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Evaluating the Predicting Value of Respiratory Symptoms in Suspected Asthma Patients in Comparison to the Results of the Methacholine Test

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Abstract

Background: Asthma is a serious and chronic lung disease that is associated with inflammation and increasing the sensitivity of airways. A number of patients, despite having clinical symptoms, do not have the spirometry criteria for a definitive diagnosis of asthma therefore, we use methacholine stimulation test. But since in different studies the relationship between the frequency of respiratory symptoms in suspected asthmatic patients and the positive results of the methacholine test is not definitely clear, in this study, we decided to evaluate the predictive value of respiratory symptoms in suspected asthmatic patients in comparison to results of its methacholine test.

Method: This study was conducted on 147 suspected asthma patients. At first, the patients were subjected to methacholine test and divided into two methacholine negative and positive groups. Then the frequency of clinical symptoms between the two groups was analyzed.

Results: In this study, out of 147 patients studied, 61 were women (41.4%) and 86 (58.6%) were men. The results of this study showed that there is a significant relationship between two methacholine positive and negative groups in terms of shortness of breath (60% versus 19.3%), wheezing (29.5% versus 7.7%) and morning sputum (30.5% against 4%).

Conclusion: The results of this study showed that there is no significant relationship between the two groups of methacholine positive and methacholine negative in terms of age and sex in suspected asthma patients, but there is a significant relationship between these two groups in terms of shortness of breath, wheezing and morning sputum. The result of our study also showed that cough as a clinical symptom in suspected asthmatic patients has no significant relationship with two groups of positive and negative methacholine test and it cannot be a suitable predictive index in patients suspected with asthmatic.

Keywords: Respiratory symptoms • Asthma • Methacholine • Chronic lung disease • Asthma

Introduction

Asthma diagnosis: Asthma is diagnosed based on symptoms and clinical examination such as wheezing, shortness of breath, cough and wheezing along reversible airway obstruction [1-6]. This reversibility is determined by spirometry as a 12% increase in FEV1 and a 200 ml increase in FVC following the consumption of two puffs of beta-adrenergic agonists [7-10]. while a number of patients, despite having clinical symptoms, do not have the spirometry criteria necessary to be definitively diagnosed as an asthma patient, so they suffer from chronic clinical symptoms without receiving appropriate treatment. In these cases, performing stimulation tests with histamine or methacholine seems necessary to diagnose reversible airway obstruction [10-12].

Methacholine: Methacholine is an airway constrictor and parasympathetic analog and a synthetic derivative of acetylcholine transporter and compared to acetylcholine, it is hydrolyzed significantly slower by acetylcholinesterase and its effect is longer [13]. positive methacholine test has diagnostic predictive value in people with asthma symptoms, while negative result of this test rejects asthma with a predictive value over 90% [14].

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In limited studies, the frequency of suspected asthma symptoms among patients who underwent the methacholine test has been investigated. Studies regarding the relationship between the results of the methacholine test and the frequency of respiratory symptoms in suspected asthma patients have not shown conclusive results, and the methacholine test is not available in all regions. In this study, we decided to examine the frequency and correlation of respiratory symptoms in suspected asthmatic patients with the results of the methacholine test in order to help improve the patient's asthma symptoms.

Materials and Methods

Inclusion criteria: A total of 147 people with suspected asthma symptoms who visited Shahid Beheshti Hospital in Kashan were included in the study. In the last two months, these people had one or more symptoms of asthma, including cough lasting more than 10 days, shortness of breath at rest and continuous or intermittent activity, wheezing, and morning sputum. After explaining the objectives of the research, they were subjected to physical examination.

All patients included in this study had a normal examination. Then, basic spirometry test was taken from all patients, and if FEV1 was more than 60% of the expected value, in the next step, methacholine test was performed on them.

Exclusion criteria: Patients with relative or absolute contraindications to methacholine test, including FEV1 less than 60% or less than one-liter, pregnant patients, breastfeeding mothers, patients with a history of heart attack or stroke in the last three months, patients with a history of smoking, patients with uncontrolled blood pressure BP>200/100 mmHg, patients using cholinesterase inhibitors (in myasthenia gravis) and patients with aortic aneurysm were excluded from the study.

Test methodology: Methacholine test was performed on patients according to ATS (American Thoracic Society) guidelines. First, a basic spirometry was performed on the patient, and if the FEV1 was more than 60% of the expected value, spirometry was performed again with normal saline control solution and methacholine dilution solution, which in our method was benzyl alcohol. After performing the above steps, if the FEV1 drop was less than 20%, the test enters the next step and then we check the continuous breathing for two minutes with doubling concentrations of methacholine (0.03, 0.06, 0.125, 0.25, 0.5, 1,2, 4, 8,16) was performed. After breathing for two minutes, from each of the mentioned concentrations, spirometry was performed on the patient, and if the FEV1 drop was more than 20% in each of the concentrations, the test would be stopped. However, if the drop in FEV1 was less than 20%, the test was performed witha higher concentration until the test was stopped after inhaling a concentration of 16 mg/ml. Then, spirometry was performed on the patient, the patient's vital signs and the concentration of methacholine that caused a drop of FEV1 were recorded. According to the convention of pc 20, less than eight positive test signs, more than sixteen negative test signs, between 8-16 were considered borderline and 20 pc less than 1 mg/ml indicated severe airway irritation. A positive test, along with clinical symptoms, strongly indicates asthma.

