Exhaled Nitric Oxide
A Predictor of Steroid Response

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Rationale: **The initial management of patients who present with persistent respiratory symptoms includes recognizing those with the potential to benefit from inhaled steroid therapy. To date, this has required undertaking a "trial of steroid" to identify responders. There is increasing evidence that steroid response is more likely in patients with eosinophilic airway inflammation, and this can be assessed indirectly using exhaled nitric oxide (F_{ENO}) measurements.** ***Objectives:*** **We aimed to assess the predictive accuracy of F_{ENO} to identify steroid response in 52 patients presenting with undiagnosed respiratory symptoms in a single-blind, fixed-sequence, placebo-controlled trial of inhaled fluticasone for 4 weeks.** ***Methods:*** **Comparisons of predictive accuracy were made between F_{ENO} and other conventional predictors: peak flows, spirometry, bronchodilator response, and airway hyperresponsiveness measured at baseline. "Steroid response" was defined as change in symptoms, peak flows, spirometry, or airway hyperresponsiveness to adenosine based on established guidelines and recommendations.** ***Results:*** **Steroid response was significantly greater in the highest F_{ENO} tertile ($>$ 47 ppb) for each endpoint. This outcome was independent of the diagnostic label. The predictive values for F_{ENO} were significantly greater than for almost all other baseline predictors, with an optimum cut point of 47 ppb.** ***Conclusions:*** **F_{ENO} measurements greater than 47 ppb provide a means of predicting steroid response in patients with undiagnosed respiratory symptoms. Assessing airway inflammation is of more practical value than diagnostic labeling when considering the potential usefulness of inhaled antiinflammatory therapy.**

Keywords: asthma; exhaled nitric oxide; inhaled corticosteroid; symptoms; treatment response

Managing patients with chronic respiratory symptoms due to airway pathology is commonplace, particularly in the primary care setting. Understandably, clinicians aim to establish a firm diagnosis in the first instance, and then proceed to offer treatment. This will often include inhaled antiinflammatory therapy, particularly if the diagnosis is believed to be asthma. However, even in the absence of a confirmed diagnosis, inhaled corticosteroids (ICSs) are often prescribed empirically.

This approach may be problematic. First, respiratory symptoms are nonspecific, with considerable overlap between conditions such as asthma, wheezy bronchitis, eosinophilic bronchitis, postviral airway hyperresponsiveness, chronic obstructive pulmonary disease, vocal cord dysfunction, and primary hyperventilation syndrome. Other related problems may contribute to confusion regarding the true etiology of the patient's symptoms (e.g., gastroesophageal reflux, chronic rhinitis with postnasal drip) (1). Second, conventional lung function tests (e.g., spirometry, peak flows) are poorly sensitive at least for the diagnosis of asthma (2), and cannot be relied on to provide supportive evidence, especially in mild cases. Even if the diagnosis of asthma is firm, there is significant heterogeneity in the response to ICS treatment (3). Thus, patients may be committed to steroid therapy inappropriately, and this is both costly and potentially harmful, particularly at higher doses (4, 5).

An alternative approach would be to identify "steroid responsiveness" in relation to underlying airway inflammation as part of the first-line assessment of patients with undiagnosed respiratory symptoms, in addition to and independently of attaching a diagnostic label. This has already been suggested for chronic obstructive pulmonary disease (6), and given that there is significant overlap between chronic obstructive pulmonary disease and asthma (7), attaching a diagnostic label *per se* is not necessarily helpful in predicting steroid responsiveness (8).

There is increasing evidence that steroid response is more likely in patients with eosinophilic airway inflammation (9), and this can be assessed, albeit indirectly, using exhaled nitric oxide (F_{ENO}) as a surrogate measurement (10–12). With ICS treatment, F_{ENO} levels are reduced in a dose-dependent manner (13, 14), and conversely, levels increase when ICS treatment is withdrawn (15).

