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Clinical Applications of Impulse Oscillometry

Constantine Saadeh and Nicole Davey-Ranasinghe

Abstract

Impulse oscillometry is a noninvasive procedure that can be performed within few minutes. The purpose of the procedure is to measure the resistance of the small and large airways, as well as the reactants of the airways. It is gradually gaining popularity in evaluating lung function, particularly in patients with asthma and COPD. In contrast to spirometry, the test performs measurement during tidal breathing. In other words, forced exhalation is not required. Other advantages include, but are not limited to, evaluating COPD patients' reversibility which is rarely noted on spirometry. IOS also is tool for chronic management of patients with asthma and COPD while on treatment. It can evaluate children with asthma even as young as 2 years old. Spirometry requires the child to cooperate and usually is of meaningful use beginning at the age of 5 years old. Other potential applications include early evaluation of transplant rejection, cystic fibrosis, and vocal cord disorder. In this chapter, we will explore the procedure itself, the settings, advantages and disadvantages, and comparative data with spirometry.

Keywords: impulse oscillometry, spirometry, asthma, COPD

1. Introduction

The expert panel 3 of the National Asthma Education and Prevention Program defines asthma as “a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment.” This definition allows for incorporation of the clinical, physiological, and pathological findings of asthma. Traditional spirometry, while the gold standard, can be unreliable in pediatric patients and is dependent on patient effort. Impulse oscillometry is a clinical tool that is independent of patient effort and allows for diagnosis and management of pediatric and adult patients with asthma. IOS can enhance the clinical evaluation for patients with asthma. IOS is a technique that measures airway impedance (resistance and reactance). IOS is a noninvasive technique that is beneficial either as a single modality or in combination with traditional spirometry for patients in the diagnosis and management of asthma.

2. Overview

Impulse oscillometry or IOS is a measure of both small and large airway resistance. In addition, resonance capacitance or reactance is also obtained via impulse spirometry. It is also referred to as forced oscillation since impulses are sent at periodic intervals into the airways. The measurement of airway resistance and reactance is performed in a noninvasive, relatively independent, and minimally intrusive manner during spontaneous tidal breathing [1].

In contrast to traditional spirometry, impulse oscillometry or IOS tracing is independent of age, height, weight, or gender in adolescents or adults 13 years or older. In other words, normal values are the same whether the patient is 13 or 60 years old. The most relevant findings include R5, R15 or higher, and AX. R5 reflects the small airway resistance. However, R5 is the summation of small and large airways. R15 or higher signifies only the larger airways. AX is low-frequency integrated impedance reactance at R5 and is referred to as purely reactance.

In this chapter, we will review briefly the IOS procedure. We will then guide the reader to the useful applications of this methodology and the diagnosis and follow-up in patients with asthma in terms of actual diagnosis, follow-up with treatment as outpatient, and documentation of response to treatment. Response to treatment can be gauged via handheld nebulizer treatment in the acute setting. In addition, treatment with inhaled corticosteroids or inhaled corticosteroid/LABA or long-acting beta agonists has also been observed independent of spirometry [2]. We will also review the literature regarding the comparison of this modality to traditional spirometry. Finally, we will briefly outline future directions in the evaluation of other respiratory disorders.

3. Impulse oscillometry

3.1 Technique

The technique of IOS is effort independent. However, it does require breathing through the mouth as noted below. The IOS technique was performed as previously described. Briefly, patients are seated comfortably in a no swivel chair (**Figure 1**).

Nose clips were applied, and a special mouthpiece was used. For IOS measurements, patients may be advised to cradle their cheeks with their hands. Patients are allowed to breathe normally while the loudspeaker delivered intermittent

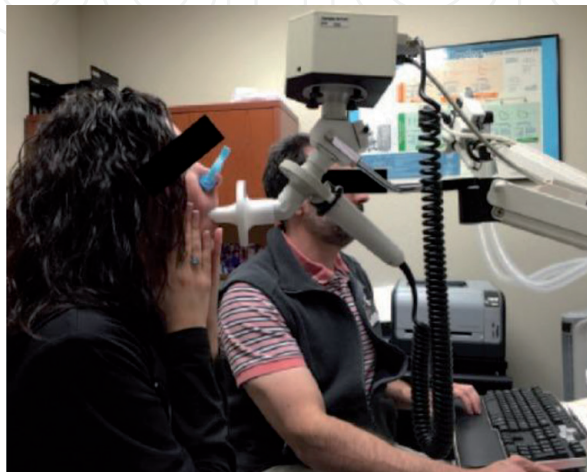


Figure 1. The subject during tidal breathing inhales and exhale in a closed system. Technician is watching the screen for the sinusoidal waves to pick up the best reading.

