



Letter to the Editor

Asthma symptom perception does not relate with type-2 bronchial inflammation

Les symptômes d'asthme ne sont pas associés à une inflammation bronchique de type 2

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Mots clés : Asthme ; Fonction respiratoire ; NO exhalé ; Perception des symptômes ; Vie réelle

Asthma is a syndrome characterized by episodic respiratory symptoms, including breathlessness, wheezing, chest tightness and cough, due to bronchial airflow limitation that in turn is sustained by bronchial inflammation and airways hyperreactivity.

The perception of asthma respiratory symptoms may be easily assessed by a psychometric tool, such as the visual analogue scale (VAS), that allows to objectively quantify the perceived symptom severity [1]. Previously, it has been reported that VAS measurement of respiratory symptom perception is significantly associated with the asthma control level [2], the bronchial obstruction documented by impaired FEV₁ values [3] and the perception of bronchodilation after administration of short acting β 2-agonist [4].

On the other hand, bronchial eosinophil infiltration defines the type 2 asthma endotype [5]. There is evidence that fractional exhaled nitric oxide (FeNO) levels are associated with eosinophilic bronchial inflammation grade [6]. So, FeNO is a surrogate biomarker commonly used to measure type 2 bronchial inflammation and to predict responsiveness to inhaled corticosteroids [7]. Moreover, it was reported that eosinophil may be a reliable marker of asthma activity, mainly concerning the asthma symptom score [8] and the asthma control [9]. However, at our best knowledge, there is no evidence of a possible relationship between respiratory symptom perception measured by VAS and bronchial inflammation assessed by FeNO in adult patients with asthma. Therefore, the current study investigated the possible association between VAS assessment of perceived asthma symptoms and FeNO in a real-life cohort of asthmatics.

The present study was conducted as a retrospective observation of a consecutive series of patients visited in a real-life setting, such as a pulmonology clinic. The visit included: history, clinical examination, symptom perception severity assessed by VAS, lung function testing, FeNO measurement, asthma control test (ACT) questionnaires and asthma control level assessment according to Global Initiative for Asthma (www.ginasthma.org) document.

In particular, the VAS evaluation system comprised a segment of length 10 cm, upon which the patient is asked to indicate his/her actual perception of asthma symptoms, by marking a point along the segment. In this study, 0 corresponded to the most severe symptoms, while 10 corresponded to optimal symptom-free breathing. The segment was without interval markers.

Patients discontinued use of long-acting bronchodilators and short acting respectively for 24 and 8 hours before measurement of lung function. The diagnosis of asthma was performed on typical symptoms and documented demonstration of reversible bronchial obstruction or methacholine bronchial challenge, according to Global Initiative for Asthma criteria (www.ginasthma.org). The study conformed to the local ethic criteria concerning the management of clinical data; all patients gave a written informed consent.

A linear regression analysis was performed on log-transformed FeNO to test the association between the FeNO and the VAS and to study the effect of demographic and clinical factors on the FeNO. The VAS and those covariates with a P -value < 0.20 were then selected for the multivariate analysis, where a linear regression model on log-transformed FeNO was used again with a forward model selection based on the Akaike information criterion. The likelihood ratio (LR) test was used as a test of statistical significance and differences, with a P -value less than 0.05, were selected as significant. Data were analysed using R 3.2.3 software environment (www.R-project.org).

Three hundred and nineteen patients were enrolled in this study. The whole population descriptive statistics were reported in Table 1. The mean age was 42.07 years; there was a predominance of female gender (58.68%), but without difference about FeNO levels. About asthma GINA control, 41% of patients were well controlled, 45.7% partially controlled, and 13.1% uncontrolled. The mean ACT value was 19.87, the mean VAS value was 6.97 and the spirometry parameters were within the normal range.

Table 1
descriptive statistics ($n = 319$) with univariate and multivariate VAS analysis.

