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Clinical Implications of Having Reduced Mid Forced Expiratory Flow Rates (FEF$_{25-75}$), Independently of FEV1, in Adult Patients with Asthma

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Abstract

Introduction
FEF$_{25-75}$ is one of the standard results provided in spirometry reports; however, in adult asthmatics there is limited information on how this physiological measure relates to clinical or biological outcomes independently of the FEV$_{1}$ or the FEV$_{1}$/FVC ratio.

Purpose
To determine the association between Hankinson’s percent-predicted FEF$_{25-75}$ (FEF$_{25-75\%}$) levels with changes in healthcare utilization, respiratory symptom frequency, and biomarkers of distal airway inflammation.
Methods
In participants enrolled in the Severe Asthma Research Program 1–2, we compared outcomes across FEF_{25-75}% quartiles. Multivariable analyses were done to avoid confounding by demographic characteristics, FEV₁, and the FEV₁/FVC ratio. In a sensitivity analysis, we also compared outcomes across participants with FEF_{25-75}% below the lower limit of normal (LLN) and FEV₁/FVC above LLN.

Results
Subjects in the lowest FEF_{25-75}% quartile had greater rates of healthcare utilization and higher exhaled nitric oxide and sputum eosinophils. In multivariable analysis, being in the lowest FEF_{25-75}% quartile remained significantly associated with nocturnal symptoms (OR 3.0 [95%CI 1.3–6.9]), persistent symptoms (OR 3.3 [95%CI 1–11], ICU admission for asthma (3.7 [1.3–10.8]) and blood eosinophil % (0.18 [0.07, 0.29]). In the sensitivity analysis, those with FEF_{25-75}% <LLN had significantly more nocturnal and persistent symptoms, emergency room visits, higher serum eosinophil levels and increased methacholine responsiveness.

Conclusions
After controlling for demographic variables, FEV₁ and FEV₁/FVC, a reduced FEF_{25-75}% is independently associated with previous ICU admission, persistent symptoms, nocturnal symptoms, blood eosinophilia and bronchial hyperreactivity. This suggests that in some asthmatics, a reduced FEF_{25-75}% is an independent biomarker for more severe asthma.

Introduction
Both the diagnosis of asthma and the monitoring of disease severity rely on the use of pulmonary function testing (PFT) data. Though the forced expiratory volume in one second (FEV₁) and the FEV₁ to forced vital capacity (FVC) ratio are the most commonly used spirometric measurements to identify both the presence and degree of airflow obstruction, other values such as the forced expiratory flow between 25% and 75% of the FVC (FEF_{25-75}) are also commonly reported [1]. Although variation in the FEF_{25-75} was previously thought to reflect changes exclusively in the small airways (< 2mm) [2–4], subsequent studies using other physiological or radiological parameters have shown that changes in FEF possibly reflect distal airflows that involve airways that have greater diameters. More importantly, there is limited information about its clinical usefulness, including the fact that current guidelines such as those from the Global Initiative for Asthma (GINA) and the Expert Panel Report 3 of the National Heart, Lung and Blood Institute do not provide specific recommendations for the use of FEF_{25-75} in the evaluation or management of asthma [5,6]. In heterogeneous populations, FEF_{25-75} is seldom discordant from FEV₁ and FEV₁/FVC [7]. However, reduced FEF_{25-75} in children with asthma has been shown to be associated with increased asthma severity, need for systemic steroid use and more frequent exacerbations in the setting of normal FEV₁. It is not known whether these results are also applicable to adult asthmatics [8].

To answer this question, we sought to determine whether the percent predicted FEF_{25-75} (FEF_{25-75}% ) is associated with clinical asthma outcomes among participants of the Severe Asthma Research Program (SARP). We hypothesized that having a reduced FEF_{25-75}% would
be associated with increased asthma morbidity independent of and beyond the severity implied by more traditional markers like FEV1%. We further hypothesized that FEF25-75% would be associated with biomarkers linked to more distal airway inflammation.

