

# Role of FEF<sub>25-75</sub> as an early marker of bronchial impairment in patients with seasonal allergic rhinitis

Giorgio Ciprandi, M.D.,\* Ignazio Cirillo, M.D.,# Catherine Klersy, M.D.,§  
Gian Luigi Marseglia, M.D.,¶ Andrea Vizzaccaro, M.D.,# Eugenio Pallesi, M.D.,\* and  
Mariangela Tosca, M.D.¶ (Italy)

## ABSTRACT

**Background:** Allergic rhinitis may be associated with asthma. Forced expiratory flow between 25 and 75% of vital capacity (FEF<sub>25-75</sub>) is a measure of small airways narrowing. The aim of this study was to evaluate whether patients with seasonal allergic rhinitis (SAR) without symptoms of asthma might, nevertheless, have airways obstruction both in and out of the pollen season.

**Methods:** Fifty patients (mean age, 23.7 ± 4.9 years) with SAR were evaluated both during and outside the pollen season. All of them had moderate-severe grade of nasal obstruction. Total symptom score, rhinomanometry, nasal lavage, nasal scraping, spirometry, and methacholine (MCH) bronchial challenge were assessed in all subjects.

**Results:** Although data on forced vital capacity and response to MCH were similar in and out of the pollen season, all other parameters were markedly different. The major finding of the study was that FEF<sub>25-75</sub> was significantly associated with nearly all of the parameters considered, including bronchial hyperreactivity, with Pearson R ranging from 31 to 75% and differences in mean FEF<sub>25-75</sub> ranging between 14.5 and 16.5% of predicted. The more significant association was with nasal airflow in the pollen season (R = 82.8%; p < 0.001). A significant association persisted for all parameters while controlling for season.

**Conclusion:** This study highlights the link between upper and lower airways and the role of FEF<sub>25-75</sub> as an early marker of bronchial impairment in those patients with SAR alone.

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Airway inflammation may be considered a *condicio sine qua non* of allergic rhinitis.<sup>1</sup> Infiltration by inflammatory cells, including T cells, mast cells, and eosinophils, characterizes the immunopathology of allergic inflammation.<sup>2</sup> The cytokine pattern is characterized typically by a Th2 polarization.<sup>3</sup> Th2-derived cytokines account for recruiting and activating eosinophils in the airways: actually, eosinophil infiltration may be considered as a reliable marker of allergic inflammation.<sup>3</sup>

Moreover, a close link between upper and lower airways is well known.<sup>4</sup> In this regard, we previously reported that 77% of conscripts with respiratory allergy suffered from allergic rhinitis and asthma.<sup>5</sup> In addition, a bronchial involvement, including slight airflow limitation and hyperreactivity, may be detected in patients with rhinitis who only perceived nasal symptoms.<sup>6</sup>

Asthma is defined as chronic inflammation of lower airways<sup>7</sup> and inflammatory infiltration also is well documented in the nasal mucosa of patients with allergic rhinitis.<sup>8</sup> Allergic airway inflammation may induce airflow limitation both at nasal and bronchial levels. In particular, nasal obstruction may be evaluated assessing both subjective complaints, using symptom severity score rating, and nasal airflow, performing active anterior rhinomanometry. On the other hand, bronchial airflow obstruction may be investigated by spirometry. Moreover, bron-

chial hyperreactivity (BHR) is a pathophysiological feature of asthma and may be evaluated by nonspecific challenge.

The forced expiratory flow between the 25 and 75% of the vital capacity (FEF<sub>25-75</sub>) measures the average flow of air through the middle lung volumes. However, FEF<sub>25-75</sub> has been shown to be more variable and less reproducible than forced expiratory volume at 1 second (FEV<sub>1</sub>) because it is influenced by changes in lung volume and the shape of the flow-volume loop and is only partially corrected by calculating flow rates at isovolume.<sup>9</sup> Moreover, because full vital capacity may not be delivered in a forced expiratory maneuver in the presence of severe airway obstruction, FEF<sub>25-75</sub> may underestimate the degree of airway obstruction. On the other hand, recently, it has been shown that FEF<sub>25-75</sub> is useful in predicting the presence of airway responsiveness.<sup>10</sup> In addition, it has been reported that asthmatic children without symptoms had decreased FEF<sub>25-75</sub> in a larger proportion of patients than peak expiratory flow rate or FEV<sub>1</sub>, suggesting that FEF<sub>25-75</sub> is a more sensitive indicator of chronic airflow obstruction.<sup>11</sup> Bahceciler provided further evidence that a low FEF<sub>25-75</sub> is a risk factor for the persistence of respiratory symptoms in allergic children with asthma.<sup>12</sup> Fonseca-Guedes showed that FEF<sub>25-75</sub> can decrease in response to exercise without changes in FEV<sub>1</sub>, mainly in children with mild asthma, whereas the agreement between FEV<sub>1</sub> and FEF<sub>25-75</sub> changes is greater in more severe forms of asthma.<sup>13</sup> Finally, we recently provided evidence that FEF<sub>25-75</sub> is frequently impaired in patients suffering from allergic rhinitis alone.<sup>14</sup> For these reasons, the aim of this study was to evaluate whether patients with SAR without symptoms of asthma might, nevertheless, have airways obstruction both in and out of the pollen season.

