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Predictive factors for a shortened methacholine challenge protocol in children

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ABSTRACT

Rationale: Although the methacholine challenge test is useful in the diagnosis of asthma, it is time-consuming in children. While protocols that quadruple methacholine concentrations are widely used in adults to shorten testing time, this has not been evaluated in children. Studies have not identified predictors associated with the safe use of a quadrupled concentration protocol.

Objectives: To identify clinical predictors associated with the preclusion of a quadrupled concentration protocol in children.

Methods: We included subjects <18 years who performed a methacholine challenge tests between April 2016 to February 2017 (derivation cohort) and March 2017 to September 2017 (validation cohort). We determined the eligibility of a subject to omit the 0.5 mg/ml and 2.0 mg/ml concentrations based on their PC20 and identified baseline characteristics that are associated with the preclusion of the quadrupled protocol using bivariate analysis. The derived algorithm was applied to the validation cohort.

Results: We included 399 and 195 patients in the derivation and validation cohorts, respectively. A baseline FEV_1 ≤90% predicted, FEV_1/FVC ≤0.8, FEF_{25-75} ≤70% predicted, and a decrease in FEV_1 ≥10% with the previous concentration significantly precluded the omission of the 0.5 mg/ml concentration. A baseline FEF_{25-75} ≤70% predicted and a drop in FEV_1 ≥10% with the previous concentration significantly precluded the omission of the 2.0 mg/ml concentration. Applying these 4 criteria to the validation cohort resulted in an overall sensitivity and specificity of 74.0% and 84.6%, respectively.

Conclusions: We identified objective pulmonary function measures that may personalize and shorten the methacholine challenge protocol in children by quadrupling concentrations.

1. Introduction

Diagnosing asthma may be challenging given that symptoms such as wheeze, shortness of breath, and cough are non-specific. Thus, international guidelines recommend the measurement of airway hyperresponsiveness to guide asthma diagnosis, particularly in patients who have symptoms consistent with asthma but normal lung function [1–5].

Methacholine bronchial provocation is a widely used, objective clinical test to assess airway hyperresponsiveness. Despite its clinical usefulness, it remains a time-consuming test because of the administration of incremental methacholine concentrations [2]. In children, particularly young children, this test can be technically challenging given their shorter attention span, taking as long as 90 min to complete. Several studies have proposed methods to shorten this test in children, including reducing the threshold to affirm the presence of airway hyperreactivity from 8 mg/ml to 4 mg/mL [6] and using more rapid nebulizers [7]. Few studies that included mostly adults demonstrated the possibility to shorten the provocation procedure by starting at a higher concentration or omitting some concentrations based on baseline lung function measurement, symptom control, and use of medication [8,9].

While quadrupling methacholine concentrations was already recommended in the first 1999 ATS methacholine guideline [3] and is a common practice in adults, no formal recommendation for or against quadrupling concentrations or doses have been made in children, possibly due to the fear of inducing severe bronchospasm. However,

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quadrupling methacholine concentrations could significantly shorten the duration of the test, decreasing the burden on the patient performing the test. It may also increase the accessibility of this test for others, ultimately leading to a more timely diagnosis and clinical management of individuals with asthma.

In this study, we identified clinical characteristics predictive of whether children can safely use a shortened methacholine provocation protocol whereby concentrations are quadrupled instead of doubled. We then validated our algorithm in a separate cohort of children. Some of the results of this study have been previously reported in the form of an abstract [10].

2. Methods

2.1. Design

We performed a retrospective study on patients having had a methacholine challenge test at the pulmonary function laboratory of Sainte-Justine University Hospital Center from April 2016 to February 2017 (derivation cohort). We subsequently validated our findings in a separate set of patients having had this test from March 2017 to September 2017 (validation cohort). We identified eligible subjects through the pulmonary function laboratory database. The institution's research ethics review committee approved this study.

2.2. Subjects

We included subjects aged 6–17 years, inclusively, referred for a methacholine challenge test, independent of the source of referral (by pulmonologists, hospitalist or community pediatricians, or general practitioners). We excluded subjects who were unable to perform a reproducible spirometry according to American Thoracic Society (ATS) guidelines and those with cystic fibrosis given their tendency to have higher airway hyperresponsiveness [11].

