Repeatability of Respiratory Impedance and Bronchodilatory Response in Asthmatic Children

by

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Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
March 2016

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Abstract

Asthma is a chronic illness that affects approximately 10% of children in the developed world. Objective assessment is recommended using spirometry to obtain the forced expired volume in 1 second (FEV1), usually combined with inhaled bronchodilator to assess airway reversibility. However this measurement is often not done, possibly due to the difficulty involved in the test. A potentially easier to perform measurement is oscillometry which obtains the respiratory system resistance, Rrs and reactance, Xrs but little evaluation has been done to compare this to spirometry. This thesis compares the sensitivity and repeatability of oscillometry to spirometry during reversibility and develops a 'signal to noise' measure assessed in children with asthma.

List of abbreviations used

ANOVA	Analysis of Variance
AOS	Airwave Oscillmetry System
ATS	American Thoracic Society
ACT	Asthmatic Control Test
BD	Bronchodilator
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
Crs	Respiratory System Compliance
Ers	Respiratory System Elastance
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
FEV1	Forced Expired Volume in One Second
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
Irs	Respiratory System Inertance
IOS	Impulse Oscillometry System
PEF	Peak Expired Flow
PFT	Pulmonary Function Test
PQSI	Pittsburgh Sleep Quality Index
RIV	Respiratory Impedance Variability
Rrs	Respiratory System Resistance

RV	Residual volume
SDRrs	Standard Deviation of Respiratory System Resistance
SDXrs	Standard Deviation of Respiratory System Reactance
TLC	Total Lung Capacity
VAR	Variation in Airway Resistance
VAX	Variation in Airway Reactance
VC	Vital Capacity
Xrs	Respiratory System Reactance
Zrs	Respiratory System Impedance

Chapter 1: Introduction

1.1 Overview

Asthma is a chronic illness that affects approximately 10% of children in the developed world. Objective assessment is recommended using spirometry to obtain the forced expired volume in 1 second (FEV1), usually combined with inhaled bronchodilator to assess airway reversibility. However this measurement is often not done, possibly due to the difficulty involved in the test. A potentially easier to perform measurement is oscillometry which obtains the respiratory system resistance, Rrs and reactance, Xrs but little evaluation has been done to compare this to spirometry. This thesis compares the sensitivity and repeatability of oscillometry to spirometry during reversibility and develops a 'signal to noise' measure assessed in children with asthma.

We measured 53 school aged children using standard spirometry and oscillometry using the tremoFlo system, with 3 repeated measures both before and after an inhaled bronchodilator. We calculated the sensitivity to BD as the %change in FEV1, Rrs and Xrs, and we calculated the variability of these measures using their coefficient of variation. We developed the signal to noise ratio as the sensitivity normalized to the COV as the SNR_BD_FEV1, SNR_BD_Rrs and the SNR_BD_Xrs. We found that, in response to BD, FEV1 increased by 7.1(6.2)%, while Rrs decreased by 25.3(10.5)% and Xrs became less negative by 26.9 (20.5)%. However both Rrs and Xrs were more variable, with their COVs about 2.5-fold and 6-fold respectively greater than the COV of FEV1. Importantly when we compared the SNR_BD between impedance measurements (FOT) and FEV1, we found that while the SNR_BD for Xrs5 and FEV1 were not

significantly different, the SNR_BD for Rrs5 was nearly 2 times greater than SNR_BD for FEV1 ($p < 0.0005$). This means Rrs at 5 Hz may be a more useful measure of the response to a bronchodilator in children with mild asthma. In conclusion, since oscillometry had better signal-to-noise, and is easier for patients to perform, and because it directly measures the difficulty of moving air in the respiratory system, we recommend oscillometry to assess reversibility in children with asthma.

1.2 The Respiratory System and the Mechanics of Breathing

The primary role of the lung is gas exchange. The lung has other functions as well; it acts as a reservoir for blood, it filters unwanted particles from the blood and it also involved in immune and metabolic functions such as collagen and elastin protein synthesis and acid base balance. Gas exchange involves the movement of oxygen into the lungs during inhalation and the removal of carbon dioxide during exhalation. For the purposes of this thesis, the respiratory system is made up of the moving elements, the conduction and the gas exchanging compartments that comprise the mechanical components responsible for movement of air. These include the conducting path from the mouth and nose to the lung via the trachea, the lungs, the pleura, the rib cage and the diaphragm. The lungs are typically thought to consist of two zones; namely the conducting zone and the respiratory zone. The conducting zone is made up of the nasal cavities, para nasal sinus, pharynx, larynx, glottis, trachea, bronchi and bronchioles while the respiratory zone where gas exchange with the blood can occur is made up of respiratory bronchioles, alveolar ducts and alveoli.

Another division of the airways is into the upper airways, the central airways and the small peripheral airways. The upper airways include the pharynx, larynx and glottis while the central airways include the trachea below the larynx and glottis and all airways greater than 2 mm in diameter. The small peripheral airways are all airways less than 2 mm in diameter.

The structure of the airways is like that of a tree, the trachea branches off into the left and right main bronchi, which then branch off into smaller bronchial tubes. When we take a cross section of any of these tubes we can see the wall components of the airway. The airway is made up of the lumen inside, while the airway wall consists of connective tissues and mucus glands. In the middle of the airway wall, there is the smooth muscle which circles around the airway and which when activated can contract excessively resulting in airway obstruction in diseases such as asthma (described in the next section).

The mechanics of how the respiratory system moves airs into and out of the lung is called the mechanics of breathing and involves the resistance to airflow through the airways, the stretch of the tissues including lungs and ribcage tissues with inflation as well as the mechanics during deflation. It is necessary to overcome the mechanical forces to move air into and out of the lungs, which allows the body to take in oxygen (inhalation) and remove carbon dioxide (exhalation). The primary muscles of breathing are mainly the diaphragms but also the muscles of the rib cage muscles known as the intercostal muscles.

When we inhale these muscles contract, which expand the lung and move the diaphragm down. The airflows down from nose and mouth to the major bronchial led to the open airways (bronchial tubes) and end into the alveoli. At the same time gas

exchange occurs between red blood cells and the alveoli located in the capillaries. The blood becomes oxygen –rich and the carbon dioxide moves into the alveoli and bronchial tubes toward to the nose and mouth is known as exhalation. In exhalation the diaphragm and rib cage muscles are relax, which make the lungs smaller.

1.3 Asthma

Asthma is one of the most common chronic conditions that occur in children, characterized by a number of variable and recurring symptoms as well as reversible airflow obstruction and bronchospasm. It is also associated with airway inflammation and airway remodelling. Individuals with asthma experience symptoms that include wheezing, coughing, chest tightness and shortness of breath[1]. The prevalence of asthma is increasing across the world and Canada is no exception to this phenomenon. The report from the International Study of Asthma and Allergies in Childhood (ISAAC) in 2007 reported on the high prevalence of childhood asthma, combining data from several studies. In the age range of 6 to 14, from 40 countries, prevalence ranged from 2.1 to 32% and was highest in English speaking countries and Latin America. Of note was the significant increase in asthma among preschool children[2].

According to statistics Canada, in the years 1994/1995, 11% of Canadian children under the age of 11 were diagnosed with asthma. By 2000/2001 the prevalence of the disease had risen to 13%. Overall statistics on the prevalence of asthma in Nova Scotia suggest that the provincial rate is higher than that of the rest of Canada with 10.8% of the population having the disease overall, compared to 8% in the rest of Canada[1,3].

In asthma, airways narrow in the lung due to inhaled allergen or can be induced from exercise [4,5]. Mucous is also produced in the airways, which leads further reduction in the lumen. Indeed, because the lumen inner surface has fluid and mucous, any reduction in the cross section of the airway leads to a greater reduction in area available for airflow, and the airway can become plugged [6]. With airway narrowing, airway resistance will become higher and the patient may have difficulty breathing. The effects of airway narrowing can be measured by a number of methods, including spirometry and the forced oscillation technique, both of which are the main technologies used in this thesis to assess asthma and are described in more detail below (Section 3).

The assessment of asthma is aided by the use of inhaled drugs, and depending on the drug can either relax or constrict the airway smooth muscle. A bronchodilator which relaxes airways smooth muscle is used for reversibility testing which uses spirometry to assess if the bronchodilator has a strong effect leading to airway dilation and improvements in airflow (described below in the following sections). In addition, inhaled bronchoconstricting agonists, or merely exercise in exercise testing can be used to assess how sensitive the airways are to narrowing, in tests known as airway hyperresponsive testing [7].

Another factor important to recognize in the constriction associated with asthma is the airway narrowing is not the same for all airways. In healthy individuals, all regions of the lungs are relatively homogenously ventilated, which means all alveoli tend to get the same amount of air or similar fractions of new air as they are stretched. However, in asthma some parts of the lungs are poorly ventilated, while others may be preferentially

ventilated, and ventilation becomes strikingly heterogeneous because of the airway narrowing [8].

1.4 Diagnosing Asthma

According to the Asthma Society of Canada, when children have colds they often cough and wheeze, but this is not necessarily asthma. Consequently it is difficult to diagnose asthma in young children, purely based on symptoms. On the other hand, reversibility of airway obstruction is an objective measurement that is strongly associated with asthma. If the airway narrowing is reversed significantly after inhaling a bronchodilator, this is strongly indicative and supports the clinician in the diagnosis of asthma[9].

Indeed, it has been recognized that asthma is substantially over diagnosed, due to the lack of use of objective measures of lung function [10]. Thus lung function tests are recommended for the diagnosis and monitoring of asthma, particularly in children. Currently the only recommended objective measurement is spirometry, described below, but several new measurements are being developed that may offer improved sensitivity, specificity, and repeatability or ease of use. However, in this study we wanted to compare one of those measurements, oscillometry to the current standard spirometry and assess its performance in reversibility testing. Forced Oscillation Technique is easily performed by children compared with spirometry, which requires a learned maneuver, and is not recommended for children less than 6 years old.

1.5 Spirometry

Spirometry is the most common of these tests to diagnose lung diseases. During the procedure, patients are asked to breathe in as deeply as they can and then to forcefully exhale as hard as they can for as long as they are able. A spirometer is a device that measures the volume of air and the speed with which it is exhaled or inhaled. A spirometry test requires that a subject breathe into a mouthpiece with a nose clip placed. The test requires that three adequate and acceptable maneuvers be completed. This is determined by no leaks observed, proper posture during the test, and each test being within 120 ml of each other. When this is achieved the largest or test with the maximal Forced expired volume in 1 second (FEV1) is reported.

There are many measured values that are obtained from spirometry. These include the Forced vital capacity (FVC), FEV_1, Forced expiratory flow 25% to 75%($FEF_{25-75\% \text{ or } 25-50\%}$), Functional residual capacity (FRC) and Peak expiratory flow (PEF). According to current guidelines, the normal range for Forced expiratory volume (FEV1) in one second is >80-120% of the predicted value for the subject (Table1.1).

Table 1.1: Common Measure of Pulmonary Function

Common Measures of Pulmonary Function Name	Abbr.	Description
Forced Vital Capacity	FVC	This is the amount of air that can be forcibly exhaled from the lungs after a deep inspiration.
Forced Expiratory Volume in 1 second	FEV1	This is the amount of air that can be forcibly exhaled from the lungs in the first second of exhalation, measured in litres.
Forced Expiratory Volume in 1 second to Forced Vital Capacity ratio	FEV1/FVC	This is the ratio of FEV1 to FVC. In healthy adults this should be approximately 75 - 80%.
FEV1 percent predicted	FEV1%	This is the ratio of the measured FEV1 to the predicted FEV1 computed from equations that use the subject's height and usually sex and age. The equations are obtained from large studies of healthy subjects.
Peak Expiratory Flow Rate	PEFR	This is the speed of the air moving out of your lungs at the beginning of the expiration, measured in litres per second.
Forced Expiratory Flow 25–75% or 25–50%	FEF25–75% or 25–50%	This is the average flow (or speed) of air coming out of the lung during the middle half of expiration also sometimes referred to as the Maximal Mid-Expiratory Flow (MMEF).
Forced Inspiratory Flow 25–75% or 25–50%	FIF25–75% or 25–50%	Measurement is similar to FEF 25%-75% or 25%-50% except that it is taken during inspiration.
Forced Expiratory Time	FET	This measures the length of the expiration in seconds.

In a study of almost 248 preschool children, it was found that 82% produce just one acceptable spirometry effort out of three [11]. Another study of 313 children with asthma, aged between 3 and 16 years old, 132 were unable to perform spirometry indicating difficulty in performing spirometry in young children [12] .

1.6 Airwave Oscillometry

Unlike spirometry, oscillometry does not require any effort, but still requires the subject to maintain a good mouth seal with the mouthpiece and requires fairly normal breathing [13]. Moreover, with oscillometry, it is potentially faster and as mentioned above it is easier to measure, thus making assessing pulmonary function in young children possible.

Airwave oscillometry (AO), also known as the forced oscillation technique (FOT) is a non-invasive method for measuring lung function by multi-frequency onto the patient's respiratory airflow [14]. The method was introduced in mid-1950 and but only recently with more advanced technology been developed successfully commercially and is currently being used more extensively for research and development as a measure of small airways function.

The principle of this technique is that generated oscillatory pressure waves of about 1 to 2 cm H_2O are superimposed at a higher frequency than the normal breathing rate. In this thesis I used the unit of cm H_2O because it is the conventional unit for pressure in the majority of North America based respiratory literature, 1 cm H_2O= 98 Pa or 0.098 kPa. Consequently the lung mechanical parameters can then be estimated from

the respiratory impedance (Zrs) calculated from the ratio of the pressure to the resulting

flow oscillations at the imposed frequencies of oscillation [15].

$$Zrs(f) = \frac{P(f)}{\dot{V}'(f)} \qquad (1.14)$$

Theoretically the impedance can be calculated from the ratio of Fast Fourier Transform

(FFT) of pressure to flow measured at the subject's airway opening, where f is the

oscillatory frequency, but in practice it is often computed from the average from repeated

windows of the ratio.

$$Zrs = \frac{1}{N}\sum_k \left(\frac{FFT(W(p_k(t)))}{FFT(W(\dot{v}_k(t)))} \right) \qquad (1.2)$$

where k is the index of an individual window, typically of 1 sec duration, W is a

windowing function, usually set to be a Hamming window, and N is the number of

windows used to compute the average Zrs [16]. It is common for the windows to be

overlapping from 50% but some use more overlap to as high as 95%.

