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Utility and efficiency of methacholine challenge testing in evaluating pediatric asthma: unraveling the diagnostic conundrum

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ABSTRACT

Objective: Interpretation of methacholine challenge testing (MCT) results depends on the patient's pretest probability of asthma as well as the provocative concentration (PC_{20}); however, ordering providers rarely understand the complexity associated with its interpretation. This study investigated the clinical utility and efficiency of MCT at a tertiary center in evaluating pediatric asthma.

Methods: Retrospective chart review was done for all MCT done at a tertiary center over a six year period (2011–2017). Demographics, referring provider, referral diagnosis, current symptoms with and without exercise, and baseline spirometry were collected. Pretest probability of asthma was assigned by author (RB) who was blinded to MCT results and PC_{20} . Post-test probability of asthma was assigned based on pretest probability, MCT result (+/–), and PC_{20} . Three assigned asthma probability categories were “unlikely”, “likely”, and “very likely”.

Results: Of 172 subjects (91 Females, age range 5–21 years), 64.9% of MCT results ($n = 111$) were negative and 35.1% ($n = 60$) were positive. One was inconclusive. Those who tested positive were shorter, lighter, younger and had lower forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio than those who tested negative ($p < 0.05$). Subjects with exercise symptoms only were less likely to test positive (OR 0.2, CI 0.1–0.5). In a majority of subjects (91.8%; 157/171), MCT increased the certainty of presence or absence of asthma.

Conclusions: In our subject population, MCT could be useful in evaluating pediatric asthma if subject's pretest probability of asthma and PC_{20} was taken into account. It was not as useful for subjects with exercise symptoms only.

Abbreviations: FEV_1 : Forced expiratory volume in one second; FVC: Forced vital capacity; MCT: Methacholine challenge testing; PC_{20} : Provocative concentration₂₀; PD_{20} : Provocative dose₂₀

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Introduction

Methacholine Challenge Test (MCT) is done to assess the presence and degree of airway responsiveness, measured by an index of bronchoconstriction. This test is most often done to exclude or confirm a suspected diagnosis of pediatric asthma. In day-to-day practice, asthma is most frequently diagnosed by clinical history, supported by reversible airflow obstruction on spirometry. However, spirometry may be inconclusive, especially in those with normal or near-normal lung function values. In this case, MCT may be appropriate to increase or decrease the probability of asthma.

Interpretation of methacholine challenge results depends on the patient's pretest probability of asthma

as well as the Provocative Concentration (PC_{20}) (1). The optimal diagnostic value of methacholine challenge testing occurs when the pretest probability of asthma is 30–70% (2). The lower the PC_{20} , the higher the probability that a positive MCT reflects asthma (3). However, ordering providers rarely understand the complexity associated with its interpretation and implications which can potentially cause unnecessary tests or misinterpretation of the results. The average cost of a methacholine challenge test is more than 1000 dollars. Although no deaths have been reported with MCT, there remains the potential of severe bronchospasm (1). Keeping the cost and safety concerns in mind, it is prudent to understand the usefulness and efficiency of MCT in evaluating pediatric asthma.

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In this retrospective study, we investigated the clinical utility and efficiency of MCT in evaluating pediatric asthma in subjects referred to our tertiary center over a six years period.

Methods

Retrospective chart review was done for all MCT done at our tertiary center located in the USA over a six year period (2011–2017). Data collected included but was not limited to demographics, referring provider, referral diagnosis, current symptoms with and without exercise, and baseline spirometry. Subjects were instructed to hold inhaled bronchodilators 24 h prior and inhaled/oral steroids one week prior to the test if they were on these medications. Antihistamines were also held one week prior to the test. Two-minute tidal breathing of a nebulized solution was used as a method of inhalation of diluent as well as for increasing concentrations of methacholine. The test was considered completed when the top concentration (25 mg/ml) was administered or the FEV₁ had fallen by at least 20%. PC₂₀ was calculated based on guidelines (1). Pretest probability of asthma was assigned by an author (RB) who was blinded to MCT results and PC₂₀. This was done based on referral diagnosis, current symptoms and whether symptoms only occur with exercise (Table 1). Current symptoms only with exercise were given lower pretest probability of asthma as many studies have shown poor correlation between self-reported exercise-induced symptoms

and exercise induced bronchoconstriction (4–6). Post-test probability was assigned based on the pretest probability of asthma, MCT result ($\pm$), and PC₂₀ (Table 2).

