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The Case for Impulse Oscillometry in the Management of Asthma in Children and Adults

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Abbreviations:

1. IOS – Impulse oscillometry
2. PAW – Peripheral airway
3. PAI – Peripheral airway impairment
4. Rrs - Resistance
5. Xrs - Reactance
6. BDR – Bronchodilator response
7. LABA – Long acting beta agonists

The Case for Impulse Oscillometry in the Management of Asthma in Children and Adults

I. Introduction

Spirometry has traditionally been employed to evaluate lung function in children and adults [1]. While spirometry is of great utility, many practitioners do not use this in their assessment of asthma [2], 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.

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 [3,4]. 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.

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 [1], have been shown to be effective in asthma in improving control and reducing morbidity, a considerable number of children [5] and adults [6] may not respond well in terms of either spirometric parameters or clinical outcomes [7].

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 [8] and inflammation [9] in persistent asthma, and therefore the delivery of standard large particle inhaled controller therapies may be inadequate [10] This area of the lung so called "silent zone", has been largely neglected primarily due to its inaccessibility to evaluation by previous techniques. More recently, newer noninvasive techniques have successfully evaluated PAW [11-15] 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 [15]. IOS has been found to have good reproducibility [3], and shows good correlation with previously established methods of assessing the PAW both in adults and older children [15-20]. To our knowledge this has not been adequately evaluated in the preschool child.

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[21]. PAI has been shown to be clinically related to airway hyper- reactivity, nocturnal asthma, exacerbations, steroid-resistant asthma, and fatal asthma [22]. However, PAI may be clinically relevant at all levels of asthma severity [23], and control [24,25], as well as predicting the persistence of childhood asthma into adulthood [26], and potential loss of lung function with age [27,28].

The primary purpose of this updated review is to demonstrate clinical situations where IOS could provide "value added" to traditional clinical and spirometric parameters. In addition, we examine the applicability of commercial IOS reference values for diverse racial/ethnic populations, as well as assess airway reactivity, and effectiveness of extrafine (EF) compared to standard aerosols measured by improvement in PAW function. A complete search in Pub Med was performed for articles for IOS in peer reviewed journals. The articles included in this review were based on the expert opinion and previous publications by the authors.

II. 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 [29]. Both lung resistance (Rrs) and reactance (Xrs), which reflect total pulmonary impedance (Z,) are measured and observed by the investigator in real-time t(s) as a function of flow volume and pressure for approximately 30 seconds, thus allowing the investigator to select the best tracings. 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 R and X values are analyzed and graphically displayed. Reproducibility in children and adults ranges between 5-15%, but should not exceed 17% [3, 30], - For further technical details see two previous excellent reviews [3, 31].

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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 [32-35]. 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.

PAW obstruction is reflected by increases in the frequency-dependent resistance with an elevated R5-R20 and AX, manifested in obstructive diseases such as asthma and COPD (Fig 1). 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.

III. Population Based Reference Values

Although a representative relationship between baseline IOS parameters and physical characteristics (i.e., height, age, weight, etc.) of children and adults without lung disease has been implemented into the commercially available IOS devices and been used for several years, reference values as mentioned are primarily based on the data obtained from Caucasians [32-35]. To compare reported IOS parameters obtained from diverse populations with commercially utilized values obtained from previously reported regression equations a PubMed database was used to search for suitable studies. Seventeen studies in healthy children [33-49] and eleven in healthy adults [30;50-59] were identified and presented in Figure 2A and B (children) and Table 1 (adults). Due to limited data, IOS parameter values other than R5 and X5 were not available at this time. As presented in Figures 2 A and B the reported R5and X5 values, the most commonly reported IOS parameters in children and adults, show wide variations at a given height and age. However, there is substantial population overlap in R5 and X5 values at a given height, regardless of geographical location and ethnic differences. Table 2 includes mean (SD) of R5 and X5 values obtained from healthy adults with diverse geographical and ethnic backgrounds. Some R5 and X5 values in Table 2 were estimated using a regression equation [30;50,59] at a given height and age. For adults, both R5 and X5 values were similar regardless of demographic or geographical differences. Furthermore, it is remarkable to note that these values for R5 and X5 are comparable to those commercially utilized regression equations for both children and adults shown in Figures 2A and B and Table 1). Thus, R5 and X5 values that exceed the currently available commercial limits of the IOS parameters in children and adults at each age or height may suggest PAI and

the need for step up therapy. However, further studies will be needed to clearly define normal limits of these IOS parameters for other ethnic and racial groups such as the African American population, as well for establishing universal reference values for the key PAW markers R5-R20 and AX.