Taken together, these data suggest the possibility that F_{ENO} measurements might be used to predict whether patients with nonspecific respiratory symptoms will respond to a trial of inhaled steroids. In this single-blind, fixed-sequence, placebo-controlled study, our aim was to evaluate the accuracy of baseline F_{ENO} measurements to predict a positive response to treatment with inhaled fluticasone.

METHODS

Subjects

We recruited consecutive patients referred by their family practitioner to the Dunedin Hospital pulmonary function laboratory for investigation of persistent, previously undiagnosed respiratory symptoms. The laboratory offers spirometry and bronchial challenge testing as a routine service for community practitioners. Patients were 12 to 75 years old and had respiratory symptoms for a minimum of 6 weeks. Exclusion criteria were as follows: use of ICSs or oral corticosteroids in the previous 4 weeks, respiratory tract infection in the previous 6 weeks, other established respiratory diagnosis, or significant comorbidity. Smokers were not excluded. The study was approved by the Otago Ethics Committee, and all subjects gave written, informed consent.

Study Design

Subjects attended the research clinic on five separate occasions. Short-acting β-agonists taken "as required" were the only inhaled medication permitted until the study was completed, but were withheld for a minimum of 6 hours before each visit. After completing a questionnaire detailing their respiratory symptoms, subjects underwent a fixed sequence of diagnostic tests (Table 1). Between Visits 3 and 4, subjects

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TABLE 1. SCHEDULE OF STUDY VISITS AND PROCEDURES

	Time Interval					
	Run-in, 7–10 d		4 wk		4 wk	
	Visit 1	Visit 2	Visit 3	Visit 4		Visit 5
Clinical assessment	X					
F_{ENO} measurement	X		X	X		X
Spirometry	X			X		X
Bronchodilator reversibility	X					
Methacholine challenge		X				
Adenosine monophosphate challenge			X	X		X
Symptom diary and peak flow measurements	X	X	X	X	X	
Inhaled matching placebo, 1 puff twice daily via spacer				X		
Inhaled fluticasone 250 μg/puff, 1 puff twice daily via spacer					X	

Definition of abbreviation: F_{ENO} = exhaled nitric oxide.

received single-blind treatment with inhaled placebo (1 puff twice daily via metered dose inhaler and spacer [Volumatic; GlaxoSmithKline, Greenford, UK]) for 4 weeks, followed by inhaled fluticasone (250 μg/puff, 1 puff twice daily via matching inhaler) for 4 weeks between Visits 4 and 5. At the final visit, asthma was diagnosed on the basis of a relevant symptom history (present in all subjects) using American Thoracic Society criteria (16) plus one or more of the following:

1. A positive response to bronchodilator, defined as an increase in FEV_1 of 12% or greater from baseline 15 minutes after inhaled albuterol (17);
2. A positive response to ICSs (fluticasone, 500 μg/day for 4 weeks), defined as an increase in FEV_1 of 12% or greater (17) or an increase in mean morning peak flow (over previous 7 days) of 15% or greater (18);
3. A positive test for airway hyperresponsiveness, defined as a provocative dose of methacholine, resulting in a 20% reduction in FEV_1 (PD_{20}) of < 8 μmol (19).

Study Procedures

Respiratory symptoms, bronchodilator use, and peak flows were recorded twice daily in a diary during the run-in and each treatment period. Diurnal peak flow variation was calculated as amplitude % mean over 7 days: a value of 20% or greater was considered clinically significant (20). Using the diary data, a composite symptom score (0 to 10) was calculated for each day (*see* online supplement). Mean values for the composite symptom scores and morning peak flows were obtained for three 7-day intervals: before commencing placebo treatment (run-in), last 7 days of placebo treatment period, and last 7 days of fluticasone treatment period.

F_{ENO} was measured using a chemiluminescence analyzer (NiOX; Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers according to current guidelines at an exhaled flow rate of 50 ml/second (21). All readings were recorded by two staff members who were blinded to the patient's identity and treatment period. Bronchodilator reversibility was calculated as the percentage of change in FEV_1 from baseline, 15 minutes after inhaling 400 μg of albuterol. PD_{20} methacholine and provocative concentration (PC) of adenosine monophosphate (AMP) resulting in a 20% reduction in FEV_1 (PC_{20}) were measured using standard protocols (22, 23).

