An Overview about Impulse Oscillometry in Pre-school Children

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Abstract

Background: Pulmonary function testing may assist in the diagnosis and follow-up of respiratory diseases. The most commonly used method to date is spirometry because it has well-established protocols for its execution and interpretation. Spirometry can be performed in children younger than six years of age, but achieving a reproducible and reliable measure in these children is a challenge since we can observe reproducible respiratory maneuvers by most children only after the age of five years. Impulse oscillometry (IOS) has been introduced as an alternative technique to assess lung function with particular application to asthma. IOS is noninvasive, easily performed during tidal breathing and requires only minimal patient cooperation. IOS being effort-independent makes it feasible even in young children. It also obviates the problems with interpreting forced mid expiratory flow rates (FEF25-75) which are highly volume dependent, as for example in patients who perform an incomplete expiratory maneuver from total lung capacity to residual volume. IOS is a useful tool for the assessment of lung function in pre-school children mainly because it is effort independent, it is performed with tidal breathing and it requires minimal patient cooperation. However, some young children still have difficulty in staying quiet during the IOS. In these cases, the use of other parameters of spirometry such as forced expiratory volume in 0.5 s (FEV0.5) instead of forced expiratory volume in 1 s (FEV1) could be more effective.

Keywords: Impulse Oscillometry

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Introduction

Spirometry has traditionally been employed to evaluate lung function in children and adults. While spirometry is of great utility, many practitioners do not use this in their assessment of asthma, which could reflect a lack of accessibility, problems with interpreting results, and difficulties at the extremes of age such as in preschool children and the elderly, who may not be able to perform spirometry, since it requires effort-dependent lung maneuvers. In addition, spirometry may be limited when clinical conditions do not allow it to be safely performed **(1)**.

In this context impulse oscillometry (IOS) has been introduced as an alternative technique to assess lung function with particular application to asthma. IOS is noninvasive, easily performed during tidal breathing and requires only minimal patient cooperation. IOS being effort- independent makes it feasible even in young children. It also obviates the problems with interpreting forced mid expiratory flow rates (FEF25-75) which are highly volume dependent, as for example in patients who perform an incomplete expiratory maneuver from total lung capacity to residual volume **(2).**

The challenge to discover more effective asthma treatment is essential for the clinician. Although inhaled corticosteroids (ICS), first line controller therapy in patients of all ages with persistent asthma, have been shown to be effective in asthma in improving control and reducing morbidity, a considerable number of children and adults may not respond well in terms of either spirometric parameters or clinical outcomes **(3).**
One possibility accounting for these observations recently proposed has been the under appreciation that the peripheral airways (PAW), less than 2mm luminal diameter, are major sites of airway obstruction and inflammation in persistent asthma, and therefore the delivery of standard large particle inhaled controller therapies may be inadequate the peripheral airways have been largely neglected primarily due to their inaccessibility to evaluation by previous techniques. More recently, newer noninvasive techniques have successfully evaluated PAW including IOS which measures airway impedance (Zrs), a composite of airway resistance (Rrs) which detects airway obstruction in the central and PAW, and reactance (Xrs) which is thought to reflect the elasticity of the PAW. IOS has been found to have good reproducibility, and shows good correlation with previously established methods of assessing the PAW both in adults and older children (**4**).
It's been suggested that IOS could detect PAW impairment (PAI) early, before clinical manifestations and spirometric abnormalities occur, primarily reflecting central airway dysfunction which may take longer to develop obstruction. PAI has been shown to be clinically related to airway hyper- reactivity, nocturnal asthma, exacerbations, steroid-resistant asthma, and fatal asthma. However, PAI may be clinically relevant at all levels of asthma severity, and control, as well as predicting the persistence of childhood asthma into adulthood, and potential loss of lung function with age. Pulmonary function testing may assist in the diagnosis and follow-up of respiratory diseases. The most commonly used method to date is spirometry because it has well-established protocols for its execution and interpretation. Spirometry can be performed in children younger than six years of age, but achieving a reproducible and reliable measure in these children is a challenge since we can observe reproducible respiratory maneuvers by most children only after the age of five years **(5).**