From the \*Azienda Ospedaliera Universitaria San Martino, Genoa, Italy, #Ospedale Marina Militare, La Spezia, Italy, §Servizio di Biometria ed Epidemiologia Clinica-Direzione Scientifica, IRCCS Policlinico San Matteo, Pavia, Italy, ¶Clinica Pediatrica, IRCCS Policlinico San Matteo, Pavia, Italy, and ||Istituto Giannina Gaslini, Genoa, Italy

Address correspondence and reprint requests to Giorgio Ciprandi, M.D., Allergologia-U.O. ORL, Dipartimento Patologie Testa-Collo, Padiglione Specialità (piano terzo), Ospedale San Martino, Largo R. Benzi 10, 16132 Genoa, Italy  
E-mail address: gio.cip@libero.it

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## MATERIALS AND METHODS

### Study Design

This study was performed during the pollen season (*i.e.*, spring) and out of the pollen season (*i.e.*, winter, the season without pollens in our geographic area).<sup>5</sup> We included subjects with allergic rhinitis due to pollen allergens only. All of them were evaluated performing skin-prick test, rhinomanometry, nasal lavage and scraping, spirometry, and methacholine (MCH) bronchial challenge during the pollen season (spring). All of them were reevaluated outside the pollen season. The study was approved by the Navy Hospital Review Board and an informed consent was obtained from all patients.

### Subjects

Fifty subjects with seasonal allergic rhinitis (SAR) were prospectively and consecutively evaluated (all men; mean age,  $23.7 \pm 4.9$  years). All of them were Navy soldiers who referred to the Navy Hospital for periodic fitness visits. A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study based on a clinical history of SAR and presence of moderate or severe nasal obstruction. All patients were sensitized to pollens only (*i.e.*, *Parietaria judaica*, grasses, olive trees, birch, and hazel). We excluded all subjects who met the following exclusion criteria: any prior history of asthma; sensitization to perennial allergens; acute or chronic upper respiratory infections; anatomic nasal disorders (*i.e.*, nasal polyps, septum deviation, etc.); previous or current smoking; previous or current specific immunotherapy; and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, and antihistamines during the previous 4 weeks. The diagnosis of SAR was made based on a history of nasal symptoms and positive skin-prick test for pollens according with validated criteria.<sup>15</sup> Skin-prick tests were performed as stated by the European Academy of Allergy and Clinical Immunology.<sup>16</sup>

Nasal symptoms were assessed by the patient, answering questions made by the investigator regarding nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated according to the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Total symptom score (TSS) being the sum of each individual symptom was considered also.

Active anterior rhinomanometry (ZAN 100 Rhino; ZAN, Messgeraete GmbH, Germany) was used to measure nasal airflow considered as the sum of the airflow through the right and left nostrils in milliliters per second at a pressure difference of 150 Pa across the nasal passage. Details are reported elsewhere.<sup>17,18</sup>

Spirometry was performed with a computer-assisted spirometer (Pulmolab 435-spiro 235; Pulmolab, Morgan, England) and according to international guidelines.<sup>7,9,19</sup> Briefly, 3 blows (every 5 minutes) were performed and the best result was considered. All subjects met the criteria for reproducibility and acceptability.