**Methods**

The study population consisted of participants ages 18 or older from the multi-center SARP study who met criteria for asthma and also had FEF measurements. Asthma diagnosis was based on having either a 12% increase in FEV1 after short acting bronchodilator or a 20% drop in FEV1 after inhalation of methacholine (PC20 25 mg/ml). The SARP 1–2 study has been previously described in detail [9]. Briefly, the study population consisted of subjects recruited at SARP participating academic centers through the use of local advertisement and from their clinics who met eligibility criteria, including being a current nonsmoker with asthma and having less than 5 pack-years of tobacco use. Study participants were classified as having either severe or not severe asthma. According to the American Thoracic Society (ATS) definition, severe asthma was defined as: at least 1 major criteria: a) Use of high-dose inhaled steroids for > 50% of the preceding year or b) continuous or near-continuous oral steroids); and at least 2 minor criteria: a) daily controller medication in addition to inhaled steroids, b) beta agonist required daily or near-daily, c) persistent airway obstruction, d) one or more urgent care visits for asthma per year, e) 3 or more oral corticosteroid bursts/year, f) clinical deterioration with reduction in oral steroid dose, and g) near-fatal asthma event in the past. Non-severe asthmatics included those with moderate (pre bronchodilator FEV1 < 80% with or without use of inhaled corticosteroids (CS)) or mild (FEV1 ≥ 80% with or without use of inhaled CS) asthma.

**Clinical Data**

After signing informed consent, study participants provided demographic information, smoking history, past medical history and frequency of respiratory symptoms in the 3 months preceding enrollment, including cough, sputum production, chest tightness, nighttime asthma symptoms, wheezing, and shortness of breath. Subjects also completed the Juniper Asthma Quality of Life Questionnaire (AQLQ). As this specific project was performed as secondary analysis of the above data following de-identification, no further patient consent or institutional review board approval was required.

**Allergy Skin Test**

All participants underwent allergy skin testing for tree mix, grass mix, ragweed, weed mix, dogs, cats, molds, dust mites, and cockroach. To control for validity, diluting fluid and histamine were respectively used as negative and positive controls. Presence of atopy was defined as having at least one skin test reaction of ≥3 mm and greater than the saline control.

**Lung Function testing**

Spirometry was done following ATS guidelines[10]. Post bronchodilator FEV1 was recorded as the maximum bronchodilator change between 4 and 8 puffs of albuterol. Patients with a baseline FEV1 > 50% and FEV1 ≥ 1.5L underwent methacholine challenge, following a 7-dose algorithm of incremental doses from 0.078mg/ml to maximum of 25 mg/ml. A provocation concentration (PC20) of <16 mg/ml was considered positive. This high value was chosen because of the high and prolonged steroid doses in the population. Because of FEV1 criteria, methacholine challenges were only done to a subset of the subjects. FEF25-75% was calculated...
using Hankinson’s regression models for each sex and by race [11]. Exhaled nitric oxide (eNO) was measured online following ATS and ERS standards [12].

Statistical Analysis

The FEF\textsubscript{25-75} distribution was divided into quartiles to determine how the variability in this measure associates with changes in healthcare utilization, frequency of respiratory symptoms and biomarkers of distal airway inflammation. Healthcare utilization included emergency department (ED) visits, hospitalizations and intensive care unit (ICU) admissions for asthma. The frequency of respiratory symptoms was defined as a binary variable for having or not having symptoms at least twice or more per week. Continuous parametric and non-parametric data were respectively compared across FEF\textsubscript{25-75} quartiles using one way ANOVA or Kruskal Wallis tests with Bonferroni pairwise comparisons. The Chi2 test was used to compare the distribution of categories.

