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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.

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 group.

According to Global initiative for Asthma guidelines (GINA) 2023 asthma is defined as a heterogenous 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 best possible treatment around 5% of patients suffer from severe asthma [1]. Severe asthma is the Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for >50% of the previous year to prevent it from becoming ''uncontrolled'' or which remains ''uncontrolled'' despite this therapy [2].

Conventionally asthma is a large airway disease but recent studies report involvement of 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 airway needs to be widespread so as to be picked up on spirometry. Secondly involvement of small airways in asthma has therapeutic implications as majority of standard inhaled corticosteroids used for the management of asthma tends to deposit predominantly in larger airways with very little deposition in distal peripheral portion of 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 is difficult to perform in all patients.

Among functional methods other than the usual spirometry, Impulse oscillometry (IOS) is an important tool for assessment of small airway disease assessment. Impulse oscillometry (IOS) is a variant of 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 the resistance to airflow and reactive parameters. It's a non-invasive test, easy to perform, and requires only minimal patient cooperation. It can differentiate easily between small and large airway obstruction and is more sensitive than spirometry for peripheral airway disease. Among asthmatics it can be used for assessment of bronchodilator responsiveness and bronchoprovocation testing [6].

In the past years there has been great interest in small airways disease and some new insights have been gained about the contribution of these small airways to the clinical expression of asthma [7]. Use of a simple non-invasive technique for the assessment of small airways in severe asthma patient is the need of the hour.

However there is paucity of knowledge in the correlation of small airway involvement and 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 patient by impulse oscillometry 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 to June 2019. Patient 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 presence of other coexisting diseases such as Chronic obstructive airway disease (COPD), Bronchiectasis, ABPA, 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 ATS/ERS guidelines and following parameters were measured; FEV1(%), FEF 25(%), FEF 50(%), FEF 75(%), RV (%), RV/TLC (%). IOS was performed using Jaeger IOS machine and the patients were categorised into large airway obstruction (LAO) small airway obstruction (SAO) or normal airway obstruction (N) on the basis of pre-defined cut offs of R5, R20, R5-20, Ax and Fres. Patients with R5 and R20 both values > 150% were categorised as large airway obstruction, R5 > 150 % and R20 < 150 % were categorised 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. FeNo levels were also measured in these patients by using HYPAIR FeNO (MEDISOFT) . Patient also underwent single point IgE testing and AEC testing, device used to measure both IgE and AEC values were MiniVIDAS and XL1000 respectively. All this was done on OPD basis when they were already on optimized treatment and single point ACT score was taken in our study. Comparative analysis was done between these groups in respect to symptoms and spirometry values, [IgE,FeNO and AEC].

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. Quantitative variables were compared using ANOVA/Kruskal Wallis Test (when the data sets were not normally distributed) between the three groups. Qualitative variables were correlated using Chi-Square test. 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.

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. Mean age of the patients was 53.8 ± 14.0 years. 58% females were there in the study group (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 (OCS) 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 (GERD), hypertension, hypothyroidism and diabetes as mentioned in Table 1.

HRCT 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, IOS parameters of these groups along with clinical and laboratory values.

Small airways disease diagnosed by IOS as per predefined criteria was in 27.3% (29/94) of severe asthmatics. Asthma control was poorest in small airway obstruction patients with more frequency of positive family history in these also. There was no statistical difference between three groups regarding symptoms or comorbidities (Table 1). Also BMI, 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 group was not statistically different but 'Small airway index' (D_{5-20}) was high in all three groups with significantly higher values in small airway disease group as compared to large airway and normal airway group patients. This signifies that even in cases with large airway obstruction small airways were involved too.

This explains abnormal reactance (X5) and Fres in both large and small airway obstruction groups, both being also markers of small airway disease. Among lung volumes, RV % predicted was statistically high in small and large group, but was normal in asthmatics with normal IOS. Spirometry indices showed reduced FEV_1/FVC ratio in all groups with no statistical difference between them. FEV_1, FEF_{25} and FEF_{50} (absolute and % predicted) were not statistically different in any group. Only FEF_{75} percent predicted was statistically different among groups but not between LAO versus 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 were not statistically different.

