



Impedance Oscillometry: Emerging Role in the Management of Chronic Respiratory Disease

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Abstract

Purpose of Review Chronic respiratory diseases affecting adults and children are widely prevalent, so lung function testing is imperative for diagnosis and management. Spirometry is the traditional standard measure of lung function; however, certain groups of patients are unable to provide accurate and reproducible exhalation maneuvers. Consequently, the impedance oscillometry system (IOS) has been developed as an effort, independent technique to assess airway function in children and the elderly. To better understand this emerging modality, the following review will compare IOS with spirometry, examine the function of the device, provide interpretation strategies, and discuss the evidence supporting its use in adults and children with chronic lung disease.

Recent Findings In a population of symptomatic adults with suspected COPD, impedance oscillometry resistance measurements correlate with FEV₁ and lung resistance increases with the severity of airflow limitation. In patients with asthma, IOS is a sensitive measure of airway hyperresponsiveness and bronchodilator response.

Summary Impedance oscillometry is evolving as an alternative measure to assess lung function pediatric and adult populations.

Keywords Impedance oscillometry · Asthma · Chronic obstructive pulmonary disease (COPD) · Pulmonary function testing (PFT) · Lung physiology

Introduction

Chronic respiratory diseases are prevalent conditions and worldwide leading causes of morbidity and mortality [1–3]. The worldwide prevalence of asthma is estimated to be 334 million according to a report by the World Health Organization (WHO) and is the most common respiratory disease in children [4]. In adults, the most common chronic respiratory disease is chronic obstructive pulmonary disease (COPD) with a spirometry-confirmed worldwide prevalence of 11.8% for men and 8.5% for women [5]. While asthma has

been reported to be more prevalent worldwide compared with COPD, the mortality associated with COPD was eight times more frequent than deaths associated with asthma [5]. Notably, between 1980 and 2014, the mortality due to chronic respiratory diseases increased and is a leading cause of death in the USA and associated with significant morbidity and financial costs [6]. Importantly, accurate and early identification of patients with chronic respiratory disease is important in order to (1) counsel on factors to prevent disease progression, (2) prescribe appropriate medical therapy, and (3) allow prognostication.

Frequent symptoms associated with chronic respiratory diseases include cough, dyspnea, and wheezing; however, these symptoms are common and non-specific, as chronic cough has been reported in 12% of the general population [7] and dyspnea accounts for ~10% of visits in ambulatory settings [8]. In clinical practice, the diagnosis of chronic respiratory disease relies on the severity and duration of symptoms, exposure history, and pulmonary function tests. However, use of self-reported symptoms to adequately diagnose COPD or asthma is fraught with limitations and can lead to misdiagnosis and medication overprescribing. Therefore, performance

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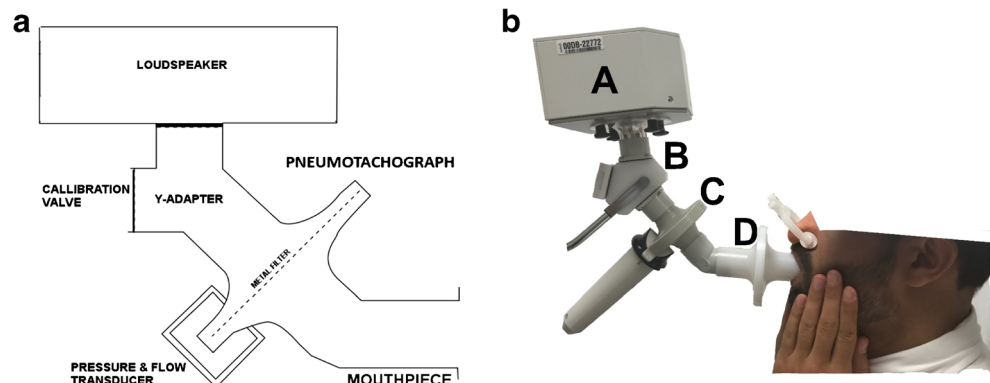
of pulmonary function tests is necessary for diagnosis of chronic respiratory disease in adults and children. For over 50 years, spirometry has been employed to measure forced expiratory volumes and resulted in a useful diagnostic test. Refinements in test performance, development of normative indices, and creation of interpretation strategies have led to establishment of spirometry as the gold standard for diagnosis of chronic respiratory disease. However, performance of spirometry is difficult for certain groups of patients as it involves performance of consistent, maximal forced exhalation maneuvers with coaching and repeated attempts that need to satisfy standards for repeatability and reproducibility [9–13]. Understandably, non-English speaking individuals and hearing or cognitively impaired adults and young children may have difficulty providing consistent and reproducible measurements. In addition, office staff require training to recognize and rectify poor test measurements and reports indicate that spirometry testing performed in a primary care clinic setting meet acceptable criteria only 60% of the time [14, 15]. Indeed, accurate and quality pulmonary function testing is crucial for diagnosis and proper patient management and there is a need for alternative measurement of lung function.