Study Measurements and Statistical Analyses

To evaluate the predictive accuracy of F_{ENO} measurements, comparisons were made against a range of other "predictors" (Table 2). The response to inhaled fluticasone was assessed using a number of outcome measures (Table 2). "Steroid response" for each endpoint was calculated as the within-treatment changes for fluticasone minus the within-treatment changes for placebo. Thereafter, categoric designation of steroid response was based on cut points obtained from international guidelines (17–19). To assess the association between F_{ENO} and the primary endpoints, subjects were stratified by tertiles for baseline F_{ENO}. This approach permits direct comparisons between the present study and another relevant investigation (6). Comparisons between tertile groups were performed using one-way analysis of variance, with linear contrasts to identify any trend across the three tertiles. For each of the four "steroid response" outcomes listed in Table 2 (A–D), sensitivities, specificities, and posi-

TABLE 2. PREDICTORS AND OUTCOME MEASUREMENTS FOR STEROID RESPONSE

Predictors

Measurements at baseline/run-in

- F_{ENO}
- FEV_1 % predicted
- FEV_1 bronchodilator response
- PD_{20} methacholine
- Diurnal peak flow variation (amplitude % mean, over last 7 d of run-in)

Outcomes

Endpoint	Cut point for significant response	Reference
A. Improvement in FEV_1	> 12%	ATS (17)
B. Improvement in mean morning peak flow (over 7 d)	> 15%	GINA (18)
C. Reduction in composite symptom score	> 1 point	—
D. Improvement in PC_{20} AMP	> 2 doubling dose shift	ERS (19)

Definition of abbreviations: ATS = American Thoracic Society; ERS = European Respiratory Society; F_{ENO} = exhaled nitric oxide; GINA = Global Initiative for Asthma; PC_{20} AMP = provocative concentration of adenosine monophosphate resulting in a 20% reduction in FEV_1; PD_{20} = provocative dose of methacholine resulting in a 20% reduction in FEV_1.

Predictor measurements were obtained at study entry. Outcome measurements were calculated as change for each parameter after 4 weeks' inhaled fluticasone minus the change after 4 weeks' placebo treatment. The cut points for a significant "steroid response" are referenced from current asthma guidelines.

tive and negative predictive values were obtained. Receiver operating characteristic (ROC) curves were then constructed for each of the five predictors. The areas under the ROC curves (AUCs) for the predictors were compared using the method described by Hanley and McNeil (24).

RESULTS

One hundred one consecutive patients were referred to the pulmonary function laboratory during the recruitment interval; of these patients, 60 were enrolled into the study. Thirteen patients could not be contacted further; 13 declined to participate; 15 did not meet the inclusion criteria (7 were taking ICSs, 4 did not have chronic symptoms, 2 had significant comorbidities, 1 had sarcoidosis, and 1 had lower respiratory tract infection). During the study, six patients failed to complete the placebo treatment period (one withdrew consent, one had respiratory tract infection, one had acute rhinosinusitis, and three were lost to follow-up). Two patients withdrew during the fluticasone treatment period (both withdrew consent). Demographic details for the 52 patients who completed the study are shown in Table 3, and have been further stratified for baseline F_{ENO} by tertiles.

A diagnosis of asthma was made in 27 of the 52 patients. The criteria used to confirm the diagnosis of asthma in individual patients are reported in Table E1 in the online supplement. The proportion of patients with asthma was greatest in the highest F_{ENO} tertile (15/17, 88%) compared with the middle (7/18, 39%) and lowest tertiles (5/17, 29%; $p < 0.001$). In the remaining 25 patients, the final diagnoses were as follows: postnasal drip (13), bronchitis (4), gastroesophageal reflux disease (4), primary hyperventilation syndrome (2), bronchiectasis (1), and left ventricular dysfunction (1).

