation and significant differences were found between all aRIC model parameters.
Meraz et al. (96)	26 children 6 to 19 years Normals, PSAI, SAI, and Asthmatics	R3, R5, R10, R3-R20, R5-R20, X3, X5, X10, AX, and eRIC and aRIC	<b>25th SBEC</b> <b>2009</b>	aRIC and eRIC model parameters for the <b>Normal/PSAI</b> group showed <b>no significant differences</b> between pre and post bronchodilation conditions. For the <b>Asthma/SAI</b> group: <b>aRIC Rp, I and Cp</b> presented <b>significant differences</b> , <b>eRIC R, Rp and Cp</b> showed <b>significant differences</b> .
Meraz et al. (97)	26 children	R3, R5, R10, R3-R20,	European Respiratory Society	<b>Children with SAI</b> manifest small

6 to 19 years  
Normals, PSAI, SAI,  
and  
Asthmatics

R5-R20, X3, X5, X10,  
AX, and eRIC and aRIC

(ERS) 19th Annual Conference  
2009

growth-related decreases in R and X  
magnitudes compared to BD responses.  
Normal children show the opposite pattern.  
IOS parameters differed consistently  
between normal and SAI children over 2 years.  
Model-derived Cp and Rp track IOS indices  
of small airway function.

### 6.2.3 Final Pre-bronchodilation work

For the final part of this research the IOS data and model parameters collected from 112 children in 2006, under pre-bronchodilation conditions were analyzed. The eRIC and aRIC models were run using frequencies from 5 to 25 Hz.

The IOS and model parameters selected to be analyzed were chosen from publications previously presented in this chapter and in previous chapters. These parameters were chosen because of their ability to evaluate respiratory system properties and impairments. The IOS and models' parameters analyzed were: R5, R5-R20, X5, AX, Fres, eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp.

Our expert clinician performed careful visual inspection of the raw data and quality assured all the acquired data from 112 children IOS data and finally classified these data into four groups, 11 children were considered to be Healthy (or Normal), 17 children were classified as having Probable Small Airway Impairment (PSAI), 54 manifested definite Small Airway Impairment (SAI) and 30 presented IOS data characteristic of asthma. Children in these four groups were either Anglo or Hispanic children as indicated by their parents in the questionnaires.

Mean  $\pm$  standard deviation and range of values for all IOS and model parameters analyzed are presented in Table 6.25 for Healthy children, in Table 6.26 for those with PSAI, in Table 6.27 for children with SAI, and in Table 6.28 for those with Asthma.

Table 6.25 Healthy Children IOS and Models Parameters Pre-B (N=11)

IOS Measurements and Model Parameters		
Healthy Group N=11		
	Range	Mean $\pm$ SD
R5 (kPa/l/s)	0.28-0.56	0.40 $\pm$ 0.09
R5-R20(kPa/l/s)	0.02-0.11	0.07 $\pm$ 0.03

<b>X5</b> (kPa/l/s)	-0.14-0.0	-0.11±0.04
<b>AX</b> (kPa/l)	0.19-0.55	0.37±0.12
<b>Fres</b> (1/s)	9.55-17.39	13.14±2.48
<b>eRIC Cp</b> (l/kPa)	0.1138-0.3480	0.1880±0.0655
<b>Rp</b> (kPa/l/s)	0.0667-0.5136	0.3462±0.1300
<b>aRIC Cp</b> (l/kPa)	0.1097-0.2041	0.1516±0.0309
<b>Rp</b> (kPa/l/s)	0.0881-0.4475	0.3089±0.1086

Table 6.26 PSAI Children IOS and Models Parameters Pre-B (N=17)

<b>IOS Measurements and Model Parameters</b>		
<b>PSAI Group N=17</b>		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.35-0.70	0.49±0.11
<b>R5-R20</b> (kPa/l/s)	0.08-0.32	0.14±0.07
<b>X5</b> (kPa/l/s)	-0.34-(-0.10)	-0.17±0.07
<b>AX</b> (kPa/l)	0.42-2.01	0.87±0.50
<b>Fres</b> (1/s)	13.35-19.02	16.70±1.94
<b>eRIC Cp</b> (l/kPa)	0.0442-0.1634	0.1118±0.0383
<b>Rp</b> (kPa/l/s)	0.2810-1.0385	0.4439±0.2146
<b>aRIC Cp</b> (l/kPa)	0.0279-0.1536	0.1000±0.0415
<b>Rp</b> (kPa/l/s)	0.2304-0.7555	0.4084±0.1685

Table 6.27 SAI Children IOS and Models Parameters Pre-B (N=54)

<b>IOS Measurements and Model Parameters</b>		
<b>SAI Group N=54</b>		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.38-0.97	0.65±0.15
<b>R5-R20</b> (kPa/l/s)	0.07-0.46	0.25±0.09
<b>X5</b> (kPa/l/s)	-0.48-(-0.13)	-0.26±0.09
<b>AX</b> (kPa/l)	0.46-3.15	1.89±0.75
<b>Fres</b> (1/s)	15.78-28.34	19.33±2.44
<b>eRIC Cp</b> (l/kPa)	0.0331-0.1772	0.0627±0.0277
<b>Rp</b> (kPa/l/s)	0.3179-1.4088	0.6375±0.2399
<b>aRIC Cp</b> (l/kPa)	0.0209-0.1762	0.0514±0.0303
<b>Rp</b> (kPa/l/s)	0.4144-1.0865	0.5966±0.1893

Table 6.28 Asthmatic Children IOS and Models Parameters Pre-B (N=54)

<b>IOS Measurements and Model Parameters</b>		
<b>Asthma Group N=30</b>		
	Range	Mean±SD
<b>R5</b> (kPa/l/s)	0.49-1.21	0.82±0.17
<b>R5-R20</b> (kPa/l/s)	0.20-0.60	0.37±0.12
<b>X5</b> (kPa/l/s)	-0.60-(-0.16)	-0.36±0.12
<b>AX</b> (kPa/l)	1.28-4.72	3.01±0.98
<b>Fres</b> (1/s)	17.44-25.17	20.91±1.67



<b>eRIC Cp</b> (l/kPa)	0.0228-0.0672	0.0403±0.0132
<b>Rp</b> (kPa/l/s)	0.3687-1.3608	0.8359±0.2630
<b>aRIC Cp</b> (l/kPa)	0.0168-0.0640	0.0320±0.0130
<b>Rp</b> (kPa/l/s)	0.3737-1.2585	0.7946±0.2293

According to our expert clinician the range of values of every analyzed feature, measured and estimated IOS parameters: R5, R5-R20, AX and Fres, and eRIC and aRIC model parameters: Rp, Cp, for the SAI and Asthmatic groups were comparable to those values observed in other asthmatic children of the same age range.

*The same pattern previously seen can be again be observed here, children classified as normal or possible SAI were relatively similar in both IOS and aRIC model parameters, with however, clear increases in R5, R5-R20, AX, Fres, and Rp, and a clear decrease in X5 and Cp going from normal to possible SAD.*

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

Even though these similarities between Normal and PSAI groups and between SAI and Asthma groups were observed, significant differences between these groups, in these previously mentioned four groups IOS and model parameters, were evaluated. Comparing Normal and PSAI groups significant differences were seen for all of the parameters with the exception of eRIC Rp and aRIC Rp. Comparing PSAI and SAI groups all of the nine analyzed IOS and model parameters presented significant differences between these groups. Also comparing SAI and Asthma groups all of the parameters showed significant differences.

The parameters used in this work seem to be sensitive and reliable indices for respiratory disease classification using Impulse Oscillometry data and model parameters.

As stated before in chapter 3, it was demonstrated by several researchers, working in establishing Reference IOS values for Normal children, that Height was the best predictor of IOS parameters. Because of this important finding in previous research works it was decided to analyze the correlations between these nine selected IOS and model parameters and Children Heights in our research. All of the

parameters showed a good correlation with children's heights. The best correlation was observed for X5 with a correlation coefficient  $r = 0.855$ , and the lowest  $r$  value ( $r = 0.486$ ) was observed for  $F_{res}$ . In Table 6.29 the values of  $R$  obtained for these correlations are presented.

Table 6.29 Correlation coefficients ( $r$ ) between IOS and Model Parameters and Height for 2006 Data

Correlation with Height	
Parameters	$r$
<b>R5</b> (kPa/l/s)	0.784
<b>X5</b> (kPa/l/s)	0.855
<b>R5-R20</b> (kPa/l/s)	0.791
<b>AX</b> (kPa/l)	0.816
<b>Fres</b> (1/s)	0.486
<b>eRIC Cp</b> (l/kPa)	0.798
<b>Rp</b> (kPa/l/s)	0.818
<b>aRIC Cp</b> (l/kPa)	0.739
<b>Rp</b> (kPa/l/s)	0.842

The correlations between AX vs both models' Cps, and R5-R20 vs both models' Rps were also evaluated. The correlation between AX and eRIC Cp was the best correlation ( $r = 0.973$ ). For the correlation between AX and aRIC Cp a value of  $r = 0.900$  was obtained. A value of  $r = 0.782$  was observed for R5-R20 vs eRIC Rp, and a better correlation was found for R5-R20 vs aRIC Rp ( $r = 0.864$ ). Figure 6.1 shows the correlation between AX and eRIC Cp.

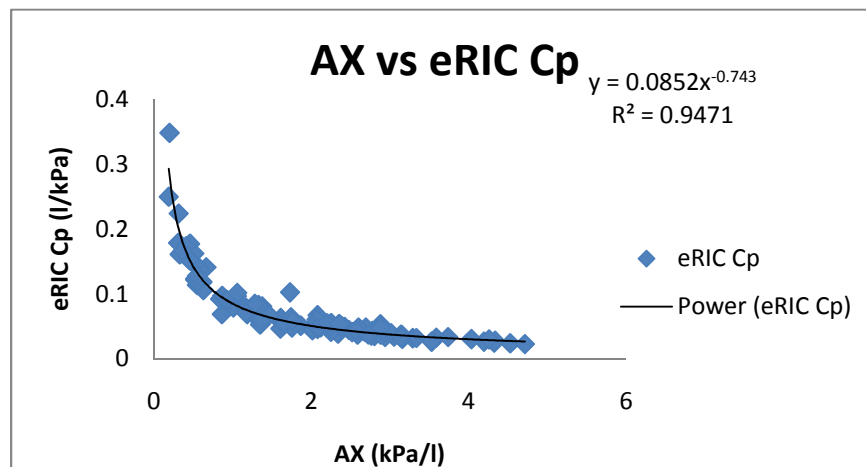


Figure 6.1 Correlation between AX vs eRIC Cp for pre-B data

#### 6.2.4 Final Pre-bronchodilation and Post-bronchodilation Work

Also for the final part of this research the IOS data and model parameters collected from 47 children in 2008, under pre-bronchodilation and post-bronchodilation conditions were analyzed. As well the eRIC and aRIC models were run using frequencies from 5 to 25 Hz.

The IOS and model parameters selected to be analyzed, were chosen from publications previously presented in this chapter and in chapter 3. These parameters were chosen because of their ability to evaluate respiratory system's properties and impairments. The IOS and models' parameters analyzed were: R3, R5, R3-R20, R5-R20, X3, X5, AX, Fres, eRIC Cp, eRIC Rp, aRIC Cp and aRIC Rp. It can be observed that IOS parameters at 3 Hz (R3, X3, R3-R20) were added to this analysis in order to evaluate their performance.

Our expert clinician quality assured the IOS data collected from all of the 47 children IOS data and classified them into four groups: 6 children were considered to be Healthy (or Normal), 4 children were classified as PSAI, 11 manifested definite SAI and 24 presented as 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 for each IOS and model parameters analyzed are presented in Table 6.30 for Healthy children, in Table 6.31 for PSAI children, in Table 6.32 for children with SAI, and in Table 6.33 for those with Asthma for this pre- and post-B data collected in 2008.

