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ORIGINAL ARTICLE

The FEF₂₅₋₇₅ and its Decline as a Predictor of Methacholine Responsiveness in Children

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Background. Methacholine challenge (MCC) is an important diagnostic tool for asthma, especially in patients in whom routine pulmonary function testing (PFT) is normal or equivocal. The basis for a positive test per American Thoracic Society (ATS) guidelines is a methacholine concentration ≤ 16 mg/mL that causes a 20% decrease in forced expiratory volume in 1 second (FEV₁) (termed the PC20 for FEV₁). There is little information in the medical literature that utilizes other flow rates during MCC, including small airway function parameters such as the forced expiratory flow rate 25–75% (FEF₂₅₋₇₅). We question whether the FEF₂₅₋₇₅ may be a useful parameter to monitor during MCC and whether it may be predictive of a positive MCC. **Hypothesis.** The baseline FEF₂₅₋₇₅ and its decline during a MCC are useful in the interpretation of a MCC. **Methods.** We retrospectively analyzed all MCC performed at this institution between December 1998 and December 2006. Parameters reviewed included age, gender, race, weight, height, baseline PFT data including FVC, FEV₁, FEF₂₅₋₇₅, and forced expiratory time, methacholine PC20 for FEV₁, the relative changes from baseline for FEV₁ and FEF₂₅₋₇₅ during the MCC, and clinical symptoms during the MCC. **Results.** A total of 532 MCC were completed during the 8-year study period in children 4 to 18 years of age. A total of 203 MCC (38%) were positive (defined by a PC20 ≤ 16 mg/mL) and 329 studies were negative (62%). The baseline % predicted FEF₂₅₋₇₅ in positive MCC was 82.4 ± 21.9 vs. 98.7 ± 21.3 in the negative studies ($p < 0.001$). The FEF₂₅₋₇₅/FVC ratio in positive MCC was 0.82 ± 0.21 vs. 0.97 ± 0.23 in negative studies ($p < 0.001$). In the positive MCC, the decrease in FEF₂₅₋₇₅ was much faster and of much greater degree than in the negative challenges. When a significant reduction in FEF₂₅₋₇₅ was defined as greater than 10% by the second concentration of methacholine (0.25 mg/mL), the sensitivity for a positive MCC was 63%, the specificity was 71%, the positive predictive value was 57%, and the negative predictive value was 76%. A comparison of the baseline FEF₂₅₋₇₅ to the PC20 for the positive MCCs revealed no statistical significance. **Conclusions.** The FEF₂₅₋₇₅ and its decline during a MCC appear to be useful information and potentially predictive of a positive MCC. We suggest that the forced expiratory flow rate 25–75% (FEF₂₅₋₇₅) be considered as an adjunct to the FEV₁ to define a positive study.

Keywords methacholine, airway responsiveness, bronchial challenge, FEF₂₅₋₇₅

INTRODUCTION

Hyperreactivity of the airway is a basic characteristic of bronchial asthma. The National Asthma Education and Prevention Program (NAEPP) guidelines recommend that spirometry be performed on all patients presenting with signs and symptoms of asthma since it may serve as an objective measure of airway obstruction (1). Spirometry is also helpful if performed before and after administration of an inhaled β -agonist, such as albuterol. If baseline pulmonary function test is normal in the face of clinical symptoms, a bronchoprovocative challenge, such as a methacholine challenge (MCC), may be valuable (2, 3).

The change in forced expiratory volume in 1 second (FEV₁) following MCC is the most widely applied criterion in the evaluation of airway hyperresponsiveness. It is easily performed and highly reproducible (4). A positive MCC is currently defined as the methacholine concentration of up to 16 mg/mL that causes a decrease in FEV₁ of 20% or more and is termed the PC20 for FEV₁ (5). Godfrey was able to show that the optimal cut off point for the dose of metha-

choline causing a 20% decline in FEV₁ was 6.6 mg/mL, with a sensitivity of 92% and a specificity of 89% (6).

