

Impulse oscillometry usefulness in small-airway dysfunction in asthmatics and its utility in asthma control

Ragia S. Sharshar

Background Small-airway affection and its relation to clinical status in asthmatic patients became an increasing interest during the last decade. Spirometry is a basic diagnostic tool for measuring pulmonary function in asthmatics but not fully illustrative especially in assessing small airways. Impulse oscillometry (IOS) can be considered a complementary and sometimes alternative technique to spirometry because it is used during quiet breathing and so gives more data about small-airways affection in asthmatic patients.

Aim To evaluate IOS usefulness in the detection of small-airways disease in asthma and its correlation to the level of disease control.

Patients and methods The study was conducted on 44 asthmatic patients who were classified into two groups: controlled asthma and uncontrolled asthma by asthma control test questionnaire (ACT score). Spirometry and IOS were performed on all patients.

Results Small-airway IOS values (R5–20, X5, and AX) were found to be statistically significant between two groups. Moreover, they strongly correlated significantly with clinical symptoms, assessed by ACT. There was high sensitivity and

specificity of (R5–20) 80 and 82%, (X5) 80 and 86%, and (AX) 86 and 89%, while for spirometric data only forced expiratory flow (FEF_{25–75%}) showed a statistically significant difference between the two groups, and not FEV₁% and there was poor correlation between ACT and FEF_{25–75%}.

Conclusion IOS provides an easy and rapid tool to diagnose and assess small-airways disease in adult, asthmatic patients
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Chest Department, Faculty of Medicine, Tanta University, Tanta, Egypt

Correspondence to Ragia S. Sharshar, MD, Chest Department, Faculty of Medicine, Tanta University, Tanta, 1221, Egypt. Tel: +20 122 365 0568; e-mail: ragia_sharshar@yahoo.com

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Introduction

Asthma is a chronic inflammatory disorder that affects the entire tracheobronchial tree, including not only central but also peripheral membranous bronchioles that represents small-airways affection. Remodelling of small-airways affecting both clinical aspect with poor asthma control, more frequent exacerbations, as well as influence functional manifestations of asthma making airflow limitation irreversible [1–3].

Functional evaluation of small-airways is still a matter of challenge, as the classical use of spirometry parameters is still not fully descriptive [4].

Impulse oscillometry (IOS), a technique first described 60 years ago, was recently used successfully to evaluate lung function in healthy individuals and asthmatics [5,6].

IOS can measure both proximal and peripheral resistance in both adults and pediatric asthmatics. The main advantage of IOS is it is simple, noninvasive, sensitive and moreover does not need a forced technique that affects the bronchial tone [7–9].

Aim

To evaluate IOS usefulness in the detection of small-airways affection in asthmatic patients and its correlation to disease control level.

Patients and methods

This prospective, cross-sectional study was done on 44 asthmatic patients, recruited from the Chest Department, Tanta University, from May 2016 to February 2017 those who fulfilled the ethics committee considerations. Exclusion criteria were smokers and ex-smokers, hospitalization in the last 1 month, respiratory tract infection, and concomitant chest diseases.

After a written, informed consent has been taken, detailed medical history, thorough clinical examination and chest radiograph, spirometry [forced expiratory volume at first second (FEV₁)/forced vital capacity (FVC), FEV₁%, forced expiratory flow (FEF_{25–75%})] and IOS (R5, R5–20, X5, AX) measurements were done on all patients.

All patients were diagnosed with asthma based on medical history, physical examination, and GINA guidelines [10].

The study patients were classified into two groups: controlled asthma and uncontrolled asthma according

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to the asthma control test, which is a five-point questionnaire applied to evaluate asthma control clinically. Each of the five questions of asthma control test (ACT) was explained to patients before completion of questionnaire, patients were considered having controlled asthma if the ACT score is more than 20 points and uncontrolled asthma if the ACT score is 19 or less (Fig. 1) [11,12].

IOS maneuver was performed using Master Lab-IOS Unit (Master Screen IOS 2001, version 4.5; Erich Jaeger GmbH, Hochberg, Germany), following standard recommendations [9].

