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Methacholine challenge testing is superior to the exercise challenge for detecting asthma in children

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ARTICLE INFO

Article history:

Received for publication July 30, 2015.

Received in revised form September 17, 2015.

Accepted for publication September 30, 2015.

ABSTRACT

Background: Exercise-induced bronchoconstriction occurs in a large proportion of children with asthma. **Objective:** To compare the predictive value of methacholine challenge testing (MCCT) and the exercise treadmill challenge (ETC) for detecting asthma in children with postexercise symptoms.

Methods: This was a prospective study of children 10 to 18 years old with postexercise symptoms. During asthma diagnosis, they underwent MCCT and ETC. There were 2 study visits. All subjects underwent ECT at visit 1 and MCCT 1 week later at visit 2.

Results: One hundred one children were included; 62.9% had a history of atopy, and asthma was confirmed in 43.6%. MCCT showed 90.9% sensitivity, 82.5% specificity, 80.0% positive predictive value, and 92.2% negative predictive value; the respective values for ECT were 77.3%, 68.4%, 65.4%, and 79.6%. Positive MCCT results showed significantly higher sensitivity and higher positive predictive value in the diagnosis of asthma in children with postexercise symptoms compared with a 10% decrease in forced expiratory volume in 1 second for ECT ($P = 0.034$). Conducting MCCT during asthma diagnosis confirmed asthma in an additional 24.3% of children with exercise-induced symptoms. With a cutoff level at 17% of forced expiratory volume in 1 second for ECT, the discrepancy was decreased and reasonable values for sensitivity, specificity, positive predictive value, and negative predictive value were attained (61.0%, 77.1%, 69.4%, and 69.8%, respectively).

Conclusion: A large number of school children with asthma and postexercise symptoms could have positive MCCT and negative ECT findings. Untreated asthma in children with exercise-induced bronchoconstriction could cause them to be discharged from physical education classes.

Trial Registration: www.ClinicalTrials.gov, identifier NCT01798823.

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Introduction

Asthma is the most frequent chronic respiratory disease in children. Exercise-induced bronchoconstriction (EIB), described as transient narrowing of the airways, occurs in a large proportion of children with asthma, and it has been widely reported in school children with postexercise symptoms.^{1–3} There are many techniques to provoke bronchial hyperreactivity (BHR).^{4–6} Direct provocation testing with methacholine has been reported to have a high sensitivity to identify BHR and a negative test result is often used to exclude asthma. In contrast, provocation tests that use

indirect stimuli (eg, exercise) have a high specificity for asthma. It has been shown that BHR to an indirect stimulus is more closely associated with airway inflammation than BHR to a direct stimulus and might have greater clinical importance in asthma diagnosis.⁶ However, the most appropriate measurement technique remains unclear, especially in children with exercise-induced symptoms. The aim of this study was to compare the predictive value of methacholine challenge testing (MCCT) and standardized exercise treadmill challenge (ETC) for detecting asthma in children with postexercise symptoms.

Methods

This was a prospective study of middle-school children 10 to 18 years old who attended the authors' allergic outpatient clinic from January 2013 to December 2014 because of postexercise symptoms such as cough and shortness of breath during or after physical education classes and could perform spirometry. Patients with

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Disclosures: Authors have nothing to disclose.

Funding Sources: This study was supported by the National Science Centre (grant UMO-2012/07/B/NZ5/02684) and the Medical University of Lodz (grant 502-03/2-056-01/502-14-220).

<http://dx.doi.org/10.1016/j.anai.2015.09.022>

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Table 1
Clinical characteristics of study population

Study group	Statistical parameter					
	Mean	Median (Q1, Q3)	SD	SE	95% CI	Minimum–maximum
Overall	13.02	8 (5, 14)	14.62	1.55	9.94–16.10	1–98
Asthma						
No	9.85	5 (4, 9)	14.69	2.12	5.59–14.12	1–98
Yes	22.00	20 (5, 32)	18.75	6.25	7.59–36.41	1–51
Atopy						
No	14.61	6 (5, 17)	19.94	3.58	7.30–21.93	1–98
Yes	8.86	6 (4, 9)	8.54	1.82	5.06–12.65	2–35
Without asthma or atopy	11.59	5.5 (5, 9)	20.03	4.27	2.71–20.47	1–98
With asthma and atopy	15.25	12.5 (7, 17.5)	12.03	2.13	10.91–19.59	3–48

