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ORIGINAL RESEARCH

Detection of Inadequately Controlled Asthma in Adults Using Impulse Oscillometry and Fractional Exhaled Nitric Oxide

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Purpose: To investigate the effectiveness of impulse oscillometry (IOS) and its combination with fractional expiratory nitric oxide (FeNO) in distinguishing inadequately controlled asthma (ICA) from well-controlled asthma (WCA) in adults.

Patients and Methods: Adult patients aged 18 and above with asthma were recruited and underwent routine blood tests, FeNO, IOS, and spirometry before and after bronchodilator administration on the same day. Asthma control level was assessed using Asthma Control Test (ACT) scores; WCA was defined as a score above 20, while ICA was defined as a score of 20 or below. Receiver operating characteristic curve (ROC) and logistic regression analyses were employed to determine the relationship between IOS and FeNO measurements and asthma control.

Results: The *z* score values of IOS parameters, specifically resistance at 5 hz (R5), resistance at 20 hz (R20), and the area under reactance curve between 5 hz and resonant frequency (AX) after bronchodilator administration were significantly different between the WCA (n = 75) and ICA (n = 77) groups. IOS parameters, R5, R20, and AX, after bronchodilation identified patients with ICA, with areas under receiver operating characteristic curve (AUC) of 0.654, 0.690, and 0.708, respectively, adjusted for smoke exposure, variable airflow limitation and fixed airflow obstruction. Combining IOS parameters with FeNO significantly increased the AUC (0.728, 0.752, and 0.763) for detecting ICA compared to IOS parameters with R5, R20, and AX, alone. Patients with abnormal IOS and FeNO values had significantly higher odds ratio (OR) of having ICA by logistic regression analyses, especially for abnormally higher AX, with an OR of 6.48.

Conclusion: IOS is useful in discriminating ICA from WCA in adults, with its effectiveness further enhanced when combined with FeNO measurements.

Keywords: Asthma, Impulse oscillometry, Fractional exhaled nitric oxide, Spirometry

Introduction

Asthma is a common chronic airway disease affecting 1–29% of the population in different countries from the Global Asthma Network Phase I, a multi-country cross-sectional population-based study.[1] It is characterized by airway obstruction accompanying airway inflammation, leading to subjective respiratory symptoms essential for assessing asthma control.[2,3] A considerable number of patients with asthma remained uncontrolled (40–80%) or partially controlled (10–40%) at each treatment step,[4] as defined by the Global Initiative for Asthma (GINA). Therefore, GINA guideline recommends that once the diagnosis of asthma has been made, asthma control should be assessed at every opportunity, which is an important component in the asthma management cycle.[5] Poor symptom control is also strongly associated with an increased risk of asthma exacerbations and increased urgent healthcare utilization,[6,7] highlighting the importance of distinguishing inadequately controlled asthma (ICA) from well-controlled asthma (WCA).

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According to GINA recommendations,[5] effective asthma control encompasses symptom control and risk reduction for future adverse outcomes. Asthma symptom control is mainly evaluated by numerical self-administered questionnaires, such as the Asthma Control Test (ACT) scale. Spirometry is the main method recommended by guidelines for evaluating respiratory function,[5] and impaired lung function is a typical risk factor for asthma exacerbations.[8,9] Variable airflow limitation which describes a positive bronchodilator response usually defined by spirometry parameter forced expiratory volume in 1 second (FEV_1) is associated with loss of asthma control.[10] And asthma patients with fixed airflow obstruction which describes abnormal post-bronchodilator spirometry is associated with greater symptom burden.[11] However, the limitations of spirometry are well described including the requirement for patient coordination to perform a maximal effort-dependent forced maneuver, as well as the lack of ability to provide more specific information about the pathophysiological changes especially in small airways, which lead a poor correlation with asthma control.[12,13]

Impulse oscillometry (IOS), a non-invasive method for measuring respiratory system impedance including resistance and reactance,[14] is especially sensitive to peripheral airway changes.[15] Thus, it correlates better with asthma symptoms and is usually considered a supplementary tool for spirometry.[11,16,17] Previous studies have shown that patients with ICA had significantly increased airway resistance and reactance, as measured by IOS.[18–22] However, there is still controversy over whether IOS could provide additional, complimentary information about the pathophysiology in order to better assess the asthma symptom among adult populations with asthma.[23–25] Additionally, fractional exhaled nitric oxide (FeNO) may reflect type 2 airway inflammation,[5,26] which is also associated with asthma control.[19,21] Patients with ICA had more severe type 2 airway inflammation, as indicated by FeNO,[20,21] rather than higher blood eosinophil (EOS) levels,[20,24] or higher sputum EOS levels[27,28] compared to those with WCA. These findings imply that IOS and FeNO may provide additional information about airway pathology and asthma symptom control that spirometry cannot capture. Although several studies on children with asthma found that combining IOS and FeNO can better identify ICA than IOS alone,[19–21] no reports focused on their roles in evaluating asthma control in adults. Thus, our study aims to investigate the effectiveness of IOS and FeNO in distinguishing ICA from WCA in adults.