The IOS device consists of measuring head, resistor, a pneumotachograph, pressure and flow transducers, and a computer. The system was calibrated for volume before data collection using a 3-L syringe. The patient was asked to breathe normally (tidal breathing) while seated in a relaxed sitting position, the head held slightly extended, with lips making a tight seal and tongue below a well-fitted mouthpiece. To avoid the compliance of cheeks, place firmly the patient's hands directly over them, with a nasal clip placed to occlude the nares. Impulses were applied for 30–45 s, IOS data were

reviewed, with rejecting segments affected by airflow leaks or swallowing artifacts. IOS used to assess respiratory resistance at 5 Hz (R_5) indicates total resistance. Respiratory reactance at 5 Hz (X_5) detects peripheral elastic recoil of airways. Reactance area (A_x) is an integration index of reactance measure from X_5 to F_{res} [13–15].

$R5-20$ is defined by the difference between low-frequency total resistance (R_5) and high-frequency central resistance (R_{20}), and hence derives peripheral airway resistance. So peripheral airway obstruction is reflected by elevated $R5-20$ because pressure waves signal passes into the distal lung, that is, R_5 , encounters more resistance than higher frequency more proximal R_{20} impulse. Peripheral airway obstruction leads to loss of elastic recoil expressed as less X_5 and more A_x . $R5-20$ is considered abnormal if higher than 0.03 kPa/l; X_5 is considered normal if it equals X_5 predicted 0.15 kPa/l; A_x was considered normal if it equals 0.33 kPa/l [15–17].

Statistical analysis

Statistical analysis was done using SPSS (IBM Corp. Armonk, New York, USA) version (20). Continuous

Figure 1

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5
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2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5
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3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5
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4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5
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5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5
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SCORE

TOTAL

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data were expressed as mean $\pm$ SD and categorical variables as percentages. Pearson's linear correlation coefficient was used for the correlation between ACT scores and lung function. *P* value of less than 0.05 was considered significant.

Results

A total of 44 asthmatics were included, their mean age was 43.3 $\pm$ 12.4 years with the percentage of women to men being 72.7–27.3%. Basic demographic data of patients in both groups are illustrated in Table 1. As for ACT, the mean value was 20.88 $\pm$ 2.191, 29 out of 44 (65.9%) cases had uncontrolled asthma while 15 out of 44 (34.1%) was controlled (Table 2).

Spirometric parameters showed that the mean value of FEV₁% was 81.27 $\pm$ 5.79 and 78.48 $\pm$ 4.64 in groups I and II, while FEF_{25–75%} was 62.93 $\pm$ 4.03 and 44.17 $\pm$ 3.55 in groups I and II, respectively. A statistically significant difference between FEF_{25–75%} in two groups was detected, and not FEV₁%. On correlation with ACT, there was poor correlation between ACT and FEF_{25–75%}, while no correlation was detected between ACT and FEV₁ (Tables 1 and 3).

Small-airway IOS parameters were statistically significant between controlled and uncontrolled asthma (*P*<0.05). Moreover, small-airways evaluated by IOS indices, R5–20, X5, and AX values strongly correlated significantly with clinical symptoms, assessed by the ACT (Tables 1 and 3 and Figs 2–4). There was high sensitivity and specificity of (R5–20) 80 and 82%, (X5) 80 and 86%, and (AX) 86 and 89% (Table 4).

Table 1 Level of control in the study groups, based on asthma control test

Level of control	Controlled asthma (group I)	Uncontrolled asthma (group II)
<i>N</i>	15/44	29/44
Percentage	34.1	65.9

Table 2 Basic demographic data of patients in both groups

Demographics	Controlled asthma (group I)	Uncontrolled asthma (group II)	<i>t</i> -Test	<i>P</i> value
<i>N</i>	15/44	29/44	–	–
Baseline spirometry				
FEV ₁ , %predicted	81.27 $\pm$ 5.79	78.48 $\pm$ 4.64	3.001	0.091
FEF _{25–75%} , %predicted	62.93 $\pm$ 4.03	44.17 $\pm$ 3.55	252.38	0.001*
Baseline IOS				
R5–20	0.68 $\pm$ 0.31	1.68 $\pm$ 0.29	156.99	0.001*
X5	–0.85 $\pm$ 0.19	–1.40 $\pm$ 0.21	70.989	0.001*
AX	4.40 $\pm$ 2.67	13.45 $\pm$ 2.56	119.95	0.001*
ACT	22.27 $\pm$ 0.80	15.48 $\pm$ 1.40	297.77	0.001*

ACT, asthma control test; FEF, forced expiratory flow; IOS, impulse oscillometry. **P* $\leq$ 0.05, statistically significant.

