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Effect of lowering Methacholine Challenge Test cutoff in children

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ABSTRACT

Background: The diagnosis of asthma is based on clinical judgment, history of personal or familial atopy, and testing, typically with a methacholine challenge test (MCT). Guidelines suggest a provocation concentration that caused a decrease in forced expiratory volume in 1 second of 20% (PC_{20}) cutoff of 4 mg/mL for a positive test result.

Objective: To investigate the effect of lowering the MCT PC_{20} cutoff from 8 to 4 mg/mL on the number of positive test results and the distribution of test results.

Methods: A retrospective study was conducted at the Montreal Children's Hospital from January 1, 2006, through June 31, 2012, on patients referred by nonrespiratory physicians. A 2-minute tidal breathing dosing protocol was used, and the PC_{20} was calculated by linear interpolation.

Results: A total of 748 patients were tested using spirometry. A total of 134 (17.9%) had a negative MCT result, and 614 (81.1%) responded at 8 mg/mL or less. A total of 570 patients (92.8% of respondents) responded at a dose of 4 mg/mL or higher (median PC_{20} of 0.47 mg/mL), with the remainder (7.2% of respondents) responding at a dose between 4 and 8 mg/mL (median PC_{20} of 6.37 mg/mL). There was no difference in the number of positive test results between the sexes, regardless of cutoff. The sensitivity of MCT was 82.1% at a cutoff of 8 mg/mL and 76.2% at 4 mg/mL. With a pretest likelihood of asthma of 75%, the specificity was 71.2%.

Conclusion: In a standard pediatric referral population, using a PC_{20} cutoff of 4 mg/mL provided a sensitivity of 76.2%, and only excluded 5.8% of all those referred for suspicion of asthma (7.2% of all test results were $\leq$8 mg/mL). This finding suggests that a PC_{20} of 4 mg/mL can reasonably be used as a cutoff for a positive MCT result in children.

Introduction

The diagnosis of asthma is based on clinical judgment, history of personal or familial atopy, and testing, typically with a methacholine challenge test (MCT). The MCT measures airway hyperresponsiveness, and standards have been published.[1,2] The test assesses the provocation concentration that caused a decrease in forced expiratory volume in 1 second (FEV_1) of 20% (PC_{20}).[3] Moderate to severe bronchial hyperreactivity is defined as a PC_{20} less than 1 mg/mL, mild bronchial hyperreactivity as a PC_{20} of 1.0 to 4.0 mg/mL, and borderline bronchial hyperreactivity as a PC_{20} of 4.0 to 16.0 mg/mL.[1]

The American Thoracic Society use data from adult studies to construct a receiver operating curve, taking into account pretest probability of asthma, to estimate the likelihood of the patient having asthma based on the PC_{20}. A PC_{20} of 8 mg/mL decreased on the diagonal, suggesting that a value of 8 mg/mL did not aid in making the diagnosis, and the guidelines suggested using a cutoff of 4 mg/mL for a positive test result. Despite this, many pediatric studies continue to use cutoffs of 4 to 16 mg/mL.[2–5]

Two studies have looked at cutoff values in children. The first study used physician assessments for pretest probability of asthma.[6] However, these physicians were allergists or allergy trainees, who performed an extensive structured history and physical examination related to personal and familial history of allergy and atopy, use of asthma medications, and prior diagnosis of asthma, and a structured physical examination. These authors found that a cutoff of 4 mg/mL was moderately sensitive in girls, regardless of whether there was a history of atopy (71%) or not (77%), and moderately sensitive in boys with a history of atopy (67%). However, 52% of the children defined as healthy (ie, no history or physical examination suggestive of asthma or rhinitis and negative skin prick test result) had a methacholine response of

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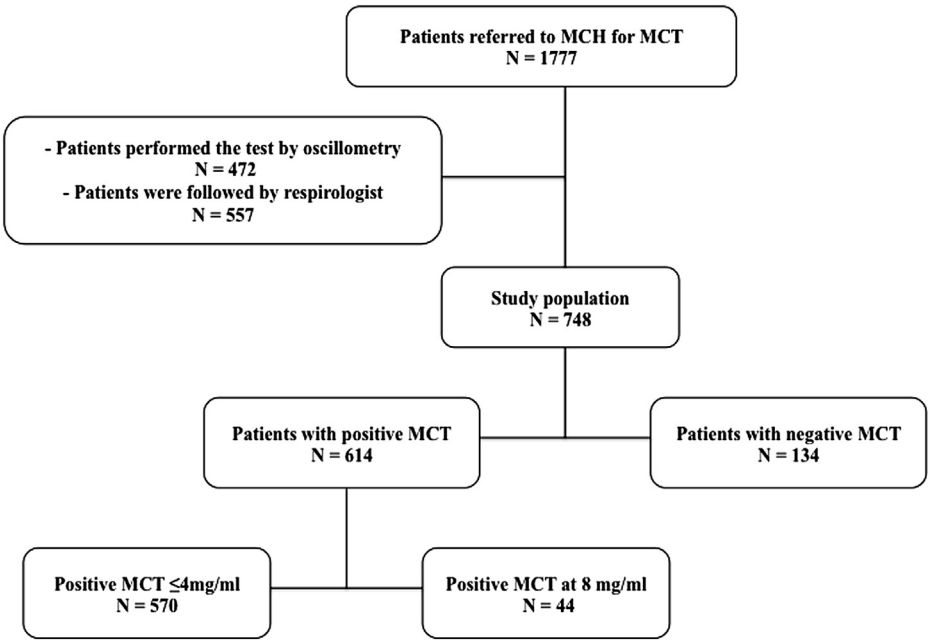

