

Nitric oxide as a clinical guide for asthma management

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Asthma is a pathologically heterogeneous disease, and the phenotype is characterized by different types of airway inflammation. Exhaled nitric oxide ($F_{E}NO$) measurements are a surrogate marker specific for eosinophilic airway inflammation. The latter is usually associated with steroid responsiveness, and hence, $F_{E}NO$ may be used to guide steroid requirements in certain clinical situations. High $F_{E}NO$ levels may be used to predict likely benefits with inhaled corticosteroid (ICS) therapy. Both high and low $F_{E}NO$ levels are prognostically significant when withdrawal of ICS treatment is being considered. Studies have shown that, just as for induced sputum, repeated $F_{E}NO$ measurements improve the cost-effectiveness of ICS therapy when used to guide dose requirements. In practice, $F_{E}NO$ measurements are useful in the management of severe or difficult asthma. High and low $F_{E}NO$ levels in symptomatic patients provide the clinician with information that enables active eosinophilic airway inflammation to be included or excluded. Either outcome is helpful in decision making. $F_{E}NO$ measurements complement the use of other tests in asthma, but more work is required to determine reference values and cut-points for appropriate interpretation. (*J Allergy Clin Immunol* 2006;117:259-62.)

Key words: Asthma, exhaled nitric oxide, $F_{E}NO$, pulmonary function

Asthma is increasingly recognized as a syndrome rather than a specific disease, and its underlying pathology, clinical manifestations, natural history, and responses to treatment exhibit considerable heterogeneity. Conventional measurements of functional abnormalities, such as airway obstruction and reversibility and bronchial hyper-responsiveness, provide information that describes the

Abbreviations used

$F_{E}NO$: Fraction of nitric oxide in exhaled air
ICS: Inhaled corticosteroid

physiological phenotype. However, because of considerable overlap between asthma and other airways diseases, these data provide only limited guidance to the clinician, both diagnostically and in terms of treatment choices.

More recently, the technique of induced sputum analysis has offered insights into the different pathological phenotypes of asthma. Although characterized predominantly by eosinophilic airway inflammation, in some cases neutrophilic and pauci-granulocytic cell populations occur.¹ The key issue appears to be not only that these entities are different but also that they define the differing capacity to respond—or not—to anti-inflammatory treatment. Airways diseases characterized by eosinophilic inflammation are more likely to benefit from corticosteroid therapy.²

It is against this background that the advent of exhaled nitric oxide ($F_{E}NO$) measurements represents a significant advance in practice. In contrast with induced sputum induction, $F_{E}NO$ measurements are easy to perform and are reproducible. Standards for measurement have been agreed.³ Importantly, measuring $F_{E}NO$ provides a useful surrogate marker for airway eosinophilia.⁴ This feature is critical to the clinical interpretation of $F_{E}NO$ measurements. In atopic asthma, $F_{E}NO$ levels are increased compared with healthy controls, increase further when asthma becomes unstable, and are reduced with steroid treatment. Just as importantly, levels are likely to be low in the absence of eosinophilic airway inflammation. This is diagnostically helpful: in such circumstances, alternative diagnoses should be considered. These include neutrophilic asthma, anxiety/hyperventilation, vocal cord dysfunction, rhinosinusitis, gastroesophageal reflux, chronic obstructive pulmonary disease, or even cardiac disease.

The role of $F_{E}NO$ measurements in the management of asthma per se is still an evolving one. However, recent studies now provide a sufficient body of evidence to support this application in clinical practice.

