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Validity of Spirometry for Diagnosis of Cough Variant Asthma

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Abstract

Background

Cough variant asthma (CVA) is a chronic or recurrent cough without wheezing accompanied by bronchial hyper-responsiveness and eosinophilic inflammation of the airways. This study aimed to evaluate the validity of spirometry in the diagnosis of CVA, as well as determining the specificity and sensitivity of spirometry parameters in CVA.

Materials and Methods

This descriptive observational study was conducted from March 2015 to February 2016. The subjects were 73 patients 5 to 15 years of age who referred to the pulmonology clinics of Tabriz Pediatric Center, Tabriz city, Iran. The patients were divided into two groups of classic asthma (n=37), and CVA (n=36). Basic spirometry parameters such as FEV1/FVC and FEF25-75% were measured and the spirometry findings of each individual were measured based on European Respiratory Society (ERS) criteria. After intervention (β2 (beta2) adrenergic receptor agonists as bronchodilator test), in two groups, spirometry was again performed. The FEV1/FVC and FEF 25-75% parameters were examined for intervention. Data analysis was performed using SPSS (version 16.0).

Results

Cut-off points for the diagnosis of CVA and classic asthma were obtained using FEV1/FVC and FEF 25-75% spirometry. The cut-off point for FEV1/FVC for the diagnosis of CVA was calculated to be 80%. When the FEV1/FVC ratio was higher than 80%, diagnosis of CVA was possible with a specificity of 94.59%, and sensitivity of 66.67%. These findings suggest a specificity and sensitivity of 94.59%, and 66.67%, respectively, for the diagnosis of classic asthma (with an FEV1/FVC ratio of below 80%). Analysis showed a positive predictive value of 100% for CVA at FEF 25-75% with a negative predictive value of 55.4%.

Conclusion

Spirometry can be a sensitive method for the diagnosis of CVA at a FEF 25-75% below 65%; however, it lacks the specificity for accurate diagnosis of CVA.

Key Words: Asthma, Children, Cough Variant, Spirometry, Validity.

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1- INTRODUCTION

One subtype ofasthma is cough variant asthma (CVA), which is a chronic or recurrent cough without wheezing accompanied by bronchial hyper-responsiveness and eosinophilicinflammation of the airways (1, 2). CVA was first described by Glauser in 1972 (3). Unlike other causes of chronic cough, such as post-nasal drip-induced, gastro-esophageal reflux disease and ectopic cough, it is responsive to bronchodilators (4-6). The cough described in CVA patients is similar to that in asthma, as it includes non-productive, exercise-induced and cold air-induced coughing. Upper respiratory infections also have been proven to be involved in the onset of symptoms. Spirometry findings have been reported to be normal in most patients diagnosed with CVA (7).

Clinical studies have reported a lower incidence of CVA than classic asthma in children (8). It has been suggested that in adults and children, CVA may be a pre-term trend for asthma. Although some children tend to show sensitivity to asthma triggers, many get relief from short-time asthma medications (9,10). Progression towards typical asthma is common in the pediatric population and these patients are associated with bronchial hyper-responsiveness (2). Therefore, the diagnosis of CVA in early visits of these patients can lead to reduced progression of symptoms towards classic asthma.

In adults and children who are able to cooperate and are over the age of six years, measuring lung function by spirometryis suggested to achieve an accurate diagnosis (11). A FEV1/FVC ratio of less than 0.8 represents significant airway obstruction. Although it has been stated in the literature that CVA spirometry findings include normal FEV1 and peak expiratory flow rates (PEFR), some studies have reported significant changes in pulmonary function tests during exercise or methacholine tests (7, 12, 13). To our knowledge, no study has evaluated the validity of spirometry parameters for CVA. The aim of this study was to evaluate the validity of spirometry in the diagnosis of CVA, as well as determine the specificity and sensitivity of spirometry parameters in CVA.

2- MATERIALS AND METHODS

2-1. Study design and ethical considerations

This study is a descriptive observational study that has been registered as a research project (ID code 11376/4/5) at the Children's Research and Health Center. This study was approved by the Ethics Committee of the Tabriz University of Medical Sciences (Ethical code: TBZMED.REC.1394.856). The parents of the patients completed an informed consent form for spirometry and intervention. This study was conducted from March 2015 to February 2016. A total of 73 patients aged 5 to 15 years (37 cases of classic asthma and 36 cases of CVA) referred to the pulmonology clinics of Tabriz Pediatric Center, Tabriz city, East Azarbaijan province, North West of Iran. Patients evaluated by conventional spirometry.