Subjects with baseline F_{ENO} levels in the highest tertile (> 47 ppb) had significantly lower FEV_1 % predicted and FEV_1/FVC ratio and significantly greater improvement in FEV_1 with bronchodilator compared with the other two tertiles. Subjects with F_{ENO} in the highest tertile also had a significantly greater response to inhaled fluticasone for all four categories of "steroid response" (increase in FEV_1, increase in mean morning peak flows, improved respiratory symptoms, and reduction in airway hyperresponsiveness to AMP) as shown in Table 3 and Figure 1.

ROC curves for each of the baseline measurements used as predictors of steroid response are shown in Figure 2. The AUCs for baseline F_{ENO}, FEV_1 % predicted, FEV_1 bronchodilator response, PD_{20} methacholine, and peak flow variation used as predictors were as follows: 0.76, 0.47*, 0.66, 0.63, and 0.63 for increase in FEV_1; 0.81, 0.68, 0.57*, 0.65*, and 0.58* for increase in morning peak flow; 0.64, 0.45*, 0.46*, 0.45*, and 0.46 for decrease in symptom score; and 0.91, 0.68*, 0.71*, 0.84, and 0.72* for improvement in PC_{20} AMP. Values with an asterisk indicate those predictors for which comparisons with F_{ENO} revealed significant differences (*see* Tables E2–E5 for *z*-scores and p values). Sensitivities, specificities, and positive and negative predictive values for each of the predictors in relation to each of the four "steroid response" outcomes are shown in Table 4. In general, baseline F_{ENO} provided greater sensitivities and negative predictive values than for each of the other predictors. Overall, the optimum F_{ENO} cut point as a predictor for each of the four study endpoints was 47 ppb (*see* Tables E6–E9). This cut point was obtained independently of the cut point for the highest F_{ENO} tertile.

DISCUSSION

The results of the present study confirm that using a wide range of possible outcomes to define "steroid response," F_{ENO} measurements provide superior accuracy compared with the majority of other predictors for identifying "responders" among patients

TABLE 3. DEMOGRAPHICS FOR THE 52 SUBJECTS WHO COMPLETED THE STUDY

		F_{ENO} (ppb) by Tertiles			
	All Subjects	< 15	15–47	> 47	p
Demographics					
No. patients	52	17	18	17	
Age, yr (range)	40.5 (14–71)	37.8 (14–67)	39.3 (17–64)	44.1 (18–71)	0.45
Sex, female	32 (76%)	13 (76%)	10 (56%)	9 (53%)	0.31
Smoking history, current/ex/nonsmokers	3/10/39	3/2/12	0/5/13	0/3/14	0.75
FEV_1, % predicted	97.8 (14.2)	101.4 (13.3)	100.8 (14.8)	90.9 (12.6)	0.05
FEV_1/FVC ratio, %	80.4 (9.1)	83.1 (9.4)	83.0 (8.0)	75.3 (8.0)	0.01
FEV_1 bronchodilator reversibility, %	5.2 (4.7)	3.9 (2.3)	4.1 (3.2)	7.5 (6.7)	0.04
Asthma diagnosed*	27	5	7	15	< 0.001
Peak flow variation (amplitude % mean over last 7 d of run-in)	6.3 (3.9)	5.7 (3.5)	5.5 (2.3)	7.8 (5.1)	0.17
Steroid response (absolute changes)†					
FEV_1, % (SEM)	6.5 (2.0)	1.7 (1.7)	2.1 (1.7)	15.9 (5.1)	0.003
Mean morning peak flow (over 7 d), % (SEM)	6.7 (2.2)	1.2 (2.2)	1.9 (2.8)	17.5 (5.0)	0.002
Composite symptom score (SEM)	0.2 (0.4)	1.0 (0.4)	−0.1 (0.7)	−1.5 (0.8)	0.01
PC_{20} AMP, doubling dose shift (SEM)	1.7 (0.4)	0.4 (0.4)	0.4 (0.3)	4.3 (0.7)	< 0.001
F_{ENO}, ppb (SEM)	−27.6 (7.9)	−2.8 (1.4)	−2.6 (3.8)	−80.4 (18.7)	< 0.001

Definition of abbreviations: F_{ENO} = exhaled nitric oxide; PC_{20} AMP = provocative concentration of adenosine monophosphate resulting in a 20% reduction in FEV_1; PD_{20} = provocative dose of methacholine resulting in a 20% reduction in FEV_1.

