ORIGINAL ARTICLE

Airway Reactance Predicts Static Lung Hyperinflation in Severe Asthma

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Abstract

Background: Static lung hyperinflation (SLH) measured using body plethysmography in patients with asthma is associated with poor outcomes. The severity of SLH may be associated with small airway dysfunction (SAD), which can be measured using impulse oscillometry (IOS).
Objective: This study aims to determine the correlation between SLH and SAD in patients with severe asthma and assess the improvement in SLH and SAD with treatment.
Methods: We analyzed data from patients who were enrolled in the Taiwan Severe Asthma Registry, which comprises a prospective observational cohort. Plethysmography and IOS were performed regularly. The relationship between spirometry and IOS parameters was determined. Changes in the clinical outcomes in response to treatment were analyzed.
Results: Of 107 patients with severe asthma, 83 (77.6%) had SLH based on an increased residual volume to total lung capacity ratio (RV/TLC). Most patients were older women with worse pulmonary function and SAD than those without SLH. SAD, defined as increased airway resistance/reactance, was significantly correlated with SLH. Airway reactance at 5 Hz (X_5) ≤−0.21 kPa/(L/s) detected SLH with an area under the receiver operating characteristic curve of 0.84 (P<.0001; sensitivity, 85.2%; and specificity, 83.3%). After 12 months, patients who received add-on biologics (vs those who did not) had significantly reduced exacerbations, fractional exhaled nitric oxide level, and blood eosinophil counts, as well as improved forced expiratory volume in the first second, X_5, and a trend toward reduced RV/TLC ratio.
Conclusion: In severe asthma, airway reactance (X_5) could be a novel parameter for assessing SLH.

Key words: Body plethysmography. Impulse oscillometry. Static lung hyperinflation. Severe asthma.

Resumen

Antecedentes: En el asma bronquial, la hiperinsuflación pulmonar estática (SLH) medida mediante pletismografía corporal (Pleth) se asocia a un peor pronóstico. La gravedad de la SLH podría estar asociada con la disfunción de las vías respiratorias pequeñas (SAD), que puede medirse mediante la oscilometría de impulsos (IOS).
Objetivo: Este estudio pretende determinar la correlación entre el SLH y la SAD en pacientes con asma grave, y la mejora de ambos parámetros en respuesta al tratamiento.
Métodos: Se analizaron los datos de los pacientes que se inscribieron en el Registro de Asma Grave de Taiwán, una cohorte observacional prospectiva. Se realizaron periódicamente mediciones de Pleth e IOS. Se determinó la relación entre los parámetros espirométricos e IOS. Se analizaron los cambios en los parámetros clínicos y funcionales en respuesta al tratamiento.
Resultados: De una muestra de 107 pacientes con asma grave, 83 (77,6%) presentaban SLH, definida mediante una relación volumen residual/capacidad pulmonar total (VR/CTP) aumentada. La mayoría de los pacientes eran mujeres de edad avanzada con peor función pulmonar y SAD, en comparación con los que no tenían SLH. El SAD por aumento de la resistencia/reactancia de las vías respiratorias se correlacionó significativamente con el SLH. La reactancia de las vías respiratorias a 5 Hz (X5) ≤-0,21 [kPa/(L/s)] detectó el SLH con un área bajo la curva ROC de 0,84 (p < 0,0001, sensibilidad = 85,2% y especificidad = 83,3%). Después de 12 meses, los pacientes que recibieron tratamiento biológico adicional presentaron una reducción significativa de las exacerbaciones, del nivel de óxido nítrico exhalado, del recuento de eosinófilos en sangre, una mejora del volumen espiratorio forzado en el primer segundo, de la X5, y una tendencia a la reducción del cociente RV/TLC en comparación con los que no recibieron tratamiento biológico.
Conclusiones: En el asma grave, la reactancia de la vía aérea X5 podría ser un parámetro novedoso para evaluar el SLH.

Palabras clave: Pletismografía corporal. Oscilometría de impulsos. Hiperinsuflación pulmonar estática. Asma grave.

Summary box

- **What do we know about this topic?**
  Small airway dysfunction (SAD), such as static lung hyperinflation (SLH), is associated with poor outcomes in patients with asthma. Impulse oscillometry (IOS) evaluates SAD in an effort-independent manner that is more patient-friendly than body plethysmography.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  Airway reactance (X_5), an IOS parameter, could be used to access SLH in patients with severe asthma.

Introduction

Asthma is characterized by chronic airway inflammation and remodeling that mainly involves the small airways [1-3]. Small airway dysfunction (SAD) can be detected using various methods [4]. Up to 90.7% of asthma patients have SAD, with increased prevalence in more severe disease [5,6]. In addition, SAD in asthma is associated with poor symptom control, more frequent exacerbations, and increased use of oral corticosteroids [5,6]. A recent study from Severe Asthma Research Program-3 showed that SAD is associated with future lung function decline in patients with severe asthma [7].

Asthma patients with static lung hyperinflation (SLH) more frequently experience wheezing and require rescue medication [8]. Emerging evidence shows that SLH determined based on increased low-attenuation areas in computed tomography (CT) images is associated with fixed airflow limitation, accelerated decline in forced expiratory volume in the first second (FEV_1), and future exacerbation in asthma, suggesting its impact on airway remodeling and parenchymal destruction [7,9]. SLH is defined as an increased volume of air trapped in the lung at the end of expiration due to the premature closure of the small airways, which is more commonly determined based on an increased residual volume to total lung capacity ratio (RV/TLC) in body plethysmography [10,11]. A previous study showed the RV/TLC ratio to be negatively correlated with FEV_1 in adult patients with obstructive lung disease [12]. In a previous study, we observed that increased small airway resistance and reactance are significantly associated with lower FEV_1 [13]. The relationship between hyperinflation and small airway function deserves further investigation.

Body plethysmography, which is used to measure lung volume, expiratory flow, and airway resistance, is effort-dependent and requires the patient's cooperation with forced expiration. The technique may prove challenging for asthma patients who are elderly or have poor lung function. Impulse oscillometry (IOS) is based on an oscillation technique that measures lung mechanics in an effort-independent manner by applying different sound waves at various frequencies to assess airway resistance and reactance during tidal breathing [14-18]. SAD has been reported to be associated with important asthma outcomes, such as asthma control and exacerbation [19]. Compared with spirometry, IOS is more sensitive in identifying SAD in asthma [5,20]. Nevertheless, it remains uncertain whether IOS is a candidate for evaluating SLH in patients with severe asthma.

In this observational study of patients with severe asthma, we aimed to determine the relationship between hyperinflation and small airway function. Changes in small airway function and hyperinflation after treatment based on Global Initiative for Asthma (GINA) guidelines [21] were also assessed.

Methods

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (IRB-TPEVGH No.: 2019-07-035CC and 2022-04-007AC) and conducted at Taipei Veterans General Hospital.

