RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

Baseline Spirometry as a Predictor of Positive Methacholine Challenge Testing for Exertional Dyspnea

John C Hunninghake, Sarah B McCullough, James K Aden, Jackie A Hayes, Edward T McCann, and Michael J Morris

BACKGROUND: There are several tests recommended by the American Thoracic Society (ATS) to evaluate for airway hyper-responsiveness (AHR), one of which is methacholine challenge testing (MCT). Few studies have examined the correlation of baseline spirometry to predict AHR in MCT, especially in the younger, relatively healthy military population under clinical evaluation for symptoms of exertional dyspnea. The study aim was to retrospectively correlate baseline spirometry values with MCT responsiveness. METHODS: This study is a retrospective review of all MCT performed at Brooke Army Medical Center/Wilford Hall Medical Center over a 12-y period; all completed studies were obtained from electronic databases. The following parameters were analyzed from the studies: baseline FEV_1, FVC, FEV_1/FVC, mid-expiratory flow ($FEV_{25-75\%}$), $FEV_{25–75\%}$/FVC. Studies were categorized based on baseline obstruction, restriction, $FEF_{25–75\%}$ lower limit of normal, and response to bronchodilator testing (if completed); these values were compared based on methacholine reactivity and severity. RESULTS: Methacholine challenge studies (*n* = 1,933) were reviewed and categorized into reactive (*n* = 577) and nonreactive (*n* = 1,356) as determined by ATS guidelines. The mean baseline FEV_1 (% predicted) with MCT reactivity was 88.0 ± 13.0% versus no MCT reactivity was 92.7 ± 13.0% ($P < .001$). The mean baseline FVC (% predicted) was 93.1 ± 13.7% versus 95.3 ± 13.5% ($P < .001$). The mean baseline $FEV_{25–75\%}$ (% predicted) was 80.0 ± 22.1% versus 89.0 ± 23.4% ($P < .001$). Based on partition analysis, methacholine reactivity was most prevalent with baseline obstruction, *n* = 115 (43%), and in the absence of obstruction, when the $FEF_{25–75\%}$ (% predicted) was below 0.70, *n* = 111 (40%). The negative predictive value with normal spirometry was 73%. CONCLUSIONS: The analysis of baseline spirometry prior to MCT proved useful in the evaluation of exertional dyspnea in a military population. The presence of airways obstruction (FEV_1/FVC < lower limit of the normal range) followed by a reduction in $FEV_{25–75\%}$ < 70% predicted showed a positive correlation with underlying AHR. In patients with exertional dyspnea and normal baseline spirometry, the use of the $FEF_{25–75\%}$ may be a useful surrogate measurement to predict reactivity during MCT and consideration for additional testing or treatment
Key words: FEF_{25-75}; airway hyperreactivity; baseline spirometry; methacholine challenge testing; exertional dyspnea; military population. [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Methacholine challenge testing (MCT) is one of several methods approved by the American Thoracic Society (ATS) to evaluate patients for evidence of airway hyper-responsiveness (AHR).[1] Other methods, including histamine challenge testing, exercise spirometry, and eucapnic hyperventilation, also assess reproduction of symptoms and objective decrease in FEV_1 of 20%. Methacholine has become the most used test for AHR based on its ease of administration and consistent reproducibility of results. Guidelines for the administration and interpretation of MCT were published in 1999 by the ATS and dictate the protocol for methacholine dosing, recommended equipment, and interpretation of results based on the level of reduction of FEV_1.[1]

Indications for MCT include evaluation for asthma or exercise-induced bronchoconstriction (EIB) when symptoms are suggestive of this disease process and methods such as spirometry and post-bronchodilator (BD) response are not diagnostic. The optimal diagnostic value when the pretest probability is 30–70% in any given patient.[2] A negative test (with no response to methacholine at the highest dose of 16 mg/mL) essentially rules out that a patient's symptoms are related to AHR. However, its positive predictive value for asthma is less reliable given AHR is seen with COPD, cystic fibrosis, sarcoidosis, bronchitis, and allergic rhinitis. Studies in asymptomatic military personnel have shown a 6–7% incidence of EIB; up to 35% of these individuals with EIB diagnosed by bronchoprovocation testing has normal spirometry at rest.[3-5] Within the military population, dyspnea precipitated by exercise is a relatively common complaint referred to military medical clinics.[4] MCT is ubiquitously used in this mostly young and physically active population to rule out underlying AHR that worsens with exercise.[4,6] Based on current military guidelines, MCT is the preferred method for EIB compared to exercise spirometry and eucapnic hyperventilation within military testing centers.[7] Generally, it should not be performed in those patients with spirometric evidence of moderate-to-severe baseline obstruction or subsequent response to post-BD testing that suggests underlying AHR.

