Published in final edited form as:

Ann Allergy Asthma Immunol. 2016 July ; 117(1): 97–99. doi:10.1016/j.anai.2016.04.029.

The Association of FEF_{25–75} and Bronchodilator reversibility with Asthma Control and Asthma Morbidity in Inner City Children with Asthma

Watcharoot Kanchongkittiphon, MD, PhD^{a,b}, Jonathan M. Gaffin, MD, MMSc^{c,d}, Lianne Kopel, MD^e, Carter R. Petty, MA^f, Mary E. Bollinger, DO^g, Rachel Miller, MD^{h,i}, Matthew Perzanowski, PhDⁱ, Elizabeth C. Matsui, MD, MHS^j, and Wanda Phipatanakul, MD, MS^{d,k}

^aChildren's Hospital of Michigan, Detroit, MI ^bDepartment of Pediatrics, Ramathibodi's Hospital, Mahidol University, Bangkok, Thailand ^cDivision of Respiratory Diseases, Boston Children's Hospital, Boston, MA ^dHarvard Medical School, Boston, MA ^eDivision of Respiratory Medicine, Montreal Children's Hospital, Montreal, Quebec ^fClinical Research Center, Boston Children's Hospital, Boston, MA ^gDivision of Pulmonology and Allergy, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD ^hDivision of Pulmonary, Allergy, Critical Care Medicine, Columbia University Medical Center, New York, NY ⁱDepartment of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY ^jDivision of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD ^kDivision of Allergy and Immunology, Boston Children's Hospital, Boston MA

Keywords

FEF₂₅₋₇₅; Bronchodilator reversibility; asthma; inner-city; children

Spirometry is recommended by the National Asthma Education and Prevention Program guidelines as a tool for assessing asthma severity and control. The guidelines assess asthma severity and control by both clinical symptoms and forced expiratory volume in 1 second (FEV₁) percent predicted. However, FEV₁ is often normal in children with asthma, regardless of severity¹.

Forced expiratory flow at 25% to 75% of forced vital capacity (FEF₂₅₋₇₅) percent predicted is regarded as a more sensitive measure of small airway obstruction. It has been shown that a

Corresponding Author: Wanda Phipatanakul, MD, MS, Division of Immunology, Boston Children's Hospital, 300 Longwood Avenue, Fegan 6, Boston, MA 02115, Telephone: 617-355-6117, Fax: 617-730-0310, wanda.phipatanakul@childrens.harvard.edu.

Conflict(s) of interest: All authors have no conflict of interest

Trial registration: Not applicable

The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

low FEF₂₅₋₇₅ was associated with increased asthma severity and that low FEF₂₅₋₇₅ may represent a risk factor for the persistence of symptoms in children with asthma².

Previous studies have also demonstrated that an elevated bronchodilator response (BDR), defined as at least a 12% increase in FEV₁ following administration of short acting beta agonist, is associated with increased airway inflammation, and poor clinical asthma outcomes^{3,4}.

We aimed to determine whether FEF₂₅₋₇₅ and BDR are associated with asthma morbidity in urban children with asthma, independent of the guidelines-endorsed measure of FEV₁ and FEV₁/FVC.

Baseline data from subjects enrolled in 2 studies, School Inner-City Asthma Study (SICAS) during 2008–2012 and the Mouse Allergen and Asthma Intervention Trial (MAAIT) during 2010–2014, were used. Full methods including inclusion and exclusion criteria for the SICAS and MAAIT are published elsewhere^{5,6}. Subjects with incomplete spirometry data were excluded. Pulmonary function testing was performed according to the recommendations of the American Thoracic Society guidelines and standardized to the Third National Health and Nutrition Examination Survey (NHANES) reference values for percent predicted⁷. Children younger than 8 years old were excluded due to limitations of NHANES reference values in this age group⁸. Post-bronchodilator spirometry was obtained approximately 15 minutes after nebulized albuterol. A normal FEF₂₅₋₇₅ was defined as 75.5% predicted according to the lower limit of normal 95% confidence interval for FEF₂₅₋₇₅ in study participants. BDR was calculated as the percent change from baseline for FEV₁ by the equation: $BDR = [(post-bronchodilator\ FEV_1 - pre-bronchodilator\ FEV_1) / (pre-bronchodilator\ FEV_1)] \times 100$. BDR was defined as positive if there was a change in FEV₁ 12%⁷.

Morbidity outcomes included the presence of any wheezing/chest tightness/cough, report of slowing down/stopping play or activities, nocturnal wheezing, and any missed school days due to asthma. We estimated unadjusted and adjusted odds ratios using logistic regression models. Statistical analyses were completed using IBM SPSS Statistics version 19.

