Exhaled NO may predict loss of asthma control: the effect of concomitant allergic rhinitis

To the Editors:

We read with great interest the recent article by MICHILS *et al.* [1] demonstrating that sequential changes in exhaled NO fraction (F_{ENO}) are associated with asthma control, even in smokers who present lower levels of F_{ENO} compared with nonsmokers. Besides tobacco smoking, we have recently shown that a significant confounding factor in the diagnosis of asthma using F_{ENO} is the presence of allergic rhinitis, since patients with allergic rhinitis have been found to have elevated F_{ENO} levels [2]. This effect may well be attributed to the underlying atopic status of those patients, since elevated F_{ENO} has been shown to be associated with a phenotype characterised by atopy and increased airway responsiveness [3]. In the present study we attempted to evaluate whether the coexistence of allergic rhinitis may affect the validity of sequential changes of F_{ENO} in predicting control in asthmatic patients.

We performed a *post hoc* analysis of a prospectively collected database of all consecutive patients evaluated in the Asthma Clinic of the Respiratory Medicine Dept, University of Thessaly Medical School (Larissa, Greece), between June 2007 and February 2009. Of the 259 patients in the database, we excluded 82 smokers, 26 patients with difficult-to-treat asthma in whom total control was never achieved during that time period, and 41 patients who were not seen at least twice. Patients were treated according to Global Initiative for Asthma (GINA) guidelines and were all receiving inhaled corticosteroids. All patients were submitted to F_{ENO} measurements using a portable analyser (NiOX MiNO; Aerocrine, Solna, Sweden) as previously described [2] and to spirometry with a dry spirometer (KoKo Legend; Ferraris Respiratory Ltd, Hertford, UK). The assessment of asthma control was based on the evaluation of an experienced physician (K. Kostikas) according to the GINA guidelines and the use of the original Asthma Control Questionnaire (ACQ) [4]. The diagnosis of allergic rhinitis was based on history and appropriate assessment of atopic status, as previously described [5].

Comparisons among groups at baseline were performed with one-way ANOVA with Bonferroni *post hoc* tests. Comparisons of F_{ENO} levels between the two visits were performed using Wilcoxon signed rank tests. For the assessment of the performance of F_{ENO} percentage changes compared to baseline (ΔF_{ENO}%) in the identification of loss of control, receiver operating characteristics (ROC) curves were created by plotting sensitivity against 100-specificity. The area under the ROC curve (AUC) with 95% confidence intervals (CI) and its difference from 0.5 were calculated. Additionally, sensitivities, specificities, and positive and negative predictive values (PPV and NPV, respectively) were calculated for specific cut-off points. Statistical analysis was performed with GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA, USA) and MedCalc 9 (MedCalc Software, Mariakerke, Belgium).

110 patients with two consecutive visits, who, at the first visit, had well-controlled asthma, were included in the analysis. Of those patients, 61 lost control in the subsequent visit (32 with rhinitis and 29 without rhinitis) and 49 remained well

TABLE 1 Patients' characteristics and loss of control

	Patients who lost control		Patients who maintained control	
	Asthma without rhinitis	Asthma and rhinitis	Asthma without rhinitis	Asthma and rhinitis
Subjects	29	32	23	26
Age	53±11	50±18	53±16	48±16
Sex male/female	9/20	11/21	9/14	10/16
FEV_1 visit 1 % pred	92±15	91±17	95±8	94±8
FEV_1 visit 2 % pred	84±19*	83±16*	95±13	96±13
FEV_1/FVC visit 1	74±10	80±10	78±7	77±7
FEV_1/FVC visit 2	72±14	78±10	72±14	81±13
$FEF_{25–75}$ visit 1 % pred	65±31	75±32	72±38	69±29
$FEF_{25–75}$ visit 2 % pred	59±30	78±10	60±30	76±35
ACQ visit 1	0.76±0.43	0.72±0.58	0.69±0.48	0.71±0.53
ACQ visit 2	1.98±0.63*	2.08±0.58*	0.71±0.51	0.72±0.46
F_{ENO} visit 1 ppb	12±7	12±8	11±5	11±6
F_{ENO} visit 2 ppb	25±21*	22±22*	12±5	13±5

Data are presented as n or mean±SD. *: $p<0.05$ compared to visit 1. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; ACQ: Asthma Control Questionnaire; F_{ENO}: exhaled NO fraction.