multi-frequency impulses over a minimum of a 30-s period. A trained technician will be guiding and assisting the patient during the procedure, which involves three to five sinusoidal readings, depending on the incidence of cough, swallowing, and holding of breath. The recordings with the best coherence at frequencies from 5 to 30 Hz were chosen. The technician was also trained to capture subclinical leaks through the mouthpiece, and leaky recordings were discarded. The pre- and post-bronchodilator assessments took at least 10 min and used ultrasonic nebulizer. The IOS parameters measured were R5, R15, and AX.

Traditionally, spirometry is utilized to evaluate lung function in both children and adults. There is no doubt that spirometry is of greater utility at least for most practitioners who diagnose and manage asthma. However, the limitations include difficulty conducting the measurement in patients who are less than 5 years old. Even in patients who are 5 years old and older, the predicted FEV1 may not be as accurate as it is in adults. On the other hand, IOS is more feasible in terms of detecting small airway dysfunction [27, 28]. Classically, small airway dysfunction is detected via the FEF 25/FEF 75. This is highly volume dependent as patients may be unable to perform a complete expiratory maneuver from total lung capacity to residual volume.

Even in adults, spirometry itself has its own limitations. FEV1 or the forced expiration volume in the first second is dependent on the ability of the patient to take a deep breath and forcefully exhale until the residual volume is reached. The FEV1 is then compared to a predicted value which is determined via statistical analysis of normal people. Therefore, patients who participate in athletics, for example, may have a higher FEV1 than the predicted value. However, these patients may also have abnormal IOS even though they have supernormal FEV1. In addition, patients with lower predicted value may show improvement in the IOS even though the spirometry may not change. The improvement can be noted acutely via handheld nebulizer or chronically through the use of maintenance inhalers such as corticosteroids.

4. Measurements

Impulse oscillometry in contrast to spirometry measures the resistance and the airways as well as the reactants. The resistance in the airways is referred to as R5 which is the resistance in the small airways. R15 or higher is a measurement of the resistance in the larger airways. It is important to note that the resistance in the small airways or R5 is the summation of the small and large airways, and therefore the difference between R5 and R15 or higher is the actual small airway measurement. The integrated impedance reactants at R5 or above are referred to as AX. AX is considered the area under the X curve from the beginning of normal inspiration. The reactants are a more sensitive guideline for patient evaluation and asthma. A normal AX is 3 cm of water or less in children who are 13 years and older throughout adulthood. Children who are 5 years or younger have poor lung compliance. Therefore, a normal AX in this age group varies, but usually it is 30 cm of water or less. Therefore, in the younger age group since there is variation in the measurement of AX, it is reasonable to always measure the AX pre-and post-bronchodilation with short-acting beta agonist. This will give better determination of the actual pulmonary status of the patient. As a result of that, children who are between the ages of 6 and 12 will have an AX in between 30 and 3 cm of water. In this group of patients, it is important to follow up these patients not only with measurement of reactance or AX at baseline but also to check that nebulizer treatment is followed with short-acting beta. These patients were on rather than of equal or less of 1000 µg per day at least 2 weeks after treatment with inhaled maintenance corticosteroids or combination. The combination in general will be inhaled corticosteroids with long-acting beta agonist **Figure 3**.

The trained technician will be able to choose the recordings with the best coherence at frequencies between 5 and 30 Hz. The ideal coherence should be 0.9, 1, 1, 1 at 5, 10, 15, and 20 Hz, respectively. The technician is also trained to capture subclinical leaks through the mouthpiece, and leak recordings should be discarded.

5. Role of IOS in asthma

Published observations by the author and colleagues have shown that patients with asthma showed improvement in the IOS values. This has been observed through the measurement of the reactance or AX immediately following nebulizer treatment as well as definite improvement 3 months or more after the start of inhaled corticosteroids or a combination of inhaled corticosteroids with long-acting beta agonist. The FEV1 in these patients showed improvement in the minority of patients, while the reactance or AX improved in all the patients who were tested. There were 39 patients who were adults in this age group. **Figure 1** above shows in office IOS. **Figures 2** and **3** below reveals the improvement in IOS immediately following nebulizer treatment and 3 months later in an individual patient [26–28].