Table 6.30 Healthy children IOS and Models Parameters Pre- and Post-B (N=6)

IOS Measurements and Model Parameters					
Healthy Group N=6					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean $\pm$ SD		Range	Mean $\pm$ SD
<b>R3</b> (kPa/l/s)	0.34-0.59	0.41 $\pm$ 0.09	<b>R3</b> (kPa/l/s)	0.30-0.54	0.38 $\pm$ 0.08
<b>R5</b> (kPa/l/s)	0.29-0.51	0.35 $\pm$ 0.08	<b>R5</b> (kPa/l/s)	0.25-0.48	0.33 $\pm$ 0.08
<b>R3-R20</b> (kPa/l/s)	0.05-0.12	0.09 $\pm$ 0.02	<b>R3-R20</b> (kPa/l/s)	0.03-0.13	0.08 $\pm$ 0.04
<b>R5-R20</b> (kPa/l/s)	-0.01-0.07	0.03 $\pm$ 0.03	<b>R5-R20</b> (kPa/l/s)	-0.02-0.08	0.03 $\pm$ 0.04
<b>X3</b> (kPa/l/s)	-0.21-(-0.09)	-0.16 $\pm$ 0.05	<b>X3</b> (kPa/l/s)	-0.22-(-0.09)	-0.15 $\pm$ 0.05
<b>X5</b> (kPa/l/s)	-0.13-(-0.07)	-0.10 $\pm$ 0.02	<b>X5</b> (kPa/l/s)	-0.13-(-0.08)	-0.10 $\pm$ 0.02

<b>AX</b> (kPa/l)	0.18-0.36	0.26±0.06	<b>AX</b> (kPa/l)	0.16-0.36	0.24±0.07
<b>Fres</b> (1/s)	10.26-13.46	11.18±1.15	<b>Fres</b> (1/s)	9.6-13.74	10.99±1.76
<b>eRIC Cp</b> (l/kPa)	0.2073-0.2816	0.2346±0.0284	<b>eRIC Cp</b> (l/kPa)	0.1894-0.2892	0.2297±0.0362
<b>Rp</b> (kPa/l/s)	0.2163-0.8016	0.5665±0.2788	<b>Rp</b> (kPa/l/s)	0.2227-0.5801	0.3501±0.1630
<b>aRIC Cp</b> (l/kPa)	0.1851-0.2331	0.2091±0.0169	<b>aRIC Cp</b> (l/kPa)	0.1436-0.2411	0.2087±0.0366
<b>Rp</b> (kPa/l/s)	0.1891-0.7206	0.3922±0.2057	<b>Rp</b> (kPa/l/s)	0.1992-0.6173	0.3151±0.1710

Table 6.31 PSAI children IOS and Models Parameters Pre- and Post-B (N=4)

IOS Measurements and Model Parameters					
PSAI Group N=4					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean±SD		Range	Mean±SD
<b>R3</b> (kPa/l/s)	0.47-0.99	0.67±0.25	<b>R3</b> (kPa/l/s)	0.37-0.96	0.60±0.27
<b>R5</b> (kPa/l/s)	0.39-0.84	0.57±0.21	<b>R5</b> (kPa/l/s)	0.30-0.87	0.50±0.26
<b>R3-R20</b> (kPa/l/s)	0.14-0.44	0.30±0.15	<b>R3-R20</b> (kPa/l/s)	0.14-0.39	0.26-0.12
<b>R5-R20</b> (kPa/l/s)	0.07-0.29	0.19±0.11	<b>R5-R20</b> (kPa/l/s)	0.07-0.30	0.17±0.10
<b>X3</b> (kPa/l/s)	-0.45-(-0.02)	-0.28±0.11	<b>X3</b> (kPa/l/s)	-0.32-(-0.20)	-0.24±0.06
<b>X5</b> (kPa/l/s)	-0.33-(-0.15)	-0.22±0.09	<b>X5</b> (kPa/l/s)	-0.24-(-0.13)	-0.17±0.05
<b>AX</b> (kPa/l)	0.57-2.57	1.31±0.95	<b>AX</b> (kPa/l)	0.43-2.20	1.11±0.82
<b>Fres</b> (1/s)	15.53-17.36	16.44±0.92	<b>Fres</b> (1/s)	12.47-17.19	15.37±2.54
<b>eRIC Cp</b> (l/kPa)	0.0445-0.1616	0.0963±0.0556	<b>eRIC Cp</b> (l/kPa)	0.0243-0.1636	0.0978±0.0621
<b>Rp</b> (kPa/l/s)	0.4398-0.6730	0.5443±0.1211	<b>Rp</b> (kPa/l/s)	0.3539-0.6174	0.4886±0.1180
<b>aRIC Cp</b> (l/kPa)	0.0389-0.1616	0.0858±0.0572	<b>aRIC Cp</b> (l/kPa)	0.0077-0.1636	0.0861±0.0690
<b>Rp</b> (kPa/l/s)	0.3561-0.6730	0.5116±0.1403	<b>Rp</b> (kPa/l/s)	0.3539-0.8784	0.5339±0.2423

Table 6.32 SAI children IOS and Models Parameters Pre- and Post-B (N=11)

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

Table 6.33 Asthmatic children IOS and Models Parameters Pre- and Post-B (N=24)

IOS Measurements and Model Parameters					
Asthma Group N=24					
Pre-Bronchodilation			Post-Bronchodilation		
	Range	Mean±SD		Range	Mean±SD
<b>R3</b> (kPa/l/s)	0.45-1.77	0.82±0.26	<b>R3</b> (kPa/l/s)	0.37-1.31	0.62±0.20
<b>R5</b> (kPa/l/s)	0.39-1.28	0.68±0.19	<b>R5</b> (kPa/l/s)	0.32-1.04	0.52±0.16
<b>R3-R20</b> (kPa/l/s)	0.14-1.24	0.44±0.22	<b>R3-R20</b> (kPa/l/s)	0.10-0.78	0.30±0.14
<b>R5-R20</b> (kPa/l/s)	0.07-0.75	0.30±0.14	<b>R5-R20</b> (kPa/l/s)	0.05-0.52	0.20±0.10
<b>X3</b> (kPa/l/s)	-0.87-(-0.13)	-0.34±0.15	<b>X3</b> (kPa/l/s)	-0.65-(-0.1)	-0.27±0.13
<b>X5</b> (kPa/l/s)	-0.81-(-0.12)	-0.29±0.14	<b>X5</b> (kPa/l/s)	-0.55-(-0.08)	-0.21±0.11
<b>AX</b> (kPa/l)	0.45-6.61	2.24±1.23	<b>AX</b> (kPa/l)	0.28-4.35	1.38±0.90
<b>Fres</b> (1/s)	14.44-24.19	19.48±2.64	<b>Fres</b> (1/s)	12.76-20.86	17.68±2.35
<b>eRIC Cp</b> (l/kPa)	0.0200-0.1782	0.0593±0.0347	<b>eRIC Cp</b> (l/kPa)	0.0047-0.2466	0.0848±0.0527
<b>Rp</b> (kPa/l/s)	0.2925-1.8113	0.6749±0.2949	<b>Rp</b> (kPa/l/s)	0.2318-1.2561	0.5050±0.2148
<b>aRIC Cp</b> (l/kPa)	0.0148-0.1522	0.0570±0.0390	<b>aRIC Cp</b> (l/kPa)	0.0047-0.2087	0.0776±0.0519
<b>Rp</b> (kPa/l/s)	0.2250-1.6536	0.5840±0.2848	<b>Rp</b> (kPa/l/s)	0.1604-1.1443	0.4288±0.2033

According to our expert clinician the range of values of every analyzed feature, measured and estimated IOS parameters: 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 observed in other asthmatic children of the same age range.

Clear increases in R3, R5, R3-R20, R5-R20, AX, Fres, and Rp, and clear decreases in X3, X5 and Cp going from normal to possible SAD were observed.

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.

All these mentioned increases and decreases of the most significant parameters are shown in Figures 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, and 6.8.