Abbreviations: CI, confidence interval; Q1, quartile 1; Q3, quartile 3.

exclusionary medical conditions, such as acute or chronic lung diseases, and active smokers were not enrolled. Diagnosis of asthma was universally established by symptoms of asthma, physical examination findings of the respiratory system, and positive reversibility test findings in all patients, according to current guidelines.⁷ All children during diagnostic procedures underwent MCCT and standardized ETC. Medical documentation of patients who were completely naive to therapy at that time was analyzed by allergist physicians who paid special attention to asthma-like symptoms. Clinical characteristics of the study population are listed in Table 1.

There were 2 study visits. All subjects underwent ETC at visit 1 and then MCCT at visit 2. There was a 1-week interval between the 2 tests.

Pulmonary Function Tests

Pulmonary function testing was performed with a Master Screen unit (Erich Jaeger GmbH, Hochberg, Germany). Flow and volume were measured with a pressure-screen-type pneumotachograph, which was calibrated daily. All measurements were performed by a trained investigator. Measurements were carried out in a familiar and quiet room. Standing height and weight were assessed: subjects wore light summer clothing and were measured without shoes. During measurements, children were instructed to sit upright, and a nose clip and a non-compressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls provided by the manufacturer of the lung function test equipment. All pulmonary function tests were performed according to American Thoracic Society and European Respiratory Society standards.^{8,9} The highest of 3 successful measurements was analyzed. The results were expressed as the percentage of a predicted value. Positive reversibility test result was defined as improvement of at least 12% of pre-bronchodilator forced expiratory volume in 1 second (FEV₁) after administration of salbutamol (200 µg) in all patients.

Standardized ETC

Exercise-induced bronchoconstriction was tested using a motor-driven treadmill (Kettler, Ense-Parsit, Germany) according to American Thoracic Society and European Respiratory Society guidelines.^{8–11} The children were instructed to run for 8 minutes with a submaximal exercise load. The exercise test consisted of a 2-minute warmup and 6 minutes of steady-state running on a treadmill inclined to produce a heart rate at least 95% of the maximum predicted for age (calculated as 220 – age [years]). The slope of the treadmill was 5.5%. Small adjustments in workload

(treadmill speed) were made, if necessary, to achieve targeted heart rates. Nasal clips were used during the test, and heart rate was continuously monitored (electronic heart rate scanner; Kettler). The ambient temperature in the air-conditioned laboratory was kept stable at 22°C, and the humidity was stable at 40% to 50% on each day of the study. FEV₁ was measured before running, immediately after, and 3, 6, 10, 15, 20 and 30 minutes after running. Maximum percentage of decrease in FEV₁ after ECT was calculated by the following formula: [(pre-exercise FEV₁ – lowest postexercise FEV₁)/pre-exercise FEV₁] × 100. EIB was defined as a decrease in FEV₁ greater than 10% from baseline within 30 minutes after the exercise.

Methacholine Challenge Testing

Methacholine challenge testing of the provocation was performed with a timesaving procedure using the dosimeter technique APS Pro (Erich Jaeger GmbH) with controlled tidal breathing. After pulverization of the physiologic diluent, methacholine was delivered in 4 cumulative doses: 0.015, 0.045, 0.18, and 0.72 mg. A negative MCCT result was defined as a provocation dose causing a 20% decrease (PD₂₀) higher than 0.72 mg. MCCT was continued at 2-minute intervals between inhalations until a decrease in FEV₁ of at least 20% was obtained. PD₂₀ was calculated by linear interpolation on a logarithmic dose–response curve.¹²

Ethics

The study was approved by the medical ethical committee of the Medical University of Lodz. Written consent from the patients and their parents was obtained.