To evaluate for possible confounders, we performed logistic regression analysis that included the following models: a) univariable, b) adjusted for demographic factors (age, gender, BMI, race), and c) full model adjusted for demographic variables + FEV\textsubscript{1} % predicted and the FEV\textsubscript{1}/FVC ratio. The covariable model selection was based a priori and whether their p value was < 0.1 or the model’s estimate changed by ≥ 10%. Given the high degree of correlation between FEF and FEV\textsubscript{1} or the FEV\textsubscript{1}/FVC ratio, all models were evaluated for collinearity using the variance inflation factor (VIF). Due to the fact that in severe asthmatics, FVC accounts for most of the FEV\textsubscript{1} reversal after bronchodilation due to air trapping [13], a separate multivariate analysis was run with adjustment for FVC rather than FEV\textsubscript{1} (S3 Table); both could not be adjusted for in the same model due to collinearity. We also performed a sensitivity analysis to determine the study outcomes of discordant subjects with low FEF\textsubscript{25-75} but no airway obstruction, defined as having FEF\textsubscript{25-75} < LLN with FEV\textsubscript{1}/FVC > the lower limit of normal (LLN). All statistics were done using Stata 13.0 (College Park, Tx).

Results

The characteristics of the study population are shown in Table 1, which consisted of 829 participants, of whom the majority was Caucasian, female and overweight. With decreasing FEF\textsubscript{25-75} quartiles, there was a greater proportion of African American race, larger BMI, longer duration of asthma and a higher proportion of moderate to severe asthmatics. There was also a strong association between FEF\textsubscript{25-75} quartiles with increased medication use health care utilization, eNO, IgE and sputum eosinophil proportions. Similarly, participants in the lower quartile distribution were more likely to have required an oral corticosteroid burst, to be seen in the emergency room or to be hospitalized for asthma. Those in the lowest FEF\textsubscript{25-75} quartile had the highest likelihood of having been previously intubated for asthma. With progressive FEF\textsubscript{25-75} decline, there was also a significant reduction in FVC, FEV\textsubscript{1} and the FEV\textsubscript{1}/FVC ratio as shown in Table 2. Adjustment for FVC rather than FEV\textsubscript{1} did not significantly change the results of the multivariate analysis (S3 Table).

Multivariable analyses

Respiratory symptoms. In the univariable analysis (S1 Table), compared to highest referent FEF\textsubscript{25-75} quartile (median 92.5 (IQR [80.1, 101.1]) category, the odds of having persistent respiratory symptoms increased in association with lower FEF\textsubscript{25-75} quartiles and remained largely significant after adjustment for age, BMI, sex, duration of asthma and ever smoking; however, after adjustment for FEV\textsubscript{1} percent predicted and the FEV\textsubscript{1}/FVC ratio, only nocturnal
symptoms and persistent symptoms remained significantly associated with the lowest FEF25-75% quartile (median 25.6 [IQR 20.4, 32.2]) as shown in Table 3 and Fig 1A.

**Healthcare utilization.** In the univariable analysis, compared to the referent category, the odds of ever requiring hospitalizations, ED visits or ICU care increased in relation to lower quartiles, as shown in Table 3 and Fig 1A.

### Table 1. Characteristics of the study population by the FEF25-75% quartile distribution.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall</th>
<th>Q1 (74–146)</th>
<th>Q2 (56–74)</th>
<th>Q3 (37–55)</th>
<th>Q4 (9–37)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 829</td>
<td>N = 207</td>
<td>N = 207</td>
<td>N = 208</td>
<td>N = 207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>36.8 (25.5, 46.6)</td>
<td>32.6 (22.2, 38.9)</td>
<td>35.3 (25.6, 42.0)</td>
<td>37.6 (26.7, 47.7)</td>
<td>41.7 (32.2, 49.6)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Sex—Female</td>
<td>65.1%</td>
<td>67.1%</td>
<td>70.5%</td>
<td>64.4%</td>
<td>58.4%</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>Race—White</td>
<td>64.9%</td>
<td>74.4%</td>
<td>69.6%</td>
<td>61.1%</td>
<td>54.6%</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 (23.9, 34.2)</td>
<td>28.0 (22.5, 32.5)</td>
<td>29.6 (23.8, 33.0)</td>
<td>30.8 (24.6, 35.0)</td>
<td>31.3 (25.1, 35.9)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Duration of asthma (yrs)</td>
<td>21.8 (11.8, 30.6)</td>
<td>17.9 (8.5, 23.8)</td>
<td>19.9 (10.6, 27.1)</td>
<td>23.0 (12.8, 32.1)</td>
<td>26.3 (15.6, 35.9)</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>20.7%</td>
<td>18.0%</td>
<td>20.3%</td>
<td>21.2%</td>
<td>23.2%</td>
<td>P = 0.6</td>
</tr>
</tbody>
</table>

