

Exertional-induced bronchoconstriction: Comparison between cardiopulmonary exercise test and methacholine challenging test

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ABSTRACT

Introduction: Exertional-induced bronchoconstriction is a condition in which the physical activity causes constriction of airways in patients with airway hyper-responsiveness. In this study, we tried to study and evaluate any relationship between the findings of cardiopulmonary exercise testing (CPET) and the response to methacholine challenge test (MCT) in patients with dyspnea after activity. **Materials and Methods:** Thirty patients with complaints of dyspnea following activity referred to “Lung Clinic” of Baqiyatallah Hospital but not suffering from asthma were entered into the study. The subjects were excluded from the study if: Suffering from any other pulmonary diseases, smoking more than 1 cigarette a week in the last year, having a history of smoking more than 10 packets of cigarettes/year, having respiratory infection in the past 4 weeks, having abnormal chest X-ray or electrocardiogram, and cannot discontinue the use of medicines interfering with bronchial provocation. Baseline spirometry was performed for all the patients, and the values of forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC were recorded. The MCT and then the CPET were performed on all patients. **Results:** The mean VO₂ (volume oxygen) in patients with positive methacholine test (20.45 mL/kg/min) was significantly lower than patients with negative MCT (28.69 mL/kg/min) ($P = 0.000$). Respiratory rates per minute (RR) and minute ventilation in the group with positive MCT (38.85 and 1.636 L) were significantly lower than the group with negative methacholine test (46.78 and 2.114 L) ($P < 0.05$). Also, the O₂ pulse rate in the group with negative methacholine test (116.27 mL/beat) was significantly higher than the group with positive methacholine test (84.26 mL/beat) ($P < 0.001$). **Conclusion:** Pulmonary response to exercise in patients with positive methacholine test is insufficient. The dead space ventilation in these patients has increased. Also, dynamic hyperinflation in patients with positive methacholine test causes the reduced stroke volume and O₂ pulse in these patients.

Key words: Asthma; Cardiopulmonary exercise testing; Dyspnea; Hyper-reactive airways; Methacholine challenge test

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INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is a condition in which vigorous physical activity stimulates acute airway narrowing in people with airway hyper-reactivity.^[1] The prevalence of EIB in patients with asthma has been reported to range from 40% to 90%.^[2,3] EIB is a well-recognized medical indication for the prophylactic use of β_2 agonists, so that its documentation would appear to justify the need for prophylaxis with a β_2 agonist before exercise. Exercise protocols based on the duration of work

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or achievement of a specific heart rate have been proposed as standards for diagnosing EIB.^[4] However, there are some limitations with respect to standardization of both the workload and environmental conditions of temperature and humidity.^[5] The eucapnic voluntary hyperpnea (EVH) test has been proposed as an alternative to exercise as a laboratory-based test to identify EIB.^[6] However, provocation with EVH requires dry gas mixture limiting its availability. Provocation with methacholine requires less expensive equipment that is easily portable. In this study, we aimed to assess the sensitivity of methacholine challenge test (MCT) to identify EIB in 59 subjects using cardiopulmonary exercise test (CPET) as gold standard.

MATERIALS AND METHODS

Subjects

Fifty-nine subjects (body mass index [BMI] <35) referring to Baqiyatallah Medical Center with signs and symptoms suggestive of asthma but without a firm diagnosis of asthma or an exclusion of the diagnosis of asthma (e.g., had an equivocal diagnosis of asthma or had been referred for further investigation of asthma-type symptoms) were included. Subjects had at least step 1 symptoms according to the National Asthma Education Prevention Program (NAEPP) expert panel II (The NAEPP Report updated its recommendations for the monitoring and treatment of asthma in February 1997), that is, a kind of asthma severity grading (symptoms ≤ 2 times/week; asymptomatic between exacerbations; exacerbations of only a few hours to a few days; and night time symptoms of ≤ 2 times/month).^[7] They were required to have a forced expiratory volume in 1 second (FEV₁) $\geq 70\%$ of the predicted value at the Screening Visit. Subjects were excluded from participating this study if they: Had any known other pulmonary disease; had smoked more than 1 cigarette/week within the past year or had a ≥ 10 pack year smoking history; had a respiratory tract infection within the previous 4 weeks; had been skin test positive to aeroallergens that were present in the environment during the time of enrollment and reported worsening of symptoms when exposed to these aeroallergens during the study; had been diagnosed at screening visit as definitively having asthma or not having asthma; had clinically significant abnormal chest X-ray or electrocardiogram; or had failed to observe washout of medications that would interfere with CPET.

