Role of FEF<sub>25-75</sub> in managing children with newly-diagnosed asthma in clinical practice

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Abstract. Background Reversible bronchial obstruction characterizes asthma. Spirometry is the gold standard to assess airflow, and FEV<sub>1</sub> is the most reliable parameter in this regard. However, many children with asthma have FEV<sub>1</sub> within the normal range despite uncontrolled asthma and worsening. Therefore, FEF<sub>25-75</sub> has been proposed as a valuable marker of early airflow impairment. This study aimed at investigating FEF<sub>25-75</sub> in a cohort of children with newly diagnosed asthma. Methods 381 children (122 females, mean age 11.6 years) were consecutively visited and had a new asthma diagnosis. In addition, Spirometry, type-2 phenotyping, asthma control assessment, and ACT were performed. Results 72 (18.9%) asthmatic children had impaired FEF<sub>25-75</sub>, such as <65% of predicted. Low FEF<sub>25-75</sub> was associated with lower FVC and FEV<sub>1</sub>/FVC values (OR 1.11 and 1.32, respectively). Children with normal FEV<sub>1</sub> but impaired FEF<sub>25-75</sub> had more frequently uncontrolled asthma (15.8% vs. 32.4%) than children with both parameters within the normal range. Conclusions FEF<sub>25-75</sub> deserves adequate and careful consideration in children with asthma, and the presence of impaired FEF<sub>25-75</sub> values suggests a more compelling approach. (www.actabiomedica.it)

Keywords: asthma, FEF<sub>25-75</sub>, FEV<sub>1</sub>, asthma control, clinical practice

Introduction

Asthma is the primary chronic disease in childhood as it affects about 10% of the pediatric population (1). Type-2 inflammation is the most common phenotype in children with asthma, and allergic rhinitis is frequent comorbidity (2). Consistently, anti-inflammatory medications, such as inhaled corticosteroids, are the most used therapy to achieve asthma control (3).

Reversible bronchial obstruction is the main functional characteristic of asthma (3). Therefore, spirometry is the gold-standard tool for detecting airflow limitation (4). In this regard, forced expiratory volume in one second (FEV<sub>1</sub>) is the most reliable marker of bronchial obstruction (5). However, FEV<sub>1</sub> often is within the normal range in the follow-up of asthmatic patients (6). Therefore, alternative parameters have been proposed to remedy this drawback, including the ratio between FEV<sub>1</sub> and the forced vital capacity (FVC). However, also FEV<sub>1</sub>/FVC is usually impaired in patients with overt obstruction (7). As a result, it has been proposed that the forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25-75</sub>) could be a reliable marker for revealing bronchial airflow impairment when FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are within the normal range (8).

In recent years, an ever-increasing body of evidence on this topic has been accumulating (9). In particular, it has been reported that FEF<sub>25-75</sub> can predict the development of chronic obstruction in subjects with lung function (10). In addition, a very...
recent study demonstrated that FEF_{25-75} was more sensitive at reflecting airway hyperresponsiveness, inflammation, and disease severity than FEV_{1} in adult patients with asthma (11). Consistently, the role of FEF_{25-75} as a reliable marker of bronchial obstruction has also been confirmed by pediatric studies (12-14).

Based on this background, the current study aimed at investigating the role of FEF_{25-75} in a cohort of children with a new diagnosis of asthma evaluated in clinical practice.

**Material and methods**

**Study design**

This cross-sectional study included children consecutively visited at a pediatric third-level allergy clinic for the first time. Primary care paediatricians sent all patients to confirm asthma diagnosis. The inclusion criterion was the asthma diagnosis, based on GINA criteria, including two key defining features: i) a history of respiratory symptoms, such as wheeze, breathlessness, cough, and chest tightness that vary over time and in intensity, and ii) variable expiratory airflow limitation (3).

The exclusion criteria were: lung disease other than asthma, recent asthma exacerbation, acute or chronic upper and/or lower respiratory infections.

The visit included careful history, clinical examination, lung function testing, self-administration of the children’s asthma control test (C-ACT) questionnaire, and asthma control assessment, according to the GINA guidelines (3). The methodological details were extensively described elsewhere (15). The local Ethics Committee approved the study (code number: 22253/2017).

