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Small airway involvement in severe asthma: how common is it and what are its implications?

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Abstract

Asthma is a prevalent chronic respiratory disease affecting all age groups globally, causing significant morbidity and mortality. Small airway involvement, often undetected by traditional spirometry, has emerged as a critical aspect of asthma pathophysiology, especially in severe cases. This retrospective observational study aimed to assess small airway dysfunction using impulse oscillometry (IOS) in 94 severe asthma patients. Results indicated that 27.3% of patients had small airway obstruction. While spirometry showed no statistical differences between groups, IOS parameters were significantly different, highlighting its sensitivity in detecting small airway disease. Patients with small airway involvement exhibited poorer asthma control, emphasizing the clinical relevance of identifying and addressing small airway dysfunction. The study underscores the need for comprehensive evaluation tools like IOS alongside spirometry, especially in severe asthma management. Further large-scale studies are warranted to validate IOS's utility in optimizing therapeutic strategies and improving asthma control, particularly in resource-limited settings. Recognizing and addressing small airway involvement could lead to individualized management approaches and better outcomes in severe asthma patients.

Key words: inspiratory oscillometry, small airway diseases, severe asthma.

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Introduction

Asthma is a common chronic disease that causes respiratory symptoms, limitation of activities, and attacks that sometimes require urgent medical care and, in some cases, may be fatal. It is a serious global health problem that involves all age groups. According to the Global Initiative for Asthma (GINA) guidelines 2023, asthma is defined as a heterogeneous disease usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

To improve the quality of life among asthmatics, appropriate control of asthma is needed. Despite the best possible treatment, around 5% of patients suffer from severe asthma [1]. Severe asthma is the asthma that requires treatment with guidelines-suggested medications for GINA steps 4-5 asthma [high-dose inhaled corticosteroids (ICS) and long-acting β-agonists or leukotriene modifier/theophylline] for the previous year or systemic corticosteroids (CS) for >50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy [2].

Conventionally, asthma is considered a large airway disease, but recent studies report involvement of the small airways in asthma [3]. The small airways are defined as airways with an internal diameter of less than 2 mm [4]. The role of small airway involvement in this condition cannot be neglected, and due to the fact that small airways contribute only a small proportion of total airway resistance, disease in small airways needs to be widespread so as to be picked up on spirometry. Secondly, the involvement of small airways in asthma has therapeutic implications, as the majority of standard inhaled corticosteroids used for asthma management tend to deposit predominantly in larger airways, with very little deposition in the distal peripheral portion of the lung [5]. To assess small airway involvement, various methods (functional and radiological methods) are available. Histopathological examination is the closest to being the "gold standard", but being an invasive test, it is difficult to perform in all patients.

Among functional methods other than the usual spirometry, impulse oscillometry (IOS) is an important tool for assessing small airway disease. IOS is a variant of the forced oscillation technique, described by Dubois over 50 years ago, that permits passive measurement of lung mechanics [6]. Sound waves are superimposed on normal tidal breathing, and the disturbances in flow and pressure caused by the external waves are used to calculate parameters describing airflow resistance and reactive parameters. It is a non-invasive test, easy to perform, and requires only minimal patient cooperation. It can differentiate easily between small and large airway obstruction (LAO) and is more sensitive than spirometry for peripheral airway disease. Among asthmatics, it can be used for assessing bronchodilator responsiveness and for bronchoprovocation testing [6].

In recent years, there has been significant interest in small airways disease, and new insights have emerged regarding the role of

these small airways in the clinical expression of asthma [7]. Use of a simple non-invasive technique for the assessment of small airways in severe asthma patients is the need of the hour. However, there is a paucity of knowledge in the correlation of small airway involvement and the severity of asthma. To answer this question, we have planned this study to assess small airway involvement by IOS in patients with severe asthma and its clinical impact on the same.

Primary objective

To evaluate small airway dysfunction in severe asthma patients by IOS and its correlation with the pulmonary function test and control of asthma.