Table 1:**Impulse Oscillometry Terminology (4).**

Impedance (Zrs)	**A calculation of the total force needed to propagate a pressure wave through the pulmonary system, comprised of resistance and reactance.**
Resistance (Rrs)	Energy required to propagate a pressure wave through the airways; to pass through the bronchi, bronchioles, and to distend the lung parenchyma. Resistance is determined when a pressure wave is unopposed by airway recoil and is in phase with airflow.
Reactance (Xrs)	Energy generated by the recoil of the lungs after distention by a pressure wave out of phase with airflow.
Area of Reactance (AX or XA)	Area under the curve between the reactance values for 5Hz and the resonance frequency.
Resonance Frequency (Fres)	The frequency at which the lung tissue moves from passive distention to active stretch in response to the force of the pressure wave signal; graphically when reactance is zero.
Coefficient of Variability (CV)	Statistical determinant of the trial-to-trial variability serving as an index of reproducibility.
Frequency Independent Change	When resistance values do not vary at different frequencies. If overall resistance is increased this may be indicative of proximal obstruction.
Frequency Dependent Change	When resistance varies with frequency more than age dependent normal values. This may be indicative of distal obstruction as shown by R5-R20.

The Impulse Oscillometry System (IOS) is a non-invasive technique that performs a mechanical assessment of airways, using pressure fluctuations during tidal breathing --- which is increasingly gaining acceptance in the scientific community employed either as an alternative method to evaluate lung function in children unable to properly perform spirometry or as an additional tool for measuring different aspects of the pulmonary physiology. The IOS evaluates the resistance of the airways based on the production of oscillations of small pressures applied in the mouth and transmitted to the lungs thus allowing the measurement of resistance and reactance of the respiratory system **(6).**

Because it is an examination that is rapidly executed and has good reproducibility, IOS can be applied to all age groups. However, there is great interest in the pediatric population since it is a non-invasive method, requiring only passive patient cooperation and not using forced expiratory maneuvers. Impulse oscillometry equipment generates pressure oscillations that are applied to the mouth and transmitted to the lungs with low (5 Hz) and high (20 Hz) signals. Lowfrequency signals are transmitted to the distal regions of the lungs and reach the peripheral airways (diameter<2 mm). High-frequency signals are transmitted to the central region of the lung and reach the central airways. Thus, it is a system that assesses the resistance of the airways of the entire tracheobronchial tree and serves as an alternative method in the evaluation of patients with asthma and cystic fibrosis. Considering the importance of lung function assessment in clinical practice and the lack of methods applicable to the pediatric age group, this study aims to present a review of the literature on the use of IOS in the assessment of respiratory diseases in children **(7).**

Structure of the Oscillometry System

There are three perspectives of the forced oscillation technique, one of them is the "typical forced oscillometry technique", which is sometimes applied as a general term describing all oscillometry techniques, but commonly points out a simple one-frequency technique, another one is impulse oscillometry (IOS), using pressure pulses, and the third one is the Pseudo-Random Noise (PRN). IOS and PRN techniques are more often used because their principle allows a quick performance of the test. The one-frequency FOT is appropriate for the use in research because of its ability to determine changes occurring at one precise frequency. The concept of oscillometry was published very first by Dubois et al in 1956, describing a technique meant to be useful in acquiring data of the respiratory system's mechanic proprieties. Further studies were published after 1990, due to the development of technology, facilitating the technical approach and the interpretation of clinical data **(5).**

The main components of the oscillometer are the loudspeaker, which forms a pulsatile stimulus through the adapter, this way pressure waves get into the airways with the airflow; and the pneumotachograph, usually attached to a mouthpiece, a face mask, or an endotracheal tube. A bias flow is used to eliminate the dead space. Data will be collected by the pressure and flow sensors **(8).**