2.3. Methacholine challenge protocol

Following the inhaled 0.9% NaCl step, methacholine at 0.06 mg/ml was given, followed by 0.25 mg/ml and subsequent doubling of concentrations. Two additional concentrations, 0.03 and 0.125 mg/ml, were optional and given only if the drop in FEV_1 was $\geq$10% with NaCl and the 0.06 mg/ml concentration, respectively. The test was stopped following the 8 mg/ml concentration or a drop in FEV_1 $\geq$20%, whichever occurs first. Methacholine was administered using a Small Volume Nebulizer VixOne™ (Westmed, Tucson, AZ) that were calibrated to obtain an output within 10% of 0.13 ml/min as per ATS guidelines [3]. Patients were instructed to breathe quietly for 2 min through the mouthpiece, after which spirometry was performed using a Jaeger MasterScope spirometer (Cardinal Health, Dublin, OH) with references values by Stanojevic et al. [12]. There was a 5-min interval between the start of each nebulization. The cumulative effect of methacholine can be considered small with this interval [13,14]. The methacholine challenge and spirometry were conducted as per ATS guidelines [3,15].

2.4. Assessment of the eligibility for a shortened protocol with quadrupling of the methacholine concentrations

In order to assess whether a subject would be eligible to skip the methacholine concentration of 0.5 mg/ml (thus quadrupling the concentrations from 0.25 mg/ml to 1.0 mg/ml), we evaluated the PC_{20} of all subjects having received the 0.25 mg/ml concentration. If the PC_{20} was $\leq$0.5 mg/ml, we considered that the subject was not eligible to skip the 0.5 mg/ml concentration and thus should be using the standard protocol. If the PC_{20} was >0.5 mg/ml, we considered that the subject would be eligible to skip the 0.5 mg/ml concentration ("shortened protocol"). Similarly, to assess whether a subject would be eligible to skip the methacholine concentration of 2.0 mg/ml and use the shortened protocol, we evaluated whether the PC_{20} of subjects having received the 1.0 mg/ml concentration was $\leq$2.0 mg/ml or >2.0 mg/ml.

2.5. Assessment of potential predictors for a shortened protocol

We considered the following objective measures as potential predictors for a shortened protocol: sex, body mass index (BMI), and baseline forced expiratory volume in 1 s (FEV_1) percent predicted, baseline forced vital capacity (FVC) percent predicted, baseline FEV_1/FVC, baseline forced expiratory flow at 25–75% of the pulmonary volume (FEF_{25-75}) percent predicted, and the percentage of decrease in FEV_1 following each methacholine concentration. While patient-reported clinical data such as physician-diagnosed asthma and current medication was available, we excluded these variables because of the potential for subjectivity and their dependence on several factors, including access to health providers, the source of referral, and medication adherence.

2.6. Statistical analyses

We performed a descriptive analysis of the derivation and validation cohorts. Using the derivation cohort, we extracted two sub-cohorts: 1) subjects who received the 0.25 mg/ml concentration and 2) those who received the 1.0 mg/ml concentration. Bivariate analysis was performed to identify predictors for having a PC_{20} $\leq$0.5 mg/ml in the first cohort and $\leq$2.0 mg/ml in the second cohort. Subsequently, using the predictors identified in the derivation cohort, we classified subjects in the validation cohort as being eligible or not for the shortened protocol (i.e. quadrupling concentrations by omitting the 0.5 mg/ml and/or 2.0 mg/ml concentrations). Based on their documented PC_{20}, we calculated the sensitivity, specificity, and positive and negative predictive values of our model. A 2-sided p-value of <0.05 was considered statistically significant. All analyses were performed with R software, version 3.5.0 (www.r-project.org).

3. Results

3.1. Derivation cohort

We identified 399 subjects meeting the study criteria, 386 and 339 of whom received the 0.25 mg/ml and 1.0 mg/ml concentrations, respectively. Baseline characteristics of the 399 subjects, the majority of whom were referrals from the community (n = 279, 69.9%) and were Caucasian, are shown in Table 1. The mean FEV_1, FEV_1/FVC, FEF_{25-75} of the cohort were within the normal range and 36.1% of the cohort had a negative methacholine challenge test (PC_{20} >8.0 mg/ml).