Study Design and Patients

We enrolled adult patients (≥20 years old) with severe asthma who underwent body plethysmography and IOS at the outpatient clinic of Taipei Veterans General Hospital from July 2019 to September 2021. All patients were enrolled in the Taiwan Severe Asthma Registry, which is a prospective observational cohort approved by the hospital's IRB. Severe asthma is defined according to the guidelines of the European Respiratory Society and the American Thoracic Society (ERS/ATS) [22]. All patients required steps 4-5 of treatment as recommended by the GINA report [21], including medium- or high-dose maintenance inhaled corticosteroids (ICS) and long-acting ß-2 agonist (LABAs) with or without add-on long-acting muscarinic antagonists (LAMAs) or leukotriene modifier/theophylline or maintenance oral corticosteroids. The exclusion criteria included the following: age younger than 20 years; mild-to-moderate persistent asthma co-occurring with chronic obstructive pulmonary disease (COPD) or other pulmonary diseases; stage IV lung cancer, or end-stage malignancy; need for long-term oxygen for more than 15 hours a day or noninvasive positive-pressure ventilation support for a least 6 hours a day; active tuberculosis or other infectious diseases; and inability to complete the consent form.

IOS, Body Plethysmography, and Spirometry

The protocols for IOS, body plethysmography, and spirometry have been described in detail elsewhere [23]. In brief, patients underwent IOS based on the manufacturer's standardized protocol (Jaeger MS-IOS) and recommendations from the ERS [14,15]. Confounding factors, such as cheek vibration or air escaping from the nose, were addressed using

nasal clips and manual cheek compression. The patients were asked to breath tidally for 30 to 45 seconds without tongue interposition or glottis contraction during activation of the loudspeaker. The loudspeaker released around 120 to 150 pulses with a frequency ranging from 5 to 35 Hz during the test and superimposed normal tidal breathing. For avoidance of the effect of forced expiration, IOS was performed before body plethysmography and spirometry [15]. Body plethysmography and spirometry were conducted using standard procedures, and the results were interpreted according to ATS/ERS strategies [24-27]. Data were analyzed using 2 flow-sensing spirometers, each linked to a computer (Jaeger MS-IOS and Vmax 22 SensorMedics). For assessment of the bronchodilator response (BDR), patients were requested to avoid inhaled bronchodilators for 12 hours before the test. During the bronchodilator test, spirometry was performed before and 15 minutes after inhalation of 400 µg of salbutamol (a short-acting ß-2 agonist [SABA]). A positive BDR result was defined as an increase in FEV_1 or FVC of more than 12% and 200 mL from baseline in response to a SABA [24]. All devices were calibrated twice daily, and 2 independent pulmonologists were responsible for assuring the quality of the tests. SLH is defined as an RV/TLC ratio of more than 0.4 [11].

Data Collection

The variables collected at baseline included age, sex, body mass index (BMI), smoking status, duration of asthma diagnosis, age of onset of asthma, comorbidities, medication, exacerbation history, Asthma Control Test (ACT) score, blood

Table 1. Baseline Characteristics of the Study Patients.[a]

	Total (n = 107)	Patients with SLH (n = 83)	Patients without SLH (n = 24)	*P* Value[b]
Female, No. (%)	64 (59.8)	56 (67.5)	8 (33.3)	.0028
Age, y	68 (55-77)	70 (61-78)	50 (40-65)	<.0001
BMI, kg/m^2	25.2 (22.8-27.9)	25.2 (22.5-28.0)	25.3 (23.0-27.4)	.9464
Ever-smoker, No. (%)	26 (24.3)	19 (22.9)	7 (29.25)	.5298
Duration of asthma, y	17.0 (6.8-34.0)	16.5 (6.0-40.0)	17.0 (7.0-31.5)	.8072
Late-onset asthma, No. (%)[c]	65 (60.7)	57 (68.7)	8 (33.3)	.0019
Atopy, No. (%)[d]	27 (25.2)	17 (20.5)	10 (41.7)	.0348
Comorbidities, No. (%)				
Allergic rhinitis	15 (14.0)	10 (12.0)	5 (20.8)	.2754
CRS	12 (11.2)	7 (8.4)	5 (20.8)	.0903
CRSwNP	4 (3.7)	2 (2.4)	2 (8.3)	.1784
GERD	37 (34.6)	30 (36.1)	7 (29.2)	.5268
OSAS	6 (5.6)	5 (6.0)	1 (4.2)	.7279
Anxiety	3 (2.8)	1 (1.2)	2 (8.3)	.0622
ACT score	22 (18-24)	22 (18-24)	22 (17-23)	.4391
≥1 exacerbation/year, No. (%)	70 (65.4)	51 (61.4)	19 (79.2)	.1082
Annual number of exacerbations	1 (0-2)	1 (0-2)	1 (1-3)	.1062
Medication				
Medium or high dose ICS/LABA/LAMA, No. (%)	82 (76.6)	63 (75.9)	19 (79.2)	.7389
OCS, NO. (%)	43 (40.2)	30 (36.1)	13 (54.2)	.1129
Biologics, No. (%)	46 (43.0)	35 (42.2)	11 (45.8)	.7506
FeNO, ppb	30 (18-60)	32.5 (17-66)	29 (21.5-39.5)	.5113
Blood eosinophils/µL	205 (98-338)	193 (102-356)	230 (92-304)	.9494

Abbreviation: ACT, Asthma Control Test; BMI, body mass index; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; ICS/LABA/LAMA, inhaled corticosteroid, long-acting ß-2 agonist and long-acting muscarinic antagonist combination therapy; OCS, oral corticosteroid; OSAS: obstructive sleep apnea syndrome; SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4

[a]Data are shown as No. (%) for categorical variables and median (IQR) for nonnormally distributed variables.

[b]*P*<.05 (Mann-Whitney), statistically significant.

[c]Late-onset asthma, defined as age of asthma onset ≥40 years old.

[d]Atopy, defined as an increase in total IgE >100 U/mL or a positive Phadiatop test result (>0.35 PAU/L)

eosinophil counts, fractional exhaled nitric oxide (FeNO), and peak expiratory flow rate (PEFR). We also recorded IOS parameters, including resistance at 5 Hz (R_5), the difference between resistance at 5 and 20 Hz (R_5-R_{20}), reactance at 5 Hz (X_5), resonant frequency (F_{res}), and area under the reactance curve between 5 Hz and resonant frequency (AX). The percent predicted values of IOS parameters were also calculated [28]. Spirometry data, including FEV_1, FVC, and forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$), were obtained from the flow-volume curve, and RV and TLC were calculated based on the volume-time curve in body plethysmography. We also collected data from patients who completed 12 months of follow-up to compare changes in these clinical parameters in response to treatment with or without biologics.