TABLE 2 Diagnostic performance of change in exhaled NO fraction for the identification of loss of control in two consecutive visits

	Optimal cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	AUC (95% CI)	p-value
Asthma without rhinitis#	>30%	0.83 (0.64–0.94)	0.87 (0.68–0.97)	0.89	0.81	0.893 (0.777–0.961)	<0.0001
Asthma with rhinitis¶	>40%	0.72 (0.53–0.86)	0.92 (0.74–0.98)	0.92	0.71	0.786 (0.657–0.884)	<0.0001

The optimal cut-off points represent values with the best combination of sensitivity and specificity. PPV: positive predictive value; NPV: negative predictive value; AUC: area under the receiver operating characteristic curve. #: n=52; ¶: n=58.

controlled (26 with rhinitis and 23 without rhinitis). Demographic characteristics are presented in table 1. Study groups did not differ in demographic and spirometric characteristics, F_{ENO} levels or ACQ scores at baseline. In both groups where control was lost in visit 2 (with and without rhinitis), F_{ENO} increased significantly ($p<0.001$ for both comparisons). In contrast, patients who maintained control at visit 2 did not present significant differences in F_{ENO} levels between visits ($p=0.100$ and $p=0.146$ for patients with and without allergic rhinitis, respectively).

In ROC analysis, ΔF_{ENO}% was associated with loss of control, since both ROC curves differ significantly from 0.5 (fig. 1, table 2). The diagnostic performance of ΔF_{ENO}% did not differ significantly between patients without and with allergic rhinitis, despite a trend in favour of the former (AUC 0.893 *versus* 0.786; $p=0.152$). In patients without rhinitis, an increase in F_{ENO} >30% from baseline was highly indicative of loss in asthma control (PPV 0.89), whereas an increase <20% was unlikely to be related to loss of control (NPV 0.81). Additionally, an increase in F_{ENO} >40% in patients with rhinitis was also highly suggestive of loss in asthma control (PPV 0.92). In contrast, an increase in F_{ENO} <20% was not as strong a predictor of maintenance of control (NPV 0.72) in patients with asthma and rhinitis as in those without rhinitis.

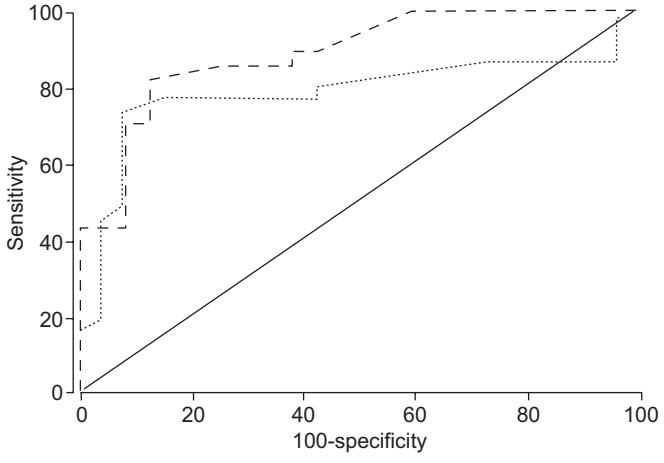

FIGURE 1. Receiver operating characteristic analysis for the assessment of the performance of exhaled NO fraction (F_{ENO}) changes compared to baseline (ΔF_{ENO}%) in the identification of loss of control between two consecutive visits. - - - -: asthma without rhinitis; ·····: asthma and rhinitis.

Our data support our previous observations suggesting that the presence of atopy, and especially allergic rhinitis, may impair the diagnostic value of F_{ENO} in asthmatics [2]. The poorer diagnostic performance of F_{ENO} in patients with concomitant rhinitis may plausibly represent cases of deterioration in rhinitis symptoms (related to increased nasal inflammation) without concurrent impairment of asthma control. Interestingly, our results independently confirm the data of MICHILS *et al.* [1] and further support the observation that an increase in F_{ENO} >40% from baseline is highly indicative of loss of asthma control, even in patients with underlying atopy, as expressed by the presence of allergic rhinitis.

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