**Biomarkers**

| Exhaled NO (ppb) | 38.0 (15.6, 48.1) | 31.1 (13.5, 36.6) | 37.1 (14.1, 49.7) | 40.1 (17.8, 52.2) | 43.8 (17.0, 49.3) | P = 0.01* |
| IgE (IU/mL blood) | 324 (54, 334) | 197 (42, 226) | 316 (52, 355) | 401 (64, 362) | 384 (56, 385) | P = 0.05* |
| Eosinophil % (blood) | 3.93 (2.5) | 3.40 (1.55, 5) | 3.95 (2.5) | 3.66 (2.5) | 4.72 (2.6) | P = 0.01** |
| Sputum eosinophil % | 4.89 (0.2, 4.1) | 3.22 (0.001, 1.9) | 3.08 (0.2, 2.8) | 3.66 (0.3, 4.0) | 9.59 (0.6, 8.6) | P = 0.001** |
| PC20 (mg/ml) | 1.15 (0.42, 3.89) | 2.25 (0.89, 6.48) | 1.28 (0.53, 3.99) | 0.84 (0.27, 2.42) | 0.46 (0.19, 1.44) | P = 0.0001* |

**Outcomes**

| ER for breathing ever | 67.9% | 61.8% | 58.5% | 68.1% | 83.1% | P = 0.001 |
| Spent night in hospital ever | 42.4% | 33.3% | 30.4% | 38.8% | 67.2% | P = 0.001 |
| ICU ever | 15.9% | 6.4% | 7.8% | 14.7% | 34.8% | P = 0.001 |
| Intubated ever | 8.3% | 4.8% | 5.8% | 4.8% | 18.0% | P = 0.001 |

Footnote: Continuous variables are shown as median (Inter quartile range). Categorical variables shown as percentage of total. Q: quartile, BMI: body mass index, NO: nitric oxide, WBC: white blood cell, PC20: provocation challenge, ER: emergency room, ICU: intensive care unit.

* P value calculated from log transformed data

**Table 2. Lung function parameters by the FEF25-75% quartile distribution.**

<table>
<thead>
<tr>
<th>Overall</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 829</td>
<td>N = 207</td>
<td>N = 207</td>
<td>N = 208</td>
<td>N = 207</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>78.6 (66, 92)</td>
<td>97.2 (90, 104)</td>
<td>87.0 (80, 94)</td>
<td>74.5 (67, 81)</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>89.4 (79, 101)</td>
<td>97.6 (89, 106)</td>
<td>94.5 (84, 103)</td>
<td>88.1 (79, 97)</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.72 (0.65, 0.80)</td>
<td>0.83 (0.80, 0.87)</td>
<td>0.76 (0.73, 0.80)</td>
<td>0.70 (0.66, 0.74)</td>
</tr>
<tr>
<td>FEF25-75 (% predicted)</td>
<td>57.0 (37.2, 73.8)</td>
<td>92.5 (80.1, 101.1)</td>
<td>64.0 (59.0, 68.5)</td>
<td>46.0 (41.8, 50.8)</td>
</tr>
</tbody>
</table>

Footnote: Values shown as median (Inter quartile range). Q: quartile, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, FEF25-75: forced expiratory flow between 25% and 75% of FVC.