Statistical Analysis

The distribution of the variables was assessed using the Kolmogorov-Smirnov goodness-of-fit test. Continuous variables are shown as mean (SD) or median (IQR) according to their distribution. For the different groups, the *t* test was

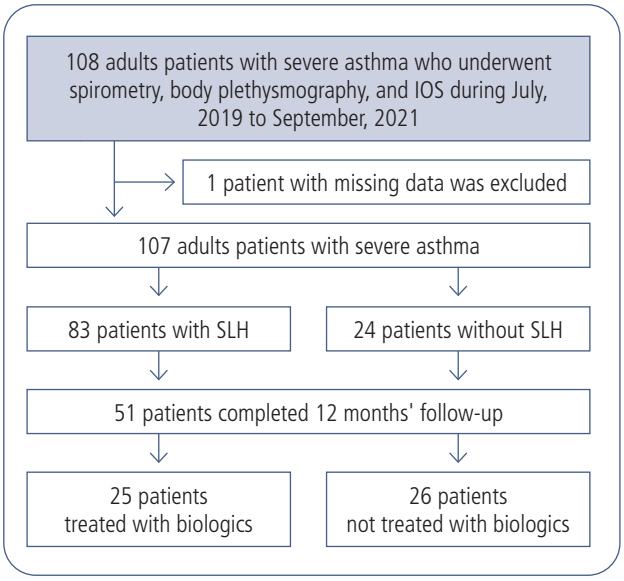

Figure 1. Flow chart of the study population. IOS indicates impulse oscillometry; SLH, static lung hyperinflation.

Table 2. Baseline Pulmonary Function Data of the Study Patients.[a]

	Total (n = 107)	Patients with SLH (n = 83)	Patients without SLH (n = 24)	*P* Value[b]
PEFR, (L/min)	250 (180-345)	220 (170-300)	340 (20-470)	<.0001
Spirometry				
FEV_1/FVC, %	62.9 (55.3-72.6)	62.1 (55.1-70.3)	69.8 (60.0-80.2)	.0358
FEV_1, % predicted	64.7 (52.9-78.3)	61.0 (49.8-70.0)	85.6 (66.1-95.1)	.0001
FVC, % predicted	79.3 (69.6-88.6)	61.0 (49.8-70.0)	85.6 (66.1-95.1)	.0001
$FEF_{25-75\%}$, % predicted	27.4 (18.6-48.6)	24.0(18.0-39.5)	46.0(22.4-74.0)	.0109
BDR (+), No. (%)	19 (17.8)	14 (16.9)	5 (20.8)	.6543
TLC, % predicted	98.5 (91.5-113)	98.0 (90.0-113.5)	105.5 (93.5-110.5)	.4090
RV/TLC	0.50 (0.42-0.57)	0.52 (0.46-0.58)	0.37 (0.34-0.38)	<.0001
Impulse oscillometry				
R_5, kPa/(L/s)	0.51 (0.42-0.67)	0.55 (0.45-0.68)	0.43 (0.36-0.48)	<.0001
R_5, % predicted	165.2 (133.9-198.6)	174.0 (136.1-206.2)	139.2 (131.2-175.1)	.0749
R_5-R_{20}, kPa/(L/s)	0.17 (0.01-0.26)	0.19 (0.13-0.27)	0.10 (0.07-0.15)	.0003
R_5-R_{20}, % predicted	239.4 (165.4-360.2)	262.4 (164.5-367.7)	206.8 (165.4-308.3)	.4132
F_{res}, Hz	19.91 (18.90-20.92)	20.2 (17.4-23.3)	16.3 (14.0-18.9)	.0003
F_{res}, % predicted	136.3 (118.5-164.4)	133.7 (114.1-162.6)	150.3 (128.4-183.5)	.1012
X_5, kPa/(L/s)	-0.27 (-0.43 - -0.20)	-0.32 (-0.46 - -0.24)	-0.15 (-0.20 - -0.10)	<.0001
X_5, % predicted	245.6 (172.2-358.1)	265.5 (184.6-366.2)	173.1 (109.0-226.0)	<.0001
AX, kPa/L	1.79 (1.03-2.30)	2.09 (1.46-3.58)	0.77 (0.36-1.27)	< .0001
AX, % predicted	422.4 (246.5-700.2)	455.2 (259.4-801.2)	320.6 (201.9-602.4)	.2031

Abbreviations: AX, area under the reactance curve between 5 Hz and resonant frequency; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC of more than 12% and 200 mL over baseline in response to a short-acting ß-2 agonist; F_{res}, resonant frequency; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of FVC; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4; X_5, reactance at 5 Hz.

[a]Data are shown as number (%) for categorical variables and median (interquartile range, IQR) for nonnormally distributed variables.

[b]*P*<.05 (Mann-Whitney), statistically significant.