Table 1 Population characteristics in and out of pollen season

| Variable*            | In Pollen Season | Out of Pollen Season | p Value |
|----------------------|------------------|----------------------|---------|
| FEF <sub>25-75</sub> | 88.3 (13.3)      | 94.6 (11.1)          | 0.011   |
| FEV <sub>1</sub>     | 97.9 (10.7)      | 101.9 (9.1)          | 0.049   |
| FVC                  | 97.2 (8.6)       | 98.5 (6.6)           | 0.399   |
| Eosinophils          | 10.5 (3.9)       | 5 (10%)#             | —       |
| Neutrophils          | 21.3 (5.9)       | 26 (52%)#            | —       |
| IL-4                 | 10.2 (3.1)       | 3.3 (1.2)            | <0.001  |
| IL-5                 | 6.5 (1.7)        | 2.9 (1.1)            | <0.001  |
| IL-8                 | 662.2 (119.8)    | 346.9 (74.4)         | <0.001  |
| IFN- $\gamma$        | 1.6 (0.6)        | 7.7 (2.1)            | <0.001  |
| TSS                  | 9.5 (1.6)        | 0.4 (0.7)            | <0.001  |
| Nasal flow           | 482.5 (111.4)    | 672.8 (79.4)         | <0.001  |
| Obstruction score    |                  |                      |         |
| 0                    | 0 (0%)           | 44 (88%)             | <0.001  |
| 1                    | 0 (0%)           | 4 (8%)               |         |
| 2                    | 24 (48%)         | 2 (4%)               |         |
| 3                    | 26 (52%)         | 0 (0%)               |         |
| MCH positivity       | 26 (54%)         | 27 (54%)             | 1.000   |

\*Mean and SD reported for continuous variables; N and (%) for categorical variables

#Out of pollen season, because of their extremely low number, both eosinophils and neutrophils were rated as present/absent.

MCH challenge was performed by administering MCH using a dosimetric computerized apparatus (MEFAR MB3; Marcos-Mefar SpA, Italy), activated by inhalation. Subjects inhaled increasing doses of MCH, starting from 30  $\mu\text{g/mL}$ . The scheduled doses consisted of the following 11 steps: 30, 30, 30, 60, 90, 150, 150, 150, 300, 300, and 300  $\mu\text{g/mL}$  as previously reported.<sup>5,6,14</sup> The procedure was stopped when FEV<sub>1</sub> value was reduced by  $\geq 20\%$  of the baseline value or a maximal cumulative dose of 1590  $\mu\text{g}$  was achieved. A computerized algorithm calculated the threshold provoking dose causing a 20% fall of FEV<sub>1</sub> (PD<sub>20</sub>/FEV<sub>1</sub>). If no response was obtained with the maximal cumulative dose of 1590  $\mu\text{g}$ , the test was considered negative.

Nasal cytological specimens were obtained by scraping the head of the inferior turbinate with a cotton swab. Smears were stained and read as described in previous reports.<sup>17,18</sup> Nasal lavage was performed using 5 mL of physiological saline, according to standard methods described elsewhere.<sup>17,18</sup> Cytokine assessment included IL-4, IL-5, IL-8, and IFN- $\gamma$ . The cytokines were measured with ELISA method (R & D Systems, Minneapolis, MN) according to a procedure previously reported.<sup>17,18</sup>

### Statistical Analysis

Descriptive statistics were computed as mean and SD for continuous variables and as absolute frequency and percentage for categorical variables. Comparison between seasons

Table 2 Results of general linear regress models for the association of FEF<sub>25-75</sub> with nasal parameters

| Variable                      | Univariate Analysis  |                |                                 |                | Bivariate Analysis                                  |                                                              |
|-------------------------------|----------------------|----------------|---------------------------------|----------------|-----------------------------------------------------|--------------------------------------------------------------|
|                               | In Pollen Season*    | <i>p</i> Value | Out of Pollen Season*           | <i>p</i> Value | Association Independent of Season ( <i>p</i> Value) | Different effect in/out Season (Interaction; <i>p</i> Value) |
| Eosinophil                    | −74.6% (−84.8/−59.0) | <0.001         | −16.5 (−26.0/−6.9) <sup>1</sup> | 0.001          | —                                                   | —                                                            |
| Neutrophil                    | −23.8% (−48.4/4.4)   | 0.096          | −4.3 (−10.6/1.9)§               | 0.172          | —                                                   | —                                                            |
| IL-4                          | −50.7% (−66.8/−26.6) | <0.001         | −56.6% (−72.9/−34.1)            | <0.001         | Yes (<0.001)                                        | Yes (0.027)                                                  |
| IL-5                          | −75.3% (−85.3/−60.1) | <0.001         | −49.1% (−67.7/−24.6)            | <0.001         | Yes (<0.001)                                        | No (0.557)                                                   |
| IL-8                          | −31.3% (−54.4/−3.8)  | 0.027          | −41.4% (−62.1/−15.4)            | 0.003          | Yes (<0.001)                                        | No (0.296)                                                   |
| IFN- $\gamma$                 | 70.0% (52.3/81.9)    | <0.001         | 35.9% (8.9/57.9)                | 0.010          | Yes (<0.001)                                        | Yes (<0.001)                                                 |
| TSS                           | −75.0% (−85.1/−59.7) | <0.001         | −35.6% (−57.7/−8.7)             | 0.011          | Yes (<0.001)                                        | No (0.742)                                                   |
| Nasal flow                    | 82.8% (71.5/89.9)    | <0.001         | 31.0% (3.5/54.2)                | 0.028          | Yes (<0.001)                                        | Yes (<0.001)                                                 |
| Obstruction symptoms          | −15.9 (−22.0/−9.8)¶  | <0.001         | −17.4 (−25.8/−8.9)              | <0.001         | —                                                   | —                                                            |
| MCH positivity                | −15.0 (−18.2/−11.5)§ | <0.001         | −14.7 (−19.5/−9.9)§             | <0.001         | Yes (<0.001)                                        | No (0.934)                                                   |
| Ln(MCH)# in positive patients | 74.0% (49.5/87.7)    | <0.001         | 75.3% (52.3/88.1)               | <0.001         | <0.001                                              | No (0.513)                                                   |

