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Exhaled nitric oxide as a marker of asthma control in smoking patients

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ABSTRACT: Exhaled nitric oxide fraction (*F*eNO), which is a reliable marker of eosinophilic airway inflammation, is partially suppressed by tobacco smoking. Consequently, its potential as a biomarker in asthma management has never been evaluated in smoking patients. In the present study, the authors tested the validity of *F*eNO to predict asthma control in this population.

***F*eNO and the Asthma Control Questionnaire (ACQ) were recorded at least once in 411 nonsmoking (345 with at least two visits) and 59 smoking (51 with at least two visits) asthma patients.**

Despite similar mean ACQ scores (1.5 *versus* 1.7), *F*eNO was reduced in smoking asthmatics (18.1 ppb *versus* 33.7 ppb). A decrease in *F*eNO of <20% precludes asthma control improvement in nonsmoking (negative predictive value (NPV) 78%) and in smoking patients (NPV 72%). An increase in *F*eNO <30% is unlikely to be associated with deterioration in asthma control in both groups of patients (NPV=86% and 84% in nonsmoking and smoking patients, respectively).

It is concluded that, even in smokers, sequential changes in *F*eNO have a relationship with asthma control. The present study is the first to indicate that cigarette smoking does not obviate the clinical value of measuring *F*eNO in asthma among smokers.

KEYWORDS: Asthma control, exhaled nitric oxide, tobacco smoking

Although the debate is not over, it is generally accepted that the exhaled nitric oxide fraction (*F*eNO) has the potential to be useful in the management of asthma [1–6]. However, several factors confounding *F*eNO measurement have been recognised [7]. Among them, tobacco smoking has been consistently shown to reduce *F*eNO levels [6, 8–15], by a factor varying from 0.63 to 0.80 according to the multivariate analyses that have compared *F*eNO in smokers and nonsmokers [6, 14, 15]. The mechanism by which smoking causes *F*eNO reduction is not fully understood, but may include reduction in nitric oxide (NO) synthesis due to feedback inhibition induced by high concentrations of NO contained in cigarette smoke [9]. NO oxidation or interaction with other molecules present in tobacco smoke might also occur [16]. However, regardless of the mechanism of *F*eNO reduction reported in smokers, it is generally assumed that *F*eNO should not be assessed in asthmatic patients who smoke. Perhaps, consequently, this population (~25% of adult asthma patients [17]) has been excluded from clinical trials that have explored the potential of *F*eNO as a biomarker in asthma management. Even in the present authors' own studies, where it has recently been shown that *F*eNO is a reliable marker of asthma control over time in unselected patients, smoking patients were not enrolled [18]. Interestingly, the present authors' previous study [18] strongly suggested that it is the change in *F*eNO values, rather than absolute cut-off points (*i.e.* individualised *F*eNO profiles), that may be meaningful for the longitudinal assessment of asthma control in daily practise. Therefore, in the present study, the authors investigated whether, despite the *F*eNO reduction reported in smoking asthma patients [6, 8–15], changes in *F*eNO might also be significantly related to changes in asthma control in this population.

To do this, *F*eNO was monitored on several occasions in smoking and nonsmoking patients attending a tertiary asthma clinic. Its ability to reflect improvement or worsening of asthma control over time was compared in both groups, using the Asthma Control Questionnaire (ACQ) as a gold standard for the assessment of asthma control [19].

METHODS

Subjects

Between January 1, 2004, and July 30, 2008, 411 adult nonsmokers and 59 adult smokers

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attending the Allergy and Asthma clinic in the Chest Dept of the Erasme University Hospital, Brussels, Belgium, for treatment of persistent asthma diagnosed according to standard criteria [20] were enrolled in the study.

The present study was approved by the local ethics committee, and patients signed to give informed consent.

Study procedures and design

Study design

The present study is a *post hoc* analysis of an existing database that is continuously updated. A significant part of the database was reported in the present authors' previously published study, which documented a relationship between asthma control and F_{ENO} in nonsmoking asthma patients [18]. The present analysis focuses on whether current smoking annuls the validity of F_{ENO} measurements to predict asthma control. ACQ scores and F_{ENO} were recorded independently on one or more occasions for each patient, including smokers who were excluded from the initial analysis for reasons mentioned earlier. At each visit, asthma treatment was adjusted according to the Global Initiative for Asthma (GINA) guidelines recommendations [20], regardless of ACQ score or F_{ENO} value, which were recorded separately.

