

Original Article

Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function

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What is already known about this topic? Compared with forced expiratory flow between 25% and 75%, impulse oscillometry (IOS) is an effort-independent utility to detect small airway dysfunction.

What does this article add to our knowledge? This study provides reference values of IOS parameters, and the IOS parameter resonant frequency is more sensitive than forced expiratory flow between 25% and 75% to detect small airway dysfunction.

How does this study impact current management guidelines? Patients with respiratory symptoms and preserved pulmonary function may have small airway dysfunction that can be diagnosed with IOS in addition to spirometry.

BACKGROUND: Asthma and chronic obstructive pulmonary disease are characterized by persistent airway inflammation and airflow limitation. Early detection of these diseases in patients with respiratory symptoms and preserved pulmonary function (PPF) defined by spirometry is difficult. Impulse oscillometry (IOS) may have better sensitivity than effort-dependent forced expiratory flow between 25% and 75% (FEF_{25%-75%}) to detect small airway dysfunction (SAD).

OBJECTIVE: To identify SAD in patients with respiratory symptoms and PPF using IOS.

METHODS: Medical records of symptomatic patients without acute or known structural lung diseases were evaluated. Patients had bronchodilator testing and IOS in the outpatient clinic between March 1 and July 31, 2017. Correlations between respiratory symptoms, spirometry, and IOS parameters were determined.

RESULTS: Among 349 patients enrolled to the study, 255 (73.1%) patients met the criteria of PPF. The IOS parameters—difference in resistance at 5 Hz and resistance at 20 Hz, reactance at 5 Hz, resonant frequency (F_{res}), and area under reactance curve between 5 Hz and resonant frequency—were significantly correlated with FEF_{25%-75%}. The cutoffs for SAD were difference in resistance at 5 Hz and resistance at 20 Hz greater than 0.07 kPa/(L/s), reactance at 5 Hz less than -0.12 kPa/(L/s), F_{res} greater than 14.14 Hz, and area under reactance curve between 5 Hz and resonant frequency greater than 0.44 kPa/L. Of the IOS parameters, F_{res} and reactance at 5 Hz had the highest sensitivity and specificity. When compared with FEF_{25%-75%}, F_{res} had greater sensitivity to detect SAD in patients with PPF. Patients with IOS-defined SAD had a significantly higher incidence of wheeze or sputum production than did those defined by FEF_{25%-75%}.

CONCLUSIONS: Patients with respiratory symptoms and PPF may have SAD, which can be identified with the aid of IOS in addition to spirometry. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Small airway dysfunction; Forced expiratory flow; Impulse oscillometry; Spirometry; Preserved pulmonary function

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are airway diseases involving the small airways.^{1,2} Early treatment, even in patients with infrequent symptoms, is associated with improved long-term outcome and reduced risk of exacerbation.^{3,4} Diagnosis of early onset asthma and COPD is challenging, because it is difficult to identify in patients with small airway dysfunction (SAD) and preserved pulmonary function (PPF). Symptomatic smokers with PPF have activity limitations, exacerbations, and evidence of airway disease.⁵ In asthma,

Abbreviations used

AX-	Area under reactance curve between 5 Hz and resonant frequency
BR-	Bronchial reversibility
COPD-	Chronic obstructive pulmonary disease
FEF _{25%-75%} -	Forced expiratory flow between 25% and 75%
FVC-	Forced vital capacity
F _{res} -	Resonant frequency
IOS-	Impulse oscillometry
PPF-	Preserved pulmonary function
R ₅ -	Resistance at 5 Hz
R ₂₀ -	Resistance at 20 Hz
R ₅ - R ₂₀ -	Difference between R ₅ and R ₂₀
SAD-	Small airway dysfunction
X-	Reactance
X ₅ -	Reactance at 5 Hz
Z-	Impedance

peripheral airway resistance is significantly associated with total airflow obstruction.⁶

Spirometry is an effort-dependent method to diagnose airflow limitation.^{7,8} Forced expiratory flow after expiration of 25% to 75% of forced vital capacity (FVC) (FEF_{25%-75%}) is used to evaluate airflow in peripheral airways.^{9,10} A value of FEF_{25%-75%} less than 65% predicted is considered abnormal and is more accurate than FEV₁ to detect SAD in asthma.¹¹⁻¹³

However, the reproducibility and comparability of FEF_{25%-75%} are limited if not adjusted for lung volume.¹⁴ Various radiological and physiological tests have been proposed as noninvasive measurements of small airway function.¹⁵ Impulse oscillometry (IOS), using sound waves at frequencies from 5 to 35 Hz, can assess respiratory mechanics during spontaneous breathing.¹⁶ When compared with spirometry, IOS is an effort-independent method that is convenient and more sensitive to detect SAD and correlates with symptoms and disease severity of asthma and COPD.^{17,18} IOS also plays a role in detection of SAD in patients with dust exposure.¹⁹

The aim of our study was to identify SAD by IOS in patients with respiratory symptoms and PPF. Although there is no criterion standard to detect SAD at present, we correlated IOS parameters with FEF_{25%-75%} and recruited nonsmoker healthy subjects for comparison. We further determined the association between IOS parameters and respiratory symptoms.