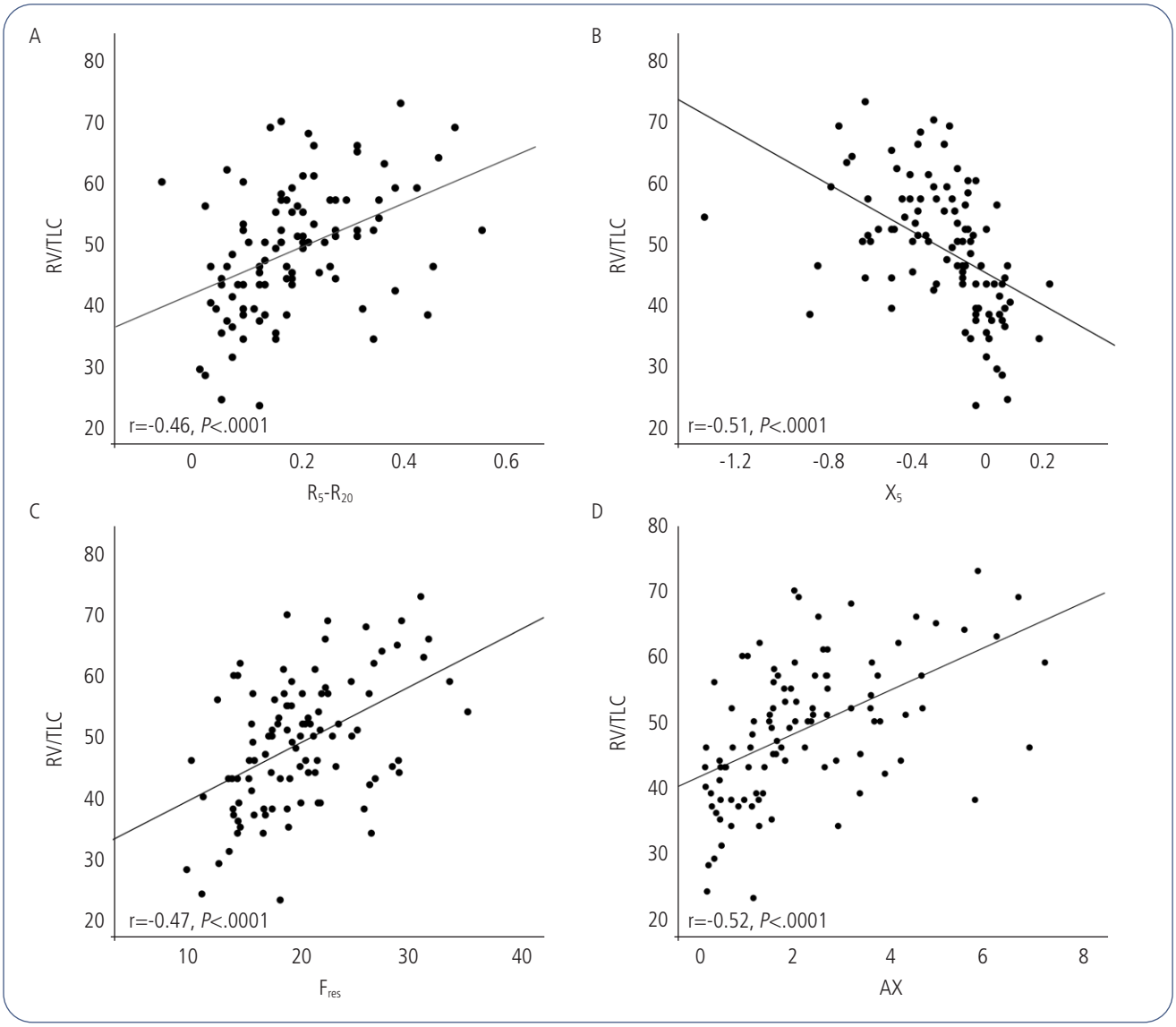

Figure 2. Correlations between RV/TLC and impulse oscillometry parameters including difference between resistance at 5Hz and 20Hz (R_5-R_{20}) (A), reactance at 5 Hz (X_5) (B), resonant frequency (F_{res}) (C), area under reactance curve between 5 Hz and resonant frequency (AX) (D). RV indicates residual volume; TLC, total lung capacity.

performed to compare normally distributed variables and the Mann-Whitney test was used to compare nonnormally distributed data. The Pearson χ^2 test was applied to compare the categorical variables, which were expressed as number and percentage. Changes in clinical parameters from baseline to 12 months' follow-up were assessed using the McNemar test and the Wilcoxon signed-rank test for categorical and continuous variables, respectively. The Spearman rank correlation coefficient (rs) was used to examine relationships between variables. To determine the capability of IOS parameters for detecting the outcome of SLH, we constructed the receiver operating characteristic (ROC) curve and calculated the optimal cut-off value with the Youden index to determine the outcome of SLH. A 2-tailed *P* value of <.05 was considered significant. All analyses were carried out using SPSS (IBM Corp.) Version 25.0 and MedCalc Statistical Software version 20.009 (MedCalc Software bv).

Results

Baseline Patient Characteristics

The study enrolled a total of 107 patients with severe asthma (Figure 1). Table 1 shows the baseline characteristics of the study patients. Most were female (59.8%), and the median age was 68 years, with a BMI of 25.2 kg/m^2. Ever-smokers accounted for 24.3%. Asthma had been diagnosed a mean of 17 years previously and was late-onset in 60.7% [21,29]. Atopy was recorded in 25.2% of patients [30], allergic rhinitis in 14%, chronic rhinosinusitis in 11.2%, chronic rhinosinusitis

with nasal polyps in 3.7%, gastroesophageal reflux disease in 34.6%, obstructive sleep apnea syndrome in 5.6%, and anxiety in 2.8%. The median ACT score was 22, and 65.4% of patients had had at least 1 exacerbation in the previous year. As for therapy, 76.6% patients took ICS/LABA/LAMA combination therapy, 40.2% patients took oral corticosteroids, and 43.0% of patients received biologics. Median FeNO was 30 ppb, and the median blood eosinophil count was 205/μL. These patients were categorized into patients with and without SLH according to their RV/TLC ratio [11].

Most patients with severe asthma (n=83, 77.6%) had SLH and appeared to be older, with more females and late-onset asthma and less atopy than patients without SLH. No differences between groups were observed for the remaining characteristics.

Baseline Pulmonary Function Data

Table 2 shows the baseline pulmonary function data. The medium PEFR was 250 L/min, and the baseline FEV_1/FVC ratio, FEV_1 (% predicted), FVC (% predicted), $FEF_{25-75\%}$, and RV/TLC ratio were 62.9%, 64.7%, 79.3%, 27.4%, and 0.50 respectively. Compared to patients without SLH, those with SLH had significantly lower PEFR, FEV_1/FVC, FEV_1 (% predicted), FVC (% predicted), and $FEF_{25-75\%}$ and a higher RV/TLC ratio.

Baseline R_5, R_5-R_{20}, F_{res}, X_5, and AX were 0.51, 0.17, 19.91, −0.27, and 1.79, respectively. Similarly, the absolute values of IOS parameters and % predicted of X_5 were significantly worse in patients with SLH than in those without SLH.

To elucidate the effect of age and sex, we analyzed the characteristics of patients with and without SLH matched by age and sex from our cohort (Table S1 in the Supplementary Material). A random number table was used to select patients from 2 groups for matching. First, we performed a 1:1 match by sex, with the result that 24 patients from each group (8 females and 16 males) were selected. Then, patients were randomly selected on a 10-year grading scale by sex, which resulted in 15 patients from each group (Table S1). The results still showed that patients with SLH had an increased RV/TLC ratio and poorer FVC than those without SLH. Of note, the IOS parameter X_5 (both absolute value and % predicted) was significantly worse in patients with SLH than in those without SLH.

Correlation Between RV/TLC Ratio and IOS Measurements

Figure 2 shows that the absolute value of IOS parameters correlated moderately with the RV/TLC ratio: the Spearman rank correlation coefficient (rs) of R_5-R_{20}, X_5, F_{res}, and AX was 0.48, –0.61, 0.45, and 0.57, respectively (all *P* values <.0001). Figure S1 shows that among the IOS parameters presented as % predicted, only X_5 still correlated moderately with the RV/TLC ratio (rs=0.46, *P*<.0001). Figure S3 demonstrates the correlations between the RV/TLC ratio and both absolute value and % predicted for R_5 and R_{20}. Similarly, the correlations were all weaker than those of X_5, both in absolute value (rs=–0.61) and in % predicted (rs= 0.46).

ROC Curve Analysis and Optimal Cut-off Value

Figure 3 and Table 3 demonstrate the ability of IOS parameters to detect SLH, as calculated by ROC curve analysis, yielding areas under the curve (AUC) of 0.84, 0.80, 0.75, and 0.74 for X_5, AX, R_5-R_{20}, and F_{res}, respectively (all

Table 3. Performance of Different IOS Parameters to Detect SLH in Patients With Severe Asthma.

Variables	Cut-off value	Sensitivity, %	Specificity, %	LR (+)	LR (–)	AUC (95%CI)	Youden Index	*P* Value
X_5, kPa/(L/s)	≤–0.21	85.2	83.3	5.11	0.18	0.84 (0.76-0.91)	0.69	<.0001
X_5, % predicted	>189.39	75.9	75.0	3.04	0.32	0.77 (0.68-0.85)	0.51	<.0001
AX, kPa/L	>1.35	76.5	83.3	4.59	0.28	0.80 (0.71-0.87)	0.60	<.0001
AX, % predicted	>384.67	60.2	66.7	1.81	0.60	0.61 (0.52-0.71)	0.27	.0976
R_5-R_{20}, kPa/(L/s)	>0.16	66.3	83.3	3.98	0.41	0.75 (0.65-0.83)	0.50	<.0001
R_5-R_{20}, % predicted	>224.89	60.2	70.8	2.07	0.56	0.62 (0.52-0.71)	0.31	.1023
F_{res}, Hz	>16.9	79.0	62.5	2.11	0.34	0.74 (0.65-0.82)	0.42	<.0001
F_{res}, % predicted	≤154.01	74.4	45.83	1.38	0.55	0.59 (0.49-0.68)	0.21	.1612

Abbreviations: AUC, area under the receiver operating characteristic curve; AX, area under reactance curve between 5 Hz and resonant frequency; IOS, impulse oscillometry; LR (+), positive likelihood ratio; LR (–), negative likelihood ratio; SLH, static lung hyperinflation, defined as the ratio of residual volume (RV) to total lung capacity (TLC) ratio more than 0.4; R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; F_{res}, resonant frequency; X_5, reactance at 5 Hz.