1.6.1 Airwave Oscillometry System (tremoFlo)

FLOW VS TIME

(FLOW L/S vs TIME (S); x-axis 0 to 20, y-axis -0.8 to 0.8)
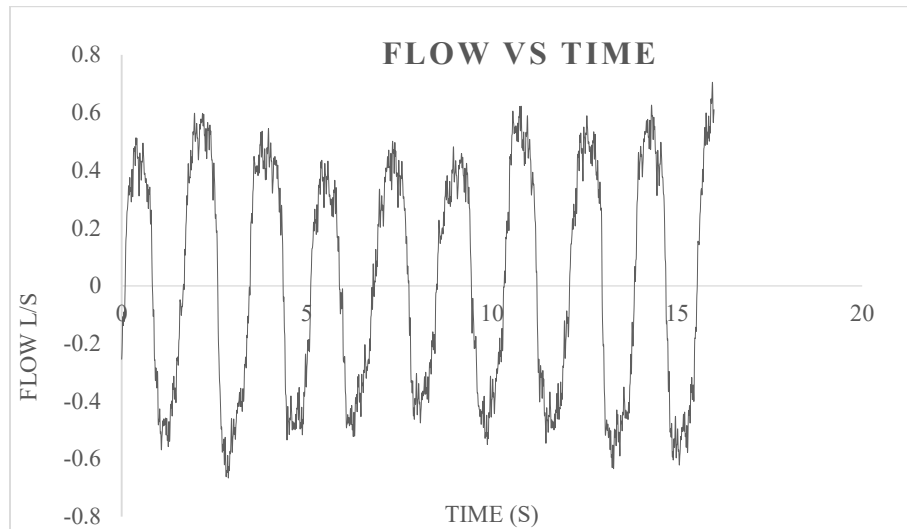
Figure 1.1: Flow versus time measured in a spontaneously breathing subject for 16 seconds. The flow perturbation signal contains 9 frequencies ranging from 5-37 Hz. The large amplitude slower oscillations represent the patient's breathing while the small faster wiggles appearing on the peak and troughs of the patient's breathing represent the perturbation signal from the tremoFlo device
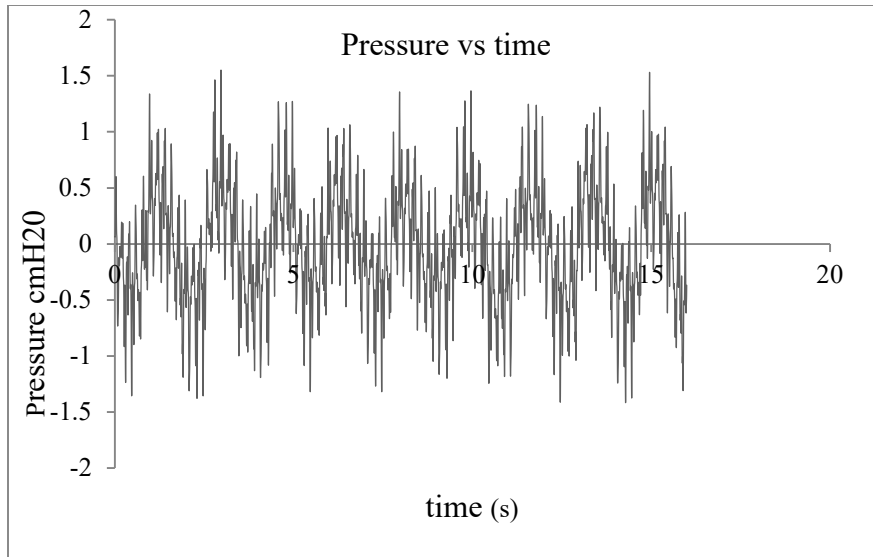
Figure 1.2: Pressure versus time measured in aspontaneously breathing subject for 16 second. A pressure wave of about 1-2 cm H20 is generated from the flow oscillations created by the oscillating screen mesh within the tremoFlo device. This pressure wave is also superimposed on the spontaneous breathing of a subject and the resulting impedance of the respiratory system (Zrs) to the flow oscillations is estimated

Figure 1.3: The hand held component of Thorasys tremoFlo ᵀᴹ with disposable anti-bacterial/anti-viral filter attached.
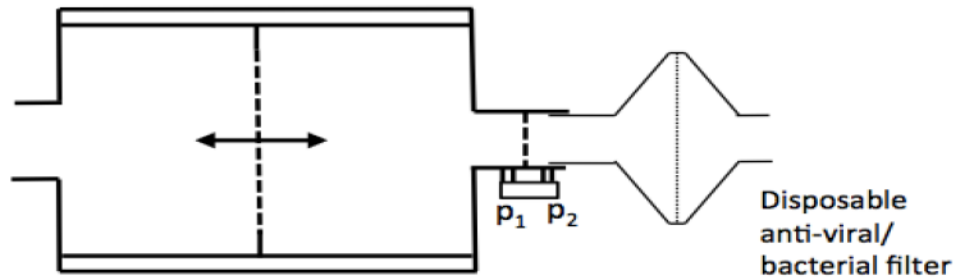
Figure 1.4: Schematic tremoFlo TM showing oscillating mesh (arrows) that generates the pressure, and the fixed front located mesh which with the differential pressure measurement at p1 and p2 is used to compute the flow, with p2 providing the oscillatory pressure measurement.

In this thesis, the system used to measure impedance was the TremoFlo airwave oscillometry device (Thorasys Thoracic Medical Equipment Inc., Montreal, Canada). In

one configuration this system produces an oscillatory wave with nine frequencies over a frequency range of 5 to 37 Hz. The hand held component of Thorasys tremoFlo [TM] is shown in Figure 1.3 with anti-viral bacterial filter attached in the front. The device consists of a handheld unit connected to a base unit or controller that contains much of the electronics responsible for controlling the hand held unit. The schematic of tremoFlo [TM] is shown in Figure 1.4. The important component of the schematic is the oscillating mesh screen, which oscillates back and forth generating the oscillatory pressure and thus oscillatory flow. The mesh is moved by an electromagnetic voice coil including fixed magnets surround, the windings surrounding the mesh. The magnets are also surrounded by a cylindrical steel core to help draw and contain the magnetic flux and complete the magnetic circuit largely within the device. Pressure used to compute the impedance is obtained at the pressure port p2 just in front of where the anti-bacterial/anti-viral disposable filter is attached to the device. Flow is measured by measuring the differential pressure (p1 and p2) divided by the resistance of the static mesh screen at the front of the device. Thus flow is computed as

$$\dot{V} = \frac{P2 - P1}{R} \tag{1.3}$$

The total resistance of the device to the subject's breathing efforts is the sum of the oscillating mesh (approximately 0.5 cmH$_2$0/l/s) and the static mesh (approximately 0.4 cmH$_2$0/l/s) and the small resistance of the anti-bacterial/anti-viral filter. The resistance is less than 1 cmH$_2$0/l/s, recommended by current guidelines [8] and ensures the subject respiratory effort is not significantly increased. As mentioned above, the device applies

nine frequencies (5, 11, 13, 17, 19, 23, 29, and 37 Hz) with a period of one-second that repeats for 16 seconds for a single measurement.

1.6.2 Calibration of the tremoFlo Device

The device is calibrated initially by the manufacturer, and this calibration was validated each day prior to each measurement with a standard reference resistance load of 5 cmH$_2$O/l/s (Thorasys, Inc., Montreal). The guidelines state that accuracy must be within 10% or 0.1 cmH$_2$O/l/s, whichever is greater [16], which is confirmed by the tremoFlo software [17].

1.7 Feasibility and reference values of FOT in children

The main advantage of FOT is that it requires minimal effort and cooperation from the subject [18]. Mochizuki et al. showed that more than 80% of preschool children could achieve reliable FOT measurements in the first attempt and the technique could help identify asthma at an early stage of the disease [19]. It is important to establish reference values so that measurements from individuals can be assessed if their impedance values are within the normal range. However, there are far fewer studies to choose from for reference values for FOT compared with the established spirometric measures. Nevertheless, several studies have evaluated the normal baseline for children to establish reference values, which depend on subject weight and sometimes differentiate values based on sex. Indeed, in a study of 255 healthy Dutch children of age between 2.3 and 12.5 years, Rrs was found to be slightly higher and Xrs more negative in young boys for the same age than in young girls [20]. Cuijpers et al[21] also showed similar results in a study involving over 370 children between the age of 5 and 12 years,

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but reported their dependence on age, sex and height. Negative frequency dependence of resistance between 8 and 28 Hz was prevalent across all heights, and was more prevalent in boys [24, 25] and Rrs was higher. Xrs was more negative in girls than in boys at 8 Hz when children were below 140 cm, but above 140 cm, this was reversed and resonant frequency was higher in boys than in girls[21]. While there were statistical differences based on sex, these were much smaller than that based on height. A third study by Nowowijska et al. [26] found similar results, and this was the study we used as reference values, principally because of the large number of subjects and large age range they used. These reference values were obtained from impulse oscillometry, which obtained the impedance at 5, 10, 15, 20, 25, and 35 Hz. Reference values are used to compute an individual's predicted value, and as mentioned above, are commonly based on their height and in some studies, also weight and sex. For example, to compute the percent predicted resistance at 5 Hz, Rr5%pred and percent predicted reactance at 5 Hz, Xr5%predicted, from the reference data of Nowowijska et al. [26] is based only on subject height, with no dependence on weight or sex. A particular subject's Rrs are usually defined to be within the normal range, if less than the 95th percentile, while for Xrs if greater than the 95th percentile. The predicted values and the 95th percentile upper limit and lower limit of normal thresholds are determined from these reference value studies in healthy subjects. In this thesis, the reference data of Nowowijska et al. [26] were used. AS an example, Smith et al. reported that Rrs at 5 Hz was abnormal if it was greater than 150% of predicted values (percent predicted resistance, Rrs%) [15].

1.8 Respiratory Impedance

The respiratory impedance (Zrs) is computed from the ratio of pressure to flow as in equation 1.1 and often using the method of equation 1.2, and is a complex number valued function which is plotted versus frequency and normally divided into the real and imaginary parts as

$$\frac{P(f)}{\dot{V}(f)} = Zrs(f) = Rrs(f) + jXrs(f) \qquad (1.4)$$

where $j = \sqrt{-1}$. The real part is the resistance (Rrs) and the imaginary part is the reactance (Xrs). Rrs represents the resistance to airflow through the airways within the lung, but there are also components due to the upper airways (predominantly the larynx) as well as some mechanical resistive losses due to tissue distortion within the lungs. Xrs is the imaginary part of the impedance, and at breathing and low oscillation frequencies largely reflects the stiffness of the tissues of the respiratory system, composed mostly of lung tissue stiffness, and the remainder largely due to chest wall stiffness comprising the diaphragm and rib cage. At higher oscillation frequencies usually above 10 Hz in adults, and 20 Hz in children, the reactance becomes dominated by the inertial acceleration of the air.

1.8.1 The Resistance of the respiratory system (Rrs)

Rrs in asthma often exhibits a slight frequency dependence where Rrs decreases nearly inversely with frequency at low oscillation frequencies [22]. This is illustrated in Figure 1.5, which shows the Rrs from a study of adults of different asthma severity [23] Appendix.1. Rrs values for children are larger than for adults since their airways are smaller, and also shows frequency dependence in asthma. The frequency dependence is

associated with increasing heterogeneity of airway diameter and ventilation that increases with airway narrowing.
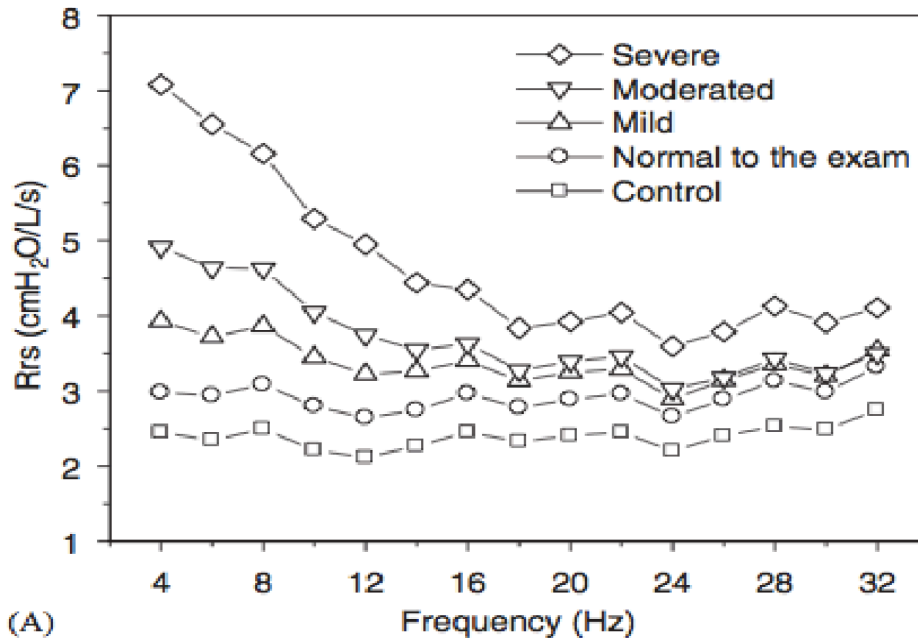
Figure 1.5: Comparisons of the mean values of respiratory system resistance as a function of frequency in control and asthmatic subjects of varying severity (reproduced with permission from (Respiratory Medicine Journal)) [23].

As described above, Rrs is the sum of resistances from the different mechanical parts of the respiratory system. Rrs is dominated in healthy subjects by the central airways, which are the trachea and first few branches (bronchi) of the airway tree, while the peripheral airway resistance is largely negligible in health, but can become very significant in disease. The contributions to resistance from the rest of respiratory system, such as the lung tissue and chest wall are usually modest [15].

1.8.2 The Reactance of the Respiratory System (Xrs)

Xrs is always frequency dependent in both health and disease in adults and children. With increasing obstruction (narrowing of airways) reactance becomes more negative [22]. This is illustrated in Figure 1.6, which compares the reactance decreasing with increasing severity of asthma [22] Appendix.1.
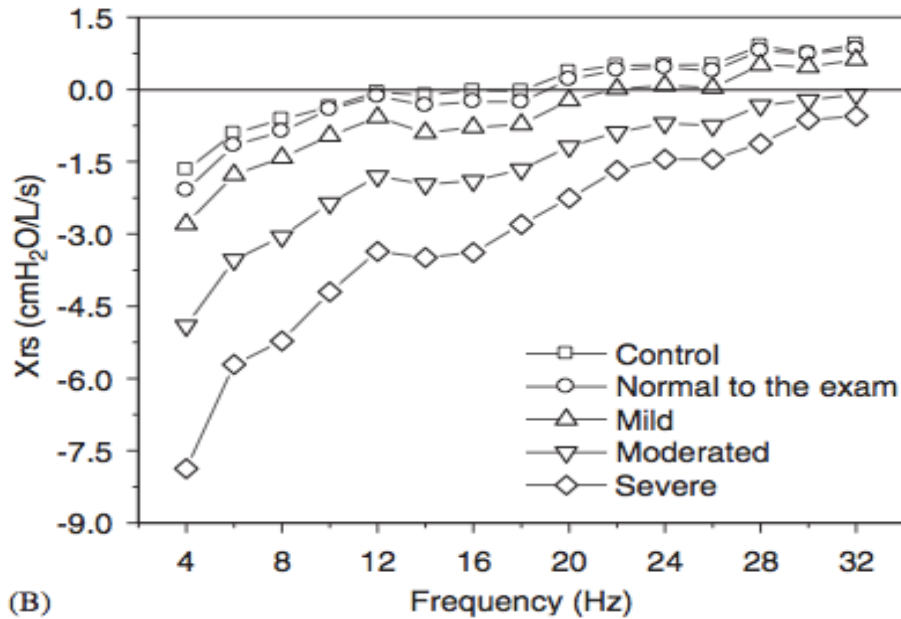
Figure 1.6: Comparisons of the mean values of respiratory system reactance as a function of frequency in control and asthmatic subjects (reproduced with permission from (Respiratory Medicine Journal))[23].