The role of small airway dysfunction in adults with asthma has been demonstrated in at least 31–47% of 196 patients who were diagnosed with asthma and had insufficient control of their symptoms. Twenty percent of these patients had poorly controlled asthma. Irrespective of their smoking history, both impulse oscillometry and nitric oxide measurements in the exhaled breath or FENO were more sensitive

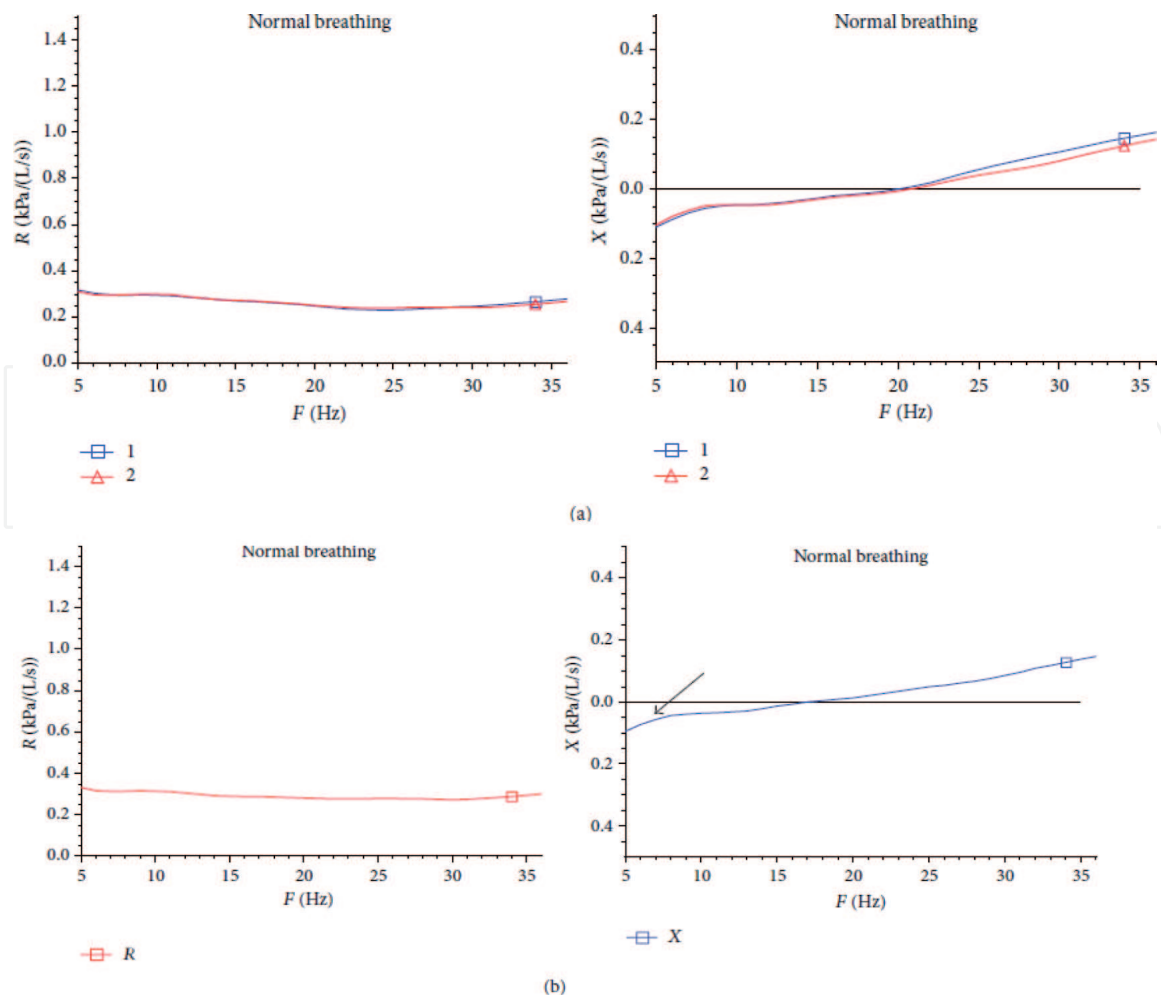


Figure 2.
(a) Patient 15 before bronchodilator. (b) Patient after bronchodilator.