The patients were divided into two groups of classic asthma (n=37), and CVA (n=36). Basic spirometry parameters such as FEV1/FVC and FEF 25-75% were measured and the spirometry findings of each individual were measured based on European Respiratory Society (ERS) criteria considering the age, gender, height and weight of each patient. Patients were asked to inhale 4 doses of 100 micrograms of $ß_2$ adrenergic agonists spray (bronchodilator test), and after 15 minutes, spirometry was again performed. The FEV1/FVC and FEF 25-75% parameters were examined for intervention. This method does not have a single gold standard, but is based on the ERS according to the age, gender, height and

weight of each patient (14). The CVA group included patients with a history of chronic non-productive cough (mostly overnight) for more than 8 weeks without wheezing and dyspnea. Patients with a history of cystic fibrosis, respiratory tract infection, pneumothorax or any previous history of treatment with asthma medications were excluded from the study.

2-2. Spirometry

Patients were divided into the two groups and underwent routine spirometry. After intervention (inhaled ß$_2$ adrenergic agonists as bronchodilator test), spirometry was again performed.

2-3. Statistical analysis

The results are expressed as mean ± standard deviation (SD). Qualitative and quantitative variables were analyzed between groups by independent t-testing and Chi-square testing, respectively. Comparison of changes in the main variables in post-interventional spirometry (inhaled ß$_2$ adrenergic agonists as bronchodilator test), and basic spirometry were analyzed using the paired t-test. Data analysis was performed using SPSS (version 16.0). A p-value of less than 0.05 was considered to be statistically significant. The cut-off point for the validity of spirometry in the diagnosis of CVA was determined using the receiver operating characteristic (ROC) curve.

3- RESULTS

In this study, 73 patients aged 5 to 15 years participated. These patients were divided into two groups. One included 36 CVA patients (49.3%). The second group included 37 patients (50.7%) with classic asthma. Forty-eight patients (65.8%) were male, and 25 (34.2%) were female.

3-1. Spirometry parameters before and after intervention

The mean FEV1/FVC and FEF 25-75% before intervention (inhaled ß$_2$ adrenergic agonists as bronchodilator test) in both groups are shown in **Table.1**. The FEV1/FVC showed a significantly higher mean in CVA patients ($p < 0.001$) in comparison with classic asthma patients. There was a non-significant difference ($p = 0.06$) between CVA and classic asthma in the FEF 25-75% with a higher mean in classic asthma group (**Table.1**).

These patients also underwent spirometry after intervention (inhaled ß$_2$ adrenergic agonists as bronchodilator test). **Table.1** compares the mean ± SD of each group before and after intervention. All comparisons before and after intervention showed a significant differences for FEV1/FVC and FEF 25-75% ($p < 0.001$).

Table-1: Spirometry parameters before and after intervention for each group of classic and cough variant asthma patients

Name of group	Spirometry parameter	Pre-intervention Mean ± SD	Post-intervention Mean ± SD	P-value
Cough variant asthma	FEV1/FVC	89.44±13.07	122.86±11.43	<0.001
	FEF 25-75%	52.17±12.16	83.72± 11.48	<0.001
Classic asthma	FEV1/FVC	72.35±8.47	114.78±17.07	<0.001
	FEF 25-75%	57.86±12.35	86.08±13.34	<0.001

SD: Standard deviation; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; FEV1/FVC: Forced expiratory volume in 1 second/ Forced vital capacity ratio; FEF25%: Forced expiratory flow at 25% of expired vital capacity; FEF75%: Forced expiratory flow at 75% of expired vital capacity; PEF: Peak expiratory flow; FEF (25-75%): Forced expiratory flow between 25% and 75% of expired vital capacity.

Using spirometry, the FEV1/FVC and FEF 25-75% cut-off points for the diagnosis of CVA and classic asthma were obtained by the ROC curve. The cut-off point for FEV1/FVC for the diagnosis of CVA was calculated to be 80%. When the FEV1/FVC ratio was higher than 80%, a diagnosis of CVA was possible with a specificity of 94.59% and sensitivity of 66.67%. The findings suggested a specificity of 66.67%, and sensitivity of 94.59% for the diagnosis of classic asthma for an FEV1/FVC ratio of less than 80% (**Figures 1, 2**).