As stated above, at low frequencies it is the elastance (stiffness) of the respiratory system that dominates the reactance, while at higher frequencies the inertial forces due to acceleration of the oscillating gas column in the airways dominate. In fact, the mechanical properties of the respiratory system can in fact be modelled as a three parameter model, comprising a resistance, elastance and inertia described in the next section.

1.8.3 The Equation of Motion and the Single Compartment Model of the Respiratory System

The equation of motion used for single compartment model, which is the most common model used in the respiratory system is the following

$$P(t) = R\dot{V}(t) + EV(t) + I\ddot{V}(t) \qquad (1.5)$$

where as before P is the pressure in cm H_2O, V is the volume in l, $\dot{V}$ is the flow in l/s and $\ddot{v}$ is the 2nd derivative of volume and thus is the acceleration of volume. R is an ideal resistance in cmH_2O/l/s E is an ideal elastance in cm H_2O/l, and is an inertance in cm H_2O/l/s^2. Here we can view the pressure applied to a simple idealized tube connected to an elastic volume. Thus the resistive pressure is

$$P_R = R\dot{V} \qquad (1.6)$$

and the portion of the pressure due to elastance is

$$P_E = EV \qquad (1.7)$$

and the portion of the pressure due to inertance is

$$P_I = I\ddot{V} \qquad (1.8)$$

Together in equation 5 these describe the mechanical properties of the respiratory system. It is largely accurate to describe the oscillatory mechanics in healthy people, but with obstructive disease the measured pressure-flow relationship exhibits deviations from the model more easily seen as frequency dependence of resistance discussed further below. Here the pressure difference due to the resistive flow is modelled as a simple linear Newtonian relationship. This is valid as during normal breathing and oscillometry, the

fluid, which is the air, moves slowly in layers through the airways without much mixing among the layers. The elastic behaviour is also modelled linearly which is valid as long as subjects are breathing normally at near the relaxed volume of the lung (known as the functional respiratory capacity, FRC) where the pressure volume relationship is fairly linear. The inertive contribution is usually small, and the linear relationship is usually valid.

Normally the parameters of the respiratory system are identified from computing the impedance in the frequency domain versus frequency. Equation 5 can be transformed to the frequency domain using the Fourier Transform and it can be shown that the equation of motion in the frequency domain follows the form:

$$Z(\omega) = R + j(\omega I - E / \omega) \hspace{2cm} (1.9)$$

where Z is the model impedance, and is the ratio between the oscillatory $P(f)$ and $\dot{V}(f)$ at all the oscillatory frequencies, with ω is the radial frequency and is equal to $2\pi f$. To identify the model parameters of the respiratory system from this equation, we fit the model impedance to the data computed from equation 5. Then, the resistance is straightforward, and Rrs can be computed as the average of the real part of the impedance. The reactance follows a functional form starting at negative values at the lowest frequency, and approaches the curve $Xrs = -Ers/\omega$ at low frequencies. With increasing frequency Xrs deviates from this pure elastance curve, crossing $Xrs = 0$ at a frequency known as the resonant frequency, and then approaches the pure inertance linear curve $Xrs = \omega Irs$ at high frequency. The resonant frequency is where the inertial pressure amplitude is equal and opposite to the elastic pressure amplitude and $Xrs = 0$. The reactance of the single compartment model thus follows this relationship as

$$Xrs = \omega Irs - Ers/\omega \qquad\qquad (1.10)$$

When impedance is obtained by measurement via FOT, the plotted impedance data Rrs and Xrs can visually indicate changes in the mechanical properties, or the estimated parameter from the least square fit (e.g. Ers) can be used to assess the level of obstruction in the respiratory system. It should be noted that obstruction is described as anything that limits the movement of air into or out of the respiratory system, whether airway narrowing, mucous plugging, or stiffening of the lung tissues. When airways narrow or the lung stiffens, the magnitude of Zrs is increased, and usually both Rrs and Xrs are affected.

The single compartment model is sufficient for describing health and mild disease such as mild asthma. However, in more obstruction such as modest and severe asthma, Rrs becomes frequency dependent., This cannot be describe by the signal compartment model since the model has a frequency independent, constant single value for Rrs.. This arises because of substantial heterogeneity in airway diameters, leading to differences in impedances amongt the multiple pathways in the lung and the single compartment model is no longer sufficient. Therefore, multi compartment models have been developed to describe this behaviour. The simplest model is the two compartment model such as described by Otis in 1956 (ref). The Otis model is a parallel two compartment model with two airways and lung compartments, providing two time constants. When the time constants are not equal, frequency dependence of Rrs in a limited range of frequencies such as measured by FOT can be modelled [24]. An alternative two-compartment model was developed in 1969 by Mead et al (ref). The Mead model has the two compartments arranged in series with a central airway resistance and compliance feeding into a

peripheral airway resistance and peripheral compliance. The upper airway compartment accounts for central airway wall shunting where some of the flow goes into stretching the airway walls of the larger airways [25]. However, for the purposes of this thesis, as my subjects had relatively mild asthma, and thus very limited frequency dependence of Rrs, the single compartment model was found to be sufficient

1.8.4 Upper airway shunt and measurement quality

An interesting problem is that the measurements are of the entire respiratory system, which includes the lungs, chest wall and upper airways (mouth structures and larynx), but in practice the clinician is usually most interested in the impedance of the lungs, and its changes in disease. Thus any change in Rrs that occurs for example following therapy or a bronchial challenge or inhaled bronchodilator will be slightly less than the change occurring within the lung. This effect is exaggerated by an effect known as upper airway shunt that can be significant with increased lung impedance that occurs in disease. The upper airway shunt occurs because some of the oscillations go to oscillating the soft tissues of the upper airway, mainly the cheeks and possibly the soft palate and sinus cavities. This effect is small in health since the impedance of the cheeks is much more than that of the lungs. However when there is airway constriction in the lungs, because of the parallel impedance path to the cheeks, the effect is increased, and changes in Zrs are not proportional to changes in lung impedance. Thus if the clinician measures an increase in a child's Zrs that is due to airway narrowing in the lungs, the percent change in the lungs is underestimated relative to the percent change in Zrs. This is since an increasing fraction of the oscillations go into oscillating the soft tissues of the upper airways, the more Zrs increases. This is particularly more important in children

who have smaller lungs than adults, and thus higher impedance. To reduce the effect of shunt, subjects must support their cheeks and use nose-clips during measurement to ensure oscillations do not escape via the nose [26].

Also for best quality of the measurements, subjects should not tilt their head down, which can compress the throat and increase upper airway resistance. Also they should not slouch forwards during the measurement, which compresses the abdomen and moves the contents upwards into the thorax, reducing lung volume and leading to some airway narrowing.

1.9 Sensitivity and reversibility of respiratory impedance

A reversibility test is a measurement of the ability to reverse airway obstruction that is associated with asthma, and is carried out using an inhaled bronchodilator (BD). Bronchodilators act by relaxing the airway smooth muscle, most commonly via beta-agonist receptor stimulation of the airway smooth muscle cells. Since the airways are pulled by the lung tissue attachments to the airway, which are normally in tension during breathing, this relaxation leads to airway dilation. The effect of the bronchodilator is measured by spirometry as a change in FEV1, or can be measured by a change in Rrs, and the effect of a bronchodilator on FEV1 or Rrs is larger in asthma than in healthy subjects [27]. Bronchodilators are used in reversibility testing as a clinical assessment in adults and in children with asthma to determine the improvement of the patient's lung function with therapy [28].

1.9.1 Sensitivity and reversibility in spirometry

For a positive BD response, (positive BDR) the standard for adults and for children> 5 years is an increase in FEV1 ≥12% [29]. While there are several studies that contributed to establishing the 12% criteria for positive BDR with spirometry, there have only been a few studies using FOT.

Oostveen et al. noted that to define reversibility in oscillometry, it is necessary to first determine the healthy response [13]. Oostveen et al. found in adults that after administration of inhaled BD, Rrs decreased on average by 11%, and they determined that the upper limit of normal defined by the 95% confidence interval as 32% for Rrs at the low frequency of 5 Hz [26]. This provided a useful threshold for a positive reversibility test using oscillometry if a subject's Rrs decreased more than 32%.

1.10 Quality control of FOT

1.10.1 Coherence

The coherence is computed at each oscillation frequency from the recorded pressure and flow, and is used to quantify the reliability and linearity of the relationship between pressure and flow. It is thus a fairly good index for assessing the reliability in Zrs estimation. The acceptable value of the coherence function at each frequency is normally recommended to be greater than 0.9 or sometimes greater than 0.95 [27]. It is decreased due to contamination by noise, or in some implementations by the effects of nonlinearities between pressure and flow. However, due to differences in calculating coherence from device to device, the absolute values may not be directly comparable. However, for comparing measurements recorded with the same settings on a given

device, the coherence is still a good indicator of data quality, for a given recording. Typically coherence is worse at lower oscillation frequencies largely due to breathing noise contamination [26] which although is mostly near breathing frequencies of 0.2-0.4 Hz, the spectrum extends high above this and some small amplitude noise can contaminate the oscillation frequencies which typically begin at about 5 Hz. Coughing as well as talking or swallowing can decrease coherence, but these are usually transient artifacts whose effects can be removed manually, or automatically by device software.

1.10.2 Coefficient of variation.

The coefficient of variation (COV) of any measure is the ratio of the standard deviation of the measure to its mean, and is thus is a measure of the variability of the measurement. It is computed from repeated measurements, and a low COV value is a good indication of measurement repeatability. In this thesis, as will be described in methods I assessed the repeatability of measurements taken during tests of bronchial responsiveness from both spirometry and oscillometry in asthmatic children. An Official American Thoracic Society/European Respiratory Society report states that the average COV from spirometry FEV1 for preschool children is 6.2% [30]. For adults the COV is much lower. The standard measurement of FEV1 requires that the measurement be repeated 3 times, and if the volume range exceeds 120 ml, then the maneuver must be repeated, eliminating outliers until this criteria is met. This procedure thus limits COV to low values in spirometry, and potentially to lower values than occurs in oscillometry if all measurements are maintained for calculation of impedance. However, in oscillometry there have been very few publications that assessed repeatability for normal impedance measurements, and fewer that included bronchodilator testing. In the guidelines and

recommendations document for clinical use of FOT, Oostveen et al. stated that the COV in Rrs is less than 15% across all frequencies [26]. The implication is that if a measured COV is outside of this range, than one measurement in the repeated recordings may be an outlier due to measurement artifacts, and possibly should be repeated and replaced or eliminated from the measurements. COV is normally only considered for Rrs, but is sometimes also computed for Xrs. However, Xrs has a significant problem in the assessment of repeatability due to the fact that average Xrs can be close to zero at frequencies near the resonant frequency, and the COV can thus approach infinity in this case. Xrs at low frequencies is negative and at high frequencies is positive and thus can cross zero within the oscillation frequency range typically at 8 Hz for adults, and at higher frequencies in children depending on lung size. In this thesis in addition to computing COV, and recognizing this limitation, we also computed the standard deviation of Xrs as an absolute measure to avoid this problem. However, the standard deviation of Xrs cannot be compared to and measure of variation from spirometry because of the difference in units. [16].

1.11 Gap in knowledge

As mentioned above, spirometry can be difficult in children because of the need for active participation from the patient. FOT does not require active participation and is a faster and easier means of measuring pulmonary function. However, in children in the age range between 5 and 14 years old there is little data on how spirometry compares to FOT, and in particular no data comparing performance, either in repeatability, or sensitivity to inhaled BD for reversibility testing. This study is designed to help fill that

gap, to assess the repeatability of FOT, and compare it to spirometry, and as well measure and compare the sensitivity to inhaled BD in subjects with asthma. Further since FOT provides both Rrs and Xrs at different frequencies with the potential to provide physiological interpretation regarding the site of airflow limitation, we wanted to compare these measures and how they changed with BD. In addition we also wanted to assess how well the single compartment model describes the frequency dependence of reactance in children. If it fits well, then the elastance or Ers could potentially be used to assess repeatability and sensitivity of this parameter derived from Xrs, avoiding the difficulty in assessing the COV of a parameter that can be near zero.

Chapter 2: Thesis Questions and Hypothesis

2.1 Thesis Questions, hypothesis and objectives

According to Farrugia et al. clinical research questions should ideally follow the FINER approach (Feasible, Interesting, Novel, Ethical and Relevant) [31]. I feel that the research questions of this thesis meet the FINER criteria. It is feasible, as subjects are readily available at the IWK health Centre, FOT is easy for subjects to do, and BD testing is part of their normal assessment in the pulmonary function lab with spirometry. It is novel as this research extends the existing research that has been done in the field. It attempts to compare FOT obtained impedance to the standard measurement of lung function, both in repeatability and in sensitivity to BD. It is also ethical and relevant since it is safe, and establishing if BD testing by FOT is sensitive and repeatable, provides either an alternate, or possibly a more useful measure of BD responsiveness in asthma, with potential physiological interpretation of the specific mechanical outcomes from FOT.

2.2 Questions

The research questions that the study seeks to answer are as follows:

Question 1

The first question will explore the sensitivity of Rrs and Xrs as an indicator of lung mechanics to an inhaled BD compared to current standard measures of lung function i.e. spirometry. Secondary to this question, I will assess if there are differences in sensitivity based on the level of asthma control of the subjects.

Question 2

The second question involves the repeatability of the equipment. The research will seek to compare repeatability of Rrs and Xrs to FEV1. The approach will be to use COV for FEV1 and Rrs, and possibly for low frequency Xrs. Although because Xrs has the potential problem in some subjects when it is close to near zero, I will also compute the standard deviation as a direct measure of variability however, this cannot be used to compare with spirometry. I will also evaluate the coefficient of variability of Ers computed from Xrs, which avoids the problem that Xrs has when Xrs is near zero. The COV of Ers can thus be used to compare to the COV from spirometry.

2.3 Hypothesis and main objective

Brief rationale: FOT is known to be more sensitive than spirometry to changes due to an inhaled bronchodilator, but it is also more variable. Here I am using the term sensitivity to describe the percent change in a measured or computed variable to the inhaled agent. If the improvement in sensitivity outweighs the impact of the increased variability, FOT may be a more reliable and useful measurement of the BD response.

Hypothesis: FOT is a repeatable measurement in children with asthma, albeit more variable than spirometry, but if the relative change in response to BD is normalized to the variation as measured by COV in the FOT parameters, FOT will have better or at least similar 'signal-to-noise' as a measure of the BD response.

Aim: I will examine the repeatability of spirometry and oscillometry in children with asthma measuring the relative change in both FEV1 and FOT measures, and also the

repeatability of each measure, and determine the ratio of relative change to the variability by COV as a measure of the 'signal-to-noise' for each method.

Chapter 3: Methodology

3.1 Selection of study participants

Fifty-three children with asthma were recruited from the outpatient clinic at the IWK Health Center. This study was approved by the IWK Health Center and the parents or guardians of children provided written consent on behalf of the children. All participants were assigned unique patient identifiers to protect their identity during this study. In this thesis, outcome measures are indicated as mean (SEM)

3.2 Inclusion and exclusion criteria

Children with poorly controlled asthma who were between the ages of 5 and 14 years were recruited to participate in this study. Subjects had clinician diagnosed asthma and were classified as either controlled or uncontrolled in accordance to the Canadian Thoracic Society 2012 guidelines (Table 3.1) for uncontrolled asthma[32]. These classifications were used with permission from the author[32] Appendix.2.