Materials and Methods

This was a retrospective observational study undertaken at Metro Centre for respiratory diseases, Noida, India. The study period was between June 2017 and June 2019. Patients aged >18 years with severe asthma [on Step 4 and 5 treatment with poor control – Asthma Control Test (ACT) <20] as per GINA guidelines available at that time were included in the trial.

Exclusion criteria were age <18 years, pregnancy, and the presence of other coexisting diseases such as chronic obstructive airway disease, bronchiectasis, allergic bronchopulmonary aspergillosis, pulmonary tuberculosis, and interstitial lung disease.

Patients' demographic data, radiographic findings, as well as clinical details, including age of onset, symptoms, and comorbidities, were recorded. Spirometry was performed in all patients as per American Thoracic Society/European Respiratory Society guidelines, and the following parameters were measured: forced expiratory volume in 1 second (FEV1) (%), forced expiratory flow at 25% (FEF25) (%), forced expiratory flow at 50% (FEF50) (%), forced expiratory flow at 75% (FEF75) (%), Residual Volume (RV) (%), and RV/Total Lung Capacity (%). IOS was performed using the Jaeger IOS machine (Vyaire Medical, Höchberg, Germany), and the patients were categorized into LAO, small airway obstruction (SAO), or normal airway obstruction (N) on the basis of pre-defined cut-offs of resistance at 5 Hz (R5), resistance at 20 Hz (R20), Small Airway Resistance Index (R5-20), area of reactance (Ax) and resonant frequency (Fres). Patients with R5 and R20, both values >150% were categorised as LAO; R5>150% and R20<150% were classified as small airway function, and both values <150% were categorised as normal. As there are no Indian equations for predicted values, western equations for predicted values were used. fractional exhaled nitric oxide (FeNo) levels were also measured in these patients by using HYPAIR FeNO (MEDISOFT, Sorinnes, Belgium). The patient also underwent single-point immunoglobulin E (IgE) testing and Absolute Eosinophil Count (AEC) testing. The devices used to measure both IgE and AEC values were MiniVIDAS (bioMérieux, Marcy-l'Étoile, France) and XL 1000 (Erba Diagnostics Mannheim, Germany), respectively. All this was done on an outpatient department (OPD) basis when they were already on optimized treatment, and a single point ACT score was taken in our study. Comparative analysis was done between these groups with respect to symptoms and spirometry values (IgE, FeNo, and AEC).

Statistical analysis

Categorical variables were presented in numbers and percentages (%), and continuous variables were presented as means ± standard deviations and medians. Normality of data was tested by the Kolmogorov-Smirnov test. Quantitative variables were compared using analysis of variance/Kruskal-Wallis Test (when the data sets were not normally distributed) between the three groups. Qualitative variables were correlated using the Chi-Square test. The Spearman rank correlation coefficient was used to assess the correlation between IOS parameters and spirometric parameters. A p-value of <0.05 was considered statistically significant. Analysis was done using Statistical Package for Social Sciences (SPSS) 21.0 (IBM, Armonk, NY, USA).

Results

A total of 94 severe asthma patients were enrolled in the study during the 2-year period (2017-2019), attending OPD and meeting the inclusion criteria. The mean age of the patients was 53.8±14.0 years. In the study group, 58% were females (n=54). Age of onset of respiratory symptoms above 30 years was seen in 70% of patients. Family history of asthma was reported in 55%. The study cohort had an average of 1.6 exacerbations in the past year. A significant proportion of the patients (84%) had previously received oral corticosteroid therapy. The average peripheral eosinophil count across the cohort was 298 cells/µL. Smoking history was present in 10 out of the 94 patients (10.6%). Shortness of breath and wheezing were reported in 2/3rd of patients, and among the comorbidities, allergic rhinosinusitis was the most common comorbidity, followed by gastroesophageal reflux disease, hypertension, hypothyroidism, and diabetes, as mentioned in Table 1.