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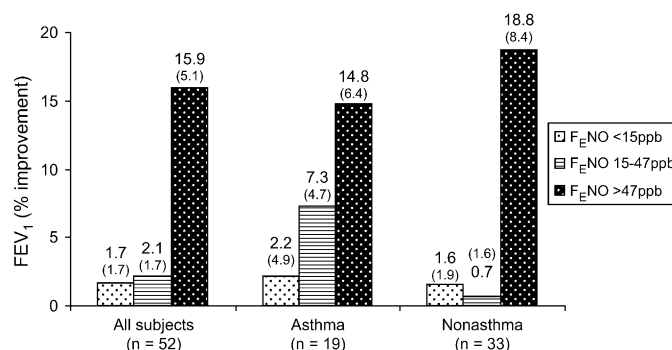


FIG 1. Changes in FEV₁ (% improvement) following 4 weeks of treatment with inhaled fluticasone 500 µg/d in 52 subjects with chronic nonspecific respiratory symptoms, stratified by baseline F_ENO (tertiles). The changes in FEV₁ were significantly higher in the group with the highest F_ENO (greater than 47 ppb) using 1-way ANOVA for trends across all 3 groups ($P < .01$). Data are also given after stratifying by clinical diagnosis made at the time of initial presentation based on symptoms, bronchodilator response, and/or a positive test for airway hyperresponsiveness (asthma versus nonasthma).⁷

STARTING AND STOPPING INHALED STEROID THERAPY

The decision to commence inhaled corticosteroid (ICS) therapy in patients with chronic symptoms of cough, wheeze, and shortness of breath is often empiric. The assumption is made that these symptoms are a result of uncontrolled airway inflammation, and in turn, that anti-inflammatory treatment is appropriate. However, this approach is flawed. First, the correlation between respiratory symptoms and airway inflammation is very weak,⁵ and second, not all airway inflammation is steroid-responsive.⁶

Recently, Smith et al⁷ showed that F_ENO measurements provide a useful guide about whether benefits will be obtained from a trial of ICS treatment. Among 52 steroid-naïve patients with chronic respiratory symptoms, the response to inhaled fluticasone for 4 weeks was significantly greater than placebo and occurred predominantly in the 1/3 of subjects whose F_ENO was greater than 47 ppb (Fig 1). The negative predictive values were high (77% for symptoms; 89% for improvement on spirometry); that is, in the absence of high F_ENO levels, a response to steroid was much less likely. These results are consistent with those of Szeffler et al,⁸ who demonstrated that the mean F_ENO levels in children who were steroid-responsive (54 ppb; 95% CI, 19-90) were significantly greater than in those who did not respond (mean F_ENO, 23 ppb; 95% CI, 10-41).

Measurements of F_ENO are also helpful when considering stopping ICS therapy if asthma appears to be in remission. Is remission the result of ICS treatment or independent of it? Can treatment be discontinued safely? Pijnenburg et al⁹ have recently addressed this issue in a study of 40 children with stable asthma. ICS treatment was withdrawn, and 9 relapsed during the 24-week follow-up interval. In contrast with the nonrelapsers, their F_ENO levels rose steadily during the postwithdrawal period, from a mean F_ENO at baseline of 14.8 ppb to 40.8 ppb at 4 weeks. The values were 10.5 ppb and

15.9 ppb, respectively, in the nonrelapsers ($P = .01$). Optimum positive and negative predictive values for subsequent relapse were obtained at a F_ENO of 49 ppb, which is remarkably similar to the cut-point for “steroid-responsiveness” obtained in the study by Smith et al.⁷ In a similar study, Zacharasiewicz et al¹⁰ concluded that the absence of sputum eosinophils, with simultaneously low F_ENO levels, predicted successful withdrawal of ICS therapy in children.

OPTIMIZING INHALED STEROID THERAPY

At least in this country, there has been a trend over recent years for increasingly high doses of ICS therapy to be prescribed in patients with persistent asthma. In addition to the economic cost, the risk of adverse systemic effects also increases significantly with higher doses.¹¹ Clearly, any practical strategy that might improve the cost-benefit ratio for ICS prescribing would be an advance.