Since optimal asthma control appears more difficult to achieve in smoking patients [21], the 1.5 optimum cut-off point identifying poorly controlled asthma [22] was selected as the reference ACQ score in the receiver operating characteristic (ROC) curve analysis. For clarity's sake, it was considered that an ACQ score of <1.5 identified asthma that is controlled (*i.e.* partly or well controlled), whereas an ACQ score of $\geqslant 1.5$ identified uncontrolled asthma. Using the ROC curve analysis, the present authors assessed the ability of F_{ENO} to: 1) reflect asthma control cross-sectionally using an ACQ threshold of 1.5; 2) detect a significant improvement or worsening of asthma control that resulted in a change from uncontrolled (ACQ $\geqslant 1.5$) to controlled (ACQ <1.5) asthma, either respectively or *vice versa*; and 3) detect a significant improvement or worsening of asthma control defined as a decrease or increase in ACQ of $\geqslant 0.5$, even though it was not large enough to result in a change of the asthma control status.

Patients treated with low ($\leqslant 500$ μg beclomethasone dipropionate (BDP) eq·day^{-1}) and high-to-moderate (>500 μg BDP eq·day^{-1}) inhaled corticosteroid (ICS) doses were considered separately. Indeed, in the present authors' previous study [18], it was found that the overall ability of F_{ENO} to reflect asthma control was reduced in patients using high ICS doses.

Study procedures

Asthma Control Questionnaire

Asthma control was assessed using a French translation of the short version of the ACQ of JUNIPER *et al.* [23]. This version does not include FEV_1 rating. Patients subjectively evaluate the degree of impairment caused by their asthma during the preceding 7 days by responding to six questions using a seven-point scale: a score of 0 indicates no impairment and a score of 6 indicates maximal impairment. The total ACQ score is the mean of the six responses, thus varying between 0 (totally controlled asthma) and 6 (totally uncontrolled asthma). A score of >1.5 is used to identify poorly controlled asthma [22]. A change of 0.5 in the ACQ score is considered to be the minimum change that is clinically relevant [22].

F_{ENO}

F_{ENO} was measured before any forced expiratory manoeuvres using a daily calibrated LR 2000 chemoluminescence analyser (Logan Research Ltd, Rochester, UK) with online measurement of a single exhalation at a flow rate of 50 mL·s^{-1} (American Thoracic Society (ATS)/European Rspiratory Society (ERS) standard) [24]. F_{ENO} levels were read at the plateau corresponding to 70–80% of the carbon dioxide curve. Absolute F_{ENO} values are expressed in ppb, and changes in F_{ENO} are expressed as a percentage of the initial value (Δ%).

Statistical methods

ROC curve analysis was performed in the whole population, as well as in the two different subgroups, *i.e.* patients treated by low and high-to-moderate doses. The area under the ROC curve (AUC) was computed, and its difference from 0.5 was statistically evaluated. For a given type of assessment, the optimal cut-off value was determined for the whole population by maximising the Youden's index [25], *i.e.* the true-positive rate (sensitivity) minus the false-positive rate (1-specificity; see online supplementary material). Geometrically, this index is the vertical distance between the ROC curve and the first bisector. The cut-off value corresponding to the maximum value of Youden's index was then used to derive sensitivity (Se), specificity (Sp), positive predictive values (PPV) and negative predictive values (NPV), and accuracy in the whole population and in the subgroups of patients. In the online supplementary material, Se, Sp, PPV, NPV and accuracy may be found for other cut-off values, as well as the amounts of true-positive, true-negative, false-positive and false-negative cases (contingency tables).

Unpaired t-tests were used when considering forced expiratory volume in 1 s (FEV_1) and log-transformed F_{ENO} values, and Mann–Whitney U-tests when considering ICS doses and ACQ scores. Proportions were compared using a Chi-squared test. The limit of significance was a p-value of 0.05.

RESULTS

Of the 411 nonsmoking patients and 59 smoking patients, 345 and 51, respectively, were seen at least twice, representing 646 and 92 pairs of successive visits for nonsmoking and smoking patients, respectively (the median time between two visits for nonsmoking patients was 88 days, range 10–1,255 days, interquartile interval 42–189; and for smoking patients it was 93 days, range 7–525 days, interquartile interval 49–182). Table 1 presents demographic data for the nonsmoking and smoking groups, as well as F_{ENO}, FEV_1, ACQ score and ICS dose values at study onset for the total studied population (included in the cross-sectional analysis) and for the subgroup of patients who were seen at least twice (included in the longitudinal analysis).