High-resolution computed tomography of the chest was reported normal in 40%, bronchial wall thickening (34%) being the most common abnormal finding, followed by air trapping and mosaic attenuation (20%), and bronchial dilatation in 6%. Table 2 shows the spirometric and IOS parameters of these groups along with clinical and laboratory values.

Small airways disease diagnosed by IOS, as per predefined criteria, was observed in 27.3% (29/94) of severe asthmatics. Asthma control was poorest in SAO patients with a more frequent positive family history. There was no statistical difference between the three groups regarding symptoms or comorbidities (Table 1). Also, body mass index, serum IgE total, AEC, and FeNO were not statistically different in any group.

IOS indices, R5, R20, X5, and Fres were statistically different in all three groups. Although total airway reactance (X5) in large as well as small airway groups was not statistically different, 'Small Airway Index' (D_{5-20}) was high in all three groups, with significantly higher values in the small airway disease group as compared to the large airway and normal airway group patients. This signifies that even in cases with LAO, small airways were involved too. This explains abnormal reactance (X5) and Fres in both large and SAO groups, both being also markers of small airway disease. Among lung volumes, RV% predicted was statistically high in both the small and large groups, but was normal in asthmatics with normal IOS.

Spirometry indices showed reduced FEV1/FVC ratio in all groups, with no statistical difference between them. FEV1, FEF25, and FEF50 (absolute and % predicted) were not statistically different in any group. Only FEF75 predicted was statistically different among groups, but not between LAO *vs.* SAO groups, indicating it as a poor marker of small airway involvement in severe asthma (Figure 1). Reversibility testing seen on spirometry indices as well as on IOS was not statistically different.

Discussion

Asthma is defined as a chronic heterogeneous inflammatory disease of predominantly large airways associated with airway hyper-

Table 1. Clinical findings in large, small or no obstruction (as per impulse oscillometry parameters).

Parameter	L (n=47), n (%)	N (n=18), n (%)	S (n=29), n (%)	Chi square test (p)
SEX				
Female	35 (37)	6 (6)	13 (14)	0.0028
Male	12 (13)	12 (13)	16 (17)	
Clinical findings				
Allergic symptoms	24 (26)	11 (12)	16 (17)	0.762
Chest tightness	28 (30)	10 (11)	22 (23)	0.2565
Cough	26 (28)	11 (12)	18 (19)	0.8193
Shortness of breath	31 (33)	14 (15)	22 (23)	0.5171
Wheeze	30 (32)	9 (10)	22 (23)	0.1913
Family h/o allergy	29 (31)	5 (5)	18 (19)	0.0328
Allergic rhinosinusitis	24 (26)	11 (12)	16 (17)	0.762
GERD	21 (22)	6 (6)	11 (12)	0.6689
Hypertension	13 (14)	5 (5)	9 (10)	0.9467
Hypothyroidism	11 (12)	8 (9)	4 (4)	0.0577
OSAHS	4 (4)	3 (3)	1 (1)	0.2876

L, large airway obstruction; S, small airway obstruction; N, no airway obstruction; h/o, history of; GERD, gastroesophageal reflux disease; OSAHS, obstructive sleep apnea-hypopnea syndrome.

responsiveness and variable airflow obstruction. While asthma has traditionally been thought of as a disease of the larger airways, there is increasing interest in identifying the role of small airway disease in asthmatics [3,4].

The overall prevalence of small airway disease in adult asthmatics varies worldwide and depends on the physiological test used to assess it. According to the systematic review by Usmani *et al*., small airways disease is highly prevalent in asthma, with a reported prevalence of 50-60% [8]. Small airways are involved across all asthma severities, with evidence of distal airway disease even in the absence of proximal airway obstruction. Hence, asthma affects the entire bronchial tree, and involvement of the small airway is being recognized as a major area of airflow limitation [4,9]. However, there is a paucity of literature on small airway dysfunction in severe asthma patients. The major reason is that small airways dysfunction remains undetected by conventional spirometry, which is used routinely to