In 1956, Dubois and colleagues described use of forced oscillation technique (FOT) to non-invasively measure lung mechanics in healthy adult subjects [16]. This involved measurement of airway, lung tissue, and chest wall resistance through use of a loud speaker that generated single-frequency sound waves which were transmitted through a mouthpiece attached to passively breathing subject. However, this technique was cumbersome due to the equipment as well as each sound frequency was tested separately and multiple frequencies were required to obtain meaningful data; thus, it was principally used as a research tool. Subsequent improvements in pressure transducers and computer technology allowed use of multiple sound frequencies at a single time that led to development of the impulse oscillometry system (IOS) [17]. This technique has undergone refinements that have generated commercially available devices.

Impedance oscillometry system is an effort, independent technique to assess airway function that is less physically taxing for patients, especially those unable to properly perform spirometry [18•]. Impedance oscillometry requires use of loud speaker that generates sound waves over a range of frequencies (2–35 Hz) that travel through a mouthpiece connected to a patient (Fig. 1). These sound waves are superimposed on a patient's normal tidal breathing with the resulting changes in pressure and flow measured by transducers. The IOS device consists of a small loud speaker that produces sound waves directed through a mouthpiece attached to a patient's open glottis. The loud speaker is connected to a Y-adaptor that is attached to a pneumotachograph that measures pressure and flow during inspiration and expiration. The loud speaker is electronically controlled by a computer and programmed with manufacturer-specific algorithms. Respiratory system impedance can be determined through computer analysis of the amplitude and phase differences of pressure and flow during spontaneous breathing [17, 19].

Sound waves generated by the loud speaker are transmitted through the oropharynx, large and small airways, and lung tissue during normal tidal breathing. Higher-frequency sound waves (> 20 Hz) move shorter distances while lower frequencies (< 15 Hz) course to reach the smaller airways and lung parenchyma. A transducer measures pressure and flow during inspiration and expiration, and these signals are separated from the respiratory pattern by a signal filter. The measured parameters include total respiratory system impedance (Z_{rs}) that is composed of the forces that limit airflow namely respiratory system resistance (R_{rs}) and respiratory system reactance (X_{rs}). The respiratory resistance represents the flow-resistive properties of the respiratory system, namely, extrathoracic and intrathoracic airways, lung parenchyma, and chest wall. This represents the energy required for a sound wave to travel through the airways, lung parenchyma, and chest wall to distend the lung. This is determined as a pressure wave that moves unimpeded by airway recoil and is in phase with airflow [20•]. In general, the measured resistance at lower frequencies, such as 5 Hz (R_5), represents total airway

Fig. 1 **a** Impedance oscillometry schematic. Schematic diagram of the impedance oscillometry system. The loudspeaker generates the pressurized sound waves as the patient breaths normally. **b** Impedance oscillometry image displaying subject performing impedance oscillometry with hands placed on cheeks. A loud speaker, B Y-adaptor, C pneumotachograph, D mouthpiece



resistance (central and distal airways) while the resistance at 20 Hz (R20) represents the large central airways. The difference between the R5 and R20 values is an assessment of the resistance of small airways in patients, typically calculated as $(R5 - R20) / R5 \times 100$. It should be noted that the boundary between “large” and “small” airways is not dictated by anatomical location or by airway diameter [17].

Respiratory reactance (Xrs) represents the elastic and inertance properties of the respiratory system. This is the energy created by the elastic recoil of the airways and lung parenchyma as well as inertance that reflects the energy required to move a column of air through the lung. In simple terms, resistance represents the energy consumptive properties while reactance represents the energy storage properties of the respiratory system. Another measured parameter is the area of reactance (AX) that represents the area under the curve for the reactance at frequencies between 5 Hz and the resonant frequency (Fres). When reactance is zero, the pressure and flow response are in phase, and this represents the resonant frequency of the respiratory system. Resonant frequency is the frequency where the magnitude of elastance and inertance are equal. Resonant frequency can vary over a range of frequencies and is a convenient marker for separation of low-frequency from high-frequency respiratory reactance [17]. In healthy adults, a normal resonant frequency of the respiratory system is 7–12 Hz and this value decreases with increasing

age [21]. In healthy children, the resonant frequency is greater than in normal adults. Of note, in adults with chronic obstructive airway disease, the resonant frequency of the respiratory system has been observed to be increased [22, 23] (Table 1).