METHODS

Study design and data collection

This retrospective study reviewed medical records from adult patients (≥ 20 years) who underwent both the bronchodilator test and IOS in the Taipei Veterans General Hospital Pulmonary Function Laboratory from March 1 to July 31, 2017.

All treatment-naïve adults with respiratory symptoms who came to our clinic were included, and received pulmonary function tests to detect whether there was a fixed airway obstruction or SAD. Exclusion criteria were patients with acute exacerbation of respiratory disease; pneumonia requiring antibiotics; hospitalization within the previous month; chronic respiratory infection; and structural lung diseases, including active or previous tuberculosis, bronchiectasis, interstitial and restrictive lung diseases, arteriovenous malformation, and surgical intervention of pulmonary lesions, and asymptomatic patients.

Moreover, we prospectively recruited never-smokers without a history of pulmonary diseases such as asthma, COPD, lung nodules, or interstitial lung diseases and with a normal chest X-ray as reference of healthy controls.

Baseline demographic variables were collected by chart review, including sex, age, weight, height, body mass index, smoking status, and respiratory symptoms including wheeze, cough, sputum production, and dyspnea. The definition of PPF included patients who met the following criteria: FEV₁/FVC greater than or equal to 0.7, FVC greater than 80% predicted, and lack of bronchial reversibility (BR) to short-acting inhaled drugs.^{5,9} An FEV₁/FVC value greater than or equal to 0.7 excludes patients with asthma and COPD, and an FVC value greater than 80% predicted minimizes misclassification of patients with restrictive lung disease. To exclude patients with asthma, we required a negative BR. Correlation between spirometry and IOS parameters in symptomatic patients with PPF was analyzed. SAD was defined as FEF_{25%-75%} less than 65% predicted,¹¹⁻¹³ and cutoff values of IOS parameters were then calculated.

The medical records were reviewed independently by 2 pulmonology specialists with assistance of the third specialist if disagreement existed. Our study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Spirometry and bronchodilator test

Patients were advised to avoid inhaled bronchodilators 12 hours before spirometry and reversibility testing. Because forced expiration can affect resistance and reactance, spirometry was conducted immediately after IOS. For data analysis, 2 flow-sensing spirometers (MS-IOS Jaeger, Würzburg, Germany, and Vmax 22 SensorMedics, Yorba Linda, Calif) connected to a computer were used. From the forced expiratory flow-volume curve, we measured peak expiratory flow, forced expiratory flow after expiration of 50% of FVC, FEF_{25%-75%}, FVC, and FEV₁. The percentage of predicted indices was obtained. Patients underwent spirometry before and 15 minutes after inhaling salbutamol (400 μ g) from a metered-dose inhaler with a valve-bearing spacer device. The BR was positive if FEV₁ or FVC or both improved 12% and 200 mL when compared with baseline values. The equipment was calibrated twice a day.

Impulse oscillometry

The IOS was conducted using combined spirometry and IOS equipment (MS-IOS Jaeger) according to the protocols of the European Respiratory Society.^{20,21} No premedication was given before IOS. Nasal clips and manual compression of the cheeks were used to reduce the confounding factors of cheek vibration and escape of air via the nostrils. Patients breathed quietly, through a loudspeaker-activated mouthpiece, for 30 to 45 seconds without contraction of the glottis or interposition of the tongue. The loudspeaker emitted 120 to 150 pulses varying from 5 to 35 Hz in frequency and overlapping normal breathing sounds (0.2-2 Hz). The resulting pressure and flow rates allow calculation of airway impedance (Z). Airway impedance includes total resistance of the respiratory system (R_{rs}), and reactance (X), which is resistance to inertia and elasticity of the tissues of the respiratory tract. Although R_{rs} at different frequencies reflects total resistance (resistance at 5 Hz [R_5]) or central airway resistance (resistance at 20 Hz [R_{20}]), the difference between R_5 and R_{20} ($R_5 - R_{20}$) reflects the resistance of small or peripheral airways.¹⁶ Resonant frequency (F_{res}) represents the frequency at which reactance is 0, indicating that the elastic and inert properties are equal and opposite. The area under reactance curve between 5