\*Measures of effect for the association of FEF and nasal parameters are Pearson R % (95% CI) for continuous variables; mean difference (95% CI) for categorical variables.

#Natural log-transformed MCH.

§Present vs absent or positive vs negative.

¶Obstruction score 3 vs 2.

||Obstruction score 1, 2 vs 0.

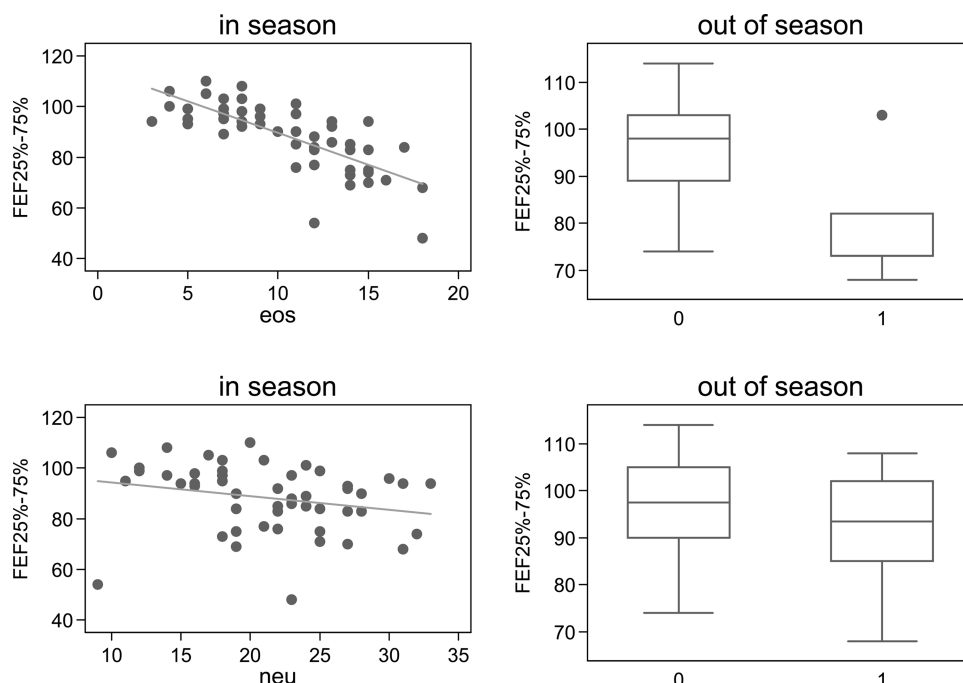


**Figure 1.** Association of FEF<sub>25-75</sub> in and out of pollen season, with eosinophiles (upper panel, left and right, respectively) and with neutrophiles (lower panel, left and right, respectively). Note that out of pollen season, because of their extremely low number, both eosinophiles and neutrophiles were rated as present (1)/absent (0). Box and whisker plot represent the median (midline), the 25th–75th percentiles (box), and the nonoutlier extremes (whisker). Dots are outliers.