Materials and Methods

Study Participants

Patients aged over 18 years with asthma were recruited from the Department of Respiratory and Critical Care Medicine, Beijing Chao-Yang Hospital between September 2021 and August 2024. Asthma was diagnosed according to a history of variable respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, along with confirmed variable expiratory airflow limitation based on GINA recommendations, which means at least one of the following: positive bronchodilator responsiveness test with spirometry, excessive variability in twice-daily peak expiratory flow (PEF) over 2 weeks, increase in lung function after 4 weeks of treatment, positive bronchial challenge test, and excessive variation in lung function between visits.[5] Exclusion criteria included patients who had exacerbations within eight weeks before study enrollment, defined as the use of oral or parenteral corticosteroids; those with smoking exposure of over 10 pack-years; or those diagnosed with other respiratory diseases, including chronic obstructive pulmonary disease, tuberculosis, and bronchiectasis. The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital (No.2022-KE-12) following the Declaration of Helsinki. All participants provided written informed consent.

Study Procedures

Participants underwent routine blood tests, FeNO, IOS, and spirometry on the same day; their demographics and medical history were collected. The count of peripheral blood EOS was measured using an automated system (XN9000; Sysmex Co., Japan). FeNO measurement and IOS were performed before spirometry to avoid the influence of forced breathing maneuvers. All patients underwent IOS and spirometry before and after the inhalation of 400 μg salbutamol according to a standard protocol.[29] Asthma control was assessed using ACT, a questionnaire consisting of five questions with lower scores indicating poorer asthma control.[30] Based on their ACT scores, patients were classified as having WCA (ACT scores ≥ 20) or ICA (ACT scores < 20).[11]

FeNO Measurement

FeNO was measured using a nitric oxide analyzer with electrochemical sensors (NIOX; Aerocrine AB, Stockholm, Sweden), according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[31] Patients performed repeated and reproducible exhalations at a constant flow rate of 50 mL/s to obtain at least two NO plateau values that agreed within 10% of each other. Abnormal FeNO was defined as more than 50 ppb or 20 ppb, indicating type 2 inflammation according to ATS[26] or GINA,[5] separately.

Impulse Oscillometry

IOS was performed to measure respiratory system impedance at different oscillation frequencies according to the recommendations of the ERS Task Force.[32] Patients who wore a nose clip breathed tidally into the IOS mouthpiece for 30 seconds, allowing recording over at least three breaths. The basic parameters evaluated in IOS included resistance at 5 hz (R5), resistance at 20 hz (R20), difference between R5 and R20 (R5-R20), reactance at 5 hz (X5), resonance frequency (Fres), and the area under reactance curve between 5 hz and resonant frequency (AX). Among these parameters, R5 reflects total airway resistance, R20 reflects the large airways only, and R5-R20 equals the resistance of the small airways. In addition, X5, Fres and AX all represent the reactance in small airways. The *z* score of IOS parameters were calculated based on reference equations from a previous multicenter cross-sectional study on IOS in Chinese adults.[33] And the abnormal values determined by values greater than the upper limit of normal (ULN) (*z* score, +1.645 for R5, R20, Fres and AX), or less than the lower limit of normal (LLN) (*z* score, −1.645 for X5), also derived from the above reference equations.

Spirometry

Spirometry was performed using a spirometer (Viasys Healthcare, Hochberg, Germany) following ATS/ERS recommendations.[29] The best measures of three reproducible forced expiratory maneuvers were recorded for FEV_1, forced vital capacity (FVC), maximum mid-expiratory flow (MMEF), and FEV_1/FVC. Similarly, the *z* score and % predicted values of spirometry parameters were calculated based on reference equations from a previous multicenter study in Chinese aged 4 to 80 years,[34] considering the similar race, age, height and weight of the population included in our study. The abnormal values determined by spirometry parameters less than the LLN also derived from the above reference equations. Variable airflow limitation was defined as greater than or equal to 200 mL and greater than or equal to 12% improvement in FEV_1 and/or FVC after bronchodilator administration following ATS/ERS recommendations.[35] And fixed airflow obstruction was defined as post-bronchodilator FEV_1/FVC below the LLN based on a previous study from Cottee et al.[11]

Statistical Analysis

Data were summarized using frequencies and percentages for categorical variables and compared using X^2 or Fisher's exact test. For continuous variables, the Shapiro–Wilk test was used to check for normality. Thus, the data with normal distribution was represented by mean ± standard deviation and compared using Student's *t*-test, and the data without normal distribution was represented by median [interquartile range] and compared using the Mann–Whitney test. Receiver operating characteristic curve (ROC) analysis was used to evaluate the effectiveness of IOS parameters, FeNO, and their combination in identifying patients with ICA. The DeLong test was used to compare the area under the ROC curve (AUC).