Spirometry

First, baseline spirometry was performed for all cases using a volume displacement spirometer according to the methods recommended by the American Thoracic

Society.^[8] The FEV₁, forced vital capacity (FVC), and FEV₁/FVC were expressed as percentage of predicted.

Methacholine challenge test

Then, challenge test with methacholine was performed for all of our subjects. Methacholine (Provocholine™, Methapharm, CA, USA) was delivered from a DeVilbiss Healthcare 100 DeVilbiss Drive Somerset, Pennsylvania, US by the dosimeter method. The concentrations were: 0.0312, 0.0625, 0.125, 0.25, 0.5, 1, 2, and 4 mg/mL. Each concentration required five inhalations from functional residual capacity to total lung capacity. Spirometry was performed within 3 min. The response to methacholine was expressed as the concentration required provoking a 20% fall in FEV₁ from the prechallenge value (provocative dose 20).

Cardiopulmonary exercise test

At the end, in all patients, a maximal, symptom-limited CPET was performed on a Collins CPX system (Warren E. Collins, Inc., Braintree, Massachusetts, USA). A ramped protocol was used with 2 min of initial, unloaded cycling, followed by a graded increase in load until exhaustion. The workload increase was arbitrarily chosen to give a maximal test in 10–12 min. During all studies, expired gases, oximetry, heart rate, heart rhythm, and blood pressure (BP) were monitored. Oxygen consumption (VO₂) was calculated and expressed as a percentage of predicted. Arterial blood gases were obtained via a catheter inserted in the radial artery or by radial puncture. Samples were obtained at rest and throughout the exercise period. All studies were interpreted by an experienced pulmonologist (Prof. Mostafa Ghanei).

The contraindications to MCT are summarized as following:

Absolute

- Severe airflow limitation (FEV₁ < 50% predicted or < 1 L)
- Heart attack (ischemic heart disease) or stroke in the last 3 months
- Uncontrolled hypertension, systolic BP >200, or diastolic BP >100
- Known aortic aneurysm.

Relative

- Moderate airflow limitation (FEV₁ < 60% predicted or < 1.5 L)
- Inability to perform acceptable quality spirometry
- Pregnancy

- Nursing mothers
- Current use of cholinesterase inhibitor medication (for myasthenia gravis).

Statistical analysis

Data were analyzed using SPSS software (version 18 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean \pm standard error of mean. Comparison between groups was performed using Student's sample *t*-test for continuous variables. $P < 0.05$ was considered statistically significant.

And also, the sensitivity and specificity of these tests were evaluated.

Ethical approval

The study was performed according to the principles of the Declaration of Helsinki, and the study protocol was approved by the local ethics review committee of Baqiyatallah University of Medical Sciences.

RESULTS

In this study, two pulmonary specialists were as consolors. The average ages in patients with positive and negative methacholine test were, respectively, 40.95 and 34.8 years ($P = 0.028$). The age ranges in patients with positive and negative methacholine tests were, respectively, between 13 and 57 and 28 and 45 years. In attention to $P = 0.028$, it is age-related test. The BMI of each person was calculated by measurement of height and weight of the patients based on the $BMI = \text{weight}^2/\text{height}$ formula. The mean BMI values in patients with positive and negative methacholine test were, respectively, 25.76 and 25.22 ($P = 0.0635$).

In basic spirometry performed on all patients, the measured mean FVC values in patients with positive and negative methacholine tests were, respectively, 3.79 mL and 4.99 L ($P = 0.001$).

Also, the mean percentage of FVC from the predicted value was equal to 85.7% in patients with positive methacholine test and 99.25% in patients with negative methacholine test ($P = 0.020$). The measured mean FEV1 values in basic spirometry testing in patients with positive and negative methacholine tests were, respectively, equal to 2.79 L and 4.06 L ($P = 0.000$). Also, the measured mean percentages of FEV1 of the predictive value in patients with positive and negative methacholine test were, respectively, equal to 79.65% and 104.13% ($P = 0.001$).

In performed CPET, the mean VO_2 values in patients with positive and negative methacholine tests were, respectively, equal to 20.45 mL/kg/min and 28.69 mL/kg/min ($P = 0.000$). The mean percentages of VO_2 in patients with positive and negative methacholine tests were, respectively, equal to 72.52% and 105.32% ($P = 0.000$).