Results

The results of statistical analysis showed that out of 147 patients studied, 61 were women (41.4%) and 86 (58.6%) were men, and the average age of the studied patients was 39.12 ± 10.25 years. Among the participants in the study, 95 people had a positive methacholine test (37.9% women and 62.1% men) and 52 people had a negative methacholine test result (48.1% women and 51.9% men).

In people with positive methacholine test, 77 people (81.1%) had cough and 18 people (18.9%) had no cough, and on the other hand, in people with negative methacholine test, 41 people (78.8%) had cough and 11 people (21.2%) were without cough. The comparison of these two groups showed that these differences are not statistically significant (P-value=0.85).

In people with positive methacholine test results, 38 people (40%) had no shortness of breath and 57 people (60%) had shortness of breath, while in people with negative methacholine test results, only 10 people (19.3%) had shortness of breath and 43 people (80.7%) of them did not show any signs of shortness of breath. The comparison of these two groups showed that these differences are statistically significant (P-value<0.01).

In the methacholine negative group, 48 people (92.3%) had no nocturnal wheezing and 4 people (7.7%) had nocturnal wheezing. In the positive methacholine group, 67 people (70.5%) did not have nocturnal wheezing, 28 people (29.5%) had nocturnal wheezing, and the comparison of these differences was statistically significant (P-value<0.01).

As can be seen in Table 1, in the group with a negative methacholine test, 96% of people, equal to 50 people, did not have morning sputum and 4%, equal to two people, had morning sputum. In the group with positive methacholine test, 66 people did not have morning sputum (69.5%) and 29 people had morning sputum (30.5%). This finding shows that the prevalence of morning sputum is higher in methacholine positive patients and the comparison of these two groups shows that these differences are statistically significant (P-value<0.01).

Symptoms/Methacholine		Positive	Negative	P-value	Predictive value
Cough	Yes	77 (81.1%)	41 (78.8%)	0.85	Positive=65%

	No	18 (18.9%)	11 (21.2%)		Negative=62%
Shortness of breath	Yes	57 (60%)	10 (19.3%)	<0.01	Positive=83%
	No	38 (40%)	42 (80.7%)		Negative=47%
Nocturnal wheezing	Yes	28 (29.5%)	4 (7.7%)	<0.01	Positive=87.5%
	No	67 (70.5%)	48 (92.3%)		Negative=58%
Morning sputum	Yes	29 (30.5%)	2 (4%)	<0.01	Positive=93%
	No	66 (69.5%)	50 (96%)		Negative=56%

Table 1. Frequency of symptoms in methacholine positive and negative patients.

Discussion

Shortness of breath is caused by the interaction of multiple environmental, chemical and mechanical signals and receptors in the central nervous system, upper and lower airways, lungs and chest wall. Various conditions such as pulmonary edema, atelectasis, congestive heart failure led to the activation of lung excitatory receptors such as pulmonary C fibers. Stimulating lung receptors directly or by modifying other sensory inputs cause shortness of breath through afferent fibers of vagus nerve. Cough also may have induced by many stimuli through inhaled air. In asthmatic patient's airway inflammation and smooth muscle contraction may trigger cough but many other conditions including respiratory infection may also contribute to cough stimuli. Wheez a continuous high frequency sound is hallmark of asthma even though it may occur in night. The less appreciated complain in asthmatic patients is morning excessive sputum production that may be is secondary to variability in autonomic nerve activity and accumulation of abnormal sputum which was not cleared by patient overnight.

In patients with asthma, the sensitivity of airways smooth muscles increases then smooth muscles of airways contract more and faster in response to stimuli and lead to a decrease in lung function and shortness of breath [15]. Currently, in the methacholine test, this substance, as a non-specific cholinergic stimulant, can cause bronchoconstriction and shortness of breath by acting on the muscarinic receptors in the smooth muscles of the airways and pulmonary c-fibers, without aggravating the inflammation. This explanation can be a suitable justification for the result of our study that shortness of breath is more common in methacholine positive people than in methacholine negative people. This result was also consistent with another study conducted in 2016 by K. Porpodis et al., on 88 suspected asthma patients. Among the symptoms related to asthma, only shortness of breath had a significant relationship in patients with a positive methacholine test, and other asthma symptoms, including age, sex, and history of smoking, did not have a significant and clear relationship in patients with a positive methacholine test [16]. Also, another study conducted in 2003 by M Waked et al. on 134 patients with asthma showed that there is a significant and direct relationship between the results of the methacholine test and shortness of breath in patients. In our study the positive predictive value of dyspnea for asthma was 83% with a negative predictive value of 47% that indicate the presence of dyspnea have a good likelihood of asthma disease but the absence of dyspnea may not clear the asthma disease.