Logistic regression analysis was also performed to further evaluate the associations of abnormal IOS parameters and FeNO with increased ICA risk, adjusted for smoke exposure, variable airflow limitation and fixed airflow obstruction. P values of less than 0.05 were considered statistically significant, and adjusted by the Holm-Bonferroni test for multiple Logistic regression. All statistical analyses were conducted using R (version 4.3.1).

Results

Demographic Characteristics of the Study Population

A total of 152 patients with asthma were enrolled in this study (Figure 1). According to ACT scores, 75 (49.3%) patients were classified as having WCA and 77 (50.7%) as having ICA. Patients' demographic and clinical characteristics

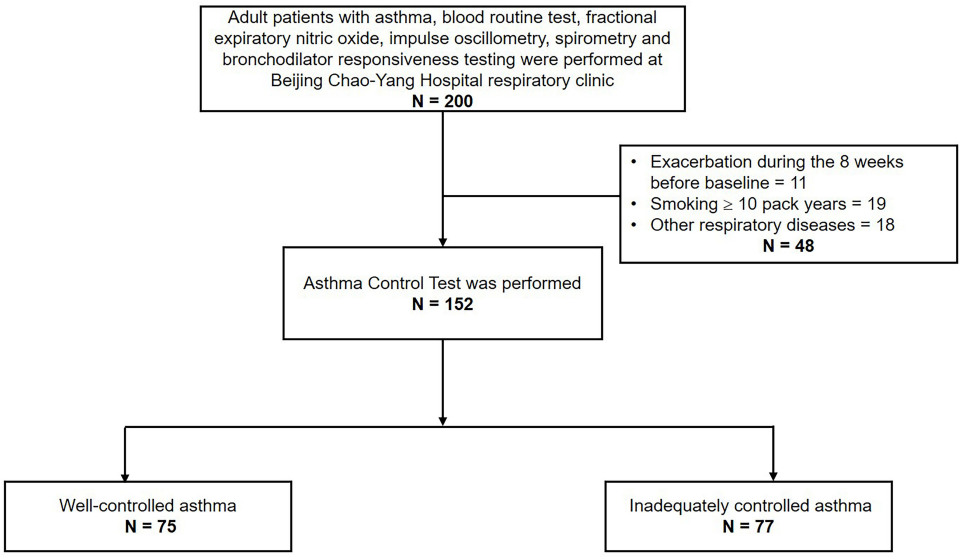

Figure 1 Study design and flow diagram.

stratified by asthma control are shown in Table 1. The average age was 46.3 ± 14.3 years; 42.8% of patients were male, and there were no significant differences in the demographics between the WCA and ICA groups. Patients with ICA had a significantly lower inhaled corticosteroid (ICS) dose and lesser requirement for additional medication use including / long-acting β agonist (LABA), anti-immunoglobulin E (IgE) or leukotriene receptor antagonist (LTRA), and only a trend of higher requirement for short-acting β agonist (SABA) which failed to reach statistical significance than patients with WCA. And there were 26 (17.1%) patients with variable airflow limitation, 58 (38.2%) patients with fixed airflow obstruction.

Table 1 Clinical Characteristics of the Study Population

Characteristics	Total (n = 152)	WCA (n = 75)	ICA (n = 77)	P value
Age (yrs)	46.3±14.3	45.5±14.7	47.0±14.0	0.5
Male (%)	65 (42.8)	30 (40.0)	35 (45.5)	0.6
Height (cm)	165.6±10.0	165.8±9.2	165.4±10.8	0.8
Weight (kg)	70.7±14.4	71.2±15.1	70.2±13.8	0.7
BMI (kg/m^2)	25.7±4.1	25.8±4.5	25.6±3.8	0.7
Smoke exposure (%)	38 (25.0)	19 (25.3)	19 (24.7)	0.9
Duration of disease (yrs)	4.6±7.8	4.8±5.7	4.4±9.5	0.7
Asthma medication				
ICS (%)	78 (51.3)	53 (70.7)	25 (32.5)	<0.01*
LABA (%)	76 (50.0)	53 (70.7)	23 (29.9)	<0.01*
SABA (%)	5 (3.3)	1 (1.3)	4 (5.2)	0.4
Anti-IgE (%)	8 (5.3)	8 (10.7)	0 (0.0)	0.01*
LTRA (%)	10 (6.6)	9 (12.0)	1 (1.3)	0.02*
ACT	18.8±4.8	22.4±2.4	15.2±3.7	<0.01*
Variable airflow limitation (%)	26 (17.1)	12 (16.0)	14 (18.2)	0.9
Fixed airflow obstruction (%)	58 (38.2)	28 (37.3)	30 (39.0)	0.9