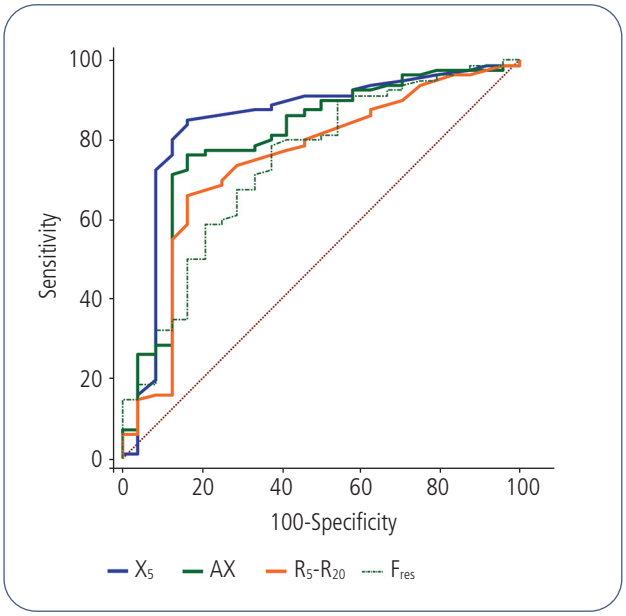

Figure 3. Receiver operating characteristic curve analysis of impulse oscillometry parameters to detect static lung hyperinflation (SLH) in patients with severe asthma. R_5 indicates resistance at 5 Hz; R_{20}, resistance at 20 Hz; X_5, reactance at 5 Hz; F_{res}, resonant frequency; AX, area under the reactance curve between 5 Hz and resonant frequency.

P values <.0001). Of the 4 variables, X_5 performed best for detecting SLH. The optimal cut-off value of X_5 was −0.21 (kPa/[L/s]), with a sensitivity of 85.2% and a specificity of 83.3%. Figure S2 also showed that X_5 (% predicted) had the highest AUC (0.77) compared with other IOS parameters for detecting SLH. Figure S4 and Table S2 show the ROC curves and the abilities to detect SLH by both absolute value and % predicted values for R_5 and R_{20}. Similarly, the AUCs were all smaller than those of X_5, both in absolute value (AUC=0.84) and in % predicted value (AUC=0.77).

Baseline Characteristics of Patients With Severe Asthma Treated With and Without Biologics

Forty-six patients (43.0%) received biologics, including omalizumab (31 [67.4%]), mepolizumab (14 [30.4%]), and benralizumab (1 [2.2%]). The average time taking biologics before enrollment was 181.3 days (95%CI, 96.7-266.0). Table 4 shows that patients who received biologics had significantly lower BMI and ACT scores than those who did not. This group was also characterized by more ever-smokers, more patients with comorbid conditions (allergic rhinitis and anxiety), more acute exacerbations (AEs), and more frequent OCS use. The other clinical characteristics and pulmonary function data had no between-group differences.

Changes in Clinical Characteristics After 12 Months of Treatment With or Without Biologics

Table 5 shows that 51 patients completed 12 months' follow-up, including 38 patients (74.5%) with SLH and 13 patients (25.5%) without SLH. Twenty-five patients (49.0%) received biologics, including omalizumab (17 [68.0%]), mepolizumab (7 [28.0%]), and benralizumab (1 [4.0%]). The remaining 26 patients (51.0%) received standard treatment other than biologics according to the GINA guideline [21]. Patients who received biologics had significantly fewer AEs and lower FeNO and blood eosinophil levels. They also had improved values for the ACT score, FEV_1, and X_5. Finally, we observed a trend toward a lower RV/TLC ratio in patients who received biologics than in those who did not (*P*=.0520).

Discussion

In this study, a high percentage of patients with severe asthma had SLH. These patients were older, mainly female, and with worse airflow obstruction, poorer lung function, and increased small airway resistance and reactance than those without SLH. We demonstrated that airway reactance (X_5) measured by IOS can be applied to assess SLH in severe asthma with high sensitivity and specificity. This diagnostic measure could be an alternative to body plethysmography, which is effort-dependent and technically demanding. After 12 months of follow-up, the changes recorded in patients who received add-on biologics (vs those who did not) were as follows: significantly reduced exacerbations, FeNO, and blood eosinophil counts; improved asthma control, FEV_1, and X_5; and a trend toward a lower RV/TLC ratio.

The clinical characteristics of patients with SLH in our study were compatible with previous evidence indicating accelerated lung function decline and lower FEV_1 [7,12]. The consequences of SLH were shown to be associated with decreased inspiratory muscle function and exercise performance, more severe breathlessness, and impaired activities of daily living, regardless of asthma severity [31]. In severe emphysema, RV/TLC, an indicator of hyperinflation, was significantly correlated with 6-minute walking distance and symptom scores [32]. During the 6-minute walking test, patients with severe asthma had significantly reduced inspiratory capacity, similar to patients with COPD, indicating dynamic hyperinflation [33]. In addition, increased RV% predicted was associated with frequent albuterol use and wheezing in patients with persistent asthma, suggesting unrelieved air trapping [8]. Moreover, recent real-world evidence from the US CHRONICLE study, an observational cohort of US adults with severe asthma, showed that females experienced more exacerbations and poorer symptom control [34]. Another international multidatabase cohort study also demonstrated that patients with late-onset asthma were more frequently uncontrolled [35]. Taken together, our results highlighted that patients with severe asthma and SLH are an important phenotype requiring intensive management.