Characteristic	Descriptive statistics		Univariate analysis		Multivariate analysis ($n = 167$)	
	Total	FeNO ppb	Exp (beta)	P-value	Exp (beta)	P-value
Age (years)	42.07 (16.34)	Rho = -0.10	1.00 (0.99: 1.01)	1.0000		
Gender				1.0000		
Male	41.32%	32.46 (26.18)	1			
Female	58.68%	33.3 (24.59)	1.05 (0.88: 1.26)			
GINA ^a				0.0381		0.3316
Well controlled	41.12%	29.56 (23.03)	1		1	
Partially controlled	45.72%	32.66 (24.23)	1.11 (0.92: 1.34)		1.07 (0.79–1.44)	
Uncontrolled	13.16%	46.74 (30.92)	1.58 (1.20–2.09)		1.36 (0.89–2.08)	
ACT ^a	19.87 (4.4)	Rho = -0.16	0.97 (0.96: 0.99)	0.0780	1.00 (0.97–1.03)	0.4094
VAS ^a	6.97 (2.3)	Rho = -0.13	0.96 (0.91: 1.01)	0.0888	0.98 (0.92–1.03)	0.8916
FVC % of predicted	100.5 (18.43)	Rho = -0.05	1.00 (0.99: 1.01)	1.0000		
FEV ₁ % of predicted	89.82 (20.83)	Rho = -0.04	1.00 (0.99: 1.01)	1.0000		
FEV ₁ /FVC	81.31 (14.63)	Rho = 0.05	1.00 (0.99: 1.01)	1.0000		

Characteristic: variable taken into account; descriptive statistics are reported as number of subjects with %, mean with standard deviation and Pearson's correlation coefficient; exp (beta): exponential beta regression coefficient with 95% confidence interval; P-value: the likelihood ratio P-value adjusted for multiple comparisons by the Bonferroni correction method.

^a Variables entering in the multivariate analysis (see the text for abbreviations and further details).

No univariate significant association between VAS and FeNO was observed (P -value = 0.0888). Moreover, the study of the demographic and clinical factor effects on the FeNO showed a significant association between the GINA asthma control level and the FeNO (P -value = 0.0381). The multivariate analysis, where VAS, GINA and ACT were taken into account, did not show any significant factor effects on the FeNO values (P -value > 0.05). The relationship between VAS and FeNO was very slight and not significant, as plotted in Fig. 1.

The current real-life study demonstrates that there is no significant association between asthma symptom perception assessed by VAS and bronchial inflammation measured by FeNO in a daily clinical practice setting.

The FeNO use in the management of asthma is still controversial, even though there is agreement about its predictive role of

ICS responsiveness and its value as biomarker for type 2 asthma endotype [5,7]. In fact, FeNO is associated with peripheral, sputum, and bronchial eosinophil [10]. In addition, the grade of eosinophil inflammation is associated with symptom severity and disease activity [8,9].

The current cross-sectional study shows that there is no association between FeNO levels and perception of asthma symptoms assessed by VAS. This outcome seems to be inconsistent with the demonstrated association between symptom severity and eosinophil inflammation grade. The possible explanation might depend on the concept of perception. Actually, symptom perception, such as a subjective evaluation, may be substantially conflicting with objective assessment of disease severity, including asthma scores. Many factors may affect the perception of symptoms, including age, asthma duration, emotional disorders, gender, and so on. In addition, it is well known that there are asthmatic patients hypo- or hyper-perceiver.

The present real life study has a limitation because it was performed as cross-sectional, so further longitudinal studies should be designed to confirm these findings.

In conclusion, the current study shows that asthma symptom perception is not associated with type 2 bronchial inflammation.

Disclosure of interest

The authors declare that they have no competing interest.

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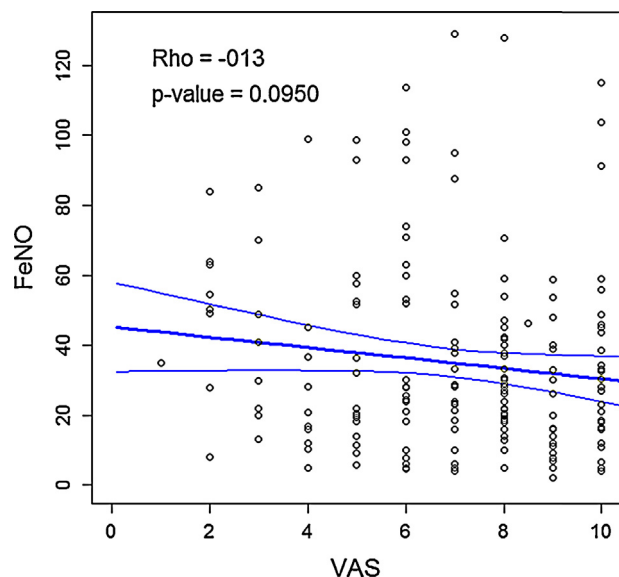


Fig. 1. The scatter plot of the FeNO versus the VAS with a regression line.

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