Although FEV₁ is the most widely used parameter, and most accepted measure in methacholine challenges, we propose that the forced expiratory flow rate 25–75% (FEF₂₅₋₇₅) may be another helpful marker. Several studies have shown that a reduced baseline FEF₂₅₋₇₅ in the context of otherwise normal spirometry is suggestive of asthma (7–10). However, very few studies have examined FEF₂₅₋₇₅ decline as a marker of bronchial reactivity during a MCC (10–13). In a group of 205 consecutive primarily adult patients who underwent a MCC, the baseline FEF₂₅₋₇₅ was lower in those who had a positive MCC (10). However, utilizing an FEF₂₅₋₇₅ below a certain percentage showed poor sensitivity in predicting a positive MCC (10). In another group of primarily adults, 89% of patients (94/106) who underwent MCC and who had positive responses in both FEV₁ and FEF₂₅₋₇₅ (positive response defined as a $\geq 20\%$ decrease in FEV₁, and $\geq 25\%$ decrease in FEF₂₅₋₇₅ at ≤ 8 mg/mL of methacholine) actually responded at a lower concentration of methacholine based on the FEF₂₅₋₇₅ (10). Easton found that of 32 patients, including children, who underwent MCC, 11 had a greater than 20% decrease in FEV₁, while 15 had a greater than 25% decline in FEF₂₅₋₇₅ (12). A recent study found that both the difference between baseline FEV₁%

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predicted and $FEF_{25-75}\%$ predicted and the ratio between these parameters could discriminate between allergic subjects with little or no bronchoreactivity during a MCC to those with moderate to severe bronchoreactivity, with relatively high sensitivity (13). This last study also primarily involved adults and none of the aforementioned studies evaluated the decline in FEF_{25-75} during the MCC. We hypothesize that the decline in FEF_{25-75} may be used as an adjunctive marker in addition to FEV_1 in methacholine challenges to diagnose airway hyperreactivity.

METHODS

We retrospectively reviewed all children between 4 to 18 years of age who had a methacholine challenge (MCC) performed at Children's Hospital of Wisconsin between December 21, 1998 and December 31, 2006. Patients were referred either to aid in the differential diagnosis of suspected asthma or to confirm the presence of hyperreactive airways.

All patients were asked to avoid dietary substances, such as caffeine, and any respiratory medications that are known to interfere with test results. Patients had to be free of any respiratory infection for at least 6 weeks before testing. Oral consent at the time of the MCC was obtained after explaining the procedure and informing patient/parents of any risks involved.

Baseline spirometry was obtained according to American Thoracic Society (ATS) criteria. The children included in

our review had normal baseline spirometry and were able to perform repeatable spirometry. Patients who had a baseline $FEV_1 < 70\%$ predicted were excluded from the study.

Forced expiratory maneuvers were recorded on a computerized spirometry system (Sensormedics Vmax; Viasys Healthcare, Yorba Linda, CA). The spirometric parameters of FVC, FEV_1 , and FEF_{25-75} were measured and referenced to the population of Polgar (14). All patients with baseline spirometry that included $FEV_1 > 70\%$ predicted performed a subsequent MCC.

The 5-breath dosimeter method (15) and a dosing schedule using methacholine concentrations of 0.025, 0.25, 2.5, 10, and 25 mg/mL Provacholine approved by the FDA for Methapharm (Brantford, ON, Canada) was used. The methacholine dilutions were administered serially using an Airlife "Misty-Neb" small volume nebulizer or Vital Signs "Respirgard II" small volume nebulizer at an airflow of 8 L/min. Five inspiratory capacity breaths (with a 5-second breath hold at total lung capacity) were administered at each concentration and spirometry was performed within 3 minutes after each dose. The MCC was completed when a 20% decrease in baseline FEV_1 was achieved with one of the concentrations or until all five concentrations were administered. Albuterol MDI or nebulized albuterol was given to reverse bronchospasm. Spirometry was repeated 15 minutes post-bronchodilator administration to verify reversal of the bronchospasm. Positive results were defined as a $PC_{20} \leq 16$ mg/mL as defined by ATS.

TABLE 1.—Demographics and baseline spirometric values stratified by positive and negative methacholine challenges.