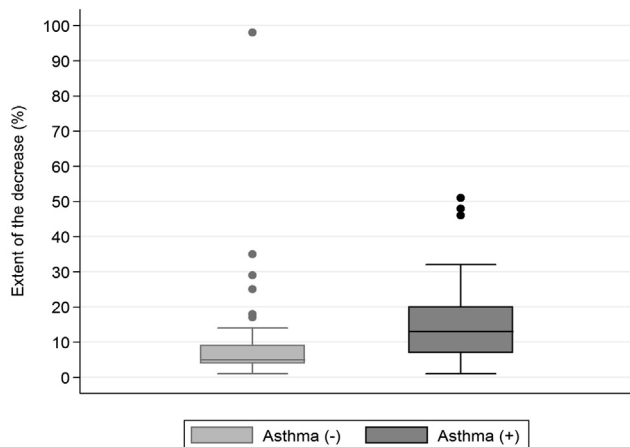
Statistical Methods

For statistical analyses, Cohen κ coefficients were used to estimate the inter-rater agreement between 2 unique raters (ie, 2 methods of diagnosis of asthma) in teenagers who attended secondary school—methacholine provocation and provocation by physical effort in relation to exercise-induced bronchial symptoms. In addition, the Wilcoxon rank-sum test was fitted to assess differences between 2 independent groups. Two receiver operating characteristic curves were drawn for binary data (eg, coded as 0 to 1) in addition to corresponding bi-normal fit lines, Youden indexes, areas under the curve, sensitivity and specificity, and a *P* value informative of the statistical significance of the difference between the 2 receiver operating characteristic curves.

All statistical computations were performed using STATA 12.1 Special Edition (StataCorp LP, College Station, Texas). A *P* value less than .05 was considered statistically significant.

Results

Of 101 children (62.4% female and 37.6% male) included in the analysis, 11 patients were excluded because testing data were incomplete. More than half the patients (62.9%) had a history consistent with atopy, which was defined as any allergy diagnosis. Asthma diagnosis was confirmed in 43.6% of children. Patients with and without asthma and with positive MCCT results constituted 90.9% and 17.5%, respectively (*P* < .001), of the sample. Patients with and without asthma and with positive standardized ETC results constituted 77.3% and 31.6%, respectively (*P* < .001; Fig 1). Of patients with a negative MCCT result, 43.1% had a positive standardized ETC result; of patients with a negative standardized ETC result, 40.8% had a positive MCCT result. A significant association was observed between positive MCCT and ETC results in the prediction of asthma diagnosis. However, the 2 tests did not necessarily identify the same patients. The MCCT showed 90.9% sensitivity, 82.5% specificity, 80.0% positive predictive value, and 92.2%



The Wilcoxon rank-sum test was performed

Figure 1. Decrease in forced expiratory volume in 1 second after a standardized exercise treadmill challenge in children with asthma and without asthma ($P < .001$ by Wilcoxon rank-sum test).

negative predictive value; for ECT, the respective values were 77.3%, 68.4%, 65.4%, and 79.6% (Fig 2).

A PD_{20} lower than 0.72 mg (positive MCCT result) showed significantly greater sensitivity and a higher positive predictive value in the diagnosis of asthma in children with postexercise symptoms compared with a decrease in FEV_1 greater than 10% in ETC ($P = .034$). This conclusion was based on the sensitivity, specificity, Cohen κ coefficient, and P values.

The MCCT during asthma diagnosis allowed confirmation of asthma in an additional 24.3% of children with exercise-induced respiratory symptoms. The sensitivity for MCCT detecting a positive ETC reaction was 60.0% overall (specificity 56.9%, positive predictive value 57.7%, and negative predictive value 59.2%).

Discussion

Recurrent dyspnea, cough, and labored breathing with viral respiratory infections or symptoms with specific allergenic exposures are often the first indication of asthma. EIB occurs commonly in patients with asthma but also can affect individuals without asthma.^{2,13–15} Response to an exercise challenge has not been

compared with that to a methacholine challenge in school children being evaluated for postexercise symptoms. The present study included a large number of children with symptoms suggestive of asthma but without a definitive diagnosis. This study investigated the sensitivity and specificity of airway responsiveness to methacholine and exercise challenges to identify the diagnosis of asthma in children with postexercise symptoms. Results showed that although the 2 tests are complementary in the diagnosis of asthma in this population, MCCT is more sensitive and specific than the ETC.