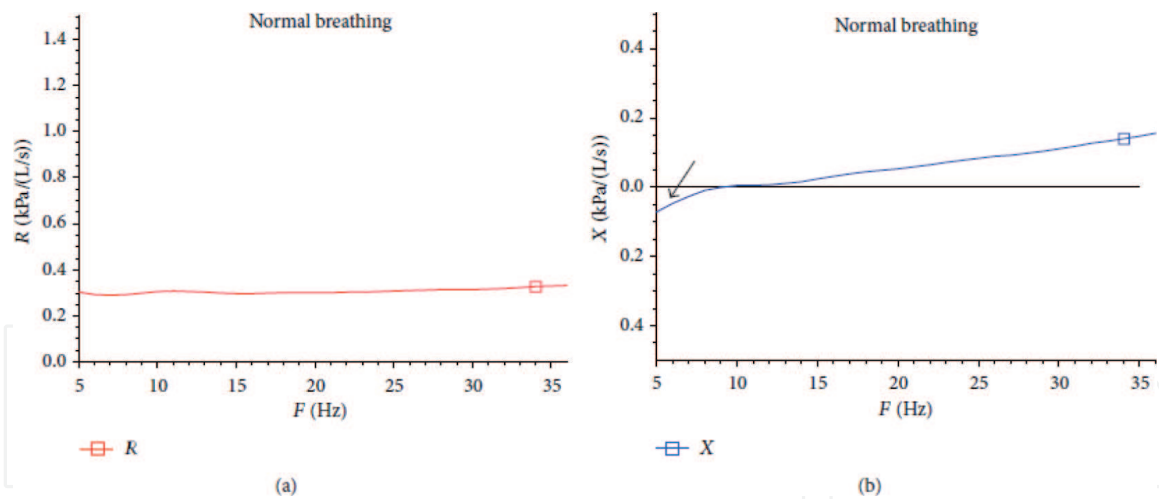


Figure 3. Patient 15 follow-up (post) (shadowed area AX). Notice normal resistance (a) and normal AX (b) following inhaled corticosteroids for at least two weeks.

in predicting small airway dysfunction than traditional spirometric measurements. The authors concluded that even though nitric oxide measurement was slightly more sensitive than IOS, both of these tests were complimentary in determining the severity of peripheral airway dysfunction. However, in this study, the risk factors for peripheral airway dysfunction were noted to be in patients who have traditionally positive smoking history, elevated blood eosinophils, and dose with low baseline FEV1. Nevertheless, the role of impulse oscillometry in this study should be strongly emphasized (**Figure 3**) [3].

In children with asthma, IOS was noted to be more useful than spirometry and identifying both the asthma and predicting loss of control and exacerbations. This can help with early intervention when the spirometry is normal, but the IOS is showing abnormality. In particular, children are known to have more peripheral or small airway dysfunction. Traditionally this has been dependent upon forced expiration flow between 25 and 75%. Recent studies have shown that IOS is a better predictor particularly in measurement of the small airways or R5 as well as the reactance or AX in the initial evaluation and response to treatment. IOS had improved diagnostic capability in identifying patients with uncontrolled asthma during select baseline values. In the longitudinal analysis of 54 children between the ages of 7 and 17 years old with mild to moderate asthma, both R5 and AX showed inadequate control of asthma 8–12 weeks after the initial visit than spirometric measurements. This included FEF 25–75%. Scholz and colleagues evaluated the value of IOS compared with spirometry and methacholine challenge as predictors of asthma exacerbation in children who are 4–7 years old during 1-year observation. R5 was more predictive of an exacerbation even at the time when the patient was not having any symptoms. The FEV1 or FEV1/FVC and methacholine challenge via spirometry were also normal in these children. In preschool children, normal IOS findings in children between the ages of 2 and 7 years old in patients with asthma are unlikely to have decreased lung function in adolescence based on their initial IOS measurements [4, 5].

Small airways of the lung are defined as the bronchial passages that are less than 2 mm in diameter. They are located beyond the seventh or eighth generation of the tracheobronchial tree. These airways account for more than 90% of the cross-sectional area of the lung and terminate with the alveolar sacs [6].