**Functional assessment**

Spirometry was performed using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England – predictive values ECCS 1993), with an optoelectronic whirl flow meter. According to the guidelines, this spirometer fulfills the ATS/ERS standards, and it was performed as stated by the European Respiratory Society (16,17).

**Asthma control level**

Asthma control level was assessed according to the GINA criteria: patients were classified as having well-controlled, partly controlled, or uncontrolled asthma (3).

**Asthma control test**

Asthma control test (ACT) and cACT questionnaires consist of five questions with five possible responses, exploring the patient’s perception of his/her asthma control (18). The result could range between 0 and 25 or 27, where 25 or 27 is, respectively, the optimal asthma control (18,19).

**Type 2 phenotype**

The type 2 phenotype was defined if allergy was documented. Allergy was defined if the symptom occurrence was consistent with the exposure to the sensitizing allergen. In patients with seasonal conditions, the demonstration was simple. Instead, in patients with persistent conditions, children were asked if they developed symptoms when approaching a pet. Alternatively, when they exposed themselves to dust (opening a closet, doing housework, opening old books), they had symptoms (15).

**Statistical analysis**

Due to the nature of this study, no sample size justification was needed as no formal *a priori* hypothesis was tested.

As appropriate, the descriptive analysis of baseline characteristics was summarized as count and percentage, mean and standard deviation, and median with range.

Univariate logistic regression model was performed to detect factors significantly associated with impaired FEF_{25-75}. Covariates with p-value <0.10 were chosen as potential candidates for the subsequent multivariate model. The same statistical approach
(univariate and then multivariate) was used for analyzing factors predicting bronchial obstruction.

Odds ratio (OR) with the corresponding 95% confidence intervals (CI) were reported to show the strength of the associations. The significance level (alpha error) was set at .05. SPSS v.24 was used for computation.

Results

This study included 381 children (122 females and 259 males; mean age 11.6 years). The main demographic and clinical outcomes are reported in Table I. Seventy-two (18.9%) children had impaired FEF$_{25-75}$ values, such as $<$65% of predicted, and 46 (12.1%) had overt bronchial obstruction, defined by FEV$_1$ <80% of predicted. Type-2 phenotype characterized 95% of children; asthma was well-controlled in 56.4% of children and partly controlled in 31.8%, but uncontrolled in 11.8%. Stratifying patients with FEF$_{25-75}$ impaired or normal values, children with abnormal FEF$_{25-75}$ had median lower FEV$_1$, (80.0 vs 99.0) FVC (93.0 vs 99.1), FEV$_1$/FVC values (88.0 vs 101.0), higher frequency of bronchial obstruction (47.2% vs 3.9%), and uncontrolled asthma (23.6% vs 9.1%) than children with normal FEF$_{25-75}$. In particular, there was an association between impaired FEF$_{25-75}$ and low FVC (OR: 1.11, 95%CI: 1.07 – 1.15; $p$ < 0.001) and FEV$_1$/FVC values (OR:1.32, 95%CI: 1.24 – 1.42; p<0.001) (Table I).

Considering only children with normal FEV$_1$ (N=335), such as without overt obstruction, the