Overall, 186 subjects from SICAS and 404 subjects from MAAIT met inclusion criteria. Regarding demographic characteristics of included subjects, mean study participants' age was 11 years old. 59% of study participants were male. The majority of the subjects were Black and Hispanic (68%) with an annual family income of less than \$25,000 per year. Minority of subjects had reported exposure to tobacco smoke (34%). Regarding spirometry indices, 24% of the study participants had FEF₂₅₋₇₅% predicted less than 75.5%. Most subjects had persistent asthma with normal lung function in which 79% of subjects had FEV₁% predicted 80%, and 63% of subjects had FEV₁/FVC 80%.

Table 1 illustrates the relationship between lung function testing and clinical symptoms. SICAS subjects with a low FEF₂₅₋₇₅ (n=54) had greater odds of asthma symptoms in the past 2 weeks compared with those with a normal FEF₂₅₋₇₅. After adjusting for sex, age, race, income, secondhand smoke exposure, and body mass index (BMI), subjects with a low FEF₂₅₋₇₅ had higher odds of nocturnal wheezing, odds ratio (OR) 2.1, 95% confidence

interval (CI) 1.0–4.2, and higher odds of school absence due to asthma, OR 4.3, 95% CI 1.2–14.8, compared with those with a high FEF₂₅₋₇₅. Similarly, MAAIT subjects with low FEF₂₅₋₇₅ (n=85) had higher odds of reporting having to slow down/stop play and/or activities in the past 2 weeks compared to those with a normal FEF₂₅₋₇₅ even adjusted for FEV₁/FVC. However, in both cohorts, low FEF₂₅₋₇₅ was not an independent predictor for poor outcomes when FEV₁ % predicted was included in the model.

Linear regression models including 130 subjects from SICAS and 404 subjects from MAAIT with BDR testing found that subjects with positive BDR (SICAS, n=33, MAAIT, n=126) demonstrated a non-significant trend for association with greater asthma symptoms for the majority of outcomes tested, and was significantly associated with school absenteeism in SICAS. BDR in children with asthma is associated with increased airway inflammation and this may mediate the association seen in our current study.

FEF₂₅₋₇₅ has recently received attention as a possible marker of worsened asthma control and risk for future morbidity in children² presenting for clinical pulmonary function testing at a tertiary care center. In the cohorts included in the current study, mainly representative of children of black and Hispanic background with persistent asthma, similar trends were observed. However, the relationship between FEF₂₅₋₇₅ and increased asthma symptoms and markers of exacerbations was not independent of the association with FEV₁ % predicted. This suggests that while the FEF₂₅₋₇₅ may be an important measure of lung function that relates to important clinical outcomes, its additive value in determining loss of asthma control is limited when the FEV₁ percent predicted is considered. Although FEF₂₅₋₇₅ may be a more sensitive marker of small and medium sized airflow limitation, the hallmark of asthma, its higher coefficient of variability⁸ may sufficiently limit its ability to specifically identify lack of control.

A strength of this study is the large and well characterized participants from 2 inner-city children population cohort. However, we acknowledge several limitations to this analysis. Although asthma morbidity outcomes were not significantly associated with low FEF₂₅₋₇₅ and positive BDR, most odds ratio values were consistently greater than 1, a trend that suggests the FEF₂₅₋₇₅ relationships are not spurious. Furthermore, there is a lack of consensus of normal range for FEF₂₅₋₇₅. While low FEF₂₅₋₇₅ and poor clinical outcomes have been previously described in asthmatic children the absolute normal cutoff level for FEF₂₅₋₇₅ has not been firmly established. Previous studies have cut-off values ranging from 60%–80%^{2, 9–10}. We chose 75.5% as a cutoff based on the findings of other published studies and the distribution of data in our cohort. Similar debate over clinically significant BDR exists¹¹, as well.

In conclusion, in urban asthmatic children, BDR might be considered in assessing asthma severity and morbidity outcomes. FEF₂₅₋₇₅ is associated with symptoms, but its utility independent of FEV₁/FVC or FEV₁ is likely limited. Future studies are necessary in order to better understand the role of FEF₂₅₋₇₅ and BDR as predictors of morbidity and markers of loss of control.

Acknowledgments

Funding: This study was supported by grants R01 AI 073964, K24 AI 106822, K24 AI 114769, K23 AI 106945, U01 AI 110397, U01 AI 083238, P30 ES009089 from the National Institutes of Health

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102, and financial contributions from Harvard University and its affiliated academic healthcare centers.

Abbreviations

FEV₁	Forced expiratory volume in 1 second
FEF₂₅₋₇₅	Forced expiratory flow at 25% to 75% of forced vital capacity
BDR	Bronchodilator response
SICAS	School Inner-City Asthma Study
NHANES	National Health and Nutrition Examination Survey
BMI	Body mass index
OR	Odds ratio
CI	Confident interval