Discussion

Asthma is defined as a chronic heterogeneous inflammatory disease of predominantly large airways associated with airway hyperresponsiveness and variable airflow obstruction. Whilst asthma has traditionally been thought of 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 also varies with the physiological test used to assess it. As per the systematic review by Usmani et al small airways disease is highly prevalent in asthma with a reported prevalence of 50 to 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 entire bronchial tree and involvement of small airway is being recognized as major area of airflow limitation [4,9]. However there is paucity of literature on small airway dysfunction in severe asthma patients. The major reason being small airways dysfunction remain undetected by conventional spirometry which is being used routinely evaluate these patients. Spirometry lacks the sensitivity to pick up small airway dysfunction till > 75 % of them being gets involved [10]. It has been shown in studies that small airways involvement in asthma is related to severity of symptoms and poor asthma control.

Impulse oscillation system (IOS) is a simple, non-invasive, and effortless technique for the assessment of small airways, which requires only passive patient cooperation. It allows the measurement of both the airway resistance and the 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 patient. IOS may provide a useful measure in identifying small airway disease in patients with severe asthma as 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. ATLANTIS study showed that lowest prevalence of SAD got diagnosed when multiple breath nitrogen wash out test was performed. The maximum number of patients were diagnosed with combination of IOS with spirometry [12]. In our study both IOS and spirometry were used for 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 average 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 year [12]. In another study by Mousa H et al, the mean age of patients in Asthma group was 44.92 years and that in control group was 34.05 years [13]. In our study, there were (54/94) 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 responsiveness and increased severity and risk of future exacerbations [3,4,14]. ATLANTIS study also showed increased prevalence of small airway involvement as the severity of the asthma amplified. More severe asthmatics had higher prevalence of SAD(12). Similar results have been found in our study where among the severe asthmatics with predominant SAD had poor ACT scores (Figure 3) as compared to the patients with normal or large airway obstruction. 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 FEV_1 varied in 3 groups but it was not statistically different between the three groups. Value of FEV_1 % predicted, pre or post were not statistically different between patients with small airway involvement vis a vis with large airway obstruction or no obstruction on IOS. Raised RV % predicted was statistically significant between small and large airway obstruction group versus no obstruction on IOS, indication air trapping in both groups. Similar trends have been found in previous studies where IOS and spirometry has been used to diagnose SAD presence in asthmatics [11,13]. This again highlights the fact that alone spirometry is insufficient in assessment of patients with severe asthma.

The impact of any inhaled medications depend upon its successful distribution to all the areas of lung involved. Targeting small airways inflammation in severe asthma is critically important as the combined surface area of small airways far exceeds the surface area of central airways. Extra-fine particle ICS seems to improve airway hyperresponsiveness more due to deposition of fine ICS particle in small airways [15]. Addition of such 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 few limitations of our study. First being a single tertiary centre study, we had referred severe asthma patients skewed from community. Secondly, ours being private centre 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 study being retrospective but still had comprehensive data for 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 was 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, R20 are available. However, 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 of 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 overall improve asthma control in severe asthmatics which otherwise have costly biologicals option or oral steroids with high morbidity.

Conclusions

Asthma conventionally being considered as large and medium sized airways disease and small airway dysfunction as an extension of disease pathophysiology to periphery of lungs is now being detected with better diagnostics. But severe asthmatics with predominant small airway involvement in nearly $1/4^{th}$ of patients is puzzling and explains why many patients despite adequate asthma therapy continue to suffer. Perhaps this is due to largely unaddressed issue of small airways by routine therapies. IOS appears to be useful tool to identify small airway involvement in patients with bronchial asthma but needs to be used in conjunction with spirometry. Recognition of small airway involvement in severe asthma would prompt in future individualised management and to improve asthma control. This is clearly another modifiable factor in Difficult to Treat algorithm in severe asthma management or a separate phenotype.

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Table 1. Clinical Findings in large, small or no obstruction (as per IOS parameters)

Parameter	L(n=47)	N(n=18)	S(n=29)	Chi square test(p-value)
SEX				0.0028
Female	35 (37%)	6 (6%)	13 (14%)	
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

Table 2. Spirometry, lung volumes and IOS 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 (pvalue)[5]	S-L (pvalue)[6]	S-N (pvalue)[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
R 20[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

[1]L (Mean±SD): provides average and standard deviation value for the parameters for Large airway group; [2]N (Mean±SD): provides average and standard deviation value for the parameters for Normal airway group; [3]S (Mean±SD): provides average and standard deviation value for the parameters for Small airway group; [4]kw.pval : is the p value for Kruskal-Wallis test. This test compares if the average value for the selected parameter (example: Age) is significantly different across the 3 study group (in our case L,N and S group). if the kw.pval is significant (i.e. <=0.05) it indicate the average value of corresponding parameter is significantly different across L,N and S group. 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 (pvalue) : Provides the p value for comparison between Normal and Large airway group for the corresponding parameter; [6]S-L (pvalue) : Provides the p value for comparison between Small and Large airway group for the corresponding parameter; [7]S-N (pvalue) : Provides the p value for comparison between Small and Normal airway group for the corresponding parameter.