Methacholine has been extensively studied in 2 groups of patients. It was first described and tested in patients with known asthma and evidence of AHR to determine the optimal testing methodology and provocative dose needed to produce a reproducible response. From these early studies, the concept of the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) was devised. Additionally, numerous studies were conducted on normal populations to determine the negative predictive value of the test. A study of 537 asymptomatic men in the Normative Aging Study[8] found a relationship between a decrease in the FEV_1 and reactivity to MCT. Wassmer and colleagues, as part of an epidemiologic survey, evaluated a large population of European individuals and found a higher percentage of females with AHR at 28% compared to 13% in males.[9] Another study specifically evaluated a population of 63 Army officer cadets and found a background AHR rate of 3%,[6] whereas Jayet et al[10] determined an overall rate of 11% in 1,567 adults with no history of smoking, asthma, atopy, or recent infections. From 6 large population studies, the overall rate of AHR was approximately 13–14%.[11]

Given the significant false-positive rate with MCT and the frequency with which it is used to evaluate active duty service members with complaints of exertional dyspnea, we hypothesized whether there were baseline spirometric findings in this cohort predictive of MCT reactivity. Identifying specific trends in spirometry would increase the pretest probability of detecting AHR in a military cohort and guide providers to selectively administer MCT. The purpose of this study was to retrospectively review MCT examinations to identify trends in baseline spirometric values that predicted underlying AHR in military personnel with exertional dyspnea.

QUICK LOOK

Current knowledge

Multiple small studies have identified a correlation between certain baseline spirometric parameters and airway hyperreactivity (AHR) in patients with asthma-like symptoms. A FEF_{25-75} <65% predicted on baseline spirometry has been established as abnormal for the pediatric population with respiratory symptoms, but there are no consistent cutoff values for FEF_{25-75} (% predicted) for adults with asthma-like symptoms that predict AHR. Specifically, there are no studies that analyze the predictive potential of baseline spirometry for AHR in the military population under evaluation for exertional dyspnea.

What this paper contributes to our knowledge

Certain baseline spirometric parameters demonstrated significant correlations with the presence or absence of AHR in a military population under evaluation for exertional dyspnea. AHR is more likely with a baseline obstructive pattern with the $FEV_1 < 90\%$ predicted or in the absence of obstruction, when the FEF_{25-75} <70% predicted and a non-obstructive pattern.

Methods

This study was conducted as a retrospective review of all MCT studies done at Brooke Army Medical Center and Wilford Hall Ambulatory Surgical Center over a designated 12-y period from 2006–2018. The study was reviewed and approved by the Brooke Army Medical Center Institutional Review Board. The majority of the completed studies was performed according to published ATS guidelines with a maximum dose of 16 mg/mL.[1] At the Wilford Hall Ambulatory Surgical Center pulmonary function laboratory, the study was terminated at 8 mg/mL if the patient

Drs Hunninghake, Hayes, McCann, and Morris are affiliated with Pulmonary/Critical Care Service, Department of Medicine, Brooke Army Medical Center, JBSA Fort Sam Houston, Texas. Dr McCullough is affiliated with Wake Forest Baptist Medical Center, Winston-Salem, North Carolina. Dr Aden is affiliated with Graduate Medical Education, Brooke Army Medical Center, JBSA Fort Sam Houston, Texas.

Dr Morris discloses relationships with Janssen Pharmaceuticals and GlaxoSmithKline. The other authors have disclosed no conflicts of interest.

Correspondence: John C Hunninghake Maj USAF MC, Pulmonary Disease Service (MCHE-ZDM-P), Brooke Army Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234. E-mail: john.c.hunninghake.mil@mail.mil.

DOI: 10.4187/respcare.09163

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

had no downward trend in FEV_1 from baseline or symptoms suggestive of bronchial reactivity. This abbreviated procedure only constituted 18% of all nonreactive studies. Per both laboratory protocols, all long-acting inhaled medications were discontinued at least 72 h prior to the study, and short-acting β-agonists were prohibited the day of the study. Subjects for this study were required to be active duty service members who were undergoing an initial MCT for evaluation of exertional dyspnea, primarily difficulty with running or inability to pass a timed military running test, as part of their overall symptom protocol. The presence of obstruction on baseline spirometry did not preclude use of the MCT if there was a nonsignificant bronchodilator response or indicated based on clinical history. If duplicate studies were identified, the initial study was used. Data obtained from the MCT studies included demographic data, baseline FVC, FEV_1, mid-expiratory flow ($FEF_{25-75\%}$), and if prior initial spirometry reported a post-BD response to FEV_1. Reference values were taken from the National Health and Nutrition Examination Survey (NHANES) III to define the lower limit of normal for baseline obstruction (FEV_1/FVC) or restriction or reduction in $FEF_{25-75\%}$.[12]

