EXHALED NITRIC OXIDE

THE UTILITY OF EXHALED NITRIC OXIDE AS A MARKER OF BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN WITH MILD TO MODERATE PERSISTENT ASTHMA

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Statement by Author

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Abstract

Asthma remains a prevalent disease with significant morbidity and mortality. Currently, the diagnosis and treatment of asthma in the clinical setting is dependent on reported symptoms, measurements of lung function, and bronchodilator response. However, a review of current literature suggests these measures may not accurately reflect the extent of BHR or underlying inflammation in the airways. Updates to current national guidelines have highlighted the potential diagnostic role of exhaled nitric oxide (ENO) measurements in pediatric asthmatic patients. A significant body of research confirms that ENO is elevated in patients with asthma and ENO has been shown to distinguish subjects with asthma from those without asthma with a high degree of discriminatory power. Moreover, ENO correlates well ($r = -0.65; p<0.0001$) with airway hyperresponsiveness, a characteristic feature of asthma. Can the measurement of ENO enable clinicians to make the diagnosis of asthma more easily, confirm the diagnosis with much greater confidence, and manage the disease more appropriately than has been possible to date? This paper reviews current literature examining the utility of exhaled nitric oxide as a marker of bronchial hyperresponsiveness in children with mild to moderate persistent asthma to help answer this question.
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CHAPTER I
INTRODUCTION

Asthma poses a growing problem for society, healthcare professionals, and those individuals directly affected by the disease in terms of the costs associated with it and escalating morbidity rates (Cicutto & Downey, 2004). The prevalence of asthma has increased sharply in the United States and around the world in the past 30 years. A review of studies performed in 17 countries during the 1960s and repeated in the 1990s confirms an international increase in asthma prevalence (Woodruff & Vahy, 2001). The International Study of Asthma and Allergies in Childhood, which examined the prevalence of asthma in 56 different countries in the 1990s, found that prevalence ranged from 2% to 3% in Eastern Europe, Indonesia, Greece, Uzbekistan, India, and Ethiopia to 20% in the United Kingdom, Australia, and New Zealand (Woodruff & Vahy, 2001).

Although some of this is certainly due to advances in the early diagnosis of the disease, epidemiological data indicates that there has been a real increase in the incidence of asthma and the reasons for this are not yet clear and likely include multiple contributing factors (Carmen & Landau, 1990).

The finding that affluent countries have higher asthma prevalence has prompted speculation about the effects of affluence, modernization, or “western lifestyle” on risk factors for asthma. Numerous authors have speculated on possible factors contributing to the increase in asthma prevalence, morbidity, and mortality. Among the factors that have been suggested as possible explanations are increasing concentrations of indoor airway allergens, changing patterns in the immune response to infections, increased consumption
of specific dietary nutrients, and changes in the organization and delivery of health care (Vollmer, Osborne, & Buist, 1998). Hypotheses that attempt to explain the rising prevalence have been advanced but remain unproven, and uncertainty about the cause of increasing asthma prevalence is a source of unease.

In the United States, data from the National Health Interview Survey shows that the annual prevalence of asthma increased from 3.1% in 1980 to 5.4% in 1994. Although the prevalence of asthma has been increasing since the early 1980s for all age, sex, and racial groups, the prevalence remains higher among children than adults, and higher among blacks than whites (National Institutes of Health National Heart, Lung, and Blood Institute, 1999). Data from the National Health Interview Study suggests that in the United States alone, the number of cases of asthma reported since 1980 has increased by 75% and that the rate among children less than 5 years of age has increased 160% (National Institutes of Health National Heart, Lung, and Blood Institute, 1999).

Morbidity and Mortality

Asthma affects 20.3 million individuals in the United States, 6.3 million of which are children (Mannino et al., 1998). Asthma is the most common chronic childhood disease in America. Recent statistics estimate that 1 out of every 20 children in the United States is affected by asthma (Asthma and Allergy Foundation of America, 2004).