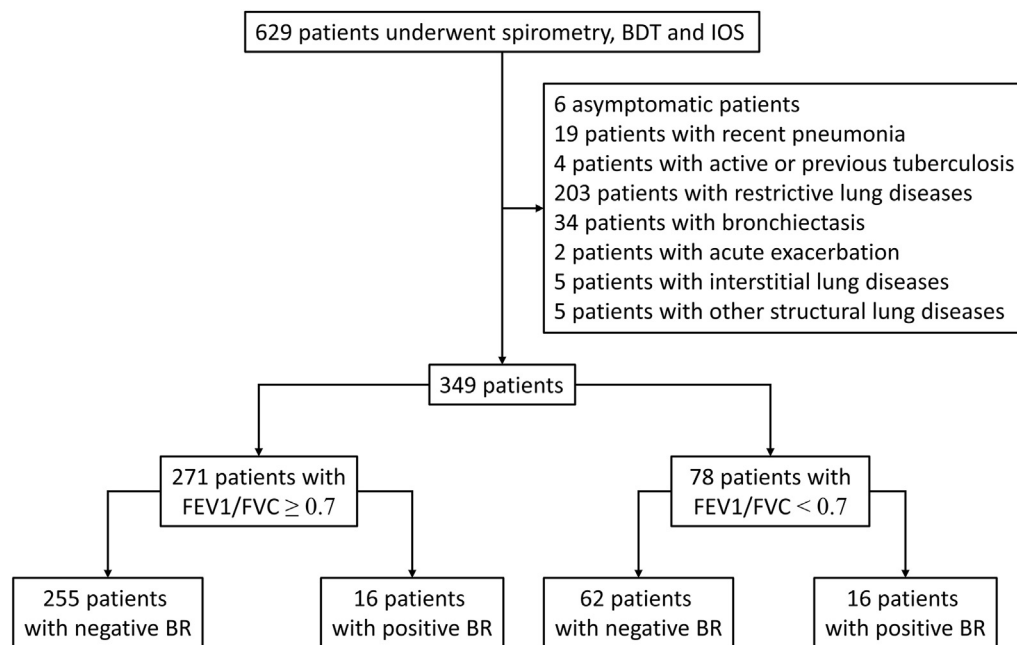


FIGURE 1. Enrollment of study population. BDT, Bronchodilator test.

TABLE I. Demographic characteristics of the study population

Characteristic	Nonobstructive group (FEV ₁ /FVC ≥ 0.7)		Obstructive group (FEV ₁ /FVC < 0.7)		P value
	BR (−) (N = 255)	BR (+) (N = 16)	BR (−) (N = 62)	BR (+) (N = 16)	
Age (y)	56 (41-64)	59 (51-70)	67 (62-75)	63 (56-80)	<.01
Height (cm)	165 (158-170)	160 (157-167)	162 (157-167)	164 (159-173)	.19
Weight (kg)	65 (56-75)	68 (57-77)	63 (57-70)	62 (54-78)	.62
BMI (kg/m ²)	24.3 (21.7-26.8)	25.8 (23.1-28.1)	24 (21.9-26.1)	22.8 (20.7-26.4)	.30
Sex: male, n (%)	133 (52.2)	7 (43.8)	44 (71.0)	11 (68.8)	.03
Smoking, n (%)	87 (34.1)	4 (25)	32 (51.6)	9 (56.3)	.02
Symptoms, n (%)					
Wheeze	34 (13.3)	0 (0)	3 (4.8)	3 (18.8)	.10
Cough	180 (70.6)	12 (75)	42 (67.7)	10 (62.5)	.85
Sputum	120 (47.1)	8 (50)	36 (58.1)	7 (43.8)	.46
Dyspnea	119 (46.7)	5 (31.3)	42 (67.7)	9 (56.3)	.01
Pulmonary function test					
FEV ₁ /FVC	0.82 (0.78-0.86)	0.77 (0.72-0.78)	0.63 (0.56-0.66)	0.58 (0.52-0.65)	<.01
FEV ₁ (L/s)	2.70 (2.16-3.22)	1.95 (1.76-2.35)	1.84 (1.54-2.13)	1.70 (1.3-2.08)	<.01
FEV ₁ (% predicted)	99.87 ± 12.36	86.86 ± 14.26	80.12 ± 14.4	72.82 ± 16.97	<.01
FVC (L/s)	3.30 (2.68-3.95)	2.66 (2.25-3.15)	3.11 (2.54-3.58)	2.97 (2.67-3.47)	<.01
FVC (% predicted)	96.1 (88-104.2)	86.4 (82.6-91.5)	97.1 (90.6-107.9)	89.6 (84.6-101.2)	<.01
PEF (% predicted)	90.6 ± 17.78	75.53 ± 12.53	64.93 ± 17.72	55.31 ± 10.55	<.01
FEF _{25%-75%} (% predicted)	82.09 ± 25.65	59.34 ± 28.39	29.89 ± 9.3	30.69 ± 13.68	<.01
FEF _{50%} (% predicted)	96.54 ± 30.17	66.83 ± 25.14	35.62 ± 12.03	34.39 ± 17.43	<.01
IOS					
R ₅ [kPa/(L/s)]	0.36 (0.3-0.45)	0.36 (0.32-0.5)	0.41 (0.34-0.53)	0.41 (0.34-0.52)	.03
R ₅ − R ₂₀ [kPa/(L/s)]	0.07 (0.04-0.11)	0.07 (0.02-0.14)	0.11 (0.08-0.17)	0.14 (0.1-0.18)	<.01
X ₅ [kPa/(L/s)]	−0.1 (−0.13 to −0.07)	−0.11 (−0.16 to −0.05)	−0.15 (−0.21 to −0.11)	−0.19 (−0.22 to −0.15)	<.01
F _{res} (Hz)	14.17 (10.66-16.72)	15.87 (11.72-18.19)	17.35 (15.46-21.06)	18.17 (17.08-21.39)	<.01
AX (kPa/L)	0.4 (0.2-0.7)	0.56 (0.23-1.29)	0.9 (0.54-1.66)	1.15 (0.94-1.83)	<.01
FEF _{25%-75%} <65% predicted, n (%)	64 (25.1)	10 (62.5)	62 (100)	16 (100)	<.01

BMI, Body mass index; FEF_{50%}, forced expiratory flow at expiration of 50% of FVC; PEF, peak expiratory flow.