Demographics	Methacholine positive (N = 203)		Methacholine negative (N = 329)		p value
	N evaluated		N evaluated		
Age*	203		329		
Mean $\pm$ SD		9.1 $\pm$ 3.2		11.0 $\pm$ 3.2	<0.001
Median (range)		9.8 (4.0 – 17.0)		11.0 (5.0 – 18.0)	<0.001
Gender, N (%)	203		329		0.111
Male		107 (53)		150 (46)	
Female		96 (47)		179 (54)	
Race, N (%)	203		329		0.287
Caucasian		180 (89)		296 (90)	
Black		22 (11)		26 (8)	
Hispanic		—		3 (1)	
Asian		1 (1)		4 (1)	
Baseline Pulmonary Function Tests					
FVC (% predicted)	203		329		
Mean $\pm$ SD		101.3 $\pm$ 14.8		103.6 $\pm$ 14.6	0.083
Median (range)		100.0 (72.0 – 143.0)		103.0 (56.0 – 166.0)	0.054
FEV_1 (% predicted)	203		329		
Mean $\pm$ SD		92.9 $\pm$ 15.4		97.5 $\pm$ 13.6	<0.001
Median (range)		91.0 (62.0 – 145.0)		97.0 (56.0 – 182.0)	<0.001
FEF_{25-75} (% predicted)	203		329		
Mean $\pm$ SD		82.4 $\pm$ 21.9		98.7 $\pm$ 21.3	<0.001
Median (range)		81.0 (38.0 – 154.0)		97.0 (48.0 – 185.0)	<0.001
FEV_1 /FVC ratio	203		329		
Mean $\pm$ SD		84.1 $\pm$ 6.8		87.5 $\pm$ 5.6	<0.001
Median (range)		84.0 (64.0 – 99.0)		88.0 (65.0 – 100.0)	<0.001
FEF_{25-75} /FVC (% predicted/% predicted)	203		329		
Mean $\pm$ SD		0.82 $\pm$ 0.21		0.97 $\pm$ 0.23	<0.001
Median (range)		0.79 (0.38 – 1.46)		0.95 (0.41 – 1.96)	<0.001
FEF_{25-75} /FVC (absolute values)	202		327		
Mean $\pm$ SD		0.91 $\pm$ 0.26		1.05 $\pm$ 0.26	<0.001
Median (range)		0.87 (0.05 – 1.81)		1.01 (0.37 – 2.10)	<0.001
Complaints/symptoms during challenge	203		329		<0.001
None		15 (7)		128 (39)	
≥ 1 complaint or symptom		188 (93)		201 (61)	

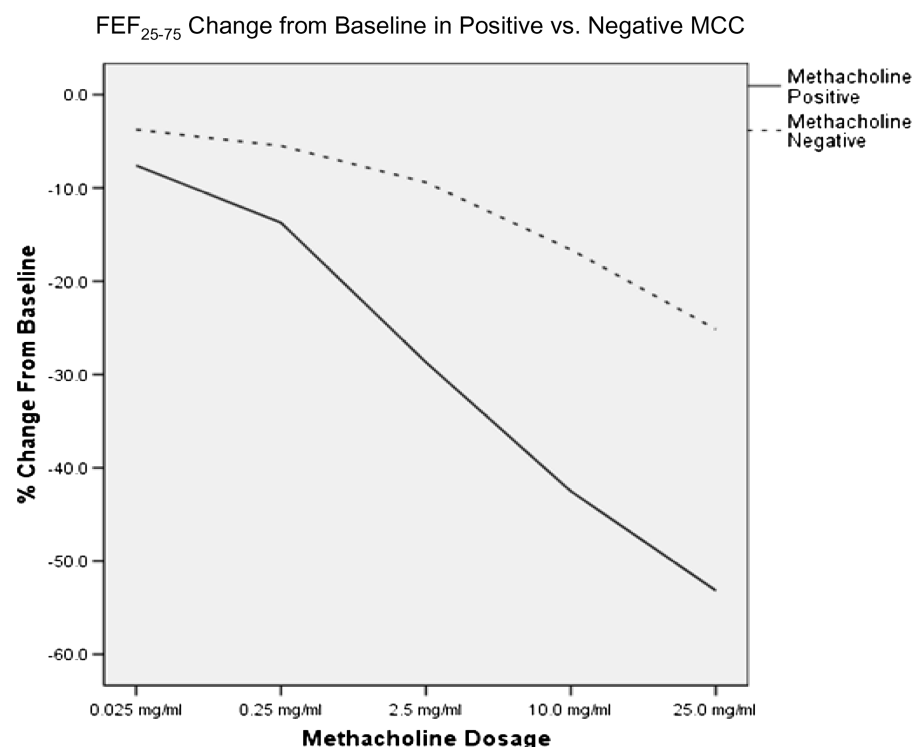


FIGURE 1.—Comparison of the FEF₂₅₋₇₅ change from baseline in the positive vs. negative methacholine challenges.