Data expressed as mean (SD) unless otherwise stated. Data are also stratified by tertiles for F_{ENO} at baseline.

*Diagnosis of asthma was defined as appropriate respiratory symptoms plus one or more of the following: (*1*) a positive response to bronchodilator, defined as an increase in FEV_1 of 12% or greater from baseline 15 min after inhaled albuterol (17); (*2*) a positive response to inhaled corticosteroid (fluticasone, 500μg/d for 4 wk), defined as an increase in FEV_1 of 12% or greater (17) or an increase in mean morning peak flow (over previous 7 d) of 15% or greater (18); (*3*) a positive test for airway hyperresponsiveness, defined as a PD_{20} of < 8 μmol (19).

† Steroid response was calculated as change with inhaled fluticasone minus change with inhaled placebo. Comparisons between tertiles were performed using one-way analysis of variance with linear contrasts to identify any trend across the three tertiles.

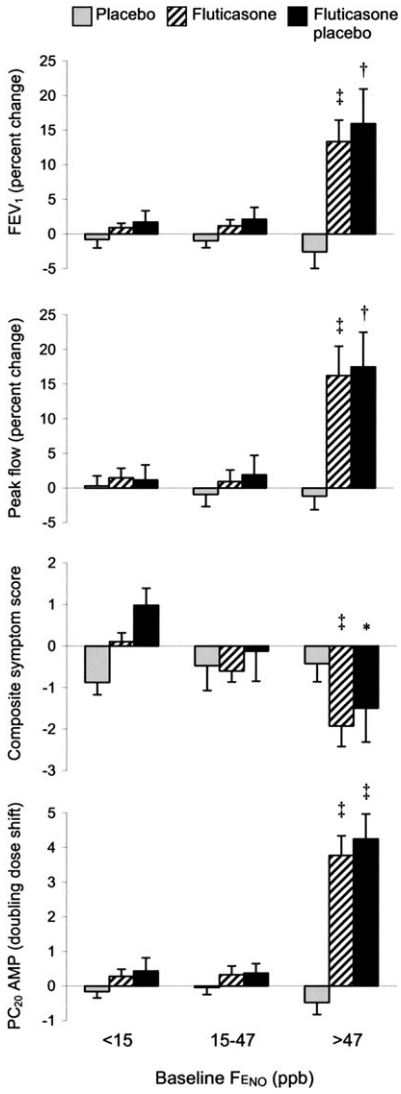

Figure 1. Mean (SEM) changes for each study endpoint. The three *bars* represent changes with placebo, fluticasone, and fluticasone minus placebo, stratified by exhaled nitric oxide (F_{ENO}; expressed as tertiles for all 52 subjects). Comparisons between tertiles were performed using one-way analysis of variance with linear contrasts to identify any trend across the three tertiles (*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$).

with previously undiagnosed persistent respiratory symptoms. First, the change in each of the major study outcomes after 4 weeks of inhaled fluticasone was significantly greater in the highest F_{ENO} tertile group. Second, the AUCs for F_{ENO} were consistently greater than for any other predictor of steroid response (FEV_1 % predicted, bronchodilator reversibility, airway hyperresponsiveness to methacholine, and peak flow variation). For F_{ENO}, the negative predictive values for steroid response ranged from 77 to 94% depending on the endpoint chosen (Table 4), indicating that, in the absence of a high F_{ENO} (> 47 ppb), steroid responsiveness is less likely to be present.