The data are described using mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables. P value is for 1-way ANOVA for 4 groups.

TABLE II. Correlation between spirometry and IOS parameters in patients with PPF (N = 255)

IOS parameter	FEV ₁ (% predicted)		FVC (% predicted)		PEF (% predicted)		FEF _{25%-75%} (% predicted)		FEF _{75%} (% predicted)		FEF _{50%} (% predicted)		FEF _{25%} (% predicted)	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
$R_5 - R_{20}$	-0.14*	.03	-0.21†	<.01	-0.11	.10	-0.13*	.04	0.26†	<.01	-0.15*	.01	-0.18†	<.01
X_5	0.13*	.03	0.11	.07	0.11	.09	0.15*	.02	-0.14*	.03	0.09	.15	0.08	.22
F_{res}	-0.22†	<.01	-0.27†	<.01	-0.11	.11	-0.21†	<.01	0.06	.34	-0.20†	<.01	-0.17†	<.01
AX	-0.16†	<.01	-0.22†	<.01	-0.14*	.04	-0.18†	<.01	0.22†	<.01	-0.16*	.01	-0.17†	<.01

FEF_{75%}, forced expiratory flow at expiration of 75% of FVC; FEF_{50%}, forced expiratory flow at expiration of 50% of FVC; FEF_{25%}, forced expiratory flow at expiration of 25% of FVC; PEF, peak expiratory flow.* $P < .05$.† $P < .01$.

Hz and the resonant frequency is AX, known as the “Goldman Triangle,”²² indicating an index related to respiratory compliance and small airways patency.²³ We evaluated the following IOS parameters: $R_5 - R_{20}$, reactance at 5 Hz (X_5), F_{res} , and AX. The morphology of R and X graphs was evaluated.

Statistical analysis

The distribution of variables was assessed by means of Kolmogorov-Smirnov goodness-of-fit test. Variables are expressed as mean $\pm$ SD or median (interquartile range). One-way ANOVA, Kruskal-Wallis test, and Pearson χ^2 test were used for comparisons. Pearson correlation coefficient (r) was used to examine relationships between measures. With FEF_{25%-75%} less than 65% as the threshold value for small airway disease, the receiver-operating characteristic curve method was used to plot the true-positive rate (sensitivity) as a function of the false-positive rate (1 – specificity) for different cutoff points of IOS parameters. A value of P less than .05 was considered significant.

RESULTS

Screening algorithm and demographic characteristics of the study population

Of the 627 individuals with respiratory symptoms and results from both the bronchodilator test and IOS, 278 were excluded (Figure 1). The remaining 349 patients were divided into 4 groups on the basis of airflow obstruction (FEV₁/FVC < 0.7) and BR. The 4 groups were as follows: nonobstructive $\pm$ BR and obstructive $\pm$ BR. In the nonobstructive group (271 of 349 [77.7%]), 255 patients had PPF without BR. The other 16 patients (16 of 271 [6%]) had BR. In the obstructive group, 62 patients had BR and 16 patients did not have BR (Figure 1).

Demographic characteristics are presented in Table I. When compared with the nonobstructive group, individuals in the obstructive group were more likely to be older and male, with a history of smoking and dyspnea. Patients in the nonobstructive group had better lung function and lesser small airway resistance. All patients in the obstructive group had SAD (100%). In contrast, in the nonobstructive group, 25.1% of patients without BR and 62.5% with BR had SAD (Table I). The between-group analysis of patients without BR in obstructive and nonobstructive groups is presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org and the analysis of patients in nonobstructive group is presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. The clinical diagnosis was made using chest X-ray, bronchodilator test, IOS, and allergen test, if indicated, and medication was given after the completion of the aforementioned tests. The data are presented in Table E3 in this article's Online Repository at www.jaci-inpractice.org.

Correlation between IOS and spirometric parameters

In symptomatic patients with PPF, the FEV₁ and FEF_{25%-75%} significantly correlated with IOS parameters (Table II). With SAD defined as FEF_{25%-75%} less than 65% predicted, the cutoffs for IOS-defined SAD were as follows: $R_5 - R_{20}$ greater than 0.07 kPa/(L/s), X_5 less than -0.12 kPa/(L/s), F_{res} greater than 14.14 Hz, and AX greater than 0.44 kPa/L. Among IOS parameters, F_{res} had a higher sensitivity (75.0%; area under the curve, 0.69) and X_5 a higher specificity (77.5%; area under the curve, 0.64) for diagnosing SAD (Table III and Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

TABLE III. Cutoff values of SAD-related IOS parameters in patients with PPF (N = 255)

IOS parameter	Cutoff value	Sensitivity (%)	Specificity (%)	LR (+)	LR (–)	AUC	Youden index	P value
$R_5 - R_{20}$	>0.07	62.5	59.7	1.55	0.63	0.62	0.22	<.01
X_5	<–0.12	46.9	77.5	2.08	0.69	0.64	0.24	<.01
F_{res}	>14.14	75.0	57.9	1.78	0.43	0.69	0.33	<.01
AX	>0.44	65.6	61.9	1.72	0.56	0.67	0.28	<.01

AUC, Area under curve; LR, likelihood ratio.