Notes: Data are presented as mean ± standard deviation or n (%). * P < 0.05.

Abbreviations: WCA, well-controlled asthma; ICA, inadequately controlled asthma; BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting β agonist; SABA, short-acting β agonist; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist; ACT, asthma control test. Variable airflow limitation was defined as greater than or equal to 200 mL and greater than or equal to 12% improvement in FEV_1 and/or FVC after bronchodilator administration following ATS/ERS recommendations;[35] Fixed airflow obstruction was defined as post-bronchodilator FEV_1/FVC below the LLN in our study following a previous study from Cottee et al.[11]

Differences in IOS, Spirometry, and FeNO Between Patients with WCA and ICA

The ICA group exhibited statistically higher *z* score values of R5, R20, and AX after bronchodilator administration, as well as the absolute values of AX than the WCA group, with no difference observed in other IOS parameters (Table 2). However, there were no significant differences in all spirometry parameters before and after bronchodilator administration between patients with WCA and ICA (Supplementary Table 1). Bronchodilator responsiveness, assessed using IOS and spirometry parameters as both absolute change and percentage change, was not significantly different between the two groups (Supplementary Table 2). FeNO levels were significantly higher in the ICA group than those in the WCA group (65.5±72.6 ppb vs 38.3±43.6 ppb, P = 0.006), whereas blood EOS levels were not significantly different between the two groups (Table 2).

Discriminative Ability of IOS Alone and Combined with FeNO in Detecting ICA

IOS parameters which were significantly different from the ICA group than those in the WCA group were further included in the ROC analysis. The ability of IOS parameters and FeNO to distinguish patients with ICA from those with WCA is shown by the ROC curves (Figure 2). After adjustment for covariates including smoke exposure, variable airflow limitation and fixed airflow obstruction, the IOS parameters with *z* score values of R5, R20, and AX after bronchodilator administration distinguished ICA, with AUC values of 0.654, 0.690, and 0.708 (Table 3).

Table 2 Comparison of IOS, EOS, and FeNO results Between the WCA and ICA Groups

Parameters	Total (n = 152)	WCA (n = 75)	ICA (n = 77)	P value
Pre-bronchodilator				
R5 (kpa/(L/s))	0.43±0.16	0.42±0.15	0.44±0.18	0.4
R20 (kpa/(L/s))	0.36±0.09	0.35±0.09	0.36±0.09	0.8
R5-R20 (kpa/(L/s))	0.08±0.10	0.07±0.09	0.08±0.11	0.3
X5 (kpa/(L/s))	−0.11 [−0.16, −0.08]	−0.11 [−0.14, −0.09]	−0.11 [−0.17, −0.08]	0.9
Fres (kpa/(L/s))	15.29±7.48	14.91±6.80	15.67±8.11	0.5
AX (kpa/(L/s))	0.37 [0.18, 0.82]	0.34 [0.19, 0.67]	0.38 [0.17, 0.97]	0.6
R5 (z score)	2.77±3.06	2.49±2.93	3.05±3.17	0.3
R20 (z score)	1.97±1.82	1.87±1.86	2.06±1.78	0.5
R5-R20 (z score)	1.80±3.53	1.53±3.42	2.06±3.63	0.4
X5 (z score)	−0.97 [−3.25, 0.10]	−1.01 [−2.22, 0.09]	−0.76 [−3.32, 0.10]	0.9
Fres (z score)	3.29±5.56	2.95±5.16	3.62±5.95	0.5
AX (z score)	0.12 [−0.02, 0.39]	0.11 [−0.01, 0.29]	0.12 [−0.02, 0.42]	0.6
Post-bronchodilator				
R5 (kpa/(L/s))	0.35±0.11	0.34±0.09	0.37±0.13	0.06
R20 (kpa/(L/s))	0.31±0.08	0.30±0.07	0.32±0.09	0.1
R5-R20 (kpa/(L/s))	0.05±0.06	0.04±0.05	0.05±0.06	0.2
X5 (kpa/(L/s))	−0.10 [−0.12, −0.07]	−0.09 [−0.11, −0.07]	−0.10 [−0.15, −0.07]	0.6
Fres (kpa/(L/s))	12.71±5.03	12.28±4.02	13.13±5.85	0.3
AX (kpa/(L/s))	0.25 [0.16, 0.53]	0.21 [0.13, 0.36]	0.30 [0.20, 0.90]	0.001*
R5 (z score)	1.03±2.12	0.42±1.53	1.62±2.44	<0.001*
R20 (z score)	0.78±1.63	0.25±1.41	1.30±1.67	<0.001*
R5-R20 (z score)	0.16 [−0.68, 1.54]	0.00 [−0.80, 1.38]	0.34 [−0.56, 1.62]	0.1
X5 (z score)	−0.19 [−1.37, 0.51]	−0.13 [−0.99, 0.53]	−0.19 [−1.71, 0.49]	0.6
Fres (z score)	1.14±3.64	0.76±2.95	1.51±4.19	0.2
AX (z score)	0.04 [−0.05, 0.16]	−0.01 [−0.06, 0.07]	0.08 [−0.02, 0.34]	<0.001*
Blood EOS (/μL)	436.3±353.1	393.1±281.8	478.4±408.3	0.1
FeNO (ppb)	52.1±61.4	38.3±43.6	65.5±72.6	0.006*