Until recently, it was thought that between two-thirds to three-fourths of those individuals with asthma had mild disease. More recent studies have suggested that the proportion of persons with mild asthma is significantly less than previously reported (Colice, Song, Stampone, et al., 1999). Fuhlbrigge et al. observed that only 10.7% of
individuals with asthma have mild intermittent disease, as defined by the National Asthma Education and Prevention Program (NAEPP) classification guidelines, while 77.3% demonstrate moderate persistent asthma (Fuhlbrigge, Adams, Guilbert, et al., 2002). This suggests that a majority of the U.S. population with asthma experience persistent rather than intermittent symptoms and that the overall burden on the health and functioning of the U.S. population is substantial. The discordance in severity of asthma symptoms reported by individuals may be related to how the NAEPP classification guidelines are operationalized (Fuhlbrigge et al., 2002). Inquiry into recent day or nighttime symptoms alone underestimates the burden of asthma and may lead to poor diagnosis and inadequate treatment of asthma (Fuhlbrigge et al., 2002).

Asthma is the only chronic disease in America, besides AIDS and tuberculosis, that continues to have an increasing death rate (Asthma and Allergy Foundation of America, 1999). From 1979 to 1992, asthma death rates in the United States increased a total of 58 percent. For children 19 years and younger, the death rate increased by 78 percent (Asthma and Allergy Foundation of America, 1999). It is estimated that over 5,000 individuals die each year due to asthma. This means that on average, fourteen Americans die each day from asthma (Asthma and Allergy Foundation of America, 1999). These statistics clearly highlight the need to aggressively diagnosis and treat this disease and its symptoms.

Pathophysiology of Asthma

Asthma, once thought of as a “simple” hypersensitive reaction, is now known to be a complex condition with a spectrum of causes and contributing factors, with airway
inflammation as its central attribute (National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, 1997). Airway inflammation causes bronchial hyperresponsiveness, which causes airway obstruction leading to recurrent episodes of wheezing, coughing, chest tightness, and breathlessness (Fig 1) (National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, 1997). These episodes are usually associated with widespread but variable airflow obstruction that is often reversible with treatment (National Heart, Lung and Blood Institute, 1997).

Figure 1: Schematic representation of underlying inflammation and BHR resulting in symptoms and exacerbations of asthma (National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, 1997).

It is hypothesized that airway inflammation can be acute, subacute, and chronic (Fig. 2). The acute inflammatory response is represented by the early recruitment of cells to the airway. In the subacute phase, recruited and resident cells are activated to cause a more persistent pattern of inflammation. Chronic inflammation is characterized by a persistent level of cell damage and an ongoing repair process. (National Institutes of
Health, 1997). This persistent but latent airway inflammation leads to the thickening of the airway wall and may account for bronchial hyperresponsiveness, which could have a substantial impact on the progression of asthma (Kharitonov, 2004). It is these structural changes in the airway that contribute to airway remodeling.

![Pathophysiology of Airway Remodeling](image)

Figure 2: Pathophysiology of Airway Remodeling

Viewed microscopically, airways are infiltrated with eosinophils and mononuclear cells, and there is vasodilation and evidence of microvascular leakage and epithelial disruption. The airway smooth muscle becomes hypertrophied, which is characterized by new vessel formation, increased numbers of epithelial goblet cells, and deposition of interstitial collagens beneath the epithelium (National Institutes of Health, 1997). Moreover, these morphologic changes may not be completely reversible. Consequently, research is currently focused on determining whether these changes can be prevented or modified by early diagnosis, avoidance of factors that contribute to asthma.
severity, and pharmacological therapy directed at suppressing airway inflammation (National Institutes of Health, 1997).

Health Care Utilization and Costs

Asthma significantly affects the quality of life of many people in the United States and places a large social and economic burden on society. Asthma exacerbations reportedly are responsible for approximately 9 million primary care provider office visits, 1.9 million emergency department visits, and 500,000 hospitalizations annually (National Institutes of Health, 1997). This health care utilization comes at substantial personal and financial cost, with asthma exacerbations leading to enormous direct expenditures as well as days of missed work and school for both the parent and the child (American Lung Association, 2004). Among children ages 5 to 17, asthma is the leading cause of school absenteeism from a chronic illness, accounting for more than 14 million missed school days annually (National Institutes of Health, 1997). Direct health care costs for asthma in the United States total more than 9.4 billion dollars annually; indirect costs (lost productivity) add another 4.6 billion dollars for a total of 14 billion dollars annually (Asthma and Allergy Foundation of America, 2004).