TABLE IV. Characteristics of healthy controls and symptomatic patients with PPF and SAD defined as $FEF_{25\%-75\%} < 65\%$ predicted (N = 43)*

Characteristic	Healthy controls (N = 43)	Symptomatic patients with PPF and SAD (N = 43)	P value
Age (y)	55 (42-63)	57 (46-66)	0.47
Sex: male, n (%)	21 (48.84)	21 (48.84)	1
Height (cm)	165 (159-172)	164 (156-170)	0.39
Smoking, n (%)	0 (0.00)	10 (23.26)	<0.01
FEV_1 (% predicted)	101.24 (94.12-108.52)	86.89 (82.05-92.25)	<0.01
FVC (% predicted)	101.14 (89.56-107.99)	92.94 (85.16-101.23)	0.02
$FEF_{25\%-75\%}$ (% predicted)	83.47 (72.65-100.07)	53.55 (45.71-59.26)	<0.01
$R_5 - R_{20}$ [kPa/(L/s)]	0.07 (0.04-0.09)	0.09 (0.05-0.15)	0.03
X_5 [kPa/(L/s)]	–0.09 (–0.13 to –0.07)	–0.11 (–0.14 to –0.08)	0.11
F_{res} (Hz)	13.14 (10.53-14.9)	15.33 (13.36-18.92)	<0.01
AX (kPa/L)	0.34 (0.16-0.57)	0.49 (0.28-1.05)	<0.01

The data are described using mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables.

*Matched by age and sex.

Comparison of patients with PPF and SAD with healthy controls

To highlight the unique characteristics of these symptomatic patients with PPF, we recruited 48 healthy subjects for comparison. An age- and sex-matched comparison between 43 healthy controls and symptomatic patients with PPF and SAD (defined by $FEF_{25\%-75\%} < 65\%$ predicted) is presented in Table IV. The spirometric values and most IOS parameters (except X_5) were different between symptomatic patients with PPF and SAD and healthy controls.

Association between SAD parameters and respiratory symptoms

Compared with $FEF_{25\%-75\%}$, $R_5 - R_{20}$, and X_5 , a cutoff value of greater than 14.14 Hz for F_{res} could detect more SAD in the nonobstructive group (Table V). As determined by F_{res} , X_5 , and $R_5 - R_{20}$, the incidence of symptoms, including wheezes and sputum, was significantly higher in those with SAD than in those without SAD. $FEF_{25\%-75\%}$ failed to identify differences (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

This study provides information on identifying patients with respiratory symptoms and PPF who may have SAD. When compared with $FEF_{25\%-75\%}$, $R_5 - R_{20}$, and X_5 , the IOS parameter F_{res} had improved sensitivity to detect SAD in the nonobstructive group. The incidence of symptoms including wheezes and sputum was significantly higher in those with SAD than in those without SAD determined by F_{res} , X_5 , and $R_5 - R_{20}$. Differences were not detected with $FEF_{25\%-75\%}$. The IOS parameters, particularly F_{res} , may be markers to detect distal

airway function, which might be affected by inflammation in early asthma, COPD, or dust/fumes exposure.

SAD, resulting from small airway inflammation and remodeling, is important in the pathogenesis of asthma and COPD.^{1,2} The presence of SAD is associated with increased disease severity, poorer symptom control, and risk of exacerbation.^{17,18,24,25} The spirometric parameter $FEF_{25\%-75\%}$ with the cutoff value of 65% predicted has been used to predict SAD,¹¹⁻¹³ and is considered an early marker of bronchial impairment in patients with seasonal allergic rhinitis.²⁶ It could be useful to predict bronchial hyperactivity in patients with allergic asthma and rhinitis.²⁷ However, the reproducibility and comparability of $FEF_{25\%-75\%}$ are limited when not adjusted by lung volume.¹⁴ Lung volume is largely influenced by inadequate effort in elderly and children.

IOS, an alternative technique to detect small airway resistance and elastance directly, is effort-independent and highly sensitive. This technique can be used in the diagnosis of asthma in young children²⁸ and COPD in geriatric patients,²⁹ and has the advantage of high sensitivity^{30,31} and good correlation to the spirometry parameters FEV_1 and $FEF_{25\%-75\%}$.³² In heavy smokers and patients with early-stage COPD, Su et al³³ demonstrated that F_{res} and $R_5 - R_{20}$ correlated well with small-airway morphological abnormalities assessed by endobronchial optical coherence tomography. Exposure to maternal smoking during pregnancy and adolescent smoking increase peripheral airway resistance measured by IOS indices.³⁴

However, it is not surprising that the correlation between spirometry and IOS parameters is not strong because spirometry is an effort-dependent measurement in contrast to effort-independent IOS. $R_5 - R_{20}$ is the only IOS parameter currently applied for the diagnosis of SAD.^{18,19} In this study, we provided the cutoffs for the other parameters— X_5 , F_{res} , and