Notes: Data are presented as mean ± standard deviation or median [interquartile range]. * P < 0.05.

Abbreviations: IOS, impulse oscillometry; EOS, eosinophil; FeNO, fractional exhaled nitric oxide; WCA, well-controlled asthma; ICA, inadequately controlled asthma; R5, resistance at 5 hz; R20, resistance at 20 hz; R5-R20, difference between the resistances at 5 hz and 20 hz; X5, reactance at 5 hz; Fres, resonant frequency; AX, the area under reactance curve between 5 hz and resonant frequency.

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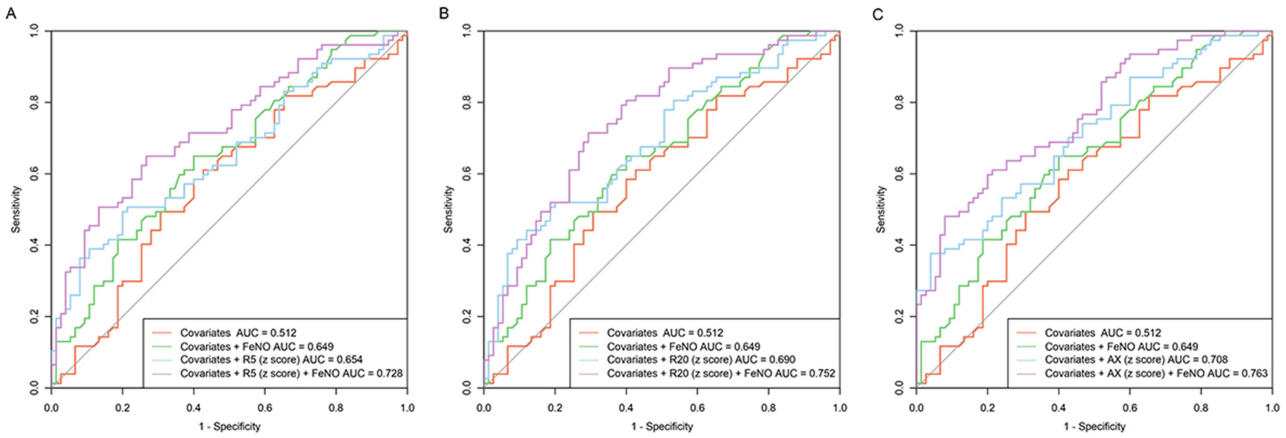

Figure 2 ROC curve analysis for the *z* score of R5 (**A**), R20 (**B**), and AX (**C**) after bronchodilator administration and the combinations of (**A**–**C**) with FeNO as continuous variables. Covariates include smoke exposure, variable airflow limitation and fixed airflow obstruction.
Abbreviations: ROC, receiver operating characteristic; R5, resistance at 5 hz; R20, resistance at 20 hz; AX, the area under reactance curve between 5 hz and resonant frequency; FeNO, fractional exhaled nitric oxide.

Additionally, FeNO combined with IOS measures (R5, R20, and AX) improved AUC values to 0.728, 0.752, and 0.763, with sensitivities of 64.9%, 71.4%, and 48.1% and specificities of 73.3%, 70.7%, and 92.0% (all $P < 0.05$) (Table 3).