Tables 2–5 display the cut-off values (resulting from Youden's index maximisation), the number of positive and total cases, and therefore the prevalence, the Se, the Sp, the PPV and NPV, the accuracy and the p-value allowing rejection (or not) of the null hypothesis AUC=0.5.

TABLE 1 Demographic data and indices values at study onset

	Total			Patients seen at least twice		
	Nonsmokers	Smokers	p-value#	Nonsmokers	Smokers	p-value#
Subjects n	411	59		345	51	
Age yrs	41±16	38±11	0.39	41±16	39±11	0.47
Male/female n	195/216	34/25	0.14	219/126	26/25	0.08
Nonatopic/atopic n	61/350	5/54	0.19	43/302	4/47	0.34
ACQ score¶	1.5 (0–5.0)	1.7 (0–5.3)	0.34	1.7 (0–5.3)	1.9 (0–5.3)	0.34
ICS dose¶,+	250 (0–2000)	500 (0–2000)	0.50	250 (0–2000)	500 (0–2000)	0.37
***F*eNO ppb§**	33.7 (14.3–79.2)	18.1 (6.9–47.5)	<0.001	34.8 (14.6–83.0)	18.5 (6.1–55.5)	<0.001
FEV1 % pred	85.6±15.7	86.2±17.9	0.80	85.0±20.6	86.5±18.0	0.79

Data are presented as mean±SD, median (range) (¶), or geometrical mean (geometrical interval) (§), unless otherwise indicated. ACQ: Asthma Control Questionnaire; ICS: inhaled corticosteroid; *F*eNO: exhaled nitric oxide fraction; FEV1: forced expiratory volume in 1 s; % pred: % predicted. #: comparison between nonsmoking and smoking group; +: ICS dose in μg equivalents beclomethasone diproprionate per day^{-1} with the exception of *F*eNO, nonsmoking and smoking groups were statistically similar.

Cross-sectional assessment of asthma control

Asthma control was cross-sectionally assessed at study onset for 411 nonsmoking and 59 smoking asthma patients. Controlled asthma (ACQ score of <1.5) was considered as a positive event. Table 2 shows that, in smoking asthma patients, *F*eNO is unable to cross-sectionally assess asthma control.

Assessment of change in asthma control between pairs of visits

Change from uncontrolled (ACQ score ⩾ 1.5) to controlled (ACQ score <1.5) asthma

In nonsmoking and smoking patients, asthma was uncontrolled at visit 1 in 283 pairs (out of 646) and 52 pairs (out of 92), respectively. A change to controlled asthma (spontaneous as well as treatment-induced) at visit 2 was considered as a positive event. In nonsmoking and smoking patients, this was observed on 133 and 17 occasions, respectively.

Table 3 shows that *F*eNO exhibits high operating characteristics in both nonsmoking and smoking groups. The cut-off values for decreases in *F*eNO which had the highest NPVs for establishing control were 30% in nonsmokers and 20% in smokers.

TABLE 2 Cross-sectional assessment of asthma control

	Nonsmokers	Smokers
Total events n	411	59
Positive cases n	197	15
Prevalence	48	25
Cut-off ppb	50	25
Sensitivity	72	66
Specificity	56	48
PPV	61	30
NPV	68	81
Accuracy	64	53
p-value#	<0.001	0.39

Data are presented as %, unless otherwise indicated. PPV: positive predictive value; NPV: negative predictive value. #: the p-value was defined as the statistical significance of rejecting an area under the curve of 0.5. A positive event was defined as controlled asthma (Asthma Control Questionnaire score <1.5). A true-positive case was defined as an exhaled nitric oxide fraction (*F*eNO) of less than or the same as the cut-off value associated with a controlled asthma. *F*eNO does not discriminate for or against cross-sectionally controlled *versus* uncontrolled asthma in smoking patients (p=0.39).

TABLE 3 Assessment of a change from uncontrolled (Asthma Control Questionnaire (ACQ) score of ⩾1.5) to controlled (ACQ score <1.5) asthma

	Nonsmokers	Smokers
Total events n	283	52
Positive cases n	133	17
Prevalence	47	33
Cut-off	-30	-20
Sensitivity	68	71
Specificity	71	66
PPV	68	50
NPV	72	82
Accuracy	70	67
p-value#	<0.001	0.016

Data are presented as %, unless otherwise indicated. PPV: positive predictive value; NPV: negative predictive value. #: the p-value was defined as the statistical significance of rejecting an area under the curve of 0.5. A positive event was defined as a change from uncontrolled (ACQ score of ⩾1.5) to controlled (ACQ score <1.5) asthma. A true-positive case was defined as exhaled nitric oxide fraction (*F*eNO) change of less than or the same as the cut-off value (*e.g.* -40%) associated with a positive event. *F*eNO exhibited similar operating characteristics in both the nonsmoking and smoking group. In particular, a high NPV was observed.