The small airways have no cartilage to support the structure and are therefore more easily collapsible upon compression. Small airway disease affects the majority of asthmatics across the spectrum of severity. The production of small particle

inhaled corticosteroids has enhanced the delivery of inhaled corticosteroids to the smaller airways. This certainly has improved lung function in both adults and children with asthma. Traditionally, high-resolution CT of the chest has been a noninvasive direct radiographic assessment of the luminal caliber and wall thickness of the medium and large airways that are more than 2 mm in diameter. However, this modality has difficulty in evaluating airways that are less than 2 mm in diameter. About 5–10% of patients with asthma are deemed to have severe disease as defined by the European Respiratory Society and the American Thoracic Society as asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy. Treatment compliance such as appropriate use of inhalers is essential for disease management [7]. Even though there is no gold standard technique for the assessment or diagnosis of small airway, impulse oscillometry in particular has been shown to be effective in the evaluation of small airways either alone or in a combination with exhaled nitric oxide measurement [8].

6. IOS and airway hyperreactivity

The role of IOS in bronchial challenge has also been studied. Bronchial challenge test with methacholine or histamine directly or indirectly such as mannitol may be used in every day clinical practice to identify the presence of airway hyperactivity. Airway hyperactivity is the hallmark of persistent asthma. It is particularly useful when the diagnosis of asthma is in doubt such as patients who are experiencing unexplained cough with normal spirometry. Theoretically, performing IOS with normal tidal breathing is much easier for patients to perform with repeated measurements during challenge. Bronchial irritation such as coughing may pose some limitation while performing the test with spirometry. Eighteen adult patients with mild to moderate persistent asthma had methacholine and histamine challenges measuring both spirometry and IOS. A decrease in the FEV₁ by 20% was almost equivalent to a 37% drop in R5 for methacholine and 35% decrease for R5 with histamine. The authors concluded that 40% decrease in R5 may be justifiable to approximately extrapolate to the drop in the FEV₁ by 20% for both methacholine and histamine challenge [9, 10]. Similar values on R5 or AX were noted in another study. Improvement by 40% or more on the AX value may carry the same significance as a drop in the FEV₁ by 20% without the risk of irritation through forced exhalation. Studies in children are very limited in this regard. One study has noted that in children between the ages of 3 and 8 years old, a change in the R5/R20 after methacholine challenge was significantly higher in those children with more severe asthma as shown by increased exercise-induced bronchospasm and short-acting beta 2 agonist use [11].

In another study, 48 young children with asthma undergoing methacholine challenge noted that a drop of 45% in R5 had the equivalents of a drop in the FEV₁ by 20%. In addition, significant increase in resistance was seen well before a change in the FEV₁ at lower methacholine dosages suggesting that IOS is more sensitive than spirometry [12].

Hyperresponsiveness was also studied in patients with mild to moderate adult asthma. Patients were recruited between the ages of 18 and 65 years old. FEV₁ was noted to be greater than 80% of what is predicted in these patients. Diurnal FEV₁ variation was less than 30%. These patients were on equal or less of 1000 mcg/day of beclomethasone dipropionate or equivalent dose. These patients were recruited prospectively. Bronchial challenge was performed with inhaled methacholine and histamine. Twenty-one participants were randomized. Eighteen of whom, ten

women and eight men, completed the protocol. All of these patients were used in this analysis, and the mean age was 36 years old. The PC 20 over the FEV1 dropped by 20% following the challenge was noted at equivalents of 43.5% drop in R5 and the methacholine challenge, while it was 45% on the histamine challenge. The magnitude of change seen was greater for all IOS indices including R5 and R5–R20 area under the curve as well as what is referred to as resident frequency or X5. X5 correlated well with the AX. The significance of this study is that these patients were identified as having mild to moderate adult asthma. These patients were well controlled with inhaled corticosteroids. Therefore, they had normal FEV1 at baseline. This study correlated with what has been reported in the literature regarding the application of IOS in SSA and hyperactivity in patients with asthma [13].

