

# Evaluation of Methacholine Challenge Test Results in Chronic Cough Patients Referring to Clinic of Pulmonary Disease

Gholamreza Derakhshan Deilami<sup>1</sup>, Mahmoud Khandashpour<sup>1\*</sup>, Om'albanin Paknejad<sup>2</sup>, and Marzie Pazooki<sup>3</sup>

<sup>1</sup> Department of Internal Medicine, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Department of Pulmonology, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>3</sup> Department of Internal Medicine, Sina Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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**Abstracts-** Chronic cough is a common problem in patients visiting physicians and its prevalence in different populations range from 3 to 40%. Postnasal drip, asthma and gastroesophageal reflux are the known cause of chronic cough. Although diagnosis of asthma is usually made by clinical signs and spirometric results, methacholine challenge test is a good diagnostic test in patients who show normal physical examination and spirometric results. In this study, the results of methacholine challenge test in chronic cough patients are investigated. This is a cross sectional study performed on patients suffering from chronic cough (over 8 weeks), who went to Pulmonary Disease Clinic of Imam Khomeini Hospital in 2006. Postnasal drip, gastroesophageal reflux was evaluated and ruled out in all patients. Then they were tested by methacholine inhalation using low to high doses of methacholine. The results of test was defined as 20% fall in FEV1 and its relationship with age, sex, history of allergic disease, family history of asthma and smoking status was investigated. 81 patients (36 female and 45 male) entered this study who had mean age of  $32.5 \pm 13.06$  years. 81.5% of patients had never smoked or closed contact with smokers, 6.2% were passive smokers, 8.6% were smokers and 3.7% had quit smoking. 37% had suffered from chronic cough less than 6 months, 11% for 6-11 months and 52% for more than 12 months. In 26% of patients, family history of asthma was present and 34.5% had a history of one type of allergy. In 29.5% the results of methacholine challenge test was positive, among them 45.8% showed an intense response and 54.2% a moderate response. The test results and its intensity had no statistically significant relationship with age, sex, smoking status, the duration of cough and family history of asthma, but the relationship between methacholine challenge test and the history of allergic disease was significant. Methacholine challenge test can be used as a diagnostic test in patients suffering from chronic cough of unknown origin and patients whose clinical and paraclinical finding are normal. A positive test indicates hyper-sensitivity of airways which can be used for planning their treatment.

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**Key words:** Asthma, chronic cough, methacholine challenge test, PC20

## Introduction

In general population in Iran, the 4th cause of death after cardiovascular diseases, cancers and accidents, is respiratory diseases that make up to 7.8% of annual death cause (1). Chronic cough is the most common symptom of respiratory disease and one of the most common reasons for seeking medical care. The prevalence of chronic cough in general population is reported differently in various studies including 10% (2, 3), 14-23% (4), 3-50% (5) and 6-14% (6). The definition of chronic cough varies too. Some reference define it as a cough which last

more than 3 weeks (2, 3,7) and others as a cough lasting 8 weeks or more (8-10). The most common causes of chronic cough are post nasal drip (PND), asthma, and gastroesophageal reflux (GERD) (5, 7-9). Asthma is defined as reversible obstruction of airway (9, 11). To diagnose asthma, in addition to presence of clinical signs such as wheezing, paroxysmal dyspnea, and chronic cough, meeting spirometric criteria is necessary. These criteria include an increase of 12% and 200cc in FEV1, or FVC after the inhalation of 2 puffs of  $\beta$ -adrenergic agonists (11). When spirometry is normal provocative airway tests can be used to detect reversible constriction

\*Corresponding Author: Omalbanin Paknejad

Department of Pulmonology, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran  
Tel: +98 21 84902460, 9121062584, Fax: +98 21 88845187, E-mail: o.paknejad@gmail.com

of airways in asthma patients. In order to perform these test, histamine, methacholine, hyperventilation, cold air exposure and physical activities can be used (12-15). Among these provoking agents, methacholine is the most widely used (12-14). Methacholine is an airway constrictor. It is a parasympathetic analog and a synthetic derivate of the neurotransmitter acetylcholine. It is slowly metabolized by methacholinesterase and its effect can be reduced or eliminated by atropine or others anticholinergic drugs (12, 14). In this study, methacholine test results are evaluated in Iranian patients suffering from chronic cough. A negative methacholine challenge test rules out asthma and its predictive value is over 90%, but a positive results is diagnostic only in patients who have symptoms and signs of asthma (for the concentrations less than 4 mg/ml about 10% and for concentrations less than 1 mg/ml about 90-98%) (12).

## Patients and Methods

This study is cross sectional study and the diagnostic method used in this study is methacholine challenge test. The study population consisted of patients who were suffering from cough for at least 8 weeks and went to pulmonary disease clinic of Imam Khomeini Hospital. The essential criteria to enter the study were: chronic cough (at least 8 weeks) and normal spirometry test results. The patients were excluded from study in patients with PND, patients of GERD who were untreated, and patients who were afflicted by respiratory infection in last three weeks and those who had any of contraindications for taking metacholine according to table 1.