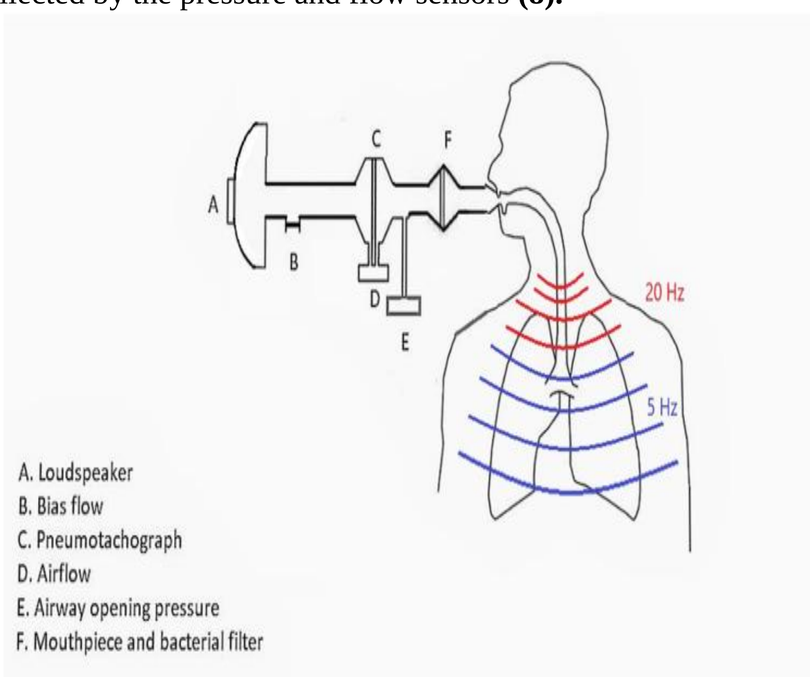

Figure 1:The main components of the oscillometer

Technique Description

Prior to the measurements, reasonable instructions should be given, patients should breathe with tidal volume and respiratory frequency as usually. The procedure should be executed with the subject seated in a relaxed but upright posture. The position of the head and neck should be neutral or a bit extended. The subjects have to support their cheeks firmly, and a nose-clip must be used. The technician must perform a visual check in order to verify that the mouthpiece is sealed and the tongue is in correct position, so there are no leaks around the mouth. During the procedure, the subjects are asked to perform tidal breathing for 30–45 seconds. Provided values of impedance are typically an average of all recorded correct measurements acquired in the course of the testing interval. It was published that technical standards for respiratory oscillometry in 2019, including a list of minimum instructions and information that should be provided to the patient prior to testing. Usually three measurements need to be performed, although in a study conducted by **Watts et al (9)** published in 2016, analyzing the effect of the period of data gathering during the measurements on FOT results, 22 asthmatics, 18 COPD patients, and 20 healthy patients were used for the control group. Their study showed that two technically sustainable measurements derive the same mean resistance and reactance values as three or more replicate measurements, no matter how long the measurement lasts. Special attention is needed when performing multiple pulmonary function tests. Numerous studies proved that volume history can affect measurements in the case of subjects with pulmonary pathology, and in the case of healthy subjects during broncho-provocation tests.

Jensen et al (10) published a study showing the effects of deep breaths and bronchial challenge on airway caliber. Their study showed that asthmatic subjects cannot maximally dilate their airways during deep inspiration, and this worsens post-constriction considerably.

Salome et al (11) also published a study 2 years later demonstrating theeffects of airway re-narrowing for asthmatic and non-asthmatic patients.

Slats et al (12) published a study showing that, in the case of asthmatic patients, inflammation in the airways is strongly associated with impaired mechanical function of the lungs through deep inspiration. Therefore, oscillometry should be performed before other pulmonary tests requiring the subject to take deep breaths.

Acceptability Criteria

Although acceptability and reproducibility criteria of oscillometry still need improvement, the accuracy of the impedance measurements can be obtained by quality control, excluding artifacts such as swallowing, glottis closure, poor cheek support, tongue movement, or the presence of leaks. Technicians can identify these artifacts by monitoring the flow, the volume, and the pressure during the procedure, and eventually repeating the measurements, until obtaining three accurate recordings. Reproducibility of impedance can be validated with coherence values. An optimal test quality requires values larger than 0.8 cm H_2O measured at 5 Hz or larger than 0.9 cm H_2O measured at 20 Hz (**13).**

Parameters

The respiratory tract's resistance and reactance values can be determined by oscillometry at given frequencies. The main parameters are: Impedance (Z) force that has to be defeated in order to mobilize gas in and out of the airways. Mathematically it can be determined as the ratio of pressure (P) to flow (V) in function of oscillation frequency (ω): (14).

Furthermore, impedance can be separated to its components, resistance (R) and reactance (Z): (14). where j-imaginary unit, √-1.

Variations of impedance can be detected depending on the respiratory tract area where the pressure is measured (upper airways, distal airways, lungs, or chest-wall). Respiratory resistance (Rrs) is the energy needed to move the pressure wave through the airways. An increase in resistance can be found in diseases affecting the airways, for example in asthma or COPD. Respiratory reactance (Xrs) is the energy determined by flow airflow dynamics in the airways, influenced by the elasticity of tissue and the interstitial forces. Values of reactance (Xrs) become more negative in diseases where elastance is increased **(15).**

where Capacitance (E), component of reactance, determines the elasticity of the lung, and it presents as a negative value. Inertance (I), also part of reactance, is determined by mass-inertive forces of the air movement in airways and it is a positive value **(14)**.