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FEF25-75% quartiles (S1 Table). After adjusting for demographics, these associations were attenuated but remained significant. After adjusting for FEV1% and the FEV1/FVC ratio, only those in the lowest FEF25-75% quartile had a significantly increased odds ratio (OR) of ever having an ICU admission for asthma (Table 3, Fig 1B).

**Biomarkers of allergic, airway inflammation and bronchial hyperactivity.** In the univariable analysis, lower FEF25-75% quartiles were significantly associated with log-transformed eNO, IgE, PC20, blood and sputum eosinophils (S1 Table). After adjustment for demographics, these remained significant with the exception of blood eosinophilia. In the fully adjusted model, the 3rd FEF25-75% quartile was associated with IgE, eNO, PC20, and marginally with sputum eosinophils. In the lowest quartile, only blood eosinophils and PC20 remained significant (Table 3 and Fig 1C), though a trend towards increasing IgE, eNO and sputum eosinophilia remained.

**Sensitivity analysis on patients with discordant FEF25-75 and FEV1/FVC.** Compared to asthmatics with an FEF25-75 > LLN and FEV1/FVC > LLN, those with a reduced FEF25-75 < LLN but FEV1/FVC > LLN, had significantly increased nocturnal symptoms and persistent symptoms. They were also more likely to visit the emergency room, to have serum eosinophilia and bronchial hyperreactivity (S2 Table).

**Discussion**

In this cross sectional study of SARP participants, reduced FEF25-75% was associated with increased frequency of respiratory symptoms, greater healthcare utilization and higher levels of biomarkers of distal airway inflammation. Although many of these associations were attenuated by adjusting for FEV1% and the FEV1/FVC ratio, having a reduced FEF25-75% was independently related to more frequent nocturnal and persistent symptoms, ICU admission for asthma, higher eNO, greater bronchial hyperreactivity and higher sputum eosinophil percentage. Further, among patients with an FEV1/FVC ratio above the lower limit of normal, having an FEF25-75 below the LLN was associated with increased symptom burden, healthcare utilization, serum eosinophilia and bronchial hyperreactivity. Together, these results show for
the first time in adults with asthma, that having a low FEF_{25-75} identifies a group of patients with higher morbidity and elevated biomarkers of distal airway inflammation.

According to the European Respiratory Society (ERS) and the American Thoracic Society (ATS) task force for standardization of lung function testing, the FEF_{25-75} is defined as the mean forced expiratory flow between the 25% and 75% of the FVC [14,15], which some have interpreted as a quantitative measure of small airways (<2mm) obstruction [4]. Indeed, since the 1970s FEF_{25-75} rates were proposed to be a marker of small airway obstruction and a more sensitive way to detect early stages of obstructive airway disease. However, others have argued that FEF_{25-75} is highly variable and neither sufficiently sensitive nor specific to diagnose obstructive lung disease [16]. Moreover, FEF_{25-75} has not been shown to correlate with other physiologic or histologic measures of distal lung inflammation [16]. Using computed tomography airway morphometric analysis, FEF_{25-75} has been shown to be moderately and inversely correlated with the bronchial wall area (WA) and WA corrected for body surface...
area, though not exclusively in the small airways [17]. Although it is possible that FEF25-75% predominantly reflects flows derived from more distal airways, there is insufficient data to support the concept that variability in this measure is specific to small airway changes. Despite these limitations, FEF25-75% continues to be part of the standard spirometry report. More importantly, there are no recommendations as to how reductions in this measure should be taken into consideration for asthma treatment or for risk stratification.

Unlike Quanjer et al [7] who have argued that FEF25-75% does not aid clinical decision making, our results support a different conclusion. Although we also found the percentage of discordant cases (low FEF25-75% with a normal FEV1/FVC) is relatively small, FEF was independently associated with several clinical, inflammatory and healthcare outcomes. Further, the study by Quanjer et al was unable to examine these associations, as their study did not include any non-physiological clinical outcomes.