Statistical Analysis

Data was analyzed using SPSS 14.0. Categorical variables were compared using Chi-square test. *t* tests (mean $\pm$ standard deviation) were used to compare continuous variables and Mann-Whitney tests used to compare the medians (and ranges). A *p* level of <0.05 was considered significant. Receiver operating curves were constructed and fractional areas under the curve calculated to determine the usefulness of both the baseline FEF₂₅₋₇₅ and the decline in the FEF₂₅₋₇₅ in defining a positive MCC. The study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Definitions

Sensitivity: proportion of people with disease who have a positive test result.

Specificity: proportion of people without disease who have a negative test result.

Positive predictive value (PPV): proportion of people with positive test result with disease.

Negative predictive value (NPV): proportion of people with negative test result without disease.

Area Under Receiver Operating Curves

0.90–1.00 = Excellent; 0.80–0.90 = Very Good; 0.70–0.80 = Good; 0.60–0.70 = Fair; 0.50–0.60 = Poor.

RESULTS

A total of 532 children underwent MCC methacholine challenge between December 1998 and December 2006. The

patients ranged in age from 4 to 18 years; 52% were females and 48% were males; participating children were predominantly Caucasian; 203 studies were positive (38%), defined as a PC20 FEV₁ $\leq$ 16 mg/mL, and 329 (62%) were negative with a PC20 FEV₁ $>$ 16 mg/mL. The demographics and baseline spirometry values stratified by positive and negative MCC are shown in Table 1. Those children who had positive challenges were younger compared to those with negative challenges, consistent with previously published data (16, 17). In addition, those with positive MCC had lower baseline spirometric values (with a trend noted for the FVC) compared to those whose MCC was negative. Of the MCC positive patients, 39% had clinical symptoms during the challenge that were suggestive of asthma versus 7% of the MCC negative patients ($p < 0.001$). The baseline FEF₂₅₋₇₅ % predicted in positive MCC was 82.4 ± 21.9 vs. 98.7 ± 21.3 in the negative studies ($p < 0.001$). The FEF₂₅₋₇₅ % predicted/FVC % predicted ratio was 0.82 ± 0.21 in MCC positive studies vs. 0.97 ± 0.23 in negative studies ($p < 0.001$). The decrease in FEF₂₅₋₇₅ was much faster and of much greater degree in the positive MCC vs. the negative challenges. (Figure 1, Table 2). When PC20 was stratified, we found that lower PC20 values correlated with more significant decreases in FEF₂₅₋₇₅ (Figure 2). Table 3 shows the sensitivity, specificity, positive predictive value, and negative predictive value for various baseline values of FEF₂₅₋₇₅, for various decreases in FEF₂₅₋₇₅ during the MCC and for various combinations of these parameters. For example, when a baseline FEF₂₅₋₇₅ $<$ 90% predicted was used as a significant value, the sensitivity was 65%, the specificity was 67%, the positive predictive value was 55%, and the negative predictive value was 76%.

TABLE 2.—Comparison of FEF₂₅₋₇₅ change from baseline during positive vs. negative methacholine challenges.

Methacholine dosage	Methacholine positive (N = 203)		Methacholine negative (N = 329)		p value
	N eval	FEF ₂₅₋₇₅ change from baseline	N eval	FEF ₂₅₋₇₅ change from baseline	
0.025 mg/mL	203		329		
Mean ± SD		-7.6 ± 11.6		-3.8 ± 8.2	<0.001
Median (range)		-6.0 (-53.0 - 33.0)		-4.0 (-51.0 - 25.0)	<0.001
0.25 mg/mL	202		329		
Mean ± SD		-13.7 ± 14.6		-5.5 ± 9.6	<0.001
Median (range)		-12.0 (-70.0 - 41.0)		-6.0 (-90.0 - 25.0)	<0.001
2.5 mg/mL	190		329		
Mean ± SD		-28.7 ± 16.0		-9.4 ± 10.6	<0.001
Median (range)		-27.0 (-73.0 - 16.0)		-10.0 (-48.0 - 39.0)	<0.001
10.0 mg/mL	135		329		
Mean ± SD		-42.5 ± 14.6		-16.6 ± 11.5	<0.001
Median (range)		-43.0 (-77.0 - 32.0)		-16.0 (-45.0 - 25.0)	<0.001
25.0 mg/mL	44		329		
Mean ± SD		-53.2 ± 8.9		-25.2 ± 14.4	<0.001
Median (range)		-53.5 (-74.0 - -35.0)		-26.0 (-84.0 - 18.0)	<0.001