The provocative concentration causing a 20% drop in FEV_1 (PC_{20}) was calculated for all reactive MCT and recorded as borderline (4–16), mild (1–4), or moderate-to-severe bronchial hyper-responsiveness (< 1) in accordance with ATS guidelines.[1]

Analysis included the following correlations for MCT reactivity and severity: (1) baseline obstruction, (2) baseline restriction, (3) baseline reduction in $FEF_{25-75\%}$ below the lower limit of normal, and (4) correlation of $FEF_{25-75\%}$/FVC. Categorical data were summarized using percentages and chi-square tests or Fisher exact test, whichever was most appropriate. Means and SD or medians and interquartile ranges were used as summary statistics for continuous variables, and they were analyzed using Student *t* test and one-way analysis of variance. Post hoc multiple comparisons were adjusted using Tukey method. Significance for results was established when *P* values were $< .05$. All analysis was performed using JMP version 13.2 (SAS Institute, Cary North Carolina). Partition analysis was performed to prioritize the spirometry parameters that best predict MCT reactivity. This algorithm chooses the optimal factor and cutoff based on the LogWorth statistic.[13]

Table 1. Demographics and Methacholine Reactivity

	Total	MCT Reactive	MCT Nonreactive
Subjects, *n*	1,933	577	1,356
Age, y	32.3 ± 9.2	27.4 ± 4.1	30.9 ± 8.9
Male	1,316 (68.1%)	360 (62.4%)	956 (70.5%)
Female	617 (31.9%)	217 (37.6%)	400 (29.5%)
BMI, kg/m^2	27.4 ± 4.1	27.5 ± 4.3	27.4 ± 4.1
White	1,141 (59.0%)	320 (55.5%)	821 (60.5%)
Black	424 (21.9%)	154 (26.7%)	270 (19.9%)
Hispanic	299 (15.5%)	86 (14.9%)	213 (15.7%)
Asian	69 (3.6%)	17 (2.9%)	52 (3.8%)

Demographic variables of the methacholine challenge studies.
MCT = methacholine challenge testing
BMI = body mass index

Results

Of the 1,933 active duty service members identified who underwent MCT for exertional dyspnea, 1,316 (68.1%) were male and 443 (31.9%) were female, and the mean age was 32.2 ± 9.2 y. Overall demographics for the study cohort are shown in Table 1. Both ethnicity and gender are consistent with the demographics of the overall active duty military population. Methacholine challenge tests were categorized according to ATS guidelines.[1] The 577 (30%) individuals with a positive test ($PC_{20} < 16$) were designated as reactive, whereas the remaining 1,356 negative MCTs were categorized as reactive. No significant differences in MCT reactivity were noted based on the demographics shown in Table 1.

Table 2 shows the baseline spirometry values based on MCT reactivity. Of the 577 individuals with reactive

Table 2. Methacholine Challenge Testing Reactivity Based on Baseline Values

	Nonreactive	Reactive	*P*	Borderline	Mild	Moderate-Severe
Subjects, *n*	1,356 (70%)	577 (29%)		272 (47%)	162 (28%)	144 (25%)
PC_{20}	NA	4.94 ± 4.49		8.83 ± 3.54	2.45 ± 0.99	0.41 ± 0.31
FEV_1 (% predicted)	92.7 ± 13.0	88.0 ± 13.0	.001	88.7 ± 12.1	88.3 ± 13.9	86.2 ± 13.7
FVC (% predicted)	95.3 ± 13.5	93.1 ± 13.7	.001	92.9 ± 12.8	94.9 ± 14.4	91.6 ± 14.5
$FEF_{25-75\%}$ (% predicted)	89.0 ± 23.4	80.0 ± 22.1	.001	81.7 ± 20.8	77.6 ± 22.8	79.3 ± 23.4
FEV_1/FVC	80.3 ± 6.6	78.8 ± 6.9	.001	79.5 ± 6.3	77.5 ± 6.7	79.1 ± 7.9
$FEF_{25-75\%}$/FVC	94.6 ± 25.7	86.8 ± 24.3	.001	88.8 ± 22.5	82.5 ± 22.9	88.1 ± 28.2

Comparison of baseline pulmonary function test values with MCT reactivity.
PC_{20} = provocative concentration with 20% decrease in FEV_1
$FEF_{25-75\%}$ = mid-expiratory flow

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

Table 3. Methacholine Challenge Testing Reactivity Based on Baseline Restrictive/Obstructive Indices