Emerging Diagnostic Tools for Asthma

Asthma clearly imposes a growing burden on society in terms of quality of life, healthcare costs, and morbidity. The development of early detection techniques and new therapeutic strategies are greatly needed in order to tackle the growing problem of asthma in the United States and globally. One of the emerging diagnostic tools that hold promise in both the diagnosis and management of pediatric asthma is exhaled nitric oxide (ENO).
ENO is very easy to perform. During online measurement of ENO the patient should be seated comfortably. Nose clips should not be used because they may allow nasal NO to accumulate and promote leakage of this NO via the posterior nasopharynx (falsely increasing the ENO value). The patient exhales to nearly residual volume (RV) into the room, then inserts the mouth piece into his/her mouth and inhales through their mouth as deeply as possible, to total lung capacity (TLC), for 2-3 seconds. After inhalation, the subject exhales rather forcefully and continuously at a steady rate for approximately 10 seconds. During expiration it is important that nasal NO is excluded. This is accomplished by exhaling against an expiratory resistance and maintaining a constant flow of 200mL/s (Cicotto & Downey, 2004). The final ENO value is based on an average of three reproducible tests (values within 5% of one another).

ENO has been introduced as a simple noninvasive means of assessing airway inflammation in both adult and pediatric asthmatic patients and there has been a great deal of discussion regarding whether ENO may enable clinicians to make the diagnosis of asthma more easily, confirm the diagnosis with much greater confidence, and manage the disease more appropriately than has been possible to date. This paper reviews current literature examining the utility of exhaled nitric oxide as a marker of bronchial hyperresponsiveness in children with mild to moderate persistent asthma to help answer this question.

NATURE OF THE PROBLEM

Asthma typically presents with a history of wheeze, shortness of breath, and cough, which are variable in severity and over time. But, this presentation may not
always be straightforward and clinicians frequently wish to validate the diagnosis using objective tests (Smith, Cowan, Filsell, et al., 2004). This is particularly so if maintenance treatment with long-term inhaled corticosteroid therapy is being considered (Smith, 2004).

Usually, the diagnosis of asthma is based on objective measurements such as, symptom scores reported by the patient, the measurement of airway obstruction by peak flow rates or forced expiratory volume in 1 second (FEV1), and/or the assessment of bronchodilator response. Bronchoprovocation with methacholine can also be used to assess bronchial hyperresponsiveness (National Institute of Health, 1997). Unfortunately, these traditional approaches are problematic for several reasons. First, self-reporting of symptoms is much dependent on perception of symptoms with the potential for both under perception and over perception (Teeter & Bleecker, 1998). Second, national guidelines recommend the measurement of serial peak expiratory flows (PEF) or spirometry to confirm the diagnosis of asthma, but obtaining serial measurements over a period of 10-14 days, as recommended, requires adequate patient compliance and it is the experience of many clinicians that this is not easily achieved (Enright, Lebowitz, & Cockroft, 1991). Third, spirometry is primarily based on demonstrating abnormal airway physiology, or airway obstruction. Particularly in mild asthma, this is often not present and for this reason the sensitivity of this test is low (Hunter, Brightling, Woltman et al., 1994). Fourth, although bronchoprovocation with methacholine is a highly reliable test to measure the degree of airway hyperresponsiveness, methacholine testing is costly, time
Exhaled Nitric Oxide is extremely difficult to perform in young children, and not without risk, precluding its use in general pediatric practice (National Institutes of Health, 1997).

Because of the numerous obstacles encountered in testing young children (<6 yr), the diagnosis of asthma in children in general practice is largely based on clinical history, with recurrent wheezing being the most predictive symptom of asthma (Malmberg et al., 2003). Recently, the measurement of ENO has been introduced as an alternative means of screening for asthma and has been especially attractive in children because of the ease of measurement (Malmberg et al., 2003).

