Non-Invasive Monitoring of Inflammation in Asthma Using Exhaled Nitric Oxide

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Abstract

Management of asthma is currently based on symptoms (in children, usually a second-hand report from parents) and lung function measurements. Inhaled steroids, targeted at controlling airway inflammation, are the mainstay of asthma management. Due to possible side effects they should be used at the lowest possible doses while asthma is adequately controlled. Fractional exhaled nitric oxide is a simple non-invasive method to assess inflammation in asthma, and its role in asthma management is increasing in popularity. The present review summarizes recent research on the use of FeNO in monitoring airway inflammation and optimizing asthma management. The addition of FeNO measurements to the conventional assessment of asthma control appears promising. The practicability of including this measuring method into everyday clinical practice is currently being evaluated.

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Since the first international publication of Asthma Management Guidelines in 1991, the assessment and management of asthma have been based solely on symptoms and lung function. Although commonly adopted and frequently used, applying these guidelines into daily practice has been difficult [1,2]. Recent guidelines published by GINA (Global Initiative for Asthma) have created a new important paradigm change in the management of asthma [3]. For the first time, these new published guidelines emphasize the importance of asthma control as the core of asthma assessment and management. Since asthma is an inflammatory disease of the airways it is now clear that in order to achieve control the major task is to reduce airway inflammation. Indeed, most of the recommended therapies to achieve control are aimed at reducing airway inflammation. Monitoring airway inflammation is necessary to assess whether therapy is effective and whether control is achieved.

How can airway inflammation be monitored? Currently there are several direct methods to detect airway inflammation, such as bronchial biopsy and bronchoalveolar lavage. However, these are time-consuming and invasive tests with a very low practical applicability, and repeating them for monitoring purposes is partly unethical. Surrogate markers of airway inflammation, such as induced sputum analysis for eosinophils and their products, are possible options in specialized practice. Other methods to monitor airway hyper-responsiveness – a prevalent feature in asthmatic subjects – have been used infrequently, for example, methacholine or adenosine monophosphate challenge tests.

In clinical practice the degree of airway inflammation is suggested indirectly by subjective parameters such as frequency and severity of symptoms (wheeze, cough, shortness of breath). This is, however, patient-derived information and does not accurately reflect the degree of airway inflammation. Moreover, the correlation between airway inflammation and either symptoms [4,5] or even lung function is weak [6,7].

It has now been established that FeNO, the fraction of nitric oxide in exhaled air, is an important marker of airway inflammation and can be measured non-invasively. FeNO measurements have emerged as a potentially important clinical tool that uses a range of commercially available analyzers. Smaller less costly hand-held devices are also becoming available. FeNO measurements can be performed online, with direct exhalation into the NO analyzer, or offline. We describe here the rationale and applicability of FeNO measurements as a non-invasive marker to assess and manage asthma, with particular reference to steroid therapy adjustment.

What is NO?

Nitric oxide is an endogenous messenger generated in the lower airways by enzymes of the NO synthase family, although non-enzymatic synthesis and consumptive processes may also influence levels of NO in exhaled breath. It has a diverse range of effects including non-adrenergic, non-cholinergic neurotransmission and vascular and non-vascular smooth muscle relaxation [8]. In pathological situations NO is a pro-inflammatory mediator with immunomodulatory effects [8]. On the other hand, under physiological conditions NO acts as a weak mediator of smooth muscle relaxation and protects against airway hyper-responsiveness [9].

In 1991, Gustafsson et al. [10] described the measurement of NO in the exhaled air of humans, rabbits and guinea pigs,

FeNO = fractional exhaled nitric oxide

leading to the eventual development of commercial instruments for the real-time measurement of FeNO. In humans, exhaled air NO appears to originate in the airway epithelium [11]. Although raised levels may occur in a number of airway or lung diseases [12], at present the most important context in which the measurement of NO is clinically useful is asthma.

Technical considerations

Initial studies of FeNO levels in normal controls and patients with asthma highlighted the importance of standardization of expiratory flow rates. At low exhaled flow rates, FeNO levels are relatively high, whereas the levels are lower with increasing exhaled flow rates. This is explained by the fact that NO reaches the bronchi and, therefore, the exhaled air, primarily by diffusing across tissue, down its concentration gradient, and in a time-dependent manner. With slow exhaled flow rates, there is ample time for NO to diffuse down its concentration gradient, and FeNO levels primarily represent bronchial NO concentrations. In the alveoli, NO levels are low and remain in a steady state because of the high avidity of NO for hemoglobin. At high flow rates, there is less time for bronchial diffusion, and the lower FeNO levels reflect a more significant alveolar component.

The need for uniform and standardized testing was recently addressed in a combined American Thoracic Society/European Respiratory Society statement [13]. It describes a standardized technique of measurement and a recommended flow rate. The statement recommends performing a minimum of three exhaled measurements at 0.050 L/sec, each with an FeNO within plateau variation of ≤ 10% or 1 part per billion, and with ≤ 5% variation between the three readings.

Routine methodology can be used in children from the age of 4–5 years. The results are highly reproducible and immediately available, and the test can be repeated easily and as often as needed. Normal reference values are available. Both of the present authors use these measurements in their routine practice.