In terms of bronchial hyperresponsiveness, cough is an important consideration. Cough is a complex reflex that typically acts as a valuable protective airway clearance mechanism. It arises from irritation of the intrapulmonary and extrapulmonary airways. When the cough reflex is activated, there is an initial inspiratory phase followed by the glottic closure. There is prompt increase in intrathoracic pressure. This is followed by forced expiration and the opening of the glottis. As a result, gas is expired at a high flow rate along with the characteristic audible sound recognized as cough. Patients with asthma or chronic cough and suspected cough-variant asthma participated in a prospective study. The purpose of the study was to compare the bronchodilating effect of deep inspiration in patients with chronic asthma, cough-variant asthma, and chronic cough using high dose of methacholine. These were patients who are between the ages of 18 and 65. Twenty-eight patients out of 56 that were screened were included in the study. Fifteen of these patients were taking inhaled corticosteroids, and nine were taking long-acting beta agonist. The total resistance did not differ significantly on any of these 3 groups. However, small airway resistance or R5 worsened in patients with cough-variant asthma and chronic asthma but did not with chronic cough. Similar findings were noted with spirometry. The purpose of the study was to show that deep inspiration can reverse the obstructive effect due to airway closure but not the obstruction due to large airway narrowing. However, as a secondary finding, impulse oscillometry reproduces the same results as spirometry with methacholine challenge with more comfort during the study. This correlated with the other findings as noted above [14].

7. IOS and pro-inflammatory mediators

Asthma is considered a chronic respiratory disease characterized by airway inflammation. Airway inflammation can lead to airway remodeling and hyperresponsiveness. Airway remodeling refers to the structural changes in the airway including but not limited to the airway smooth muscle, airway epithelia, blood vessels, as well as the extracellular matrix. This can manifest itself as an increase in the airway smooth muscle mass, epithelial injury, epithelial cell hyperplasia, goblet cell hyperplasia, thickening of the basement membrane, and angiogenesis. The mechanism of airway remodeling is still unclear. It is noted that multiple cytokines, chemokines, and transcription factors as well as growth factors are released from inflammatory cells. Structural cells are also involved in the airway remodeling. For example, TGF-beta and vascular endothelial growth factor or VEGF are released by the structural cells.

Follistatin-like protein 1 or FSTL1 is also known as transforming growth factor-beta 1-stimulated clone 36. It is a secreted glycoprotein of 308 amino acids. The function of FSTL1 is not completely understood. It has been shown to play a key role in tumor propagation and bone metastasis, chronic pain hypersensitivity,

inflammation and insulin resistance, and obesity and regulation of erythropoiesis as well as physical development. Several studies have shown that FSTL1 may play an important role in the respiratory system. It is important in lung development, cartilage formation, and alveolar maturation. No count of FSTL1 and mice is embryonic clear lethal, and these mice display multiple developmental abnormalities of the respiratory and skeletal systems. In a recent study, 32 asthmatics and 25 controls were enrolled for routine blood testing. Spirometry and impulse oscillometry were performed. Fiberoptic bronchoscopy was also performed in the 32 asthmatics. The study was aimed at measuring FSTL1 levels. However, it was noted that IOS measurements in these patients were more sensitive than that of spirometry. FSTL1 levels were higher in asthmatics and improved with treatment. IOS showed more improvement than FEV1 in the same patients where the FSTL1 was decreased. Indirectly, therefore IOS may be considered a more accurate measurement of the inflammatory process and airway remodeling in the lung than spirometry [15].

8. IOS and beta-2 receptor polymorphism

Gly16Arg beta-2 receptor genotype is a variant allele in the polymorphism of Beta 2 adrenergic receptor family. In other words, in asthmatic children, the presence of this LDL is associated with sub-sensitivity response following exposure to regular long-acting beta-2 agonist in asthmatic patients receiving concurrent inhaled corticosteroids. In a study involving 112 patients treated with inhaled corticosteroids with a mean age of 43 years old, there was no difference in response to treatment with inhaled corticosteroids or combination of inhaled corticosteroids with long-acting beta agonist in terms of IOS response. In other words, allelic variation of the beta-2 adrenergic receptor did not influence the IOS outcomes [16].

9. IOS and observations in pre-asthma

In a recent study, 21 school children participated in a 6-minute walk with a measurement of spirometry and IOS before the 6-minute walk, post 6-minute walk, followed by 30-minute of rest, and an additional 6-minute walk, IOS, and spirometry. One hundred twenty-three children participated, but only 21 school children were able to perform the spirometric maneuvers according to preestablished inclusion criteria. Of the 21 children, 9 were able to perform the 6-minute walk with no changes in the IOS. Significant increase in R5 as well as R20 was noted in the rest of the children who participated. Spirometry did not change, but there was a decrease in the FEF 25–75%. The importance of this study is that it suggests that greater attention should be given to submaximal test particularly in children who are predisposed to airway alterations [17].

