

Does exhaled nitric oxide measurement have a role in asthma care?

John Oppenheimer, MD,* and Christine A. Sorkness, PharmD†

Recent guidelines have highlighted the importance of attaining and maintaining control in asthma, yet there currently is no perfect measure of control.^{1–3} One issue that is clearly gleaned from the literature is that although correlation exists among various measures of asthma control, no single variable can provide the complete picture. A composite of several indicators of control is required.⁴ These components include patient history, such as nocturnal awakening, β_2 -agonist rescue use, limitations in daily activity (and/or validated tools such as the Asthma Control Test or Asthma Therapy Assessment Questionnaire), and objective measures of lung function. It is hoped that in the future we will have a generally agreed on validated tool to better evaluate asthma control. Future evaluation of asthma control will likely include measures beyond medical history and lung function, such as indicators of airway inflammation.³ Because asthma is predominantly an inflammatory disorder, it is intuitive that a noninvasive biomarker evaluation of inflammation needs to be an integral component of diagnosis and management strategies.

A study by Sont et al⁵ catalyzed interest in measures of inflammation as a tool for titrating maintenance therapy. These investigators examined adjustment of controller medicine using a standard guidelines approach compared with controller medicine adjustment directed to minimize airway hyperresponsiveness (AHR) via methacholine challenge. Their hypothesis was that control of AHR would correlate with improved asthma outcomes. This premise proved true; a 1.8-fold reduction in mild exacerbations and a greater reduction in thickness of the subepithelial reticular layer (obtained via bronchial biopsy) were achieved in the AHR-directed group. Similarly, in a study by Green and colleagues,⁶ normalizing sputum eosinophil counts also resulted in a reduction in asthma exacerbations. Unfortunately, both of these procedures are cumbersome and thus impractical in standard clinical practice. For this reason, efforts are ongoing in the search for a surrogate measure of inflammation that is reproducible and practical in “real-world” asthma care. Many had

hoped that measurement of exhaled nitric oxide (eNO) would fill this role. With an initial positive study and several Food and Drug Administration–approved devices that are not cost prohibitive, many specialists have added this measure to their evaluation of patients with asthma. A great deal of enthusiasm followed the positive study by Smith and colleagues,⁷ who demonstrated that when comparing standard guidelines–directed care to the addition of eNO, the latter group demonstrated a statistical reduction in maintenance therapy required, while simultaneously achieving a trend toward decrease in asthma exacerbations. The results of this study supported the hypothesis that control of a surrogate of inflammation translated to improved asthma control.

However, several more recent studies have questioned the utility of eNO. In the first, Shaw and colleagues⁸ examined the addition of eNO to standard care in a primary care setting and found no significant improvement in asthma control or medicine titration. The most recent study by Szeffler and colleagues⁹ further questions the contribution of eNO measures. In this multicenter trial, which compared guidelines based care alone with a strategy directed toward a decrease in eNO, the authors examined a large cohort of inner-city residents with asthma. Like Shaw et al, they were unable to demonstrate added benefit with the use of eNO measures. In their 46-week study, they demonstrated no difference in number of days with asthma symptoms, pulmonary function, or asthma exacerbations, despite the fact that the eNO group received approximately 80 μg more of inhaled corticosteroids (ICSs) daily. Thus, physicians are left to question whether eNO provides any added benefit to the present measures of asthma control.

Potential concerns come to mind when considering the present use of eNO in the care of patients with asthma. The first issue is that we may be using the wrong protocol for interpreting eNO. Currently, we rely on an eNO cutoff level (generally between 20 and 30).¹⁰ It is well known that eNO is sensitive to the use of ICSs and that significant variation in levels occur in the population with asthma.^{11,12} Thus, possibly a change in the level of eNO vs a specific cutoff would provide a more useful measure. This premise is demonstrated in a study by Jones et al¹³ that evaluated the usefulness of eNO in diagnosing and predicting loss of control in asthma after ICS withdrawal. These investigators found that analysis

Affiliations: * Pulmonary and Allergy Associates, New Jersey Medical School, Cedar Knolls, New Jersey; † Department of Pharmacy and Medicine, University of Wisconsin, School of Pharmacy, Madison, Wisconsin.

