FEF$_{25-75}$ and Asthma in Clinical Practice

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There is growing interest about the practical role exerted by forced expiratory flow between 25% and 75% of forced vital capacity (FEF$_{25-75}$), mainly as potential surrogate marker for small airways.[1] A recent robust longitudinal study evidenced an association among low FEF$_{25-75}$, long-term asthma persistence, and poor asthma outcomes independently of FEV$_1$.[2] Actually, it is known that the main limitation with FEF$_{25-75}$ is a low reproducibility, but it could be partially compensated for correct technique and well-trained staff.

There is evidence that FEF$_{25-75}$ may have a clinical relevance especially when FEV$_1$ values are normal.[3] Indeed, it has been proposed that reduced FEF$_{25-75}$ might precede FEV$_1$ impairment, so indicating early disease and poor prognosis.[4] Allergic rhinitis (AR) model is paradigmatic as it is a main risk factor for asthma onset. Indeed, it has been reported that reduced FEF$_{25-75}$ values (defined as <65% of predicted in this series of studies) were associated with bronchial hyperreactivity,[5] positive response to bronchodilation testing,[6] and increased fractional exhaled nitric oxide[7] in AR patients. Thus, reduced FEF$_{25-75}$ might be a surrogate functional marker of early bronchial involvement in AR. More recently, it has been also reported that impaired FEF$_{25-75}$, such as <65% of

predicted, is associated with airway inflammation in subjects with asthma-like symptoms.[8] 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 FEF$_{25-75}$ as a predictive marker of newly diagnosed asthma.

The present study concerned a group of 602 asthmatics (355 females, mean age 40.05 ±16.3 years), consecutively evaluated. The aim was to evaluate the possible impact of reduced FEF$_{25-75}$ (evaluated as continuous variable) on some parameters (including: lung function, perception of respiratory symptoms assessed by the visual analogue scale (VAS), age, gender, body mass index (BMI), current bronchial and/or nasal symptoms, rhinitis comorbidity, asthma control grade, ACT, FeNO, and anxiety and depression assessed by HADS). The study conformed to the ethic criteria concerning the management of clinical data, all patients gave a written informed consent.

Data were acquired and analysed by R 3.3.3 software environment (R: A Language and Environment for Statistical Computing. Vienna, Austriahttps://www.R-project.org).

The FEF$_{25-75}$ significantly impacted on: asthma control grade, presence of current symptoms, rhinitis comorbidity, early onset, age, BMI, FVC, FEV$_1$, FEV$_1$/FVC, and VAS (data not showed; *p*-values<0.05). Briefly, a FEF$_{25-75}$ one-unit increase was associated with decreased chances 2% and 3% of having partially controlled and uncontrolled asthma grade respectively (OR(95%C.I.)= 0.98 (0.98: 0.99), and 0.97 (0.96: 0.98), respectively). Regarding rhinitis comorbidity and early onset outcomes, a FEF$_{25-75}$ one-

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unit increase was associated with increased chances 2% and 3% of having rhinitis comorbidity and early onset (OR (95%C.I.)=1.02 (1.01: 1.03), and 1.03 (1.02:1.04), respectively). Moreover, a one-unit increase in FEF_{25-75} value was also linked with decreased chances 2% and 1% of having current asthma and asthma+rhinitis symptoms respectively (OR (95%C.I.)=:.98 (0.98:0.99), and 0.99 (0.98:0.99), respectively). A one-unit increase in FEF_{25-75} value was also associated with a 21%, 49%

25% and 2% increase of FVC, FEV_1, FEV_1/FVC and VAS (β: 0.21, 0.49, 0.25 and 0.02, respectively). It was also observed that a one-unit increase in FEF_{25-75} value was linked with a 19% and 3% decrease of age and BMI (β:-0.19, and -0.03, respectively).

Considering the 568 (94.4%) patients with normal FEV_1 value, such as$\geq$80% of predicted, FEF_{25-75} significantly impacts on asthma control grade, age, FEV_1, FEV_1/FVC, and VAS (Table 1).

Table 1. Impact of the FEF25-75 (as predictor variable) effect on the demographic and clinical characteristics in patients with normal FEV1 (such as > 80% of predicted)