Associations of IOS and FeNO with the Increased Risk of ICA

To further identify the relationship between IOS and FeNO measurements and the increased risk of ICA among adults, the odds ratio (OR) in the univariate and multivariate analyses are shown in Table 4. Classification as normal versus abnormal was based on ULN (*z* score, +1.645 for R5, R20, and AX) for IOS parameters and 50 ppb for FeNO as the definition of type 2 inflammation from ATS,[26] respectively. Compared with patients with normal values, those with abnormally higher R5, R20, and AX or abnormally higher FeNO levels were more likely to suffer from ICA. The relationship was best demonstrated by abnormally higher AX (OR: 6.48; 95% CI: 2.61–18.59) in the multiple logistic analysis after adjusting for smoke exposure, variable airflow limitation and fixed airflow obstruction, whereas the weakest relationship with ICA was observed for abnormally higher FeNO levels (OR: 2.94; 95% CI: 1.42–6.35). The abnormal FeNO also defined as more than 20 ppb according to the definition of type 2 inflammation of GINA,[5] which showed the similar result in univariate analysis but not significant after the adjustment in the multiple logistic analysis (Supplementary Table 3).

Table 3 AUC Comparisons: IOS Parameters Alone Versus IOS Parameters Combined with FeNO for Detecting ICA

Parameters (Post-Bronchodilator)	ROC Curve for IOS Parameters[#]			ROC Curve for IOS Parameters Combined with FeNO[#]			P value[£]
	Sensitivity	Specificity	AUC (95% CI)	Sensitivity	Specificity	AUC (95% CI)	
R5 (z score)	49.4%	80.0%	0.654 (0.567–0.741)	64.9%	73.3%	0.728 (0.649–0.808)	0.02*
R20 (z score)	41.6%	90.7%	0.690 (0.607–0.774)	71.4%	70.7%	0.752 (0.675–0.830)	0.04*
AX (z score)	37.7%	96.0%	0.708 (0.627–0.789)	48.1%	92.0%	0.763 (0.689–0.837)	0.02*

Notes: [#]AUCs were obtained from separate multivariate logistic regression models that included the covariates of smoke exposure, variable airflow limitation and fixed airflow obstruction in the study population. [£] A comparison of AUCs was done using the DeLong test.* $P < 0.05$.
Abbreviations: AUC, area under the receiver operating characteristic curve; IOS, impulse oscillometry; FeNO, fractional exhaled nitric oxide; ICA, inadequately controlled asthma; ROC, receiver operating characteristic; R5, resistance at 5 hz; R20, resistance at 20 hz; AX, the area under reactance curve between 5 hz and resonant frequency.

Table 4 Odds Ratio of ICA Association with Abnormal IOS Parameters and FeNO Levels

Abnormal Parameters	n (%)		Univariate Analysis (Crude)		Multiple Analysis (Adjusted)[#]	
	WCA (n = 75)	ICA (n = 77)	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value[##]
IOS (Post-bronchodilator)						
R5 (z score) ≥ ULN	12 (16.0)	31 (40.3)	3.54 (1.64–7.62)	0.001*	4.00 (1.81–9.42)	0.004*
R20 (z score) ≥ ULN	9 (12.0)	30 (39.0)	4.68 (2.03–10.77)	<0.001*	5.85 (2.44–15.40)	<0.001*
AX (z score) ≥ ULN	9 (12.0)	31 (40.3)	4.94 (2.15–11.36)	<0.001*	6.48 (2.61–18.59)	0.004*
FeNO ≥ 50 ppb	14 (18.7)	31 (40.3)	2.94 (1.40–6.14)	0.004*	2.94 (1.42–6.35)	0.02*

Notes: [#]Covariates include smoke exposure, variable airflow limitation and fixed airflow obstruction. [##]P value was adjusted by the Holm-Bonferroni test * P < 0.05.
Abbreviations: ICA, inadequately controlled asthma; IOS, impulse oscillometry; FeNO, fractional exhaled nitric oxide; WCA, well-controlled asthma; CI, confidence interval; R5, resistance at 5 hz; ULN, upper limit of normal; R20, resistance at 20 hz; AX, the area under reactance curve between 5 hz and resonant frequency.

Discussion

To our knowledge, this study is the first to investigate the efficacy of IOS and FeNO in distinguishing ICA from WCA among adults. The study shows that post-bronchodilator IOS is useful in identifying ICA, with efficacy further enhanced by its combination with FeNO measurements. Additionally, abnormal IOS parameters (particularly abnormally high AX) and abnormally high FeNO levels are associated with an increased risk of ICA.