Alternatively, when a significant reduction in FEF₂₅₋₇₅ was defined as a greater than 10% decrease by the second concentration of methacholine (0.25 mg/mL), the sensitivity for a positive MCC was 63%, the specificity was 71%, the positive predictive value was 57%, and the negative predictive value was 76%. Additionally, if we used either a baseline FEF₂₅₋₇₅ < 90% predicted or a greater than 10% decrease by the second concentration of methacholine (0.25 mg/mL), the sensitivity increased to 88% and the negative predictive value increased to 86%, although the specificity and the positive predictive value decreased. Figure 3 shows that when comparing baseline FEF₂₅₋₇₅ % predicted to the PC20 for the positive MCC, there was no statistical significance ($r =$

0.069, $p = 0.33$). In addition, no statistical difference was found when comparing FEF₂₅₋₇₅/FVC to PC20 for the positive MCC. Figure 4 shows the receiver operating curves for the baseline FEF₂₅₋₇₅ and the decrease in FEF₂₅₋₇₅ during the second concentration of methacholine (0.25 mg/mL) as predictors of a positive MCC. The area under the curve was 0.71 and 0.74, respectively, suggesting a good fit for using these data as predictors for methacholine responsiveness.

DISCUSSION

In our study, we demonstrated that both the baseline FEF₂₅₋₇₅ and the decline in FEF₂₅₋₇₅ during methacholine challenges may be helpful markers, in addition to the standard

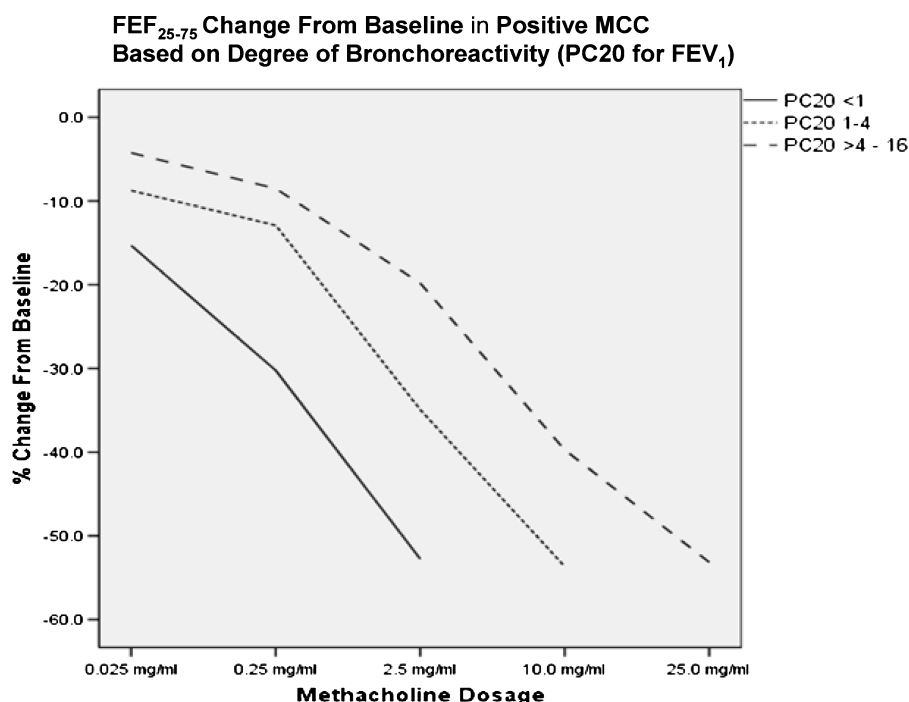


FIGURE 2.—Comparison of the FEF₂₅₋₇₅ change from baseline in the positive methacholine challenges based on the degree of bronchoreactivity. Stratification was done based on PC20 for FEV₁ values where <1 (mg/mL) is considered moderate-severe bronchoreactivity, 1–4 (mg/mL) is considered mild bronchoreactivity, and >4–16 (mg/mL) is considered borderline bronchoreactivity.