We have previously demonstrated that F_{ENO} measurements may be used helpfully to diagnose asthma (2). Furthermore, the combination of F_{ENO} and spirometric testing provides even higher levels of diagnostic accuracy (25). However, in practice, it is arguably just as important to identify patients who may or may not benefit from inhaled antiinflammatory therapy as it is to attach a diagnostic label. This has been confirmed in the present study. As we have demonstrated, steroid response occurred in relation to baseline F_{ENO} measurements independently of the final diagnosis. This highlights the limitations of using diagnostic labeling to predict treatment response. Rather, it emphasizes the need to assess airway inflammation, even indirectly, to direct treatment (6, 9).

Measuring F_{ENO} is potentially very useful in this regard given that it correlates well with eosinophilic airway inflammation (11, 12). Previously, Pavord and colleagues (9) have confirmed that, in a group of 23 patients with asthma, the response to a short-term trial of inhaled budesonide was greatest in patients with significant sputum eosinophilia. A similar outcome was reported by Meijer and coworkers (26) who studied 120 patients with asthma whose inhaled steroid therapy was withdrawn. High levels of sputum eosinophils were predictive of steroid response. This underlines that, even within a group of patients with diagnosed asthma, steroid response is related to particular characteristics of airway inflammation. Little and colleagues (27) have also confirmed that in patients with asthma, most of whom were taking inhaled steroids, both F_{ENO} and sputum eosinophil counts had high predictive values for any additional available improvement in airway caliber with a trial of oral prednisolone. However, close comparisons with the present study are difficult, given the differences in selection criteria for our study population as well as in the cut points for both F_{ENO} and steroid response measurements. In the study by Meijer and coworkers (26), F_{ENO} levels were not found to provide predictive accuracy, but this may have been influenced by differences in the methods used for F_{ENO} measurement. The strength of the present study is that unselected, steroid-naive patients both with and without asthma were enrolled. This permitted the assessment of airway inflammation *de novo* (albeit indirectly) to be confirmed as a means of predicting steroid response.

Our study design was influenced by a number of factors. First, it has been shown that with a trial of inhaled or oral steroid, a significant carryover effect is likely to occur (8, 28). To avoid this would have required a washout period of at least 1 month. Because our patients were presenting with undiagnosed, untreated symptoms, it was not considered ethical to extend the study (to 3 months) to conduct a random-order crossover study. Rather, a fixed-sequence, single-blind design was used, with placebo given during the first treatment period. In practice, a "trial of steroid" does not usually include placebo comparisons. In our study, the within-treatment placebo response was subtracted from the within-treatment response to fluticasone. This enabled issues of regression to the mean as well the true placebo responses to be taken into account. We chose to report the relationship between steroid response outcomes and baseline F_{ENO} levels using tertiles. This was to facilitate comparisons with a previous study (6). Analysis of our data using F_{ENO} either as a continuous variable or divided into smaller groups (e.g., quintiles) did not alter the statistical significance of the association between F_{ENO} levels and study outcomes.

Clearly, our results were dependent on the criteria used to define "steroid response." These were derived from current international guidelines (17–19). Using these criteria, the specificities for a significant steroid response using F_{ENO} as predictor ranged from 71 to 91%, implying that up to 30% of patients with a high F_{ENO} failed to demonstrate steroid responsiveness (Table 4). This may be explained in part by the fact that many patients had normal lung function, and there was therefore little room for significant improvement with fluticasone. The cut points used to define "response" may therefore have been inappropriate in these patients. Arguably, such individuals might still