On the other hand, body mass index status can play an important role in the baseline reactance curve in children who are between the ages of 8 and 16 years. At the age of 16 years, there was increased blood neutrophil count in overweight obese girls but not in boys. However, both genders showed increased reactance or AX even though these patients were not complaining of symptoms to suggest asthma. The nitric oxide washout was normal in this population. The R5 was higher in this age group. IOS therefore can be a predictor of possible asthma in adolescence with high BMI [18].

Passive smoking may result in alteration of pulmonary function in infants born preterm. A study of 139 children between the ages of 3 and 7 years old who were born late preterm were categorized whether they had presence or absence of exposure to passive smoking. Patients who are exposed to passive smoking had a

higher R5 and are 5/20 as well as a higher AX than patients who were not exposed to passive smoking. Passive smoking therefore can be a factor in early asthma development particularly in this patient population [19].

In conclusion, IOS or impulse oscillometry has been shown to reflect improvement in lung function following short-acting beta agonist treatment, as well as with long-term use of inhaled corticosteroids or combination of inhaled corticosteroids with long-acting beta agonist. The improvement was noted in multiple studies to be independent of the change or status of routine spirometry. It may also provide a better assessment of small airways through its R5 and AX measurements.

In addition, IOS can be more useful and effort independent in measurement of airway hyperresponsiveness in adults and children. It appears to be along with the measurement of nitric oxide exhalation to be reflective of the status of airway inflammation. The observed improvement and IOS are independent of the allele change or polymorphism of the beta-2 adrenergic receptor. It can play a role in the detection of early asthma particularly in children who are obese or exposed to passive smoking. This can be detected either by baseline IOS measurement or following 6-minute walk.

Monoclonal antibodies have been used in the treatment of severe asthma. These are patients who are either unresponsive to high-dose inhaled corticosteroids or are unable to be weaned off by oral corticosteroids. These patients have at least two exacerbations within 6 months. In following these patients, there is very limited data about the role of IOS at baseline and during follow-up. We have published data in an abstract form on 12 patients who were on omalizumab that showed improvement in the IOS but not spirometry with follow-up. These patients also improved in terms of tapering high-dose inhaled corticosteroids or oral steroids and had a decrease in their exacerbations even though there was no change in their FEV1. Future studies in this regard in patients with high IgE and eosinophilic asthma are warranted.

10. Role of IOS and COPD

In patients with COPD, it is well known that spirometry can be used to define the GOLD criteria. In other words, the FEV1 and the FVC are important parameters in defining the stage of the GOLD criteria. However, in general patients with COPD or chronic obstructive pulmonary disease had very little change upon follow-up in terms of improvement in the lung function based on the spirometry. Therefore, the most reliable current guidelines include quality of life, smoking cessation, 6-minute walk, oxygenation, and perhaps improvement in the FEV1. There have been several reports that showed that the impulse oscillometry can improve even though the spirometry does not change both in terms of short-term treatment with short-acting beta agonists and long-acting beta agonist/long-acting muscarinic antagonists with or without inhaled corticosteroids.

A study of 215 participants IOS was studied in the setting of chronic obstructive pulmonary disease or COPD of which 18, 83, 78, and 36 patients were classified under the GOLD criteria as grade 1, 2, 3, and 4, respectively. IOS parameters showed worsening of R5 and reactance or AX depending upon the severity of their COPD. There was a negative correlation with spirometry at baseline. This study recorded IOS at baseline, and it showed good correlation with traditional pulmonary parameters. The conclusion was that IOS can be used as an alternative methodology for evaluation of patients with COPD [1].

The diagnosis of COPD can be difficult at times particularly in the early stages. Thirty-five patients who had moderate to severe COPD showed improvement both in the AX and the resistance in the small airways following treatment with

long-acting beta agonist/long-acting muscarinic antagonist combination. The improvement was more prominent than the improvement noted in the FEV1. In fact, FEV1 and FVC statistical significance for the small sample size was not present. IOS improvement was noted in follow-up visit of these patients [20].

Another study evaluated IOS in a pediatric patients, in the use of combination of fluticasone and salmeterol combined with tiotropium, there was significant improvement in R5 and AX in patients who received the triple combination as compared to patients who only received tiotropium by itself. In this study, spirometric findings were also noted to improve with the triple combination. However, IOS findings appear to be more significant. The conclusion by the authors is that IOS may provide a physiological point of view that is different from spirometry and seemed to be applicable as an additional assessment tool targeting COPD patients [21].