Discussion

Poor evaluation of asthma control is a crucial element of suboptimal asthma management, so the challenge now is to shift to a management approach based on the level of control [18].

Symptoms and lung function assessment considered the different domains of asthma that correlate poorly over time, so both clinical and functional assessment need to be monitored by physicians to evaluate asthma control [19].

Although no comprehensive tool exists to define asthma control sharply, many tools were used for this purpose, one of these was a five-item self-administered asthma control test [11,12].

In our study according to the ACT score, 65.9% patients had uncontrolled asthma while 34.1% patients had controlled asthma. Similar findings were reported by many previous authors, some reported 37% well-controlled asthma and another hospital-based study found only 28% well-controlled asthma. This was in contrast to other studies that showed controlled asthma was from 47% up to 80% in the studied patients [12,20–22].

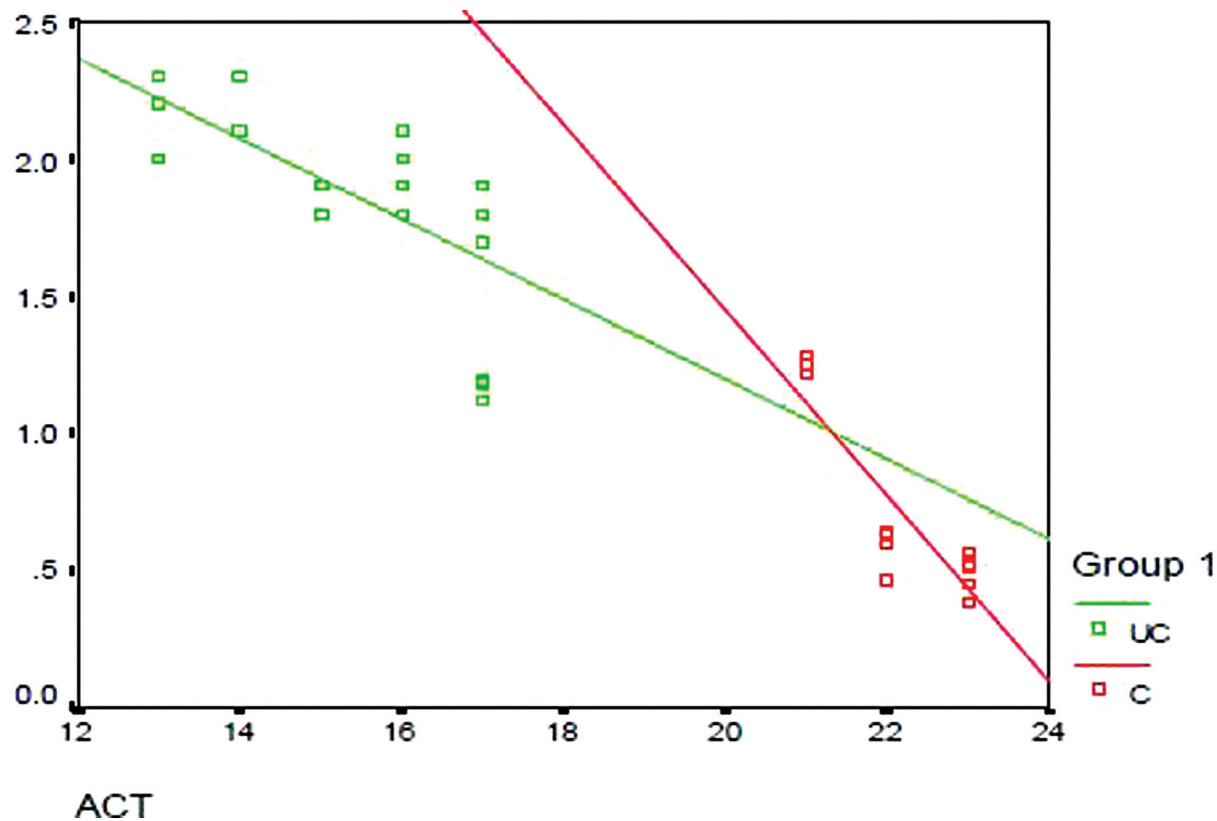
Regarding spirometric values, we analyzed FEF_{25–75%}, the most commonly used indicator of small-airways affection and FEV₁%, where we found that FEF_{25–75%} was statistically significant between the two groups