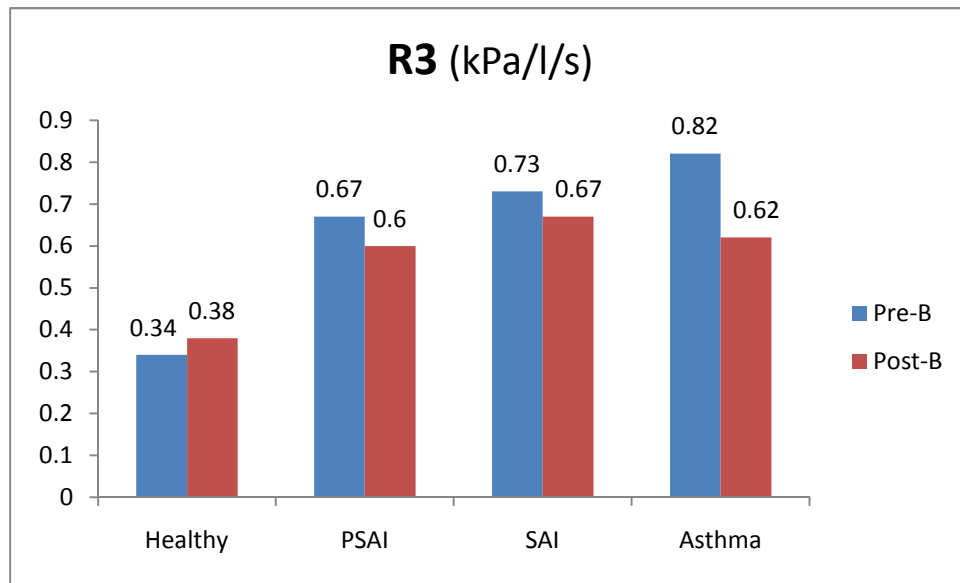


Figure 6.2 R3 mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

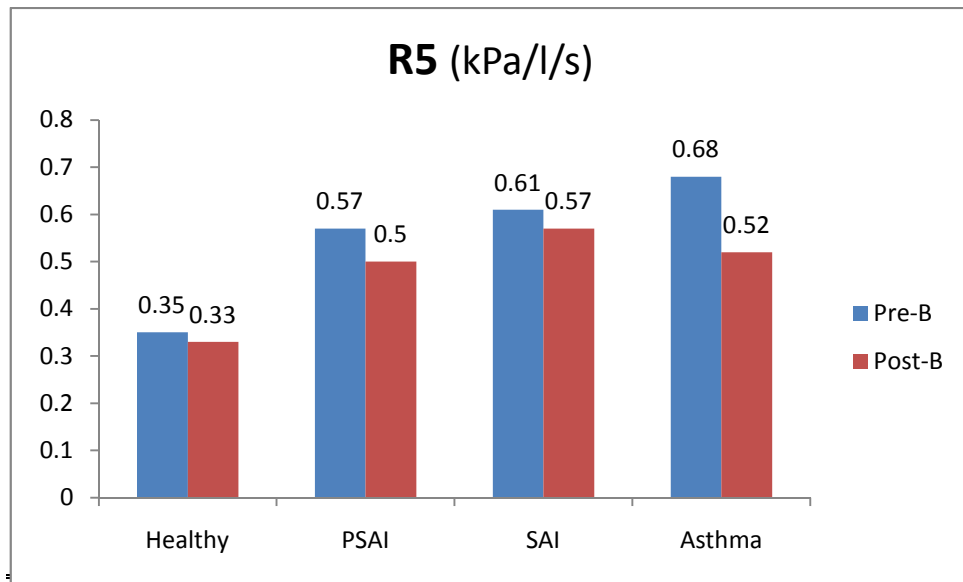


Figure 6.3 R5 mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

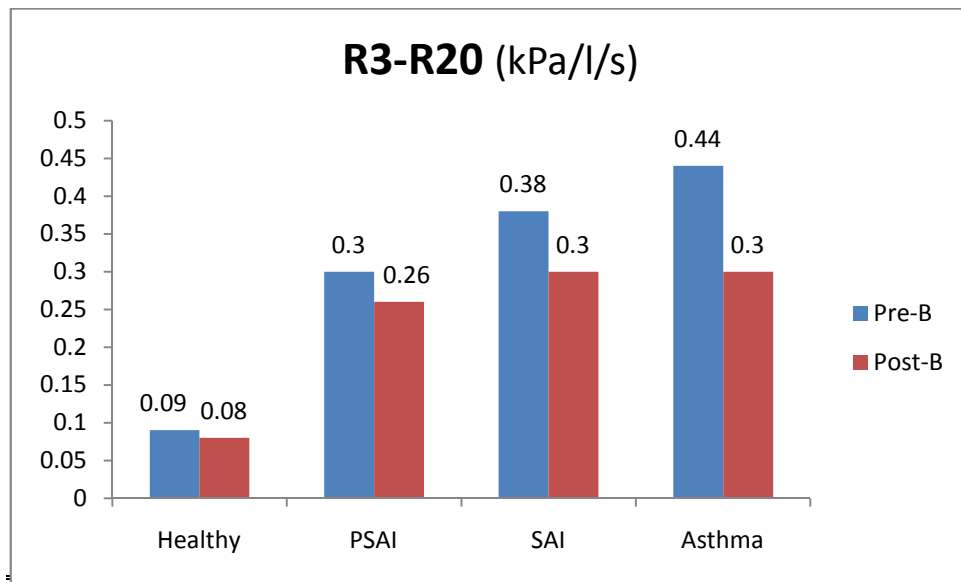


Figure 6.4 R3-R20 mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

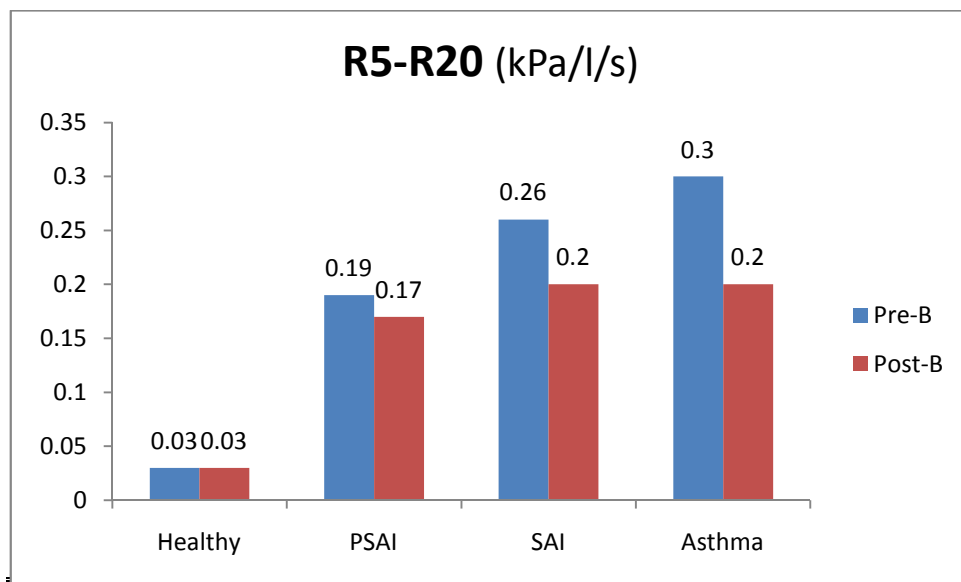


Figure 6.5 R5-R20 mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

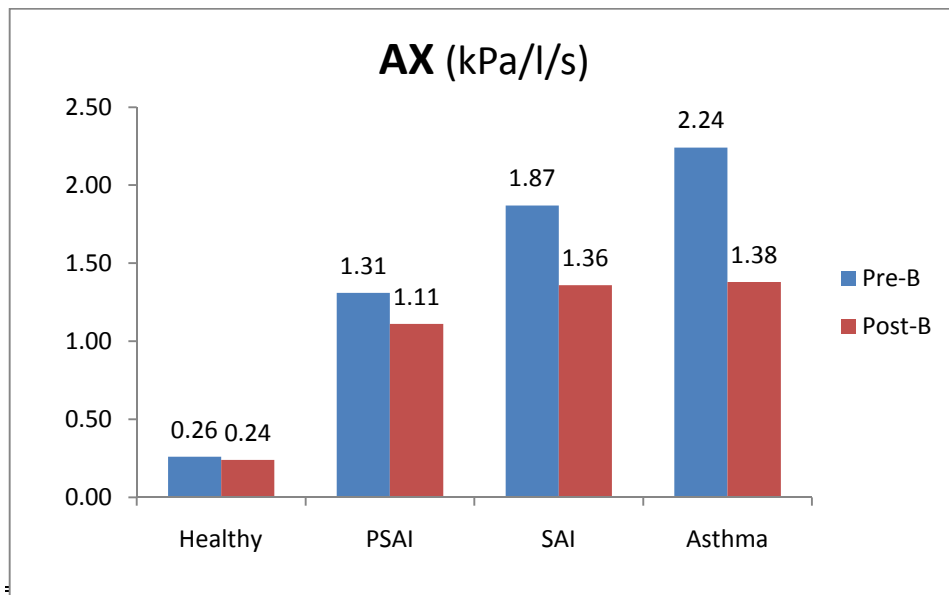


Figure 6.6 AX mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

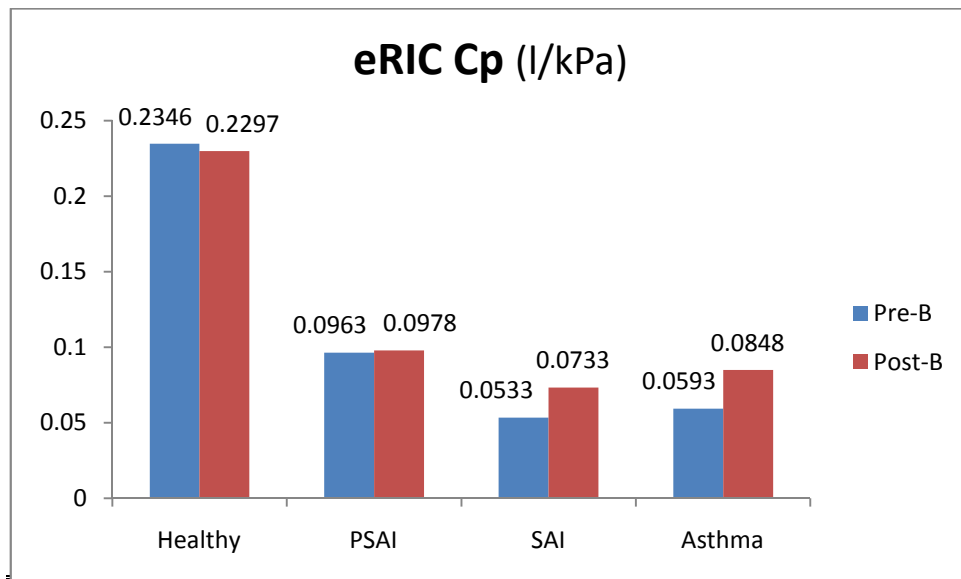


Figure 6.7 eRIC Cp mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions



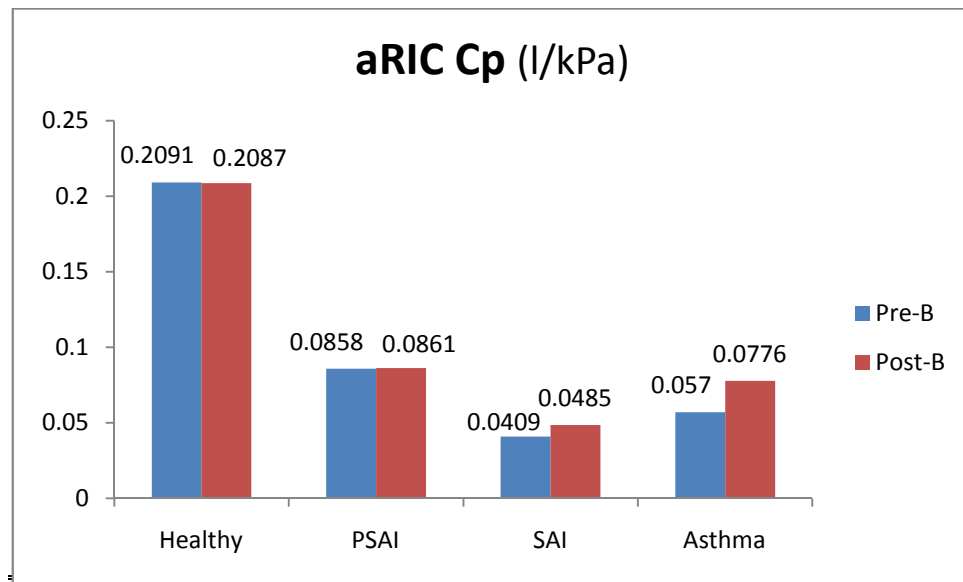


Figure 6.8 aRIC Cp mean values for the H, PSAI, SAI and Asthma children under Pre- and Post-B conditions

Comparing Pre- and Post-B IOS and eRIC and aRIC model parameters in the Normal group, no significant differences were observed (see Table 6.34).

Table 6.34 Healthy Group p values

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

Comparing Pre- and Post-B IOS and eRIC and aRIC model parameters for the PSAI group only R3, R35 and eRIC Rc presented significant differences (see Table 6.35).

Table 6.35 PSAI Group p values

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

Comparing Pre- and Post-B IOS and eRIC and aRIC model parameters for the SAI group the following parameters presented significant differences: R3,R5,X3,X5,X10,X15,R3-R20,R5-R20,AX,aRIC Rp, eRIC Rp, eRIC I and eRIC Cp (see Table 6.36).

Table 6.36 SAI Group p values

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

Comparing Pre- and Post-B IOS and eRIC and aRIC model parameters for the Asthmatic group all of the parameters presented significant differences with the exception of aRIC Ce and eRIC I (see Table 6.37).

Table 6.37 Asthma Group p values

Asthmatic Group	
	Pre-B vs Post-B p value
<b>R3</b> (kPa/l/s)	<1.5E-9
<b>R5</b> (kPa/l/s)	<1.6E-10
<b>R10</b> (kPa/l/s)	<9.7E-08
<b>R15</b> (kPa/l/s)	<0.0002
<b>R20</b> (kPa/l/s)	<0.0002
<b>R25</b> (kPa/l/s)	<3.9E-07

<b>R35</b> (kPa/l/s)	<1.7E-06
<b>X3</b> (kPa/l/s)	<0.005
<b>X5</b> (kPa/l/s)	<0.002
<b>X10</b> (kPa/l/s)	<0.0003
<b>X15</b> (kPa/l/s)	<1.4E-6
<b>X20</b> (kPa/l/s)	<0.0002
<b>X25</b> (kPa/l/s)	<0.01
<b>X35</b> (kPa/l/s)	<0.003
<b>R3-R20</b> (kPa/l/s)	<5.6E-06
<b>R5-R20</b> (kPa/l/s)	<2.5E-06
<b>AX</b> (kPa/l/s)	<3.1E-08
<b>Fres</b> (1/s)	<0.0002
<b>aRIC Rc</b> (kPa/l/s)	<0.006
<b>Rp</b> (kPa/l/s)	<4.5E-07
<b>I</b> (kPa/l/s <sup>2</sup> )	<0.002
<b>Cp</b> (l/kPa)	<0.0003
<b>eRIC Rc</b> (kPa/l/s)	<0.002
<b>Rp</b> (kPa/l/s)	<4.5E-06
<b>Cp</b> (l/kPa)	<0.0003

Similarities between Normal and PSAI groups and between SAI and Asthma groups were also observed. Significant differences between these groups in these previously mentioned IOS and model parameters were calculated. Comparing Normal pre-B to PSAI pre-B all of the IOS and model parameters presented significant differences, with the exception of aRIC Rp and eRIC Rp. Comparing Normal post-B and PSAI post-B the majority of the parameters presented 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 presented significant differences between these groups, Fres, eRIC and aRIC Cp. For PSAI post-B and SAI post-B only Fres presented significant differences. Finally comparing SAI pre-B vs Asthma pre-B, and SAI post-B vs Asthma post-B no significant differences were observed.

These selected parameters seem to be sensitive and reliable indices for respiratory disease classification using Impulse Oscillometry data and eRIC and aRIC model parameters.

The correlation between Height and these parameters IOS and model parameters was also analyzed. The parameters presented a good correlation, even though a smaller R values than the R

values presented for the Pre-Bronchodilation work in the previous section. The best correlation was observed for R5 with  $R = 0.764$ , and the lowest  $R$  value ( $R = 0.542$ ) was observed for X5. In Table 6.38 the values of  $R$  obtained for these correlations are presented.