The mean $VEVO_2$ (ventilatory equivalent for oxygen) values in patients with positive and negative methacholine tests were, respectively, equal to 38.75 and 37.44 ($P = 0.525$). The mean $VEVCO_2$ (ventilatory equivalent for carbon dioxide) values in patients with positive and negative methacholine tests were, respectively, equal to 39.6 and 38.22 ($P = 0.590$). The anaerobic threshold mean values in patients with positive and negative methacholine tests were, respectively, equal to 29.85 L/min and 33.44 L/min ($P = 0.334$). The maximum average rates in patients with positive and negative methacholine tests were, respectively, equal to 88.85 bpm and 89.25 bpm ($P = 0.83$). The mean O_2 pulse values in patients with positive and negative methacholine tests were, respectively, equal to 84.26 mL/beat and 116.27 mL/beat ($P = 0.000$) [Figure 1].

The mean heart rate reserve values measured in patients with positive and negative methacholine tests were, respectively, equal to 19.25 bpm and 20.11 bpm ($P = 0.777$). The VEMAX (MAX minute ventilatin) mean values in patients with positive and negative methacholine tests were, respectively, equal to 69.16 L/min and 80.66 L/min ($P = 0.039$) [Figure 2].

The mean ventilator threshold (VT) values measured in patients with positive and negative methacholine tests were, respectively, equal to 1.63 L and 2.11 L ($P = 0.021$). The mean percentage values of VT in patients with positive and negative methacholine tests were, respectively, equal to 87.5% and 87.11% ($P = 0.968$). The mean maximum RR values in patients with positive and negative methacholine tests were, respectively, equal to 38.85 and 46.78 ($P = 0.026$) [Figure 3].

The mean respiratory reserve volume in patients with positive and negative methacholine tests were, respectively, equal to 28.5 and 26.33 ($P = 0.798$). The mean $ETCO_2$ values in patients with positive and negative methacholine tests were, respectively, equal to 33.38 mmHg and 37.18 mmHg ($P = 0.008$). The mean ETO_2 values in patients with positive and

negative methacholine tests were, respectively, equal to 93.79 mmHg and 95.811 mmHg ($P = 0.151$).

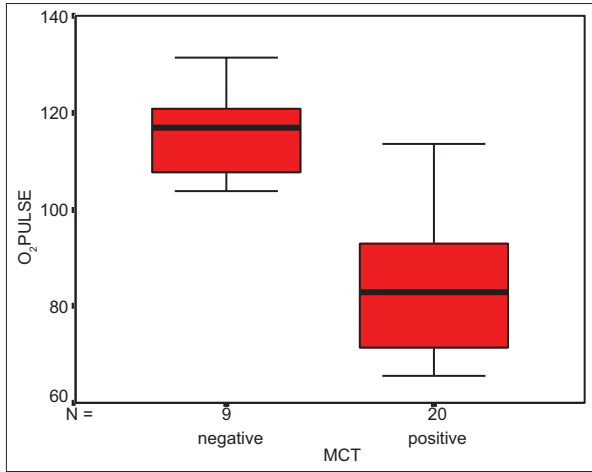


Figure 1: O₂ pulse in two groups of negative and positive methacholine challenge tests

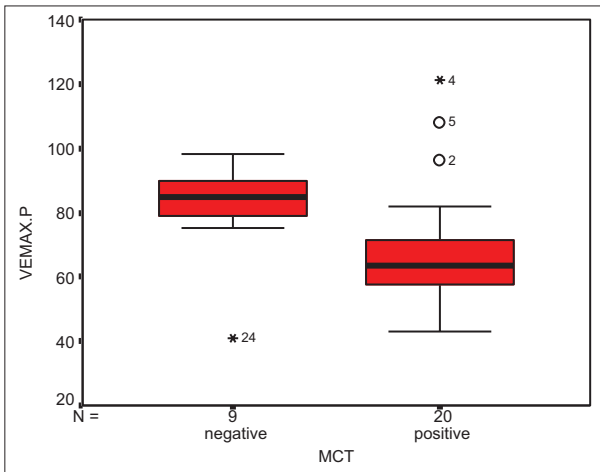


Figure 2: Ventilator equivalent max index in two groups of negative and positive methacholine challenge tests

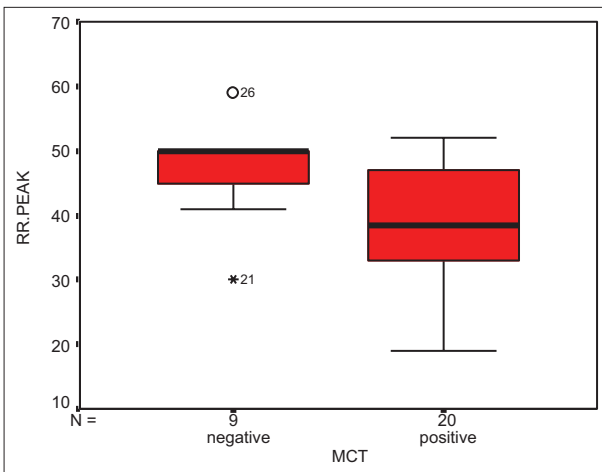


Figure 3: Respiratory rate peak in two groups of methacholine challenging test positive or negative

The mean VD.VT values at rest in patients with positive and negative methacholine tests were, respectively, equal to 25.97 and 22.35 ($P = 0.818$). The mean maximum VD.VT values in patients with positive and negative methacholine tests were, respectively, equal to 37.35 and 38.92 ($P = 0.002$).