Table 3 Correlation between spirometric, impulse oscillometry parameters, asthma control test in both groups

Asthma control test	Controlled asthma		Uncontrolled asthma	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
FEV ₁ %	–0.147	0.214	–0.026	0.893
FEF _{25–75%}	0.297	0.107	0.324	0.064
R5–20	–0.814	0.001*	–0.789	0.001*
X5	0.828	0.001*	0.681	0.001*
AX	–0.895	0.001*	–0.658	0.001*

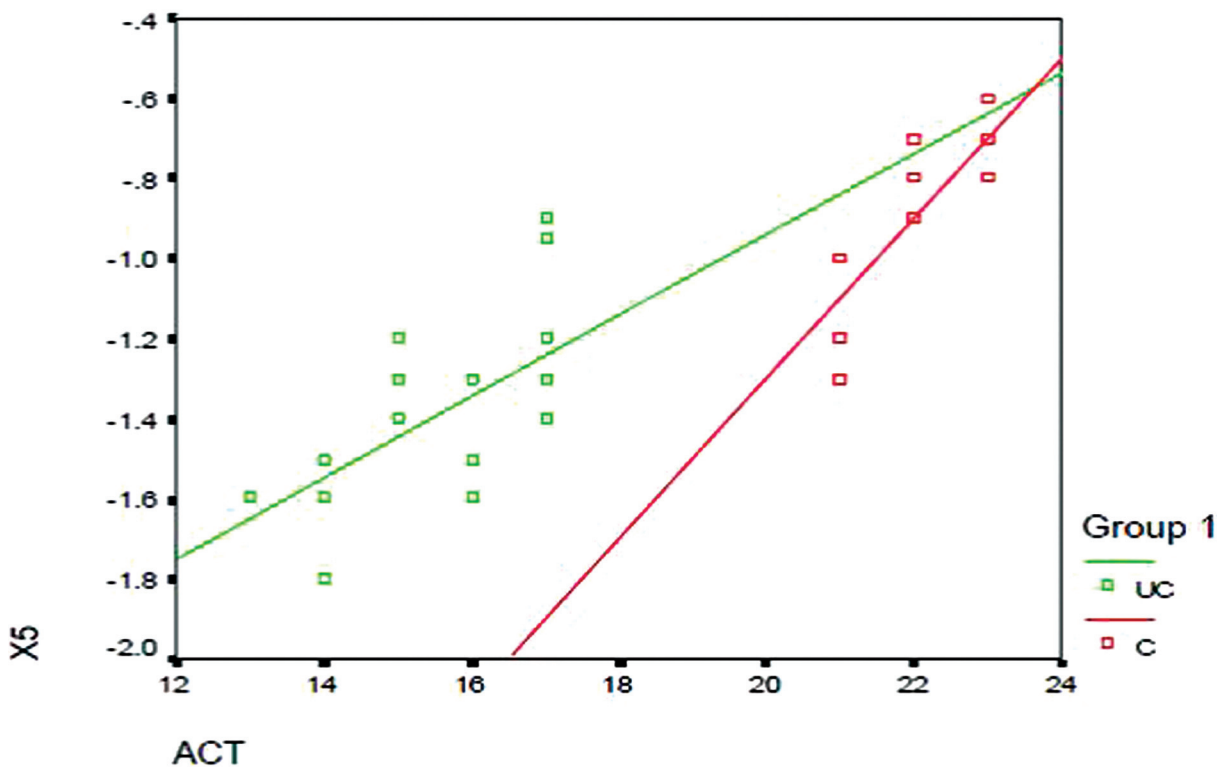
FEF, forced expiratory flow. **P* $\leq$ 0.05, statistically significant.