Table 6.38 Correlation Coefficients ( $r$ ) between Height and IOS and Models' Parameters for 2008 Data

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)	0.620
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

The statistical correlation between AX vs both models' Cps, and R3-R20 and R5-R20 vs both models' Rps were also evaluated. The best correlation observed was the correlation between AX and eRIC Cp with  $R = 0.909$ . The correlation between AX and aRIC Cp had a lower  $R$  value equal to 0.760. For the correlation between R3-R20 vs eRIC Rp,  $R$  was equal to 0.589. The correlation between R5-R20 vs eRIC Rp had a  $R = 0.516$ . For R3-R20 vs aRIC Rp,  $R = 0.787$ . And finally the correlation between R5-R20 vs aRIC Rp had a  $R = 0.731$ . Figure 6.9 illustrates the best correlation AX vs eRIC Cp.

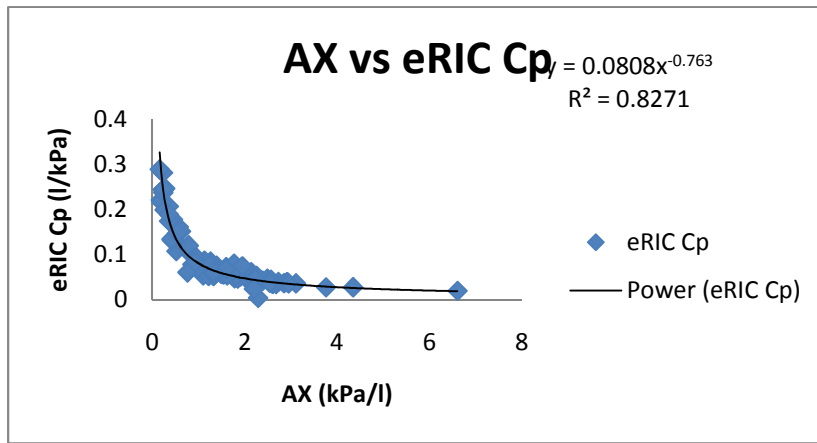


Figure 6.9 Correlation between AX and eRIC Cp for pre- and post-B data

### 6.3 RESULTS AND DISCUSSIONS FROM HYPOTHESIS 3

#### Hypothesis 3

✚ The expected growth-related improvement in IOS and eRIC/aRIC parameter estimates will be greater in Normal/PSAI children than in SAI/Asthmatic children.

#### 6.3.1 Pre- and Post-bronchodilation work over a 2 years period

To address hypothesis 3 the work previously presented in the ERS conference in 2009 was expanded (97) . From this expanded work based on IOS, eRIC and aRIC model changes over a two-year period, a Journal Paper was developed. It was recently published in the Biomedical Engineering Online Journal in March 2011 (98).

This Journal Paper focused on determination of the sensitivity of IOS parameters to show growth-related changes (increases or decreases), over a two-year period, and to analyze eRIC and aRIC model parameter estimates of lung function in Healthy (H) and Small Airway Impaired (SAI) children, to evaluate the performance of these models in quantifying airway function in this population and to show the correlation of these model parameters with IOS measures. In this paper we use the terms Healthy (H) and Normal (N) interchangeably.

For this investigation, twenty six children were recruited and tested. A total of 15 males and 11 females were included in this study. Children were first classified, by our expert clinician, as being part of one of four groups: Healthy (Normal), probable SAI (PSAI), SAI and Asthmatic, based on initial baseline IOS studies in 2006 using data of Clement et al (35) as a guide to normality. We requested subjects studied in 2006 to return in 2008 for more complete IOS testing pre- and post-bronchodilation. All twenty six subjects returned for re-evaluation in 2008.

In a previous study by our research group (92) it was observed that children classified as H or PSAI were relatively similar in both IOS and aRIC model parameters. In the same way it was observed that differences between SAI and asthmatic children were similarly modest. Therefore, it was concluded then that while expert clinician diagnostic classification distinguished between children based on 4 levels of perceived normality or absence thereof from the visual patterns of IOS data, group mean IOS and aRIC data appear to fall into two distinctly different groups: either healthy or small airway impaired. For this reason children in this research were classified as being part of one of two groups: H or SAI. Nineteen children were IOS classified as SAI, and seven as H. Age, height and weight Mean  $\pm$  SD values and ranges for this population, in 2006, are presented in Table 6.39.

Table 6.39 Demographics for the 26 children tested in 2006 and 2008.

<b>Subject Demographics</b>	<b>Males and Females</b>	
	<b>Range</b>	<b>Mean <math>\pm</math> SD</b>
Age (years)	5 to 14	8.7 $\pm$ 2.8
Height (cm)	110.7 to 171.7	135.2 $\pm$ 20.4
Weight (kg)	19.1 to 72.7	36.1 $\pm$ 16.9

In their first tests, in 2006, children were tested without the use of a bronchodilator (B), and in their second tests in 2008 children were tested before and after using a B (pre-B and post-B). The bronchodilator used was levalbuterol.

The parameters for the eRIC and aRIC ( $R_c$ ,  $R_p$ ,  $I$ ,  $C_p$ , and  $C_e$ ) models were estimated using average resistance and reactance values of the IOS parameters at different frequencies (5, 10, 15, 20, 25 Hz) for the 26 children, using the upgraded Models' codes.

The following IOS parameters:  $R_5$  (Resistance at 5Hz),  $R_5 - R_{20}$  (an index of frequency-dependence of resistance) and Reactance Area, AX (an integrative index of low-frequency reactance or the "Goldman Triangle"), were tabulated to assess expected growth-related, and Bronchodilation-related (B-related) changes in R and X magnitudes. Also  $R_p$  and  $C_p$  were selected to be analyzed in this research.

Table 6.40 shows average values of IOS parameters ( $R_5$ ,  $R_5-R_{20}$ , and AX) and statistical significance of differences between *Healthy (H)*, also called *Normal (N)*, and SAI subjects at baseline in 2006 pre-B and at pre-B and post-B conditions in 2008. It is observed that all IOS parameters ( $R_5$ ,  $R_5-R_{20}$  and AX) showed significant differences between SAI and the *H or N* group.

Table 6.40 Average Values and Statistical Significance (SAI vs H) of IOS parameters.

Tests	R5		p-value	R5-R20		p-value	AX		p-value
	(kPa/l/s)			(kPa/l/s)			(kPa/l/s)		
	SAI	H		SAI	H		SAI	H	
2006 pre-B	0.73	0.52	<0.002	0.31	0.15	<0.001	2.51	1.09	<0.0003
2008 pre-B	0.63	0.43	<0.001	0.27	0.13	<0.003	2.00	0.80	<0.002
2008 post-B	0.53	0.38	<0.02	0.20	0.08	<0.002	1.34	0.57	<0.01

Table 6.41 illustrates the statistical significance between *H* and SAI children in 2006 (baseline pre-B) and at pre-B and post-B conditions two years later for the eRIC and aRIC model parameters: Peripheral Resistance ( $R_p$ ) and Peripheral Compliance ( $C_p$ ).  $R_p$  failed to detect statistical significances between SAI and *H* groups, no significant differences were found between these two groups ( $p>0.05$ , NS) in both models; while  $C_p$  showed significant differences between these two groups in both models.

Table 6.41 Average values and Statistical Significance (SAI vs H) of the eRIC and aRIC Model Parameters.

Tests	aRIC Rp (kPa/l/s)		p-value	aRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)		p-value	eRIC Rp (kPa/l/s)		p-value	eRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)		p-value
	SAI	H		SAI	H		SAI	H		SAI	H	
<b>2006 pre-B</b>	0.592	0.451	>0.05	0.053	0.100	<b>&lt;0.02</b>	0.824	0.501	<b>&lt;0.03</b>	0.045	0.115	<b>&lt;0.0002</b>
<b>2008 pre-B</b>	0.470	0.438	>0.05	0.056	0.136	<b>&lt;0.003</b>	0.601	0.472	>0.05	0.056	0.155	<b>&lt;0.0002</b>
<b>2008 post-B</b>	0.359	0.316	>0.05	0.067	0.162	<b>&lt;0.001</b>	0.472	0.386	>0.05	0.076	0.173	<b>&lt;0.0001</b>

Table 6.42 demonstrates significant differences between 2006 pre-B and 2008 pre-B, and between 2008 pre-B and post-B data for IOS parameters. R5, R5-R20 and AX showed significant differences for SAI group comparing both scenarios (2006 pre-B vs 2008 pre-B; and 2008 pre-B vs 2008 post-B). In the *H or N* group R5, R5-R20 and AX showed no significant differences ( $p>0.05$ ) in both scenarios with the exception of 2006 pre-B and 2008 pre-B for R5.

Table 6.42 Significance difference between 2006-2008 pre-B, and 2008 pre-B and post-B data for IOS parameters.

Tests	R5 (kPa/l/s)		R5-R20 (kPa/l/s)		AX (kPa/l/s)	
	p-value		p-value		p-value	
	SAI	H	SAI	H	SAI	H
<b>2006-2008 pre-B</b>	<b>&lt;0.0002</b>	<b>&lt;0.02</b>	<b>&lt;0.05</b>	>0.05	<b>&lt;0.0005</b>	>0.05
<b>2008 pre-B/post-B</b>	<b>&lt;0.0001</b>	>0.05	<b>&lt;0.002</b>	>0.05	<b>&lt;0.00005</b>	>0.05

Table 6.43 demonstrates significant differences between 2006 pre-B and 2008 pre-B, and between 2008 pre-B and post-B data for model parameters. For *H or N* children both models parameters, Rp and Cp, presented no significant differences ( $p>0.05$ ) between 2006-2008 pre-B conditions and 2008 pre-B and post-B data. In SAI children both model parameters, Rp and Cp, showed significant differences between 2006-2008 pre-B situations and 2008 pre-B and post-B data, with the exception of aRIC Cp, which showed no significant differences ( $p>0.05$ ) between 2006-2008 pre-B data.



Table 6.43 Significant differences between 2006-2008 pre-B, and 2008 pre-B and post-B data for model parameters.

Tests	aRIC Rp (kPa/l/s)		aRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)		eRIC Rp (kPa/l/s)		eRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)	
	p-value		p-value		p-value		p-value	
	SAI	H	SAI	H	SAI	H	SAI	H
<b>2006-2008 pre-B</b>	<b>&lt;0.002</b>	>0.05	>0.05	>0.05	<b>&lt;0.002</b>	>0.05	<b>&lt;0.01</b>	>0.05
<b>2008 pre-B/post-B</b>	<b>&lt;0.000002</b>	>0.05	<b>&lt;0.05</b>	>0.05	<b>&lt;0.003</b>	>0.05	<b>&lt;0.02</b>	>0.05

In Table 6.44 we can observe the growth and bronchodilation percentage of change for *H* or *N* and SAI children from 2006 pre-B to 2008 pre-B, and from pre-B and post-B in 2008. A negative sign represents a decrease in magnitude, and a positive sign represents an increase.

Table 6.44 Growth and bronchodilator percentage of change in H and SAI children.

IOS and Model Parameters	2006 pre-B – 2008 preB	2008 preB – 2008 postB	2006 pre-B – 2008 preB	2008 preB – 2008 postB
	% of change for Healthy	% of change for Healthy	% of change for SAI	% of change for SAI
R5	-17	-12	-14	-16
R5-R20	-13	-38	-13	-26
AX	-27	-29	-20	-33
aRIC Rp	-3	-28	-21	-24
aRIC Cp	35	19	4	20
eRIC Rp	-6	-18	-27	-21
eRIC Cp	35	12	25	35

From Tables 6.42, 6.43 and 6.44 we can make the following observations:

\*In **children with SAI**, the three IOS parameters analyzed decreased from 2006 pre-B to 2008 pre-B: R5 (14%,  $p<0.0002$ ), R5-R20 (13%,  $p<0.05$ ), and AX (20%,  $p<0.0005$ ). Comparing 2008 pre-B and post-B data, post-B decreases in all IOS parameters were larger (16-33%,  $p<0.002$ ). Within the eRIC and aRIC model parameters eRIC Rp had a higher decrease from 2006 pre-B to 2008 pre-B (27%,  $p<0.002$ ) than aRIC Rp (21%,  $p<0.002$ ); similarly, eRIC Cp had a significantly higher increase (25%,  $p<0.01$ ) than aRIC Cp (4%), showing no significant differences ( $p>0.05$ ) between groups. Comparing 2008 pre-B and post-B data, eRIC Rp had a decrease (21%,  $p<0.003$ ) and aRIC Rp had a slightly higher decrease (24%,  $p<0.000002$ ), while eRIC Cp had a higher increase (35%,  $p<0.02$ ) than aRIC Cp (20%,  $p<0.05$ ).