TABLE 4 Assessment of a change from controlled (Asthma Control Questionnaire (ACQ) score <1.5) to uncontrolled (ACQ score ⩾1.5) asthma

	Nonsmokers	Smokers
Total events n	360	40
Positive cases n	65	10
Prevalence	18	25
Cut-off	+50	+50
Sensitivity	42	68
Specificity	75	87
PPV	26	63
NPV	86	89
Accuracy	69	83
p-value[#]	0.001	0.017

Data are presented as %, unless otherwise indicated. PPV: positive predictive value; NPV: negative predictive value. [#]: the p-value was defined as the statistical significance of rejecting an area under the curve of 0.5. A positive event was defined as a change from controlled (ACQ score <1.5) to uncontrolled (ACQ score ⩾1.5) asthma. A true-positive case was defined as an exhaled nitric oxide fraction (F_{ENO}) change of more than or the same as the cut-off value associated with a positive event. F_{ENO} exhibited similar operating characteristics in both the nonsmoking and smoking group. In particular, a high NPV was observed.

Change from controlled (ACQ score <1.5) to uncontrolled (ACQ score ⩾1.5) asthma

In nonsmoking and smoking patients, asthma was controlled at visit 1 in 360 pairs (out of 643) and 40 pairs (out of 92), respectively. A change to uncontrolled asthma at visit 2 was considered as a positive event. In nonsmoking and smoking patients, this was observed on 65 and 10 occasions, respectively.

Table 4 shows that F_{ENO} exhibits high operating characteristics in both nonsmoking and smoking groups. The cut-off values for an increase in F_{ENO}, which had the highest NPVs for a change to uncontrolled asthma was 50% in both nonsmokers and smokers.

Improvement of asthma control (ΔACQ <-0.5)

A significant improvement in asthma control between two consecutive visits was considered to be a positive event. As a whole, in nonsmoking and smoking patients, this occurred on 257 and 40 occasions, respectively.

Table 5 shows that, in the entire population, F_{ENO} exhibited similar operating characteristics in nonsmoking and smoking patients. Figure 1 illustrates this feature.

When considering the subgroup of smoking patients treated with >500 μg eqivalents BDP·day^{-1}, F_{ENO} was no longer significant in assessing an improvement of asthma control.

Worsening of asthma control (ΔACQ >0.5)

A significant worsening of asthma control between two consecutive visits was considered a positive event. As a whole, in nonsmoking and smoking patients, this occurred on 161 and 26 occasions, respectively.

Table 6 shows that, as for improvement assessment, F_{ENO} exhibited analogous operating characteristics in nonsmoking and smoking patients. With a cut-off value at 30% change, a high NPV was observed in both groups. When considering the subgroup of smoking patients treated with >500 μg eqivalents BDP·day^{-1}, F_{ENO} operating characteristics in assessing asthma control worsening are less significant.

In both improvement (table 5) and worsening (table 6) assessment of asthma control, the present authors considered a subgroup of pairs of visits with an initial ACQ score of <2 as well as a subgroup of pairs of visits without ICS dose

TABLE 5 Assessment of asthma control improvement (change in Asthma Control Questionnaire (ΔACQ) <-0.5)

	Nonsmokers[#]					Smokers[#]				
	Total	D ⩽500[¶]	D >500[¶]	ACQ <2[+]	ΔD 0[§]	Total	D ⩽500[¶]	D >500[¶]	ACQ <2[+]	ΔD 0[§]
Total events n	643	306	337	432	301	92	35	57	53	47
Positive cases n	257	116	141	112	108	40	14	26	18	15
Prevalence	40	38	42	26	36	43	41	46	34	32
Sensitivity	64	74	55	60	53	57	62	50	56	67
Specificity	71	67	74	70	66	74	84	71	77	75
PPV	61	58	60	41	47	62	75	59	56	57
NPV	74	80	70	83	72	70	78	63	77	83
Accuracy	68	70	66	66	65	66	77	61	70	72
p-value[f]	<0.001	<0.001	<0.001	<0.001	0.002	<0.001	<0.001	0.070	<0.001	<0.001