Figure 1. Selection of study population. MCT, methacholine challenge test.

8 mg/mL or less. This finding likely contributed to the low reported specificity. The second study evaluated a group of 7-year-olds being followed up because of a high risk of asthma.[7] Physician-diagnosed asthma was made by a single allergist based on symptoms, use of medications, and physical examination findings. These authors found an optimal cutoff of 3 mg/mL, with a sensitivity of 80%, in this population. In their asthmatic population, 92% responded at or below 8 mg/mL, with 11% responding between 4 and 8 mg/mL. In the nonasthmatic population, 73% responded at or below 8 mg/mL, with 15.5% responding between 4 and 8 mg/mL.

Certainly in patients at high risk for asthma, a positive test result is more likely, and in those with allergic rhinitis, a test result between 4 and 8 mg/mL is frequent.[8–13] It is unclear what happens in an unselected population, largely referred from general pediatric and family medicine physicians, rather than a population referred by second-line respiratory specialists. We hypothesized that lowering the threshold of a positive MCT result from 8 to 4 mg/mL would not significantly change the frequency of respondents and nonrespondents. Specifically, we hypothesized that lowering the threshold from 8 to 4 mg/mL would misclassify less than 10% of referrals. The following retrospective study was conducted to investigate the effect of lowering the cutoff from 8 to 4 mg/mL on the sensitivity, number of positive test results, and the distribution of test results in an unselected pediatric population referred to the hospital pulmonary function laboratory by nonrespiratory physicians for MCTs.

Methods

Study participants consisted of all patients referred by their physicians to the Montreal Children's Hospital for MCTs from January 1, 2006, through June 31, 2012. The request for testing was made without additional information concerning symptoms or severity as to why asthma was suspected in the referred patient. All patients needed to be older than 4 years, to be able to perform spirometry according to American Thoracic Society standards,[1] and to have a baseline FEV_1 of at least 70% predicted.[8,14] The study was approved by the research ethics review committee of the institution. No patient consent was required because the study used retrospective laboratory data with all patient identifiers removed.

Patients needed to be free of factors that could increase bronchial hyperreactivity, including current airway infection or use of antibiotics in the previous 2 weeks. Patients were advised to stop taking the following medications before testing: short-acting β_2-agonists for 6 hours, long-acting β_2-agonists and leukotriene receptor antagonists for 24 hours, short-acting antihistamines for 4 days, and long-acting antihistamines for 15 days.

Methacholine Challenge Test

Spirometry (Jaeger APS; CareFusion Respiratory Care, California) was conducted using a Hans-Rudolph nonrebreathing valve (Hand Rudolph Inc. Kansas City Missouri) attached to a Misty-Neb Medication nebulizer set (CareFusion Respiratory Care) with a flow meter at 7 L/min. A 2-minute tidal breathing dosing protocol was used based on Canadian Thoracic Society and American Thoracic Society recommendations. Doubling concentrations of methacholine were delivered, starting with a concentration of 0.25 mg/mL up to 8 mg/mL or a 20% decrease in FEV_1 from baseline. A starting concentration of 0.06 mg/mL was used if (1) the baseline forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) was equal or less than 50% predicted in patients 8 years or older, (2) the baseline $FEF_{25\%-75\%}$ was equal or less than 65% in patients 6 to 8 years of age, or (3) the patient was younger than 6 years. This was done because lower $FEF_{25\%-75\%}$ values at baseline suggest decreased flows at low lung volumes, due to more narrow airways, and an increased risk for a greater decrease in FEV_1 with methacholine provocation.

At the end of the test, nebulized salbutamol (2.5 mg) was administered. If the FEV_1 did not return to within 5% of the baseline value, spirometry was performed again 5 minutes later. If the FEV_1 was still less than 5% of baseline, the patient was evaluated by a respiratory physician, and a second treatment with salbutamol was administered, after which spirometry was performed again. Oxygen saturation was monitored throughout the challenge and for at least 10 minutes after the challenge and continued until values were greater than 95%.

The PC_{20} was calculated using a linear interpolation[15] with the following formula to include all patients who responded at the first dose of methacholine: $PC_{20} = (20-R1)\ (C2-C1) + C1$