On the other hand, what our study showed was that cough, as a clinical symptom in patients with suspected asthma, has no significant relationship between the two groups of positive and negative methacholine test, and it cannot be a suitable predictive index in patients with suspected asthma positive and negative predictive value of 65% and 62% respect. The result of our study was consistent with the study conducted by Lagziel-Golan in 2021 because also, in this study there was no significant relationship between cough in people with positive methacholine test [17]. The results of this study were parallel to the results of Paknejad et al. This research also did not find a significant relationship between cough and positive methacholine test [18]. In justifying this topic, it can be estimated that based on the studies, the sensitivity of cough receptors in the surface membrane of the airways in patients with asthma, including patients with asthma Variant cough, was "normal" [19]. And what is the main determinant in the pathophysiology of cough in suspected asthmatic patients is the presence of eosinophilic inflammation in the airways, which has been observed in the examination of sputum, bronchial mucus and BAL samples of these patients in various studies. Also, several inflammatory mediators such as prostaglandin E2, F2 and thromboxane A2 are also involved in this inflammatory process and increase the expression of TRPV1 capsaicin receptor and decrease the pH of the liquid covering the airways, which themselves can lead to the activation of TRPV1 that can play an important role in causing cough [20]. Since methacholine shows its effectiveness by acting on the muscarinic receptors in the smooth muscle of the airways and has no effect on the inflammation of the airways, it cannot play a role in coughing.

On the other hand, nerve endings related to cough stimulation, which are non-myelinated RAR nerves, are stimulated by various stimuli including stretching, impact, edema, and inflammation, so methacholine does not specifically stimulate these endings. (Its mechanism is not very clear).

Airway mucus is secreted from goblet cells in the airway epithelium and from seromucous glands in the subepithelial connective tissue. The nasal mucosa and airways have many sensory nerve endings.

The stimulation of the terminals of these nerves by the particles in the breathing air leads to the stimulation of cough or sneeze reflex, as a result, mucus and sputum are removed from the airway wall and pushed out. Since the production of sputum is proportional to the increase in the stimulation of parasympathetic terminals, therefore, in the methacholine test, this substance stimulates the production of sputum by stimulating the terminals of muscarinic nerve receptors in the airways. Therefore, it can be a suitable justification for this result of our study, why the prevalence of morning sputum has been seen more in methacholine positive patients. According to present study the positive predictive value of morning sputum was higher than other symptoms it was 93% but a low negative predictive value about 56%.

Therefore, from the above evidence, it can be estimated that methacholine does not have much effect on airway inflammation and the release of inflammatory mediators. In some cases, the use of this test may lead to false negative results.

In order to solve this problem and considering that it is not possible to stimulate the inflammation of the airways in the clinic, inhaled corticosteroid sprays can be used as a diagnostic and therapeutic method in examining suspected asthmatic patients. Its effect on the patient's symptoms led to the correct diagnosis of the disease.

According to the obtained results, a significant number of patients with positive methacholine test did not have any nocturnal wheezing but the positive predicting value for nocturnal wheezing was 87.5% a high index for suspected asthma. A low negative predictive value for this symptom may indicate the absence of night wheez does not preclude asthma. Therefore, in spite of the absence of the mentioned symptoms, in case of strong clinical suspicion of asthma, according to the fluctuations of the patient's symptoms, in the presence of normal spirometry, it seems necessary to perform the methacholine test.

Conclusion

In this study, it was found that in suspected asthma patients, the symptoms of shortness of breath, morning sputum and nocturnal wheezing had a direct relationship with a positive methacholine test. Then if there are these symptoms even in presence of normal spirometry and no access to the methacholine test, after ruling out other causes related to shortness of breath, sputum and wheezing, asthma treatment can be started for the patient.

Our study showed that cough as a clinical symptom in suspected asthmatic patients has no significant relationship between two groups of positive and negative methacholine test and cannot be a suitable predictive index in suspected asthmatic patients.

Future Studies

According to the results of the present study, which shows the high prevalence of symptoms of shortness of breath and nocturnal wheezing in patients with a positive methacholine test, the following are suggested:

- Regular examination of positive signs and symptoms for quick and timely identification of people at risk of asthma and providing consultation services and necessary help when necessary.
- Encouraging patients to go to medical centers and have an annual checkup
- Holding meetings and providing information to patients to cure and prevent asthma.
- Providing necessary social support to patients when positive respiratory symptoms occur.
- Due to lack of samples, it is recommended to conduct similar studies with a larger sample size.

Ethical Consideration

This study was approved by the local research and ethics committee. Since the interventions were performed on HCWs –not patients- written consent was not necessary. The chief of the hospital was informed about the study before starting it.

Conflict of Interest

None.

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