|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X || International Journal of Medical and Biomedical Studies Available Online at www.ijmbs.info

NLM (National Library of Medicine ID: 101738825) Index Copernicus Value 2019: 79.34

Volume 5, Issue 3; March: 2021; Page No. 163-166



Original Research Article

EVALUATION OF SMALL AIRWAY REVERSIBILITY AMONG ASTHMATIC PATIENTS WITH NON-OBSTRUCTIVE PATTERNS OF SPIROMETRY

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Article Info: Received 08 February 2021; Accepted 20 March 2021

DOI: https://doi.org/10.32553/ijmbs.v5i3.1809 Corresponding author: Prof. Tarig H Merghani Conflict of interest: No conflict of interest.

Abstract

Background: Although the forced expiratory flow parameters are increasingly used in the diagnosis of small airway disease (SAD), the reversibility of these indicators is rarely described. The aim of this study is to evaluate the association of small airways reversibility with the presence of SAD and bronchodilator reversibility (BDR) of the proximal airways.

Methods: The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and the indicators of SAD (FEF25%, FEF50%, FEF55%, FEF25-75%, and FEF75-85%) were measured before and 20 minutes after salbutamol administration (200 mcg by using inhaler/Spacer). Positive BDR was accepted when FEV1 or FVC was increased \geq 12% and > 200 ml, indicating responsive proximal airways. Positive small airway reversibility was diagnosed when any of the small airway indicators is increased \geq 30% above the baseline results. All measurements were performed with the All-flow spirometer (Clement Clarke International, Harlow, UK).

Results: Evidence of SAD was found in 62.1% of all participants and in 75.2% of those who showed responsive proximal airways. The positive predictive value of the SAD in diagnosing responsive proximal airways was 67.8%. The reversibility of the small airway indicators showed insignificant association with the FEV1 or FVC BDR. The reversibility of FEF50%, FEF75% and FEF25-75% showed significant association with the diagnosis of SAD, with specificities ranging from 75.5%-81.1%.

Conclusion: SAD has a significant association with positive reversibility of both the proximal and the peripheral airways. Further studies are needed to evaluate the clinical significance of positive small airway reversibility in the diagnosis and management of obstructive lung diseases.

Keywords: Asthma; Small airway disease; Bronchodilator Reversibility, FEV1, FVC; FEF25-75%

Introduction:

Asthma is a chronic airway disease that affects about 300 million people worldwide and cause negative impact on their social, economic and overall quality of life (1). The diagnosis of asthma continues to be a problem for the clinicians, as there are many asthma phenotypes that present with different clinical scenarios (2). Although spirometry plays a pivotal role in the diagnostic workup, it is not recommended to rule out asthma based on negative spirometry results (3). The bronchodilator reversibility (BDR) testing is recommended to be performed as part of spirometry (4). A positive BDR is a valuable step in asthma diagnosis. It is reported when either FEV1 or FVC is increased \geq 12% (and 200 ml absolute value) after inhalation of a short acting bronchodilator. The FEV1 and FVC BDR evaluates obstruction within the proximal airways. It is also helpful in the diagnosis of significant proportions of asthmatic patients, who present with normal or non-obstructive patterns on spirometry (5).

The term small airways refers to the distal airways of the lungs that have less than 2 mm internal diameter. They include the small airways of the respiratory zone and the

terminal bronchioles of the conducting zone. Because of their slight contribution to the total respiratory resistance, they rarely produce symptoms during the early stages of their inflammation; that is why they are described as the "silent zone". Many of the chronic respiratory diseases are characterized by airway remodeling within the small airways (6). The inflammation and obstruction within the small airways contribute significantly to the clinical presentation of asthma (7).

When an airway inflammation occurs predominantly within the small airways, the FEV1 and the FVC values could be normal and might show weak improvement after inhalation of a bronchodilator; however, the forced expiratory flow parameters that include FEF25%, FEF50%, FEF75%, FEF25-75% are likely to be significantly reduced (8). In this study, we aimed to determine the presence of SAD among a sample of symptomatic asthma patients presenting with non-obstructive patterns on spirometry and to investigate the associations of proximal airway reversibility and SAD with reversibility of the small airways.