Comparing IOS and Spirometry

Traditional pulmonary function testing consists of spirometry and lung volume measurements that allow recognition of lung disease patterns (obstructive, restrictive, non-specific). Clinically important parameters obtained from spirometry include forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and ratio of FEV₁/FVC. The forced vital capacity is the volume of air that is forcefully and completely exhaled with maximal effort after a full inspiration while the FEV₁ measures the exhaled volume after 1 s of the FVC maneuver. Spirometry has been the gold standard for diagnosis of airflow limitation in symptomatic patients. Since airflow limitation is partially caused by an increase in airway resistance [24], evaluation of airway resistance can also be diagnostically useful.

Airway resistance has been traditionally derived in pulmonary function testing from body plethysmography. Resistance is broadly defined as the ratio of driving pressure to flow. Airway resistance is calculated as the difference between alveolar and mouth pressure divided by constant flow rate

Table 1 Respiratory parameters measured by impedance oscillometry

Parameter	Abbreviation	Definition	Reference values
Respiratory impedance	Zrs	Impedance of the respiratory system that consists of in phase and out of phase resistance Airway resistance and elastic and inertive behavior of the lungs and chest wall as a function frequency	
Respiratory resistance	Rrs	Consists of airway, lung tissue, and chest wall resistances R5: resistance at frequency of 5 Hz Represents the proximal (large) and distal (small) airways R20: resistance at frequency of 20 Hz Represents the proximal airways	Normal: R5 ≤ 150% predicted values R20 ≤ 150% predicted values Abnormal: R5 > 150% predicted values R20 > 150% predicted values
	R5–R20	Calculated as $(R5 - R20) / R5 \times 100$ Represents resistance of small airways	Adults: Normal if ≤ 20% Abnormal if > 20% Children: Normal if ≤ 30% Abnormal if > 30%
Respiratory reactance	Xrs	Represents the elastic and inertive properties of the airways and lung tissue X5: reactance at frequency of 5 Hz	Abnormal if X5 if > 150% of predicted values
Resonant frequency	Fres	Frequency at which elastic and inertive impedances are equal	Adults: Normal < 12 Hz Abnormal > 20 Hz Children: Normal < 20–25 Hz Abnormal > 25 Hz
Reactance area	AX	Area defined as width of Xrs 5 and height of Fres under the reactance curve	No clearly set normative values
Coherence	Co	Quality control indicator Co 5 Hz: coherence at frequency of 5 Hz Co 20 Hz: coherence at frequency of 20 Hz	Results are reliable and reproducible when Co 5 Hz 0.7–0.9 Co 20 Hz 0.9–1.0

measured at the mouth. Determining flow and resistance in the human airways can be complex as these factors depend on gas composition, flow turbulence, and lung volumes. Additionally, resistance is more complex as the airways are connected in series and in parallel. Specific airway resistance is airway resistance corrected for lung volumes. An alternative method of measuring airway resistance involved use of IOS. Respiratory resistance (R_{rs}) measured by IOS includes resistance of the airways, lung parenchyma, and chest wall. Since IOS is performed during tidal breathing, changes in lung volumes are minor and thus do not interfere with the measurement. This property of IOS is thought to explain its high sensitivity to changes in bronchial tone compared to other measurements [24] (Table 2).

Quality standards for acceptable spirometry require that for the FVC maneuver to be properly performed requires inspiration to maximal inhalation followed by maximal forced exhalation. Three acceptable maneuvers are required to ensure quality of testing. Acceptable maneuvers must reflect maximal effort from the start to the end of the maneuver and must last at least 6 s. Furthermore, spirometry must be free of coughs, leaks, or early termination to be technically acceptable [14, 15, 25, 26].

In contrast, proper performance of IOS requires normal, tidal breathing with lips tightly sealed over the mouthpiece while wearing a nose clip in an upright seated position. Importantly,

a patient's cheeks must be supported by a set of hands to reduce artifact signals [27]. A minimum of three tests are performed to achieve technically acceptable measurements.