	LAO			NAO			SAO		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
FEF75 (L/s)	2.3	1.82	94	4.04	2.97	94	2.41	2.05	94

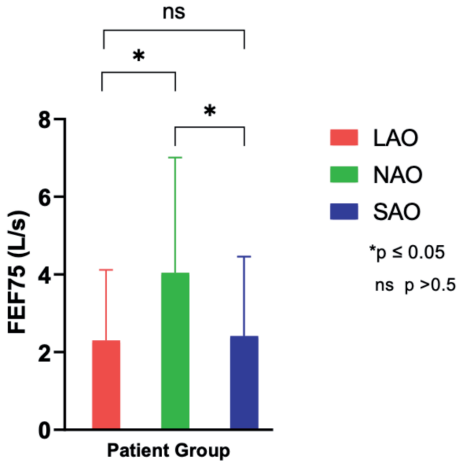

Figure 1. Forced expiratory flow at 75% (FEF75) predicted was statistically different among groups but not between large airway obstruction (LAO) vs. small airway obstruction (SAO) groups, indicating it as a poor marker of small airway involvement in severe asthma. SD, standard deviation; NAO, no airway obstruction; ns, not significant (p>0.05).

evaluate these patients. Spirometry lacks the sensitivity to pick up small airway dysfunction till >75% of them are involved [10]. It has been shown in studies that small airway involvement in asthma is related to the severity of symptoms and poor asthma control.

IOS is a simple, non-invasive, and effortless technique for assessing small airways that requires only passive patient cooperation. It allows measurement of both airway resistance and reactance. IOS is based on the physiologic principles of the forced oscillation technique. It uses sound waves for evaluating airway characteristics and requires only the normal tidal breathing from

Table 2. Spirometry, lung volumes and impulse oscillometry parameters in large airway, small airway and no obstruction groups in severe asthma.