Similar to previous studies where SAD in asthma was associated with worse clinical outcomes [6,7], our data indicated that patients with SLH were characterized not only by poorer spirometry parameters, but also by more severe impaired small airway function measured by IOS. These functional parameters in the small airways (R_5-R_{20}, X_5, F_{res}, and AX) were significantly correlated with FEV_1 and FVC, as shown in our previous study [13]. In addition, increased airway resistance/reactance measured by IOS was significantly correlated with the RV/TLC ratio. The results are consistent with those observed in patients with COPD,

Table 4. Baseline Characteristics of the Study Patients With and Without Biologics.[a]

	Total (n = 107)	Patients with biologics (n=46)[b]	Patients without biologics (n=61)	*P* Value[c]
Female, No. (%)	64 (59.8)	27 (58.7)	37 (60.7)	.8385
Age, y	68 (55-77)	67 (51-78)	69 (56-75)	.5007
BMI, kg/m^2	25.2 (22.8-27.9)	24.1 (21.8-26.9)	26.0 (23.6-28.2)	.0482
Ever-smoker, No. (%)	26 (24.3)	16 (34.8)	10 (16.4)	.0289
Duration of asthma, y	17.0 (6.8 - 34.0)	13.0 (7.0 – 25.0)	20.0 (5.0- 43.0)	.2600
Late-onset asthma, No. (%)[d]	65 (60.7)	32 (69.6	33 (54.1)	.1239
Atopy, No. (%)	27 (25.2)	10 (21.7)	17 (27.9)	.4702
Comorbidities, No. (%)				
Allergic rhinitis	15 (14.0)	10 (21.7)	5 (8.2)	.0464
CRS	12 (11.2)	3 (6.5)	9 (14.8)	.1823
CRSwNP	4 (3.7)	0 (0.0)	4 (6.6)	.0774
GERD	37 (34.6)	16 (34.8)	21 (34.4)	.9689
OSAS	6 (5.6)	3 (6.5)	3 (4.9)	.7210
Anxiety	3 (2.8)	3 (6.5)	0 (0.0)	.0434
ACT score	22 (18-24)	20 (16-22)	22 (20-24)	.0010
≥ 1 exacerbation/y, No. (%)	70 (65.4)	34 (73.9)	36 (59.0)	.1094
Annual number of exacerbations	1 (0-2)	2 (1-4)	1 (0-1)	.0002
Medication				
Medium or high dose ICS/LABA/LAMA, No. (%)	82 (76.6)	37 (80.4)	45 (73.8)	.4200
OCS, No. (%)	43 (40.2)	26 (56.5)	17 (27.9)	.0034
FeNO, ppb	30 (18-60)	33.5 (20-69)	28.5 (16.5-47)	.2499
Blood eosinophils/µL	205 (98-338)	242 (103-339)	188 (94.8-315)	.5584
PEFR, L/min	250 (180-345)	255 (180-310)	245 (175-360)	.9390
Spirometry				
FEV_1/FVC, %	62.9 (55.3-72.6)	65.2 (54.3-72.9)	62.1 (55.9-71.6)	.5333
FEV_1, % predicted	64.7 (52.9-78.3)	65.6 (54.7-82.2)	64.0 (52.4-72.6)	.4427
FVC, % predicted	79.3 (69.6-88.6)	79.3 (72.2-89.5)	79.0 (67.0-88.4)	.5333
$FEF_{25-75\%}$, % predicted	27.4 (18.6-48.6)	29.0 (15.3-46.6)	27.2 (20.0-50.8)	.9839
BDR (+), No. (%)	19 (17.8)	10 (21.7)	9 (14.8)	.3494
TLC, % predicted	98.5 (91.5-113)	98.5 (94.0-114.0)	98.5 (87.5-112.0)	.3941
RV/TLC	0.50 (0.42-0.57)	50.0 (41.0-56.5)	48.5 (41.5-56.0)	.6285
Impulse oscillometry				
R_5, kPa/(L/s)	0.51 (0.42-0.67)	0.54 (0.42-0.73)	0.51 (0.41-0.65)	.7321
R_5, % predicted	165.2 (133.9-198.6)	174.5 (136.5-216.6)	161.7 (132.7-193.4)	.1502
R_5-R_{20}, kPa/(L/s)	0.17 (0.01-0.26)	0.17 (0.10-0.28)	0.18 (0.12-0.25)	.5836
R_5-R_{20}, % predicted	165.4 (239.4-360.2)	280.3(151.6-391.2)	222.9(169.7-307.9)	.4457
F_{res}, Hz	19.91 (18.90-20.92)	19.5 (15.7-23.5)	18.9 (16.8-21.8)	.7541
F_{res}, % predicted	136.3 (118.5-164.4)	138.7 (118.1-189.5)	134.8 (117.7-154.4)	.3232
X_5, kPa/(L/s)	–0.27 (–0.43 to –0.20)	–0.25 (–0.42 to –0.16)	–0.30 (–0.44 to –0.20)	.3539
X_5, % predicted	245.6 (172.2-358.1)	247.4 (152.0-350.5)	233.4 (182.9-364.7)	.6644
AX, kPa/L	1.79 (1.03-2.30)	1.60 (0.70-3.58)	2.01 (1.10-2.90)	.5038
AX, % predicted	422.4 (246.5-700.2)	449.0 (214.8-861.3)	409.1 (266.0-619.2)	.7773

Abbreviations: ACT, Asthma Control Test; AX, area under the reactance curve between 5 Hz and resonant frequency; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC of more than 12% and 200/µL over baseline in response to a short-acting ß-2 agonist; BMI, body mass index; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of FVC; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS/LABA/LAMA, inhaled corticosteroid, long-acting ß-2 agonist and long-acting muscarinic antagonist combination therapy; OCS, oral at; OSAS, obstructive sleep apnea syndrome; PEFR, peak expiratory flow rate; RV/TLC, the ratio of residual volume to total lung capacity ratio; R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; F_{res}, resonant frequency; X_5, reactance at 5 Hz.

[a]Data are shown as No. (%) for categorical variables and median (IQR) for nonnormally distributed variables

[b]A total of 46 patients received biologics for severe asthma, including omalizumab (n=31 [67.4%]), mepolizumab (n=14 [30.4%]), and benralizumab (n=1 [2.2%]).

[c]*P*<.05 (Mann-Whitney), statistically significant.

[d]Late-onset asthma, defined as age of asthma onset ≥40 years; atopy, defined as an increase in total IgE >100 IU/mL or a positive Phadiatop test result (>0.35 PAU/L).

Table 5. Clinical Characteristics of Patients Who Completed 12 Months of Follow-Up.[a]