Interpretation of IOS

In adults, normal values of respiratory resistance and reactance are influenced by height [13, 21, 28] and to a lesser extent, age, sex, and weight [13]. Reference values for children and adults without lung disease have been developed and been incorporated into commercially available IOS devices [10, 28–31]. There is limited data concerning IOS parameters, and reference values for populations of healthy adults and children are primarily available for R_5 and X_5 and there is a need to develop reference values for R_{20} and R_5 – R_{20} . Another limitation concerning the reference values are that they are principally based on data from white, European descent population, and additional studies are needed to outline normal parameters for other racial and ethnic groups. As for reproducibility, the intra-individual variability for resistance in healthy adults and children ranges from 5 to 15% [19] and this is similar to the variability observed with measurement of airway resistance by body plethysmography [19]. Similarly, the day-to-day variability of airway resistance measurements by IOS has been reported to be 10% for adults and 16% for

Table 2 Comparison of impedance oscillometry and spirometry

	Impedance oscillometry	Spirometry
Measured variables	Z_{rs} , R_{rs} , X_{rs}	FVC, FEV_1 , PEFr
Maneuver	Normal tidal breathing of ambient air with lips tightly sealed over mouthpiece while wearing a nose clip, sitting upright, and with supported cheeks for of 20–30 s Minimum of three technically acceptable tests	Deep maximal inhalation followed by rapid forced exhalation and continued exhalation for at least 6 s Exhalation must be free of coughs, leaks, or early termination Minimum of three technically acceptable tests
Availability	Not widely available	Widely available
References of normal databases	Smaller number of patients evaluated for normal values	Substantial number of patient data
Dependent on:		
Age	Yes	Yes
Height	Yes	Yes
Weight	Yes (IOS may be abnormal due to obesity alone)	No
Ethnicity	Yes	Yes
Measurement of airway resistance	R_{rs} airways resistance in addition to chest wall and lung tissue Predominantly influenced by small airway resistance	Raw resistance of extrathoracic and intrathoracic airways Predominantly influenced by large airway than small airway resistance
Bronchodilator response	Decrease in R_5 by 40% from baseline	Increase in FVC or FEV_1 by 12% and 200 ml
Bronchoprovocation response	Increase in R_5 by 50% from baseline	Decrease in FEV_1 by 20% from baseline

Z_{rs} respiratory impedance, R_{rs} respiratory resistance, X_{rs} respiratory reactance, FVC forced expiratory volume, FEV_1 forced expiratory volume in the first second, PEFr peak expiratory flow rate, Raw airway resistance

children [19]. Currently, normal values for respiratory resistance at 5 and 20 Hz and respiratory reactance at 5 Hz have been established as $\leq 150\%$ of predicted. Reactance measurements are negative and as reactance becomes more prominent, this value becomes more negative. The normal value regarding the difference between respiratory resistance at 5 and 20 Hz ($R5 - R20$) in adults and children are ≤ 20 and $\leq 30\%$ of predicted, respectively. As with other pulmonary function testing, changes in resistance following inhaled bronchodilator administration is an important parameter. Using IOS parameters to determine the response to bronchodilators reveals a decrease in resistance that includes respiratory resistance at 5 and 20 Hz, the difference between respiratory resistance at 5 and 20 Hz and reactance at 5 Hz. After bronchodilator administration, a significant response in adults and children is considered as a decline in R5 by $\geq 40\%$, but this should not be used as a parameter to distinguish asthmatic from non-asthmatic patients. Another clinical application of IOS involves assessment of bronchial hyperresponsiveness with methacholine and histamine as a means of identifying a patient with asthma. With regard to bronchoprovocation studies, testing a significant increase in resistance is considered when R5 increases by $> 50\%$.

Accurate interpretation of IOS can be supplemented by pattern recognition of resistance and reactance graphs. In normal airways, the resistance curve should remain flat across all frequencies (Fig. 2). Similarly, in healthy young children, the resistance curve will remain flat but will have some curvature as this is related to smaller size of the airways and not disease. The reactance measurements are curvilinear across all frequencies. A quality IOS study is illustrated in Fig. 2 along with corresponding table with normal IOS and spirometry values. This was performed by an asymptomatic, non-smoking, 30-year-old Caucasian male without airflow limitation on spirometry. The software package will also generate a