Figure 2



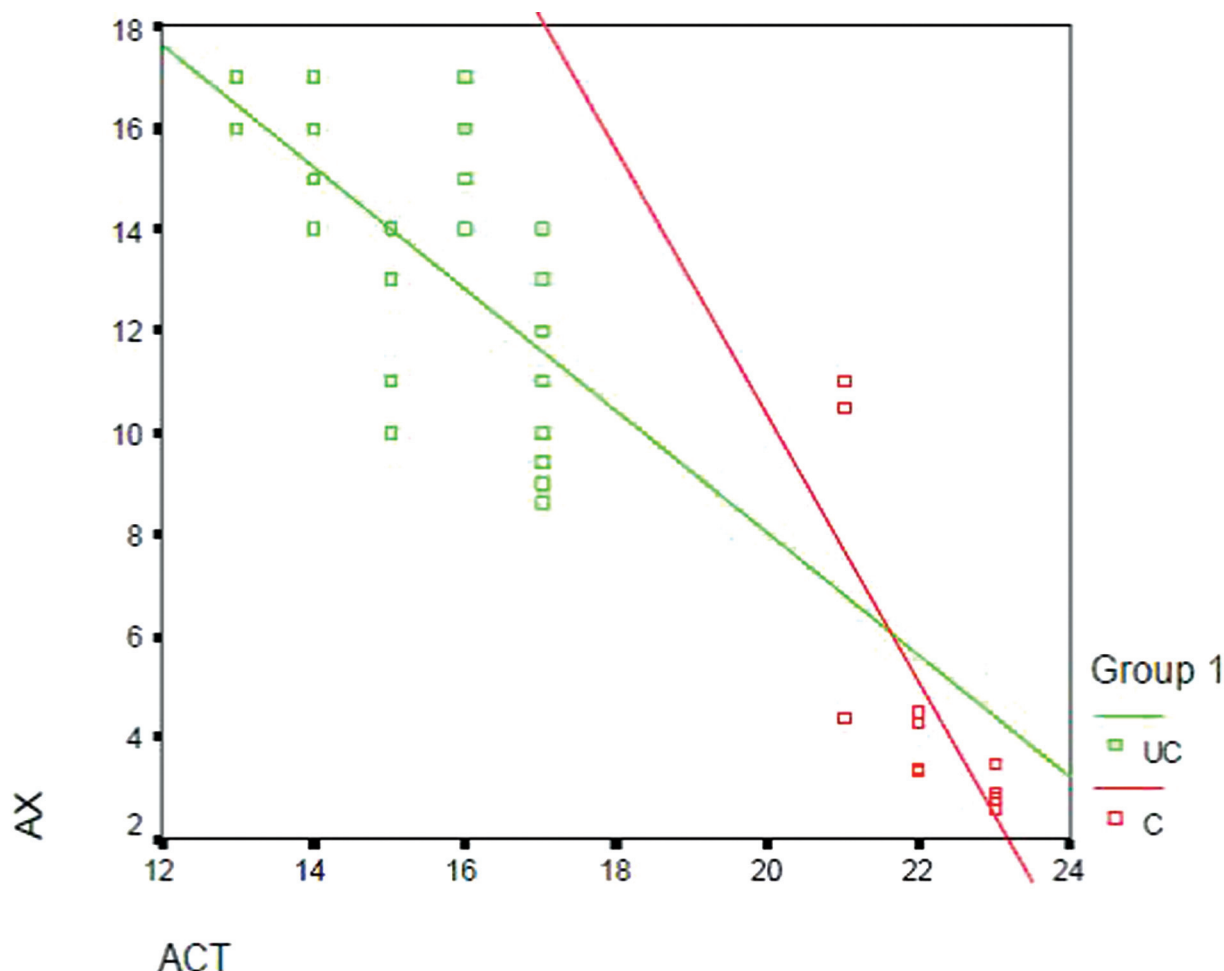
Correlation between R5-20 and asthma control test in both groups.

Figure 3



Correlation between X5 and asthma control test in both groups.

Figure 4



Correlation between AX and asthma control test in both groups.