One of the children was excluded from the study because he had taken a long-acting bronchodilator within 8-12 hours of pulmonary function testing. Two subjects were excluded from the study as they were unable to perform the forced exhalation manoeuvres of spirometry, and three subjects were excluded due to inability to complete the study protocol due to cognitive limitations that prevented accurate completion of the study questionnaires.

Table 3.1: Asthma control criteria (reproduced with permission from (The Canadian Respiratory Journal)) [33]

Asthma control criteria

Characteristic	Frequency or value
Daytime symptoms	<4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a fast-acting beta$_2$-agonist	<4 doses/week
FEV$_1$ or PEF	≥90% personal best
PEF diurnal variation*	<10%–15%
Sputum eosinophils†	<2%–3%

Diurnal variation is calculated as the highest peak expiratory flow (PEF) minus the lowest divided by the highest peak flow multiplied by 100 for morning and night (determined over a two-week period). †Consider in adults with uncontrolled moderate to severe asthma who are assessed in specialist centres. FEV$_1$ Forced expiratory volume in 1s. Adapted from reference 4

3.3 Study Design

This is a cross-sectional, prospective observational study. The study protocol is outlined in Figure 3.1. Briefly, the protocol began with the oscillometric assessment of lung mechanics, followed by spirometric evaluation of lung function. 200 mcg of the bronchodilator (BD) – salbutamol was then administered to the subject via metered dose inhaler with a spacer and a 10 minute break was given for the drug to take effect in the patient [13]. This was followed by post-BD assessments of lung mechanics and function with oscillometry and spirometry, respectively.
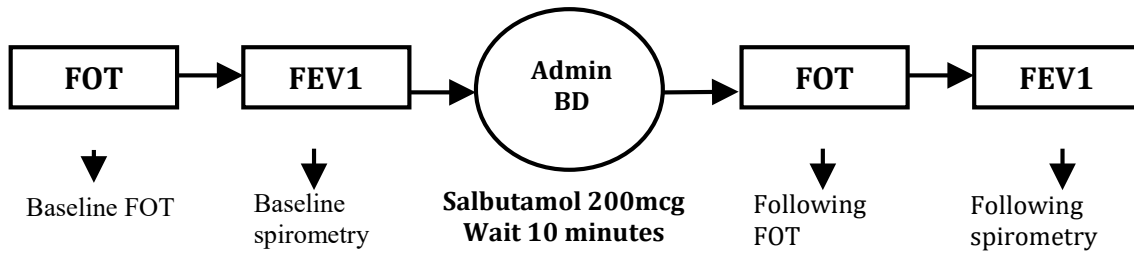
Figure 3.1: The study protocol

3.3.1 Asthma Control Test (ACT) Questionnaire

Study participants were asked to complete the asthma control test (ACT) questionnaire during the 10-minute break period given after administration of the bronchodilator, but in some cases also did the questionnaire after the above protocol was completed [32] Appendix.3. The ACT is a 7-item questionnaire containing 4 questions of which the child is expected to answer and 3 questions for the parent or guardian to answer. A score of 19 or less on the ACT indicates that the child's asthma is not well controlled while a score greater than 19 is suggestive of well-controlled asthma. Children with uncontrolled asthma exhibit frequent exacerbation of their asthma symptoms and do not respond well to rescue medication, while children with well-controlled asthma have less frequent exacerbation of their asthma symptoms and respond well to rescue medication.

The ACT is typically used in the clinical setting for routine tracking of asthma because it is stated to be a sensitive tool for assessing the level of asthma control in children. According to Schatz *et al*, the ACT has an internal consistency reliability of 0.85 at baseline and 0.79 at follow-up with a test retest reliability of 0.77 [34].

3.3.2 Weight and height measurements

The weight and height of study participants were measured without wearing shoes or heavy clothing.

3.3.3 Pulmonary function tests

Spirometry was performed according to recommended guidelines using a spirometer-equipped body box (SensorMedics Corporation, Yorba Linda, CA, USA) [30]. Forced expiratory flows, including forced expiratory volume in 1 s (FEV1) and expiratory flow at 50 % (FEF50), 75 % (FEF75), and 25 – 75 % (FEF25–75) of vital capacity (VC) were obtained. The best FEV1 and forced expiratory flows were selected as the final result from three technically acceptable measurements and expressed as percentiles of predicted values.[35].

3.3.4 Oscillometry

The impedance of the respiratory system (Zrs) was measured according to recommendations using the tremoFlo^{TM} developed by THORASYS, (Montreal, QC, Canada) [13]. During each measurement, subjects were comfortably seated with their head in the neutral position or slightly extended forwards which may help to move the tongue forwards from the back of the throat. They wore a nose-clip to prevent airflow through the nose and were instructed to firmly hold their cheeks and mouth floor so as to minimize the upper airway shunt artefact. Nowowiejska allowed children to support their own cheeks, and if necessary for the youngest children, allowed the researcher to support the cheeks [36]. To ensure that the measurements taken with the device are accurate and

viable, the children were given some time to prepare and breathe through the device before measurements were started. Measurements consisted of 16 seconds recordings, once breathing was observed to be stable, followed by a short rest of about 16 seconds. This was repeated four times or occasionally five times if artifacts such as a cough or poor seal of the mouth around the mouthpiece were observed.

As mentioned in the literature review, the tremoFlo device waveform consists of a multi-frequency composite oscillatory pressure waveform of about 0.5 to 1 cm H_2O amplitude (1 to 2 cmH$_2$O peak-peak) which was generated by a self-actuated oscillating mesh-screen piston within the device. This is called airwave oscillometry or AOS by Thorasys, referred within this thesis as either the forced oscillation technique, or specifically AOS. This pressure waveform was superimposed on the subject's normal breathing and as described above consisted of oscillatory components at 5, 11, 13, 17, 19, 23, 29, 31 and 37 Hz for 16 seconds. The oscillation frequencies of the pressure waveform are significantly higher than the normal breathing frequency, which is about 0.2-0.3 Hz, although small components exist to much higher frequencies as breathing is broad-band, but the great majority of the breathing noise was filtered out during the signal processing of the TremoFlo software using [2 Hz] bandpass filtering similar to previous studies [37,38].

As previously described in Chapter 1, Zrs was estimated from the spectral ratio of the fast Fourier transform (FFT) of pressure and flow measured at the mouth, with 1 second Hamming windows with 50% overlap (Eq. 2). The coherence was calculated from each 16 sec measurement, and if it was greater than 0.90 it was accepted as valid. The average of at least three repeated measurements was used as the reported impedance.

Oostveen et al. recommended that at least three measurements should be taken to ensure a reliable measure [13].

3.3.5 Predicted values

The predicted values for the AOS measurements were calculated according to Nowowiejska et al. [36]. Nowowiejska et al method used the coefficients of a regression equations for both boys and girls was a linear regression model of the form

$$Rrs_{pred} = aH + b \qquad (3.1)$$

While that for reactance used an exponential regression model of the form

$$Xrs_{pred} = e^{cH+d} \qquad (3.2)$$

Where a, b, c and d were coefficients, and were provided by Nowowiejska for each oscillation frequency, and H was the height in meters [36]. Coefficients were slightly different for boys compared to girls. Through this equation, the measured Rrs and Xrs can be expressed as percentage of the subject's predicted values, known as the percent predicted value. The reference values were computed at 5, 10, 15, 20, 25, and 35 Hz. Thus to compute the R5% and X5% we simply used the predicted values at 5 Hz from the above equations However in our study we used the tremoFlo^{TM} with nine frequencies at 5, 11, 13, 17, 19, 23, 29, 31 and 37 Hz. Thus for frequencies not in common, the predicted values were calculated using linear interpolation.

3.3.6 Variability and repeatability of respiratory resistance

The variability and repeatability of respiratory system resistance was determined from the percent coefficient of variation (COV) obtained from the repeated oscillometry measurements. The coefficient of variation (COV) was computed from all acceptable repeated measures as: (SD/mean)*100, where SD was the standard deviation of each patient's measured variables (e.g., Rrs5) for both pre and post bronchodilator measures. An average COV was also computed averaging the pre and post SD.

The majority of our subjects had COV in Rrs at any of the recorded frequencies of less than 10%. However it has been reported that COV is sometimes greater than 10%[27]. Here we found two subjects that had very large COV of more than 20%. Upon inspection of the data, this occurred always because one of the three measurements was substantially different from the other measurements. In one case, one of the measurements for resistance was more than twice as high as the remaining two. Upon examination of the time course of R5 and resistance at other frequencies, the values in this one case were quite variable with very large standard deviation, and it appeared there were repeated interruptions in flow, indicating swallows, and this measurement was thus eliminated from the average. Upon re-examination of the recording notes, the second subject had obvious swallowing during recording; therefore the measurements containing the artifacts were removed from the analysis.

3.3.7 Bronchial reversibility test

Lung mechanics and function was assessed before and 10 minutes after inhaling 200 mcg of salbutamol – a short acting bronchodilator (BD). As described above, the BD was

administered with a metered-dose inhaler and valve-holding chamber spacer device
according to recommended guidelines GINA [29].

3.3.8 Signal to noise

We developed a "signal to noise" or SNR, as a way to compare the sensitivity in a
measure relative to its variability. We normalized the percent change in response to BD
to the respective COV%. Here the signal is the response to BD, but the noise is the
variation in the measurement and the SNR is unitless calculated this way, allowing us to
compare spirometry to oscillometry. We did this using both the COV% from the 3
measures before BD (SNR,pre-BD), and after BD (SNR,post-BD) separately, and also
calculated the average COV from the COV before and COV after BD, to provide a more
comprehensive number for the full reversibility test which includes the repeatability
considering both the before and after measurements of the test (SNR,BD).

3.3.9 Single compartment model

We also wanted to know if the single compartment model for the respiratory system
could be used to describe the reactance data. As described in the literature review, the
single compartment model has a constant Rrs with frequency, and a nonlinear frequency
dependent relationship for Xrs with frequency. We computed the fit of the single
compartment model to the Xrs data by conducting a nonlinear least-squares fitting
procedure in Matlab using the Curve Fitting Toolbox^{TM} as follows:

$$[y] = sing\_comp(f, I, E) \qquad (3.3)$$

$$y = I\,2\pi f - E/(2\pi f) \qquad (3.4)$$

Where y is the curve fit model Xrs value fitted to the mean Xrs(f) from the measured values either before or after BD.

3.4 Statistics

We used a mixed design ANOVA with one factor (BD) and two groups (controlled asthma and poorly controlled asthma) to determine if the different groups responded differently to a BD. We used student-test with two tails and unequal variance test, to compare the sensitivities of oscillometric measures (Rrs and Xrs) to FEV1. However when we compared the signal-to-noise measures, since the SNR_BD_FEV1 was not normally distributed, we chose to compare the medians using the Wilcoxon rank sum test. A significant difference was taken as $p < 0.05$, for all comparisons.

Results

Chapter 4: Results

4.1 Demographics

The demographics, anthropometric characteristics and spirometric values of the study participants are given in Table 4.1.

Table 4.1: Demographics, anthropometric characteristics and spirometry results of the study participants

Participant Demographics	Mean (SD)
N	53, 29f
Age (years)	9.4 range (5-14)
Height (cm)	142 (24.1)
Weight (kg)	40.5 (20.4)
FEV1%	99.7 (18.2)
FVC%	109.7(16.8)
FEV1/FVC%	79.7(8.3)

4.2 Asthma Control Test (ACT) Questionnaire

The ACT questionnaire was used to discriminate between well-controlled and poorly controlled (uncontrolled) asthmatic children [34,39]. The ACT questionnaire has been well-characterized and standardized, and a score of 19 or less defined to be uncontrolled asthma, while a score of greater than 19 indicates well-controlled asthma. In this study, 14 children presented with an ACT score of less than 19 and were categorized as uncontrolled asthmatics, while 39 children were well-controlled asthmatics.

4.3 Pulmonary function tests

Table 4.2 Baseline spirometry of all subjects

	Baseline (SD)
FVC	109(16.56)
FEV_1	99.5(17.4)
PEF	101.6(21.6)
FEF_{25-75}	80(25.5)
FEF_{50}	91(32.8)
FEF_{75}	75(32)

At baseline our subjects were normal with percent predicted near 100 in all pulmonary function tests except for FEF_{25-75} FEF_{50}, and FEF_{75} which were 80 (25.5), 91 (32.8) and 75 (32)%, respectively. We found by ANOVA that controlled and poorly controlled asthma were not different for spirometric measurements, and thus the data could be pooled.

4.3 Baseline lung mechanics assessed with oscillometry
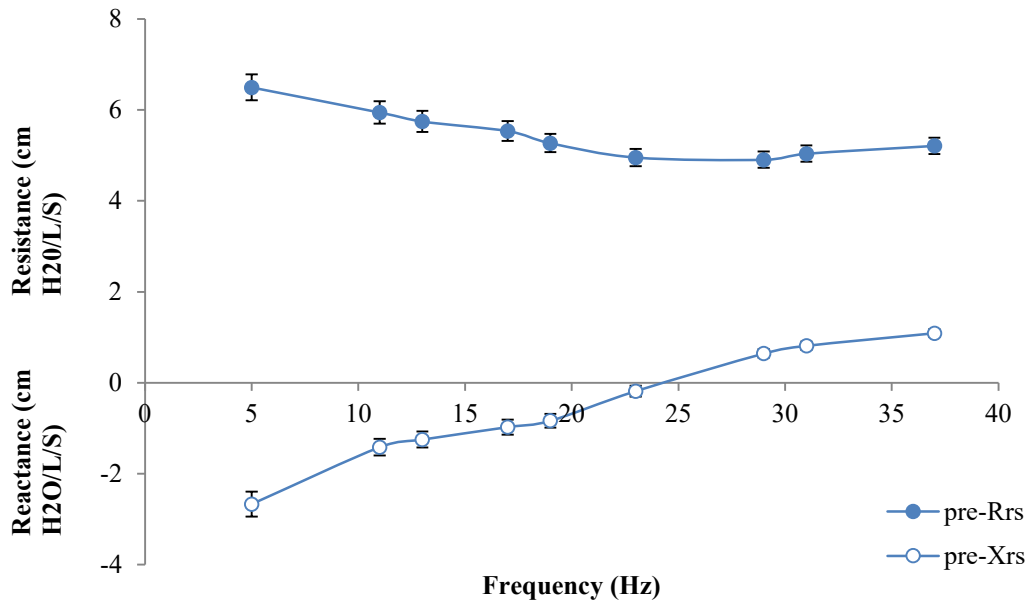
Figure 4.1: Baseline Rrs (top) and Xrs (bottom) for all subjects. Error bars indicate SEM. All subjects in this study demonstrated slight decreasing frequency dependence in Rrs

At low frequencies the Rrs was high, while at high frequencies the Rrs was slightly lowered. Rrs at 5Hz was higher than both Rrs at 19 Hz and 37 Hz ($p < 0.05$). Xrs exhibited the expected increasing inverse frequency dependence then crossed zero, and continuing approximately linearly with frequency above the crossing point, which is the resonant frequency.

4.4 Bronchial reversibility testing

4.4.1 Pulmonary function tests

We present the uncontrolled and controlled results in this thesis separately. However as we found that there were no statistically significant differences between uncontrolled and controlled results, we also present them pooled. (Tables 4.3-4.6, and Figures 4.2-4.4).