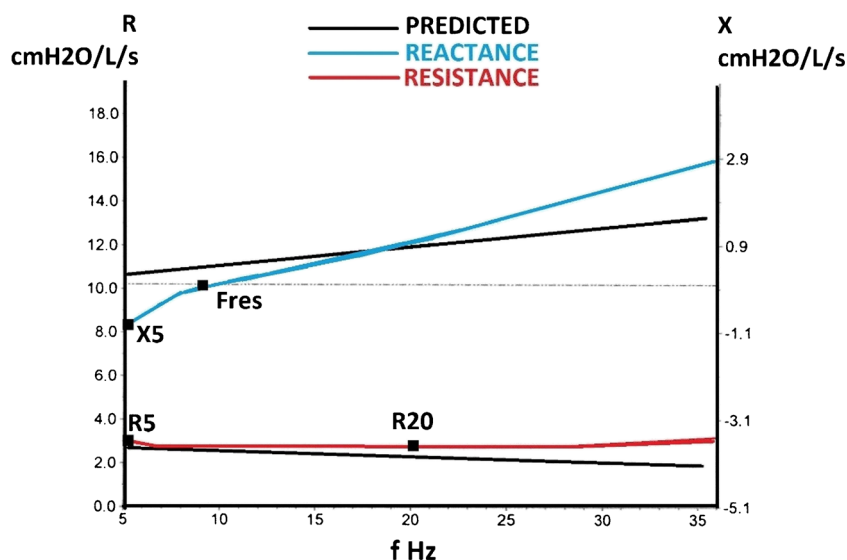
graph termed the “Goldman graph” that displays frequency (Hz) on the y-axis and a split x-axis demonstrating resistance and reactance [32] (Fig. 3). Lastly, an indicator of test quality is a function of the coherence values at 5 and 20 Hz. A reliable test is recognized when coherence at 5 Hz is between 0.7 and 0.9 and at 20 Hz between 0.9 and 1.0.

In patients with asthma or COPD in which the central and peripheral airways are involved, the resistance graph will demonstrate elevated values across all frequencies. The resistance R5 and R20 values will also be elevated at $\geq 150\%$ of predicted. In individuals with predominantly small airways disease, there is frequency dependence of resistance and in such a situation, the resistance measurements will be elevated at low frequencies (R5) and resistance will fall with higher frequencies (R20) (Fig. 4). Resistance curves that demonstrate frequency dependence are indicative of distal airway obstruction [20•]. Frequency dependent resistance is depicted in Fig. 4, and the resistance measurements have curvilinear shape across the frequency range.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive inflammatory response of the lungs to harmful air particles or gases characterized by increased airway resistance and airflow limitation that is not fully reversible [8, 25]. While spirometry is commonly used to identify symptomatic patients, there are patients with daily symptoms that do not have airflow limitation as assessed by spirometry. Woodruff and colleagues performed spirometry and COPD assessment test in a large cohort of current and former smokers and reported that 20% the cohort had no measurable airflow limitation but had similar severity of symptoms and exacerbation rates compared to patients with airflow limitation as detected by

Fig. 2 Graphic representation of IOS measurements in a healthy, asymptomatic, non-smoking 30-year-old male. The graph demonstrates resistance (red) and reactance (blue) spectra on y-axis and frequency on x-axis. This is characteristic graph for normal resistance and reactance values. R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, Fres = resonant frequency



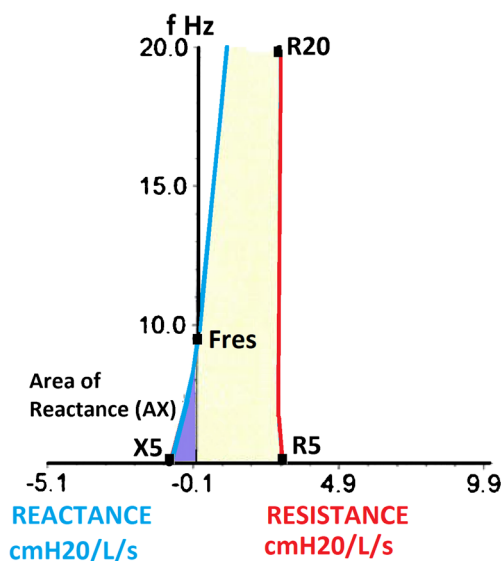


Fig. 3 A representative IOS graph from a healthy non-smoking individual. The values obtained for this graph are identical to those obtained in Fig. 2. The x-axis is split into resistance (R5 and R20) and reactance (X5), while the y-axis represents frequency. This graph is termed the Goldman graph and was generated to facilitate interpretation. This is frequently provided as part of the interpretation scheme by commercial impedance oscillometry. R5 = resistance at 5 Hz, R20 = resistance at 20 Hz, X5 = reactance at 5 Hz, Fres = resonant frequency

spirometry [34]. Moreover, current or former smokers with daily symptoms represent a group of patients in which the IOS device may be able to identify respiratory disease. Consequently, proposals have been made to implement IOS as a diagnostic tool to screen or identify early obstructive lung disease [30, 31, 33, 35].