	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

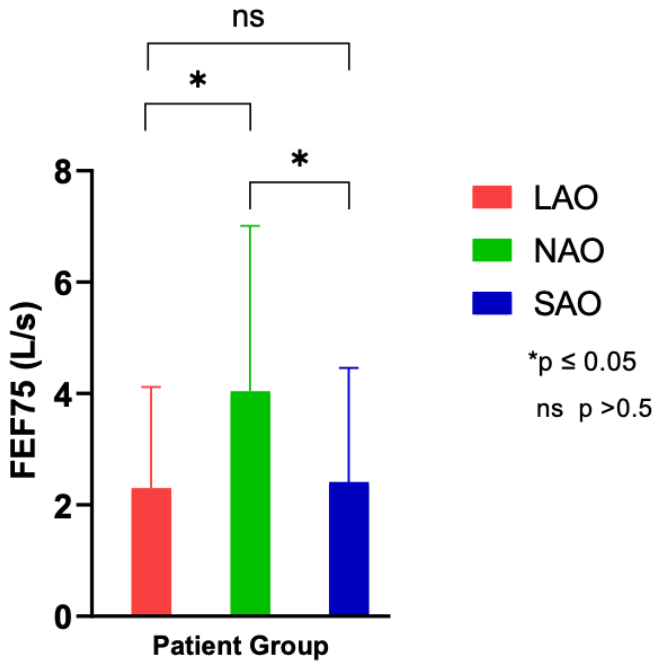

Figure 1. FEF_{75} percent predicted was statistically different among groups but not between LAO versus SAO groups, indicating it as a poor marker of small airway involvement in Severe asthma

	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

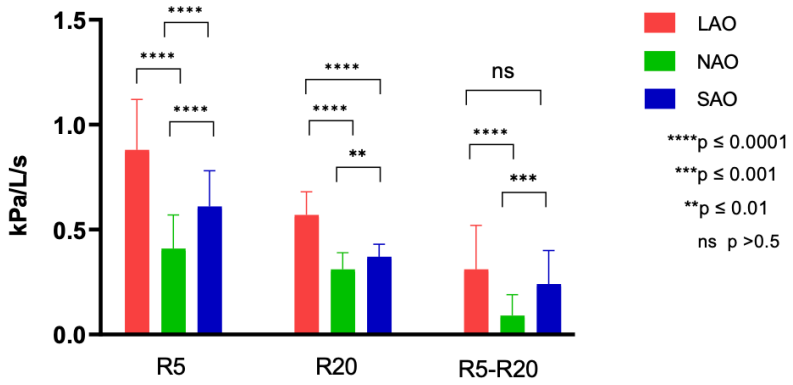

Figure 2. Small airway index(R5-R20) is elevated in all groups.

	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

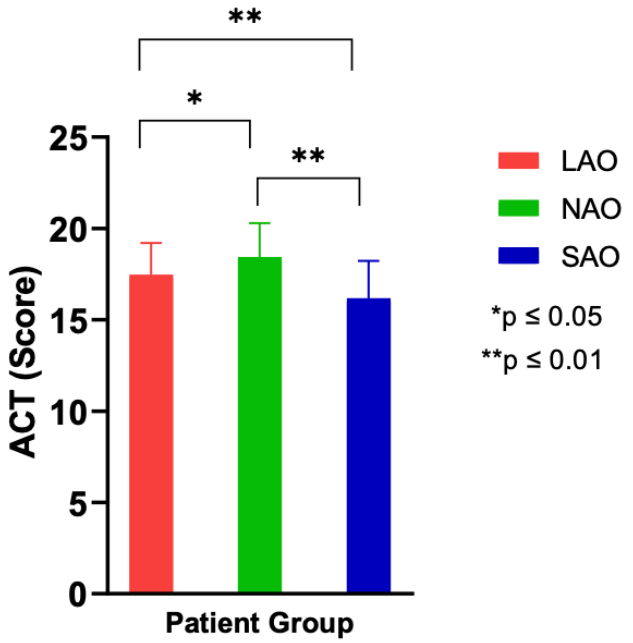

Figure 3. ACT score is lowest in patients with small airway obstruction.