Table 4 Sensitivity and specificity of impulse oscillometry parameters

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
R5-20	1.2	80	82	70	88	81
X5	-1.0	80	86	75	89	84
AX	10	86	89	81	92	88

NPV, negative predicted value; PPV, positive predicted value.

with no significant correlation between ACT and FEV₁%. These results were highlighted by several studies, indicated only weak correlations between clinical symptoms, and airflow limitation evaluated by FEV₁ [23,24].

Other previous studies by Johnbull *et al.* [20] showed that the correlation between the asthma control test and pulmonary function tests was not significant. This was also in accordance with the findings reported by Green *et al.* [25], Reznik *et al.* [26], and Osborne *et al.* [27].

Unlike our study, Mendoza *et al.* [12], found a correlation between FEV₁ and ACT. This

significant correlation probably was due to a larger study and it was a prospective cohort study. Moreover, Chalise reported positive correlations between FEV₁ and ACT test [12,28].

The poor correlation between ACT and FEF_{25-75%} may be partly due to that asthma symptoms lack specificity and also due to variations in magnitude and time of response to therapy [29].

This poor correlation can be explained first by the presence of marked measurement variability over age range, second by the fact that forced expiratory maneuver tends to exaggerate volume-dependent small-airway closure, which means FEF_{25-75%} degree of variability is affected by effort-dependent expiration from total lung capacity to residual volume. So FEF_{25-75%} is dependent on FVC, and if not adjusted it gives poor reproducibility; moreover, it is frequently normal if the FEV₁/FVC ratio is more than 75%; lastly, there is poor correlation with other markers of small-airways such as FVC and residual volume

(RV)/total lung capacity (TLC) due to the alteration of FVC with air trapping; therefore, there is much doubt about the ability of $FEF_{25-75\%}$ to clarify small-airways affection [30–32].

As for IOS parameters, we found that small-airway IOS parameters were statistically significant between controlled and uncontrolled asthma ($P < 0.05$) with high sensitivity and specificity. Also, these values correlated significantly with clinical symptoms, assessed by ACT. Many previous studies have shown obvious relationship between small-airway assessed by IOS and uncontrolled asthma [33].

Takeda *et al.* [2] found that IOS correlated better with clinical symptoms and disease control in contrast to spirometry FEV_1 that did not contribute to clinical status or dyspnea. Another study by Alferini *et al.* [14] showed that asthmatics with increased peripheral resistance had poorly controlled asthma. Moreover, they did not differ from patients with normal values of peripheral resistance measured by spirometric FEV_1 and FEV_1/FVC .

Explanation

Asthma is considered a complex clinical syndrome, a heterogeneous group of phenotypes and endotypes that shows different responses to therapy, rather than specific disease entity. Nowadays there is a move toward personalizing asthma treatment according to each phenotype [34–36].

So, asthmatic patients with poor control and more exacerbations have persistent airways inflammation. More specifically, those patients show a ‘small-airways phenotype,’ where there is continuous unopposed small-airways inflammation that is not being targeted or controlled by current regular therapies [37].

Small-airways may be site of ventilatory heterogeneity in asthma that shows increases in peripheral airflow resistance even in patients who have normal FEV_1 [30].

Three mechanical factors may explain more airway narrowing: first, more contractility of smooth muscle; second, less of normal inhibiting factors so the muscles never reach maximum force and degree of shortening; third, decreased elastic load, provided by cartilage and the parenchyma. These three mechanisms are intensified in small-airways as they are without cartilage and in asthma they are a site of extensive processes of inflammation and remodeling resulting in destabilization of airways, and so are more liable to bronchospasm [14,38,39].

Many studies suggest the presence of a ‘small-airway asthma phenotype’ that may show normal parameters for conventional pulmonary tests, that is, preserved FEV_1 but poor asthma control and disproportionate, persistent, small-airway affection [40].

Conclusion

IOS provides a useful tool as a marker of asthma control in persistent asthmatic patients. It should be used as a complementary test with spirometry to clarify patients with small-airway asthma phenotype. So, this can focus on recommendations on the importance of a multidimensional control-based strategy in asthma approach of personalized management.

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Conflicts of interest

There are no conflicts of interest.

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