\*For **children without SAI** (*H or N*), growth-related R and X magnitudes decreased from 2006 pre-B to 2008 pre-B (13-27%,  $p < 0.02$  for R5 only), R5-R20 and AX showed no significant differences ( $p > 0.05$ ); post-B decreases were larger (12-38%), and all IOS parameters showed no significant differences. In this group of children, the eRIC and aRIC model parameters presented the following changes from 2006 pre-B to 2008 pre-B: eRIC Rp decreased (6%,  $p > 0.05$ ) more than aRIC Rp (3%,  $p > 0.05$ ) both with no significant differences; while eRIC Cp and aRIC Cp showed equal increases and no significant differences (35%,  $p > 0.05$ ). Comparing 2008 pre-B and post-B eRIC Rp had a smaller decrease (18%,  $p > 0.05$ ) than aRIC Rp (28%,  $p > 0.05$ ) both showing no significant differences; eRIC Cp had also a smaller increase (12%,  $p > 0.05$ ) than aRIC Cp (19%,  $p > 0.05$ ) and also no significant differences.

It was observed that in 2006 one child was overweight, he was classified into the group of SAI subjects, and it was interesting to analyze the impact of including him or not in the calculation of the R and X results for 2006. In Table 6.45 the impact of including or excluding the overweight subject on calculation of the R and X averaged values in 2006 can be observed. The table shows that the average values for R and X are very similar. Therefore, including a child with overweight did not have a considerable impact on the results presented in this research.

Table 6.45 Impact on calculation of R and X (averaged values) by including or excluding an overweight child in 2006 (OC=Overweight child included and NOC=No overweight child included).

Frequency (Hz)	Resistance (kPa/l/s)		Reactance (kPa/l/s)	
	2006 SAI		2006 SAI	
	OC	NOC	OC	NOC
3	0.86	0.86	-0.40	-0.41
5	0.72	0.71	-0.32	-0.33
10	0.55	0.54	-0.21	-0.21
15	0.43	0.42	-0.12	-0.12
20	0.41	0.40	0.02	0.02
25	0.47	0.46	0.11	0.12
35	0.59	0.59	0.20	0.21

In Figures 6.10 and 6.11 IOS Resistance (R) and Reactance (X) are shown as a function of different oscillation frequencies in 2006 (baseline) for averaged *H or N* and averaged SAI children.

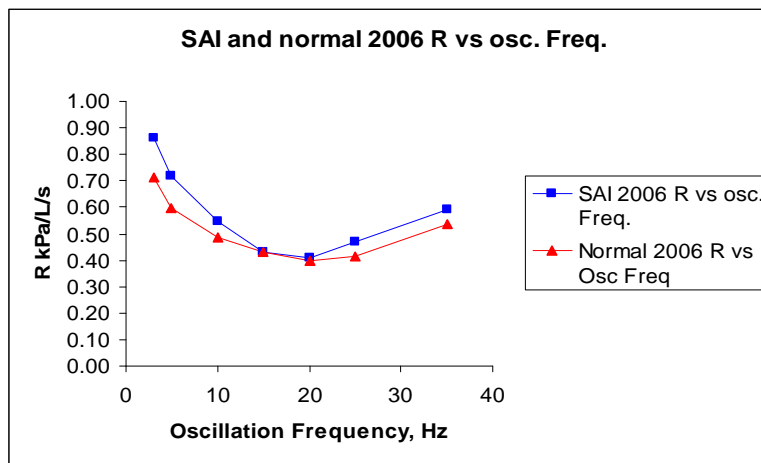


Figure 6.10 R vs Oscillation Frequency in 2006 for averaged SAI and averaged H subjects.

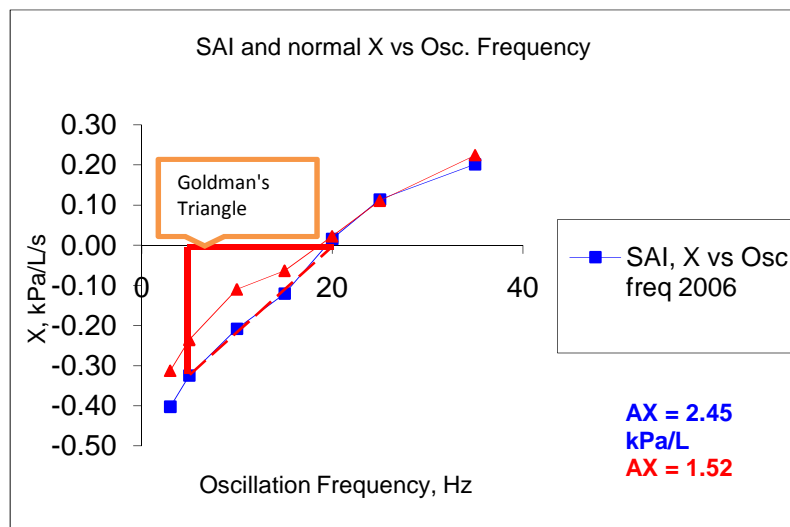


Figure 6.11 X vs Oscillation Frequency in 2006 for averaged SAI and averaged H subjects.

Figure 6.11 exemplifies the values of AX, showing that it is larger, as expected, for children with SAI (AX can be visualized as the triangular area from X5 to Fres: the point at which X = 0).

Figures 6.12 and 6.13 illustrate 2008 IOS data for R (Rrs) and X (Xrs) vs. oscillation frequency under pre-B and post-B conditions, for averaged *H* and averaged SAI children. It can be observed, in both graphs, that H pre-B line is close to SAI post-B line.

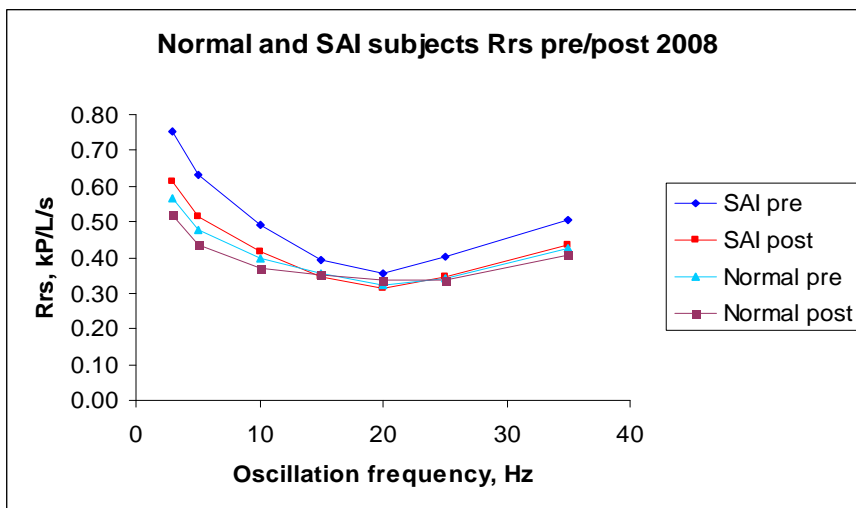


Figure 6.12 R vs Oscillation Frequency in 2008 for Averaged SAI and Averaged H Subjects.

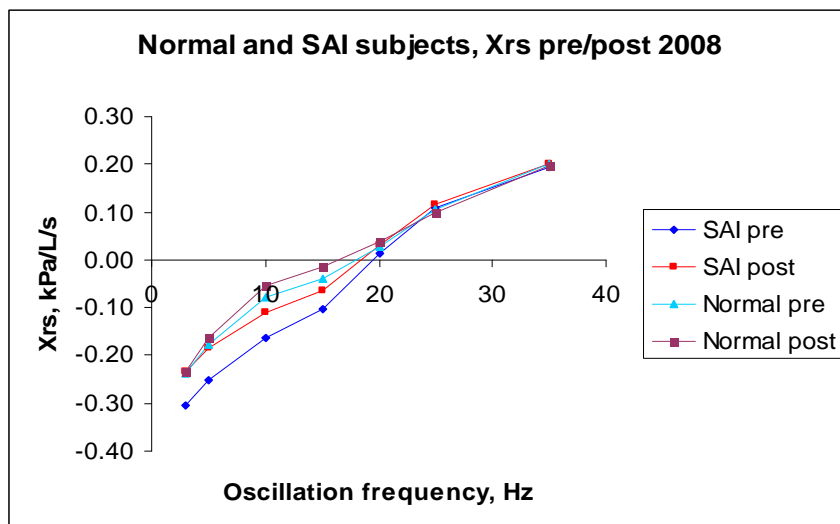


Figure 6.13 X vs. Oscillation Frequency in 2008 for Averaged SAI and Averaged H Subjects.

In Figure 6.14 we can observe the regressions between AX and Cp for both models (eRIC and aRIC) in all subjects and measurements (2006 pre-B, 2008 pre-B, and 2008 post-B) can be observed. The regression for Cp as a function of AX is very similar in both models, but a better correlation was found for the eRIC Cp ( $r = 0.935$ ) than for the aRIC Cp ( $r = 0.780$ ).

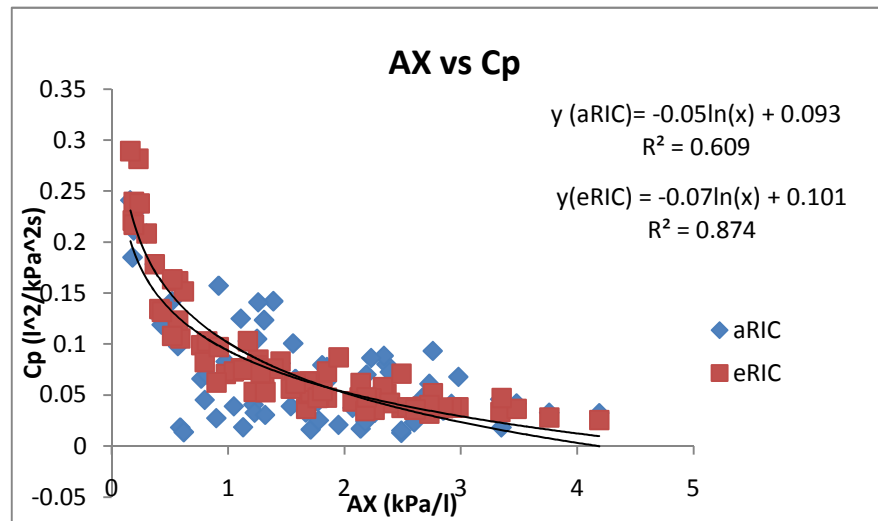


Figure 6.14 Cp as a function of AX for the eRIC and aRIC models in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B).

Figure 6.15 shows the regressions for both models (eRIC and aRIC) Rp and R5-R20 in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B), where both produced smaller correlations than the previous correlations presented in Figure 6.7 (AX vs Cp). We can observe that both model Rp regressions vs. R5-R20 are almost the same (eRIC  $r = 0.616$  and aRIC  $r = 0.594$ ).

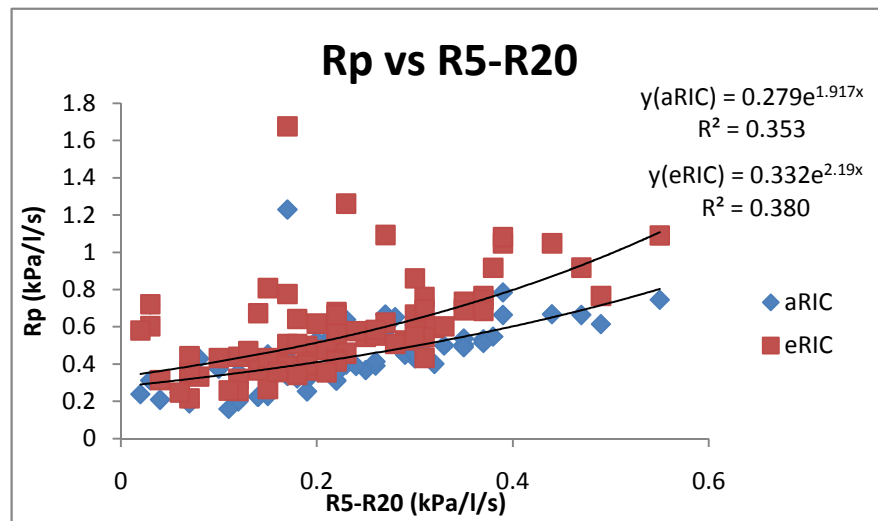


Figure 6.15 Rp as a function of R5–R20 for the eRIC and aRIC models in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B).