Methods:

We conducted a cross sectional study on adult patients who attended the asthma referred clinic in Khartoum, Sudan for follow up. All the approached patients are known asthmatics for at least one year. The patients had spirometry for evaluation of their lung function at presentation and then 20 minutes after administration of 200 mcg salbutamol by inhalation using a metered dose inhaler and spacer (4). Those who showed non-obstructive spirometric patterns were included in the study. Exclusion criteria were patient's age<18 years, non-physician diagnosed asthma, typical obstructive pattern on spirometry, failure to do the spirometry and history of inhalation of a bronchodilator within the past 8-12 hours before presentation. Positive BDR of the proximal airways was accepted when the FEV1 or FVC ≥ 12% and 200 ml improvement following the inhalation. Small airway disease was diagnosed when FEF50% & FEF25-75% were < 60% (9). Reversibility of the small airways was accepted for improvement $\geq 30\%$ of the small airway parameters FEF25%, FEF50%, FEF75%, FEF25-75% and FEF85%. The cutoff point was defined arbitrarily based on the cutoff points used in previous

studies (10-12). All measurements were carried out with the portable all flow spirometer (Clement Clarke International, UK).

The research conforms to the ethical principles of medical research involving human subjects that was developed by the World Medical Association Declaration of Helsinki (13). The Institutional Ethics Committee approved the study. Written consents were obtained from the participants before entry into the study. The data obtained were analyzed using the Statistical Package for the Social Sciences version 16 (SPSS Inc. Chicago, IL, USA). The chi square test was used to test distribution of categorical variables. Statistical significance was accepted when the P value was less than 0.05.

Results

A total of 280 adult patients (63.2% females) participated in this study. Their general characters (age, height, weight, and BMI), and their predicted and initial test values (mean, SD) are shown in table 1.

Table 1: General characteristics of the participants

Parameter	Mean	SD (test)
Age (y)	42.086	16.2932
Height (cm)	164.636	9.5776
Weight (kg)	76.761	17.1373
BMI (kg/m^2)	27.943	6.3751
FVC (test/ pred) (L)	2.55/ 3.561	0.9064
FiVC (test/ pred) (L)	3.58/ 3.661	0.9995
FEV1 (test/ pred) (L)	2.25/ 3.036	0.7551
Ratio (test/ pred) (%)	85.5/ 80.527	3.0723
FEF25% (test/ pred) (L/s)	4.28/ 6.428	1.1370
FEF50% (test/ pred) (L/s)	3.02/ 4.329	0.6741
FEF75% (test/ pred) (L/s)	1.3/ 1.842	0.4763
FEF25-75% (test) (L/s)	2.586	1.041
FEF75-85% (test) (L/s)	0.974	0.559

Table 2 shows the prevalence of small airway disease (SAD) among all participants. The patients were divided into two groups based on the results of FEV1 and FVC BDR testing that assess the proximal airways. The SAD was detected in 75.2% of those who showed positive FEV1 or FVC BDR and in 43.8% of those who showed negative BDR. The overall prevalence of SAD was 62.1%. The association was statistically significant (p< 0.001).

Table 2: The small airway disease in relation to FEV1 and/ or FVC bronchodilator reversibility

	FEV1 &/ or FVC Reversibility				
Small Airway Disease	Positive	Negative	Total		
Present (n, %)	118 (75.2%)	56 (43.8%)	174 (62.1%)		
Not present	39 (24.8%)	67 (52.2%)	106 (37.9%)		
Total	157 (100%)	123 (100%)	280 (100%)		

P< 0.001

Table 3 shows the association between the reversibility of the small airway indicators and the reversibility of the proximal airways. The BDR of the small airway indicators (FEF25%, FEF50%, FEF55%, FEF25-75% & FEF85%) showed insignificant associations with the results of FEV1 and FVC reversibility testing. The reversibility indicators of the small airways showed low sensitivities (9.6% to 22.9%), but high specificities (79.7%-92.7%) for detection of the true negative FEV1 and FVC BDR. The reversibility of FEF25% showed the highest positive predictive value (62.5%).

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Table 3: Reversibility of the small airways in relation to reversibility of the proximal airways

		BDR of proxin	nal airways				
BDR of small airways		Positive	Negative	P	Sensitivity	Specificity	PPV*
revFEF25%	Positive	15 (9.6%)	9 (7.3%)	0.507	9.6%	92.7%	62.5%
	Negative	142 (90.4%)	114 (92.7%)				
revFEF50%	Positive	21 (13.4%)	15 (12.2%)	0.770	13.4%	87.8%	58.3%
	Negative	136 (86.6%)	108 (87.8%)				
revFEF75%	Positive	29 (18.5%)	21 (17.1%)	0.762	18.5%	82.9%	58%
	Negative	128 (81.5%)	102 (82.9%)				
revFEF25-75%	Positive	15 (9.6%)	13 (10.7%)	0.779	9.6%	89.4	53.6%
	Negative	142 (90.4%)	110 (89.4%)				
revFEF85%	Positive	36 (22.9%)	25 (20.3%)	0.600	22.9%	79.7%	59.0%
	Negative	121 (77.1%)	98 (79.7%)				

PPV*= Positive predictive value

N

The association of SAD with reversibility of the small airways parameters (FEF25%, FEF50%, FEF75%, FEF25-75% & FEF85%) showed strong associations with FEF50%, FEF75% and FEF25-75% reversibility (p< 0.001), table 4. The sensitivities ranged from 4.6% to 18.4%, whereas the specificities ranged from 72.6% to 88.7%. The reversibility of FEF85% showed the highest positive predictive value (52.5%).