Table 4.3: Percent change in spirometric indices following administration of bronchodilator; Data are mean across subjects (SD)

	Pre-BD	Post-BD	%Percent Change	T-test (p value)
FVC	109.11(16.63)	109.59(17.02)	0.5(3.9)	0.20
FEV_1	99.5(17.44)	106.4(18.01)	7.11 (6.15)	$p < 0.001$
PEF	101.6(21.6)	104.74(21.23)	1.82(17.9)	$p < 0.001$
FEF_{25-75}	80.11(25.62)	99(27.9)	26.19(20.6)	$p < 0.001$
FEF_{50}	88.88(29.15)	111.24(34.34)	24.79(29.3)	$p < 0.001$
FEF_{75}	74.83(32.17)	100.29(34.73)	40.78(29.11)	0.02
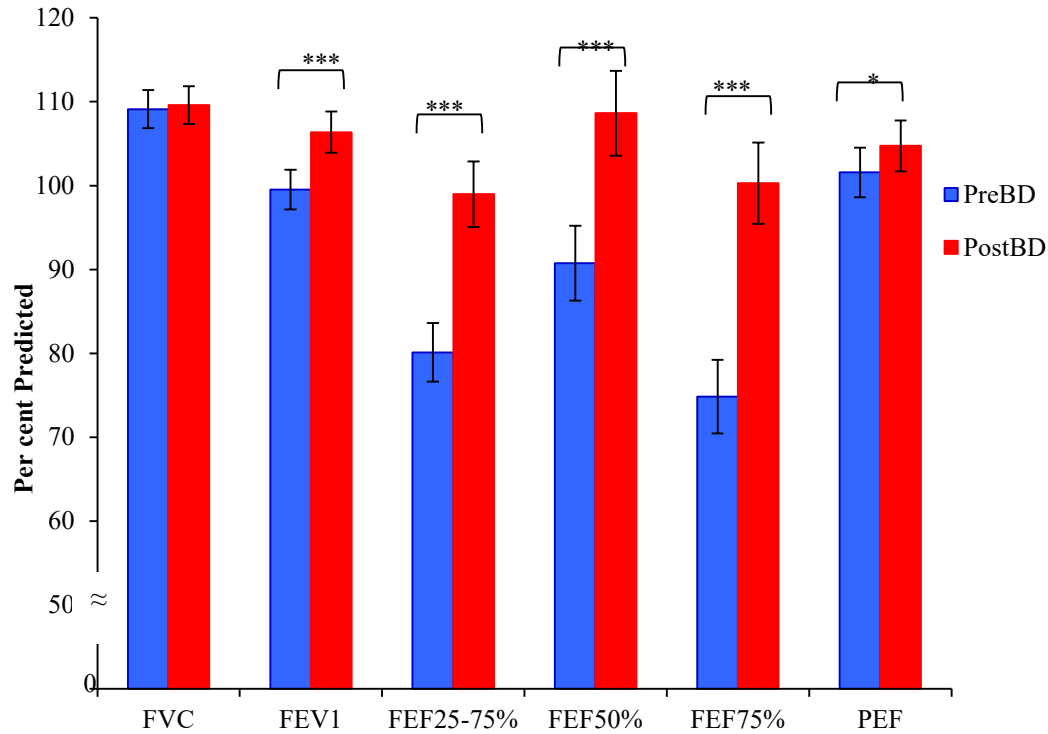
Figure 4.2: Forced vital capacity and forced expiratory flow measurements recorded before and after BD from all subjects, Error bars indicate SEM. * p <0.05, ** p < 0.01, *** p < 0.001

We show that in response to BD the FVC did not change, but the forced expired flow measures all changed, but also exhibited large variability amongst subjects. FEV1% only exhibited a change of 7% (SD = 6.2%), and was also variable. Thus the majority of the subjects were in the normal range with ten individuals having a change in FEV1% greater than 12%, the threshold for positive bronchodilator response [29].

Table 4.4: Spirometric indices in well-controlled and poorly-controlled asthmatics following administration of bronchodilator. Data are mean across subjects (SD)

	Pre-BD (well-controlled)	Post-BD (well-controlled)	Pre-BD (poorly-controlled)	Post-BD (poorly-controlled)
FVC	108.37(13.09)	108.57(13.89)	111.21(24.64)	112.5(24.29)
FEV_1	99.65(14.06)	106.5(13.96)	99.14(25.42)	106(27.16)
PEF	105.3(19.94)	107.83(19.21)	91(23.5)	96(24.84)
FEF_{25-75}	82.13(24.66)	101.1(25.04)	74.35(28.36)	93(35.19)
FEF_{50}	91.6(28.54)	114.37(33.04)	81.14(30.56)	102.28(27.63)
FEF_{75}	77.25(32.60)	102.87(332.51)	68(30.98)	93(38.34)
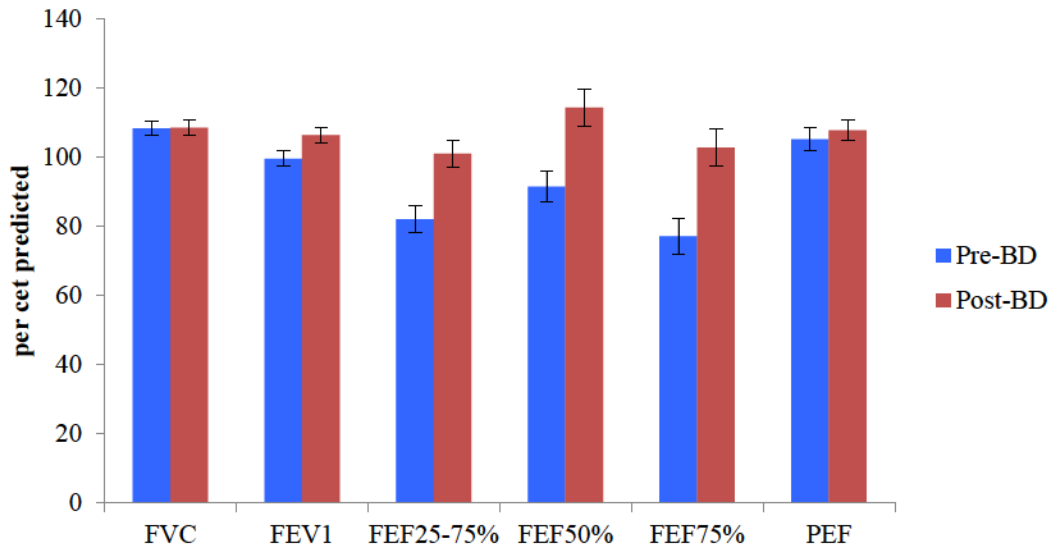
Figure 4.3: Pulmonary function tests recorded before and after BD in well-controlled asthmatic subjects (n=39). We did not for significant differences pre and post BD in controlled or uncontrolled subjects since there were no differences between the groups, and only tested this in the pooled data.

Figure 4.4: Pulmonary function tests recorded before and after BD in poorly-controlled asthmatic subjects (n=14)

Table 4.5: Percent change and p value in spirometric indices in well-controlled and poorly-controlled following administration of bronchodilator. Data are mean across subjects (SD)

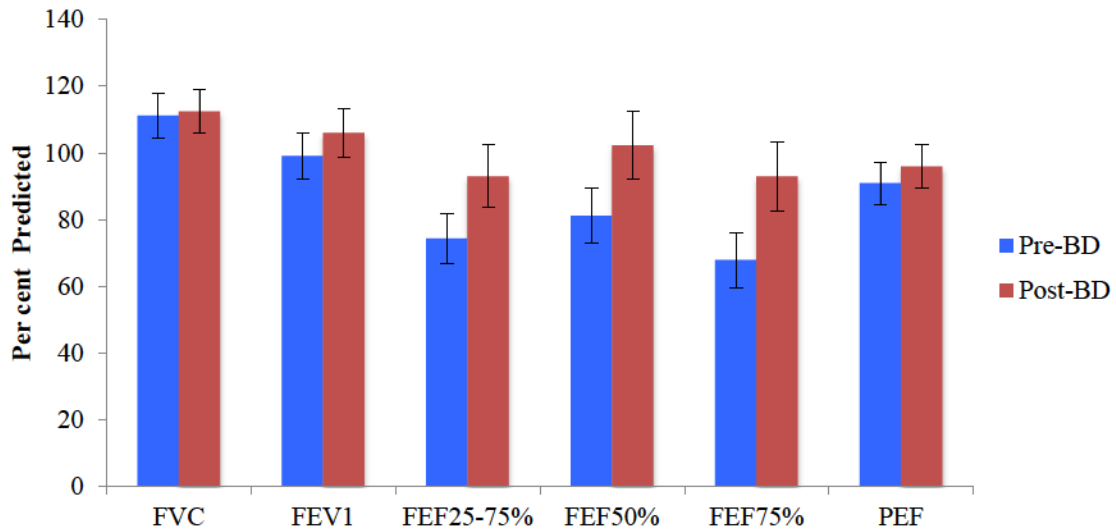|	%Change well-controlled	T-test (p value)	%Change poorly-controlled	t-test (p value)
FEV_1	7.18(6.00)	3E-09	6.88(6.79)	$p < 0.001$
PEF	2.80(8.20)	5E-12	6.15(17.08)	$p < 0.001$
FEF_{25-75}	26.7(21.4)	4E-09	24.7(18.7)	$p < 0.001$
FEF_{50}	28.3(25.8)	1E-11	27.4(17.9)	$p < 0.001$
FEF_{75}	40.6(31.8)	0.05	41.3(20.6)	0.10

4.4.2 Bronchial Reversibility of Lung Mechanics Assessed with Oscillometry

Table 4.6: Percent change in oscillometry indices following administration of bronchodilator. Data are mean across subjects (SD)

	Pre-BD	Post-BD	%Per cent Change	P value
Rrs5	6.5(2.1)	4.8(1.5)	25.3(10.5)	$p < 0.001$
Xrs5	-2.7(1.8)	-1.90(1.18)	26.9(22.5)	$p < 0.001$
Rrs19	5.24 (14)	3.9(1.9)	25.8(32.13)	$p < 0.001$
Rrs37	5.2(1.3)	4.09(1.7)	21.6(28.3)	$p < 0.001$
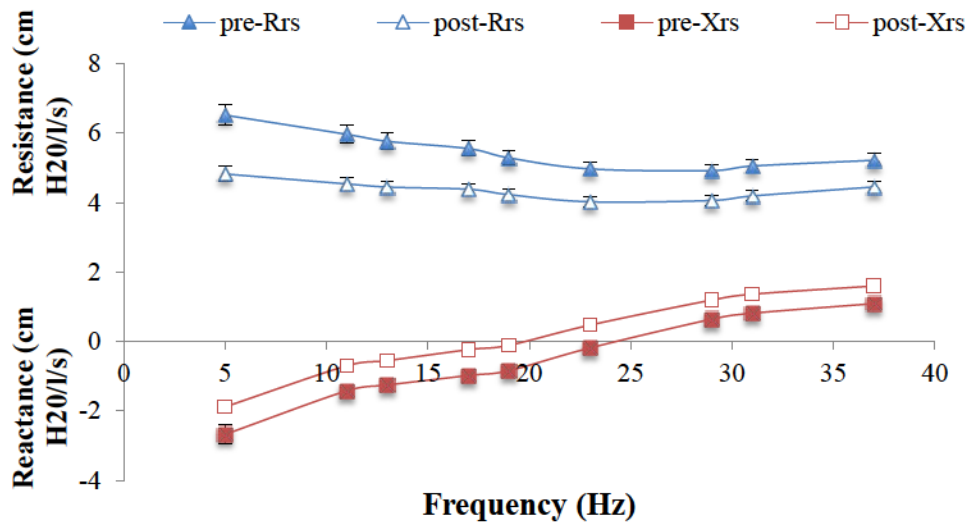
Figure 4.5: Rrs (top) and Xrs (bottom) before and following bronchodilation in all subjects
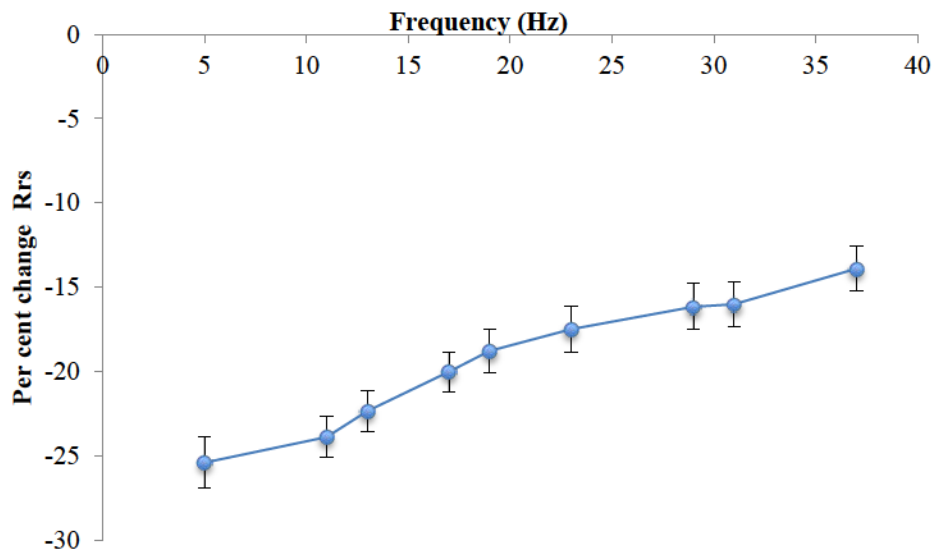
Figure 4.6: The percent change for resistance in response to BD from all subjects at each oscillatory frequency

Compared with spirometry, BD induced significant changes in both Rrs and Xrs. For instance, before BD, mean Rrs5 was 6.5(SD=2.1) cmH$_2$O/l/s which was 110 %

predicted and after BD, it decreased to 5.24(SD=1.4) cmH$_2$0/l/s, corresponding to a

25.3(SD=10.5) % change. In the mid-frequency range, mean Rrs19 before BD was

5.27(SD=1.5) cmH$_2$O/l/s (120 % predicted) and 3.88 (SD=1.99) cm H$_2$0/l/s, after BD,

corresponding to a 25.8(SD=32.1) % change. However, in the high-frequency range,

mean Rrs37 before BD was 5.2(SD=1.2) cmH$_2$O/l/s and after BD, decreased to 4.1

(SD=1.7) cmH$_2$0/l/s, corresponding to a 21.6(SD=28.3) % decrease (Table 4.6). The

sensitivity to BD was greatest at low frequencies and was reduced with increasing

frequency (Figure 4.6).

The BD also caused an upward shift in the Xrs versus frequency curve. At 5 Hz,

for example, Xrs increased from -2.77(SD=1.81) cm H$_2$O/l/s to -1.89(SD=1.17) cm

H$_2$O/l/s.