Parameter	L (mean±SD)[1]	N (mean±SD)[2]	S (mean±SD)[3]	kw.pval[4]	N-L (p-value)[5]	S-L (p-value)[6]	S-N (p-value)[7]
Age (years)	50.17±13.03	59.17±13.3	56.34±14.83	0.0169	0.0190	0.1175	0.3518
BMI (Kg/m^3)	29.13±6.89	28.22±5.79	27.1±4.15	0.6404	0.8486	0.8486	0.8486
IGE (IU/ml)	284.49±349	337.83±403.43	245.76±260.59	0.7784	0.7565	0.7565	0.7565
AEC (/cumm)	291.68±218.54	252.72±179.57	360.34±398.42	0.7521	0.7782	0.8390	0.7782
ACT	17.47±1.74	18.44±1.85	16.17±2.05	0.0007	0.0438	0.0098	0.0022
R5 [kPa/L/s]	0.88±0.24	0.41±0.16	0.61±0.17	0.0000	0.0000	0.0000	0.0000
R5 [in percentage]	248.36±64.04	124.33±16.07	182.24±39.25	0.0000	0.0000	0.0000	0.0000
R20 [kPa/L/s]	0.57±0.11	0.31±0.08	0.37±0.06	0.0000	0.0000	0.0000	0.0028
R20 [in percentage]	188.23±34.43	114.33±18.08	127.07±16.34	0.0000	0.0000	0.0000	0.0191
R5 MINUS R20	0.31±0.21	0.09±0.1	0.24±0.16	0.0000	0.0000	0.0851	0.0001
D5-20	65.25±36.33	41.24±31	82.97±75.97	0.0153	0.0175	0.4704	0.0296
x5	-0.39±0.33	-0.17±0.23	-0.34±0.25	0.0001	0.0001	0.1517	0.0064
Fres	31.79±6.86	19.78±6.09	24.21±8.36	0.0000	0.0000	0.0000	0.0373
FEV_1/FVC	60.38±11.25	64.45±8.49	56.22±12.23	0.0547	0.2067	0.1626	0.0722
FEV_1	1.32±0.62	1.66±0.88	1.41±0.73	0.5146	0.6460	0.6884	0.6460
%	55.7±18.7	61.5±22.13	50.24±16.78	0.1801	0.3671	0.3310	0.2231
FEF25	0.32±0.23	0.4±0.34	0.3±0.21	0.6527	0.6431	0.6431	0.6431
%	17.49±10.53	23.33±15.56	16.34±9.82	0.3292	0.3649	0.5886	0.3649
FEF50	0.99±0.85	1.44±1.09	0.95±0.79	0.1886	0.2230	0.7082	0.1884
%	25.96±18.24	34.39±22.81	23.52±15.78	0.2613	0.4166	0.5779	0.2218
FEF75	2.3±1.82	4.04±2.97	2.41±2.05	0.0451	0.0406	0.7687	0.0406
%	39.62±26.43	52.28±32.02	36.83±27.35	0.1194	0.1827	0.3774	0.1541
DLco[%]	82.3±13.63	88.28±14.54	80.28±12.05	0.0766	0.1000	0.5559	0.0808
RV[L]	2.57±1.29	2.11±0.63	2.6±0.89	0.1730	0.3792	0.3923	0.1429
RV[%]	144.11±68.46	112.11±38.48	138.34±46.16	0.0399	0.0342	0.9659	0.0342
RV/TLC[L]	52.27±15.2	49.78±16.58	52.26±14.39	0.8907	1.0000	1.0000	1.0000
RV/TLC[%]	143.36±32.54	134.5±36.9	142.9±31.09	0.4814	0.4476	0.9191	0.4476
Post FVC	2.43±0.84	2.48±1.13	2.58±0.84	0.7707	0.8286	0.8286	0.8286
Post % pred	83.63±18.37	76.28±26.56	76.75±14.73	0.1049	0.1805	0.1805	0.8043
Post %change	8.93±8.25	9.94±13.48	11.46±13.73	0.6623	0.7288	0.7627	0.7288
Post FEV1	1.64±0.71	1.68±1.02	1.68±0.8	0.921	0.9422	0.9422	0.9422
Post %pred	67±20.89	61.61±25.05	59.07±17.43	0.2857	0.5433	0.3798	0.8306
Post % change	11.63±9.64	9.89±12.94	11.64±12.69	0.2685	0.2578	0.5881	0.2578
MMEF	30.41±32.46	20.56±21.37	28.43±29.11	0.1323	0.1095	0.5	0.412
Ax Pre	4.43±3.21	2.77±3.8	3.2±3.38	0.0153	0.0275	0.0613	0.4898
Ax post	2.77±2.31	1.86±2.91	2.23±2.23	0.0362	0.0425	0.248	0.1519
Ax % Change	38.34±26.43	41.24±26.75	328.37±1458.35	0.9063	0.885	0.885	0.885

SD, standard deviation; BMI, body mass index; IgE, immunoglobulin E; AEC, absolute eosinophil count; ACT, Asthma Control Test; R5, resistance at 5 Hz; R20, resistance at 20 Hz; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25, forced expiratory flow at 25% of forced vital capacity; FEF50, forced expiratory flow at 50% of forced vital capacity; FEF75, forced expiratory flow at 75% of forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; RV, residual volume; TLC, total lung capacity; MMEF, maximum mid-expiratory flow (FEF25–75); Ax Pre, area of reactance (pre-bronchodilator); Ax post, area of reactance (post-bronchodilator). [1]L (mean±SD) provides average and standard deviation value for the parameters for the large airway group; [2]N (mean±SD): provides average and standard deviation value for the parameters for the normal airway group; [3]S (mean±SD) provides average and standard deviation value for the parameters for the small airway group; [4]kw.pval: is the p-value for Kruskal-Wallis test. This test compares whether the average value for the selected parameter (example: age) is significantly different across the 3 study groups (in our case, L, N, and S groups). If the kw.pval is significant (*i.e.*, ≤0.05), it indicates that the average value of the corresponding parameter is significantly different across the L, N, and S groups. If kw.pval is not significant (*i.e.*, >0.05) it indicate the average value of corresponding parameter is not statistically/significantly different across L, N and S group; [5]N-L (p-value) provides the p-value for comparison between the normal and large airway groups for the corresponding parameter; [6]S-L (p-value) provides the p-value for comparison between Small and Large airway group for the corresponding parameter; [7]S-N (p-value) provides the p-value for comparison between Small and Normal airway group for the corresponding parameter.