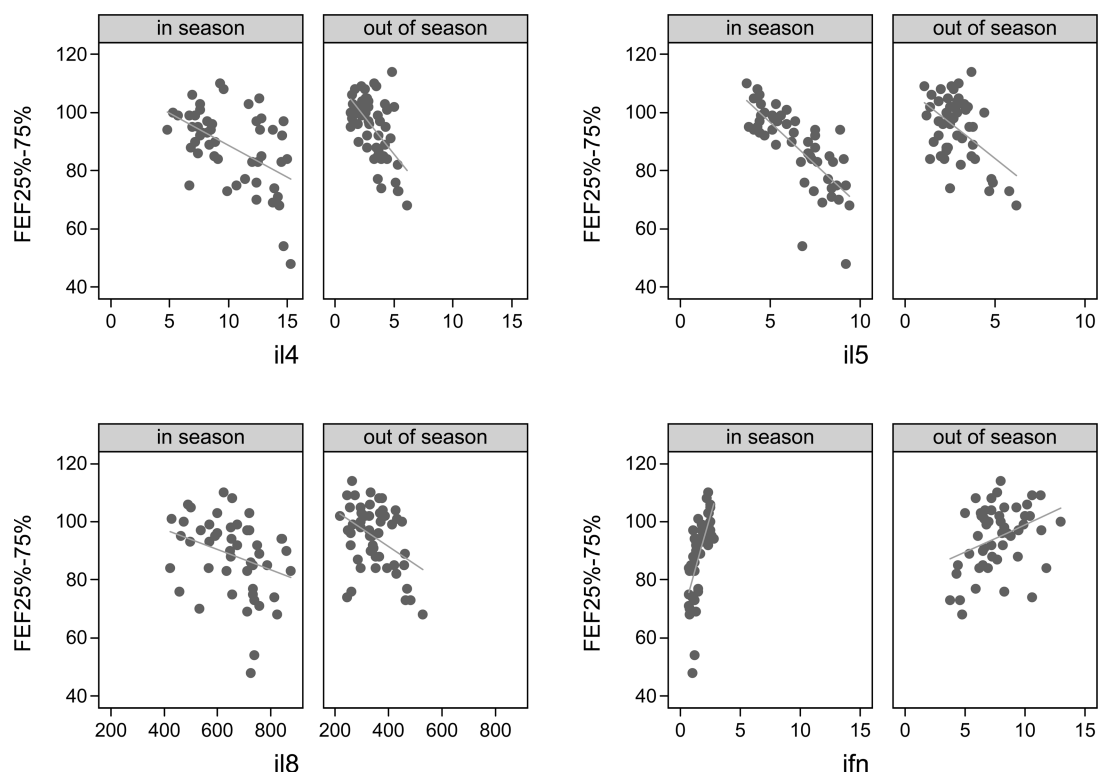


**Figure 2.** Association of  $FEF_{25-75}$ , in and out of pollen season, with IL-4 and IL-5 (upper panel, left and right, respectively) and with IL-8 and IFN- $\gamma$  (lower panel, left and right, respectively)

was performed by means of Student's *t*-test (with unequal variances correction) or Fisher's exact test, respectively. A general linear regression model was fitted to assess the association, in and out of pollen season, of  $FEF_{25-75}$  with a series of nasal parameters, *viz.*, inflammatory cells, cytokines, obstruction symptom, TSS, nasal airflow, and results of MCH bronchial challenge. The Pearson correlation coefficient and its 95% CI were computed to quantify the association for continuous variables and the difference between groups (with 95% CI) for categorical variables. In addition, a bivariate model was fitted for each nasal parameter to verify whether the association was independent of season. The interaction between each nasal parameter and season was tested also to assess whether the association of  $FEF_{25-75}$  and nasal parameter was significantly different in and out of the pollen season. Residual analysis was performed to verify model assumptions. Multicollinearity between nasal parameters hampered further multivariate analysis. Out of pollen season both eosinophils and neutrophils were rated as present/absent, because of their extremely low number. Stata 8.2 (StataCorp, College Station, TX) was used for computation. A two-sided value of  $p < 0.05$  was considered statistically significant.

## RESULTS

The nasal variables and ventilatory function both in and out of pollen season are summarized in Table 1. In season, all SAR subjects were symptomatic: 24 subjects had moderate nasal obstruction and 26 subjects had severe nasal obstruction. All of them showed typical allergic inflammation characterized by Th2 polarization (low levels of IFN- $\gamma$  and high

levels of IL-4, IL-5, and IL-8) and eosinophilic infiltration (Table 1). A clear decrease of nasal airflow was present in all subjects: the mean of airflow values were  $482.5 \pm 111.4$  mL/s. Normal values are  $742.8 \pm 128.4$  mL/s in our laboratory.<sup>17,18</sup> Normal values of  $FEV_1$  ( $97.9 \pm 10.7\%$  of predicted) and forced vital capacity (FVC;  $97.2 \pm 8.6\%$  of predicted) were found in all subjects.  $FEF_{25-75}$  mean values were  $88.3 \pm 13.3\%$  of predicted. Twelve subjects had  $FEF_{25-75}$  values  $<80\%$  of predicted. Twenty-six patients with rhinitis showed a positive MCH challenge.