Resonance frequency (Fres) is the value of Hertz at which inertance and peripheral capacitance of the lungs have equal values, and the total reactance becomes zero. Reference values of resonance frequency for adults are between 7 and 12 Hz. Values of resonance frequency can be higher in the case of lung disorders, both restrictive and obstructive. The area of reactance (AX) includes the area under the reactance curve from lowest frequency to Fres; increased values were correlated with distal obstruction. Practically 5 Hz frequency signals reach distal airways so R5 equals the total airway resistance, while high-frequency signals like 20 Hz can only reach the central airways and R20 equals the resistance of the proximal airways. In order to acquire the resistance of the distal airways, the difference between R5 and R20 is needed. In practice, a higher increased R5 than R20 means the disease of small airways, and the increase of both parameters (R20 and R5) indicates proximal airway disease. On the other hand, reactance (Xrs) at low frequencies (5Hz) determines the elastic and interstitial proprieties of the lung. Diseases that affect the elasticity of the lung (for example: interstitial lung diseases) will increase capacitance negatively (X5 will be more negative). Values of reactance are also influenced by age and weight (increase of age and weight will determine a less negative reactance) **(16).**

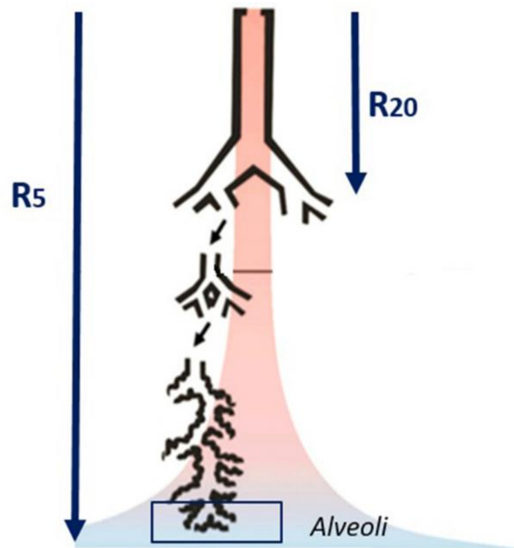

Figure 2: resistance of the proximal airways

Interpretation and Reference Values

Last year the European Respiratory Society elaborated new "technical standards for respiratory oscillometry". **King et al (13)** recommend in their article determination of predicted values for any oscillometry device in the population where it is used. Values can be different depending from the type of device that is used. Although there are publications on reference values, especially in the case of children, but also in the case of adults, normative values have not yet been published.

Kalchiem-Dekel and Hines (17) published a review article on reference values for oscillometry collecting published data from 1977 to 2017. In their research they included 14 studies of forced oscillometry technique, 19 studies of impulse oscillometry, and one study providing values for both. The majority of publications were from Europe and Asia, applied on small groups of subjects (median=264 subjects). They concluded that the measurements and the test performance were inconstant. Prediction equations were influenced by the height of the subjects and also by the gender. The age variation was not conclusive due to the poor representation of elderly subjects in the studies.

A German study conducted on a large number of subjects (1990), aged between 45–91 years, established significant differences in values of Rrs5 (29%), Rrs20 (33%), and Xrs5 (76%) compared to previous publications.

A Canadian study conducted by **Dandurand et al (18)** demonstrated that there are significant differences between oscillometry devices and measurement performances, reducing the ability to compare between studies using different equipment and formation of oscillometric-parameter databases device-independently. There are also situations when subjects performing the test have multiple lung diseases (overlap).

Table 2: Main Publications Reporting Reference Values on Healthy persons Since 2010

Authors	Technique	Frequency Range (Hz)	Number of Subjects	Age Range	Etnicity/ Nationality	Parameters
Brown et al, (19)	FOT, PRN	6–19	904	18–92	Caucazian	R6, R11, R19, X6, X11, X19
Fujiwara, (20)	IOS	5–35	420	20–89	Japanese	R5, R20, FDRrs, X5
Crim et al, (21)	IOS	5–20	555	55±9	Multinational	R5, R20, FDRrs, X5, AX, Fres
Li and Wang, (22)	IOS	5–20	920	56±13	Chinese	R5, R20, FDRrs, X5, Fres
Oostveen et al, (8)	IOS, PRN	–	368	18–84	Caucazian	mRrs, mXrs, Fres, AX mRrs, R4–R26, X4–X14, Fres, AX4, AX5
Schulz et al, (23)	IOS	5–35	397	45–91	Caucazian	R5, R20, FDRrs, X5, AX, Fres
Xue, 2014	IOS	–	6945	40–65	Chinese	mZrs, R5, X5, Fres
Zheng et al2015	IOS	5–20	362	18–78	Chinese	R5, R20, X5, X20, Fres
Geng et al,2016	IOS	5–20	409	20–60	Chinese	R5, R20, X5, Fres
Shu et al,2016	IOS	5–20	431	48 ± 14	Chinese	R5, R20, FDRrs, X5, Fres
Ribeiro et al, (24)	PRN	4–32	288	20–86	Brazilian	R4, R22, X8, X22