TABLE 3.—Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) based on the baseline FEF₂₅₋₇₅, decreases in FEF₂₅₋₇₅, both parameters combined, and either parameter, during the methacholine challenges.

	Sensitivity	Specificity	PPV	NPV
Baseline FEF ₂₅₋₇₅ % predicted:				
Baseline FEF ₂₅₋₇₅ <90%	65.5%	66.9%	55.0%	75.9%
Baseline FEF ₂₅₋₇₅ <80%	49.8%	82.7%	63.9%	72.7%
Baseline FEF ₂₅₋₇₅ <70%	29.6%	91.2%	67.4%	67.7%
Baseline FEF ₂₅₋₇₅ <60%	13.8%	98.2%	82.4%	64.9%
Percent decrease in FEF ₂₅₋₇₅ *:				
> 10% decrease	63.4%	70.5%	56.9%	75.8%
> 15% decrease	40.6%	88.2%	67.8%	70.7%
> 20% decrease	29.7%	95.4%	80.0%	68.9%
> 30% decrease	10.9%	99.4%	91.7%	64.5%
Baseline FEF ₂₅₋₇₅ % predicted and percent drop in FEF ₂₅₋₇₅ *:				
Baseline FEF ₂₅₋₇₅ <90% and >10% decrease	41.1%	90.3%	72.2%	71.4%
Baseline FEF ₂₅₋₇₅ <90% and >15% decrease	25.7%	97.0%	83.9%	68.0%
Baseline FEF ₂₅₋₇₅ <80% and >10% decrease	31.5%	94.8%	79.0%	69.2%
Baseline FEF ₂₅₋₇₅ <80% and >15% decrease	19.7%	98.5%	88.9%	66.5%
Baseline FEF ₂₅₋₇₅ % predicted or Percent drop in FEF ₂₅₋₇₅ *:				
Baseline FEF ₂₅₋₇₅ <90% or >10% decrease	87.7%	47.1%	50.6%	86.1%
Baseline FEF ₂₅₋₇₅ <90% or >15% decrease	80.3%	58.1%	54.2%	82.7%
Baseline FEF ₂₅₋₇₅ <80% or >10% decrease	81.7%	58.4%	54.6%	83.8%
Baseline FEF ₂₅₋₇₅ <80% or >15% decrease	70.8%	72.3%	61.1%	80.1%

*Decrease is at the 2nd concentration of methacholine during the MCC (0.25 mg/mL).

FEV₁, in detecting bronchial hyperreactivity in the pediatric population. We noted that the baseline FEF₂₅₋₇₅ is significantly lower in positive vs. negative MCC. However, using only the baseline FEF₂₅₋₇₅ to predict a positive MCC has a relatively low sensitivity (e.g., an FEF₂₅₋₇₅ < 80% predicted has a sensitivity of only 50%). Alternatively, when using a particular decline in FEF₂₅₋₇₅ during the MCC (e.g., a > 10% decrease at the second methacholine dosage of 0.25 mg/mL), the sensitivity and specificity are both relatively high, which suggests that this marker in addition to FEV₁ may be useful in predicting the presence or absence of bronchial hyper-

sponsiveness. In addition, the negative predictive value in this scenario is 76%, which corroborates the utility of using FEF₂₅₋₇₅ in predicting the absence of disease. Finally, if either the baseline FEF₂₅₋₇₅ or the decline in FEF₂₅₋₇₅ are used, the sensitivity and negative predictive value are both quite high, approaching 90%. This shows that this combination is useful in predicting both the presence and absence of bronchoreactivity during a MCC.