Data are presented as %, unless otherwise indicated. PPV: positive predictive value; NPV: negative predictive value. [#]: cut-off value of -20%; [¶]: inhaled corticosteroid (ICS) dose (D) in μg equivalents of beclomethasone diproprionate·day^{-1}; [+]: ACQ <2 tested the subgroup with an initial ACQ score of <2; [§]: ΔD 0 tested the subgroup without treatment modification between consecutive visits; [f]: the p-value was defined as the statistical significance of rejecting an area under the curve of 0.5. A positive event was defined as an improvement in asthma control. A true-positive case was defined as an exhaled nitric oxide fraction (F_{ENO}) change of less than or the same as a cut-off value (*e.g.* -25%) associated with an improvement of asthma control between consecutive visits. When smoking patients were treated with a high ICS dose, F_{ENO} lost its ability to assess a control improvement (p=0.07).

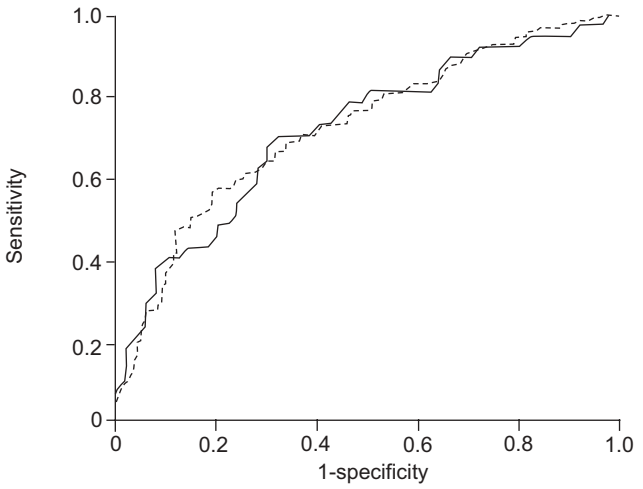

FIGURE 1. Receiver operated characteristic curve characterising the ability of exhaled nitric oxide fraction (F_{ENO}) to assess an improvement of asthma control defined as a significant Asthma Control Questionnaire (ACQ) score decrease (ΔACQ score of >0.5) between two consecutive visits. F_{ENO} exhibits similar operating characteristics in both populations. ——: nonsmoking patients; ------: smoking patients.

modification. Overall, F_{ENO} characteristics were found to be only mildly affected compared with the total group.

DISCUSSION

The present study confirms that, compared with nonsmokers, F_{ENO} is reduced in smoking asthma patients. However, this reduction does not appear to suppress its ability to reflect asthma control in smoking patients, provided changes in F_{ENO} values detected by repeated measurements are considered.

F_{ENO} is a reliable marker of eosinophilic airway inflammation [26] and has the potential to be useful in the management of asthma [1–5]. However, tobacco smoking, which affects around 25% of the asthma population [17], leads to a decrease in F_{ENO} [6, 8–15] and is considered to be a confounding factor. Therefore, it is generally assumed that F_{ENO} should not be assessed in asthmatic patients who smoke.

At first glance, the present results seem to support this common paradigm. F_{ENO} levels were in fact substantially reduced in smoking compared with nonsmoking asthma patients and to an extent that is similar to that found in previous studies [6, 14, 15]. Furthermore, whereas a single F_{ENO} value was confirmed to be significantly related to asthma control in the nonsmoking population (*i.e.* F_{ENO} level >50 ppb indicates uncontrolled asthma in most cases [18]), such a relationship could not be found in the smoking population.

However, in the present authors' previous study [18], which involved nonsmoking patients, it was shown that sequential F_{ENO} assessments are more useful than isolated measurements in demonstrating asthma control. In the current study, this was also found to hold true for smoking asthma patients. Indeed, repeated F_{ENO} measurements do appear helpful with regard to indicating change in asthma control over time in both populations. Thus, when asthma is uncontrolled in nonsmoking patients, an F_{ENO} reduction of >30% would predict that asthma is controlled in two out of three cases. The degree of change in F_{ENO} that should be considered for smoking patients is different to that for nonsmoking patients: an F_{ENO} reduction of <20% would indicate that asthma remains uncontrolled in most cases. Conversely, when asthma is controlled, an F_{ENO} increase of <50% would indicate that asthma remains controlled in either population.