PURPOSE

The aim of this project is to review current literature examining the utility of exhaled nitric oxide as a marker of bronchial hyperresponsiveness in children with mild to moderate persistent asthma, followed by a discussion on practice and policy implications.

BACKGROUND LITERATURE

Diagnosing asthma is not always easy, and objective tests are typically used to confirm the diagnosis in children >6 years of age in most pediatric pulmonary practices. The most common strategy that is employed to support a clinical diagnosis of asthma is to demonstrate the presence of an abnormal, short-term variable airflow limitation. Spontaneous variable airflow obstruction can be assessed using peak expiratory flow (PEF) monitoring at home, or treatment-induced variable airflow obstruction can be assessed in the laboratory by measuring the bronchodilator response to a beta2-agonist (Juniper, Cockroft, & Hargreave, 1994). Unfortunately, the standard measures of lung
function, such as FEV1 and PEF, only assess airway patency and not necessarily airway inflammation or the extent of bronchial hyperresponsiveness, a characteristic feature of asthma.

Persistent inflammation of the airway often exists despite normal or near normal lung function and it is this persistent or chronic inflammation that upregulates bronchial hyperresponsiveness (Vignola, Chanez, Campbell, et al., 1998). Furthermore, a significant amount of evidence exists indicating that the level of airway hyperresponsiveness correlates with the clinical severity of asthma (National Institute of Health, 1997). Patients with increased airway hyperresponsiveness not only have a higher degree of airway inflammation, but also generally have more variable airflow obstruction and require higher doses of inhaled corticosteroids to control symptoms (Juniper et al., 1983).

Bronchial hyperresponsiveness (BHR) and airway inflammation are considered the ultimate driving force behind the symptoms associated with asthma, the disability of asthma, and the sequelae of airway remodeling (Nogami, Shoji, & Nishima, 2003). BHR is an exaggerated bronchoconstrictor response to a wide variety of stimuli (National Institutes of Health, 1997). This propensity for airways to narrow too easily and too much is a major feature of asthma (National Institutes of Health, 1997). Bronchial hyperresponsiveness leads to clinical symptoms of wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Research indicates that BHR is important in the pathogenesis of asthma and that the level of BHR usually correlates with the clinical severity of asthma (National Institutes of Health,
Provocation testing with methacholine can be used to assess the degree or severity of bronchial hyperresponsiveness resulting from airway inflammation. Bronchoprovocation with methacholine is a highly reliable test with positive results in nearly all individuals with current symptomatic asthma. It has been reported that methacholine testing has a specificity of 100% and a sensitivity of 85% (Goldstein, Veza, Dunsky, et al., 2001). Whereas, postbronchodilator responses (increase of FEV1 > 12%) and PEF variation (> 20%) have a reported sensitivity of 6% and 10% respectively (Goldstein et al., 2001).

A number of epidemiological studies have also reported similar results. Higgins et al. showed that methacholine airway hyperresponsiveness identifies twice as many subjects with physician-diagnosed asthma than PEF variations (Higgins, Britton, Chinn, et al., 1992). Cameron et al. concluded that in adults with asthma who have normal or near-normal spirometric values, methacholine challenge (methacholine PC20) and sputum eosinophil count are the most useful for discriminating patients with asthma from those with “pseudoasthma” (Hunter et al., 2002).

Although methacholine challenge and induced sputum are undoubtedly of value in the diagnosis and treatment of asthma, both are typically reserved for research studies and specialized clinics. In pediatrics, the management of asthma is primarily based on symptoms reported by the patient and/or parents and if possible (>6 yrs), pulmonary function tests.
Exhaled Nitric Oxide

Recently, there has been great interest in the analysis of exhaled breath constituents as a non-invasive, simple way of monitoring inflammation and oxidative stress in the lungs (Kharitonov, 2004). Incorporating the measurement of exhaled breath constituents, such as exhaled nitric oxide, into routine pediatric pulmonary care may possibly allow the clinician or nurse practitioner the ability to diagnosis asthma more easily, confirm the diagnosis with much greater confidence, and treat the disease more appropriately than has been possible to date (Smith et al., 2004).