The FEF₂₅₋₇₅ is traditionally intended to isolate the effort-independent portion of the curve and detect the presence of obstructive disease in the small airways. The earliest change

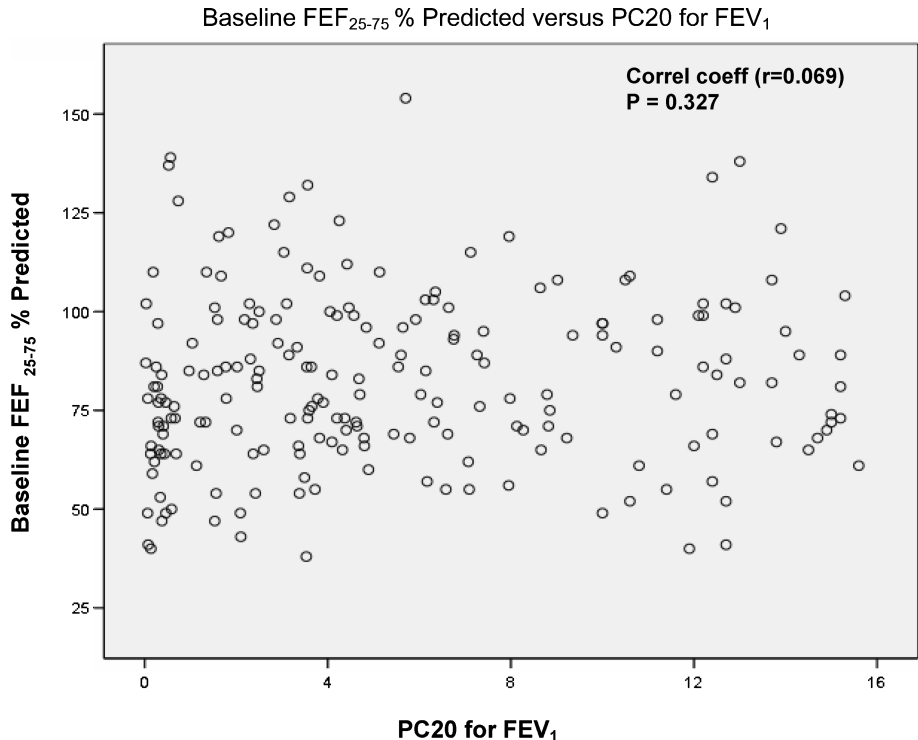


FIGURE 3.—Comparison of the baseline FEF₂₅₋₇₅ % predicted and the PC20 for FEV₁ in the MCC-positive patients.

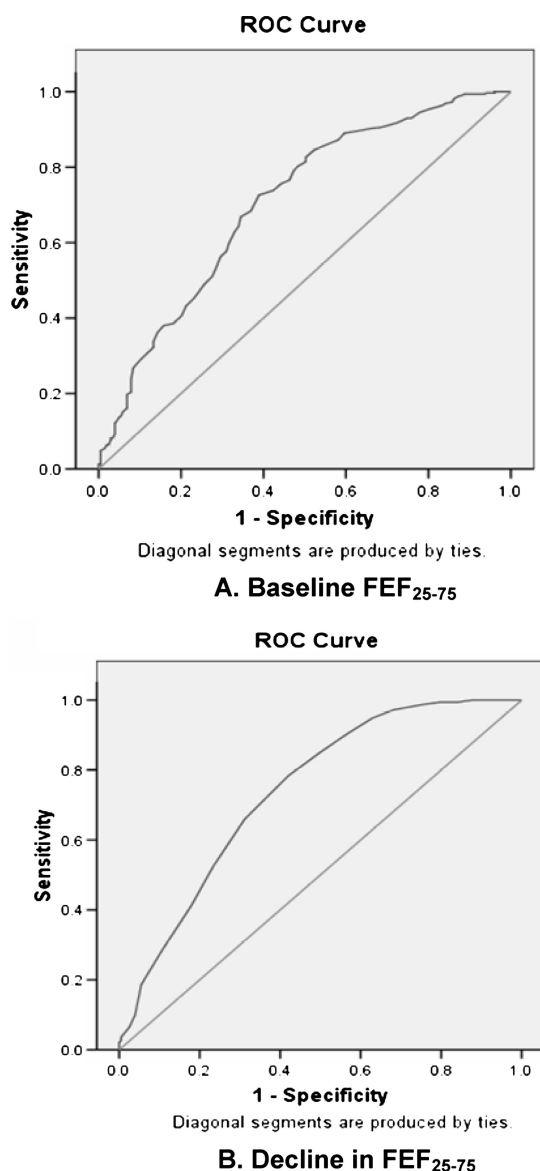


FIGURE 4.—Receiver operating curves (ROC) for the (A) baseline FEF₂₅₋₇₅ as a predictor of methacholine responsiveness. The fractional area under the curve was 0.71. The green line represents where true positives (sensitivity) equal false positives (1-specificity); (B) the FEF₂₅₋₇₅ at the second concentration of methacholine (0.25 mg/mL) as a predictor of methacholine responsiveness. The fractional area under the curve was 0.74. The green line represents where true positives (sensitivity) equal false positives (1-specificity).