	With biologics (n=25)[b]			Without biologics (n=26)		
	Baseline	12 mo	*P* Value	Baseline	12 mo	*P* Value
Female, No. (%)	17 (68.0)			15 (57.7)		.4512[d]
Age, y	67 (56-77)			71 (66-76)		.2281[d]
BMI, kg/m^2	24.0 (21.9-27.9)			26.3 (24.1-28.5)		.0883[d]
Smoking, No. (%)	9 (36.0)			3 (11.5)		.0401[d]
ACT score	18 (14-21)	22 (20-23)	.0009	23 (20-24)	23 (22-24)	.2687
No. of annual exacerbations	3 (1-4)	0 (0-1)	.0001	1 (0-2)	0 (0-1)	.0138
FeNO, ppb	41 (23.0-108.5)	32.5 (14.0-45.5)	.0009	29.0 (17.5-43.5)	22.5 (15.3-37.0)	.6578
Blood eosinophils/μL	316 (206-503)	129 (34-330)	.0032	150 (81-261)	135 (78-250)	.2309
PEFR, L/min	260 (180-325)	305 (186-458)	.3378	235 (158-373)	225 (140-375)	.0887
Spirometry						
FEV_1/FVC, %	63.1 (52.4-71.2)	71.6 (56.6-75.9)	.2758	59.4 (55.8-71.8)	63.2 (55.5-71.9)	.7533
FEV_1, % predicted	65.0 (47.8-71.5)	71.0 (55.5-86.8)	.0102	64.0 (56.3-79.0)	69.0 (57.4-82.0)	.4692
FVC, % predicted	75.3 (66.0-88.9)	83.0 (71.7-91.7)	.0875	83.9 (72.8-93.8)	85.5 (77.6-92.0)	.5172
$FEF_{25-75\%}$, % predicted	23.0 (15.0-40.7)	34.0 (21.5-54.8)	.3702	23.5 (17.8-50.5)	25.5 (18.0-43.8)	.8194
BDR (+), No. (%)	6 (24.0)	2 (8.0)	.1019	4 (17.4)	0 (0.0)	.0457
TLC, % predicted	98.0 (94.0-115.3)	101.0 (86.0-110.7)	.3176	102.5 (89.0-119.5)	101.5 (93.0-105.0)	.5029
RV/TLC	0.52 (0.44-0.59)	0.48 (0.40-0.54)	.0520	0.48 (0.41-0.55)	0.48 (0.45-0.53)	.7533
Impulse oscillometry						
R_5, kPa/(L/s)	0.55 (0.42-0.70)	0.49 (0.41-0.61)	.7863	0.55 (0.37-0.67)	0.56 (0.42-0.64)	.6202
R_5, % predicted	168.6 (125.8-194.2)	156.9 (124.6-186.0)	.8401	159.1 (133.5-202.0)	162.9 (136.5-195.9)	.6379
R_5-R_{20}, kPa/(L/s)	0.18 (0.10-0.34)	0.17 (0.09-0.26)	.6071	0.22 (0.12-0.26)	0.18 (0.13-0.25)	.9893
R_5-R_{20}, % predicted	288.9 (171.0-394.6)	218.4 (151.5-317.6)	.1579	244.8 (173.4-366.1)	243.8 (186.9-336.1)	.6381
F_{res} (Hz)	20.48 (14.49-26.52)	19.54 (15.63-22.64)	.4576	19.65 (17.42-22.28)	20.85 (17.98-23.78)	.2692
F_{res}, % predicted	136.3 (113.9-184.3)	132.2 (108.4-170.3)	.5272	132.2 (120.9-162.2)	139.1 (123.7-162.9)	.5341
X_5, kPa/(L/s)	–0.24 (–0.54 to –0.18)	–0.13 (–0.29 to -0.05)	.0152	–0.27 (–0.42 to –0.13)	–0.35 (–0.46 to –0.18)	.2427
X_5, % predicted	252.5 (183.0-372.1)	208.9 (71.8-276.5)	.1662	227.1 (112.9-313.7)	256.1 (146.9-359.4)	.8089
AX, kPa/L	1.73 (0.81-4.32)	1.73 (0.82-3.18)	.5390	2.12 (1.12-3.18)	2.19 (1.30-3.30)	.6204
AX, % predicted	447.4 (263.9-899.9)	467.5 (276.8-678.2)	.4432	408.4 (209.2-583.8)	421.4 (262.8-627.8)	.7901

Abbreviations: ACT, Asthma Control Test; AX, area under the reactance curve between 5 Hz and resonant frequency; BDR (+), a positive bronchodilator response, defined as an increase in FEV_1 or FVC of more than 12% and 200/μL over baseline in response to a short-acting ß-2 agonist; BMI, body mass index; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of FVC; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; RV/TLC, the ratio of residual volume to total lung capacity ratio; R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; F_{res}, resonant frequency; X_5, reactance at 5 Hz.

[a]Data are shown as No. (%) for categorical variables and median (IQR) for nonnormally distributed variables.

[b]Twenty-five patients received biologics for severe asthma and completed 12 months follow-up, including omalizumab (n=17 [68%]), mepolizumab (n=7 [28%]), and benralizumab (n=1 [4%]).

[c]*P* values were calculated from a comparison between patients at baseline and at 12-month follow-up by the McNemar's test for categorical variables and the Wilcoxon signed-rank test for continuous variables. Values <.05 were considered statistically significant.

[d]*P* values were generated from a comparison between patients treated with and without biologics.

for whom a significant correlation between R_5-R_{20}, F_{res}, X_5, and the RV/TLC ratio has been reported [36]. While R_5 represents total airway resistance involving both large and small airways, R_{20} is a measurement of resistance from large airways; therefore, their difference (R_5-R_{20}) reflects resistance in the small airways [16]. Figures S3 and S4 and Table S2 showed that the absolute value of R_5 was more significantly correlated with the RV/TLC ratio and better able to detect SLH than R_{20}, pointing to a dominant effect of small airway resistance and reflecting the nature of airway obstruction (medium FEV_1/FVC ratio of 62.9%) in patients with severe asthma. It is noteworthy that, of all these IOS parameters, X_5 performed best for detecting SLH in patients with severe asthma. Reactance (X) reflects airway dissipation responding to pulses delivered by loudspeaker at different pressures and frequencies and is composed of both inertance and capacitance (elasticity) [18]. X_5 is the inertia and elasticity of the tissues of both small and large airways at 5 Hz [16,18]. Our previous study showed that, compared with other IOS parameters, X_5 had the highest specificity for SAD in symptomatic patients with preserved pulmonary function [13]. Another study also found that the change in X_5, instead of airway resistance, was independently correlated with the change in volume and gas trapping after methacholine challenge in asthma patients [37]. According to the equations applied to calculate the percent predicted values of IOS parameters, factors including sex, age, height, and weight must be considered [28]. Adjusting for these factors reveals a significant difference in both X_5 and X_5 (% predicted) between patients with and without SLH (Table S1). Besides, compared with other IOS parameters, both X_5 and X_5 (% predicted) correlate more strongly with RV/TLC and perform better in detecting SLH for patients with severe asthma. In summary, SLH is associated with the degree of SAD, and the IOS parameter X_5 can provide supplementary information in the assessment of SLH.

Emerging evidence, as shown in our study, demonstrated that biologics targeting type 2 cytokines provided major benefits, including reducing exacerbations and improving symptom control and lung function in patients with severe asthma [38,39]. Previous studies also showed that treatment with ICS and biologics improved SLH in patients with different severities of asthma [40,41]. Of note, our results showed a more significant improvement in X_5 than in the RV/TLC ratio after 12 months of treatment with biologics than in those who did not receive biologics. This finding is consistent with those of a previous study, which showed that changes in IOS parameters after bronchodilator inhalation were more sensitive than spirometry for evaluating asthma control [20]. Moreover, a study by Shirai et al [42] showed that improvement of small airway function preceded the change in FEV_1 in patients who received benralizumab for their severe asthma. Our results reinforced the role of IOS parameters, especially X_5, in evaluating SLH and response to biologics in patients with severe asthma.

Our study is subject to limitations. First, only patients who successfully completed body plethysmography were reviewed. The results await further validation in patients who cannot perform forced expiration in a prospective setting. Nevertheless, our study did show the potential role of IOS as an alternative to body plethysmography in evaluating SLH in patients with severe asthma. Second, the number of patients who completed 12 months of follow-up was small, and the 12-month treatment response may not reflect the long-term effects of treatment. However, our results highlighted the importance of IOS as a more sensitive tool for detecting response to treatment in patients who received biologics.