Measurements and Interpretation

The forced oscillation technique (FOT) developed over 60 years ago by Dubois et al was the first methodology to employ superimposition of pressure fluctuations on the airway over the subject's tidal breathing to determine lung function. IOS is one type of FOT which delivers a square wave of pressure 5 times per second, thus emitting a continuous spectrum of frequencies that generate a larger sample of measurements, thus providing more detailed characteristics of respiratory function. The IOS system (MasterScreen Impulse Oscillometry by CareFusion, Yorba Linda, CA or Tremolo by Thorasys, Montreal, Canada) is routinely calibrated, as suggested by the manufacturer. Testing and analysis is performed in accordance with ERS/ATS guidelines. Both lung resistance (Rrs) and reactance (Xrs), which reflect total pulmonary impedance (Zrs,). Values of Rrs and Xrs for frequencies of 5 to 20 Hz are derived from each trial and stored. An average of 3 adequate trials of Rrs and Xrs values are analyzed and graphically displayed. Reproducibility in children and adults ranges between 5-15%, but should not exceed 17%, Further technical details have been published elsewhere **(5).**

Children as young as 3 years can generally perform IOS with accurate and objective results. Commercially available predicted values for Rrs and Xrs are based primarily on height (cm) according to the equipment's default normal reference values as recommended by the manufacturer based on existing reference values reported primarily in Caucasians. However, several recent studies suggest that these reference values for R5 and X5 may be appropriate across diverse populations. See section III on Population Based Reference Values **(26)**.

PAW obstruction is reflected by increases in the frequency-dependent resistance with an elevated R5-R20, an expression defined by the difference between low frequency at 5HzR5, and high frequency at 20Hz R20, and AX, manifested in obstructive diseases such as asthma and COPD. This is because the pressure waves' signal propagating into the distal lung, demonstrated by R5, encounters greater resistance than the higher frequency more proximal R20 impulse. In addition, PAW obstruction results in loss of elastic recoil shown by a lower X5 and an increase in the AX, an integration index of reactance measure from X5 to Fres. In contrast proximal or upper airway obstruction alone exhibits frequency- independent elevations in Rrs across frequencies (Hz), and little to no effect on Xrs.

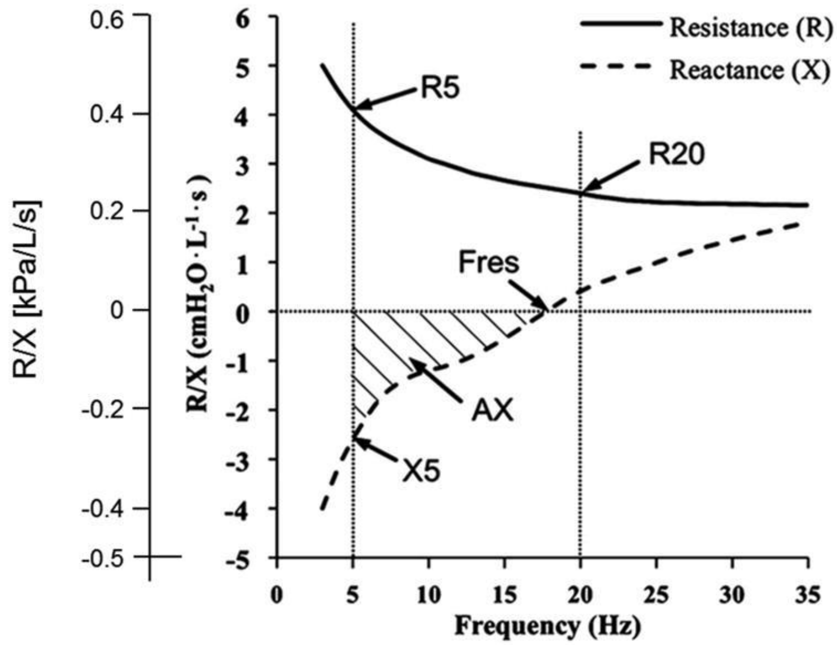

Figure 3: *Schematic illustration of IOS indices over oscillation frequency (Hz), including R5, R20, Fres, X5, and AX. Shown is a typical IOS tracing produced during a 30 second trial.*