These patients were noted at baseline to improve in terms of IOS even though the spirometry did not change. There was also improvement in the impulse oscillometry or AX with follow-up. Statistical significance was noted with improvement in AX, R5, and R15 despite the lack of improvement in FEV1. In conclusion, there was improvement in the impulse oscillometry at baseline as well as maintenance follow-up therapy in patients with mild to moderate COPD.

Peripheral airway dysfunction was also noted in COPD patients who experience sleep disturbance. Fifty patients were evaluated in the morning after sleep. Questionnaires were given about the quality of sleep. IOS measurements were noted to be abnormal particularly increased AX and R5. The study demonstrated that sleep disturbances due to COPD symptoms are associated with airway constriction which is reflective of peripheral airway dysfunction [22].

On the whole, the studies suggest that impulse oscillometry may offer a new clue in the diagnosis and follow-up of patients with COPD. The limitation of the studies is that a combination of asthma and COPD cannot be entirely excluded. It has been suggested that nitric oxide measurement is helpful in the differentiation of combination of asthma/COPD and COPD. In patients with COPD by itself, nitric oxide measurement in the exhaled breath is usually very low and is in general less than 5. However, further studies in this regard are needed to reaffirm these findings.

11. IOS and other respiratory conditions

Cystic fibrosis is a multisystem disease with respiratory system involvement responsible for 90% of morbidity and mortality. Conventional spirometry is considered the main method to evaluate airway disease in patients with cystic fibrosis. FEV1 has been recognized as an objective parameter to evaluate the course of the disease and response to treatment. Forty-nine cystic fibrosis patients between the ages 3 and 18 were compared to 45 healthy controls. IOS was performed in both groups. Spirometry was also performed in patients who are more than 6 years old, while patients who were less than 6 years old only had IOS. In both groups, it was noted that the resistance increased and so did the AX during exacerbation and decreased after treatment. This was independent of the bronchodilator effects. IOS therefore may be useful to evaluate pulmonary function and detect acute exacerbation in cystic fibrosis patients [23].

Hypersensitivity pneumonitis is a complex clinical syndrome that results from abnormal immune lung function to diverse inhaled antigens. It can be related to protein antigens denied from birds as well as air conditioning and can progress to pulmonary fibrosis. Small airway involvement is associated with interstitial mononuclear infiltrate with non-necrotizing poorly formed granulomas and varying degree of fibrosis. Therefore, detection of small airway dysfunction is essential in

establishing the severity of the disease process. In a study of 20 consecutive patients with established diagnosis of hypersensitivity pneumonitis, there was ventilation perfusion mismatch. IOS was obtained, and it did show elevated AX at baseline and improved with treatment particularly with azathioprine and prednisone. It is noted that lung volume also improved but not gas exchange [24].

A case report in 2005 demonstrated a lung transplant patient who had deterioration in the IOS even though the spirometry did not change. The AX was worse and so was the resistance in the small and large airways. This was reflective of early transplant rejection. The usefulness of IOS in monitoring lung transplant patient was evaluated by Dr. Ochman and published in 2018. The study involved 25 consecutive patients with successful lung transplantation, and 88% of these patients were noted to have increased AX indicating peripheral airway obstruction. There was an increase in the small airway resistance or R5 as well. The median age was 46 years old. This was a baseline study but suggested that IOS measurements may also be important in evaluating possible early rejection in patients with lung transplant [25].

Finally, it is well noted that vocal cord disorder in patients with chronic cough, uncontrolled COPD, or severe asthma can be a contributing factor to the worsening of the symptoms. We have noted that a ratio of AX on inspiration/AX expiration of greater than 2 is consistent with vocal cord disorder. Improvement in vocal cord disorder such as treatment of asymptomatic reflux, increased postnasal drip, and vocal cord dysfunction can lead to secondary improvement in asthma and other related conditions.

12. Conclusion

The clinical utility of IOS in asthma is well established. IOS is a noninvasive tool that is independent of patient effort and reproducible in pediatric and adult patients. IOS serves as a technique that can be used with spirometry or independently to diagnose and manage asthma. In addition, the utility of IOS is expanding and has shown to be useful in COPD and other inflammatory lung diseases.

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