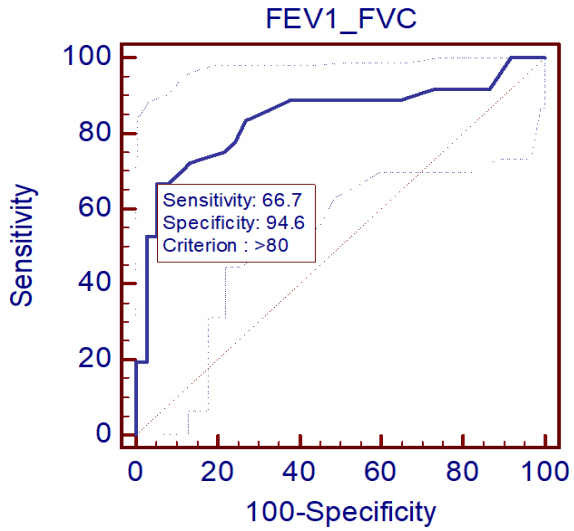

Fig.1: ROC curve for FEV1/FVC spirometry parameter in patients with cough variant asthma.

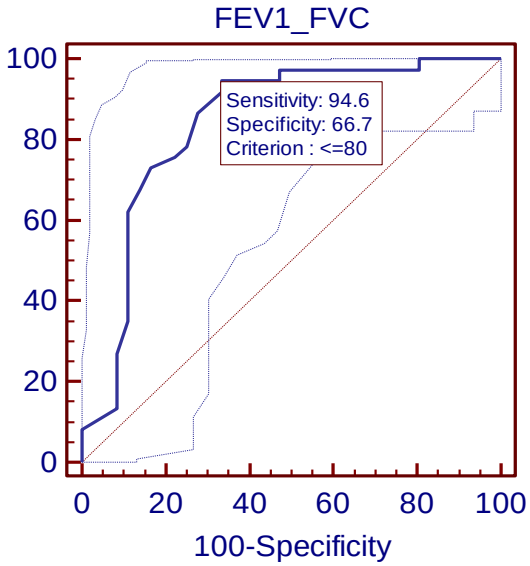

Fig.2: ROC curve for FEV1/FVC spirometry parameter in patients with classic asthma.

The FEF 25-75% parameter for the diagnosis of CVA showed a cut-off point of 65%. Values below 65% produced a diagnosis of CVA with a specificity of 21.62% and sensitivity of 100%. Analysis showed a positive predictive value of 100% for CVA using FEF 25%-75%, while the negative predictive value was 55.4% (**Figures 3, 4**).

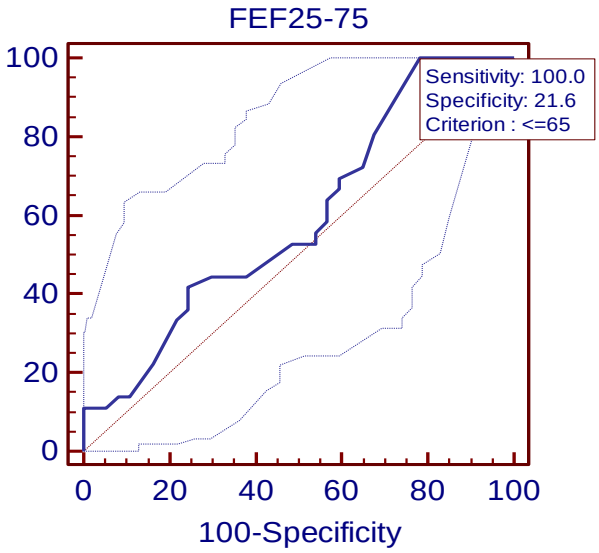

Fig.3: ROC curve for FEF 25-75% spirometry parameter in patients with cough variant asthma.