	Normal	Restrictive (FVC < Lower Limit of Normal)	Obstructive (FEV_1/FVC < Lower Limit of Normal)	$FEF_{25-75\%}$ < Lower Limit of Normal
Subjects, *n*	1,372	320	265	277
Reactive	366 (26.7%)	110 (34.4%)	114 (43.0%)	125 (45.1%)
Nonreactive	1,006 (72.3%)	210 (63.6%)	151 (57.0%)	152 (54.9%)
FEV_1 (% predicted)	96.1 ± 10.9	74.9 ± 8.2*	83.6 ± 11.9*	76.6 ± 9.3*
FVC (% predicted)	97.9 ± 10.7	74.6 ± 6.5*	100.3 ± 13.5	89.7 ± 13.4*
$FEF_{25-75\%}$ (% predicted)	92.7 ± 20.9	79.1 ± 22.8*	58.4 ± 14.4*	71.3 ± 6.1*
FEV_1/FVC	81.3 ± 4.9	82.1 ± 7.0	69.0 ± 4.3*	53.2 ± 8.8*
$FEF_{25-75\%}$/FVC	95.0 ± 20.4	106.4 ± 30.5*	58.3 ± 12.4*	60.6 ± 13.2*

Comparison of baseline pulmonary function test indices with methacholine challenge testing reactivity. *$P < .05$.
$FEF_{25-75\%}$ = mid-expiratory flow

studies, 272 (47%) were borderline reactivity, 162 (28%) with mild reactivity, and 144 (25%) with moderate-to-severe reactivity based on PC_{20}. There was significant difference for baseline FEV_1 ($P < .001$) and $FEF_{25-75\%}$ ($P < .001$) for the presence of reactivity. No statistical differences were identified based on the severity of the MCT (borderline, mild, or moderate-severe).

Comparison of baseline pulmonary function tests is shown in Table 3 based on the presence of obstruction (FEV_1/FVC < lower limit of normal), restriction (FVC < lower limit of normal), and reduction in the $FEF_{25–75\%}$ < lower limit of normal. Notably, there were 1,372 (71.0%) studies with normal spirometry, 320 (16.6%) with restrictive indices, and 265 (13.7%) with obstructive indices. When further categorized based on the $FEF_{25–75\%}$ (% predicted), 277 (14.3%) were below the predicted lower limit of normal; there was overlap with obstructive indices in 168 (63%) of these studies. Application of the $FEF_{25–75\%}$/FVC index was also conducted to determine if this was an independent predictor of MCT reactivity. The negative predictive value for MCT reactivity with normal spirometry was calculated at 73%.

Further analysis was conducted on the use of post-BD testing in this cohort. Of the 1,933 studies, 621 (32%) had previously completed post-BD testing prior to the MCT study. From this group, 170 (27%) had at least a change of 8% in the FEV_1 post-BD. The presence of an 8% bronchodilator response was more prevalent but did not predict reactive MCT. In the nonresponsive bronchodilator group ($n = 451$), 117 (26%) had a reactive MCT. In the responsive bronchodilator group ($n = 170$), 59 (35%) had a reactive MCT.

Final analysis was completed using partition analysis along with the corresponding optimized cutoff based on the LogWorth statistic as shown in Figure 1 The first separation is based on the presence ($n = 577$) or absence ($n = 1,356$) of baseline spirometry obstruction (FEV_1/FVC < lower limit of normal). Here the number of reactive MCT was 115 of 265 (43%). In the presence of obstruction ($n = 265$), an $FEV_1 \geq 100\%$ provided the ideal cutoff. In the absence of obstruction ($n = 1,668$), the next cutoff was identified with the $FEF_{25-75\%} < 70\%$ ($n = 279$). This analysis demonstrated 111 (40%) with reactive studies.

Discussion

This retrospective review of MCT in this cohort of active duty service members with exertional dyspnea revealed that baseline obstruction (with or without bronchodilator response) and reduction in the $FEF_{25–75\%}$ (% predicted) on baseline spirometry correlated with AHR. Whereas certain baseline values were associated with a positive MCT, they did not predict the severity of AHR, which is consistent with prior studies.[14-15] These results demonstrate an important role of interpreting abnormal baseline spirometric values in the absence of an obstructive pattern. Many previous studies have established the performance characteristics of spirometric and MCT indices in subjects with known asthma[1]; however, our study establishes the relevance of these markers, particularly $FEF_{25–75\%}$, in a younger patient population with exertional dyspnea undergoing clinical evaluation for AHR. The unique feature of this study, unlike prior studies, is the adult military population who may only present with symptoms with exertional dyspnea. Both the presence of baseline obstruction and reduction in the $FEF_{25-75\%}$ identified a trend toward MCT reactivity.