IV. Assessing Airway Reactivity

A. Defining the Positive Bronchodilator Response

The Bronchodilator Response (BDR) is a standard measure of airway reversibility which has traditionally been used to define the presence of asthma [1]. The BDR has been reported to be useful in identifying asthma [60], those with uncontrolled asthma [61], ICS responsiveness [62], and may reflect airway remodeling [63]. In adults the ATS defines a positive BDR as a ≥ 12% and 200ml increase in FEV1, based on the 95% confidence interval BDR value in the general population [64].

Less is known about the magnitude effect of a short acting beta2 agonist on PAW. However, the PAW contains a high a density of beta2 adrenergic receptors [65], and thus IOS may exhibit a greater beta2 effect than spirometry, which primarily measures the more central large airways. The BDR assessed by IOS is demonstrated by the reduction of resistance Rrs including R5, frequency dependent R5-R20, and reactance (Xrs) AX (Figure 3). Previous studies have reported great variability in defining a clinically relevant BDR as expressed by IOS ranging from 8.6% [66] to over 40% [30] depending on whether describing the upper limits of the normal population [30] or differentiating the

asthmatic patient from non-asthmatic controls [66]. In order to clarify this further, we define a positive BDR as greater than the 95% confidence interval response for low frequency R5 in healthy children and adults. Low frequency resistance was selected since it is thought to reflect the caliber of PAW and is commonly used to define a positive BDR. Six pediatric [34-36;66-68] studies, and 1 adult [30] study reporting the mean and standard deviation (SD) BDR, were analyzed. The 95% upper limits (95% CI) was calculated from the mean + 1.96 residual SD. For preschool and school age children the mean of these BDR values was 39%, and for the single adult study 32%. These data suggest that a BDR response greater than a 40% decrease in R5 be considered a positive BDR, signifying significant airway reversibility in children and adults, but this cut-off may not be applicable in differentiating the asthmatic from the non-asthmatic. This situation is similar to our previous BDR study utilizing spirometry, which showed lower BDR values were more effective in identifying asthmatic children than those recommended by ATS guidelines. [60]

B. Use of IOS for Bronchial Challenge Testing

Bronchial challenge testing with direct (eg methacholine or histamine) [69] or indirect acting (eg mannitol) [70] agents may be used in everyday clinical practice to identify the presence of airway hyperreactivity which is the hallmark of persistent asthma, particularly useful when the diagnosis of asthma is in doubt as in cases of unexplained cough or lack of apparent response to escalating treatment.

Performing IOS with normal tidal breathing is much easier for patients to perform with repeated measurements during challenge, especially where coughing occurs due to

bronchial irritation. When using methacholine or histamine challenge the threshold is conventionally measured using spirometry to determine the provocative concentration (or dose) required to produce a 20% fall in FEV1 (PC20 FEV1).

- Adult Studies

  18 adult patients with mild to moderate persistent asthma had methacholine and histamine challenges, measuring both spirometry and IOS [71]. A mean 23.3 (95% CI 18.7-27.9%) fall in FEV1 was associated with a mean 43.5 (95% CI 29.4-57.5%) increase in R5, all of which were significant. Corresponding data for histamine challenge were 25.9 (95% CI 21.0-30.8%) and 44.9 (95%CI 24.0-65.8%). A PC20 FEV1 equated to a PC37 R5 for methacholine and PC35 R5 for histamine. Hence for practical purposes a PC40 R5 may be used to approximately extrapolate to a PC20FEV1 for either methacholine or histamine challenge.

  Boudewijn et al performed a cross-sectional evaluation of symptomatic and asymptomatic adult patients with mild asthma who had a similar degree of methacholine hyper-reactivity. Patients with symptoms had worse PAW function (R5–R20 and X5) pre and post challenge in comparison to asymptomatic patients, with there being no difference in either R20 or FEV1, which primarily reflect the central airways [72].

  . Pediatric Studies

Although less performed in children, the IOS response after methacholine challenge has been found useful particularly in young children. For example, Kalliola et al examined the relationship between methacholine sensitivity by IOS and asthma severity in children 3 to 8 years of age [73]. They found that the increase in PAW, primarily R5-R20 after methacholine challenge was significantly higher in those children with more severe asthma as shown by increased exercise induced bronchospasm (EIB) and short acting beta 2 usage. This suggests that the change in R5-R20 following methacholine challenge could identify a population of more severe asthmatic children. In addition, Schultz et al demonstrated in 48 young asthmatic children undergoing methacholine challenge that the PD45 R5 showed the optimal combination of sensitivity and specificity to detect a PD20 FEV1[71]. Furthermore, significant increases in resistance were seen well before an FEV1 response at lower methacholine doses, suggesting that IOS was more sensitive than spirometry. [74] Free running is a more natural way of challenging the airway for bronchial hyper-reactivity and is highly specific for pediatric asthma, particularly in those who experienced exercise induced bronchospasm EIB [75]. Exercise challenge as assessed by IOS has been shown to determine respiratory status in preschool children who may not be able to perform spirometry [76]. These studies suggest that assessing PAW reactivity by IOS is feasible even in young children as well as adults, may be more sensitive than spirometry, and more useful in detecting more severe asthma.