Table 4.7: Effect of BD in selected oscillometric indices in well-controlled and poorly-controlled asthma at 3 key frequencies. Data are mean across subjects (SD)

	Pre-BD (well)	Post-BD(well)	%Per cent Change(well)	Pre-BD(poorly)	Post-BD (poorly)	%Per cent Change (poorly)
Rrs5	6.19(1.79)	4.75(1.44)	23.4(11.2)	7.24(2.54)	5.11(1.58)	28.1(10.1)
Xrs5	-2.50 (1.02)	-1.80(0.68)	21.9(22.5)	-3.44(2.94)	-2.20(1.93)	33(20)
Rrs19	5.09(1.44)	3.69(2.15)	19.8(25.5)	5.5(1.3)	4.45(0.89)	18.6(11.2)
Rrs37	5.05(1.30)	3.9(1.9)	15.3(22.5)	5.4(1.3)	4.7(1.1)	13.2(11.5)
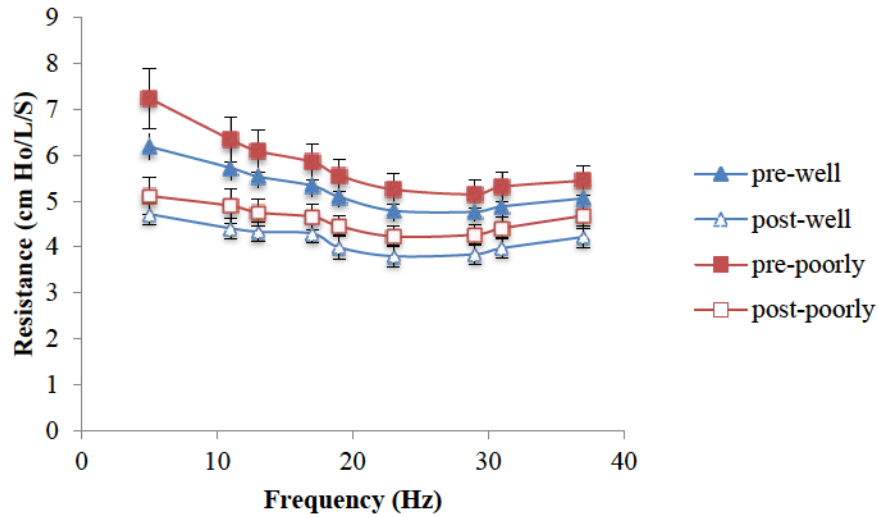
Figure 4.7: Rrs before and following BD in well-controlled and poorly-controlled subjects
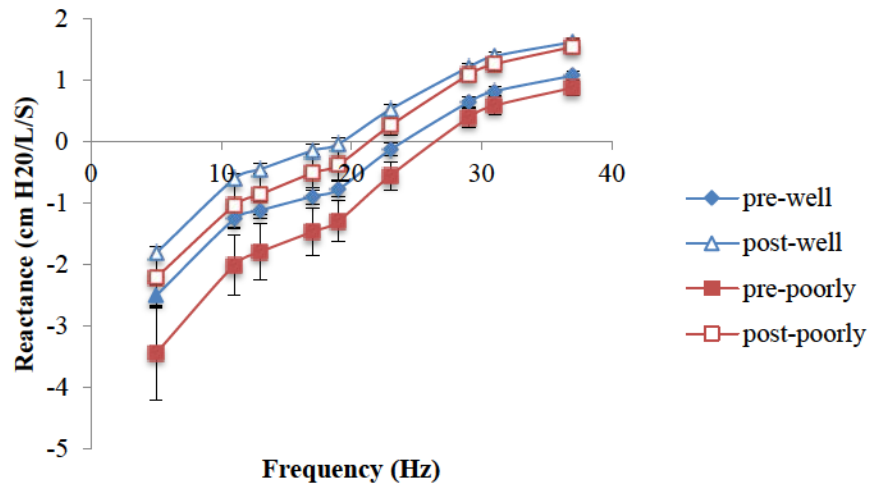
Figure 4.8: Xrs before and following BD in well-controlled and poorly-controlled subjects

Figure 4.7 compares the percentage change of Rrs in well-controlled asthma and poorly controlled asthma before and after administration of BD. We found for Rrs5,

Rrs19 and Rrs37 that there was no difference in response to BD between controlled and poorly controlled asthma (Table 4.7).

Also Figure 4.8 compares the percentage change in Xrs in well-controlled asthma and poorly controlled asthma before and after administration of BD. While Xrs5 seems to be higher in well-controlled subjects than poorly-controlled, this did not reach significance (Table 4.7).

The mixed design ANOVA showed that there was no significant difference in % change in FEV1, Rrs5 or Xrs5 between pre and post BD in both controlled and uncontrolled asthma subjects. Therefore, we pooled the groups for comparisons of sensitivity or repeatability for oscillometry to spirometry.

4.4.3 Coefficient of variation before and after bronchodilator
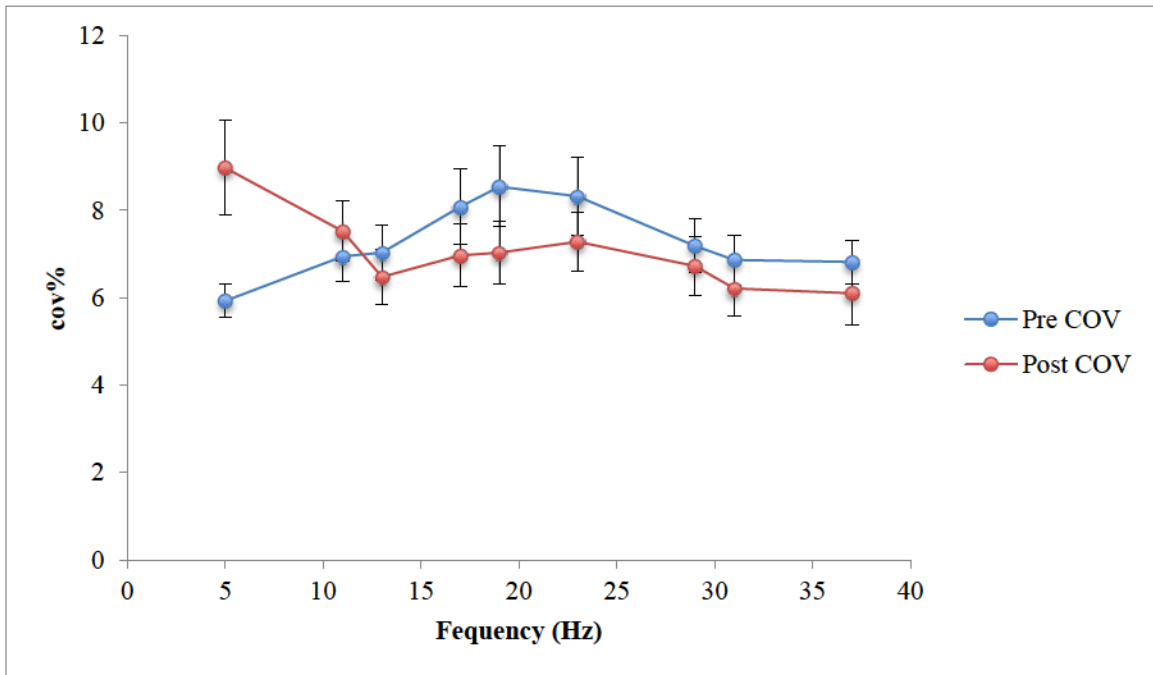
Figure 4.9: COV of Rrs before and following bronchodilation in all subjects
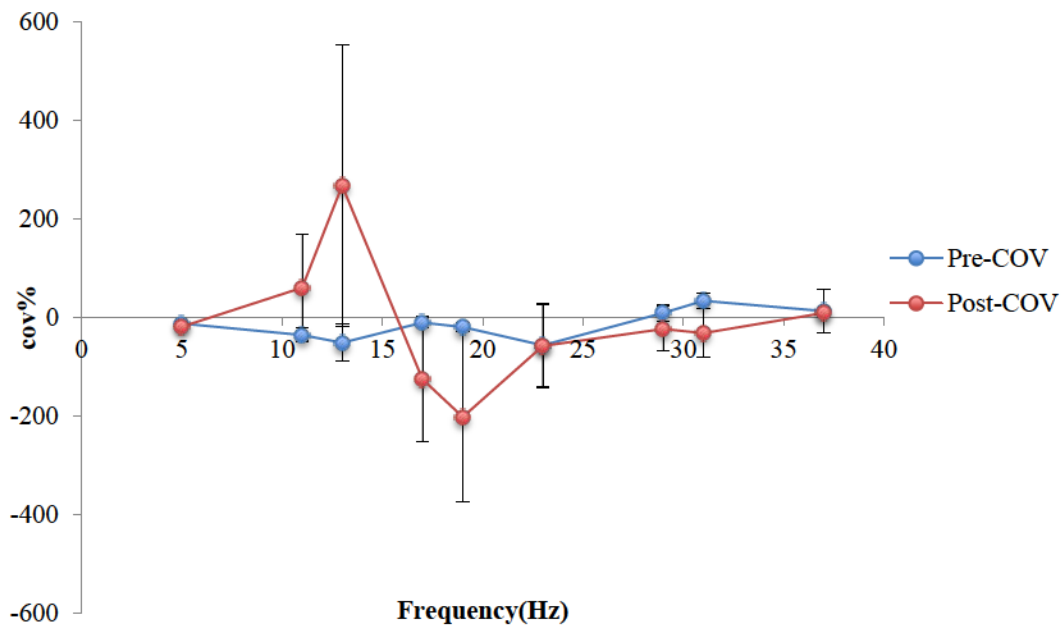
Figure 4.10: COV% of Xrs before and following bronchodilation in all subjects

As can be seen the COV% for Xrs is widely variable for much of the frequency range, but at 5 Hz, it became more consistent across subjects indicated by the similar values pre and post BD, and by the very small standard error bars.

We used the COV% from the repeated measures of spirometry and of FOT impedance as a measure of variability and repeatability. The COV% for FEV1 was found to be 2.1 (SD=1.4)% and 3.1 (SD=2.5)% recorded before and after BD, respectively. The COV% for both pre- and post-BD Rrs was ≤ 15% for all subjects at all frequencies. In particular, Pre-BD, the COV% at 5Hz, 19Hz and 37Hz was 5.9(SD=2.7)%, 8.5(SD=6.7) %and 6.8(SD=3.6)%, respectively while the post-BD COV% at those frequencies were 8.9(SD=7.9)%, 7.03(SD=5.2) %and 6.10(SD=5.3)%, respectively. The COV% for Xrs was variable at many frequencies as can be seen from Figure 6.10. However at 5 Hz, the COV% was somewhat more consistent, and pre- BD Xrs at 5 Hz, was not different between pre and post BD with 11.7 (SD=10.8) cm H_2O/l/s pre-BD and 18.39(SD=18.5) cmH_2O/l/s post-BD. The COV% for Ers was found to be 17(SD=15)% and 16(SD=16)% recorded before and after BD.

We found that both spirometric indices and FOT values changed significantly, but Rrs and Xrs demonstrated greater variability than spirometry. We calculated the SNR_BD as the ratio of the sensitivity or % change in response of a measurement relative to its COV. Because the COV of Xrs5 is negative due to the negative mean value we multiplied this by -1, which provided a positive SNR_BD_Xrs5 for ease of comparison, and because the changes in Rrs5 and Ers were negative (they decreased), we also multiplied these by -1. The distributions of the SNR_BD for Xrs5 and FEV1 were not normal, thus we compared these using the nonparametric Wilcoxon rank sum test and

report the median for the SNR_BD measures. Since the sensitivity of Rrs was greatest at 5 Hz observed in Figure 4.4, but the COV% was reasonably constant with frequency as seen in Figure 4.6a, we calculated the SNR_BD at 5 Hz only. For Xrs, due to the high variability at most frequencies we computed this also at 5 Hz only.

Table 4.8: Average percent change across subjects in response to BD for FEV1%, Rrs5 and Xrs, and their coefficients of variation (cov) pre and post BD, and median SNR-BD for FEV1, Rrs5 and Xrs5, with the SD indicated in brackets

	% Change (SD)	Pre BD COV%	POST BD COV%	Ave COV%	Median %change/Ave COV% (SNR-BD)
FEV1	7.1 (6.2)%	2.1(1.4)	3.1(2.5)	2.6(1.6)	2.0 (2.8)
Rrs5	-25.3 (10.4)%	5.9(2.8)	8.9 (7.9)	7.3(4.4)	3.8 (2.4)
Xrs5	26.8 (22.5)%	-11.7(10.3)	-18.2(18.5)	-14.9(10.1)	2.2 (3.4)
Ers	-19.7 (43.8)%	17(15)	16(16)	16.7(13.0)	1.8(2.2)

Examining the table, it can be seen that Rrs5 had a larger %change than FEV1, 25.3(SD=10.4)% compared with 7.1(SD=6.2)%. But as indicated above, Rrs5, Xrs5 and Ers appeared more variable with 7.3(SD=4.4)%, 14.9(SD=10.1)% and 16.7(SD=13.0)% average COV% respectively compared to FEV1 with only 2.6(SD=1.6)% COV%. While Xrs had a magnitude change of about 27%, Ers changed by 20% but with considerable variability in the response to BD. The average COV for Ers was comparable to the percent change. However when computed on a subject by subject basis the SNR_BD for Ers of 1.8 (SD=2.2) was very comparable to the SNR_BD for Xrs of 2.2(SD=3.4), but with less variability. However the variability in SNR_BD appeared about the same as that for Rrs5. Thus amongst the SNR_BD values, comparing FEV1, Rrs5, Xrs5 and Ers, it is

Rrs5 that is the best value. Indeed we compared SNR_BD_FEV1 to SNR_BD_Rrs, SNR_BD_Xrs and SNR_BD_Ers, and we found that while the SNR_BD for Xrs5, Ers and FEV1 were not significantly different, the SNR_BD for Rrs5 was nearly 2 times greater than SNR_BD for FEV1 ($p < 0.0005$).