Figure 6.16 illustrates aRIC Cp values plotted as a function of eRIC Cp. Both models' parameters presented a close correspondence (slope = 0.8486 and  $r = 0.840$ ).

An almost equal correlation was found between aRIC Rp and eRIC Rp (slope = 1.223 and  $r = 0.830$ ). Lower regression values were found for central (large airway) resistance Rc and large airway

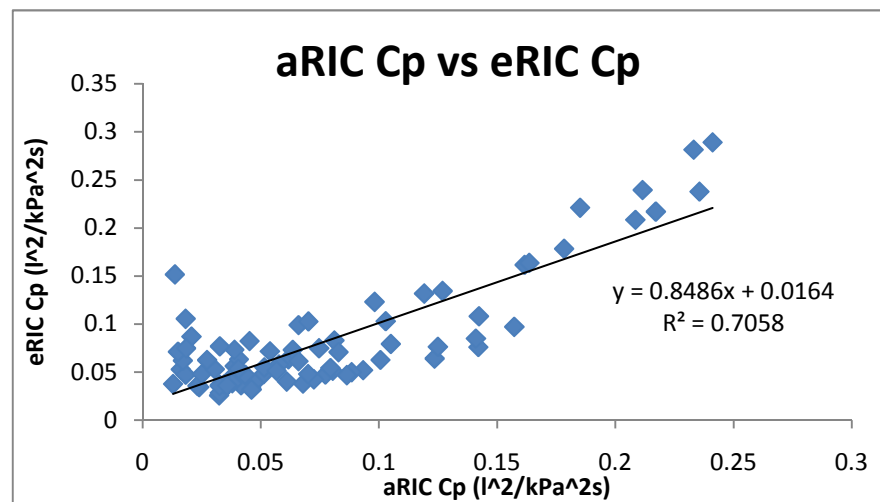


Figure 6.16 Regression line for both models (aRIC and eRIC) Cp in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B).

inertance I, Rc's slope was 0.457 and  $r = 0.544$ , meanwhile for Inertance, the slope was 0.208 and  $r = 0.480$ . These results demonstrate very similar parameter estimates for Cp and Rp from both models and comparable estimates for Rc and I from both of them as well.

Figure 6.17 shows AX vs Height in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B), while figure 6.11 depicts eRIC Cp vs Height in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B). As it can be observed from both graphs, AX and Cp provide good discrimination between the SAI and *H or N* children. We can observe in figure 6.17 that *H* children have smaller values of AX as mentioned before and as expected. In figure 6.18 we can observe that *H* (Normals) children have higher values of Cp than SAI children, suggesting that SAI subjects present reduced respiratory compliance due to small airway inflammation and lumen diameter reduction. The overlapping points between SAI and *H* children trend lines in both graphs for Cp and AX (points where the trend lines are close together) could be explained by the previous observation made about pre-B data in *H* children being similar to post-B data in SAI children.

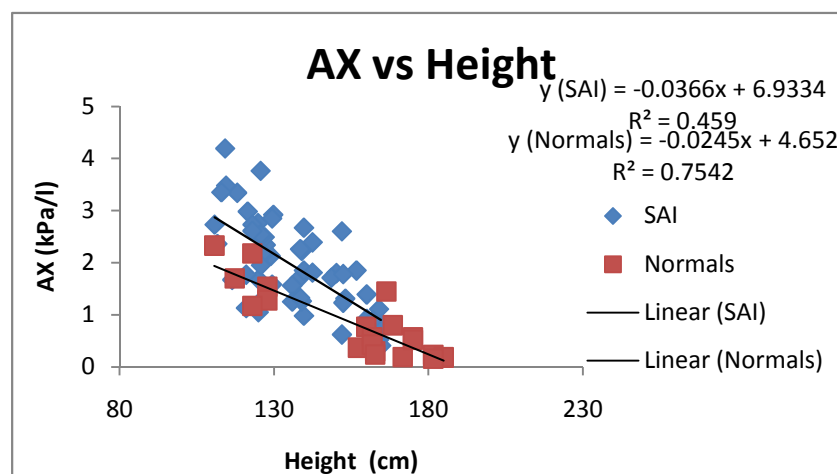


Figure 6.17 AX vs Height in all subjects and measurements (2006 pre-B, 2008 pre-B and 2008 post-B)

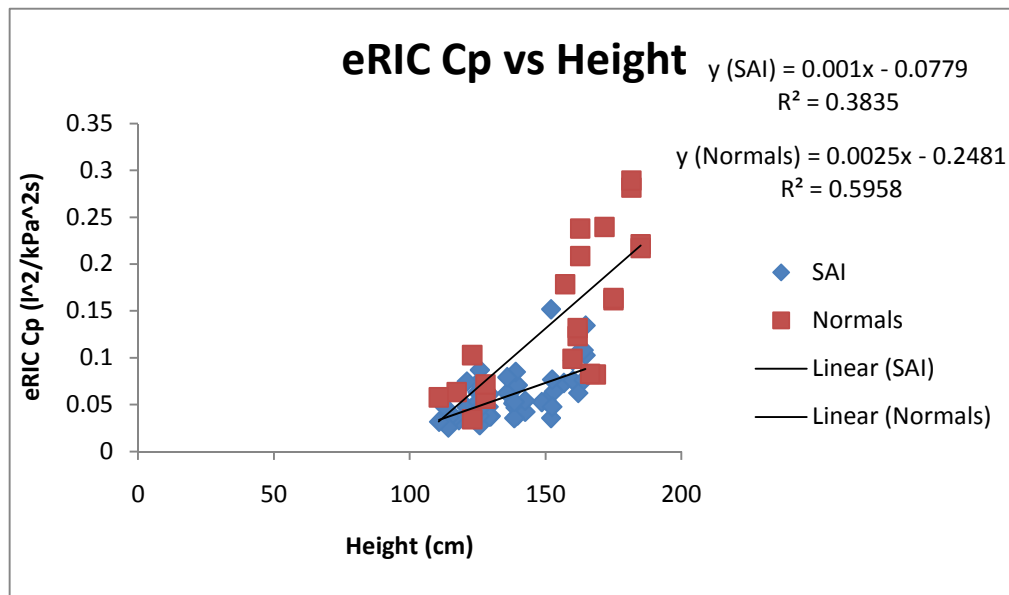


Figure 6.18 eRIC Cp vs Height in all Subjects and Measurements (2006 pre-B, 2008 pre-B and 2008 post-B).

In Table 6.46 we can observe the time change in R5, AX and eRIC Cp averaged data for SAI and *H* children. It can be observed that values of R and AX decreased with time (from 2006 pre-B to 2008 pre-B) and also showed a decrease with bronchodilation (2008 pre-B and 2008 post-B data) as expected; noticing that the largest decrease occurs in AX and is observed in pre- and post-B data for SAI children suggesting that AX can be a better discriminating parameter than R5 between SAI and *H* children.

For the eRIC Cp parameter we can see an increase with time (from 2006 pre-B to 2008 pre-B) and also with bronchodilation (2008 pre-B and 2008 post-B data) also as expected. We can observe the largest increase in *H* children with time change (from 2006 pre-B to 2008 pre-B) meaning that *H* children's peripheral compliance increases with growth better than with bronchodilation and to a better extent than for children with SAI.

Table 6.46 Time change in SAI and *H* children IOS and model parameters (averaged values)

Tests	SAI			Healthy		
	R5 (kPa/l/s)	AX (kPa/l/s)	eRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)	R5 (kPa/l/s)	AX (kPa/l/s)	eRIC Cp (l <sup>2</sup> /kPa <sup>2</sup> s)
<b>2006 pre-B</b>	0.73	2.51	0.045	0.52	1.09	0.115
<b>2008 pre-B</b>	0.63	2.00	0.056	0.43	0.80	0.155
<b>2008 post-B</b>	0.53	1.34	0.076	0.38	0.57	0.173



Zeltner et al. (99) performed a study about postnatal development and growth of the human lung, concluding that this process is made of three overlapping stages: (a) the *alveolar formation stage*, which begins in the final stage of the fetal life (36<sup>th</sup> week) and ends between 1 and 1.5 years post partum, (b) a *stage of microvascular maturation*, thought to extend from the first month after birth to the age of 2 to 3 years, (c) the *normal growth period* starts after the microvascular maturation stage and lasts until body growth stops, during this period lung development is considered complete, then normal growth comprises only normal increase in lung size. Then it merges into a period of stable lung dimensions, until aging sets in. This study confirms a previous study about postnatal human lung growth (100) where it is stated that there is rapid alveolar multiplication during the first two years of life, and there is little or no increase in the total number of alveoli after the age of 2 years. It was also stated by Zeman et al. (101) in a more recent study about small airways and alveoli that from childhood (age 6 years) to adulthood, the number of respiratory units is maintained constant, while both the smallest bronchioles and alveoli increase in size to produce the enlarged lung volume with increased age and height. In healthy children growth resistance of the lungs is expected to decrease with age.

Mild to moderate asthma results in a pattern of airway obstruction that increases in magnitude from age 5 to 18 years (102). Several studies have shown that asthma results in a reduced acceleration of lung growth (103). Lung function in children with severe asthma is reduced in childhood years and decline in adult life to levels consistent with adult obstructive lung disease. This is the reason why early detection and treatment to prevent airway remodelling in childhood is extremely important as it may reduce the risk of long term complications of childhood asthma (104).

Elastic recoil (compliance) of the lungs is low in young children and increases with age; therefore it is possible that asthma could result in a failure for this increase in elastic recoil development (103). For this reason in this research it was decided to analyze Cp (peripheral Compliance) as a measure of lung periphery elastic properties in the two years period.

Figures 6.19 and 6.20 exemplify growth related changes in eRIC Cp in all *H* and SAI children. A better correlation was found for eRIC Cp *H* children (slope = 1.053 and  $r = 0.796$ ), comparing 2006 pre-B vs 2008 pre-B data, than for SAI children (slope = 1.2151 and  $r = 0.654$ ).

A similar but slightly better correlation was found for aRIC Cp in *H* children (slope = 0.877 and  $r = 0.70$ ), comparing 2006 pre-B vs 2008 pre-B data, than for SAI children (slope = 0.562 and  $r = 0.426$ ).

Figure 6.19 illustrates growth development in Healthy children, and Figure 6.20 could imply a reduced acceleration of lung growth in children with SAI.

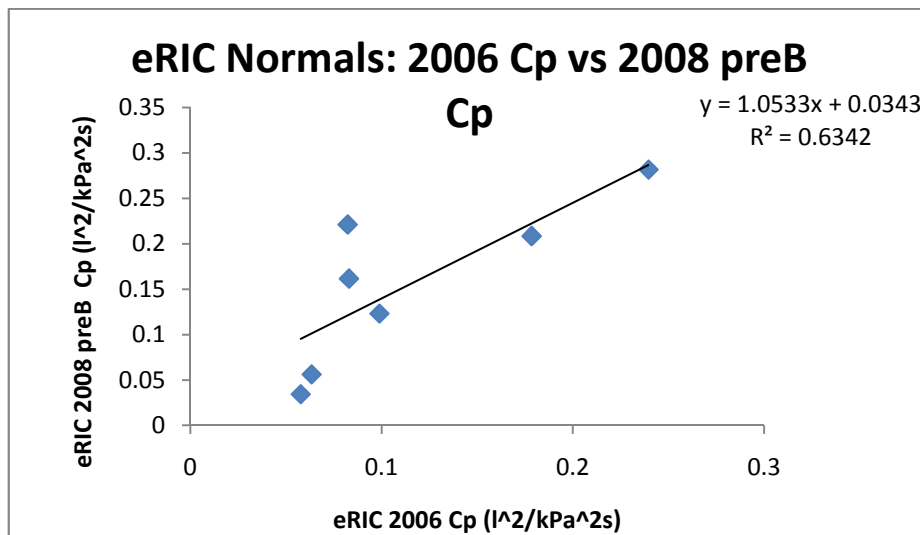


Figure 6.19 Growth changes in eRIC Cp for all H Children.