3.2. Factors precluding the omission of the methacholine concentration of 0.5 mg/ml or 2.0 mg/ml

Among subjects who received the 0.25 mg/ml concentration, 56 (14.5%) had a PC_{20} $\leq$0.5 mg/ml. A baseline FEV_1 $\leq$90% predicted, FEV_1/FVC $\leq$0.8, FEF_{25-75} $\leq$70% predicted, and a decrease in FEV_1 $\geq$10% with the 0.25 mg/ml concentration were positively associated with a PC_{20} $\leq$0.5 mg/ml (Table 2). Thus, these factors preclude the omission of the 0.5 mg/ml concentration.

Among subjects who received the 1.0 mg/ml concentration, 130 (38.3%) had a PC_{20} $\leq$2.0 mg/ml. A baseline FEF_{25-75} $\leq$70% predicted and a drop in FEV_1 $\geq$10% with 1.0 mg/ml were associated with a PC_{20} $\leq$2.0 mg/ml (Table 3). Thus, these factors preclude the omission of the 2.0 mg/ml concentration.

3.3. Validation cohort

We included 195 subjects in the validation cohort, 191 and 164 of

Table 1
Baseline characteristics of the derivation and validation cohort.

	Derivation cohort (n = 399)	Validation cohort (n = 195)
Male, n (%)	200 (50.1)	102 (52.3)
Age, mean (SD; range)	10.8 (3.3; 5.2–18.9)	12.4 (3.1; 5.7–18.6)
Race/ethnicity, n (%)		
Caucasian	333 (83.5)	165 (84.6)
Black	23 (5.8)	11 (5.6)
Asian	8 (2.0)	3 (1.5)
Other	35 (8.8)	16 (8.2)
BMI, median (IQR)	18.3 (16.8, 21.2)	19.8 (17.2, 23.07)
Baseline spirometry, mean (SD) unless otherwise specified		
FEV_1 percent predicted	101.8 (12.9)	102.2 (13.1)
FEV_1 percent predicted ≤90%, n (%)	62 (15.5)	34 (17.4)
FEV_1/FVC	86.0 (7.0)	85.6 (6.2)
FEV_1/FVC ≤80%, n (%)	62 (15.5)	29 (14.9)
FEF_{25-75} percent predicted	92.2 (22.7)	93.0 (21.3)
FEF_{25-75} percent predicted ≤70%, n (%)	71 (17.8)	28 (14.4)
Negative methacholine challenge test (PC20 >8.0 mg/ml), n(%)	144 (36.1)	59 (30.3)

Table 2
Association between baseline characteristics and PC20 ≤0.5 mg/ml (thus precluding the omission of this concentration) among the subjects who received the 0.25 mg/ml concentration.

	PC_{20} >0.5 mg/ml	PC_{20} ≤0.5 mg/ml	p-value
Number of subjects	330	56	
Male sex			
Number	166	27	
Percent	50.3	48.2	
Crude odds ratio (95% CI)	1 (Ref)	0.92 (0.52, 1.62)	0.77
Body mass index			
Median (IQR)	18.4 (15.8, 21.4)	17.7 (15.7, 19.6)	
Crude odds ratio (95% CI), per 1 unit	1 (Ref)	0.95 (0.88, 1.03)	0.20
Baseline FEV_1 percent predicted ≤90%			
Number	46	15	
Percent	13.9	25.4	
Crude odds ratio (95% CI)	1 (Ref)	2.26 (1.16, 4.41)	0.02
Baseline FEV_1/FVC percent predicted ≤0.8			
Number	42	18	
Percent	12.7	32.1	
Crude odds ratio (95% CI)	1 (Ref)	3.25 (1.70, 6.21)	<0.01
FEF_{25-75} percent predicted ≤70%			
Number	46	23	
Percent	13.9	41.1	
Crude odds ratio (95% CI)	1 (Ref)	4.30 (2.32, 7.97)	<0.01
≥10% decrease in FEV_1 percent predicted with the 0.25 mg/ml concentration			
Number	20	46	
Percent	6.1	82.1	
Crude odds ratio (95% CI)	1 (Ref)	71.30 (31.41, 161.86)	<0.01
Referral from within the institution			
Number	97	19	
Percent	29.4	33.9	
Crude odds ratio (95% CI)	1 (Ref)	1.23 (0.68, 2.25)	0.49