References

1. Bacharier LB, Strunk RC, Mauer D, et al. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *American journal of respiratory and critical care medicine*. 2004; 170(4):426–32. [PubMed: 15172893]
2. Rao DR, Gaffin JM, Baxi SN, et al. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2012; 49(6):586–92. [PubMed: 22742446]
3. Sharma S, Litonjua AA, Tantisira KG, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *The Journal of allergy and clinical immunology*. 2008; 122(5):921–8. e4. [PubMed: 18848350]
4. Galant SP, Morpew T, Newcomb RL, et al. The relationship of the bronchodilator response phenotype to poor asthma control in children with normal spirometry. *The Journal of pediatrics*. 2011; 158(6):953–9. e1. [PubMed: 21232757]
5. Phipatanakul W, Bailey A, Hoffman EB, et al. The school inner-city asthma study: design, methods, and lessons learned. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2011; 48(10):1007–14. [PubMed: 22010992]
6. Sedaghat AR, Matsui EC, Baxi SN, et al. Mouse Sensitivity is an Independent Risk Factor for Rhinitis in Children with Asthma. *The journal of allergy and clinical immunology In practice*. 2016; 4(1):82–8. e1. [PubMed: 26441149]
7. The Expert Panel Report 3 (EPR—3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma was developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. 2007; NIH Publication Number 08-5846.

8. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. *American journal of respiratory and critical care medicine*. 2008; 177(3):253–60. [PubMed: 18006882]
9. Ciprandi G, Capasso M, Tosca M, et al. A forced expiratory flow at 25–75% value <65% of predicted should be considered abnormal: a real-world, cross-sectional study. *Allergy and asthma proceedings : the official journal of regional and state allergy societies*. 2012; 33(1):e5–8. [PubMed: 22370528]
10. Marseglia GL, Cirillo I, Vizzaccaro A, et al. Role of forced expiratory flow at 25–75% as an early marker of small airways impairment in subjects with allergic rhinitis. *Allergy and asthma proceedings : the official journal of regional and state allergy societies*. 2007; 28(1):74–8. [PubMed: 17390762]
11. Tse SM, Gold DR, Sordillo JE, et al. Diagnostic accuracy of the bronchodilator response in children. *The Journal of allergy and clinical immunology*. 2013; 132(3):554–9. e5. [PubMed: 23683464]

Table 1Association of FEF₂₅₋₇₅ and BDR with asthma morbidity in last 2 weeks

Symptoms	FEF ₂₅₋₇₅ < 75.5%				BDR > 12%			
	odds ratio (95% CI)	adjusted ^a odds ratio (95% CI)	adjusted ^b odds ratio (95% CI)	adjusted ^c odds ratio (95% CI)	odds ratio (95% CI)	adjusted ^a odds ratio (95% CI)	adjusted ^b odds ratio (95% CI)	adjusted ^c odds ratio (95% CI)
SICAS cohort								
Any wheezing/chest tightness/cough	1.1 (0.6–2.1)	1.1 (0.6–2.2)	1.2 (0.5–2.9)	0.9 (0.4–2.0)	1.0 (0.4–2.5)	1.2 (0.4–3.4)	1.2 (0.4–3.9)	1.0 (0.3–3.1)
Slow down/stop play/activities	1.4 (0.8–2.7)	1.6 (0.8–3.2)	1.2 (0.5–2.8)	1.6 (0.7–3.6)	1.2 (0.5–2.9)	1.1 (0.4–2.9)	0.7 (0.2–2.2)	1.1 (0.3–3.3)
Nocturnal wheezing	1.8 (0.9–3.4)	2.1 (1.0–4.2)*	1.4 (0.6–3.5)	1.8 (0.8–4.2)	2.2 (0.9–5.6)	2.4 (0.9–6.8)	1.2 (0.4–4.0)	2.4 (0.7–7.7)
Missed school day due to asthma	2.6 (0.9–8.0)	4.3 (1.2–14.8)*	1.7 (0.3–8.5)	3.7 (0.8–16.8)	7.2 (1.8–29.2)*	18.8 (2.5–138.6)*	9.6 (1.1–86.7)*	13.5 (1.5–120.2)*
MAATI cohort								
Any wheezing/chest tightness/cough	1.6 (0.9–2.8)	1.5 (0.8–2.6)	1.1 (0.6–2.2)	0.8 (0.3–1.8)	1.3 (0.8–2.2)	1.3 (0.8–2.2)	1.3 (0.8–2.2)	1.3 (0.8–2.1)
Slow down/stop play/activities	1.8 (1.1–2.9)*	1.7 (1.0–2.9)*	1.7 (0.9–3.2)	1.5 (0.7–3.2)	1.4 (0.9–2.2)	1.6 (1.0–2.5)	1.5 (0.9–2.4)	1.5 (0.9–2.3)
Nocturnal wheezing	1.7 (1.1–2.8)*	1.8 (1.1–2.9)*	1.5 (0.8–2.6)	1.1 (0.5–2.2)	1.4 (0.9–2.2)	1.5 (1.0–2.3)	1.4 (0.9–2.2)	1.3 (0.9–2.1)

* p<0.05

^a Adjusted for BMI, Gender, Age, Race, Income, Smoking^b Adjusted for BMI, Gender, Age, Race, Income, Smoking, FEV₁/FVC^c Adjusted for BMI, Gender, Age, Race, Income, Smoking, FEV₁