Out of season, only six patients had nasal obstruction, but with grade 1 or 2. No other nasal symptoms were reported. There was reversal of Th1- and Th2-dependent cytokine values. Slight infiltration was detected (eosinophils,  $0.10 \pm 0.3$ , and neutrophils,  $0.7 \pm 0.9$ ). A clear increase of nasal airflow was present in all subjects: the mean of airflow values was  $672.8 \pm 79.4$ . All subjects showed normal values of  $FEV_1$  ( $101.9 \pm 9.1\%$  of predicted), FVC ( $98.5 \pm 6.6\%$  of predicted), and  $FEF_{25-75}$  ( $94.6 \pm 11.1\%$  of predicted). Twenty-seven patients with rhinitis showed a positive MCH challenge. Although data on FVC and response to MCH test were almost similar in and out of pollen season, all other parameters were markedly different.

$FEF_{25-75}$  and  $FEV_1$  values significantly increased outside the pollen season as well as nasal airflow values. Symptoms, inflammatory cells, and Th2-dependent cytokines normalized out of season. BHR was not modified by season. The association of  $FEF_{25-75}$  with nasal parameters is summarized in Table 2.

A significant association was observed in all cases (but for neutrophils), with Pearson *R* ranging from 31 to 75% and

differences in mean FEF<sub>25-75</sub> ranging between 14.5 and 16.5. The most significant association was with nasal airflow in season ( $R = 82.8\%$ ;  $p < 0.001$ ). A significant association persisted for all parameters while controlling for season, at the bivariate analysis.

Finally, the strength of the association was shown to be different in and out of pollen season for IL-4, IFN- $\gamma$ , and nasal airflow, while it was not in the other cases (Figs. 1–4).

DISCUSSION

Allergic rhinitis and asthma should be considered as a single syndrome involving two parts of the respiratory tract.<sup>4</sup> Patients with allergic rhinitis frequently present BHR, even in absence of asthma symptoms. In these subjects with normal FEV<sub>1</sub> values, BHR may be envisaged as a predictive marker of susceptibility to asthma.<sup>20</sup>

Very recently, we showed that subjects with allergic rhinitis alone quite frequently show impaired FEF<sub>25-75</sub> values.<sup>6,21,22</sup> Thus, the present findings offer some considerations concerning

the link between upper and lower airways and the variations of respiratory parameters consequent to allergen exposure.

First, evaluating a large cohort of subjects with SAR alone, Th2-dependent inflammation and symptoms are clearly present during the pollen season and disappear outside the pollen season. This confirms the close relationship between pollen exposure and allergic inflammation in those patients.

Second, airflow limitation, through nasal and the bronchial airways up to a point, behave similarly. In particular, considering the evaluation of FEF<sub>25-75</sub> we showed that some patients with rhinitis (24%) show an initial degree of bronchial obstruction during the pollen season. It is noteworthy that these subjects did not perceive any lower respiratory complaint. This issue is consistent with the concept that chronic nasal inflammation due to allergen exposure may involve the bronchial tree.

Third, BHR affects one-half of subjects, this finding underlines and confirms the close link between allergic rhinitis and bronchial involvement.<sup>6,14,17,18</sup>