The advantage of IOS is that it could measure small airway function including resistance and reactance during tidal breathing, which is non-invasive and very sensitive.[15] In this study, we showed that IOS parameters can discriminate ICA from WCA in adults, as evidenced by significant differences in the *z* score values of R5, R20, and AX after bronchodilator administration, as well as AX absolute values between the WCA and ICA groups. ROC analysis showed that post-bronchodilator AX and R5 exhibited the highest and lowest accuracy, respectively, in discriminating ICA from WCA, reflecting low-frequency reactance in small airways, where elastance exceeds inertance, and the resistance in both large and small airways, respectively. This finding implies that asthma control may be more dependent on increased reactance in small airways rather than total airway resistance. This partially aligns with the report of Chaiwong et al[23] which included 142 adult patients aged over 20 years with asthma and defined ICA as an ACT score ≤ 19 plus pulmonologist assessment according to GINA.[5] They reported significant differences in all parameters of spirometry and IOS between the ICA and WCA groups, except for FEV_1/FVC, and found that R5-R20 and AX were useful in identifying ICA with an AUC of 0.911 and 0.904, respectively. Similarly, DÍaz et al[24] classified adults with asthma into three groups: uncontrolled, partially controlled, and controlled groups based on GINA criteria[5] and found significant differences in all parameters of spirometry and IOS, except for R20% predicted. However, the accuracy of IOS and/or spirometry in discriminating controlled from uncontrolled and partially controlled asthma was low (AUC = 0.61). And in a longitudinal study of adult patients with GINA step 1–2 asthma, there was a significant correlation between asthma symptom measured by validated visual analogue scales and R5-R20% predicted in symptomatic periods (r = 0.43, P = 0.019), but not in less symptomatic periods (r = 0.04, P = 0.825),[36] further indicating the relationship between small airway function evaluated by IOS and asthma control. Several studies on children with asthma also consistently showed that IOS parameters, indicative of small airway function, could identify ICA from WCA.[19–21] Direct comparisons between our findings and these studies are challenging because of not only differences in assessment tools and asthma control classifications, but also the specific physiologic features in children, such as less airflow limitation, less resistance to airflow, and greater hyperinflation.[37]

One of the challenges in promoting IOS as an assistant test to daily clinical practice for identifying ICA in adults with asthma is the shortage of clinically relevant, standardized cut-off values across various studies. In this study, the *z* score values for IOS parameters were determined using published reference equations from a multicenter cross-sectional study on Chinese adults,[33] which were deemed to best represent the race, age, weight, and height of those included in our study. Thus, we classified IOS parameters as normal versus abnormal based on the ULN (*z* score, +1.645 for R5, R20, and AX) from the same reference equations. Among IOS parameters, post-bronchodilator abnormal AX (OR: 6.48; 95% CI: 2.61–18.59) and abnormal R5 (OR: 4.00; 95% CI: 1.81–9.42) showed the highest and lowest increased risk of ICA, respectively, by logistic regression. This supports the notion that asthma control depends more on increased reactance in

the small airway rather than any pathological change in the large airways. And small airway dysfunction defined after bronchodilator administration was less than before the bronchodilator administration,[38] indicating the potential for adjusting a portion of asthma populations with variable airflow limitations. Therefore, the asthma patients with abnormal IOS parameters after bronchodilator administration might represent more severe airway dysfunction compared to those before bronchodilator administration, which may indicate more pathological information related to poor asthma control. This was mostly consistent with a study from Cottee et al,[11] they found post-bronchodilator reactance identified more patients with ICA compared with spirometry. A possible explanation is that IOS parameters, particularly AX, correlate better with small airway remodeling, represented by airway luminal narrowing and wall thickening than spirometry in patients with bronchiolitis.[39] Additionally, a study demonstrated that unsuspected microscopic mild centrilobular emphysema which was occurred in small airway was the sentinel cause of loss of lung elastic recoil from autopsy of adults with asthma.[40] And it was possible that the proinflammatory proteolytic cascade which results in the loss of the terminal bronchiolar-alveolar attachments. Eller et al[41] found that the airway smooth muscle chymase$^+$ mast cell density correlated positively with ACT, suggesting an association between airway remodeling and asthma control. Thus, post-bronchodilator IOS parameters are particularly valuable for assessing ICA in adults due to their association with small airway remodeling.