The aim of asthma treatment is to achieve full asthma control (*i.e.* an ACQ <0.75). In smoking patients, however, optimal control is usually more difficult to achieve [21, 27, 28]; this is most likely to be due to the reduction in anti-asthma drugs

TABLE 6 Assessment of asthma control worsening (change in Asthma Control Questionnaire (ΔACQ) >+0.5)

	Nonsmokers[#]					Smokers[#]				
	Total	D ⩽500[¶]	D >500[¶]	ACQ <2[+]	ΔD 0[§]	Total	D ⩽500[¶]	D >500[¶]	ACQ <2[+]	ΔD 0[§]
Total events n	643	306	337	432	301	92	35	57	53	47
Positive cases n	161	64	97	130	99	26	11	15	17	14
Prevalence	25	21	29	30	33	28	31	26	32	30
Sensitivity	51	67	42	54	48	67	70	64	71	57
Specificity	76	76	78	73	70	77	84	91	86	73
PPV	37	43	44	47	34	52	78	43	71	47
NPV	84	90	77	79	80	86	87	85	86	80
Accuracy	70	74	68	67	65	74	86	70	81	68
p-value[f]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.037	<0.001	0.025

Data are presented as %, unless otherwise indicated. PPV: positive predictive value; NPV: negative predictive value. [#]: cut-off value of +30%; [¶]: inhaled corticosteroid (ICS) dose (D) in μg equivalents of beclomethasone diproprionate·day^{-1}; [+]: ACQ <2 tested the subgroup with an initial ACQ score <2; [§]: ΔD 0 tested the subgroup without treatment modification between consecutive visits; [f]: the p-value is the statistical significance of rejecting an area under the curve of 0.5. A positive event is defined as a worsening of asthma control. A true-positive case was defined as an exhaled nitric oxide fraction (F_{ENO}) change of more than or the same as the cut-off value associated with a worsening of asthma control between consecutive visits. When smoking patients were treated with a high ICS dose, F_{ENO} ability to detect a worsening of control was somewhat reduced (p=0.037).

effectiveness that has recently been documented in this population [27, 28]. The present study confirms this: well-controlled asthma (ACQ score <0.75) was achieved in only 15% of smoking patients compared with 33% in nonsmokers ($p<0.001$; data not shown). Treatment adjustments resulted in asthma that could no longer be considered poorly controlled in as many as 33% of smoking patients (data not shown). For this reason, the present authors felt that an ACQ cut-off score of 1.5 (which identifies poorly controlled asthma) was more appropriate for the present data analysis and, thus, selected it for the current study. As this level of control was achieved in only 33% of patients in the present study, the authors also considered the ability of F_{ENO} to detect any significant improvement in asthma control [22]. In this respect, repeated F_{ENO} assessments again appear to be helpful in both populations: in most cases, an F_{ENO} reduction of <20% indicates that no significant improvement in asthma control has occurred. Conversely, F_{ENO} increases of <30% are helpful to rule out mild deteriorations of asthma control. The results of the present study may be summarised as follows: if F_{ENO} does not change as indicated, the level of asthma control is not modified. This seems to remain true regardless of whether the initial ACQ score was high or low, and whether or not the ICS dose was modified.

Interestingly, when patients were treated with high-to-medium ICS doses, F_{ENO} no longer had the ability to reflect an improvement in asthma control for smoking patients, whereas for nonsmoking patients, its ability was only slightly reduced. A similar trend was observed with respect to asthma control deteriorations. These results confirm the overall reduction of the ability of F_{ENO} to reflect asthma control in patients treated with high-to-medium ICS doses, as was documented by the present authors in their previous study [18]. In addition, it appears that confounding factors, such as high ICS doses [29, 30] and tobacco smoking [6, 8–15], which are known to reduce F_{ENO}, would have a cumulative interfering effect that may eventually suppress the ability of F_{ENO} to reflect asthma control. This suggests that the effect of these confounding factors might have to be taken into account when using F_{ENO} to assess asthma control. This needs to be clarified by appropriately designed studies.

In conclusion, the present study is the first to indicate that cigarette smoking does not obviate the clinical value of measuring F_{ENO} in asthma. Indeed, it is shown that even in smokers, sequential changes in F_{ENO} have a relationship to asthma control. The results also suggest that factors, such as smoking and inhaled corticosteroid dose, act cumulatively to influence the ability of F_{ENO} to be used to assess asthma control. Overall, the importance of sequential F_{ENO} measurements in both smokers and nonsmokers is to distinguish whether or not ongoing changes or a sudden change in respiratory symptoms are/is due to changes in airway inflammation, possibly requiring a change in anti-inflammatory therapy. The present data provide evidence that enables the magnitude of changes in F_{ENO} to be more accurately interpreted when addressing this important question.

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