TABLE V. Incidence of SAD defined by $FEF_{25\%-75\%}$ and IOS parameters

Small airway parameter	Nonobstructive group ($FEV_1/FVC \geq 0.7$)		Obstructive group ($FEV_1/FVC < 0.7$)	
	BR (–) (N = 255)	BR (+) (N = 16)	BR (–) (N = 62)	BR (+) (N = 16)
$FEF_{25\%-75\%} < 65\%$ predicted, n (%)	64 (25.1)	10 (62.5)	62 (100)	16 (100)
$R_5 - R_{20} > 0.07$, n (%)	127 (49.8)	7 (43.8)	50 (80.6)	14 (87.5)
$X_5 < -0.12$, n (%)	74 (29.0)	7 (43.8)	39 (62.9)	14 (87.5)
$F_{res} > 14.14$ Hz, n (%)	128 (50.2)	11 (68.8)	54 (87.1)	15 (93.8)
$AX > 0.44$, n (%)	111 (43.5)	10 (62.5)	51 (82.3)	15 (93.8)

AX—to consider the diagnosis of SAD because there is no criterion standard at present.

The previous cutoff value for SAD in patients who are exposed to dust/fumes¹⁹ and have COPD with different severity¹⁸ was $R_5 - R_{20}$ greater than 0.07 kPa/(L/s). In our study, with FEV_1/FVC less than 0.7 (obstructive group), 82.1% of patients had $R_5 - R_{20}$ greater than 0.07. In comparison to the nonobstructive group, the peripheral resistance $R_5 - R_{20}$ was significantly higher and the midexpiratory flow $FEF_{25\%-75\%}$ was significantly lower. Our results were different from those reported by Crisafulli et al¹⁸ who reported that 73.8% of all patients with COPD have SAD as defined by $R_5 - R_{20}$ greater than 0.07.

However, in the study designed to detect early COPD, self-reported symptoms were associated with higher values of $R_5 - R_{20}$, X_5 , and AX among subjects with or without COPD. These results are consistent with our report, suggesting that IOS may detect SAD associated with COPD earlier than spirometry.³⁵

SAD has been associated with excessive bronchoconstriction, presented as wheezing, in patients with asthma.³⁶ Van der Wiel et al³⁷ reported that higher scores on wheezing were significantly associated with higher values of IOS parameters, including $R_5 - R_{20}$ and AX. These results are compatible with our finding that $R_5 - R_{20}$, X_5 , F_{res} , and AX were significantly correlated with symptoms of wheezing and sputum production. Furthermore, in male smokers without or with mild COPD, airway wall thickening determined by computed tomography was associated with more wheezing and lower FEV_1 ,³⁸ suggestive of SAD.

Among the IOS parameters, F_{res} has the best diagnostic performance in comparison to $R_5 - R_{20}$, X_5 , and AX. While F_{res} was set at 14.14 Hz determined by the receiver-operating characteristic curve method, the incidence of SAD in the nonobstructive group was 51.3% compared with 49.4% determined by $R_5 - R_{20}$ greater than 0.07, 29.9% by X_5 less than -0.12 , and 44.6% by AX greater than 0.44. Resonant frequency had the highest sensitivity to detect SAD in the obstructive group. In addition, F_{res} had better correlation to FEV_1 and $FEF_{25\%-75\%}$ when compared with the other IOS parameters, suggesting that F_{res} could be a promising marker to detect distal airway function.

Our study had several limitations. First, there is no criterion standard to diagnose SAD. The SAD in symptomatic patients with or without airway obstruction was defined by $FEF_{25\%-75\%}$ and IOS parameters. The sensitivity and specificity of IOS parameters were measured with SAD defined by $FEF_{25\%-75\%}$ less than 65% predicted. Second, this was a retrospective study and subjects may have had early asthma, COPD, bronchitis, or exposure to smoke or dust/fumes. The causes of SAD were heterogeneous, which might reflect the variation in IOS

parameters. Third, respiratory symptoms were recorded as categorical variables rather than continuous variables using the St George's Respiratory Questionnaire or COPD assessment tests. For example, either dyspnea at rest or dyspnea with exercise was captured as symptom "dyspnea" from the medical record of the outpatient department. Finally, we did not have treatment responses for IOS-defined SAD. The next step required is to investigate the pathogenesis of these SADs and to determine the patients' response to what kind of treatment and the improvement in IOS parameters.

CONCLUSIONS

This study provides reference values of IOS parameters, and the IOS parameter F_{res} is more sensitive than $FEF_{25\%-75\%}$ to detect SAD. Patients with respiratory symptoms and PPF may have SAD, which can be diagnosed with IOS in addition to spirometry.