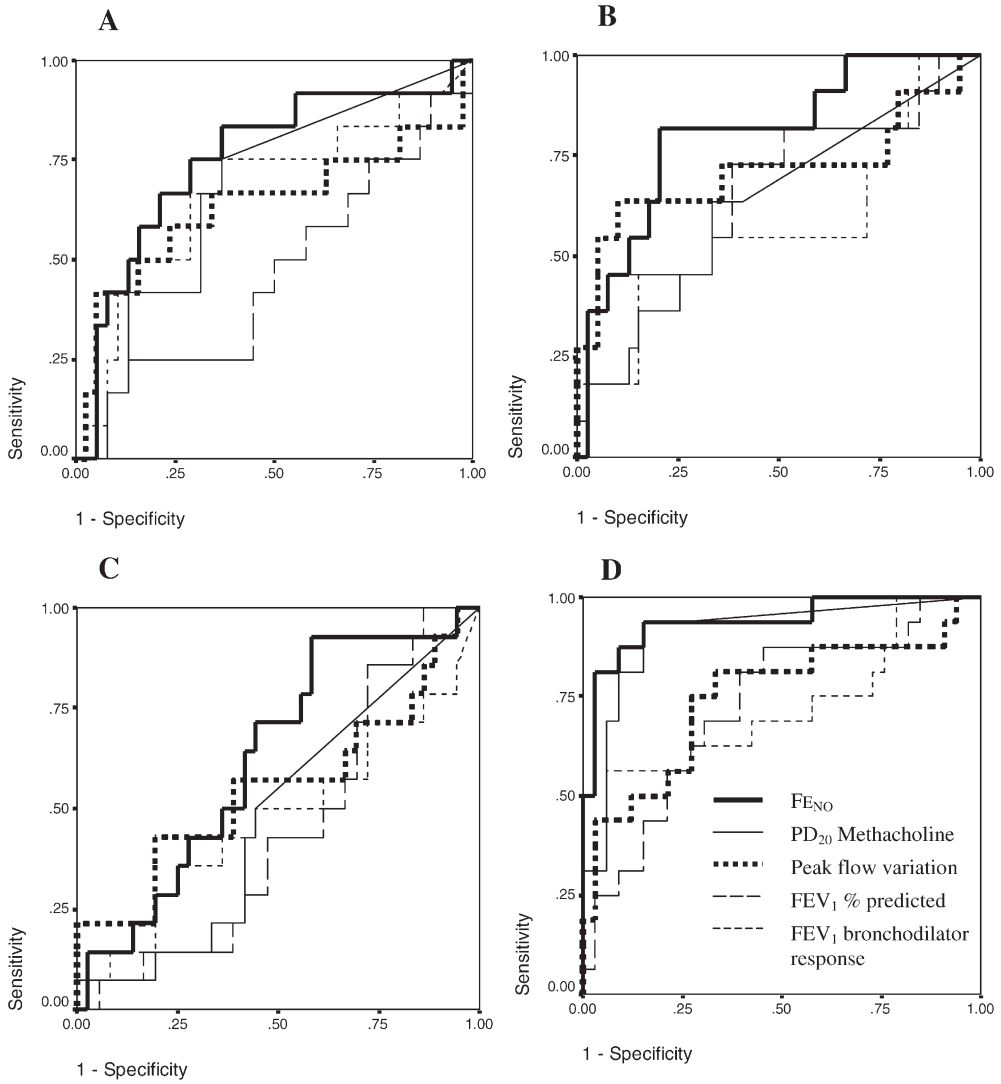

Figure 2. Receiver operator characteristic curves demonstrating the utility of FE_{NO}, PD_{20} methacholine μmol, peak flow variation (amplitude % mean over last 7 days of run-in), FEV_1 % predicted, and FEV_1 change with bronchodilator for predicting response to inhaled fluticasone in patients with nonspecific respiratory symptoms. "Steroid response" was defined as increase in FEV_1 of 12% or greater (*A*) (17); increase in mean morning peak flows (over 7 days) of 15% or greater (*B*) (18); reduction in mean composite symptom score of 1 point or greater (over 7 days; *C*); increase in PC_{20} AMP (mg/ml) of two doubling doses or greater (*D*) (19). FE_{NO} was significantly different from the following: (*A*) FEV_1 % predicted ($p < 0.05$) and PD_{20} methacholine (borderline significance: $p = 0.08$); (*B*) FEV_1 bronchodilator response ($p < 0.01$), PD_{20} methacholine, and peak flow variation ($p < 0.05$); (*C*) PD_{20} methacholine, FEV_1 % predicted, FEV_1 bronchodilator response ($p < 0.05$), and peak flow variation (borderline significance: $p = 0.06$); and (*D*) FEV_1 % predicted ($p < 0.01$), FEV_1 bronchodilator response, and peak flow variation ($p < 0.05$).

benefit from inhaled steroid treatment using criteria for response that were not used in our study. For example, we did not include longer term improvement in symptoms or quality of life as part of our study protocol.