Finally, FEF<sub>25-75</sub> is significantly associated with all evalu-

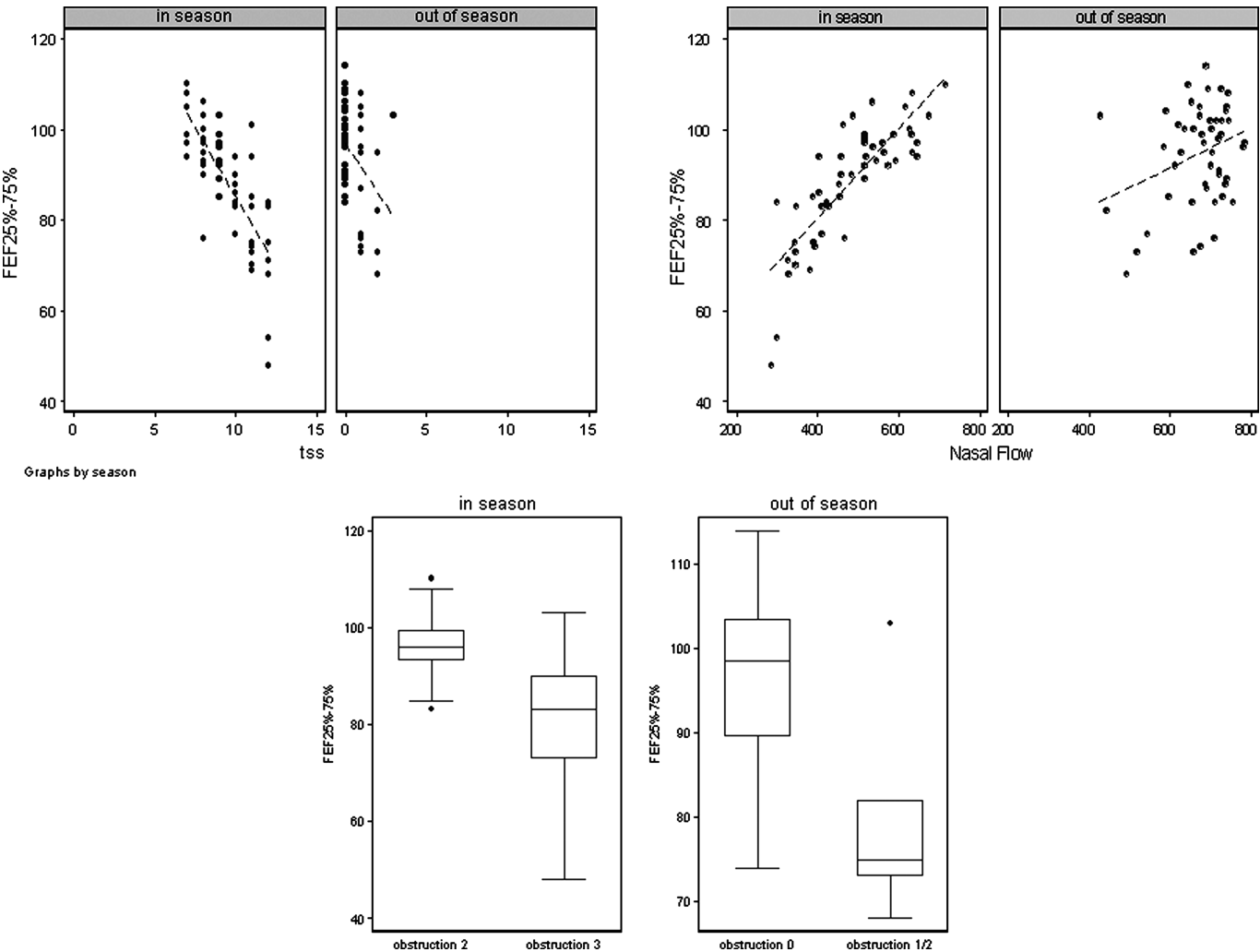


**Figure 3.** Association of FEF<sub>25-75</sub>, in and out of pollen season, with TSS and nasal flow (upper panel, left and right, respectively) and with obstructive symptom (lower panel, left). Box and whisker plot represents the median (midline), the 25th–75th percentiles (box), and the nonoutlier extremes (whisker). Dots are outliers.