the patient. IOS may provide a useful measure in identifying small airway disease in patients with severe asthma as an add-on to spirometry. The IOS values obtained are sensitive, reproducible, and correlate well with spirometry [11]. The resistance at 5 Hz (R5) reflects the total airway resistance; whereas, the resistance at 20 Hz (R20) reflects the large airways resistance. So, small-airways resistance can be measured by subtracting R20 from R5, and can be used with X5, Fres, and AX to assess the degree of peripheral airway obstruction. The ATLANTIS study showed that the lowest prevalence of SAD was diagnosed when a multiple-breath nitrogen washout test was performed. The maximum number of patients were diagnosed with a combination of IOS with spirometry [12]. In our study, both IOS and spirometry were used for the evaluation of small airway involvement in severe asthmatics, and it was found that the incidence of small airway disease is 27.3% (Figure 2).

The mean age of severe asthmatics in our study was 53.8±14.0 years. This finding is similar to the previous study by Nikkhah *et al*., where the mean age was 45±19 years [12]. In another study by Mousa *et al*., the mean age of patients in the asthma group was 44.92 years, and that of the control group was 34.05 years [13]. In our study, there were 57.45% females and 42.55% males. Similar findings have been found in multiple studies, with predominance of female cases being more frequently having severe asthma [11,13].

Inadequate control of asthma is associated with increased risk of exacerbations, impaired quality of life, increased health-care utilization, and reduced productivity. Studies and systematic reviews have found that small airway involvement in asthmatics leads to poor asthma control, more severe bronchial hyper-responsivity, and increased severity and risk of future exacerbations [3,4,14]. The ATLANTIS study also showed increased prevalence of small airway involvement as the severity of the asthma amplified. More severe asthmatics had a higher prevalence of SAD [12]. Similar results have been found in our study, where among the severe asthmatics with predominant SAD, there were poor ACT scores (Figure 3) as compared to the patients with normal or LAO. The ACT of the small airway group was 16.17±2.05 *vs.* 17.47±1.74 in the normal airway group, with a significant p-value (0.002).

In our study, it was also found that, though FEV1 varied in the three groups, it was not statistically different across them. Values of FEV1% predicted, pre or post, were not statistically different between patients with small airway involvement, *vis-à-vis* LAO or no obstruction on IOS. Raised RV% predicted was statistically significant between the SAO and LAO group *vs.* the no obstruction on IOS, indicating air trapping in both groups. Similar trends have been found in previous studies where IOS and spirometry have been used to diagnose SAD presence in asthmatics [11,13]. This again highlights the fact that alone, spirometry is insufficient in the assessment of patients with severe asthma.

The impact of any inhaled medications depends on their successful distribution to all the areas of the lung involved. Targeting small airway inflammation in severe asthma is critically important, as the combined surface area of small airways far exceeds that of central airways. Extra-fine particle ICS seems to improve airway hyperresponsiveness more due to deposition of fine ICS particles in small airways [15]. Addition of such a therapeutic strategy may improve asthma control in patients with severe asthma due to significant small airway disease and would require further large-scale studies.