The ETC has some advantages over other challenge tests. EIB diagnosed during ETC has a high positive predictive value for identifying patients with asthma. However, there are many differences of opinion as to the appropriate cutoff point to be considered significant for asthma diagnosis. In the present study, EIB was defined by a decrease in FEV_1 greater than 10%. This is compatible with the American Thoracic Society and European Respiratory Society recommendations, but not with Global Initiative for Asthma criteria (12%) or with the only meta-analysis on the subject. In a study by Johansson et al,¹⁶ exercise testing was found to be an unsuitable screening method for children with undiagnosed asthma. Fuentes et al¹⁴ suggested ETC sensitivity could be increased by adding a 28% decrease in forced expiratory flow between 25% and 75%. It also has been shown that a single exercise test does not rule out EIB and a second exercise test under the same conditions can identify more patients.¹⁷ The relation between asthma and exercise shows wide inter- and intra-patient variabilities and is likely influenced not only by the disease but also by additional psychosocial and physical variables. One must remember that postexercise symptoms can occur for reasons other than asthma.¹⁸ Hence, ETC sensitivity varies. This could be due to the fact that when performing exercise tests, conditions such as temperature and humidity in a room are very important and should be considered. The present study showed that the ETC with a 10% FEV_1 cutoff has a high positive predictive value for asthma diagnosis in children with postexercise symptoms, with high sensitivity and specificity, but these values were much higher for MCCT.

The standard ETC used is not rigorous enough to elicit a decrease in many children who might have EIB. Some protocols use cool dry air during exercise or mannitol administration.^{19–21} These diagnostic tests show similar diagnostic properties, suggesting their inter-complementary roles for asthma; however, methacholine has been shown to be more sensitive than mannitol for the evaluation of BHR in children.²¹ A positive MCCT result is often considered in the clinical setting of asthma-like symptoms with normal or near-normal spirometry findings or when the post-bronchodilation FEV_1 improves but is not greater than 12% and 200 mL.⁵ Some study results have suggested that bronchial provocation tests with methacholine in association with a physician's clinical assessment can be very useful to separate patients with from those without asthma if they are properly used.^{22,23} In the present subjects with postexercise symptoms of asthma, the MCCT was handier for confirming an asthma diagnosis. In patients with postexercise symptoms after standardized ETC and MCCT, MCCT demonstrated better sensitivity and specificity for an asthma diagnosis. The superiority of bronchial provocation testing with methacholine or histamine compared with exercise tests in the diagnosis of asthma has been observed by others.^{12,24,25}

This study has some limitations. Some children could have been in better physical condition than others, which could have affected the decrease in FEV_1 from exercise (eg, athletes can have a 5% to 6% decrease in FEV_1 , which could be significant for them). There also could be inherent bias by performing the ETC before MCCT; however, the 1-week interval between tests is long enough to perform the MCCT, which is a stronger and longer airway constrictor than exercise.

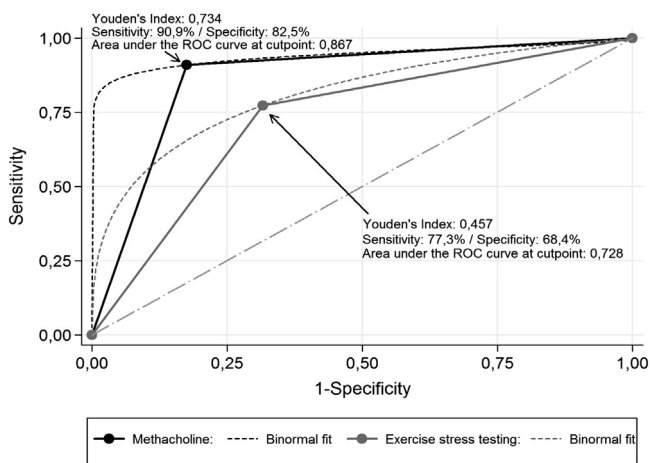


Figure 2. Receiver operating characteristic (ROC) curves in addition to the Youden indexes, sensitivity and specificity, and areas under the curve for the exercise treadmill challenge vs methacholine provocation in children with asthma and without asthma ($P = .034$).

The MCCT during asthma diagnosis allowed confirmation of asthma in an additional 24.3% of children with exercise-induced respiratory symptoms but with a negative ETC result. This has important clinical consequences. Untreated asthma in children with postexercise symptoms could cause them to be discharged from regular physical education classes.

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