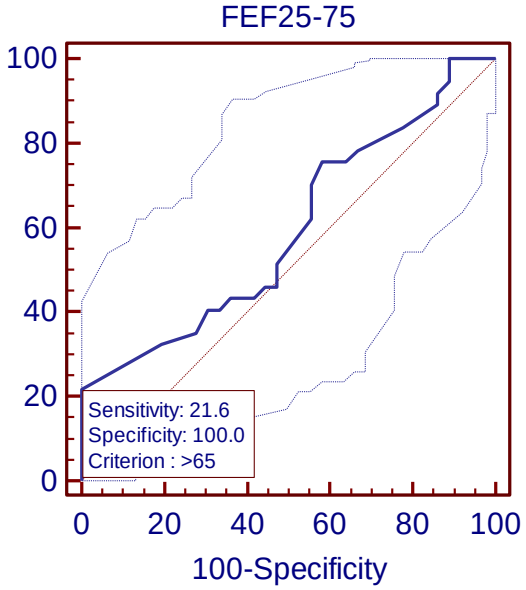

Fig.4: ROC curve for FEF 25-75% spirometry parameter in patients with classic asthma.

4- DISCUSSION

This study evaluated the validity of spirometry findings in patients with CVA with a focus on FEF 25-75%. The validity of spirometry was also assessed for CVA and classic asthmatic patients using FEV1/FVC, which showed that for a FEV1/FVC ratio higher than 80%, the diagnosis of CVA showed a specificity of 94.59%, and sensitivity of 66.67%. The current findings suggest a specificity of 94.59%, and sensitivity of 66.67% for the diagnosis of classic asthma (with an FEV1/FVC ratio below 80%).

The most important finding of this study was evaluation of the FEF 25-75% parameter for the diagnosis of CVA. A cut-off point of 65% was obtained, meaning that a FEF 25-75% value of below 65% produced a diagnosis of CVA with a specificity of 21.62% and sensitivity of 100%. Some studies have evaluated the role of spirometry in the diagnosis and evaluation of CVA in comparison with classic asthma. Chen et al.(15), reported no significant differences in the FEV1, FVC and PEFR values of CVA and classic asthma patients. The progress of both groups was reported after treatment with corticosteroids.

In another study, spirometry parameters of FEV1, FVC, FEF 25-75% and MMEF 25-75% (maximal mid-expiratory flow) were compared for an asthma attack, recovery phase of asthma and CVA. All parameters were found to be lower than 80% in the classic asthma group, but the values for FEF 25-75% decreased significantly. The mean predicted percentage of FVC, FEV1, MMEF 25-75%, FEF 25% for CVA and the recovery phase of classic asthmatic patients were lower than for the control group; however, no differences were observed between the latter two groups (16). Other studies have evaluated airway response to methacholine by comparing classic asthma and CVA patients. It has been stated that maximal airway response plays a greater role than the degree of airway hyper-sensitivity in the progression of CVA to classic asthma (6, 17). Mochizuki et al. (5) evaluated bronchial reactivity in children with CVA and compared it to that of asthma patients. They found out that bronchial reactivity in CVA patients tended to be lower and might be related to the elongated duration of cough without wheezing in CVA cases.

Some studies have investigated methods other than spirometry. Li et al. (18) reported that eosinophil infiltration and increased expression of NGF (nerve growth factor), and intrleukin-4 (IL-4) in the induced sputum of patients shows their possible role in the diagnosis and treatment of patients with CVA. Another study reported increased levels of serum immunoglobulin E (IgE), interleukin 4 and interleukin 5 (IL-5) in the peripheral blood smear of CVA patients in the acute phase in comparison with CVA patients in the recovery phase. No significant differences were stated between acute phases of asthma and CVA patients (19).

4-1. Limitations of the study

The spirometry maneuver is highly dependent on patient cooperation and effort. The most important limitation of this study was the inability and poor competition of children at the time of spirometry.

5- CONCLUSION

The cut-off point for FEF 25-75% for the diagnosis of CVA was calculated to be 65%. Values below 65% produced a diagnosis of CVA with a specificity of 21.62%, and sensitivity of 100%. When the FEV1/FVC ratio was higher than 80%, a diagnosis of CVA was possible with a specificity of 94.59%, and sensitivity of 66.67%. Thus Spirometry can be sensitive method for the diagnosis of CVA for FEF 25-75% values of below 65%; however, it lacks specificity for the diagnosis of CVA.

6- ABBREVIATION

FEV1/FVC: Forced expiratory volume in 1 second/ Forced vital capacity ratio,

FEF 25-75%: Forced expiratory flow between 25% and 75% of expired vital capacity.

MMEF 25-75%: Maximal mid-expiratory flow between 25% and 75% of expired vital capacity.

7- CONFLICT OF INTEREST

The authors declare no conflict of interest.

8- ACKNOWLEDGMENTS

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