The Impulse Oscillometry System (IOS)

The principles of IOS are based on the concepts published by **Dubois et al. (26)** in 1956 when describing a technique whose objective was to measure the mechanical properties of the lungs and thorax. This technique was forgotten until the mid-1970s and was re-studied in 1980, but it was only recognized and applied in clinical practice in the 1990s. In the last 15 years, there has been a large increase in the number of studies and publications with IOS due to the computational technological rise that facilitated its technical applicability and clinical interpretation **(2).**

The IOS equipment consists of a pneumotachograph containing a Y-shaped adapter piece, a nozzle piece, and an impedance tube. The external generator, comprised of the loudspeaker, is responsible for generating the pulsatile stimulus through the Y-adapter. Pressure waves that propagate through the movement of the air column in the conduction airways are applied, resulting in the response that will be recorded by the sensors (**27**).

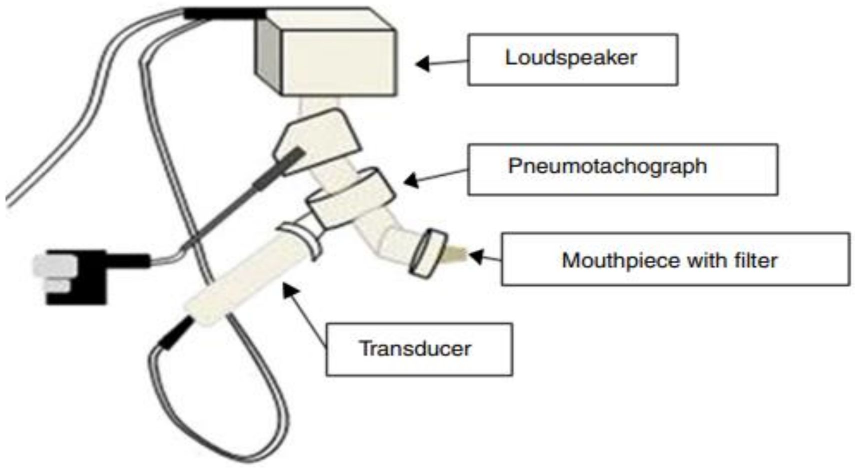

Figure 4: Scheme of the impulse oscillometry system.

Description of the technique

Oscillometric measurements are performed during tidal breathing, with the patient sitting, breathing quietly. Three to five sequences of breaths lasting at least 30 s are suitable for analysis. Bronchodilator response can be measured 15 minutes after the administration of aerosolized 2-agonist (200---400 g). For reproducible and reliable measurements, patients must be instructed not to put their tongues into the mouthpiece, breathe only through the mouth, and contain their cheeks with their hands **(7).**

Oscillometric parameters

Impedance (Z): total respiratory resistance measured by IOS. It corresponds to the sum of all forces opposing the generated impulse. Impedance varies according to the region where the pressure is measured, for example, oropharynx, larynx, trachea, proximal and distal airways, lung and chest wall. It is composed of pulmonary resistance --- known as the real part of the impedance --- which is the energy needed to propagate the pressure wave through the airways, and reactance --- known as the imaginary part of the impedance --- and which reflects the energy generated by the movement of the air in the airways and is determined by the elastic properties of lung tissue and inertial forces **(16).**