The mean respiratory quotient values in patients with positive and negative methacholine tests were, respectively, equal to 1.14 and 1.18 ($P = 0.246$). The mean oxygen saturation rates at rest in patients with positive and negative methacholine tests were, respectively, equal to 97.4% and 98% ($P = 0.068$). The mean oxygen saturation rates during the maximum activity test in patients with positive and negative methacholine tests were, respectively, equal to 96.55% and 96.75% ($P = 0.626$). All values of CPET were shown in Table 1.

MCT has high false negative (low sensitivity) and low false positive but CPET has low false negative (high specificity) with moderate sensitivity.

DISCUSSION

One of the indications for use of the cardiorespiratory exercise test is to examine the patient with dyspnea after activity. Numerous tests have been suggested to examine and study this group of patients, but all of them faced with some limitations. The CPET has been recognized as a complete test that evaluates various parameters during rest and activity. Evaluation of patients with exercise-induced dyspnea by this test can provide an appropriate assessment of the conditions of the patient's body different systems. This test has been already used in many clinical situations, including assessments before or after heart surgeries and evaluation of patients with interstitial lung disease.

No study has been performed so far aiming at comparing the CPET parameters in patients with different responses to methacholine test. We first studied and compared the CPET parameters in both groups of patients with positive and negative methacholine test and came to the conclusion that the positive response to the methacholine test can be the sign of a poor response of lung to the activity. In other words, it may be possible to overcome the symptoms of patients with bronchoconstriction by strengthening the lung response to the exercise.

Table 1: Cardiopulmonary exercise test result based on two groups of positive and negative MCT

	MCT	n	Mean	SD	P
Age (years)	Positive	20	40.95	10.913	0.028
	Negative	10	34.80	5.653	
BMI (m ² /kg)	Positive	20	25.7626	4.24861	0.635
	Negative	10	25.2255	1.87595	
FVC (L)	Positive	20	3.7970	0.78366	0.001
	Negative	8	4.9963	0.64283	
FVC.P (%)	Positive	20	85.70	12.798	0.020
	Negative	8	99.25	13.957	
FEV1 (L)	Positive	20	2.7965	0.70132	0.000
	Negative	8	4.0650	0.63146	
FEV1.P (%)	Positive	20	79.65	14.496	0.001
	Negative	8	104.13	18.833	
VO ₂ (mL/min)	Positive	20	20.455000	4.8550001	0.000
	Negative	9	28.697778	4.3969358	
VO ₂ P.H.P (mL/min)	Positive	20	72.5205	12.60739	0.000
	Negative	9	105.3216	16.93725	
VEVO ₂	Positive	20	38.75	5.056	0.525
	Negative	9	37.44	5.053	
VEVCO ₂	Positive	20	39.60	6.508	0.590
	Negative	9	38.22	5.740	
AT.P (mL/min/kg)	Positive	20	29.85	9.252	0.334
	Negative	9	33.44	8.734	
PEAKHR.P (%)	Positive	20	88.85	3.843	0.830
	Negative	8	89.25	5.651	
O ₂ pulse (%)	Positive	20	84.2607	14.31402	0.000
	Negative	9	116.2786	9.73503	
HRR.M (mL)	Positive	20	19.25	6.742	0.777
	Negative	9	20.11	9.089	
VEMAX.P (L/min)	Positive	20	69.160	19.4218	0.039
	Negative	9	80.667	16.4393	
VT.M (mL)	Positive	20	1.636	0.378	0.021
	Negative	9	2.114	0.672	
VT.P.P (%)	Positive	20	87.50	21.414	0.968
	Negative	9	87.11	30.056	
RR.PEAK	Positive	20	38.85	8.580	0.026
	Negative	9	46.78	7.981	
BR (L)	Positive	20	28.50	22.322	0.798
	Negative	9	26.33	16.800	
ETCO ₂ .PE (mmHg)	Positive	20	37.180000	2.5879478	0.008
	Negative	9	33.388889	4.5892386	
ETO ₂ .PEA (mmHg)	Positive	20	93.795	2.9422	0.151
	Negative	9	95.811	4.2899	
VD.VT@RE	Positive	20	153.35	25.974	0.818
	Negative	9	155.67	22.136	
VD.VT@PE	Positive	20	133.65	37.359	0.002
	Negative	9	80.22	38.929	
RQ	Positive	20	1.143500	0.0855493	0.246
	Negative	9	1.183333	0.0790569	
O ₂ SAT.R (%)	Positive	20	97.40	0.754	0.068
	Negative	8	98.00	0.756	

Contd...