FeNO as an inflammometer in asthma

There is a significant relationship between FeNO and eosinophilic airway inflammation, and there is an equally important relationship between eosinophilic airway inflammation and steroid responsiveness. Hence, it is now well established that FeNO is the first bedside test to indirectly assess eosinophilic airway inflammation in the bronchial mucosa in asthmatics. Allergic asthmatics usually have high FeNO levels when untreated. These levels are expected to show a rapid dose-dependent response to corticosteroids. Possible applications of FeNO include screening for asthma and diagnosis of asthma, monitoring of treatment response and treatment compliance, steroid dose titration, and prediction of exacerbation or relapse.

A strategy where inflammometry identifies the patient with airway inflammation would potentially prevent over-treatment and allow for titration towards the lowest effective dose of steroids. It may also alert for under-treatment or non-compliance. A remarkable study in adults by Smith and colleagues [14] has shown that FeNO can be used as a non-invasive marker to adjust inhaled corticosteroid treatment. The final mean daily doses of ICS after one year of following patients using conventional methods in one group and FeNO in the other treatment group was significantly lower in the FeNO group without higher exacerbation rates. Hence the authors concluded that with the use of FeNO measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control. Pijnenburg et al. [15] used FeNO to adapt the steroid dose in children but followed a protocol that was close to normal asthma management. Children with asthma had their steroid doses altered according to either FeNO or symptoms, and both the patients and the doctors were blinded to group allocation. For ethical reasons, symptoms could overrule FeNO results if the symptom scores were high; in that case (high symptom scores) therefore, the doses were not reduced even when FeNO was low. In all other situations, it was the FeNO level that determined steroid dose in the FeNO group. While no difference in the cumulative steroid dose was found after 1 year, interestingly however, a striking 2.5-doubling dose improvement in hyper-responsiveness was seen in favor of the FeNO group. Elevated levels of FeNO were found in the control group, probably indicating worse inflammation after one year of steroid dose titration on the basis of symptoms alone. Severe exacerbations, defined as the need for a course of oral prednisone, were more frequent in the control group (18 versus 8 in the FeNO group), but the study was not powered to detect significant differences in severe exacerbations. Therefore FeNO monitoring every 3 months in addition to conventional asthma management reduced airway inflammation without the need for more steroids. These results can be compared to a study conducted by one of the present authors, where a different longitudinal observational study design was used to assess the clinical use of FeNO measurements during stepwise steroid reduction in children [16]. We measured various non-invasive markers including FeNO at each study visit. Treatment decisions were not based on the result of these measurements, but ICS reduction was performed merely according to symptoms and lung function test results. A retrospective analysis of the visits prior to loss of control showed that using an elevated FeNO level ≥ 22 ppb as part of the clinical assessment of the individual patient could help optimize therapy, as 78% children above this level failed dose reduction despite fulfilling clinical guideline criteria. On the other hand, in 39% of the cases treatment reduction was successful despite elevated levels [16].

Predicting loss of control

Proof of concept that the use of FeNO to monitor airway inflammation can help predict success or failure of ICS reduction is now available [16]. Zacharasiewicz and co-authors [16] reported FeNO ≥ 22 ppb to be a significant predictor for failed ICS reduction in children with apparently well-controlled asthma. Using a cutoff of ≥ 22 ppb, the sensitivity for FeNO to predict loss of control was 78.6%, with a specificity of 68.6%. Following this report Pijnenburg

ICS = inhaled corticosteroid treatment
ppb = parts per billion

et al. [17] published similar data showing that FeNO at 2 and 4 weeks after discontinuation of ICS predicts relapse. The highest sensitivity and specificity for FeNO in their study using a cutoff level of FeNO of 49 ppb was 71% and 93% respectively. This considerably higher cutoff level could be explained by the wide range of FeNO values in children who are currently off steroids and are asymptomatic, as the relevance of an increased FeNO in asymptomatic children off treatment still remains unclear. In a recent study by Fritsch and co-authors [18], FeNO was related to important markers of asthma control. A therapy regimen aimed at lowering FeNO in children with asthma improved parameters of small airway function but was not able to improve clinical markers of asthma control. Data in adults suggest combining FeNO and forced expiratory volume in the first second (percentage of predicted) can stratify risk for asthma exacerbation [19].

Pitfalls

It is very important to note that some patients have persistently high FeNO levels despite treatment, implying that FeNO cannot simply be incorporated in current treatment guidelines [20]. It has even been shown that some adults in clinical remission of asthma may have elevated FeNO levels [4]. Also in children with asthma, FeNO has shown a varied response to ICS. Allergy and bronchial hyper-responsiveness influence FeNO level independently of high dose steroid treatment. This should be considered when using FeNO for steroid dose titration [21]. Several studies have shown that atopic asthmatic patients have higher FeNO values than patients with asthma without atopy [22]. Also, atopic smokers without asthma have been shown to have higher FeNO levels as compared to non-atopic individuals [23]. Another important aspect is that elevated FeNO levels in patients on ICS may simply reflect poor compliance, and confounding factors such as disease activity and inhaler technique need to be carefully considered [24]. It may thus prove clinically more useful to compare FeNO values with a subject's previous values than to compare them with a population-based normal range.

Larger more statistically powerful studies are urgently needed to further validate the best cutoff levels and to assess to what extent individual monitoring rather than group cutoff levels could improve asthma outcome.

In summary, it seems the time has come to start introducing FeNO into the routine clinical assessment of asthma in specialist practice, and to take FeNO levels into account when deciding on treatment.

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