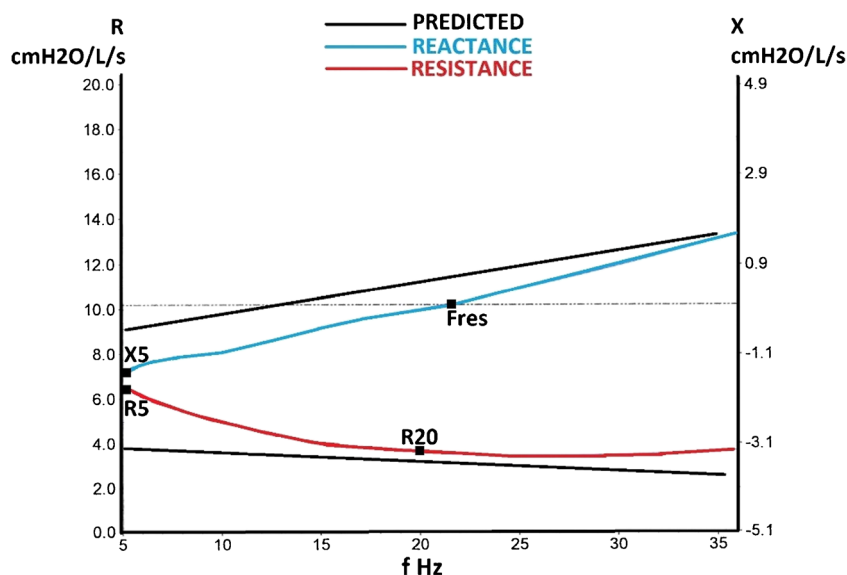
An initial report described the relationship of IOS parameters to spirometry measurements in 58 patients with COPD at baseline and 1-year follow up [35]. The mean age of the group

was 63.8 years with mean FEV₁ of 57.9%. The authors reported significant correlations at baseline between FEV₁ and IOS parameters; R5, X5, and resonant frequency, but not with R20. At 1-year follow up, there was no significant change in FEV₁, R5, X5, and resonant frequency. The authors' findings revealed that in patients with COPD, R20 was unrelated to the severity of airflow limitation, and airway reactance measurements were more closely related to spirometry than IOS measures of resistance [35].

In order to relate lung mechanics and patient symptoms, a group of investigators performed spirometry and IOS measurements in 450 individuals with and without symptoms [33]. They reported that symptomatic smokers without airflow limitation had similar R5, R20, R5–R20, and X5 values compared to asymptomatic patients with airflow limitation, defined as FEV₁/FVC < 0.70. Furthermore, symptomatic patients with airflow limitation demonstrated significant differences in reactance compared to other groups and had similar IOS measurements of resistance (R5, R20, and R5–R20) compared with symptomatic patients with preserved lung function (no airflow limitation) [33]. Notably, the authors revealed that IOS measurements could not distinguish between symptomatic patients with preserved lung function and asymptomatic patients with airflow limitation. They concluded that reactance may be a useful parameter to distinguish patients with airflow limitation from those without airflow limitation.

The role of IOS in the management of COPD patients was not well delineated and a multicenter, international clinical trial was developed to compare IOS, spirometry, and quantitative chest CT imaging as a means of diagnosing and staging disease severity [36••]. These investigators compared spirometry and IOS measurements at baseline and at a 3-month follow up in 2054 COPD patients, 233 healthy non-smokers, and 322 healthy current smokers. Patients with COPD were older

Fig. 4 A representative IOS graph from a 60-year-old female with a 40-pack year smoking history. The graph reveals resistance measurements (red) with frequency dependence. Reactance measurements (blue) are more negative across all frequencies



with mean age of 63.4 years compared to non-smokers (54.3 years) and current smokers (55.2 years). In the COPD cohort, patients were stratified according to severity of disease with 45% classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II, 43% were GOLD stage III, and 14% were GOLD stage IV. Chest CT imaging identified greater degree of emphysema in subjects with COPD compared to healthy non-smokers. As a group, patients with COPD were noted to have elevated resistances (R5, R20) and reactance parameters compared to non-smokers and current smokers. However, an appreciable number of patients with COPD were noted to have normal IOS measurements. They concluded that IOS has a limited usefulness in evaluating the degree of pathologic disease in COPD patients [36••].

Recently, Liu and colleagues evaluated the clinical application of IOS in a population of Chinese patients > 65 years [37]. Overall, patients with COPD had increased resistance and reactance compared to healthy controls; however, the resistance or reactance parameters in patients with COPD GOLD stage I did not differ significantly from age-matched healthy control subjects [37]. As the severity of COPD classified by spirometry progressed, respiratory resistance increased and reactance worsened [37]. In another set of investigative studies, IOS was used to evaluate airway resistance and the response to bronchodilators in patients with COPD patients and the response correlated with spirometry findings [38, 39].