There are a few limitations of our study. First, being a single tertiary centre study, we had referred severe asthma patients skewed from the community. Secondly, our private center had patients from middle and upper socio-economic strata with minimal representation from poor strata. Thirdly, the total number of cases was low; the results of IOS cannot be extrapolated to identify small airway dysfunction in the general population. Fourth, though the study was retrospective, it still had comprehensive data for the

	R5 (kPa/L/s)			R20 (kPa/L/s)			R5 minus R20 (kPa/L/s)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
LAO	0.88	0.24	94	0.57	0.11	94	0.31	0.21	94
NAO	0.41	0.16	94	0.31	0.08	94	0.09	0.1	94
SAO	0.61	0.17	94	0.37	0.06	94	0.24	0.16	94

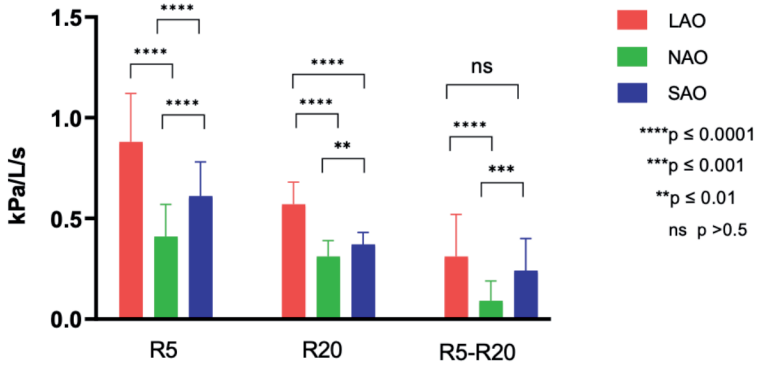

Figure 2. Small airway index (R5-R20) is elevated in all groups. SD, standard deviation; LAO, large airway obstruction; NAO, no airway obstruction; SAO, small airway obstruction.

	LAO			NAO			SAO		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
ACT Score	17.47	1.74	94	18.44	1.85	94	16.17	2.05	94

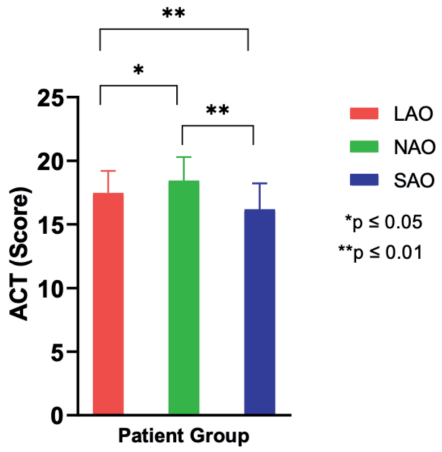

Figure 3. Asthma Control Test (ACT) score is lowest in patients with small airway obstruction. SD, standard deviation; LAO, large airway obstruction; NAO, no airway obstruction; SAO, small airway obstruction.

evaluation of small airways, as patients in our severe asthma clinic had protocols in place for complete evaluation of every new case coming to the clinic, but no data were available to clarify therapeutic actions and responses in these patients. Lastly, we used IOS parameters with predicted equations from western data, as no Indian predicted normal for R5 and R20 are available. However, the small airway index (D5-20) used in our study is expected to adjust for this shortcoming of R5 and R20 parameters.

The cost of the IOS equipment is of major importance in resource-limited settings in India. Large and multi-centric studies are needed to validate the utility of IOS in identifying small airway dysfunction and its subsequent impact on changes in therapeutics to improve overall asthma control in severe asthmatics, who otherwise have costly biological options or oral steroids with high morbidity.

Conclusions

Asthma, conventionally considered a large- and medium-sized airway disease, and small airway dysfunction as an extension of disease pathophysiology to the periphery of the lungs, is now being detected with better diagnostics. However, severe asthmatics with predominant small airway involvement in nearly one-fourth of patients is puzzling and explains why many patients, despite adequate asthma therapy, continue to suffer. Perhaps this is due to the largely unaddressed issue of small airways by routine therapies. IOS appears to be a useful tool to identify small airway involvement in patients with bronchial asthma, but it needs to be used in conjunction with spirometry. Recognition of small airway involvement in severe asthma would prompt future individualized management and improve asthma control. This is clearly another modifiable factor in the difficult-to-treat algorithm in severe asthma management or a separate phenotype.

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