whom received the 0.25 mg/ml or 1.0 mg/ml concentrations, respectively. The baseline characteristics of these patients are shown in Table 1 and were comparable to those of the derivation cohort, including the proportion of subjects with a negative methacholine challenge test (30.3%). Based on the findings in the derivation cohort, subjects with a baseline FEV_1 >90%, baseline FEV_1/FVC >0.8, baseline FEF_{25-75} >70% and FEV_1 drop <10% with the previous methacholine concentration were deemed to be hypothetically eligible to omit the 0.5 mg/ml and/or 2.0 mg/ml concentrations.

Table 3
Association between baseline characteristics and PC20 ≤2.0 mg/ml (thus precluding the omission of this concentration) among the subjects who received the 1.0 mg/ml concentration.

	PC_{20} >2.0 mg/ml	PC_{20} ≤2.0 mg/ml	p-value
Number of subjects	226	113	
Male sex			
Number	109	63	
Percent	48.2	55.8	
Crude odds ratio (95% CI)	1 (Ref)	1.35 (0.86, 2.13)	0.19
Body mass index			
Median (IQR)	18.9 (16.5, 21.6)	17.1 (15.2, 20.7)	
Crude odds ratio (95% CI), per 1 unit	1 (Ref)	0.95 (0.90, 1.01)	0.10
Baseline FEV_1 percent predicted ≤90%			
Number	31	15	
Percent	13.7	13.3	
Crude odds ratio (95% CI)	1 (Ref)	0.96 (0.50, 1.87)	0.91
Baseline FEV_1/FVC percent predicted ≤0.8			
Number	25	17	
Percent	11.1	15.0	
Crude odds ratio (95% CI)	1 (Ref)	1.42 (0.73, 2.76)	0.30
FEF_{25-75} percent predicted ≤70%			
Number	23	23	
Percent	10.2	20.4	
Crude odds ratio (95% CI)	1 (Ref)	2.26 (1.20, 4.23)	0.01
≥10% decrease in FEV_1 percent predicted with the 0.25 mg/ml concentration			
Number	32	98	
Percent	14.2	86.7	
Crude odds ratio (95% CI)	1 (Ref)	39.61 (20.48, 76.61)	<0.01
Referral from within the institution			
Number	65	35	
Percent	28.8	31.0	
Crude odds ratio (95% CI)	1 (Ref)	1.11 (0.68, 1.82)	0.67

Among the 191 subjects who received the 0.25 mg/ml in the validation cohort, 122 (63.9%) were hypothetically assigned to the shortened protocol. Among the 164 subjects who received the 1.0 mg/ml, 95 (57.9%) were hypothetically assigned to the shortened protocol (Fig. 1). Based on the actual PC_{20} of the subjects, the algorithm correctly assigned 205 steps of the methacholine challenge to the shortened protocol out of 277 steps that should have been assigned to the shortened protocol (sensitivity = 74.0%) and 66 steps to the standard protocol out of 78 steps that should have been assigned to the standard protocol (specificity = 84.6%). The positive and negative predictive value of the algorithm 94.5% and 47.8%, respectively.

With the application of the selection criteria for a shortened protocol, we would have omitted the 122 nebulizations of methacholine at 0.5 mg/ml and 95 nebulizations at 2.0 mg/ml. Considering that a total of 1083 methacholine nebulizations were administered in the validation cohort, 20.0% of the nebulizations would have been omitted with the shortened protocol.

Within the validation cohort, 12 (6.2%) subjects would have received the quadrupled concentration while their FEV_1 actually dropped by ≥20% with the doubled concentration. The mean drop in FEV_1 with the previous methacholine concentration among these patients was 21.4%.