| Table I | Demographic and clinical characteristics in children with asthma, in the global population and in patients with impaired (<65% of predicted) or normal FEF$_{25-75}$. |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | Total N = 381                                                                                                                                          | Impaired N = 72 | Normal N = 309                                                                 | Univariate* | Multivariate** |
| Sex     |                                                                                                                                                    |                |                                                                                                                                   |            |               |
|         | Females                                                                                                                                            | 122 (32.0)     | 21 (29.2)                                                                                                                          | 0.56       |               |
|         | Males                                                                                                | 259 (68.0)     | 51 (70.8)                                                                                                                          |            |               |
| Age, years |                                                                                                                                                    | 11.6 ± 2.94    | 11.5 ± 2.67                                                                                                                        | 0.58       |               |
| BMI (kg/m$^2$) |                                                                                                                                                    | 19.9 ± 4.07    | 19.2 ± 3.55                                                                                                                        | 0.10       |               |
| FEV$_1$ (% of predicted) |                                                                                                                                                    | 96.0 (51.0 - 142.0) | 80.0 (61.0 - 105.0)                                                                 | < 0.001    |               |
|         | Bronchial Obstruction                                                                                                                                  | 335 (87.9)     | 38 (52.8)                                                                                                                          | < 0.001    |               |
|         | FEV1 ($\geq$ 80%)                                                                                                                                     | 46 (12.1)      | 12 (3.9)                                                                                                                            |            |               |
|         | FEV1 ($< 80\%$)                                                                                                                                       | 86.0 (1.8 - 166.0) | 50.5 (1.8 - 64.5)                                                                 | 0.39       |               |
| FVC (% of predicted) |                                                                                                                                                    | 98.9 (71.2 - 122.1) | 88.0 (71.2 - 104.2)                                                                 | < 0.001    | 1.11 (1.07 - 1.15), <0.001 |
| FEV$_1$/FVC |                                                                                                                                                    | 98.0 (60.0 - 141.0) | 93.0 (70.0 - 124.0)                                                                 | < 0.001    | 1.32 (1.24 - 1.42), <0.001 |
| FEF$_{25-75}$ (% of predicted) |                                                                                                                                                    | 86.0 (1.8 - 166.0) | 50.5 (1.8 - 64.5)                                                                 | 0.002      |               |
|         | Type-2 phenotype No                                                                                                                                  | 19 (5.0)       | 5 (7.0)                                                                                                                            | 0.39       |               |
|         | Yes                                                                                                                                                | 360 (95.0)     | 66 (93.0)                                                                                                                          |            |               |
| Asthma control (GINA) | Well-controlled                                                                                                                                       | 215 (56.4)     | 34 (47.2)                                                                                                                          | 0.002      |               |
|         | Partly controlled                                                                                                                                   | 121 (31.8)     | 21 (29.2)                                                                                                                          |            |               |
|         | Uncontrolled                                                                                                                                       | 45 (11.8)      | 17 (23.6)                                                                                                                          |            |               |
| Childhood Asthma Control Test (adjusted age) |                                                                                                                                                    | 21.2 ± 4.10    | 20.0 ± 4.93                                                                                                                        | 0.06       |               |

Impaired: FEF$_{25-75}$ <65%; Normal: FEF$_{25-75}$ $\geq$65%  
* $p$ value  
** OR (95% CI), $p$ value
comparison between subjects with impaired or normal FEF$_{25-75}$ showed that children with low FEF$_{25-75}$ had lower BMI (18.7 vs 20.0), FEV$_1$ (89.0 vs 100.0), FEV$_1$/FVC (88.9 vs 101.0) than children with normal FEF$_{25-75}$. In particular, children with normal FEV$_1$ but impaired FEF$_{25-75}$ had higher odds of having low BMI (OR: 1.13, 95%CI: 1.01 – 1.26; p = 0.043) and FEV$_1$/FVC (OR: 1.23, 95%CI: 1.15 – 1.31; p <0.001) (Table II).

Notably, all children with impaired FEF$_{25-75}$ but normal FEV$_1$ had type-2 phenotype.

Discussion

Spirometry is a mandatory examination for diagnosis asthma and thoroughly managing patients with asthma. Even if FEV$_1$ and FEV$_1$/FVC are reliable markers of bronchial obstruction, there is growing interest in the diagnostic and prognostic role of FEF$_{25-75}$ in practical asthma management (20).

The current study investigated the role of FEF$_{25-75}$ in a cohort of children with a new diagnosis of asthma. It is interesting to note that only 12% of children present overt obstruction, such as FEV$_1$ <80% of predicted values, at the moment of the diagnostic workup. This outcome underlines the need to implement the tools to accomplish asthma diagnosis. Moreover, the type-2 phenotype affects almost all children (95%), but asthma is well-controlled only in 56% of children. This finding underscores the relevance of this issue and requires adequate attention in clinical practice. Stratifying asthmatic children by FEF$_{25-75}$ values, children with impaired FEF$_{25-75}$ had lower spirometry