Resistance (R) and reactance (X): these parameters can be measured at different frequencies evaluating different portions of the respiratory system. Almost 80% of the resistance is composed of central airways and only 20% by distal airways (<2 mm diameter) in adults. However, in children, the contribution of distal airways is greater than in adults. When measured at 5 Hz, for example, they are designated as R5 and X5, respectively. Low-frequency signals (5 Hz) penetrate the periphery of the lung, while high-frequency signals (20 Hz) reach only the proximal airways. Therefore, R5 represents the total resistance of the airways, while R20 represents resistance of the proximal airways. We can infer the resistance of the distal airways through the difference between R5 and R20. A disease isolated from the distal airways will increase R5 more than R20; on the other hand, in a disease isolated from the proximal airways, there will be an equivalent increase in R5 and R20.Reactance includes the inertia of the air column (inertance) and the capacitance of the lung, which result from the movement of the aerial column during air conduction. Capacitance is related to the elasticity of the lung. The capacitance component of the reactance presents negative signal, and the inertia component presents positive signal. Reactance is frequency-dependent. At low frequencies, capacitance dominates, therefore total lung reactance is negative, whereas at higher frequencies, the air column inertia in the proximal airways dominates and total reactance is positive. Reactance at 5 Hz (X5) relates to both the elastic and inertial properties of the lungs, reflecting the elastic recoil of the peripheral airways. Diseases that reduce the elasticity of the lung, such as fibrosis and hyperinflation, cause the capacitance to increase negatively, turning X5 more negative. With increasing age and weight, reactance becomes less negative. Resistance and reactance can be measured in pascal (Pa) or cmH2O/L/s. **(28).**

IOS variability

In general, the repeatability of IOS measurements is good,25 especially when the mean values are calculated from three acceptable data sets, ranging from 6% to 10% for the main parameters. Meanwhile, it tends to be worst in very young children. Klug and Bisgaard, 1998, found that the coefficient of variation (CV) was 9.8% in children at age of four years or less whereas it was 6.9% in oldest children (age six years or more) **(29).**

Interpretation of results

To interpret the results, it is recommended to initially observe if R and X values are in the normal range. It was demonstrated that R5 decreases with age and height, while X5 becomes less negative. R values up to 150% of predicted values are usually considered within the limits of normality. In diseases with peripheral obstruction, such as asthma, an increase of R5 and Fres and a reduction of X5 is observed. In these cases, R20 values may be increased, but to a lesser extent than R5 values. The IOS allows the identification of central obstructive disorders, observed in some diseases such as sleep apnea. In this type of disorder, there is a proportional increase of R5 and R20 and, unlike distal obstruction, there are no changes in the values of X5 and Fres. When R5 and R20 are within normal limits, and X5 is below these limits, restrictive disorder may be suggested. It is recommended that local reference values should be employed in the interpretation of IOS, based on local genetic and ethnic characteristics (ref). At the moment several authors have already published references values and equations **(30).**

IOS in pre-school children

IOS is a useful tool for the assessment of lung function in pre-school children mainly because it is effort independent, it is performed with tidal breathing and it requires minimal patient cooperation. However, some young children still have difficulty in staying quiet during the IOS. In these cases, the use of other parameters of spirometry such as forced expiratory volume in 0.5 s (FEV0.5) instead of forced expiratory volume in 1 s (FEV1) could be more effective **(31).**

Clinical applications

A. IOS in asthma

One of the main indications of IOS in children is the assessment of patients with asthma. Considering that an increase in airway resistance occurs in asthma, especially in peripheral airways, patients with asthma show an increase in R5 when compared to controls, especially during exacerbations. In addition to R5 increase, it is common to find normal R20, more negative X5, and increase in Fres. In patients with well-controlled asthma, these findings are not always observed. The most sensitive IOS parameters to detect airway obstruction and to evaluate the severity of asthma, its control, quality of life, and exacerbations are R5, R5-R20 and AX. R5-R20 and AX may be useful for early detection of pulmonary function abnormalities **(32).**

1. Correlation with spirometry

Many studies have compared the results of IOS with spirometry in the diagnosis of asthma in children and adults, although each exam assesses different aspects of lung function: The IOS assesses the mechanical properties of the lung and spirometry reflects the characteristics of the airflow. In studies using both IOS and spirometry, there is a significant association between IOS parameters and spirometric indices, especially forced expiratory volume in 1 second (FEV1). It has been shown that IOS parameters are more sensitive to identify patients with asthma and to exclude those without asthma than the parameters of spirometry. In addition, IOS is useful in the follow-up of these patients and may detect airway obstruction earlier than spirometry. Another relevant aspect refers to the fact that young children perform the IOS technique more easily than spirometry. According to **Tomalak et al., (33**), 61% of children between three and four years of age performed the IOS assessments properly, while only 3.6% did itin the spirometry assessments (**33)**

2. The IOS in bronchodilator response assessment

Studies in young children have shown that IOS was better than spirometry when assessing the bronchodilator response, an important predictor of asthma, and helping to identify patients who will benefit from drug treatment and environmental intervention. The main parameter to evaluate the bronchodilator response is R5. There is no consensus as to the best cut-off limit for positive bronchodilator response to IOS. This limit may vary, depending on the study, between 20% and 50% decrease in R5 values **(34).**