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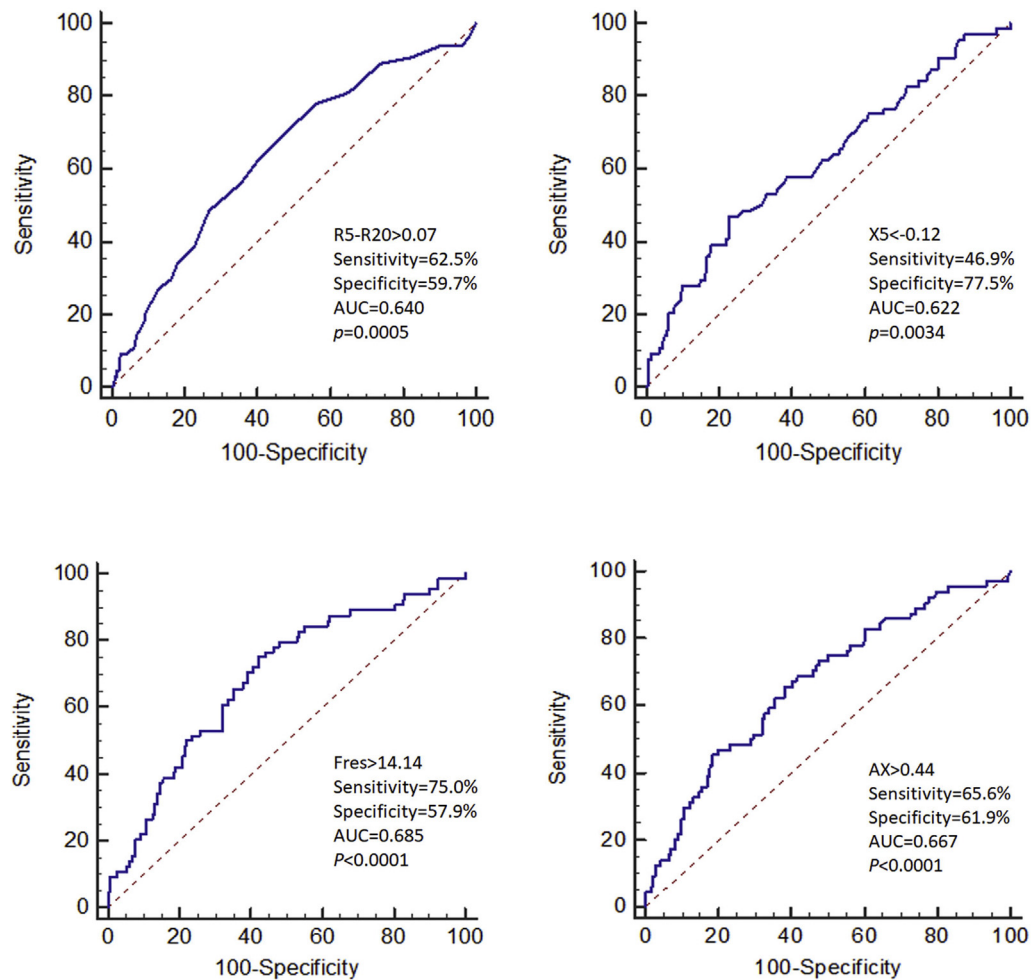


FIGURE E1. Small airway dysfunction defined by $FEF_{25-75\%} < 65\%$ predicted detected by impulse oscillometry (IOS) parameters. AUC, Area under curve.

TABLE E1. Between-group analysis with Scheffe method in patients without BR

Characteristic	Nonobstructive group (N = 255)	Obstructive group (N = 62)	P value
Age (y)	53 ± 16.1	68.2 ± 9.7	<.01
Height (cm)	163.9 ± 8.9	161.8 ± 8	.40
Weight (kg)	67 ± 13.7	64.1 ± 11.4	.47
BMI (kg/m ²)	24.9 ± 4.3	24.4 ± 3.7	.81
Sex: male, n (%)	133 (52.2)	44 (71)	.01
Smoking, n (%)	87 (34.1)	32 (51.6)	.01
Symptoms, n (%)			
Wheeze	34 (13.3)	3 (4.8)	.06
Cough	180 (70.6)	42 (67.7)	.66
Sputum	120 (47.1)	36 (58.1)	.12
Dyspnea	119 (46.7)	42 (67.7)	<.01
Chest tightness	91 (35.7)	17 (27.4)	.22
Pulmonary function test			
FEV ₁ /FVC	0.82 ± 0.06	0.6 ± 0.09	<.01
FEV ₁ , % predicted	99.87 ± 12.36	80.12 ± 14.4	<.01
FVC, % predicted	97.13 ± 11.06	99.5 ± 12.08	.53
PEF, % predicted	90.6 ± 17.78	64.93 ± 17.72	<.01
FEF _{25%-75%} , % predicted	82.09 ± 25.65	29.89 ± 9.3	<.01
FEF _{50%} , % predicted	96.54 ± 30.17	35.62 ± 12.03	<.01
R ₅ – R ₂₀ [kPa/(L/s)]	0.08 ± 0.07	0.14 ± 0.11	<.01
X ₅ [kPa/(L/s)]	–0.1 ± 0.06	–0.18 ± 0.13	<.01
F _{res} (Hz)	14.59 ± 5.66	18.53 ± 5.41	<.01
AX (kPa/L)	0.56 ± 0.54	1.32 ± 1.24	<.01

BMI, Body mass index; FEF_{50%}, forced expiratory flow at expiration of 50% of FVC; PEF, peak expiratory flow.

The data are described using mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables.

