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Original article

Role of FEF_{25-75} 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_1 is the most reliable parameter in this regard. However, many children with asthma have FEV_1 within the normal range despite uncontrolled asthma and worsening. Therefore, FEF_{25-75} has been proposed as a valuable marker of early airflow impairment. This study aimed at investigating FEF_{25-75} 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_{25-75}, such as <65% of predicted. Low FEF_{25-75} was associated with lower FVC and FEV_1/FVC values (OR 1.11 and 1.32, respectively). Children with normal FEV_1 but impaired FEF_{25-75} had more frequently uncontrolled asthma (15.8% vs. 32.4%) than children with both parameters within the normal range. *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. (www.actabiomedica.it)

Key words: asthma, FEF_{25-75}, FEV_1, 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_1) is the most reliable marker of bronchial obstruction (5). However, FEV_1 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_1 and the forced vital capacity (FVC). However, also FEV_1/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_{25-75}) could be a reliable marker for revealing bronchial airflow impairment when FEV_1 and FEV_1/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_{25-75} 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 paediatric 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)	101 (32.7)	0.56	
	Males	259 (68.0)	51 (70.8)	208 (67.3)		
Age, years		11.6 ± 2.94	11.5 ± 2.67	11.7 ± 3.01	0.58	
BMI (kg/m^2)		19.9 ± 4.07	19.2 ± 3.55	20.1 ± 4.18	0.10	
FEV_1 (% of predicted)		96.0 (51.0 - 142.0)	80.0 (61.0 - 105.0)	99.0 (51.0 - 142.0)	< 0.001	
Bronchial Obstruction	**FEV1 (≥ 80%)**	335 (87.9)	38 (52.8)	297 (96.1)	< 0.001	
	FEV1 (< 80%)	46 (12.1)	34 (47.2)	12 (3.9)		
FVC (% of predicted)		98.0 (60.0 - 141.0)	93.0 (70.0 - 124.0)	99.1 (60.0 - 141.0)	< 0.001	1.11 (1.07 - 1.15), <0.001
FEV_1/FVC		98.9 (71.2 - 122.1)	88.0 (71.2 - 104.2)	101.0 (76.6 - 122.1)	< 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)**	**92.0 (65.0 - 166.0)**		
Type-2 phenotype	**No**	19 (5.0)	5 (7.0)	14 (4.5)	0.39	
	Yes	360 (95.0)	66 (93.0)	294 (95.5)		
Asthma control (GINA)	**Well-controlled**	215 (56.4)	34 (47.2)	181 (58.6)	0.002	
	Partly controlled	121 (31.8)	21 (29.2)	100 (32.4)		
	Uncontrolled	45 (11.8)	17 (23.6)	28 (9.1)		
Childhood Asthma Control Test (adjusted age)		21.2 ± 4.10	20.0 ± 4.93	21.5 ± 3.84	0.06	

Impaired: FEF_{25_75} <65%; Normal: FEF_{25_75} ≥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

Table II Demographic and clinical characteristics in children without overt bronchial obstruction (defined by <80% of predicted), in the global population and in patients with impaired or normal FEF_{25-75}.

		Total N = 335	Impaired N = 38	Normal N = 297	Univariate*	Multivariate**
Sex	**Females**	107 (31.9)	11 (28.9)	96 (32.3)	0.67	
	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	1.13 (1.01 – 1.26), 0.043
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)	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	1.23 (1.15 – 1.31), <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	
	Yes	320 (95.8)	38 (100.0)	282 (95.3)		
Asthma control (GINA)	**Controlled**	304 (90.7)	32 (84.2)	272 (91.6)	0.14	
	Uncontrolled	31 (9.3)	6 (15.8)	25 (8.4)		
Childhood Asthma Control Test (adjusted age)		21.4 ± 4.00	20.4 ± 5.37	21.5 ± 3.78	0.73	

Impaired: FEF25_75 <65%; Normal: FEF25_75 ≥65%

** p value*

*** OR (95% CI), p value*

^ FEV1 at baseline was not considered as an independent variable in the multivariate logistic regression model due to its high collinearity with FEV1/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, FEV1/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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