Conclusion

This study provides evidence that X_5 could be a potential surrogate for evaluation of SLH, which is usually assessed using body plethysmography. The improvement in X_5 could be a sensitive parameter indicating response to treatment in patients with severe asthma.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391:783-800.
2. Burgel PR, de Blic J, Chanez P, Delacourt C, Devillier P, Didier A, et al. Update on the roles of distal airways in asthma. Eur Respir Rev. 2009;18:80-95.
3. Yanai M, Sekizawa K, Ohrui T, Sasaki H, Takishima T. Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure. J Appl Physiol (1985). 1992;72:1016-23.
4. Cottini M, Lombardi C, Micheletto C. Small airway dysfunction and bronchial asthma control : the state of the art. Asthma Res Pract. 2015;1:13.
5. Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? Ann Allergy Asthma Immunol. 2012;109:185-9.e2.
6. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med. 2019;7:402-16.
7. Krings JG, Goss CW, Lew D, Samant M, McGregor MC, Boomer J, et al. Quantitative CT metrics are associated

with longitudinal lung function decline and future asthma exacerbations: Results from SARP-3. J Allergy Clin Immunol. 2021;148:752-62.
8. Vempilly JJ, Abejie BA, Rashidian A, Jain VV, Bhakta N. Air Trapping Correlates With Increased Frequency of Albuterol Use and Severity of Wheeze in Persistent Asthma. Respir Care. 2020;65:994-1000.
9. Shimizu K, Tanabe N, Oguma A, Kimura H, Suzuki M, Yokota I, et al. Parenchymal destruction in asthma: Fixed airflow obstruction and lung function trajectory. J Allergy Clin Immunol. 2022;149:934-42.e8.
10. O'Donnell DE, Laveneziana P. The clinical importance of dynamic lung hyperinflation in COPD. COPD. 2006;3:219-32.
11. Albuquerque ALP, Nery LE, Villaça DS, Machado TYS, Oliveira CC, Paes AT, et al. Inspiratory fraction and exercise impairment in COPD patients GOLD stages II-III. Eur Respir J. 2006;28:939-44.
12. Dykstra BJ, Scanlon PD, Kester MM, Beck KC, Enright PL. Lung volumes in 4,774 patients with obstructive lung disease. Chest. 1999;115:68-74.
13. Chiu HY, Hsiao YH, Su KC, Lee YC, Ko HK, Perng DW. Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function. J Allergy Clin Immunol Pract. 2020;8:229-35.e3.
14. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22:1026-41.
15. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55:1900753.
16. Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. Breathe (Sheff). 2015;11:57-65.
17. Hellinckx J, Cauberghs M, De Boeck K, Demedts M. Evaluation of impulse oscillation system: comparison with forced oscillation technique and body plethysmography. Eur Respir J. 2001;18:564-70.
18. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: interpretation and practical applications. Chest. 2014;146:841-7.
19. Kraft M, Richardson M, Hallmark B, Billheimer D, Van den Berge M, Fabbri LM, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respir Med. 2022;10:661-8.
20. Cottee AM, Seccombe LM, Thamrin C, King GG, Peters MJ, Farah CS. Bronchodilator Response Assessed by the Forced Oscillation Technique Identifies Poor Asthma Control With Greater Sensitivity Than Spirometry. Chest. 2020;157:1435-41.
21. Global Initiative for Asthma. 2022 GINA Report, Global Strategy for Asthma Management and Prevention. 2022. Available at https://ginasthma.org/gina-reports/. Accessed June 23, 2022.
22. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343-73.
23. Hsiao YH, Lin YJ, Jeng TH, Su KC, Ko HK, Yang SN, et al. Potentiality of impulse oscillometry to evaluate bronchodilator reversibility in untreated adult patients with newly diagnosed asthma. J Chin Med Assoc. 2022 Jun 6. doi: 10.1097/JCMA.0000000000000757. Epub ahead of print.
24. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68.
25. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.
26. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200:e70-e88.
27. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26:511-22.
28. Schulz H, Flexeder C, Behr J, Heier M, Holle R, Huber RM, et al. Reference values of impulse oscillometric lung function indices in adults of advanced age. PloS One. 2013;15;8(5):e63366.
29. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther. 2017;43:39-45.
30. Wang TN, Lin MC, Wu CC, Leung SY, Huang MS, Chuang HY, et al. Risks of exposure to occupational asthmogens in atopic and nonatopic asthma: a case-control study in Taiwan. Am J Respir Crit Care Med. 2010;182:1369-76.
31. van der Meer AN, de Jong K, Hoekstra-Kuik A, Bel EH, Ten Brinke A. Dynamic hyperinflation impairs daily life activity in asthma. Eur Respir J. 2019;53:1801500.
32. de Weger WW, Klooster K, Ten Hacken NH, van Dijk M, Hartman JE, Slebos DJ. Determining Static Hyperinflation in Patients with Severe Emphysema: Relation Between Lung Function Parameters and Patient-Related Outcomes. Lung. 2020;198:629-36.
33. Benfante A, Di Marco F, Terraneo S, Centanni S, Scichilone N. Dynamic hyperinflation during the 6-min walk test in severely asthmatic subjects. ERJ Open Res. 2018;4:00143-2017.
34. Lugogo N, Judson E, Haight E, Trudo F, Chipps BE, Trevor J, et al. Severe asthma exacerbation rates are increased among female, Black, Hispanic, and younger adult patients: results from the US CHRONICLE study. J Asthma. 2022:59(12):2495-508.
35. Baan EJ, de Roos EW, Engelkes M, de Ridder M, Pedersen L, Berencsi K, et al. Characterization of Asthma by Age of Onset: A Multi-Database Cohort Study. J Allergy Clin Immunol Pract. 2022;10:1825-34.e8.
36. D'Ascanio M, Viccaro F, Calabrò N, Guerrieri G, Salvucci C, Pizzirusso D, et al. Assessing Static Lung Hyperinflation by Whole-Body Plethysmography, Helium Dilution, and Impulse Oscillometry System (IOS) in Patients with COPD. Int J Chron Obstruct Pulmon Dis. 2020;15:2583-9.
37. Downie SR, Salome CM, Verbanck S, Thompson BR, Berend N, King GG. Effect of methacholine on peripheral lung mechanics and ventilation heterogeneity in asthma. J Appl Physiol (1985). 2013;114:770-7.

38. Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022;386:157-71.
39. Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma-A Real-Life Evaluation. J Allergy Clin Immunol Pract. 2021;9:1194-1200.
40. Tunon-de-Lara JM, Laurent F, Giraud V, Perez T, Aguilaniu B, Meziane H, et al. Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. J Allergy Clin Immunol. 2007;119:583-90.
41. Pelaia C, Busceti MT, Crimi C, Carpagnano GE, Lombardo N, Terracciano R, et al. Real-Life effects of benralizumab on exacerbation number and lung hyperinflation in atopic patients with severe eosinophilic asthma. Biomed Pharmacother. 2020;129:110444.
42. Shirai T, Akamatsu T, Hirai K, Watanabe H, Tamura K, Kishimoto Y, et al. Oscillometry improves earlier than spirometry after benralizumab initiation in severe asthma. Allergy. 2020;75:2678-80.

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