4. Discussion

In this study, we identified baseline pulmonary function characteristics that could predict the possible omission of certain steps in the methacholine provocation test in children. Specifically, based on the baseline pulmonary function of the child and the magnitude of the decrease in FEV_1 with the previous methacholine concentration, children could be assigned to a shortened protocol that would quadruple the methacholine concentrations.

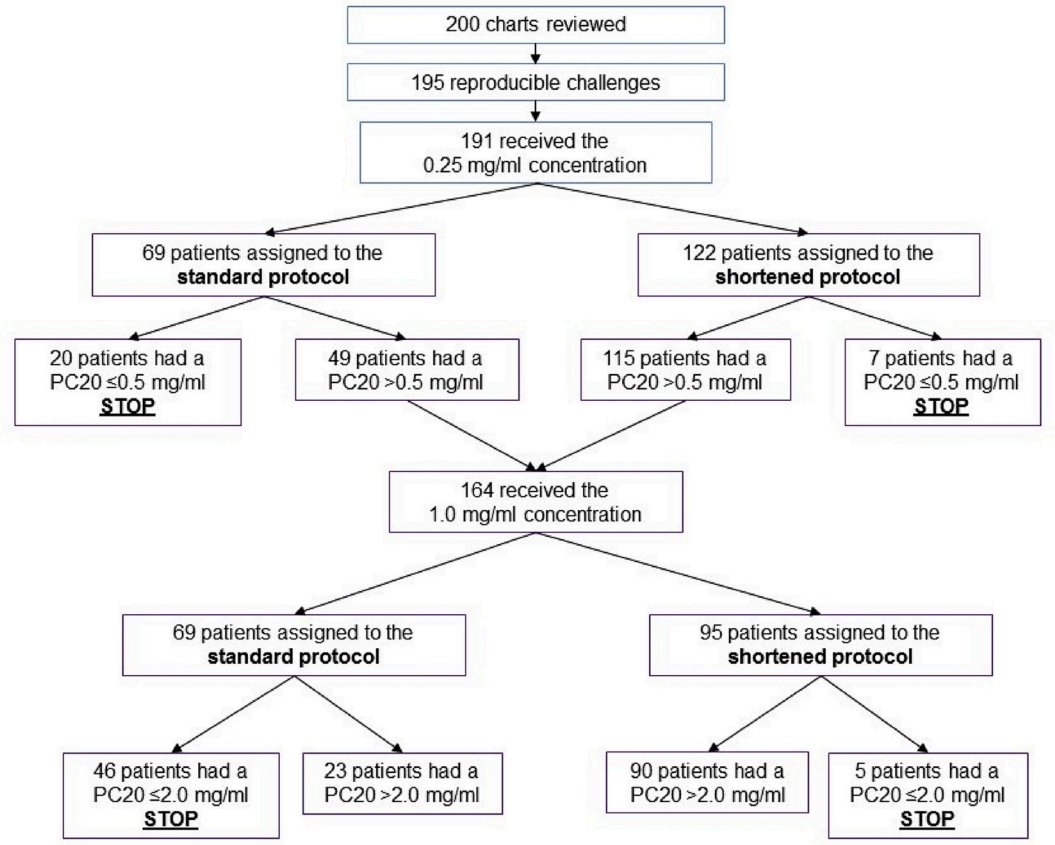

Fig. 1. Flow chart illustrating the hypothetical assignments to the standard or shortened methacholine challenge protocol in the validation cohort.

While the methacholine provocation test is a widely used objective measure to assess airway hyperresponsiveness, it can be time-consuming in children who have relatively short attention span, particularly in young children. In the recent ERS technical standard on bronchial challenge that was endorsed by the ATS [2], quadrupling increments are recommended for clinical testing, in light of previous studies showing no increased risk of severe bronchoconstriction with fewer concentration steps [16,17]. To our knowledge, this regimen is infrequently used in pediatrics and has not been evaluated. Thus, whether this regimen is safe in children and whether it should be used in all patients are questions that remain unanswered. Kivastik et al. demonstrated the feasibility and safety of a protocol which tripled methacholine concentrations in preschool children [18], however, the provocative concentration was determined by the appearance of audible wheeze and not by objective pulmonary function measures.