In children, a low FEF25-75% has been associated with greater odds for systemic steroids and ED visits, despite having a normal FEV1 [18]. Similarly, our study found that even when controlling for FEV1 and the FEV1/FVC ratio, asthmatics with lower FEF25-75% have greater odds of having been admitted to the ICU and to have persistent respiratory symptoms. In addition, we have shown that lower FEF25-75% is independently associated with eNO. As shown by Dweik et al [19], eNO is associated with increased asthma morbidity when levels are above 35 ppb. When taken into consideration with increased persistent and nocturnal symptoms, we speculate that FEF25-75% is indeed related to more distal airway inflammation either not fully captured or not yet evident by FEV1; however, further work must be done to evaluate this hypothesis. If proven in prospective investigation, the clinical implications would include both prognosis and identification of an at-risk asthma population for more intensive therapy.

There are significant limitations that need to be considered when evaluating the results from this study. First, given the cross-sectional nature of this study, no causal implications can be made between FEF25-75% and asthma severity. This question will need to be answered in the ongoing longitudinal SARP 3 study. Also, reliance on questionnaire responses may contribute to recall bias, though this should be a non-differential bias with regards to the FEF25-75% distributions. Additionally, our results may lack external validity, as the SARP study population is enriched with a higher proportion of participants with severe asthma and is not representative of the general adult asthma population. Though this limits the generalization of these findings, it should be noted that SARP still represents a broader spectrum of asthma than most studies, which may help with distinguishing effects.

Conclusions

Independent of FEV1 and FEV1/FVC, FEF25-75% predicted identifies a population of adult asthmatics with more severe symptoms, greater health care utilization and elevated biomarkers of distal airway inflammation. Further research is needed to determine if this information can be used clinically to guide treatment decisions or for prognostic evaluation; these questions are currently undergoing longitudinal analysis within SARP 3.

Supporting Information

S1 Table. Symptoms, Health Care Utilization and Biomarkers across FEF Quartiles unadjusted and adjusted for demographics. Footnote: Multivariable logistic (odds ratio) and linear regression (beta coefficient) models were adjusted for age, sex, body mass index, duration of asthma, history of smoking, FEV1 and FEV1/FVC. Bolded values represent p-values < 0.05. * Multivariate analysis odds ratios and 95% confidence intervals. ** Linear regression beta coefficients and 95% confidence intervals. Q: quartile, SOB: shortness of breath, Sx: symptoms, ER:


(2) S3 Table. Multivariable analysis of respiratory symptoms, healthcare utilization and biomarkers by FEF25-75% quartile distribution with FVC instead of FEV1. Footnote: Multivariable logistic (odds ratio) and linear regression (beta coefficient) models were adjusted for age, sex, body mass index, duration of asthma, history of smoking, FVC and FEV1/FVC. Q: quartile, SOB: shortness of breath, Sx: symptoms, ER: emergency room, ICU: intensive care unit, eNO: exhaled nitric oxide, Eos: eosinophils, PC20: provocative challenge, FEF quartiles: Q1: 88 (74–146), Q2: 64 (56–74), Q3: 46 (37–55), Q4: 27 (9–37).

(3) S4 Table. Demographic and lung function characteristics of non-obstructed patients with normal vs low FEF25-75. Footnote: Continuous variables are shown as median (Inter quartile range). Categorical variables shown as percentage of total. BMI: body mass index, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, FEF25-75: forced expiratory flow between 25% and 75% of FVC. P-values shown calculated by chi-squared for categorical variables and t-test for continuous variables.

Author Contributions

Conceived and designed the experiments: CMR FH SCE SEW. Performed the experiments: CMR FH. Analyzed the data: CMR FH. Wrote the paper: CMR FH SCE SEW. Contributed with participant recruitment: ERB WWB WJC MC AMF BG EI NNJ WCM SPP WGT KFC SCE SEW RS.

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