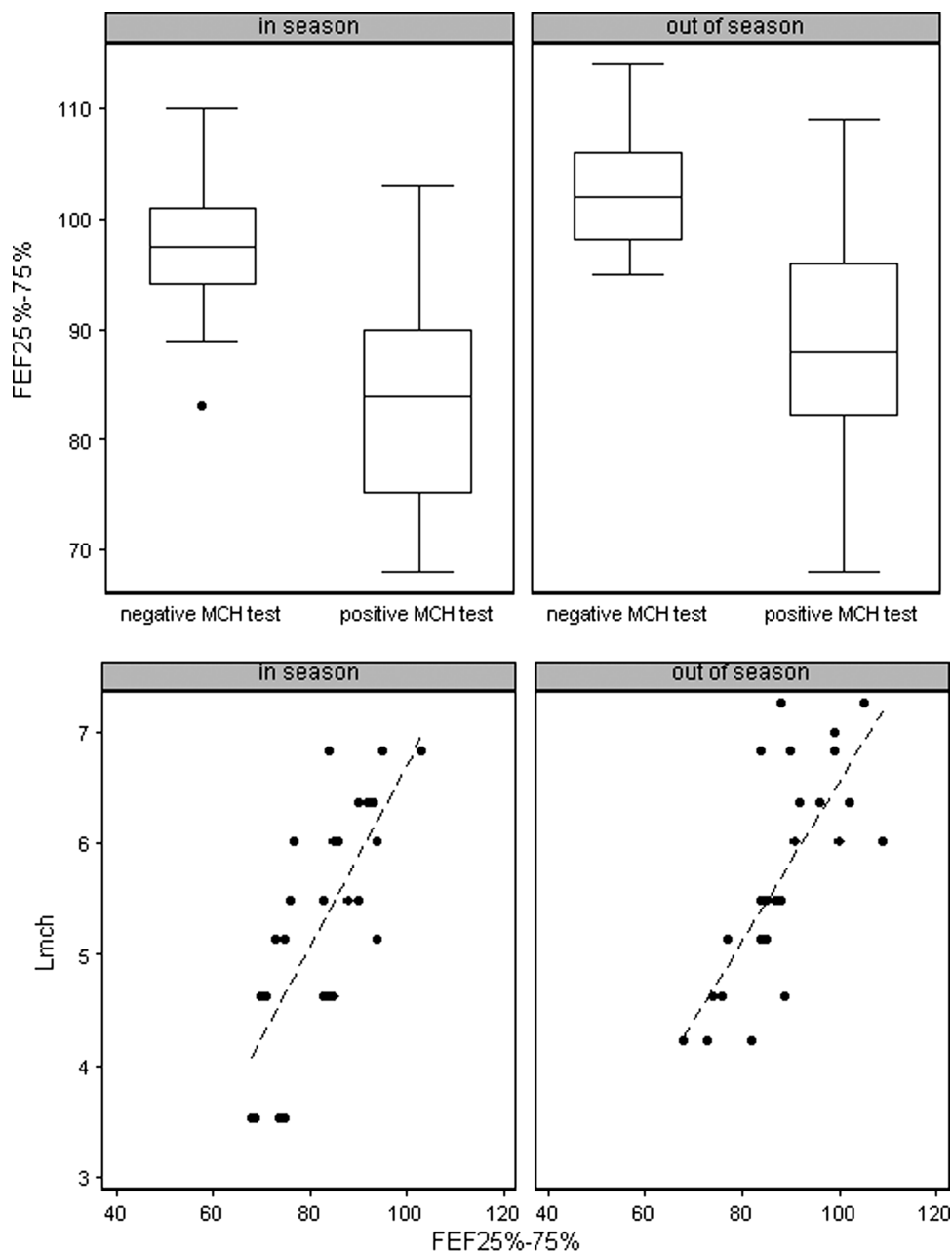


**Figure 4.** Association of FEF<sub>25-75</sub>, in and out of pollen season, with MCH<sup>+</sup> test (upper panel, left and right, respectively) and with log-transformed MCH in positive patients (lower panel, left and right, respectively). Box and whisker plot represents the median (midline), the 25th–75th percentiles (box), and the nonoutlier extremes (whisker). Dots are outliers.

ated parameters, including BHR. Thus, this finding may be considered the most important outcome of this study. This aspect underlines the link between upper and lower airways and provides evidence that early bronchial involvement may occur in subjects with nasal symptoms alone. In particular, nasal airflow is the parameter that best relates to FEF<sub>25-75</sub>. This highlights the role of airflow limitation in allergic rhinitis. Moreover, this finding confirms previous results observed in patients with SAR and perennial allergic rhinitis associated with asthma.<sup>21,22</sup> In addition, we have to underline that the association of FEF<sub>25-75</sub> with nearly all the parameters considered is independent of season.

This issue increases the strength of the role of FEF<sub>25-75</sub> as a marker of early bronchial involvement in patients suffering from isolated allergic rhinitis. Moreover, the functional dichotomy Th2–Th1 and nasal airflow mainly interacts with FEF<sub>25-75</sub>; this issue supports the concept that airway allergic inflammation and airflow impairment are closely associated. Therefore, our findings suggest that FEF<sub>25-75</sub> may be considered a reliable marker of early involvement of bronchi in allergic rhinitis. In conclusion, this study highlights the link between upper and lower airways and the role of FEF<sub>25-75</sub> as an early marker of bronchial involvement in patients with SAR alone.

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