The concept that “inflammometry” might be used to guide anti-inflammatory therapy in asthma—as an alternative to a conventional approach based on symptoms, bronchodilator use, and peak flows—is entirely rational. Anti-inflammatory treatment ought to be guided by ongoing assessment of airway inflammation or appropriate surrogates. Previously, Sont et al¹² and Green et al¹³ have investigated the use of regular bronchial hyperresponsiveness testing and induced sputum eosinophil counts, respectively, as the basis for ICS dose adjustment in asthma. Both investigators demonstrated that using the alternative strategy, outcomes with ICS treatment were improved. In the study by Green et al,¹³ a 68% reduction in asthma exacerbation rates was obtained in the strategy group compared with the conventional group. However, this was achieved using comparable doses of ICS in both treatment groups.

The results of these studies indicate the potential advantages of adjusting ICS dose on the basis of regular “inflammometry” rather than clinical parameters.

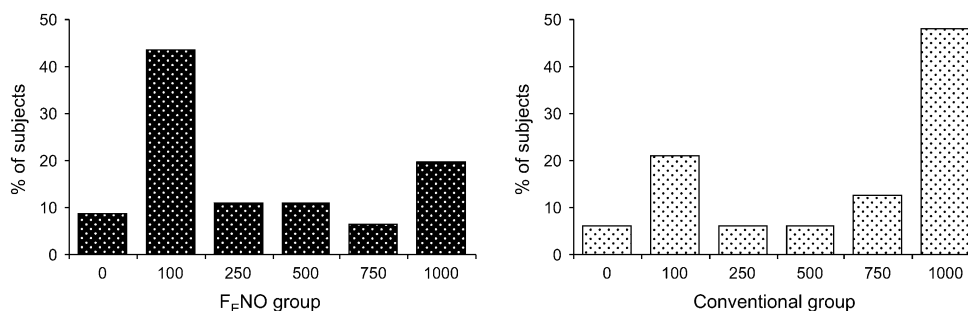


FIG 2. Distribution of mean inhaled fluticasone doses (over 12 months) in 2 asthma management groups, one using F_ENO measurements (n = 46) and the other conventional group in which symptoms, bronchodilator use, and lung function were used in accordance with a priori criteria (n = 48). There was a highly significant difference between the 2 groups ($P = .008$). Downward dose adjustments were made in the F_ENO group if the F_ENO level was less than 35 ppb.¹⁴

However, their application is clearly limited: frequent bronchial hyperresponsiveness testing or sputum induction is impractical. So what about F_ENO? In a recent study by Smith et al,¹⁴ a similar hypothesis was tested, namely that repeated measurements of F_ENO as a guide to treatment would improve the cost-effectiveness of ICS use. In that study, a somewhat different but nonetheless significant outcome was achieved. In the F_ENO group, there was a 46% reduction in the number of exacerbations, but this was nonsignificant. However, simultaneously, there was a highly significant reduction in the mean daily dose of inhaled fluticasone (over 12 months): 370 μ g/d for the F_ENO group (95% CI, 263-477) versus 641 μ g/d for the control group (95% CI, 526-756), a difference of 270 μ g/d (95% CI, 112-430; $P = .003$). The distribution of dose requirements was strikingly different between the 2 groups (Fig 2).

There are a number of explanations for these results. First, the choice of cut-point for F_ENO may have been inappropriately high (it was 35 ppb). If a lower cut-point for downward dose titration had been used in the F_ENO group, then the mean daily fluticasone dose would have been increased, and arguably the exacerbation rate in that group would have been reduced, possibly to the point of statistical significance. The overall result might then have mirrored that of Green et al.¹³ Alternatively, it could be argued that the between-group dose difference resulted from the control group receiving inappropriately high doses of ICS—but this calls into question the thresholds for ICS dose adjustment that are currently specified in conventional guidelines to determine poor asthma control and hence the need for increased anti-inflammatory treatment.¹⁵

Whatever the interpretation, the study by Smith et al⁷ provides evidence to support the view that “inflammometry,” this time using F_ENO measurements, rather than the use of clinical parameters, may provide for more effective management in chronic persistent asthma.