All patients meeting the criteria to enter the research who were not excluded were studied and no special method for sample taking was applied. There are different methods to perform methacholine challenge test. In this study patients inhaled 10 different concentration of me-

thacholine each for minutes. These methacholine solutions were prepared with concentrations of 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/ml. At first, patients underwent spirometry after inhalation of normal saline solution and then a diluted solution (phenol + normal saline). Subsequently, 3 ml of solution with lowest concentration of methacholine which was taken out of refrigerator half an hour ago and kept in room temperature was nebulized. The solution was inhaled for two minutes through nebulizer and after 2 minutes interval, spirometry was done. To obtain the optimal result, patients could practice the maneuver 3-4 times but the whole procedure did not last more than 3 minutes and to preserve accumulations were not more than 5 minutes intraval between to stips of test. If FEV1 drop was less than 20%, the next dose of methacholine was given to the patient but if FEV1 drop exceeded 20% or the highest dose of methacholine (16 mg/ml) was given, the test was stopped, patients' vital signs were recorded, albuterol inhalation was given and spirometry was repeated. The concentration of methacholine solution which induced 20% drop in FEV1 was considered provocative concentration or PC 20. In different references, the various amounts for PC 20 were considered as positive test result (12-14, 16, 17). In our study, based on ATS criteria (12), test results was considered positive if PC 20 was 4 mg/ml or less, negative if PC 20 was 16 mg/ml or more and borderline provocation was recorded if PC 20 was 4-16 mg/ml. PC 20 amounts less than 1 mg/ml was considered intense and between 1 and 4 mg/ml was considered moderate.

The test was done by a single technician using O.Acethyl methacholine- Fluka solution (Germany) and phenol and normal saline solution as diluted solutions. Micro quark cosmed (Italy) was used as spirometry and PARI set (Germany) for provocation.

**Table 1.** Metacholine test contraindications

Absolute contraindications:
-Sever restriction of airway FEV1<50% of expected or less than 1 liter.
-Heart or brain attack in last 3 months
-Uncontrolled Hypertension (systolic blood pressure >200mmHg and/or diastolic -blood pressure >100 mmHg.
-Known Aortic aneurism.
Relative contraindications:
-Relative restriction of air flow: FEV1<60% of expected or less than 1.5liter.
- Pregnancy
- Lactation
- Recent usage of cholinesterase inhibitors for Myasthenia Gravis

**Table 2.** The ratio and frequency of different smoking status according to the methacholine challenge test results

Smoking status	Methacholine test		total
	negative	positive	
Never smoked or never contact with smokers	45(68%)	21(32%)	66(100%)
Have smoked before	3(100%)	0(0%)	3(100%)
Close contact with smokers	3(60%)	2(40%)	5(100%)
Smokers	6(86%)	1(14%)	7(100%)
Total	57(70%)	24(30%)	81(100%)

## Results

According to the data of this study, 81 patients entered the study. 36 patients (44.5%) were women and 45 (55.5%) were men. Patients' mean age was  $32.5 \pm 13.1$  years. 66 patients (81.5%) have never smoked or had never close contact with smokers. 3 patients (3.7%) had quitted smoking, 5 patients (6.3%) were passive smokers and 7 patients (8.6%) were smokers. Considering the duration of cough, 30 patients (37%) had cough for less than 6 months, 9 patients (11%) for 6-12 months and 42 patients (52%) for more than 12 months. The family history of asthma in close relative including father mother brother sister, siblings, aunt, uncle, ground mother, ground fathers was negative in 60 patients (74%) and positive in 21 patients (26.1%). For the history of allergy, 28 patients (34.5%) had experienced one kind of allergy and 53 patients (65.5%) had no history for it. The results of methacholine challenge test were as follow: 11 patients (13.6%) showed intense response, 13 patients (16%) moderate response. In 14 patients (17.3%) borderline and in 43 patients (53.1%) negative response was reported. 36.4% of male patients (12 of 45) and 33.3% of female (12 of 36) patients showed

positive response. In comparison, these difference were not statistically significant ( $P > 0.05$ , 95% CI 0.92, 0.28-1.9, odds = 0.73). The mean age of patients with positive methacholine challenge test was  $29.5 \pm 12$  years and that of patients with negative methacholine challenge test was  $33.72 \pm 3$  years which did not vary significantly ( $P > 0.05$ ). The ratio and frequency of different smoking status according to the methacholine challenge test results is showed in table 2 which do not vary significantly ( $P > 0.05$ ).

The ratio and frequency of cough duration according to methacholine test results is showed in table 3 with do not vary significantly ( $P = 0.108$ ).

Positive methacholine test was reported in 38% (8 of 21) of patients who had a family history of asthma and 27% (16 of 60) of patients with no family history. The different was not significant ( $P > 0.05$ , CI 90%, 0.59-4.84, odds = 1.7). 46.4% (13 of 28) of patients who had a history of allergic disease and 21% (11 of 53) of patients with no history of allergic disease had positive methacholine test results. These differences were statistically significant ( $P=0.016$ , CI 90%, 1.2-8.9, odds =3.31). The methacholine test results and its intensity in different variables and their  $P$  value are shown in table 4.