Table 1: Contd...

	MCT	n	Mean	SD	P
O ₂ SAT.P (%)	Positive	20	96.55	0.887	0.626
	Negative	8	96.75	1.165	

BMI: Body mass index, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, FVC.P: Forced vital capacity predicted, FEV1.P: Forced expiratory volume in 1 second predicted, VO₂: Volume of oxygen consumption, VO₂ P.H.P: Pulmonary oxygen uptake high pressure, VEVO₂: Ventilator equivalent/ventilation per unitary change in oxygen consumption, VEVC₂: Ventilator equivalent/ventilation per unitary dioxide carbon production, VT.P.P: Ventilator threshold peak predicted, PEAKHR.P: Peak heart rate predicted, O₂ pulse: Pulse oximetry, HRR.M: Heart rate reserved mean, VEMAX.P: Maximum ventilation during exercise predicted, VT.M: Ventilator threshold, mean, VT.P.P: Tidal volume peak predicted, RRPEAK: The peak of respiratory rate, BR: Breathing reserve, ETCO₂.PE: Partial pressure of carbon dioxide, ETO₂.PEA: Partial pressure of end tidal oxygen, VD.VT: Volume of dead space, RQ: Respiratory quotient, O₂ SAT: O₂ saturation, MCT: Methacholine challenging test, SD: Standard deviation

The study results show that the VO₂ rate in positive methacholine group is significantly lower compared to the normal group, which is mostly due to inadequate pulmonary responses to the exercise. This becomes clear by lower minute ventilation and respiratory rates that despite using adequate pulmonary reserve has failed to create adequate minute ventilation. However, a part of such a difference can be at least attributed to the age difference between the two groups.

We showed in our study that despite the VEVC₂ value's closeness in both groups, the levels of ETCO₂ in positive methacholine group was higher, which reflects the inadequacy of the lungs to excrete CO₂ that confirms the increased dead space ventilation. This is confirmed with significantly increased VD at peak exercising in positive methacholine group compared to the control group.

In our study, the O₂ pulse in the positive methacholine group showed a significant decrease compared to the control group that its explanation seems to be difficult due to the instability of CPET findings in patients and controls. However, the increase in dead space ventilation in these patients could cause reduced cardiac output through increased dynamic hyperinflation, thereby leading to the drop in O₂ pulse stroke volume. The main reason for the decline in O₂ pulse is related to decline in stroke volume. However, any reason that leads to disruption in the rate of oxygen uptake by the tissues, including, musculoskeletal diseases, can cause a decline in the O₂ pulse, which is not true regarding our patients.

In a study, Sill *et al.*^[9] compared the CPET findings in 105 patients with exercise-induced dyspnea with 69 normal volunteers and observed that the use of CPET in patients with exercise-induced dyspnea causes the increased specificity and the reduced diagnosis sensitivity. They stated that the CPET has not the required sensitivity in diagnosis of mild illness in young people.

In another study on 50 patients that the cause of their dyspnea had not detected by routine diagnostic methods, Martinez *et al.*^[10] used the CPET results. They observed that people with normal CPET had higher VO₂ max and O₂ pulse than those with diagnosis of heart disease, de-conditioning, or hyper-active airway disease. They stated that the CPET is useful for the diagnosis of heart and lung diseases, but has not the required sensitivity to differentiate the heart disease from de-conditioning cases.

There are some limitations in our study:

- First, given the small sample size in our study, making definitive conclusions seems to be a little difficult and further studies with larger sample size are needed in the future
- Second, identifying and selecting the patients with dyspnea after exercise is so difficult and there are a lot of conflicts regarding the available tests for diagnosis. Therefore, our study may be affected by selection bias, and the results might have been somewhat distorted.

Finally, we conclude that pulmonary response to exercise in patients with the positive methacholine test is insufficient. The dead space ventilation in these patients has increased. Also, dynamic hyperinflation in patients with positive methacholine test causes the reduced stroke volume and O₂ pulse in these patients.^[11]

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Conflicts of interest

There are no conflicts of interest.

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