Several longitudinal studies of both military and civilian populations have confirmed a significant percentage of subjects with childhood asthma have persistent symptoms in adulthood. This includes military personnel with a prior history of asthma who may have continued symptoms and positive bronchoprovocation testing after entering military service.[16] An accurate diagnosis of asthma or EIB has extensive ramifications for the military as the medical condition can result in duty limitations and separation from the service.

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

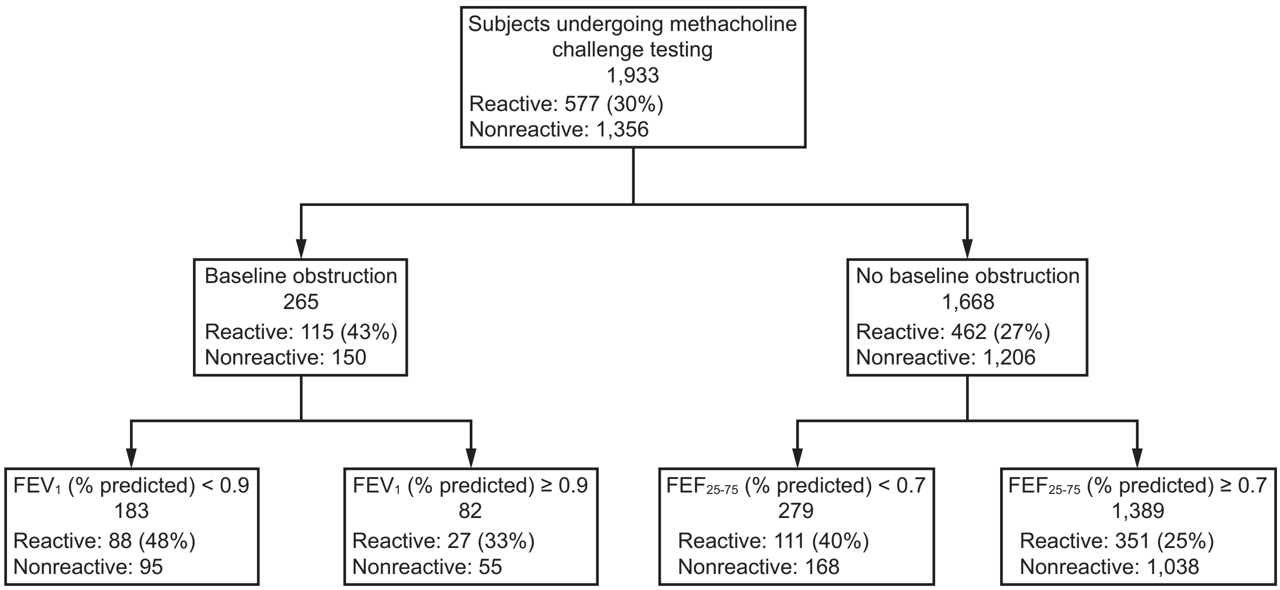

Fig. 1. Flow chart demonstrating primary separation based on presence of obstruction (FEV_1 < 1.0) and reduction in $FEF_{25-75\%}$ (% predicted) < 70% in the absence of obstruction.

Exercise-induced bronchospasm may be triggered by a number of military activities including biannual fitness testing, extended exposure to outdoor environments, and deployments to austere locations.[16] In an evaluation of 192 new recruits, asthma was diagnosed in 59% of military recruits who failed the fitness assessment test during basic training.[17] Many military personnel have either symptomatic or asymptomatic AHR, primarily manifested as exertional dyspnea, but are reluctant to disclose their symptomatology or any prior history of asthma.

As the presence of AHR is an indicator of future difficulties in meeting fitness or retention standards, many studies have evaluated various bronchoprovocation tests in both symptomatic and asymptomatic military personnel to screen for and diagnosis AHR. A randomized crossover study of 40 participants compared various bronchoprovocation tests and found that MCT and eucapnic hyperventilation were more sensitive than exercise challenge testing in determining AHR in military personnel.[18] This was validated in a direct comparison between MCT and exercise challenge testing that found 59% of subjects with a negative exercise challenge testing had a positive MCT.[5] Morris et al evaluated the utility of portable spirometry and exercise challenge testing in a cohort of 220 active duty soldiers undergoing combat medic training. In this asymptomatic cohort with a small prevalence of an asthma history, they found a large proportion (14%) of soldiers had mild airway obstruction in addition to almost one-third developing AHR with exercise.[16] Whereas these studies have evaluated the standard measures of baseline spirometry (FEV_1, FVC, and FEV_1/FVC) with bronchoprovocation testing, there were not evaluations of additional baseline spirometric measures ($FEF_{25-75\%}$, $FEF_{25-75\%}$/FVC) in this population.