TABLE E2. Between-group analysis with Scheffe method in patients without airflow limitation

Characteristic	BR (–) (N = 255)	BR (+) (N = 16)	P value
Age (y)	53 ± 16.1	57.6 ± 19.1	0.72
Height (cm)	163.9 ± 8.9	161.7 ± 7.3	0.80
Weight (kg)	67 ± 13.7	66.9 ± 10.4	1.00
BMI (kg/m ²)	24.9 ± 4.3	25.5 ± 3.4	0.94
Sex: male, n (%)	133 (52.2)	7 (43.8)	0.51
Smoking, n (%)	87 (34.1)	4 (25)	0.45
Symptoms, n (%)			
Wheeze	34 (13.3)	0 (0)	0.12
Cough	180 (70.6)	12 (75)	0.71
Sputum	120 (47.1)	8 (50)	0.82
Dyspnea	119 (46.7)	5 (31.3)	0.23
Chest tightness	91 (35.7)	4 (25)	0.39
Pulmonary function test			
FEV ₁ /FVC	0.82 ± 0.06	0.77 ± 0.06	0.05
FEV ₁ , % predicted	99.87 ± 12.36	86.86 ± 14.26	<0.01
FVC, % predicted	97.13 ± 11.06	87.74 ± 6.22	0.02
PEF, % predicted	90.6 ± 17.78	75.53 ± 12.53	0.01
FEF _{25%-75%} , % predicted	82.09 ± 25.65	59.34 ± 28.39	<0.01
FEF _{50%} , % predicted	96.54 ± 30.17	66.83 ± 25.14	<0.01
R ₅ – R ₂₀ [kPa/(L/s)]	0.08 ± 0.07	0.09 ± 0.08	0.99
X ₅ [kPa/(L/s)]	–0.1 ± 0.06	–0.11 ± 0.07	0.95
F _{res} (Hz)	14.59 ± 5.66	15.05 ± 4.72	0.99
AX (kPa/L)	0.56 ± 0.54	0.73 ± 0.61	0.85

BMI, Body mass index; FEF_{50%}, forced expiratory flow at expiration of 50% of FVC; PEF, peak expiratory flow.

The data are described using mean (SD) for normally distributed variables and median (interquartile range) for nonnormally distributed variables.

TABLE E3. Clinical diagnoses of the participants

Diagnosis	Nonobstructive group (FEV ₁ /FVC ≥ 0.7)		Obstructive group (FEV ₁ /FVC < 0.7)	
	BR (–) (N = 255)	BR (+) (N = 16)	BR (–) (N = 62)	BR (+) (N = 16)
Allergy history, n (%)	39 (15.3)	6 (35.7)	8 (12.9)	2 (12.5)
Allergic rhinitis, n (%)	108 (42.4)	7 (43.8)	21 (33.9)	8 (50)
Clinical diagnosis, n (%)				
Bronchitis	104 (40.8)	3 (18.8)	2 (3.2)	1 (6.3)
Asthma	122 (47.8)	10 (62.4)	28 (45.2)	6 (37.4)
COPD		3 (18.8)	27 (43.5)	4 (25)
ACO			5 (8.1)	5 (31.3)
Other diagnosis	29 (11.4)	0	5 (8.1)	5 (31.3)

ACO, Asthma-COPD overlap.

Other diagnoses include allergic rhinitis, gastroesophageal reflux disease, and upper respiratory tract infection.

TABLE E4. Respiratory symptoms and SAD detected by different parameters in patients with PPF

Parameter	SAD (–)	SAD (+)	P value
FEF _{25%-75%} < 65% predicted	191	64	
Wheeze, n (%)	23 (12.0)	11 (17.2)	.30
Cough, n (%)	136 (71.2)	44 (68.8)	.71
Sputum, n (%)	88 (46.1)	32 (50)	.59
Dyspnea, n (%)	86 (45.0)	33 (51.6)	.36
FEF _{50%} < 60% predicted	226	29	
Wheeze, n (%)	28 (12.4)	6 (20.7)	.22
Cough, n (%)	160 (70.8)	20 (69.0)	.84
Sputum, n (%)	103 (45.6)	17 (58.6)	.19
Dyspnea, n (%)	103 (45.6)	16 (55.2)	.33
R ₅ – R ₂₀ > 0.07 [kPa/(L/s)]	128	127	
Wheeze, n (%)	11 (8.6)	23 (18.1)	.03
Cough, n (%)	86 (67.2)	94 (74.0)	.23
Sputum, n (%)	51 (39.8)	69 (54.3)	.02
Dyspnea, n (%)	55 (43.0)	64 (50.4)	.24
X ₅ < –0.12 [kPa/(L/s)]	181	74	
Wheeze, n (%)	17 (9.4)	17 (23)	<.01
Cough, n (%)	124 (68.5)	56 (75.7)	.25
Sputum, n (%)	77 (42.5)	43 (58.1)	.02
Dyspnea, n (%)	83 (45.9)	36 (48.6)	.69
F _{res} > 14.14 Hz	126	128	
Wheeze, n (%)	7 (5.6)	27 (21.1)	<.01
Cough, n (%)	87 (69)	93 (72.7)	.53
Sputum, n (%)	51 (40.5)	69 (53.9)	.03
Dyspnea, n (%)	54 (42.9)	65 (50.8)	.21
AX > 0.44 kPa/L	142	111	
Wheeze, n (%)	13 (9.2)	21 (18.9)	.02
Cough, n (%)	101 (71.1)	78 (70.3)	.88
Sputum, n (%)	59 (41.5)	61 (55)	.03
Dyspnea, n (%)	63 (44.4)	56 (50.5)	.34