Outcome		FEF_{25-75}	Regression analysis		
Characteristic	Total	Mean(SD) or Rho	Estimate (95%CI)	Unadjusted *p*-value	*p*-value
Asthma control-GINA				0.0021	0.0318
Well Controlled	51.83%	82.14 (23.51)	1		
Partially Controlled	40.84%	77.94 (26.09)	0.99 (0.99 - 1.01) §		
Uncontrolled	7.33%	67.78 (19.4)	0.97 (0.96 - 0.99) §		
Gender				0.1302	1.0000
Male	37.83%	81.78 (24.81)	1		
Female	62.17%	78.28 (24.19)	0.99 (0.98 : 1.01) ◊		
Current symptoms				0.0228	0.3414
None	25.44%	85.07 (24.07)	1		
Asthma	18.33%	75.93 (26.41)	0.99 (0.98 – 1.01) §		
Rhinitis	16.01%	77.93 (26.61)	0.98 (0.97 - 1.01) §		
Asthma + Rhinitis	40.21%	78.08 (22.44)	0.99 (0.98 - 1.01) §		
Diagnosis				0.0149	0.2234
Asthma alone	29.73%	74.65 (22.72)	1		
Asthma + Rhinitis	70.27%	80.97 (24.85)	1.01 (1.00 : 1.02)		
Early Onset				0.0176	0.2635
No	34.07%	74.6 (25.9)	1		
Yes	65.93%	83.58 (24.44)	1.02 (1 - 1.03) ◊		
Age	39.11 (16.08)	rho = -0.27	-0.18 (-0.24 : -0.12) *	<0.0001	<0.0001
FeNO	33.04 (25.62)	rho = -0.05	-0.05 (-0.19 : 0.09) *	0.5069	1.0000
ACT	20.12 (4.29)	rho = 0.05	0.01 (-0.01 : 0.02) *	0.2566	1.0000
BMI	24.67 (4.79)	rho = -0.14	-0.03 (-0.04 : -0.01) *	0.0054	0.0807
FVC	106.5 (14.69)	rho = 0.02	0.01 (-0.04 : 0.06) *	0.6844	1.0000
FEV_1	99.63 (12.32)	rho = 0.56	0.29 (0.25 : 0.32) *	<0.0001	<0.0001
FEV_1/FVC	82.18 (10.19)	rho = 0.48	0.19 (0.16 : 0.22) *	<0.0001	<0.0001
VAS	7.49 (1.71)	rho = 0.23	0.01 (0.01 : 0.02) *	0.0001	0.0019
HADS-A	6.38 (4.02)	rho = 0.07	0.01 (-0.01 : 0.03) *	0.2615	1.0000
HADS-D	3.58 (2.75)	rho = -0.06	0.01 (-0.01 : 0.02) *	0.3723	1.0000

The FEF_{25-75} effect on the demographic and clinical characteristics in patients with normal FEV1 were assayed using logistic or nominal multinomial regression for categorical outcomes and linear regression analysis for continuous outcomes. The estimated *p*-values were adjusted for multiple comparisons by the Bonferroni correction method. Characteristics=outcome considered; Total=Outcome descriptive statistics, % and mean with standard deviation were reported for categorical and continuous outcome, respectively. FEF_{25-75}=FEF_{25-75} mean with standard deviation in the levels of categorical outcomes and Pearson's correlation coefficient (Rho) among FEF_{25-75} and continuous outcomes were showed. Estimate (95%CI)=linear regression coefficient with 95% Confidence Interval (marked with *) and odd ratios, estimated using logistic (marked with ◊) or multinomial (marked with §) regression, were reported; Unadjusted *p*-value=the Likelihood Ratio p-value; p-value = the Likelihood Ratio p-value adjusted for multiple comparisons by the Bonferroni correction method.

In particular, a FEF$_{25-75}$ one-unit increase was associated with decreased chances 3% of having uncontrolled asthma grade (OR=0.97). Moreover, a one-unit increase in FEF$_{25-75}$ value was linked with a 29%, 19% and 1% increase of the FEV$_1$, FEV$_1$/FVC and VAS score (β: 0.29, 0.19, and 0.01, respectively). It was also observed that, a one-unit increase in FEF$_{25-75}$ value was associated with an 18% decrease of the age (β=-0.18).

Therefore, the current real-life experience confirms the clinical relevance of FEF$_{25-75}$ assessment in asthmatics. Really, low FEF$_{25-75}$ values may suggest an asthma poor outcome, concerning symptoms, control level, and lung function. Notably, low FEF$_{25-75}$ is associated with uncontrolled asthma and seldom may it be the only impaired functional parameters. Overall, considering patients with normal FEV$_1$ (such as the gold standard functional parameter) values, low FEF$_{25-75}$ is associated with uncontrolled-partially controlled asthma and symptom perception severity.

Thus, even though FEF$_{25-75}$ data are not robust and does not contribute usefully to clinical decision making over and above information from FEV$_1$, FVC, FEV$_1$/FVC ratio, and the flow/volume loop,[9] a low FEF$_{25-75}$ value could induce the suspect that the patient is not well controlled, in other words it might be considered as a warning light. On the other hand, our experience has a main limitation: the cross-sectional study design, so further longitudinal real life studies should be performed to confirm the prognostic role of FEF$_{25-75}$ in the common practice.

We believe that FEF$_{25-75}$ may deserve an adequate and careful consideration in patients with asthma and/or allergic rhinitis as low values can add fruitful information about asthma control assessment, mainly when FEV$_1$ is normal.

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