Leuallen and Fowler[19] introduced the forced expiratory flow between 25% and 75% of the FVC, abbreviated as the $FEF_{25-75\%}$, as the maximal mid-expiratory flow. Due to its measurement of the most effort-independent portion of the flow volume expiratory curve, it has been purported to be a sensitive marker for medium-to-small airways disease and, therefore, might be a more sensitive way to detect early stages of obstructive lung disease. However, the $FEF_{25-75\%}$ demonstrates wide variation in the normal population, which diminishes its value in identifying small airways disease that might appear as mild AHR on provocation testing.[14]

Whereas previous studies have suggested that the $FEF_{25-75\%}$ may be too variable in its measure of air flow obstruction at baseline compared to FEV_1, it is partially dependent on the FVC due to the proportional relationship between lung volume and airway size when assessed in $FEF_{25-75\%}$/FVC.[20] Simon et al[20] found that the $FEF_{25-75\%}$ and $FEF_{25-75\%}$/FVC were more sensitive but less specific than the FEV_1 as indicators of a positive response to MCT; however, the $FEF_{25-75\%}$/FVC was less closely correlated with a significant decrease in FEV_1 than the $FEF_{25-75\%}$ alone. The partition analysis data from our study identified the presence of obstruction (reduction in the FEV_1/FVC) followed by reduction in the $FEF_{25-75\%}$, but the $FEF_{25-75\%}$/FVC did not show a significant correlation.

Whereas previous studies have evaluated the association between baseline spirometry, AHR, and the severity of AHR, there is a significant amount of heterogeneity as seen in Table 4. A 2012 study of 700 pediatric subjects (median age of 11) with allergic asthma suggested that an $FEF_{25-75\%}$ value of

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

Table 4. Key Studies Utilizing $FEF_{25-75\%}$

Author/Year	Study Type	*N*	Population	Median Age, y	Median Baseline FEV_1 (% Predicted)	Reactive +MCT (%)	Baseline $FEF_{25-75\%}$ Reactive (% Predicted)	Baseline $FEF_{25-75\%}$ Nonreactive (% Predicted)	Key Findings
Alberts, 1994[14]	Retrospective	205	Symptomatic,suspected asthma/AHR	N/A	> 80	93/205 (45%)	77.6 ± 27.2	95.4 ± 27.5	Baseline mean $FEF_{25-75\%}$ is lower for pts with AHR; no correlation between +MCT and level of severity
Litonjua, 1999[21]	Retrospective	929	Unclear symptomatology, VA Normal Aging Study	60.5 ± 7.7	94.40	112/929 (12%)	N/A	N/A	$FEF_{25-75\%}$/FVC associated with +MCT and level of severity
Parker, 2003[22]	Retrospective	764	Symptomatic,suspected asthma/AHR	40.8 ± 19.6	93.90 ± 15.10	N/A	N/A	N/A	Lower $FEF_{25-75\%}$/FVC associated with high AHR regardless of gender and age; $FEF_{25-75\%}$ alone not associated with +AHR
Simon, 2006[20]	Retrospective	121	Symptomatic,suspected asthma/AHR	44.4 ± 15.1	88.50 ± 14.20	N/A	N/A	N/A	> 25% decrease in $FEF_{25-75\%}$ and $FEF_{25-75\%}$/FVC is more sensitive but less specific than 20% decrease in FEV_1 for +MCT
Drewek, 2009[23]	Retrospective	532	Symptomatic,suspected asthma/AHR	10.1 ± 3.2	> 80	203/532 (38%)	82.4 ± 21.9	97.5 ± 13.6	Pediatric cohort: +MCT and 10% decrease in $FEF_{25-75\%}$ with PPV 57%, NPV 76%
Malerba, 2016[24]	Retrospective	400	Symptomatic,suspected asthma/AHR	29.6	104.30	224/400 (56%)	N/A	N/A	$FEF_{25-75\%}$ < 65% predicted had odds ratio 13.38 for +MCT, along with higher F_{ENO} and higher sputum eosinophil levels for +AHR
Raji, 2018[15]	Retrospective	236	Symptomatic,suspected asthma/AHR	28.4 ± 12.3	> 80	182/236 (77%)	70.9 ± 19.2	84.2 ± 22.7	Baseline mean $FEF_{25-75\%}$ is lower for pts with AHR; no correlation between +MCT and level of severity

MCT = methacholine challenge testing
$FEF_{25-75\%}$ = mid-expiratory flow
AHR = airway hyper-responsiveness
PPV = positive predictive value
NPV = negative predictive value
F_{ENO} = fraction of exhaled nitric oxide