Data analysis included calculation of summary statistics and distributional assessments for continuous data and of frequencies and percentages for categorical data. The *T*-Test with an assessment of variance was used for two group comparisons of continuous data, and to account for departures from normality, the Wilcoxon Rank Sum Test was utilized to verify results of *T*-Test. Chi² Test of Independence and Fisher's Exact Testing were utilized for examination of potential associations of MCT with categorical covariates. Statistical analyses were completed using SAS 9.4/13.2©. Unless otherwise noted all testing was two-tailed and evaluated at the Type I Error Rate of the $\alpha = 0.05$ level of statistical significance. The Institutional Review Board reviewed and approved the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [RB], upon reasonable request.

Results

One hundred seventy-two subjects were included in the study (91 Females, age (mean $\pm$ SD, 12.6 $\pm$ 3.6 years;

Table 1. Criteria for assigning pretest probability of asthma based on available clinical history.

Pretest probability of asthma	Referral diagnosis	Current symptoms
Unlikely	Shortness of breath, Chest pain	Shortness of breath with exercise only, symptoms other than respiratory (i.e. vomiting, dizziness, feeling faint, etc.)
Likely	Asthma/reactive airway disease, chronic cough	Chronic cough and shortness of breath with exercise
Very likely	Asthma	Typical symptoms of asthma-wheezing, coughing, chest tightness, shortness of breath with activity

Table 2. Criteria for assigning post-test probability of asthma based on the pretest probability of asthma, MCT results ($\pm$) and PC₂₀ as well as number of subjects, *n* (%) in each category.

Post-test probability of asthma	Pretest probability of asthma (based on clinical criteria)			Total <i>n</i> (%)
	Unlikely <i>n</i> (%)	Likely <i>n</i> (%)	Very Likely <i>n</i> (%)	
Unlikely <i>n</i> (%)	MCT (–) or MCT (+) with PC ₂₀ > 16 mg/ml 42 (24.5%)	MCT (–) 61 (35.7%)	MCT (–) 10 (5.9%)	113 (66.1 %)
Likely <i>n</i> (%)	MCT (+) with PC ₂₀ 4–16 mg/ml 9 (5.3%)	MCT (+) with PC ₂₀ > 16 mg/ml 5 (2.9 %)	N/A	14 (8.2%)
Very likely <i>n</i> (%)	MCT (+) with PC ₂₀ ≤ 4 mg/ml 5 (2.9%)	MCT (+) with PC ₂₀ ≤ 16 mg/ml 35 (20.5%)	MCT (+) 4 (2.3%)	44 (25.7 %)
Total <i>n</i> (%)	56 (32.7 %)	101 (59.1%)	14 (8.2%)	171 (100%)

MCT, methacholine challenge testing; PC₂₀, provocative concentration₂₀.

Table 3. Demographic and baseline spirometry variables for the subject population as well as T-test results (*p* values) assessing differences in these variables based on MCT results.

Variables	Mean $\pm$ SD (range)	<i>p</i> -value (T-Test)*
Age (years)	12.6 $\pm$ 3.6 (5–21)	<0.001
Weight (kg)	53.2 $\pm$ 21.4 (17.5–137.1)	<0.001
Height (cm)	150 $\pm$ 2.0 (110–190)	<0.001
BMI (kg/m ²)	21.3 $\pm$ 5.3(13.1–45.8)	0.098
FVC (% predicted)	102 $\pm$ 11.9 (64–140)	0.599
FEV ₁ (% predicted)	99.9 $\pm$ 11.6 (71–134)	0.068
FEV ₁ /FVC %	85.4 $\pm$ 6.2(67–99)	0.006

FVC, forced vital capacity; FEV₁, forced expiratory volume in one second.

*Significant *p* values are highlighted in bold.

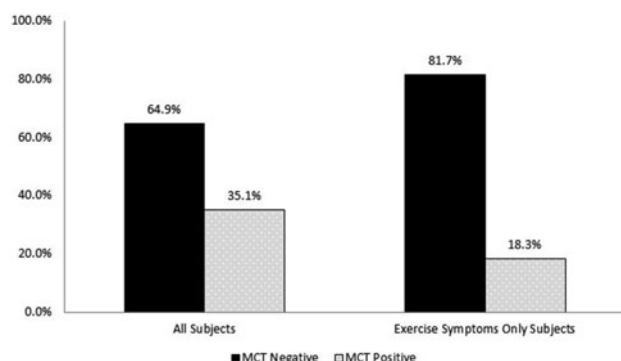


Figure 1. MCT results in all subjects as well as in subjects with exercise symptoms only.

range 5–21 years) (7). Only 9% of tests were ordered by an asthma specialist, the rest were ordered by general providers outside of the institution. 34% had been referred with a presumptive diagnosis of

asthma or reactive airway. Mean forced expiratory volume in one second (FEV₁) (99.9% predicted) and FEV₁/forced vital capacity (FEV₁/FVC) ratio (85.4%) for the group as a whole were in the normal range (Table 3).