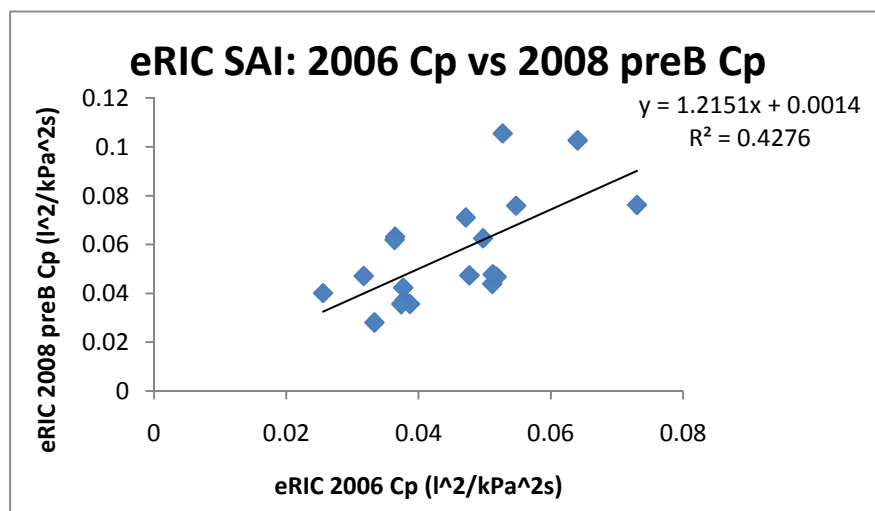


Figure 6.20 Growth Changes in eRIC Cp for All SAI Children

For a long time, small airways have been considered to be the area of focus in asthma and there is already a substantial body of evidence to support the importance of small airways disease in asthmatic patients (80) (105). Small (peripheral) airways refer to about 7 to 19<sup>th</sup> generation airways with an inner diameter of about 2 to 0.5 mm (53) (106) (107). These airways are considered to be an important site of inflammation in both early chronic obstructive pulmonary disease and asthma. It is estimated that small

airways resistance contributes 15 to 24% of airway resistance in healthy (normal) people and much higher in patients with severe diseases. It has also been stated that for subjects with nonasthmatic allergic disease (atopy) early manifestation prior to asthma could be early Small Airway Disease (SAD) also known as Small Airway Impairment and then if inflammation persists, asthma would appear (53).

Even though the importance of the small airways in asthma and other pulmonary diseases is established, clinical assessment of the peripheral airways continues to be a challenge to date (107) and a means of studying the small airways have never been readily available to clinicians (105). The silent zone of the lung (small airways) can become a seat of inflammation and fibrosis from varied sources like Small Airway Impairment leading to small airways distortion ending in functional abnormalities. These abnormalities are evident because of the increased resistance to airflow at a lately detected stage when the condition has become severe. Such circumstances demand early diagnosis to prevent pulmonary complications (108).

Asthmatic patients present a progressive deterioration of lung function, and this deterioration seems to be more evident in younger asthmatics whose disease is not well controlled. Therefore, early evaluation and therapy for small airways might be even more effective when started earlier in the course of the disease (105).

It is observed that in healthy lung growth, airway resistance decreases with age. Peripheral resistance increases significantly in asthmatics with airflow obstruction compared with central resistance, suggesting that the peripheral airways are the predominant site of airflow obstruction in asthma (107).

An effective means to evaluate small airways performance could be achieved by integrating realistic models of lung function based on physiological measurements made by FOT and other techniques (80). In this research we aimed to analyze and offer sensitive measures for healthy and impaired respiratory conditions such as SAI, by using the well-established IOS parameters R5, R5-R20 and AX, as well as the aRIC and eRIC model parameters such as Cp and Rp.

The significant differences found between SAI and *H* groups, illustrated in tables 6.36 and 6.37, confirm the ability of the analyzed IOS parameters: R5, R5-R20 (fdR) and AX, as well as model parameter Cp (for both aRIC and eRIC models) to differentiate between obstructed and non-obstructed airways. It is also demonstrated in these tables that values of IOS parameters and both Rps in both models are higher in children with SAI than in *H* children. It is also clear that Cps for both models are higher in *H* children than in children with SAI, as expected.

In Tables 6.42 and 6.43, the significant differences observed in the SAI group in all IOS parameters (R5, R5-R20 and AX) and model parameters (eRIC and aRIC Rp, and eRIC Cp), comparing baseline (pre-B) data in 2006 with pre-B 2008 data suggest an abnormal lung growth development due to the presence of the illness in the two year period. In contrast no significant differences were seen for *H* children in the same parameters during the same period of time, with the exception of R5, which may be attributed to the noise previously reported to occur in low frequency resistance and reactance measurements (73).

As illustrated in Figure 6.11, the AX parameter is greater in children with SAI than in *H* children. An improvement in lung function will imply a decrease in AX value and AX, as stated before, reflects small airway function (73). In Table 6.44 it can be observed that the AX decrease presented as percentage of change in baseline (pre-B 2006 and pre-B 2008) IOS data, is greater in *H* children than in children with SAI, a -27% for *H* children and a -20% for children with SAI (a negative sign means a decrement). These results imply that AX demonstrated a higher decrease in the two years period in *H* children, indicating improved lung function that could be attributed to normal lung growth in this group. Furthermore, AX showed a lower decrease in children with SAI suggesting an impaired lung growth due to their illness. In addition, as stated before, significant differences were observed in the SAI group comparing 2006 and 2008 baseline data and no significant ( $p>0.05$ ) differences were found in the *H* group in the same period. These results suggest that AX might be a good IOS index used to differentiate changes over time (2 years) in lung function (impaired and non-impaired).

These findings agree with a recent study performed by Larsen, et al. (26) comparing IOS AX parameter with spirometry parameters, where it was concluded that the pattern of improvement seen in AX (XA), over the course of therapy, suggests that IOS might detect alterations in airway mechanics not reflected by spirometry. In a study on clinical applications of FOT, Goldman developed an integrated response index for X, AX (73), now called the “**Goldman Triangle**”, previously explained in this study. Goldman also explained the history of the phenomenon called “frequency-dependence of resistance (fdR)” in this study.

There are several studies which are in agreement with the results presented here about the IOS parameters fdR (R5-R20) and AX being the indices most closely related to small airway function (26) (74) (109) (110) (111) (72) (112) (97). Even though these research studies suggest the potential effectiveness of IOS parameters there are still concerns about the effects of upper airway structures (like upper airway shunt) (71) (112); and additionally there is a necessity for establishing normal values as well as reproducibility studies for IOS parameters (71).

Infant's airways structure and proportions are different than those of the adult, and the relative greater lung compliance may accentuate the functional differences (113). In children with SAI, lung compliance is lower than that in normal or healthy children. As it is observed in table 6.41 for both models, the  $C_p$  is higher in  $H$  than in SAI children. An improvement in lung function will produce an increment in  $C_p$  value. In table 6.44 it can be observed that the eRIC  $C_p$  increment presented as percentage of change in baseline (2006-2008) IOS data, is greater in  $H$  children than in children with SAI, a 35% for  $H$  children and a 25% for children with SAI. This higher percentage of improvement in  $H$  children for  $C_p$  may indicate (as AX would), an improved lung function in  $H$  children (normal lung growth). Whereas a lower increment in SAI group could represent impaired lung function and growth. Similarly significant differences were observed for SAI group in eRIC  $C_p$  parameter comparing 2006 and 2008 baseline data. These results also suggest that the eRIC  $C_p$  may be a good index capable of differentiating changes over time (2 years) in lung function (impaired and non-impaired).

Goldman et al. (112) developed a similar study closely related to this research, in adolescents and young adults with Cystic Fibrosis, and in asthmatic adults, obtaining very similar results to our results previously reported, and stating that the eRIC model parameters are reliable and present a slightly better correlation with IOS parameters compared to the aRIC model parameters, concluding that the less complex and more intuitive eRIC model may be more suitable for clinical diagnosis and evaluation after treatment. Goldman et al. concluded that IOS indices of SAI are modelled similarly well with and without upper airway shunt capacitance ( $C_e$ ) for good quality IOS data, and do not seem to be dependent on upper airway shunt capacitance. This is to be expected since the IOS indices are based on low frequencies up to 20 Hz, whereas the upper airway shunt capacitance in the aRIC manifests significant, increasing effects on respiratory impedance only at higher frequencies (above the resonant frequency).

## Chapter 7: Conclusions

The results from this research work suggest that R5-R15 (frequency-dependence of resistance) seemed to be a sensitive index for gender differences in lung function between asthmatic males and females in Anglo subjects. As high correlation between  $AX_{\text{measured}}$  and  $AX_{\text{calculated}}$  values was observed, it is stated that  $AX_{\text{calculated}}$  is a good approximation to the measured AX value.

Significant differences were found between the eRIC and aRIC model parameters in several of the published papers. Statistically significant differences between Anglo nonasthmatic (normal) and Anglo Asthmatic children were found for almost all of the model parameters with the exception of  $C_e$  (R,  $R_p$ , I, and  $C_p$ ). Similarly, statistically significant differences in the same model parameters between normal Hispanic and asthmatic Hispanic children were found. It seems that differences between Normal and Asthmatic children were larger, by a factor of two, for peripheral airways than for large airways. After these results were observed, it was concluded that the aRIC model allows clear discrimination between Normal and Asthmatic Anglo and Hispanic children.

Comparing Anglo and Hispanic adolescents IOS data and model parameters, R5, R5-R15 and AX did not present significant differences between these groups. Therefore, it is concluded in this research that despite a slightly greater BMI in Hispanic adolescents, there were no differences in lung function parameters reflective of peripheral airway dysfunction that might suggest genetic differences in adolescents living in similar urban environments.

Similarly it was observed that in an urban environment with diminished air quality, Hispanic and Anglo children whose R and X were normal for age and size do not differ. Among children whose IOS R and X are consistent with significant SAI, Hispanic children are more severely affected than Anglos, with increased large and small airway resistances.

The present study has shown that equivalent electrical circuit model parameters were able to track changes in respiratory system function after bronchodilation. Both the eRIC and aRIC models clearly distinguished between children who were normal (or possibly had mild small airway impairment (SAI), who showed no significant changes with bronchodilator (BD)), and those who were asthmatic with SAI, both at baseline and regarding the pre- to post-BD changes in lung function. The eRIC model

showed an apparently larger peripheral airway compliance ( $C_p$ ) than the aRIC model, probably because it might include some of the “extrathoracic airway compliance” ( $C_e$ ). eRIC model also failed to show significant change in inertance ( $I$ ) post-BD in the Asthmatic group, while the aRIC did. On the other hand, the eRIC model is more parsimonious, and the parameter,  $C_e$ , 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 or possible SAI were relatively similar in both IOS and the aRIC model parameters, with however, clear increases in  $R_3$ ,  $R_5$ ,  $R_3$ - $R_{20}$ ,  $R_5$ - $R_{20}$ ,  $AX$ ,  $F_{res}$ , and  $R_p$ , and a clear decrease in  $X_3$ ,  $X_5$  and  $C_p$  going from normal to possible SAD.

Going to increasingly abnormal levels of "diagnostic classification,"  $R_5$ ,  $R_5$ - $R_{20}$ ,  $AX$ ,  $F_{res}$  and  $R_p$  continue to increase from PSAI to SAI to Asthma, while  $X_5$  and  $C_p$  decrease in this progression. Differences between SAI and Asthmatic children were modest.

While expert clinician diagnostic classification distinguished between children based on 4 levels of perceived normality of 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.

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  $C_p$  was the best correlation in both pre-B work and pre- and post-B work.

According to our expert clinician the range of values of every analyzed feature, measured and estimated IOS parameters:  $R_3$ ,  $R_5$ ,  $R_3$ - $R_{20}$ ,  $R_5$ - $R_{20}$ ,  $X_3$ ,  $X_5$ ,  $AX$ ,  $F_{res}$ , eRIC  $C_p$ , eRIC  $R_p$ , aRIC  $C_p$  and aRIC  $R_p$  obtained for the SAD and Asthmatic groups were comparable to those values observed in other Asthmatic children of the same age range.