DIFFICULT ASTHMA

We have recently introduced F_ENO measurements into the range of tests provided in our local pulmonary function

laboratory. Apart from their diagnostic role in the work-up of patients with nonspecific respiratory symptoms, they are also helpful in ongoing asthma management, particularly if it is severe, difficult, or both.

There are now sufficient data¹⁶ to provide a provisional schema for interpreting F_ENO results in patients with asthma. To summarize, low F_ENO levels (<25 ppb) in an asymptomatic individual indicate that ICS dose may be reduced, or even withdrawn altogether. Low levels in a symptomatic patient indicate that whatever the cause of persistent symptoms, it is unlikely that eosinophilic airway inflammation is one of them. The diagnosis of atopic asthma ought therefore to be questioned, and/or other factors should be sought, to explain ongoing symptoms such as uncontrolled rhinosinusitis, gastroesophageal reflux, and anxiety-hyperventilation. Often these factors coexist, but having F_ENO measurements provides a helpful alternative to guessing which of them is the most important. Why? Because none of these other entities will benefit from increased doses of ICS treatment.

High F_ENO levels (>45-50 ppb) in an asymptomatic individual do not necessarily imply the need for clinical intervention and should be interpreted strictly with reference to the clinical history. Unfortunately, in a patient with active asthma, they do not necessarily predict an imminent exacerbation,¹⁷ although as previously stated, they appear to be relevant in predicting the outcome with steroid withdrawal if the asthma is in remission.^{9,10} High levels in a symptomatic patient imply inadequate ICS treatment. In the first instance, poor compliance and/or poor inhaler technique are the most likely explanations. Thereafter, high levels indicate the need for increasing the dose of inhaled or even oral corticosteroid therapy. Only rarely do they indicate true steroid resistance.

PRACTICAL PROBLEMS

A number of important questions regarding the application of F_ENO measurements in asthma still remain to be resolved. Perhaps the most important of these is the issue of clinically meaningful cut-points. This is an important issue in the design and interpretation of clinical studies. It

is also problematic in practice. The interpretation of intermediate values (in the range 25–50 ppb) remains unclear. The suggested cut-points for low and high $F_{E}NO$ have been obtained in either healthy populations or those with mild to moderate asthma. Do they apply in severe or difficult asthma? In the study by Kharitonov et al,¹⁸ the upper limit of normal for $F_{E}NO$ was 33 ppb, and the between-sitting variability was ± 4 ppb. However, in the study by Jones et al,¹⁷ changes in $F_{E}NO$ between stability and poor control in 77 patients ranged from -10 ppb to $+141$ ppb (mean, 24.9 ppb), indicating very high interindividual variation with deteriorating asthma. Thus, using group mean data to derive meaningful thresholds for clinical decision making may be inappropriate. An individual $F_{E}NO$ type may be more relevant for determining what constitutes a clinically important change in specific patients.

CONCLUSION

Measurements of $F_{E}NO$ provide a perspective on airway pathology that complements conventional assessment of airway function in the diagnosis and ongoing management of asthma. They shed light on whether symptoms are attributable to uncontrolled eosinophilic airway inflammation, and in turn on whether the patient may benefit from more or less inhaled corticosteroid—or none at all. The technique is coming of age, and $F_{E}NO$ measurements now have a useful place in day-to-day practice. But we are still learning.

All numeric references to $F_{E}NO$ are reported in parts per billion at or corrected for the recommended expiratory flow rate of 50 mL/s.

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Correction

With regard to the November 2005 supplement entitled “Attaining optimal asthma control: A practice parameter” (2005;116:S3–S11): The following entry should have appeared under the list of Reviewers:

Bradley E. Chipps, MD, Sacramento, Calif

Our apologies to Dr Chipps for the inadvertent omission.