V. The Clinical Value of IOS

A. Pediatric Population

Although IOS may correlate with spirometry, each is thought to measure different aspects of lung function, IOS assessing airway caliber, while spirometry reflects airflow characteristics. In studies utilizing both IOS and spirometry, IOS has been shown to be more useful than spirometry in children in differentiating asthma from normal cohorts, particularly utilizing the BDR decrease in R5 or R10 of 20%in preschool children,[77,78] and 8.6% in school age children [66]. IOS also proved more diagnostic in identifying uncontrolled asthmatic patients utilizing baseline values [25,36]. These studies suggest that in children IOS detection of PAI maybe more reflective of an earlier event than central airway pathology in asthma identified by spirometry. This observation could have important therapeutic implications to suggest earlier introduction of therapy with EF ICS, for example.

Several more recent studies have suggested a predictive role for IOS. In a longitudinal analysis we demonstrated in 54 children (ages 7-17 years) with mild to moderate asthma, who were considered to be in good control by clinical symptoms and spirometry, that R5-R20 and AX were more predictive of loss of control 8 to 12 weeks after the initial visit than spirometric measures including FEF25-75.[79]

Schultz and colleagues evaluated the value of IOS compared to spirometry and methacholine challenge as predictors of asthma exacerbation in children 4 to 7 years over a 1 year observation period. R5 and R5-R20 were more predictive of an exacerbation,

even at a time when the patient was asymptomatic, than FEV1, FEV1/FVC or methacholine challenge [21].

Longitudinal measures suggest that irreversible changes in the lung function may develop before school age, and in fact may be present in the newborn in those destined to develop asthma [27]. Decreased FEV1, and FEV1/FVC are considered key indicators of future exacerbation, and decreased lung function over time. Spirometry may be limited however, in the preschool child and reflects primarily central airway disease, while studies have suggested that the PAW may also play a role in the development and control of asthma. Thus, Knihtila et al has recently reported that IOS findings of peripheral airway obstruction at ages 2- 7 years in asthmatic children were significantly related to abnormal post bronchodilator spirometry in those patients as adolescents , ages of 12-18 years [28]. Based on a negative predictive value of 98% the authors concluded that asthmatic children with normal preschool lung function are unlikely to have decreased lung function in adolescence. Thus, IOS could be used by the clinician to target those young asthmatic children with evidence of PAI for early therapeutic intervention to prevent further pulmonary and clinical sequelae. Taken in totality these studies suggest that in children IOS may be clinically useful even when spirometry can be performed. .

B. Adult Population

In this section we consider the proportion of adult asthmatic patients who have abnormal IOS values, and the association with asthma severity, asthma control, and loss of asthma control. In tandem we compare the utility of IOS with spirometry in these adult asthma patients.

A cross sectional evaluation of 368 patients evaluated the prevalence of small airway obstruction with community managed persistent asthma, who were receiving steps 2-4 of British Thoracic Society (BTS) guidelines [80]. An abnormal physiological value for peripheral airway resistance (R5-R20) of 0.03 kPa/L/swas defined as the upper 95%CI from healthy volunteers.[23] This showed that across BTS severity steps there was a high prevalence of peripheral airway dysfunction with 65%, 64% and 70% of abnormal values in mild, moderate and severe asthma, respectively. Peripheral airway resistance was significantly higher at step 4 than step 3 (0.12 vs 0.08 1)kPa/L/s, while no significant differences were observed with FEF25-75. Hence despite a relatively well preserved FEV1 across BTS steps, there appears to be evidence of persistent small airways dysfunction which can be detected using IOS.

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The relationship of IOS and spirometry to asthma control as measured by the Asthma Control Questionnaire (ACQ) was evaluated by cross sectional analysis of 108 patients with uncontrolled, moderate to severe persistent asthma attending a secondary care clinic[20] The mean ACQ score of 2.37 was higher than the cut point of 1.5 for poor control. IOS measurements (R5-R20, AX, RF), but not spirometry, were significantly discriminatory in terms of worse control, while only R5-R20 was discriminatory for increased albuterol use.