The role for oscillometry to screen for airway disease was discussed in a point-counterpoint discussion. Berger proposed the use of IOS, citing reports and his findings that patients with respiratory symptoms exposed to the dust from World Trade Center collapse had abnormal IOS parameters while spirometry measurements were normal [40]. In the report by Oppenheimer regarding airway measurements after dust exposure to the World Trade Center disaster, the authors described elevated R5 and R5–R20 values in 62 and 27% of subjects with normal spirometry [41]. In his argument, Berger concluded that IOS is a useful screening tool for early diagnosis of small airway abnormalities compared to spirometry. In contrast, Enright pointed out that rigorous longitudinal studies to evaluate progression of chronic airway obstruction with spirometry have been performed in smokers and that the prediction models are well established, unlike those with impedance oscillometry [42••]. Enright also pointed out the findings of the ECLIPSE trial that showed a substantial amount of COPD patients with airway obstruction confirmed on spirometry had normal parameters with oscillometry [36••]. Lastly, IOS has a greater coefficient of variability reported to be 5–15% [20••] compared to spirometry: 3% [19]. Reference values for IOS are quite lacking compared to the hundreds of thousands of patients measured with spirometry [25, 26, 43, 44]. In conclusion, there is not sufficient data to indicate that IOS can replace spirometry in the diagnosis and staging of COPD; however, it may have a role in symptomatic patients

with suspected airflow limitation unable to perform spirometry for whom a diagnosis can lead to a structured treatment.

Asthma

Asthma is considered as a small airways disease, and use of impedance oscillometry would be a suitable modality for early detection in adults as well as children or monitoring the response to medical interventions. In adults and children with asthma, IOS measurements have demonstrated elevated R5, R20, resonant frequency and more negative X5 values compared with healthy subjects [45–47]. Traditionally, asthma has been defined as reversible airflow obstruction after bronchodilator administration as measured by spirometry. Investigators have examined the relationship between spirometry and IOS in patients with asthma following bronchodilator and reported improvements in FEV₁ and R5 values [45]. After administration of an inhaled bronchodilator, the response as determined with IOS has demonstrated a decrease in R5, as well as frequency-dependent R5–R20 and Xrs [48, 49].

Bronchodilator Response Assessment with IOS

Earlier reports that have attempted to define a significant bronchodilator response have described a variability in resistance that ranges from 8.6 to 40%. Additional clarification was provided in a review on the topic, and the authors defined a significant bronchodilator response as greater than the 95% confidence interval for R5 in healthy children and adults [20••]. The selection of R5 as a measure of a bronchodilator responsiveness was based on physiologic principles that resistance at 5 Hz represents the small, peripheral airways and has been frequently used by investigators as the standard for bronchodilation. Clinical investigations that reported a bronchodilator response reported a mean decrease in R5 of 39% in children and of 32% in adults [20••]. Consequently, a significant bronchodilator response as measured by IOS has been defined as a decrease in respiratory resistance at 5 Hz or respiratory reactance at 5 Hz by 40% from baseline.

Bronchoprovocation Assessment with IOS

The role of IOS in bronchoprovocation testing has been examined in adults and children. In adults receiving methacholine or histamine, the airway response demonstrated an increase in R5, R5–R20, and resonant frequency [50]. Short and colleagues examined 18 adult patients with mild to moderate persistent asthma with methacholine and histamine challenges using spirometry and IOS as measures of airway

function [50]. After methacholine provocation, they reported a mean decrease in FEV₁ of 23.3% and this was associated with a mean increase in R5 of 43.5%. Similar data for histamine bronchoprovocation revealed a decrease in FEV₁ of 25.9% and an increase in R5 of 44.9%. Based on their findings, the authors concluded that the bronchoprovocation concentration resulting in 20% decline in FEV₁ was similar to dose leading a 40% decline in R5 compared to baseline [50]. Additional studies have measured methacholine-induced dyspnea using IOS and demonstrated increases in R5 that correlate better with symptoms than spirometry measurements of FEV₁ [51, 52]. One clinical investigation examined 20 adults with asthma and established bronchial hyperresponsiveness to methacholine with a provocative concentration associated with a 20% decrease in FEV₁ (PC20) of ≤ 16 mg/ml [52]. These investigators found that resistance and reactance correlated significantly with methacholine-induced symptoms while no significant change was seen in FEV₁. When cold air is used to induce bronchial hyperresponsiveness, IOS measurements of R5 are able to distinguish between asthmatic patients and healthy controls with better specificity and sensitivity (89 and 88%) compared to spirometry (88 and 73%), respectively [53]. Likewise, other investigators have compared lung function measurements with IOS, plethysmography, and spirometry after bronchoprovocation and reported IOS to be a more sensitive test [12, 54]. Therefore, use of IOS for bronchoprovocation testing is reported to be more sensitive and to detect airway hyperresponsiveness at lower bronchoprovocation doses compared with spirometry.