64.9% of tests (*n* = 111) were negative and 35.1% (*n* = 60) were positive (Figure 1). One was inconclusive. Of positive tests, 43% (26/60) showed PC₂₀ of $\leq$ 4 mg/ml, another 43% (26/60) had PC₂₀ of 4–16 mg/ml and rest 14% (8/60) had PC₂₀ >16 mg/ml. MCT (–/+) status was affected by age, weight, height, and FEV₁/FVC ratio. Those who tested positive were shorter, lighter, younger and had lower FEV₁/FVC ratio than those who tested negative (*p* < 0.05) (Table 3).

Of the 122 subjects for whom symptoms during exercise were available, 61(50%) had symptoms during exercise only. The MCT positive rate in these subjects was 18.3% in contrast to 35.1% in all subjects (Figure 1). The Chi² Test of Independence showed that subjects with exercise symptoms only were less likely to have a positive test (*p* < 0.001; OR 0.2, CI 0.1–0.5).

Pretest and post-test probabilities of asthma were assigned based on criteria listed in Table 1 and 2. Prior to MCT results, 32.7% subjects were in the “unlikely” category, 59.1% in “likely” category and only 8.2% in “very likely” category based on pretest

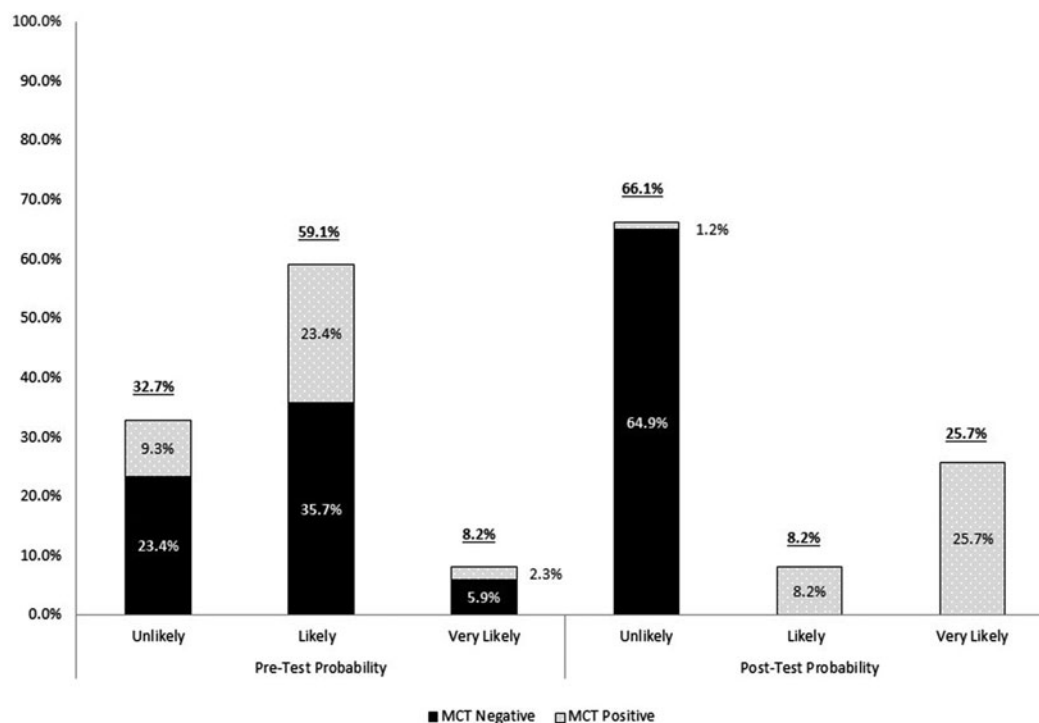


Figure 2. Distribution of pretest and post-test probability of asthma showing “unlikely” and “very likely” categories rose to 66.1% and 25.7% respectively whereas the “likely” category fell to just 8.2% post MCT results.

probability of asthma. With MCT results, “unlikely” and “very likely” categories rose to 66.1% and 25.7% respectively whereas the “likely” category fell to just 8.2% (Figure 2). Thus, in the majority of subjects ($66.1 + 25.7\% = 91.8\%$; 157/171), MCT was able to increase the certainty of presence or absence of asthma.

Discussion

In our study, approximately one-third of the tests were positive and the rest were negative. Those who tested positive were shorter, lighter, younger and had lower FEV₁/FVC ratio than those who tested negative. Subjects whose symptoms were only present during exercise were less likely to have a positive test. In the majority of the subjects, MCT results were able to increase the certainty of presence or absence of asthma.