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In a subgroup analysis, a cohort of 302 patients were then identified who had a preserved FEV1 (>80% predicted) to evaluate the predictive value of peripheral airways dysfunction defined as either R5-R20 > 0.07 kPa.l.s-1kPa/L/sor FEF25-75 <70%. [81] These patients were then evaluated for one year pre and post the index measurement. In this cohort with a mean age of 40 years and an FEV1 of 97% predicted, the proportion across BTS steps 1-4 were 6%, 38%, 28 %, and 28% respectively. An abnormal value for R5-R20 in 135 patients (45%) was associated with 44(95%CI 8-66) % and 47 (95%CI 13-67)% increased likelihood of oral corticosteroid and albuterol use respectively, while an abnormal FEF25-75 value in 157 (52%) patients was associated with a corresponding 33 (95%CI 9-60)% and 48 (95%CI 26-67)% increase, all of which were significant. Abnormal values for both R5-R20 and FEF25-75 in 83 patients (28%) were associated with 57(95%CI 17-78)% and a 68(95%CI 39-83)% increased risk of oral corticosteroid and albuterol use respectively which were numerically, but not significantly greater than R5-R20 or FEF25-75 alone. These data suggest that IOS and spirometry may provide complimentary information on small airways function, suggesting perhaps that neither measurement should be taken in isolation. In addition, these studies demonstrate that IOS may be particularly useful when the FEV1 is normal.

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VI. Effectiveness of Impulse Oscillometry in Stratification of Inhaled Corticosteroids Therapy Response

The peripheral airways of asthmatics have high receptor density of both beta 2 [65] and corticosteroid [82] receptors in airway structural cells and have been shown in pathological

studies to be a site of corticosteroid responsive eosinophilic airway inflammation and corticosteroid non-responsive airway remodeling [83-84].

These observations underpin the potential value of targeting the peripheral airways with long acting inhaled bronchodilators (LABA) and ICS in asthma, while highlighting the need to develop therapies that may attenuate airway remodeling and potentially modify disease progression.

Impulse oscillometry may be a useful biomarker of therapeutic response to inhaled therapies in asthma, which is underpinned by its ability to partition both central and peripheral airways dysfunction. In addition, the rapid proliferation of inhaled devices in asthma [85] with varying formulation chemistry (particle size and fine particle fraction) and post actuation properties (e.g. plume duration) that may influence total lung deposition, has created a need to develop stratified approaches to identify therapeutic responsiveness. A variety of radiolabelled ligand studies as well as imaging based simulation studies have suggested that extra-fine and Softmist™ inhalers demonstrate superior deposition in the lung and peripheral airways [86-87].

A variety of studies have evaluated the role of ICS with or without LABA with IOS R5-R20 as peripheral airway outcome measures [86-90]. These studies are summarized in Table 2, with additional information on the treatment 'effect size' on the peripheral airway R5-R20 and the standard deviation of R5-R20.

It is evident that the majority of studies are open label with/without randomization and that few studies have been conducted in a double blind double randomized fashion. A number of studies have compared EF with non-EF ICS, ICS/LABA inhaled therapy [88-92]. These studies have shown a consistent effect size, favoring EF therapy by a mean of 0.02-0.03kPa/L/sfor R5-R20. In addition, the studies demonstrate an effect upon IOS R5-R20 LABA [91], and ICS with or without LABA [88] when comparing EF vs non-EF therapy suggesting that this outcome may be representative of both bronchodilator sensitive and inflammatory disease in the peripheral airways. To date, studies evaluating IOS therapy response in children with asthma are lacking.These studies clearly suggest the superiority of EF ICS ± LABA in reducing PAI which should improve clinical asthma outcomes. What is needed now are studies that demonstrate that this is indeed the case.

VII. Limitation of IOS

In comparison to spirometry there are several limitations of IOS that need to be addressed to improve the general acceptance of this tool. These include interference from upper airway artifacts from tongue movement or swallowing which requires coaching, expense of the equipment, consistent reimbursement by the insurance industry, despite the fact that CPT codes are currently available, interpretation of currently available reference values, and the need to further establish universal reference values not only for R5 and X5, but the major markers of PAW function R5 –R20 and AX.

VIII. Conclusion

The PAW are the major sites of airway inflammation and obstruction in asthma. IOS offers an in-office tool that can assess PAI even in young children, and may detect airway obstruction earlier than spirometry. In children, IOS may be superior to spirometry in determining asthma status, and predicting loss of control and exacerbations, while in adults it appears to be complimentary to spirometry, particularly FEF25-75 for these outcomes. IOS may be particularly useful when the FEV1 is normal. Commercially available reference values R5 and X5 seem appropriate for the diverse geographical populations we evaluated. Improvement in PAW obstruction as determined by R5-R20, appears to consistently show the superiority of EF ICS +/-LABA aerosol therapy. However, this effect needs to be translated into clinical outcomes. Finally, detecting PAI with IOS may target young asthmatics who may benefit from early therapeutic intervention which may prevent further pulmonary and clinical sequelae.