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

< 65% predicted could be considered abnormal; however, only 45% of the subjects actually met the $FEF_{25–75\%}$ threshold on baseline spirometry.[25] In a 1994 study of mostly adult subjects with respiratory symptoms, a specific $FEF_{25–75\%}$ cutoff value of < 60% predicted was found to have a 73% positive predictive value for AHR; however, the $FEF_{25–75\%}$ did not correlate with the degree of AHR.[14] In a recent study of 236 adult subjects with respiratory symptoms during allergy season, Raji et al[15] found that a mean $FEF_{25–75\%}$ on baseline spirometry is lower for subjects with AHR based on a positive MCT. There was a higher likelihood of AHR if the $FEF_{25–75\%}$ is < 65% predicted; however, a specific cutoff value for $FEF_{25–75\%}$ could not be established that distinguished AHR from non-AHR subjects. Ultimately, whereas a baseline $FEF_{25–75\%}$ < 65% predicted is still considered impaired in the pediatric asthmatic population, there are no guidelines that have established consistent cutoff values for an abnormal $FEF_{25–75\%}$ value in non-asthmatic adults with respiratory symptoms.[14,15,26]

There have been several studies looking at predictability of baseline $FEF_{25–75\%}$ as a surrogate of AHR. Alberts et al[14] compared the baseline $FEF_{25–75\%}$ % predicted with the results of the subsequent MCT in 205 consecutive subjects referred for testing. The mean baseline $FEF_{25–75\%}$ % predicted in 112 subjects with a negative MCT was 95.4 ± 27.5%. In the 93 subjects with a reactive MCT, the mean $FEF_{25–75\%}$ was significantly lower at 77.6 ± 27.2% (P < .001). Drewek et al[23] also showed that a lower $FEF_{25-75\%}$ was also predictive of positive study. However, in a 2018 study of over 230 adult subjects with asthma symptoms, no specific $FEF_{25–75\%}$ cutoff value was identified that predicted AHR.[15] This study of active duty service members with exertional dyspnea, in addition to the other studies evaluating for asthma, adds to this growing body of evidence that an abnormal $FEF_{25-75\%}$ is predictive of MCT reactivity but does not directly correlate with the severity of AHR.

Similar to other studies, we speculate that an abnormal $FEF_{25-75\%}$ in symptomatic non-asthmatic subjects with a normal FEV_1 could be considered a marker of early airway obstruction without involvement of proximal/central airways. In a study of 400 subjects with asthma-type symptoms and non-obstructive baseline spirometry, those with an abnormal $FEF_{25-75\%}$ had increased markers of eosinophilic airway inflammation including a higher fraction of exhaled nitric oxide and higher number of sputum eosinophils.[24] Likewise, in patients with a known history of asthma, a reduced $FEF_{25-75\%}$ has been shown to be an independent marker for more severe asthma outcomes in some patients. In a cross-sectional study of over 800 adults with asthma enrolled in the Severe Asthma Research Program, subjects with a normal FEV_1/FVC but an abnormal $FEF_{25-75\%}$ were found to have an independent association with increased symptom burden, AHR, and health care utilization; however, this subgroup of subjects was relatively small.[27]

There are a number of limitations to our study, including lack of comparison with other diagnostic tools like exhaled nitric oxide and blood eosinophilia, longitudinal follow-up after initiation of treatment, and absence of short- and long-term patient outcomes to determine progression of symptoms. Future prospective studies should evaluate the role of serial assessments of $FEF_{25-75\%}$ and associated spirometric parameters in young adult patients with exertional dyspnea treated with daily versus as-needed inhaler therapy.

Conclusions

The use of baseline spirometry in an MCT proved useful in the evaluation of a young adult military population with exertional dyspnea. The presence of airway obstruction with or without bronchodilator response favored a reactive test. Additionally, a reduction in the $FEV_{25-75\%}$ < 70% predicted without obstruction also showed a positive correlation with underlying AHR. In patients with exertional dyspnea and normal baseline spirometry, the use of the $FEF_{25-75\%}$ may be a useful surrogate measurement in this population to predict MCT reactivity.