Historically, the cutoff values used in adults have also been used in children without any dose adjustment. Many studies argue that this practice is inappropriate (8,9). Our smaller and younger subjects received a larger dose, relative to their lung size in comparison to bigger and older subjects. The increased incidence of positive tests in these subjects could be a consequence of increased relative dose rather than increased airway reactivity. Our study along with previous studies argue that the methacholine dose used for adults may be inappropriate for use in children especially younger children and some kind of dose adjustment need to be done based on age (8,9). A recent large study done on Korean children suggested different cut off values of PC₂₀ based on age for diagnosis of asthma (10). Another study concluded that in children a PC₂₀ of 4 mg/ml can reasonably be used as a cut off value for positive MCT (11). Airway caliber is also important in MCT response (3). A reduction in airway caliber at baseline (lower FEV₁/FVC ratio) will result in a greater increase in airway narrowing for the same degree of muscle shortening (12,13). Thus, incidence of MCT positive is higher in subjects with lower FEV₁/FVC ratio as shown in our study group.

Subjects with exercise symptoms only were less likely to be positive on MCT in our sample population. Methacholine directly interacts with muscarinic receptors on airway smooth muscle, resulting in contraction and airway narrowing. Therefore, it is considered a direct challenge test along with histamine. Both exercise and eucapnic hyperventilation cause airway drying and cooling, which leads to bronchoconstriction through an osmolar change in the airway

epithelium resulting from water loss. Those are examples of indirect challenge tests. Individuals may respond differently to direct and indirect challenge tests based on what stimuli are involved in clinical symptoms. Since exercise triggers bronchoconstriction through an inflammatory mechanism instead of direct stimulation, the likelihood of false negative MCT is high in subjects with exercise-induced symptoms only (14). Anderson et al. performed MCT and exercise challenge testing in subjects with clinical asthma across 25 sites in the USA to compare MCT and exercise challenge testing results in the same population. Similar to our findings, they showed that 45% of subjects (73/163) with positive exercise test had negative MCT results (15). With this information in mind, the efficiency of MCT can be increased in the future by carefully choosing patients who are referred for the test. For patients with only exercise-induced symptoms, indirect challenge tests like exercise challenge test or cardiopulmonary exercise testing may be more effective in establishing the diagnosis (16).

In more than 90% of subjects in our sample, MCT results could be helpful in clinical decision making. However, careful consideration of the pretest probability of asthma, current symptoms, and PC₂₀ needed to be taken into account. There is a general notion to consider MCT results as an absolute which can be misleading. On the other hand, the concept of pretest and post-test probability uses the test results to raise or lower the probability of asthma instead of deciding unequivocally whether a patient does or does not have asthma. This approach also highlights the importance of knowledge about the patient when interpreting the results which may not be available to the interpreting specialist. It becomes more critical in a situation as in our study population where almost all subjects (>90%) were referred from outside general providers who were not asthma specialists. There is a need for educating ordering pediatric providers as well as interpreting physicians regarding this complexity in interpretation as well as its implications.

Limitations to this study include those inherent in an exploratory analysis on a retrospective chart review. No data were available upon which to perform an *a priori* sample size analysis. Therefore this study was not necessarily fully powered for the analysis of a specific hypothesis and as such, the results may not be generalizable. We could not confirm or refute the diagnosis of asthma given by the referring provider. Although Provocative dose (PD₂₀) is preferred now instead of PC₂₀, we could not employ PD₂₀ as the institutional standard during the study period was to

calculate and follow PC₂₀ (17,18). Since top concentration used in our study was 25 mg/ml, few subjects were considered MCT positive despite PC₂₀ > 16 mg/ml which we understand is not optimal. However, we have taken this into account while assigning post-test probability (Table 2). Pretest and post-test probability for asthma were assigned by one of the author (RB) based on clinical criteria chosen by experience as there is no standard validated norms in literature to calculate these. Some investigators have calculated post-test probability based on Bayes' theorem but this approach is clinically impractical (19, 20). Therefore, this author tried to make these criteria as simple and objective so that these can be reproduced in future studies (Tables 1 and 2) although we understand that these criteria are not optimal.

In conclusion, incidence of positive tests was higher in shorter, lighter and younger subjects in our sample which poses the question if reconsidering the age specific dosing of methacholine for children is needed. Overall, MCT could be useful in evaluating pediatric asthma if the subject's pretest probability of asthma and PC₂₀ was taken into account. It was not as useful for subjects who only exhibited symptoms with exercise. Our study provides evidence that MCT is a useful test provided the ordering physician understands the complexity of its interpretation and the patient population in which it can be most efficient. Future studies are needed to test specific dosing of methacholine in children. There is also a need for specific well-validated criteria for assigning pre and post-test probability of asthma in children to help with the interpretation of this test.

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