| Total N = 335 | Impaired N = 38 | Normal N = 297 | Univariate* | Multivariate** |
|---------------|----------------|----------------|-------------|---------------|
| Sex Femaless | Females 107 (31.9) | 11 (28.9) | 96 (32.3) | 0.67          |
| Sex Masles   | Males 228 (68.1) | 27 (71.1) | 201 (67.7) |              |
| Age, years   | 11.7 ± 2.94 | 11.7 ± 2.58 | 11.7 ± 2.99 | 0.86          |
| BMI (kg/m^2) | 19.9 ± 3.87 | 18.7 ± 3.54 | 20.0 ± 3.89 | 0.048         |
| FVC (% of predicted) | 100.0 (76.0 - 141.0) | 100.5 (82.0 - 124.0) | 100.0 (76.0 - 141.0) | 0.86          |
| FEV$_1$ (% of predicted) | 89.0 (80.0 - 105.0) | 89.0 (80.0 - 105.0) | 100.0 (80.0 - 142.0) | <0.001^      |
| FEV$_1$/FVC | 100.0 (78.2 - 122.1) | 88.9 (78.2 - 102.3) | 101.0 (81.5 - 122.1) | <0.001         |
| FEF$_{25-75}$ (% of predicted) | 89.0 (1.8 - 166.0) | 57.0 (1.8 - 64.5) | 92.0 (65.0 - 166.0) | //            |
| Type-2 phenotype | No 14 (4.2) | 0 (0.0) | 14 (4.7) | 0.17          |
| Asthma control (GINA) | Controlled 320 (95.8) | 38 (100.0) | 282 (95.3) |              |
| Childhood Asthma Control Test (adjusted age) | 21.4 ± 4.00 | 20.4 ± 5.37 | 21.5 ± 3.78 | 0.73          |

Impaired: FEF$_{25-75}$ <65%; Normal: FEF$_{25-75}$ ≥65%

*p value

**OR (95% CI), p value

^ FEV$_1$ at baseline was not considered as an independent variable in the multivariate logistic regression model due to its high collinearity with FEV$_1$/FVC at baseline.
parameters than children with normal FEF$_{25-75}$ and more frequently uncontrolled asthma. These results were confirmed after excluding children with overt bronchial obstruction, such as with impaired FEV$_1$ values. Namely, children with impaired FEF$_{25-75}$ but normal FEV$_1$ had lower FEV$_1$ and, interestingly, FEV$_1$/FVC values than children with both FEF$_{25-75}$ and FEV$_1$ within the normal range. Notably, all children with impaired FEF$_{25-75}$ were allergic. Examining in-depth the 72 children with impaired FEF$_{25-75}$, 38 of them had normal FEV$_1$ values. These subjects deserve greater attention as they will usually be approached with lesser caution than children with overt bronchial obstruction. Even though lung function is normal, the percentage of children with uncontrolled asthma (15.8%) is higher than in the total population (11.8%) of new-diagnosed children. In appearance, the difference seems to be slight, but, considering the high prevalence of asthma in the general population, such as about 10%, this number becomes relevant.

These data confirm the clinical relevance of FEF$_{25-75}$ as sustained by a series of studies that have been conducted both in asymptomatic subjects, in asthmatics, and in AR patients. Indeed, reduced FEF$_{25-75}$ value might precede FEV$_1$ impairment, indicating early asthma and poor prognosis in current asthma (7,21). Furthermore, in AR, reduced FEF$_{25-75}$ was associated with bronchial hyperreactivity, positive response to bronchodilation testing, and increased fractional exhaled nitric oxide (22-24). Thus, it was proposed that reduced FEF$_{25-75}$ might be a surrogate functional marker of early bronchial involvement in AR, such as impaired FEF$_{25-75}$ could predict the asthma development in patients suffering from AR. So, it has been concluded that abnormal FEF$_{25-75}$ might be considered an early marker of airflow limitation related to eosinophilic inflammation, suggesting a role for impaired FEF$_{25-75}$ as a predictive marker of newly diagnosed asthma. In addition, all children with impaired FEF$_{25-75}$ and normal FEV$_1$ were allergic. This finding was consistent with a previous study, conducted on Navy cadets, that demonstrated that impaired FEF$_{25-75}$ may predict (OR 7.43) sensitization and allow early identification of subjects with subclinical asthma (25).

The present study has some limitations, including the cross-sectional design, the lack of measuring inflammatory biomarkers, mainly concerning the FeNO assessment, and the assessment of few clinical data. Actually, FeNO is a reliable biomarker for type 2 phenotype and has many applications in pediatric asthma (26).

However, the population was homogeneous as composed of children with a new diagnosis of asthma. Therefore, the outcomes may highlight the role of FEF$_{25-75}$ as an early marker of asthma worsening.

**Conclusions**

FEF$_{25-75}$ deserves adequate and careful consideration in children with asthma, and the presence of impaired FEF$_{25-75}$ values suggests a more compelling approach.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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