3. *Assessment of asthma control*

The association between uncontrolled asthma and dysfunction of small airways is well established. For this reason, IOS presents great potential in assessing the level of asthma control. **Shi et al. (35)** compared distal airway IOS indices (such as R5-R20, X5, Fres, and AX) with the level of asthma control in children and found that R5-R20 and AX were able to correctly classify asthma control in more than 80% of the studied population. Also, the loss of asthma control can be suspected in patients with increased R5-R20 and AX --- parameters that assess the peripheral airways. These findings suggest that both decreased caliber of small airways and increased tonus contribute to the onset of symptoms in children with asthma **(35).**

4. *IOS in bronchoprovocation testing*

Airway hyperresponsiveness (AHR) is a clinical feature of asthma. It can be confirmed by bronchoprovocation tests which can be performed with methacholine, histamine, exercise, allergens. Studies suggest that an increase of 50% of baseline R5 values showed a significant correlation with a 20% fall in FEV1 and could be used in bronchial challenge testing. Furthermore, several studies found that IOS may be more sensitive than spirometry in detecting bronchoconstriction induced by methacholine or allergens, as the increase in resistance values preceded the fall in FEV1 **(36).**

5. *Assessment of response to asthma treatment*

One of the IOS parameters, reactance area (AX) can be used to assess the response to asthma treatment. A study conducted in children with asthma between the ages of six and 14 assessed the long-term response to fluticasone and montelukast therapy demonstrated that there was a steady and continuous improvement of AX during the study period, especially in patients who used fluticasone. Similar findings were not found for spirometry parameters, suggesting that IOS can identify improvement in lung function early after treatment initiation **(37).**

B. The IOS in patients with cystic fibrosis

A study conducted in patients with cystic fibrosis (CF) has shown that R5, R20, Fres, and AX values increase, and X5 values decrease during the period of symptom exacerbation. After the treatment of the exacerbation, baseline levels return, indicating that IOS can document deterioration of lung function during acute exacerbation and improvement after treatment in CF patients **(38).**

C. Other indications for oscillometry

In research, IOS was used to detect decreased lung function due to early infection by rhinovirus (before three years of age) in children aged 4---8 years old of a cohort at high risk for developing asthma. There was a decrease in X5, which was confirmed by spirometry values. In patients with post-infectious bronchiolitis obliterans (PIBO) assessed with IOS, the values of Z5, R5 increased and X5 was more negative, indicating an increase in the peripheral airways resistance. The reactance values of children with congenital malformations submitted to surgery had significant differences when compared to healthy children (mean X5: −2.11 kPa/l/s in patients and −0.11 kPa/l/s in controls, $p < 0.01$) **(39).**

IOS has been used in the pulmonary evaluation of adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID). This disease can cause bronchial inflammation, pulmonary fibrosis, and enlargement of the alveoli. Patients may present alterations in the peripheral airways indicated by the measurement of resistance and reactance at low frequencies (R5, R10, and X5). The impact of gastroesophageal reflux disease (GERD) on severe asthma was assessed using IOS. It was shown that even when there were no differences between patients with or without reflux by the ACT (Asthma Control Test), FEV1 and FVC, patients with reflux showed higher values of R5 and R5- R20. These findings were corroborated by other authors who found that 50% of patients with GERD esophagitis presented increased airway resistance (R5 and R20) despite having normal spirometry **(2).**

In children with obesity IOS can be an integrative method to the spirometry. Several studies have shown that even when the spirometric parameters are within the normal range, IOS may show evidence of lung function abnormalities, probably due to its better assessment of distal airways **(7).**

In addition to indications in children, IOS has been used in the assessment of patients with COPD in recent years. Patients at stage 0 COPD documented high values of Fres, Z5, R5, and R5-R20 when compared to controls, and X5 values significantly lower than those in the control group, demonstrating that these parameters may be useful in the evaluation of patients with COPD. It can be difficult to differentiate between asthma and COPD in elderly patients, and these two diagnoses often overlap. The performance of IOS in these patients may contribute to a more accurate diagnosis, since X5 and Fres correlate better with COPD (sensitivity of 67% and 77%, and specificity of 68% and 65%, respectively, for the diagnosis of COPD), whereas R5 correlates with asthma (sensitivity of 72% and specificity of 61% for the diagnosis of asthma). **(40).**

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