Table 4: Reversibility of the small airways in relation to small airway disease

		Small airway d	isease				
BDR of small airways		Present	Absent	P	Sensitivity	Specificity	PPV*
revFEF25%	Positive	12 (6.9%)	12 (11.3%)	0.200	6.9%	88.7%	50.0%
	Negative	162 (93.1%)	94 (88.7%)				
revFEF50%	Positive	10 (5.7%)	26 (24.5%)	0.000	5.7%	75.5%	27.8%
	Negative	164 (94.3%)	80 (75.5%)				
revFEF75%	Positive	24 (13.8%)	26 (24.5%)	0.025	13.8	75.5%	48%
	Negative	150 (86.2%)	80 (75.5%)				
revFEF25-75%	Positive	8 (4.6%)	20 (18.9%)	0.000	4.6%	81.1%	28.6%
	Negative	166 (95.4%)	86 (81.1%)				
revFEF75-85%	Positive	32 (18.4%)	29 (27.4%)	0.078	18.4%	72.6%	52.5%
	Negative	142 (81.6%)	77 (72.6%)				

PPV*= Positive predictive value

Discussion

Many of the asthmatic patients who attend asthma clinics with respiratory symptoms might show non-obstructive patterns on spirometry; however, a significant proportion of them might be responsive to the bronchodilator (14). For this reason, it is recommended that all patients who perform spirometry should also do the BDR testing, even when there is no evidence of obstruction. This study shows that the could also BDR testing be useful when bronchoconstriction is predominantly found in the small airways. Such presentation is described as the "small airways phenotype" of asthma (15). There is a possibility that difficult to treat cases could be due to SAD. Hence, the use of inhaled corticosteroids (ICS) of small particles for treatment might be better than the ICS with standard particles (16). In this study, we found evidence of SAD in nearly two thirds all participants and in 75% of those with confirmed proximal airway reversibility. A recent review study reported SAD in more than 50% of asthmatic patients with various levels of severity (17). The small airway spirometry parameters differ from the proximal airway parameters in that they are effort independent. The obstruction within the small airways appears in the spirogram as slowing in its terminal portion. Other methods that can diagnose SAD include the plethysmography, nitrogen washout technique, resistance measurements, alveolar nitric oxide and radiological studies; however, there is no method accepted as the gold standard. Similarly, there is no internationally recommended criteria for diagnosing reversibility of the small airways. We used the 30% cutoff value of improvement based on the values used in previous studies (10-12).

Although the SAD correlates with asthma symptoms and scores of Asthma Control Test (7,18), but there is still a paucity of data regarding the correlation with atypical presentation of asthma. We evaluated SAD in a cohort of known asthma patients who showed non-obstructive patterns on spirometry and our results showed insignificant association between the indicators of small airway reversibility and reversibility of the proximal airways; however, the small airway reversibility tests showed high specificities ranging from 79.7% to 92.7%. The high specificity can be utilized in the exclusion of airway obstruction.

The finding that the reversibility of FEF50%, FEF75% & FEF25-75% have significant association with the presence of SAD is a valuable finding. It can justify the use of inhaled drugs that target the small airways in a selected patients (16,18). In addition, the high specificities (75.5% to 81.1%) could be useful in detecting the true negative cases. Since the presence of SAD strongly correlates with the clinical presentation of asthma (7,18), revisiting of the SAD and all the related tests is recommended (19).

This study has many limitations. The participants are known asthmatic for at least one year, but we cannot confirm the diagnosis. The non-responsive group could still suffer from bronchoconstriction. In addition, the possibility of Chronic Obstructive pulmonary disease cannot be excluded. Other limitations include that the criteria for diagnosing small airway reversibility is not commonly used in clinical practice and smoking effects were not considered.

It is concluded that the reversibility of small airways has strong association with FEV1 & FVC BDR and with the presence of SAD. This finding could be useful in asthma diagnosis and in guiding small airway targeted therapy in selected patients, especially those who present with atypical spirometric patterns.

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