**Table 3.** The ratio and frequency of cough duration according to methacholine test results

Cough duration	methacholine test		total
	negative	positive	
6 months>	20(67%)	10(33%)	30(100%)
6-12 months	4(44%)	5(56%)	9(100%)
>12 months	33(78%)	9(22%)	42(100%)
total	57(70%)	24(30%)	81(100%)

**Table 4.** The methacholine test results and its intensity in different variables and their P value

variable	Response intensity				P value	
	sever	moderate	Borderline	no response		
gender	female	7(19.5%)	5(13.9%)	5(13.9%)	19(52.7%)	>0.05
	male	4(8.9%)	8(17.8%)	9(20%)	24(53.3%)	
history of allergy	positive	7(25%)	6(21%)	5(17.8%)	10(35.7%)	0.062
	negative	4(7.5%)	7(13.2%)	9(17%)	33(62.3%)	
family history of asthma	positive	3(14.3%)	5(23.8%)	5(23.8%)	18(38.1%)	>0.05
	Negative	8(13.3%)	8(13.3%)	9(15%)	35(58.7%)	
smoking status	Never	10(15.1%)	11(16.7%)	12(18.2%)	34(50%)	>0.05
	History of smoking	0(0%)	0(0%)	0(0%)	3(100%)	
	Passive smoker	1(20%)	1(20%)	1(20%)	2(40%)	
	smoker	0(0%)	1(14.3%)	1(14.3%)	5(71.4%)	
Cough duration	6 months>	6(20%)	4(13.3%)	4(13.3%)	16(53.4%)	>0.05
	6-12 months	2(22.2%)	3(33.3%)	0(0%)	4(44%)	
	>12 months	3(7.1%)	6(14.3%)	10(23.8%)	23(54.8%)	

## Discussion

According to the results of our study, 29.5% of patients with chronic cough had positive methacholin test results. In Lundbak *et al.* study (1993) (16) this ratio in patients who met diagnostic criteria of asthma was 61% that was different from our results because the patients who entered our study was not selected according to diagnostic criteria of asthma, therefore many of them were not asthmatic. If the results of our study are compared with those of the second part of Lundbak *et al.* (1993) (16) study, one could notice that the ratio of positive methacholine test response in patients of chronic cough who did not meet diagnostic criteria of asthma was 20% too. Having a look at the results of other surveys, we notice that the frequency of positive methacholine test vary from 32% in Haque study (14) to 57.5% in Lin *et al.* (2002) study (17). The various results are due to different factors such as:

1- Different prevalence of asthma: According to some studies, Iran is one of the regions with low prevalence of asthma while Scandinavian countries, united state, Australia, south eastern Asia, where Lin *et al.* (2002) (17), Lundbak *et al.* (1993) (16) and Koh *et al.* (2002) (18) surveys were done, have high prevalence of asthma.

2- The differences of inclusion and exclusion criteria: These criteria are mostly based on ATS but for example regarding smoking, our patients had to avoid smoking 24 hours before test while ATS demand some hours.

3- The various methacholine administrated, different apparatus and manufacturers.

In Lin *et al.* study (2002) (17) no difference were reported in age, sex, weight, smoking history and methacholine test results. Our findings show no significant relationship between sex and methacholine test results and its intensity. Although according to Irwin *et al.* (2006) (19) the progression of chronic cough and the sensitivity of cough reflex was more prominent in women, it dose not seem that there exist a pathophysiologically significant relationship between sex and methacholine test response. Besides, there is no other study available obtaining the results similar to those of Irwin *et al.* (2006) (19).

Our finding revealed no significant relationship between age and methacholine test results. The relationship between the status of exposure to smoking and methacholine test results and its intensity was not significant too, though it is expected that age and history of smoking exposure affect the response of receptors in respiratory airways and as a result affect the methacholine test result. According to our test results, there is no significant relationship between cough duration and methacholine test results, in spite of our prediction that the less cough duration was the more positive response to methacholine test would be detected and the frequency of positive methacholine test would decrease as the cough duration increased.

According to our findings, the family history of asthma is not significantly related to methacholine test results and its intensity, although, because of consider-

able hereditary factors in asthma, it was expected to detect higher intensity and more frequent positive methacholine test results in patients who had a family history of asthma. We detected a significant relationship between methacholine test results and history of allergy and almost significant relationship between the intensity of methacholine test responses and history of allergy. To be more precise, patients with a history of allergic disease had more positive methacholine test results and their response were more intensity. It seems that considering the same pathophysiology and origin of allergic disease and asthma and chronic cough as a symptom of some allergic disease such a finding is compatible with our knowledge of allergic disease.

It seems that methacholine challenge test dose not cause complication and the frequency and intensity of its response is not affected by sex, age and family history. It can be used as a reliable test to evaluate hyperresponsiveness of airway. Moreover, in patients showing positive test, one can perform spirometry after administration of  $\beta$ -agonists to evaluate their response to therapy. In patients who have a strong history for asthma with negative methacholine test results, complementary evaluation (such as eosinophilic examination of sputum for diagnosis of eosinophilic bronchitis) can be performed that warrants further investigations in future.

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