4.5 Single compartment model

When we fit the single compartment model to each subject individually, we found that the average R-squared value in pre-BD and post-BD was 0.84(SD=0.11) and 0.90(0.09) respectively. The average Ers values in pre-BD and post-BD was 107.7(65.1) cmH_2O/l and 75.8(45.2) cmH_2O/l respectively. Additionally the average Irs in pre-BD and post was 0.005(0.002) $cmH20/l/s^2$ and 0.007(0.002) $cmH20/l/s^2$, respectively. Below are two examples of a representative fit for the single compartment model:
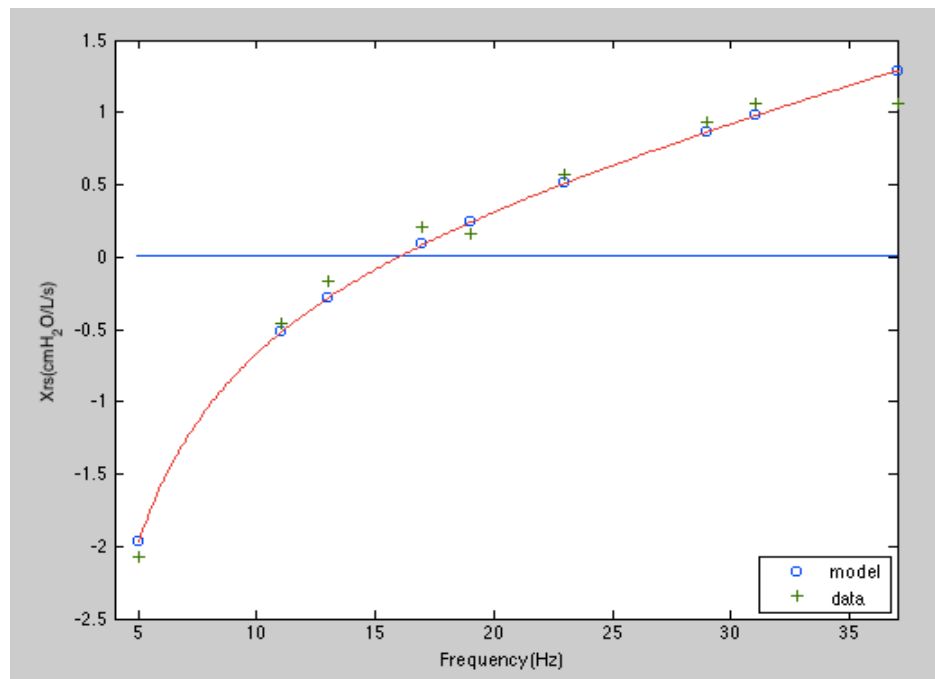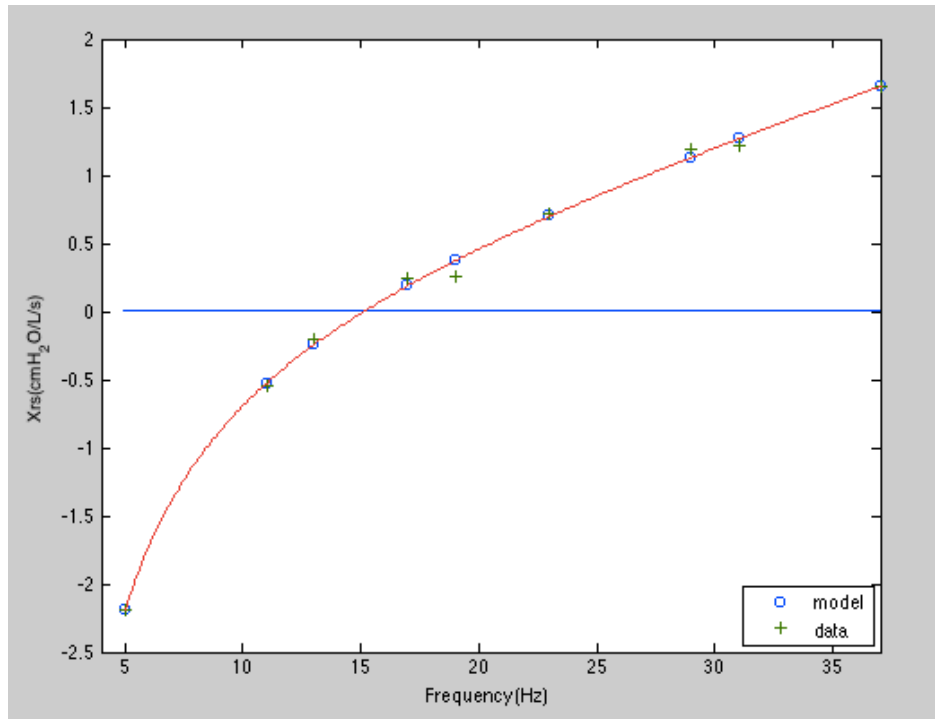
Figure 4.11: Fit of the single compartment model to the Xrs data from two representative subjects

4.6 Correlations between spirometry to oscillometry

The following demonstrates the correlation or lack of correlations we found between changes in oscillometry and FEV1 measures in response to bronchodilator.
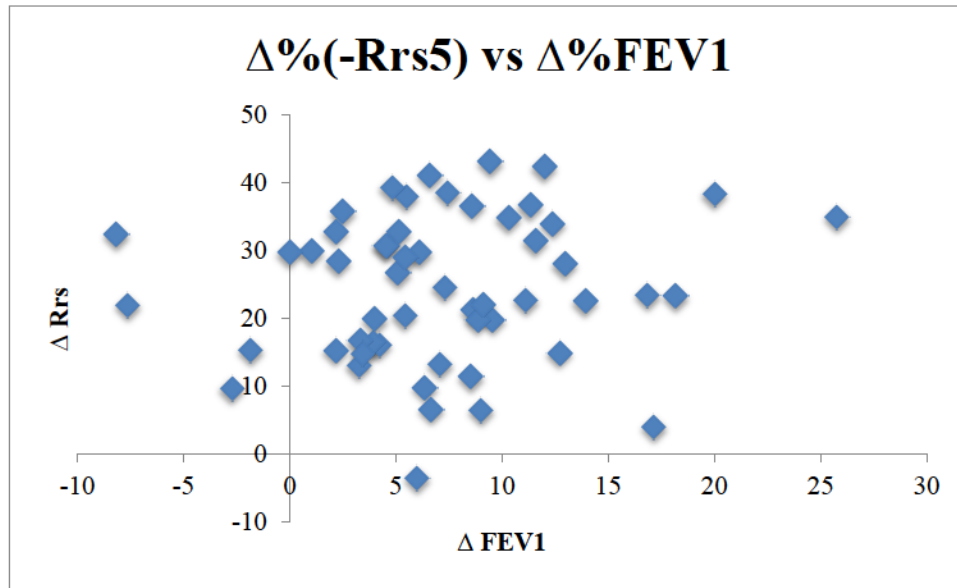
Figure 4.12: Correlations between the percent changes in Rrs and FEV1 i.e. Δ%(-Rrs), Δ%Xrs and Δ%FEV1
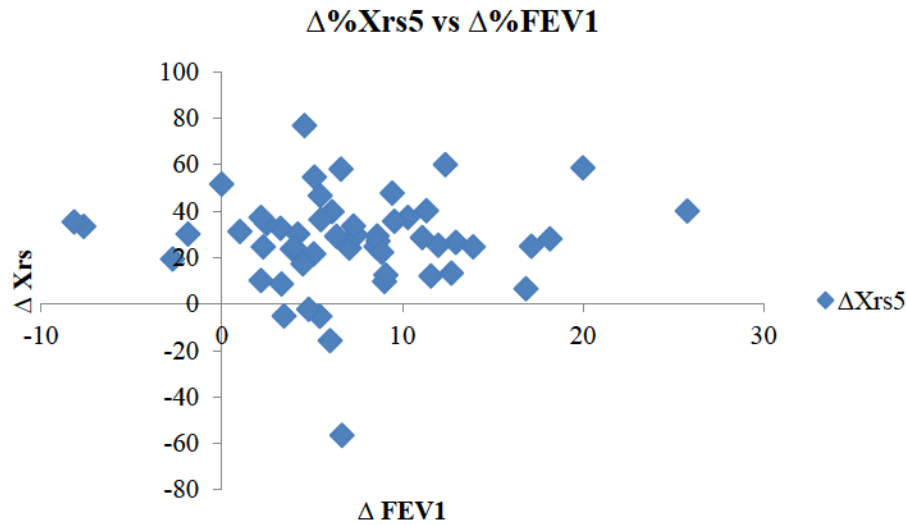
Figure 4.13: Correlations between the percent changes in Xrs and FEV1 i.e. Δ%(-Rrs), Δ%Xrs and Δ%FEV1

The percent change in Rrs was not correlated with the percent change in FEV1 (r^2=0.015, p=0.5). Similarly the percent change in Xrs was not correlated with the percent change in FEV1 (r^2=0.002, p=0.7. 4.8).

Chapter 5: Discussion

Children less than six years old have difficulty with spirometry, which is the current standard test of airflow obstruction in lung function. An alternative method to measure airflow obstruction and indeed to obtain the mechanical properties of the respiratory system is the forced oscillation technique. However, only recently has progress been made in establishing this method clinically, and understanding it's measures and how it performs in standard respiratory testing. This study was to validate the method using a novel portable forced oscillation device, and to compare it directly to spirometry in children – and in particular compare it's performance in bronchial reversibility testing. Here we assessed the degree of changes using both techniques in response to BD, the repeatability recorded in both measurements, and introduced the signal to noise bronchodilator measure, SNR_BD as a method to assess the sensitivity to the bronchodilator intervention relative to the variability in each technique. We also examined the ability of the reactance data to be described by the single compartment model.

The principle findings that arise from this thesis are: (i) Oscillometry using resistance at 5 Hz in children with asthma was more sensitive than spirometry to bronchodilator induced changes in the lung mechanics and although oscillometry was more variable than spirometry, the higher sensitivity in Rrs at 5Hz, more than made up for this variability. This was not the case for Xrs or Ers at 5 Hz. In the following section we first discuss the similarities and differences of our findings to the literature. After that, we discuss the novel findings, and finally some limitations of our study.

5.1 Similarities and differences with previous studies

5.1.1 Baseline spirometry

We found that even though we enrolled children with asthma, they demonstrated normal spirometry defined as FEV1% values > 80% [29]. Indeed, our values were close to 100 % predicted. This is likely because the subjects were reasonably well controlled in agreement with Fitzpatrick, et al (Fitzpatrick, 2006) where school children aged from 6 to 17 with stable asthma had FEV1% of 95(SD =12)% [40].

5.1.2 Bronchial reversibility assessed with spirometry

Subjects demonstrated a response to BD in FEV1% of 7.11(6.15) %. This is below the recommended cut-off for positive reversibility in subjects > 5 years of age [29]. Indeed only 10 subjects had a positive response to BD. This may reflect that some subjects who are less than the cut-off still took their short-acting beta medication agonist for control asthma such as salbutamol (SABA) or long-acting beta medication agonist for control asthma such as salmeterol xinafoate (LABA) prior to measurement despite indicating otherwise. However, it is more likely this is because they were generally well-controlled. Despite 12% being the recommended threshold according to GINA, other reports are suggestive that a lower cut-off may be appropriate. Dundas shows that 9% is a reasonable threshold with good sensitivity (50%) and specificity (86%) for associating reversibility with wheeze in a study of 142 asthmatic and healthy subjects aged from 5 to10 years old [41]. Another study in 6-year-olds with current asthma children suggested 7.8% [42]. However, even if we choose 7.8% as a threshold for reversibility, this would still result in only 23 of our 53 subjects would be positive for reversibility. The BD

response we found was in agreement with the Youn Ho Shin et al study. In that study, the subjects were clinician-diagnosed asthma, both controlled and uncontrolled with 29 % well controlled. The pooled data showed a 5.3% average response in the preschool children [43]. Thus despite the fact that our subject were in between preschool and adult, the subjects in our study thus appear to have comparable spirometry and BD responses to other reports.

5.1.3 Baseline Lung Mechanics Assessed with Oscillometry

Similarly our values of impedance at baseline were similar to other studies in children with asthma. Robinson et al reported Rrs5 of 6.04(1.43), and Xrs5 of -1.43(0.64) similar to our data in Figure 4.1 [44]. Our predicted Rrs values were higher than 100%, but only on average 109.8%, which is still in the normal range according to Smith et al. who stated values > 150% were abnormal. Thus similar to the findings in spirometry, that baseline mechanics does not well distinguish asthma from health, particularly in mild disease and the lung mechanics of our subjects at baseline were within the normal range [15].

5.1.4 Bronchial Reversibility of Lung Mechanics Assessed with Oscillometry

We found a decrease in Rrs with BD at 5Hz of 25.0(10.8)% comparable to another study in 3-6.5 years old children with asthma, which reported a 21% decrease [45]. To my knowledge there is no study measuring the change in BD using oscillometry in our school age range. Xrs5 increased by 26.9(22.5)% following BD, and this increase in Xrs5 was comparable to the 27% increase in Xrs6 reported by Hellinckx and colleagues [45].

5.2 Novel finding

Oscillometry was more sensitive than spirometry to bronchodilator. In terms of comparing spirometry to oscillometry, there are only a few studies that have estimated the reversibility in children between 5 to 14 years old. In adults, many studies comparing bronchial reversibility measured with spirometry and oscillometry have been published. These studies report that oscillometry is more sensitive because the magnitude of the change induced by bronchodilator is bigger in oscillometry than spirometry [46]. However, although we found a similar result, that the magnitude of response to bronchodilator in oscillometry was larger than spirometry, we also point out here that the measurement was more variable. However, when we compare the sensitivity relative to the variability by normalizing the percent change in response to BD to the coefficient in variation from the repeated measurements used in both spirometry and oscillometry, the higher in variability in oscillometry was not increased as much as the sensitivity, which implies that oscillometry was a more sensitive measure and better measure than spirometry for measuring the response to inhaled bronchodilator-in reversibility testing. There are no studies that establish an appropriate threshold for discriminating asthma from health for the age group 5 to 14. Oostveen *at el* found the Rrs decreased by 11% in healthy control adults. In using that population to define the normal distribution of Rrs in healthy adults, she determined the upper limit of normal (the 95% percentile) in the BDR to be 32% for Rrs at low frequency. This can thus be used as a threshold for a positive BDR response, but it should be recognized that this does not mean this threshold determined only as the abnormal response from healthy subjects is the best value for discriminating between healthy and asthmatic subjects, which might be better determined

by comparing the response with both healthy subjects and subjects with asthma [26]. Indeed, if we used this as a cut off, only 13 of 53 of our subjects would be defined to have abnormal BDR. However, Oostveen's subjects were adults, and thus the appropriate threshold may be different in children in our age range. Also our subjects included well-controlled and uncontrolled asthma, which may affect the BDR, although we did not find the BDR to be larger in our uncontrolled group, although the number of subjects may have not been sufficient. Since asthma is a multifactorial clinical diagnosis, it is also possible that some of these patients were misdiagnosed and likely other factors contributed to their asthma diagnosis independent of the BDR. However, over the larger range of BD responsiveness, we were able to show that comparing oscillometry to spirometry, oscillometry was more sensitive than spirometry, relative to its variability.

5.2.1 The similarities and differences with the literature on repeatability and reversibility

Repeatability is a measure of quality control of a measurement. However, there are no studies comparing the repeatability of oscillometry to spirometry in children. The Standardization of Spirometry guideline indicates the limit for acceptable repeatability of spirometry is assumed 6% in adults [44]. However for preschool children the quality is worse. According to the American Thoracic Society/European Respiratory Society the average COV in preschool children is 6.2%. [30]. As there is no specific criteria for school aged children, 6% must be assumed to be the standard, implying that at ages close to 5 years of age, fewer measurements would meet this criteria. With regard to oscillometry there are not many publications describing the repeatability. In 2009, the recommendation by Oostveen et al. stated that the COV in Rrs should be ≤ 15% across

all frequencies [13]. A recent study conducted by Holmgren et al. for subjects aged 8–15 years recorded the COV in Rrs at 4Hz to be 7.5%[47]. Also in a study of children 7-17 years old, Lebeque et al. [48] showed COV in Rrs was 9.3%. Similar to spirometry, the variability of FOT in preschool children is large. Hall et al. [27] reported that the mean COV of Rrs in subjects aged 3 to 6 years old is between 9% and 10%. These are all average values, and thus do not represent the upper value that should be used as acceptable. In contrast, assessing variability in Xrs using COV is prone to problems as there are because the average Xrs value its value can be close to zero. However at 5 Hz the Xrs may be sufficiently below zero that the COV is still reasonably estimated. In our study Xrs was -2.7 (SD= 1.8) at 5 Hz, with the highest Xrs 5 Hz value being -0.77 in any subject. We found the COV for spirometry to be 2.13(SD 1.42) %, while with oscillometry, the COV for Rrs5 was 5.93 (2.75)% and for Xrs5 and Ers were -11.71 (10.26)% and 0.17(0.15)% respectively.