FeNO, a biomarker of type 2 airway inflammation, reflects both large and small airway inflammation.[42] We found that FeNO levels were significantly different between the WCA and ICA groups, with an estimated AUC for ICA of 0.649 after adjusting for smoke exposure, variable airflow limitation and fixed airflow obstruction, suggesting that FeNO was useful in discriminating ICA from WCA in adults. These findings align with several previous studies conducted on children with asthma. For example, Zeng et al[20] reported significant differences in FeNO levels between the two groups, with FeNO effectively distinguishing ICA from WCA (AUC = 0.783) in children aged 3–6 years with mild to moderate asthma. Similarly, Lin et al[21] reported that FeNO levels above 20 ppb could better identify ICA (AUC = 0.714) in children aged 6–12 years with asthma. Nevertheless, another study including 142 stable adults aged 14–82 years with asthma did not find significantly different FeNO levels between the three asthma control groups, which had relatively higher average FeNO levels from 53.2 ppb to 54.1 ppb.[24] This inconsistency may be due to the asynchronous changes in FeNO levels and symptom control in patients with asthma. FeNO may significantly reduce as asthma symptoms become controlled through ICS treatment;[43,44] though this decrease may lag behind symptom improvement. For example, Shimizu et al[45] conducted a prospective three-month switching therapy trial with fluticasone furoate and vilanterol in symptomatic adult patients with asthma under routine management and found that FeNO decreased eight weeks after symptom improvement, as measured by ACT at four weeks. This study revealed that abnormal FeNO, as defined by GINA guidelines (more than 20 ppb),[5] also showed an increased risk of ICA by logistic regression. Additionally, a longitudinal study including adult patients with GINA step 1–2 asthma found that FeNO was significantly higher in symptomatic periods than less symptomatic periods,[36] further indicating the relationship between type 2 airway inflammation and asthma control.

Our study also observed that combining IOS parameters after bronchodilator with FeNO levels significantly improved the AUC for discriminating ICA, aligning with previous studies conducted on children with asthma.[19–21] FeNO represents type 2 inflammation, which may produce excessive amounts of cytokines, interleukin (IL)-4 and IL-13, potentially involved in goblet cell metaplasia and airway smooth muscle contractility.[46] Additionally, chronic allergic airway inflammation may result in airway remodeling characterized by goblet cell hyperplasia, subepithelial fibrosis, and hyperplasia and hypertrophy of airway smooth muscle cells.[47,48] The IOS parameters exhibit a good relationship with small airway remodeling.[39] Thus, the underlying chronic inflammatory process and airway remodeling contribute to wheezing, shortness of breath, cough, and chest tightness,[49] and the additional objective information from the combination of IOS and FeNO may be beneficial for assessing asthma control in adults.

Our study has several limitations. First, patients with asthma were enrolled from a tertiary hospital, with potentially more impaired lung function, more severe airway inflammation, and/or greater symptom burden than the general population with asthma. Hence, further studies should explore whether the results apply to community or primary care settings. Second, there were only almost 30% of asthma patients with ICA are persistently treated with ICS for the past three months in our study, indicating the asthma control may be lost due to the poor adherence in longitudinal

observation. And this cross-sectional study had a relatively small sample size, limiting the ability to assess a causal relationship between asthma control and IOS and FeNO. Thus, future studies with a large-scale longitudinal design are needed.

Conclusion

Combining IOS and FeNO measurements may be a practical application for identifying adults with ICA. Abnormal IOS parameters, particularly abnormally high AX, and increased FeNO levels correlated with relevant ICA risks. This suggests that small airway dysfunction and type 2 airway inflammation might contribute to the pathophysiology of ICA in adults.

Abbreviations

GINA, Global Initiative for Asthma; ICA, inadequately controlled asthma; WCA, well-controlled asthma; ACT, Asthma Control Test; FEV_1, forced expiratory volume in 1 second; IOS, Impulse oscillometry; FeNO, fractional exhaled nitric oxide; EOS, eosinophil; PEF, peak expiratory flow; ATS, American Thoracic Society; ERS, European Respiratory Society; R5, resistance at 5 hz; R20, resistance at 20 hz; R5–R20, difference between R5 and R20; X5, reactance at 5 hz; Fres, resonance frequency; AX, and the area under reactance curve between 5 hz and resonant frequency; ULN, upper limit of normal; LLN, lower limit of normal; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; ROC, receiver operating characteristic curve; AUC, the area under the ROC curve; ICS, inhaled corticosteroid; LABA, long-acting β agonist; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist; SABA, short-acting β agonist; OR, odds ratio; IL, interleukin.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Ethics committee approval from the Beijing Chao-Yang Hospital (No.2022-KE-12) was obtained prior to study initiation. The study was performed in accordance with the Declaration of Helsinki and informed consent was obtained from all study participants prior to study commencement.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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