Disclosures: Authors have nothing to disclose.

Received for publication December 17, 2008; Received in revised form January 6, 2009; Accepted for publication January 7, 2009.

of change from baseline in eNO level had a higher positive predictive value compared with an absolute value cutoff.

The second potential pitfall could be the fact that asthma is a heterogeneous illness and, as a consequence, not all asthmatic patients are significant producers of eNO. This circumstance should come as no surprise, because the eosinophil (which is the major source of eNO) is not the principal inflammatory cell in 50% of those with asthma.¹⁴ These facts do not diminish the potential utility of this measure. Certainly in the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial, Szeffler and colleagues¹⁵ identified eNO as a biomarker that predicted effectiveness of asthma pharmacotherapy. Specifically, children with elevated eNO levels (>25 ppb) demonstrated an odds ratio of ICS response of 2.8 compared with children without elevated eNO levels. In a recent analysis of the Pediatric Asthma Controller Trial, baseline eNO predicted the differential treatment response for fluticasone over montelukast regarding the gain in asthma control days (adjusted $P = .01$).¹⁶ Thus, eNO may aid the physician in differentiating asthma phenotype and guiding therapy selection. Likewise, in a recent study by van Veen and colleagues,¹⁷ the authors found that in a group of patients with difficult-to-treat asthma, those with normal lung function and elevated eNO levels (despite high-dose ICS use) demonstrated an accelerated decline in lung function when compared with those with low levels of eNO. Measurement of eNO may also prove a valuable tool in determining adherence with ICS therapy because it is sensitive to its use. Silkoff and colleagues¹¹ demonstrated utility of this biomarker. Prompt reduction in elevated eNO levels occurred with introduction of ICSs, which once again became elevated with discontinuation of ICS therapy.

The third potential concern is that eNO is not a useful intermittent measure of future control but may be beneficial in the measure of "real-time" control via daily in-home measurements. In essence, it is not analogous to a hemoglobin A_{1C} measure but more synonymous to home glucose measurements via a glucometer. This issue is exemplified in a study that monitored eNO on a daily basis and examined its association with asthma instability.¹⁸ Mean morning eNO before an asthma event was significantly higher than those with asthma stability. Having a reliable home device is of import because currently there is no good home-based measuring tool. Although daily peak flow measurements are recommended by some, a study by Buist et al¹⁹ demonstrated that the addition of peak flow measurements provided no added benefit to standard symptom-based care. Thus, exploration of other home controls is still warranted.

Lastly, eNO may not provide added benefit in the care of patients with asthma. If this is true, it would not rule out the utility of other measures of exhaled secretagogues. Reinforcing this concept are several preliminary reports have explored additional exhaled secretagogues. Studies have demonstrated the value of exhaled leukotriene (LT) C₄ and the pH of exhaled breath condensate (EBC).^{20,21} In a study by Čáp et al,

patients with mild to moderate persistent asthma treated with ICSs and age-matched healthy controls had their EBC analyzed for LTB₄, LTC₄, LTD₄, and LTE₄ via gas chromatography/mass spectrometry.²⁰ Concentrations of LTC₄ in EBC were either close to or below the detection limit of 1 pg/mL, whereas median exhaled LTD₄, LTE₄, and LTB₄ concentrations in adults with asthma were increased 4.1-fold, 1.8-fold, and 2.6-fold, respectively, compared with values in healthy adults. In the case of EBC pH, Hunt and colleagues²¹ demonstrated that the pH measures were found to be more than 2-log orders lower in patients with acute asthma exacerbation compared with control subjects and that the EBC pH normalized with corticosteroid therapy.

In conclusion, it is evident that improvement in our present diagnostic evaluation of asthma control is needed. Although the recent study by Szeffler and colleagues questions the utility of eNO as an intermittent measure of asthma control, it does not rule out alternative applications and reinforces the need to find other surrogate measures of inflammation in the quest to attain and maintain asthma control for our patients.

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- Requests for reprints should be addressed to:*
John Oppenheimer, MD
Pulmonary and Allergy Associates
8 Saddle Rd
Cedar Knolls, NJ 07927
E-mail: nallop@optonline.net
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