For the pre- and post-B work comparing Pre- and Post-B IOS and eRIC and aRIC model parameters in the Normal group, no significant differences were observed. Also comparing Pre- and Post-B for the PSAI group only  $R_3$ ,  $R_{35}$  and the eRIC  $R_c$  presented significant differences. Similarly

evaluating Pre- and Post-B for the SAI group the following parameters presented 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 for the Asthmatic group all of the parameters presented 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) presented a good correlation with children Height.

In the pre- and post-B work over a two-year period the following conclusions were reached:

IOS parameters differed consistently between Healthy and SAI children over a two-year period. SAI children showed smaller trend of “growth” in IOS parameters R5, R5-R20 and AX comparing 2006 pre-B and 2008 pre-B data; and larger trend of bronchodilator responses than H children in R5, AX, the eRIC Rp and Cp, as well as the aRIC Cp parameters. The AX and eRIC Cp parameters showed larger differences between pre-B and post-B data.

The eRIC and aRIC model parameters Cp and Rp track IOS indices of small airway function. Peripheral airway compliance (Cp) is a more sensitive index than peripheral airway resistance (Rp). The eRIC and aRIC Cp are significantly larger in H or Normal than SAI children, showing larger p values for the eRIC Cp; while for both models, Rp did not show significant differences between H and SAI children.

Model calculated parameters Rp and Cp are narrowly comparable between both analyzed models (aRIC and eRIC). In the same manner Rc and I similarly present a good correlation in both models. Both the eRIC and aRIC Cp parameters showed significantly good correlations with AX; with the eRIC model resulting in a higher r value than the aRIC model.

In this research study in 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, it may be considered a more suitable diagnostic tool for clinical applications than the aRIC model.

IOS lung function data are similarly well-modelled 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  $C_e$ . The eRIC model is a more parsimonious and equally powerful model in capturing the differences between SAI and H children, therefore it is presented 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  $C_p$  are the most reliable parameters to track small airway function in children before and after bronchodilator and over a time period (2 years). AX (the "Goldman Triangle"), representing the integrated low frequency respiratory reactance magnitude between 5 Hz and  $F_{res}$ , and the eRIC  $C_p$  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 of 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 to evaluate changes over time (two-year period) and a statistical analysis should be carried out 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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## Appendix A

### IOS Calibration

1. Assemble the IOS equipment, if it is required, and be sure that all the equipment components are airtight. This is extremely important for the proper operation of the equipment.
2. Turn on the computer. Double-click the LAB Jaeger Lab Manager Icon and you will be placed in the initial (star-up) IOS screen. Wait 5 minutes to allow the system to warm up. You can see a clock showing the time countdown at the top center of the screen. You will automatically be placed into the main IOS screen.
3. Look at the bottom of the main screen and you will find several tabs: Main group, Data Base, Calibrations, Generation, and Utilities.
4. The first thing you need to do is the Calibration of the equipment. Double click the Calibration tab and you will see two icons: Ambient Conditions and Volume Calibrations.
5. If the equipment has been moved to a different location, as is the case in the home visits made in this project, it is important to check if the Ambient Conditions have changed. If you move the equipment to another location into the same city, it is probable that the only parameter that may change is the Temperature. Measure the temperature inside the room where you placed the IOS equipment with a regular thermometer, then double click the Ambient Conditions icon and update the temperature, if it is required, erasing the old temperature number and entering the new value. Be sure you enter the temperature in the correct units set in the equipment (e.g. °C or °F). Click OK and this will bring you back to Calibration screen. If the equipment has not been moved to a different location, as is the case for the test performed in the clinic set in this project, you do not need to check the ambient conditions once they are set.
6. The calibrations that need to be set every day, before you start doing any IOS test, are the Volume and Pressure Calibrations.
  - a. Volume Calibration:
    - i. Open the terminal resistor door at the back of Y-connector (white plastic connector with a moveable Terminal Resistor door)
    - ii. Double click on Volume Calibrations. On the left you will see a screen flow vs volume diagram, and on the right the calibration factors. The Flow vs Volume diagram has a dashed white marker at 3L.
    - iii. Click on the number one icon shown in the upper left of the screen to begin the volume calibration. You will see a dialog box indicating you should press ok to begin the zero measurement and click OK.
    - iv. Use the fixed resistance straight beige plastic tube attached the 3L syringe to the open end of the plastic angle connector. Fit it tightly to avoid any air leakage and be sure this attachment is airtight for the proper operation of the equipment.
    - v. Pull the syringe back and forward at a speed similar to your normal inspiration and expiration. You will see, in the Flow and Volume diagram, a flow-volume loop traced. Make sure the end of the syringe stroke corresponds closely to the vertical dashed white marker (3L), if it does not correspond it could be because you forgot to open the terminal resistor door.
    - vi. Pull on the syringe back and forth. The first strokes are erased and the last 6 strokes will be saved. After this the new calibrations factors will appear at the right portion of the screen.
    - vii. In the calibration factors screen you will see a table with the Corrections factors CorrIN (Correction factor for Inspiration) and CorrEX (Correction factor for



- Expiration) in the first two rows, and three columns: Old (old calibration values), New (new calibration values), and %Old (difference between new and old calibration). The important issue that we have to carefully check is that the New CorrIN and New CorrEX should not be different by more than 3% from the Old values. If everything goes ok you will see a message at the bottom of the screen saying “Calibration successful”.
- viii. To verify the stability of the calibration repeat the calibration immediately, after finishing the previous calibration. Click icon 10, and you will see a window asking “Save Calibration?” Click on yes to save the calibration and go back to the calibration screen. Repeat the previous steps to perform the calibration again.
  - ix. After finishing the calibration process, click on main group tab in the bottom of the screen to go back to IOS main screen.
- b. Pressure Calibration:
- i. The Pressure Calibration ought to be done after you perform the Volume Calibration.
  - ii. Double click on the Patient Data icon. This will take you to the Patient Data Screen.
  - iii. Enter CAL in last and first name. Enter any 3-6 digit number for Identification and enter a birth day month/day/year (use four digits for the year), and press enter
  - iv. You will see a tab highlighted with the sex in it saying “Female”. Press enter if you want to leave it like this, or press the space bar if you want to choose male.
  - v. Next, enter a height and weight (it can be your own height and weight).
  - vi. Click on icon 10 (or press F10) to go back to the main IOS screen to perform the Pressure Calibration.
  - vii. You will see in the top of the screen the last and first name you just entered to do the Pressure Calibration, CAL, CAL. Check this every time you do the pressure calibration, this will make you sure that you are saving the pressure calibration data in the correct place.
  - viii. The Calibration Pressure is done by performing an IOS test using the Fixed Reference Resistance as patient.
  - ix. Close the terminal resistor door.
  - x. Position the 0.2 kPa/L/s reference (fixed) resistance over the end of the angle connector using the same fixed resistance straight beige plastic tube you just used to attached the syringe; make sure the connection be airtight.
  - xi. Double Click on Impulse Oscillometry Icon to enter to the IOS test screen. You will see a dialog box asking you to not approach the mouthpiece to do the zero adjustment. Be sure you always allow the system to do the zero adjustment before the patient places his/her mouth on the mouthpiece.
  - xii. After this you will hear a continuous popping from the loudspeaker. Wait a couple of seconds and press icon 2 to begin data saving. Do this test for 10 seconds and click on icon 7.
  - xiii. After this you will see 5 windows in the screen. Check that the calculated numerical values be 0.2kPa/L/s for R displayed in the upper right window. In doing IOS tests in homes you will find that this value changes up to 0.21kPa/L/s. This is because of the increased temperatures inside the houses, but if the value goes up more than this amount go to Reference Manual Troubleshooting.
  - xiv. Click on icon 10 to exit this screen. This will show you a dialog box saying “Save measurement?” Check that the adjacent circle to New Test has a black dot, and be

sure the saving primary data and default box inside this dialog box be checked, this is extremely important otherwise your data will not be properly saved, after this click yes.

### **Archiving IOS Data**

1. First check where the data are being saved following the next steps:
  - a. Press Control, Alt, Shift and S. This will show you Service tools
  - b. You will see the Icon DatGen highlighted in upper left. Double click on it and you will see a window labeled Database-Generation -V4.xx This window has two columns: to the left is Local and to the right is Network.
  - c. Look at the Local site to see where the data are being. You will enter this as “source database.” In this research, we found that the data was stored in C:\LAB\DB for the computers we used, the Utep laptop and WSMR Clinic PC.
2. To back up your IOS data do the following:
  - a. Double click Windows Explorer.
  - b. Select My Computer.
  - c. Select Local Disk (C:)
  - d. Click on FILE (upper left).
  - e. Select New, and then click Folder.
  - f. Place the cursor in new folder and type DATAforMDG and hit enter. For this research several folders were created inside this folder and approximately the IOS data for 5 children was saved in each one. The name chosen for each folder had the next information:
    - i. Folder number
    - ii. The place where the original data was stored (PC2 WSMR or Laptop)
    - iii. Race
    - iv. Children number saved in each folder (e.g. 1-5)
  - g. Exit Windows Explorer.
  - h. Go into LabManager and to the main IOS screen.
  - i. Click on Actions (upper left top bar).
  - j. Select Generate Lab Manager.
  - k. Enter password (abcd) and press enter; you will now see a screen of main group icons with rectangles all over screen.
  - l. Double click on any empty rectangle to get a new dialog box.
  - m. In this new dialog box entitled Add New Program, click on down arrow next to blue bar.
  - n. Select Database Utility Merge from resulting menu and press OK.
  - o. This new created icon will appear in previously empty rectangle on main screen.
  - p. Click Generation (upper left top bar).
  - q. Select End Generation Mode at bottom of drop down menu.
  - r. You will now have main group screen (without rectangles) with the new added icon. Once you create this icon you will just double click it every time you want to do a data base back up.
  - s. Double click this Database Utility Merge icon and in resulting dialog box entitled settings, click Select button under Source Data Base.
  - t. In resulting dialog box entitled Open, double click C in middle window, scroll down to Lab and select it with a double click.

- u. Double click DB and then click OK
- v. C:\LAB\DB will now appear under Source Database
- w. Click select button under Destination data base
- x. Double click C in middle window and scroll down to DATAforMDG data and double click it, scroll down again to select the appropriate folder were you are going to store the data and double click it and then click OK.
- y. C:\ DATAforMDG\ (folder name) will now appear under Destination Database
- z. Now click Create Database button under Destination Database
- aa. **NOTE!! NEVER click create database when c:\LAB4\DB (your main database on your hard drive) is listed as destination database, or you will ERASE ALL YOUR DATA if you execute this command!!**
- bb. Now look two thirds of the way down the dialog box and find "Consider date." Enter appropriate dates in the box next to FROM and in the box next to UNTIL and click OK (upper right). This will transfer data from the beginning date to the until date to your new archive on C.
- cc. If you or somebody else has tested patients on a given date that are NOT to be included in the data you wish to transfer, then look just below the Consider Data box and use the Single Patient box. Enter the exact patient ID in the small window labeled Identification and NOT enter anything in the Test number small window if you want that all tests on this patient on all dates are transferred. Then click OK.
- dd. Exit out from this by clicking on X in upper right
- ee. This newly copied data can be checked by examining it under Windows Explorer. It will have 18 files, with the largest one named MLDATA.DAT

**This whole folder can then be zipped and then copied to the USB stick.**

## **Vita**

Erika Guadalupe Meraz Tena earned her Bachelor of Engineering degree in Electronics Engineering from the Technological Institute of Chihuahua, Mexico in 1999. She received her Master of Sciences degree in biomedical engineering in 2003 from the University of Surrey, United Kingdom. In 2006, she joined the doctoral program in electrical and computer engineering at the University of Texas at El Paso.

While pursuing her degree, Dr Meraz Tena worked as a research assistant on a National Institute of Health funded project on border asthma. She is currently a researcher professor at the Autonomous University of Ciudad Juarez where she has been teaching since 2004. Most recently, Dr Meraz Tena, was a receipt of a Dodson Dissertation Fellowship. Dr Meraz Tena has presented her research at international conferences and workshop meeting in biomedical engineering and pulmonary medicine. She has authored and co-authored several conference papers and was recently publishe in BioMedical Engineering Online Journal.

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