Pediatric Asthma

Childhood asthma is often diagnosed on symptoms and clinical presentation without use of objective diagnostic testing. The information concerning pediatric lung function may lead to improved awareness and earlier treatment that could provide additional information for providers to adequately treat and alter the natural history of asthma. However, lung function testing is challenging in preschool children. While spirometry is the most commonly used method to assess lung function, it is an effort-dependent technique and children often have difficulty meeting the quality control criteria [29•]. IOS has been proposed as an alternative approach that is reliable, easy to perform, and effort independent and may fulfill these needs.

An initial clinical investigation examined IOS use in children presenting to the emergency department with an asthma exacerbation. Investigators performed spirometry and IOS measurements in 114 children aged 3–17 years and identified elevated resistance and decreased FEV₁ measurements thereby demonstrating the use of this modality in the acute care setting [55]. Another group described use of IOS in children diagnosed with asthma in the outpatient setting and

demonstrated significantly greater R5 measurements compared to healthy control subjects [48]. Other investigators have also reported that compared to healthy subjects, children with asthma or recurrent wheezing demonstrate significantly higher Rrs and lower Xrs values [56].

The ability to distinguish between asthmatics and non-asthmatics has been examined by Knihtila and colleagues, and they indicated that R5–R20 and the area of reactance demonstrated greater sensitivity in distinguishing children with current or past lower respiratory tract infection compared to healthy children [56]. The response to inhaled bronchodilators has been used to indicate the presence or absence of asthma. As a result, two reports examined the ability of IOS to discriminate between asthmatic and healthy children using the response to inhaled bronchodilators [47, 57]. However, additional studies are required to determine the discriminant qualities of IOS.

Predicting uncontrolled asthma is a useful tool to determine when to step up asthma management and/or treat an acute exacerbation; however, identifying poorly controlled asthma with questionnaires is challenging in this population as the pediatric population has poor symptom perception and parental reporting is variable [58]. IOS measures of R5–20 and area of reactance have been demonstrated to be more sensitive and not only determine loss of control but predict future loss of control compared with spirometry [59•]. Schulze et al. also demonstrated that between acute asthma flares, IOS had an 80% accuracy when distinguishing which patients would have asthma exacerbations [60]. However, future studies are needed to provide insight to the role of IOS in the management of pediatric patients.

Limitations

Despite many benefits, IOS has several limitations. The parameters for IOS in other populations including gender, race, and ethnicity have not been delineated. Height as a variable can affect test results and thus impacts on study interpretation [61]. Other factors that are not fully characterized include smoking [62] and environmental pollution [63]. In addition to intrinsic variability in patients with a diagnosis of asthma, IOS has not been comprehensively evaluated in other adult and pediatric pulmonary disorders such as bronchiectasis [64], cystic fibrosis, diffuse parenchymal lung disease, or bronchopulmonary dysplasia. [65] Other practical considerations would be the actual utilization of IOS since it is not commonly available in specialists' offices; therefore, primary care physicians may not even be aware of its existence or possible value. Even when employed in specialists' offices, the difficulty in interpretation of a new diagnostic modality can be a barrier. Additionally, while IOS is effort independent, it does still require voluntary participation from the patient and

this may not always be possible with an anxious child or uncooperative patient. Another limitation concerns billing since insurance carriers will not reimburse for performance of IOS on the same day as spirometry or other pulmonary function tests [18•].

Conclusions

In summary, impedance oscillometry is an emerging, alternative test to assess lung function pediatric and adult populations. IOS is non-invasive and effort independent and makes this an appealing tool for use in children and older adults. Yet, spirometry and impedance plethysmography measure different aspects of lung function and should be viewed as complementary. Commercially available devices include measurement equipment and software packages with normative reference values and material to assist with interpretation. Bronchoprovocation and airway responsiveness are measures of airway function that IOS appears to be well suited to assess. In adults and children, the role for IOS is evolving and additional clinical investigations are needed to identify its role in the identification and management of chronic respiratory disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

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