In conclusion, our data provide further evidence of the usefulness of FE_{NO} measurements in clinical practice. The likelihood of steroid responsiveness, or perhaps unresponsiveness, may be helpfully predicted using single FE_{NO} measurements in patients with previously undiagnosed respiratory symptoms. The cut point for optimum predictive accuracy was 47 ppb, which is notably higher than the upper limit of the so-called normal range (35 ppb) (29). This finding does not preclude the possibility that steroid responsiveness may occur at lower FE_{NO} levels, but clearly this is less likely. Using FE_{NO} measurements provides an alternative to securing and applying a diagnostic label, particularly that of asthma, as a guide to treatment. Of course, there is still the need to arrive at an accurate diagnosis in the overall management of patients with ongoing respiratory symptoms, but whether or not to treat with inhaled steroids may be better served by surrogate assessment of airway inflammation using FE_{NO} measurements.

Conflict of Interest Statement: A.D.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.O.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.P.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

TABLE 4. SENSITIVITIES, SPECIFICITIES, AND POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR EACH OF THE BASELINE MEASUREMENTS ("PREDICTORS") USED TO PREDICT "STEROID RESPONSE"

Steroid Response Endpoint	Predictors	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
FEV_1, increase of ⩾ 12%	BD reversibility > 12%*	8	95	33	78
	FEV_1 < 80% predicted†	17	88	29	78
	PD_{20} methacholine < 8 μmol‡	58	69	37	84
	PEFR variation > 20%§	0	97	NA	76
	F_{ENO} > 47 ppb	67	78	47	89
Mean morning peak flow, increase of ⩾ 15%	BD reversibility > 12%	18	98	67	82
	FEV_1 < 80% predicted	36	93	57	84
	PD_{20} methacholine < 8 μmol	55	68	32	84
	PEFR variation > 20%	9	100	100	80
	F_{ENO} > 47 ppb	82	81	53	94
Composite symptom score, reduction of ⩾ 1 point	BD reversibility > 12%	7	95	33	74
	FEV_1 < 80% predicted	7	84	14	71
	PD_{20} methacholine < 8 μmol	29	60	21	69
	PEFR variation > 20%	7	100	100	74
	F_{ENO} > 47 ppb	43	71	35	77
PC_{20} AMP, increase of 2 doubling doses or more	BD reversibility > 12%	18	100	100	71
	FEV_1 < 80% predicted	24	91	57	71
	PD_{20} methacholine < 8 μmol	82	85	74	90
	PEFR variation > 20%	6	100	100	69
	F_{ENO} > 47 ppb	82	91	82	91

Definition of abbreviations: BD reversibility = percent change in FEV_1 with bronchodilator; F_{ENO} = exhaled nitric oxide; NA = not available; PC_{20} AMP = provocative concentration of adenosine monophosphate resulting in a 20% reduction in FEV_1; PD_{20} = provocative dose of methacholine resulting in a 20% reduction in FEV_1; PEFR variation = diurnal peak flow variation (amplitude % mean, over last 7 d of run-in).

The cut point for each of the predictors is derived from current guidelines as indicated by the table footnote symbols. The criteria for "steroid response" for each of the study endpoints were increase in FEV_1 by 12% or greater (17), increase in mean morning peak flow of 15% or greater (18), reduction in composite symptom score of 1 point or greater, increase in PC_{20} AMP of two doubling doses or greater.

* Reference 17.

† Reference 17.

‡ Reference 19.

§ Reference 20.

G.M.-S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.P.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.R.T. has a potential conflict of interest in that Aerocrine, the manufacturer of NiOX analyzers, has recently agreed to donate NO analyzers to his laboratory for evaluation in the course of a future research study. This equipment was not available during the course of the present study, and Aerocrine has had no involvement in the design, execution, or analysis of the present study.

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