REFERENCES

1. American Thoracic Society. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 19992000;161 (1):309-329.
2. Irvin CG. Bronchial challenge testing. Respir Care Clin N Am 1995;1 (2):265-285.
3. O'Donnell AE, Fling J. Exercise-induced airflow obstruction in a healthy military population. Chest 1993;103(3):742-744.
4. Morris MJ, Grbach VX, Deal LE, Boyd SY, Johnson JE, Morgan JA. Evaluation of exertional dyspnea in the active duty patient: the diagnostic approach and the utility of clinical testing. Mil Med 2002;167 (4):281-288.
5. Brown LL, Martin BL, Morris MJ. Airway hyperresponsiveness by methacholine challenge testing following negative exercise challenge. J Asthma 2004;41(5):553-558.
6. Roth BJ, Dillard TA, Hammers LM. Methacholine challenge testing in reserve officer training corps cadets. Chest 2001;119(3):701-707.
7. Army Regulation 40–501. Standards of Medical Fitness. Washington, District of Columbia: Headquarters, Department of the Army; 22 Dec 2016.
8. O'Connor GT, Sparrow D, Weiss ST. Normal range of methacholine responsiveness in relation to prechallenge pulmonary function. The normative aging study. Chest 1994;105(3):661-666.
9. Wassmer G, Jorres RA, Heinrich J, Wjst M, Reitmeir P, Wichmann HE. The association between baseline lung function and bronchial responsiveness to methacholine. Eur J Med Res 1997;2(2):47-54.
10. Jayet PY, Schindler C, Künzli N, Zellweger JP, Brändli O, Perruchoud AP, et al; SAPALDIA team. Reference values for methacholine reactivity (SAPALDIA study). Respir Res 2005;6(1):131-138.
11. Hewitt DJ. Interpretation of the "positive" methacholine challenge. Am J Ind Med 2008;51(10):769-781.
12. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159(1):179-187.

RESPIRATORY CARE Paper in Press. Published on January 18, 2022 as DOI: 10.4187/respcare.09163

13. Westfall PH, Tobias RD, Wolfinger RD. Multiple comparisons and multiple tests using SAS, 2nd ed. Cary, North Carolina: SAS Institute; 2011.
14. Alberts WM, Ferris MC, Brooks SM, Goldman AL. The $FEF_{25-75\%}$ and the clinical diagnosis of asthma. Ann Allergy 199473(3):221-225.
15. Raji H, Shoushtari MH, Idani E, Tavakol H, Afrakhteh S, Dastoorpoor M, Borsi SH. Forced expiratory flow at 25–75% as a marker for airway hyper-responsiveness in adult patients with asthma-like symptoms. Tanaffos 2018;17(2):90-95.
16. Morris MJ, Schwartz D, Nohrenberg JA, Dooley SN. Asymptomatic airway hyper-reactivity in military personnel. Mil Med 2007;172 (11):1194-1197.
17. Nish WA, Schwietz LA. Underdiagnosis of asthma in young adults presenting for USAF basic training. Ann Allergy 1992;69 (3):239-242.
18. Eliasson AH, Phillips YY, Rajagopal KR, Howard RS. Sensitivity and specificity of bronchial provocation testing. An evaluation of four techniques in exercise-induced bronchospasm. Chest 1992;102(2):347-355.
19. Leuallen EC, Fowler WS. Maximal mid-expiratory flow rate. Am Rev Tubercul 1955;72(6):783-790.
20. Simon MR, Havstad S, Cotronei C, Krell W, Johnson CC, Peterson EL. Assessment of mid flow rate measurements in patients undergoing methacholine challenge. Allergy Asthma Proc 2006;27(4):404-410.
21. Litonjua AA, Sparrow D, Weiss ST. The FEF_{25-75}/FVC ratio is associated with methacholine airway responsiveness. Am J Respir Crit Care Med 1999;159(5):1574-1579.
22. Parker AL, Abu-Hijleh M, McCool FD. Ratio between forced expiratory flow between 25% and 75% of vital capacity and FVC is a determinant of airway reactivity and sensitivity to methacholine. Chest 2003;124(1):63-69.
23. Drewek R, Garber E, Stanclik S, Simpson P, Nugent M, Gershan W. The FEF_{25-75} and its decline as a predictor of methacholine responsiveness in children. J Asthma 2009;46(4):375-381.
24. Malerba M, Radaeli A, Olivini A, Damiani G, Ragnoli B, Sorbello V, Ricciardolo FL. Association of $FEF_{25-75\%}$ impairment with bronchial hyper-responsiveness and airway inflammation in subjects with asthma-like symptoms. Respiration 2016;91 (3):206-214.
25. Ciprandi G, Capasso M, Tosca M, Salpietro C, Salpietro A, Marseglia G, La Rosa M. A forced expiratory flow at 25–75% value < 65% of predicted should be considered abnormal: a real-world, cross-sectional study. Allergy Asthma Proc 2012;33(1):e5-e8.
26. Ciprandi G, Tosca MA, Castellazzi AM, Cairello F, Salpietro C, Arrigo T, Miraglia Del Giudice M. FEF(25-75) might be a predictive factor for bronchial inflammation and bronchial hyperreactivity in adolescents with allergic rhinitis. Int J Immunopathol Pharmacol 2011;24(4 Suppl):17-20.
27. Riley CM, Wenzel SE, Castro M, Erzurum SC, Chung KF, Fitzpatrick AM, et al. Clinical implications of having reduced mid forced expiratory flow rates (FEF_{25-75}), independently of FEV_1, in adult patients with asthma. PLoS One 2015;10(12):e0145476.