Taken alone, the higher variability in FOT vs spirometry would indicate that FOT was not as reliable, however when used for assessing reversibility, this must be compared against the sensitivity of the measurement. Here we found that the signal to noise ratio in responsiveness to a BD measured using Rrs at 5 Hz was approximately two times greater than the signal to noise ratio in responsiveness to a BD measured using FEV1 ($p <$ 0.0005).

Another interesting aspect in our study was the consistency of the measurement across the subjects. We showed an average change in FEV1 with BD of 7.1(SD = 6.2)% in our asthmatic subjects compared to 25.3(10.5)% in Rrs at 5 Hz for oscillometry. Here the standard deviations indicate the variation across subjects, and show that in fact the

variation relative to the magnitude of the measure was lower in oscillometry, indicating oscillometry was a more consistent measurement. This does not necessarily mean it is more reliable as a measure of BDR, but it may mean that in this case, since this improvement in consistency matches the improvement in signal to noise when we compare SNR_BD Rrs to SND_BD FEV1. Thus overall, while oscillometry for Rrs5 was more variable than spirometry, it was more sensitive and more consistent, and less affected by the variability in its measurement

5.2.2 Single compartment model

The single compartment model accounted for the Xrs data reasonably well, with an r-squared value of 0.87, which means the model, accounted for 87% of the variance of the data of the Xrs. This quality of fit implies that computing the elastance value from subjects with mild asthma may provide a useful physiological parameter to describe changes in the lung mechanics in asthma. Many authors fit FOT data to the single compartment model to identify Xrs and Rrs. This is despite the fact that in disease such as asthma it is now known that the lung is very heterogeneous and this increases with asthma severity, leading to a frequency dependent Rrs rather than the constant value predicted by the model [49]. By definition, a single compartment model is a homogenous model, rather than heterogeneous. Thus the elastance must be interpreted to represent an equivalent elastance of the respiratory system. Furthermore, the quality of fit would be expected to decrease with greater heterogeneity expected in more obstructed, higher impedance subjects. Also it would be expected to improve with bronchodilator, which should decrease any heterogeneity as airways are dilated.

Here we also found that R-squared for the model fit to Xrs for pre-BD was 0.83(0.11) and

for post was 0.90(.09). Thus the model fit appeared to improve post-BD. While this may

be because, the lung became more homogenous and better described by the single

compartment model after BD, it may also be because the signal to noise was better after

the bronchodilator. With more obstructed patients, the signal to noise in the flow signal

would be worse as the flow amplitude is lower, which would lead to larger noise in the

signal worsening estimates of Xrs, and thus poorer fits, independent of any underlying

heterogeneity. The single compartment model is often used to analyze changes in

respiratory mechanics in small animals. To my knowledge, it is not applied in the

measurement of respiratory impedance in children. This work indicates that it may be a

reliable parameter of the respiratory mechanics in children, at least in mild asthma.

However, it may be just as reasonable to use Xrs at 5 Hz, (Xrs5) as an index of lung

elasticity, since this value dominates the curve fit of Xrs, and thus largely represents the

elastic contribution to the reactance. Indeed an estimate of Ers is sometimes used that

does not employ the curve-fit, but simply estimates Ers as -2*pi*f*Xrs [50], which is

reasonably accurate as long as Xrs is not much affected by inertance, which is true when

Xrs is strongly negative. In this study 98% of the subjects had an Xrs5 that was greater

than -1, and the mean Xrs5 in pre_BD was -2.7 (1.8) and post_BD it was -1.90 (1.18).

5.2.3 Correlations between spirometry to oscillometry

Oscillometry and spirometry measurements both change in response to BD, but

we did not find that they were well-correlated. This is likely because they measure

different aspects of the underlying physiology. FEV1 is dominated by the central airways,

and largely reflects the unidirectional expiratory airflow limitation occurring at higher

lung volumes than tidal breathing during a maximal forced expiration, while Rrs reflects

the resistance to oscillatory flow, and of flows of much smaller magnitude, and is

measured at normal lung volumes that occur during breathing, and with no forced

manoeuvre. Thus these separate measures reflect different airways at different diameters

at different sites and at different lung volumes, under quite different flow magnitudes,

which nevertheless both change on average in response to a bronchodilator, but not well-

correlated.

5.3 Benefits of the Approach

This study attempted to characterize the differences between spirometry and oscillometry

in typical school aged children that come to the pulmonary function clinic. Because we

found that oscillometry for Rrs5 had higher signal to noise during reversibility testing, it

may be that oscillometry is more preferable, demonstrated here in children with mild

asthma. Since oscillometry is relatively effort independent, FOT offers a more

comfortable and convenient way of evaluating lung function, particularly useful in

children. In very young children, there are no recommended tests because of the

difficulty involved in performing them. While this study did not explore FOT in

preschool children, it does provide it in the next best age group, and indeed provides a

comparison when spirometry can be well performed. A comparison in younger children

may provide less repeatability in spirometry and also in oscillometry than we report here,

which is likely to further decrease the SNR_ BD for both measures in younger children. It

is not known if oscillometry would still have the advantage of higher SNR_BD over

spirometry in pre-school although it is more likely, given the greater feasibility for

oscillometry in this age. The addition of this technique to the repertoire of methods of testing for airway obstruction would improve the range of options for testing in this group.

5.4 Limitations of the Approach

According to Kim et al. (2001), a key limitation of the FOT method is that it is not effectively sensitive to detect pathologic conditions of the chest wall and restrictive lung diseases [18]. However its strength is that it directly measures the mechanics of the respiratory system, that is by measuring the impedance to airflow it is measuring the difficulty of moving air into and out of the airways, and provides the resistance to airflow and also the reactance which at low frequencies is governed by the elastic properties, and thus describes the elastance (or its inverse the compliance) of the respiratory system. In addition, if Rrs exhibits inverse decreasing frequency dependence, (that is Rrs at low frequencies such as 5 Hz is higher than at high frequencies such as 20 Hz) this means that there is heterogeneity in the airways, which would most likely occur with small airway narrowing. Thus with observed frequency dependence, the respiratory resistance can be divided into two compartments, the central resistance and the peripheral resistance[51]. However, there are a number of problems that could potentially affect the measurement of respiratory impedance. Although our subjects were diagnosed with asthma, they did not all have a positive reversibility result, as defined by a greater than 12% response to BD in FEV1. This may be due to some subjects not withholding their inhaled medications 8h before the measurement. Before being tested, if the asthmatic subjects used their bronchodilator medications less than 8h prior, the measurement of reversibility

would be potentially invalid, particularly for long acting beta-agonist therapy because the effect of the bronchodilatory therapy could potentially still be present reducing the BD response [52]. However it should also be noted that while the 32% threshold has been established for adults, it is possible that school aged children should have a different threshold.

Also, swallowing, glottis closure, and an inadequate seal on the nose clip, leakage around the mouth, or breathing that is different from normal breathing, such as hyperventilation, would have some effect on the mean impedance from any 16 second measurement. However in this study we rejected such artefacts detected at the time of recording, and if too many artefacts were present in a single measurement, we redid the measurement. We also eliminated outliers within the 16 sec measurements, which would remove most, if not all, artefacts that significantly affect the measured impedance. Together these approaches should provide a robust estimate of the mean impedance. Factors that affect the repeatability can be due to a lack of consistency in important steps such as supporting the cheeks, placing a nose clip properly and sitting in a good position without moving during the test. Thus similar to spirometry, which has standard requirements regarding the quality of the maneuver, oscillometry also has its requirements. Further, spirometry must be measured at least 3 times with consistency for the 3 repeated measures. We examined the oscillometry data for inconsistency in the 3 repeated measurements of both Rrs and Xrs, and in two cases removed outlier values as described in Results [13,53]. Potentially with improvements in software these could potentially be flagged or removed automatically to help operators know to repeat a given measurement.

Chapter 6: Conclusion

The conclusions of this study are briefly summarized in this chapter together with a description of their significance. Also, recommendations and possible future directions from this study are provided here.

6.1 Project Summary

The forced oscillation technique uses oscillations of air into and out of the mouth to measure respiratory impedance, Zrs which is comprised of respiratory resistance (Rrs) and reactance (Xrs). Spirometry is a well-standardized manoeuvre during which a subject inhales to maximum lung volume and then forcefully exhales as hard as possible, and the volume of the exhaled breath in the first second is measured as the FEV1. The aim of this thesis was to compare the sensitivity and repeatability of oscillometry to spirometry in reversibility testing children with asthma.

We found that following inhalation by BD, while FEV1 increased by 7.11%, Rrs and Xrs were more sensitive, and decreased more by a factor 3-fold larger. However, the repeatability as measured by COV% for FEV1 was very good at 2.13%, but was less consistent for oscillometry, being larger by a factor again of nearly 2.5-fold larger (5.93 %) for Rrs and 6-fold larger (11.7%) for Xrs. Thus while oscillometry was more sensitive, it was more variable, which we characterized with the SND_BD. Since oscillometry had a larger signal-to-noise in Rrs5, and is easier for patients to perform, and because it directly measures the difficulty moving air into and out of the respiratory

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system, we recommend that oscillometry can be used to assess and monitor reversibility in children with asthma.

6.2 List of contributions

1) This is one of a few reports of bronchodilator response of children in this age range with asthma and it is the first report using the tremoFlo.

2) I quantified the BDR in children with asthma by measuring, analyzing and reporting Rrs and Xrs. I found that percent changes in Rrs were larger than in FEV1 but more variable. I developed the SNR_BD to compare both measures, and found that oscillometry was superior to FEV1 in measurement of the response to a BD for Rrs5.

3) I also found that while the changes in Xrs5 were comparable to those of Rrs5, the SNR_BD was not as high as Rrs5, but this may be due to the fact that COV is normalized to the mean which can be close to zero for Xrs, leading to higher apparent variability than actual.

4) I also did not find any difference in FEV1, Rrs or Xrs between well-controlled and poorly controlled asthma.

5) I also found that the single compartment model fit reasonably well to the Xrs data pre and post BD for children with mild asthma.

6.3 Significance

The fact that oscillometry had superior SNR_BD for Rrs5 was important to establish as clinicians want to know if the greater sensitivity of the measurement makes up for its

increased variability. The added benefit of this technique is that it provides an easier to perform, objective measurement for airway function comparable in utility to spirometry.

6.4 Future Directions and Recommendation

This study generated a few possible ideas for future research studies. In this section, I briefly discuss new ideas, improvements for analyzing data and suggested directions for future work.

6.4.1 FOT studies

1) This thesis indicated that oscillometry was superior in signal to noise for BD response for Rrs5 compared with FEV1 in the pulmonary function lab. We did this only for the measurement of reversibility. This does not mean the method is superior for all 'signals' that clinicians are interested in that could be measured using FOT. For example a clinician is interested if a change in therapy reduces symptoms. Thus perhaps would be interested if oscillometry corresponded to changes in symptoms following a change in therapy. Thus one possible future study could assess the effects of changes in therapy on resistance Rrs and reactance Xrs. While our study which shows the measurement of BD responsiveness is better assessed with FOT, and predicts it should be better to assess therapy effectiveness, this should be confirmed. Similar to this thesis, one could compare the changes in impedance that occur with the changes in therapy, again normalized to the COVs, and compare this signal to noise to the same measured with FEV1, and also see how well each measure correlated with any changes in symptoms.

2) Also, both patients and doctors tend to significantly overestimate the level of asthma control in the patient, suggesting that more people need to make changes to their asthma treatment therapies, and perhaps on a more frequent basis. This failure to achieve consistent asthma control itself has remained consistent in the Canadian Medical landscape, despite the fact that it is generally possible to control the disease. If airway diameter, and thus respiratory impedance, is related to the changes in asthma control, then respiratory impedance it may be an effective measure of airway hyperactivity and thus respiratory impedance could be a measure lung function related to symptoms. That is, perhaps the COV of the Rrs or Xrs from multiple time-points can be used, if tracked over sufficient time as a measure of lack of asthma control that is the COV maybe related to lack of asthma control over days. Indeed, Robinson et al. [37] found that the variation of Rrs was related to asthma severity and asthma control over a period of X days. Thus it would be interesting to use the COV to help guide therapy in an interventional study to see if improved control could be achieved using COV in oscillometry relative to current standard of care based on spirometry.

3) My study measured BDR in children between 5 to 14 years of age. There is no study for this age group for healthy subjects. It might be useful to establish the normal reference values not only for baseline impedance, but also for the bronchodilator response with a large number of subjects.

4) We assessed the single compartment model, using the frequency dependence of Xrs to identify Ers from subjects with mild asthma, and we found elastance may be a useful physiological parameter to describe changes in the lung mechanics in

asthma. We assessed the signal to noise for Ers for BD, as we did for Rrs and Xrs. Unfortunately there was not any improvement in COV from Ers compared with Xrs amongst our subjects. It would be also useful to assess comparing Ers across a wider range of asthma severity, as the curve fit with Xrs in more severe asthma may be too poor to evaluate Ers despite its advantage in not crossing zero. However at this time, if a measure of elastance is desired, it is also recommended that Xrs at 5 Hz may used as an index of Ers, particularly in children or obstruction where Xrs is well below zero.

5) While I did my study with BD, it may be possible to compare oscillometry to spirometry using bronchoconstriction with methacholine as done in hyperresponsiveness testing. It would be useful to know if the increase in sensitivity reported in the literature for Rrs in response to methacholine compared to FEV1 outweighs any increase in variability that occurs, or vice versa.

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Appendix.1

Appendix.2

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To: ■ Marwa AlAmer; ⌄

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Appendix.3

How to take the Childhood Asthma Control Test

Step 1 Let your child respond to **the first four questions (1 to 4)**. If your child needs help reading or understanding the question, you may help, but let your child select the response. Complete the remaining **three questions (5 to 7)** on your own and without letting your child's response influence your answers. There are no right or wrong answers.

Step 2 Write the number of each answer in the score box provided.

Step 3 Add up each score box for the total.

Step 4 Take the test to the doctor to talk about your child's total score.

If your child's score is 19 or less, it may be a sign that your child's asthma is not controlled as well as it could be. No matter what the score, bring this test to your doctor to talk about your child's results.

Have your child complete these questions.

1. How is your asthma today?

				SCORE
0 Very bad	**1** Bad	**2** Good	**3** Very good	☐

2. How much of a problem is your asthma when you run, exercise or play sports?

0 It's a big problem, I can't do what I want to do.	**1** It's a problem and I don't like it.	**2** It's a little problem but it's okay.	**3** It's not a problem.	☐

3. Do you cough because of your asthma?

0 Yes, all of the time.	**1** Yes, most of the time.	**2** Yes, some of the time.	**3** No, none of the time.	☐

4. Do you wake up during the night because of your asthma?

0 Yes, all of the time.	**1** Yes, most of the time.	**2** Yes, some of the time.	**3** No, none of the time.	☐

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5 Not at all	**4** 1-3 days	**3** 4-10 days	**2** 11-18 days	**1** 19-24 days	**0** Everyday	☐

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5 Not at all	**4** 1-3 days	**3** 4-10 days	**2** 11-18 days	**1** 19-24 days	**0** Everyday	☐

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

5 Not at all	**4** 1-3 days	**3** 4-10 days	**2** 11-18 days	**1** 19-24 days	**0** Everyday	☐

TOTAL ☐