associated with flow limitation in the small airways is thought to be slowing in the terminal portion of the spirogram, even when the initial part of the spirogram is unaffected (18). Therefore, it stands to reason that this would be an important factor in detecting bronchial hyperreactivity in asthmatic patients. Although there is significant variation in the normal population with wide confidence intervals, the FEF₂₅₋₇₅ is still an important early indicator of inflammation in the peripheral airways.

Airway size is one of the factors that determine airway hyperresponsiveness to bronchial provocation agents, such

as methacholine. Airway size could account for intersubject variability of maximal expiratory flow volume curves. Green and colleagues suggested that there were differences in airway size from individual to individual, and that this was independent of lung parenchymal size (19). They termed this “dysanapsis” and showed that differences in airway-parenchymal relationship might influence the pathogenesis of airway diseases. Tager et al. demonstrated that the ratio of FEF₂₅₋₇₅ to FVC could be used as a surrogate measure of dysanapsis (20). Previous studies have found that the FEF₂₅₋₇₅/FVC ratio, which essentially measures airway size relative to lung size, was negatively associated with the degree of methacholine airway responsiveness (21, 22). Our study is consistent with this observation, where FEF₂₅₋₇₅/FVC was significantly lower in the positive methacholine challenges.

There have been studies in the past looking at the usefulness of small airway markers detecting exercise-induced asthma. Exercise and methacholine challenges are performed similarly, except that in exercise challenges, the provocative agent is exercise, and not a chemical agent. Soferman showed that a decrease of 21% in FEF₅₀ post-exercise may be superior to the currently accepted definition of EIA, which is based on a change in FEV₁ (23). Fonseca-Guedes was able to show that FEF₂₅₋₇₅ could decrease in response to exercise without changes in FEV₁, mainly in children with mild asthma. That study demonstrated good correlation between the changes in FEV₁ and FEF₂₅₋₇₅ after exercise and also found that the decrease in these parameters increased as the severity of asthma increased (24). This suggests that using more than one flow volume parameter may be helpful in detecting hyperresponsiveness of the airways.

Although FEV₁ is known to have a high sensitivity and specificity in detecting hyperresponsiveness of the airways in methacholine challenges, we were able to show that the decline of FEF₂₅₋₇₅ is faster and greater than FEV₁. This information might be valuable, especially when conducting this diagnostic study in the pediatric population. In younger children, there are occasions when the patient is not able to complete the methacholine challenge, and the test is terminated prematurely. This might be owing to fatigue, lack of concentration, or onset of symptoms. In these cases, a significant (>20%) decline in FEV₁ may not occur, although a significant decrease in FEF₂₅₋₇₅ (e.g., >10%) is noted. In these children, bronchoreactivity would be diagnosed based on the FEF₂₅₋₇₅ response, and proper medical management would be initiated despite a shortened MCC and lack of significant FEV₁ decline.

The main limitation of this study is that it was a retrospective design. Therefore, we were unable to follow the patients' clinical status and response to medical management. Sequential methacholine challenge data were not available for us to include in the study. It would also be important to determine whether standard spirometry and/or symptoms improved after bronchodilators were administered and if so, the time course over which these changes occurred, although this was not the purpose of this retrospective study. Additionally, although the definition of a significant change in FEF₂₅₋₇₅ during a methacholine challenge is debatable, physicians may base a significant change on the baseline variability of the particular measurement. In this study, unfortunately,

repeated measures of FEF₂₅₋₇₅ were not calculated at baseline, and therefore, this method of determining a significant change in FEF₂₅₋₇₅ was not possible.

In conclusion, FEF₂₅₋₇₅ may be a useful marker in the evaluation of methacholine challenges and should be considered in addition to FEV₁. Prospective studies in the future would be useful to more fully determine the utility of FEF₂₅₋₇₅.

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