In this study, we found that a baseline FEV_1 ≤90% predicted, FEV_1/FVC ≤0.8, FEF_{25-75} ≤70% predicted, and a decrease in FEV1 ≥10% with the previous concentration would preclude the use of quadrupling increments in children undergoing this test. Among these predictors, a decrease in FEV_1 ≥10% with the previous concentration was the strongest predictor. This is not surprising as this fall in FEV_1 represents a partial hyperreactivity, the extent of which would likely be greater with the subsequent higher concentration. We did not find studies that assigned patients to a standard or shortened protocol based on clinical features or baseline lung function test. However, two retrospective studies with mostly adult patients noted that the starting methacholine concentration could be modified according to the baseline FEV_1 [8] or FEV_1/FVC [9], corroborating our findings by suggesting that personalization of the provocation test may be feasible. While we did not assess the selection of a higher, safe starting concentration in this study, this may be another method by which the methacholine challenge test could be shortened in children.

A shortened bronchoprovocation protocol has to be first and foremost safe. Thus, while we acknowledge the likely overlap between the 4 criteria in our algorithm and their interdependence, we decided to keep all 4 criteria such that a subject meeting any one of these criteria would be excluded from the shortened protocol. In the validation cohort, only 12 of the 191 subjects (6.2%) assigned to the shortened protocol actually should have been assigned to the standard protocol. This is reflected in the high specificity (84.6%) and positive predictive value (94.5%) of our model. While none of them had a severe decrease in FEV_1 with the last concentration received, it is difficult to predict what their response to a quadrupled rather than a doubled concentration would be. Reassuringly, Jörres et al. tested a standard (doubling concentrations) and a rapid (quadrupling) protocols in young adults and found that the mean decrease in FEV_1 was similar in the doubling and quadrupling protocols [16]. This suggests that the relationship between methacholine concentrations and FEV_1 is not necessarily linear and that the decrease in FEV_1 cannot be extrapolated. A prospective study is needed to further evaluate the safety of the shortened protocol in children.

While a proportion of patients assigned to the standard protocol could have actually safely benefited from the shortened protocol, reflected in the modest sensitivity of 74.0% and negative predictive value of 47.8%, our model already represent a significant improvement from our current protocol, whereby every patient undergoes the standard protocol. In fact, our model would allow the omission of 20.0% of the nebulizations, leading to significant time and money savings.

Our study has several limitations that are noteworthy. First, we excluded patient-reported clinical variables such as previous asthma diagnosis, respiratory symptoms, and current medications in our algorithm. While we acknowledge that these variables may improve our predictive model, such clinical data may be subjective and subject to recall bias. A previous asthma diagnosis and current medications taken may be dependent on the patient's previous health care encounters and

the source of referral. Furthermore, previous studies have demonstrated that asthma symptoms correlate poorly with methacholine results [19, 20]. Thus, we decided to focus on reliable, objective measures to define our model. Second, this is a retrospective study and we acknowledge that prospective studies are needed to further evaluate the safety of a shortened, quadrupled concentrations protocol. Reassuringly, the results in our validation were consistent with those in the derivation cohort, speaking to the robustness of the model. Finally, this is a single institution study and care must be exerted when generalizing findings to other centers with different population compositions. However, our institution is a large tertiary pediatric care and referral center, with the majority of patients being referred from community physicians. To our knowledge, this reflects the practice of most centers providing methacholine provocation testing in Canada and North America.

5. Conclusion

In conclusion, we identified 4 objective pulmonary function criteria that could determine whether a child could used a shortened, quadrupled methacholine concentration protocol. While our algorithm needs to be validated prospectively, our findings suggests that a more personalized approach to the methacholine challenge protocol is feasible in children. This could lead to important time savings for families, increased accessibility for other patients, and decreased costs for health care systems.

Authors' contributions

FP contributed to the study design, data collection and analysis, interpretation of the results, drafted the manuscript. SL contributed to the study design and interpretation of the results. NM contributed to data collection and analysis. SMT contributed to the study design, data analysis, interpretation of the results, and drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.105823.

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