Nitric oxide (NO) was originally recognized as an environmental pollutant that destroyed the ozone layer and was implicated in acid rain (Kharitonov, 2004). However, it is now recognized as an important physiological mediator with a wide spectrum of action. NO was described in the 1980s as “endothelial derived relaxation factor” when it was discovered to be the agent responsible for the vasodilatation of arterioles (Furchgott, R. & Zawadzki, J., 1980). Early studies demonstrated that endothelial cells are able to release endothelium derived relaxing factor (EDRF) that diffuses to the adjacent muscle layer and relaxes it at least in part by stimulating the formation of cyclic guanosine monophosphate (cGMP) (Ricciardolo et al., 2004). Similarly, biochemical experiments showed that nitroglycerine elicits blood vessel relaxation after its conversion to NO with the subsequent formation of cGMP (Ricciardolo, Sterk, Gaston, et al., 2004). Shortly after the publication of landmark papers proposing EDRF to be NO, several investigators made observations suggesting that nitrogen oxides are important to respiratory biology (Ricciardolo et al., 2004).
Role of Exhaled Nitric Oxide in Asthma

In the respiratory system, NO participates in a broad range of important physiologic processes, including vasodilatation, neurotransmission, and host defense (Fabio et al., 2004). The release of endogenous NO in the respiratory tract may play an important signaling role in the physiologic control of airway function and in the pathophysiology of asthma.

Under physiologic conditions NO is generated from L-arginine by the enzyme nitric oxide synthase (NOS), of which there are three known isoforms: 1) constitutive neuronal nNOS; 2) inducible iNOS; and 3) constitutive endothelial eNOS. This distinction is important because NO synthesized by eNOS and nNOS is associated with physiological effects while NO synthesized by iNOS is associated with the pathological effects of NO in bronchial airways (Cicutto et al., 2004). In the human lung NOS isoforms are expressed in the vascular, airway, and parenchymal compartments (Hart, 1999).

Types nNOS and eNOS, found predominately in neurons and endothelium, respectively, are constitutively expressed and are dependent upon calcium for activity. nNOS is localized in airway nerves and is the major mediator for neural smooth muscle relaxation. eNOS is localized in the epithelium of human nasal mucosa, primarily at the basal membrane of ciliary microtubules, where it is thought to contribute to the regulation of ciliary beat frequency (Ricciardolo et al., 2004). The third isoform, iNOS is found in many different cells within the airways. iNOS is expressed in alveolar epithelial cells, lung fibroblasts, vascular smooth muscle cells, macrophages, mast cells, neutrophils, and
chondrocytes (Ricciardolo et al., 2004). Various stimuli cause transcriptional activation of \(i\)NOS in these cells. They include endogenous mediators, such as chemokines and cytokines, as well as exogenous factors such as bacterial toxins, virus infections, allergens, environmental pollutants, and hypoxia.

The protective effects of NO synthesized by \(n\)NOS and \(e\)NOS include, neuromodulation by mediating inhibitory noncholinergic nonadrenergic nerve activity, smooth muscle relaxation, attenuating airway hyperresponsiveness to bronchconstrictor stimuli, downregulating Th1 cells and their proinflammatory activity, and the killing of invading microorganisms (Fabio, Ricciardolo, Sterk, et al., 2004).

The potential detrimental effects of NO synthesized by \(i\)NOS include pro-inflammatoty activities such as, vasodilatation and plasma extravasation of the bronchial circulation, increased airway secretions, impaired ciliary motility; promoting Th2 cell-mediated eosinophilic inflammation, necrosis and apoptosis (Fabio et al., 2004).

The role of NO in the pathogenesis of asthma is currently under intense debate. In healthy subjects, ENO seems to originate mainly from \(e\)NOS in the upper airways (nasal mucosa) whereas; the contribution from \(i\)NOS in alveolar epithelial cells in the lower airways is small (Lundberg, Farkas-Szallasi, Weitzberg, et al., 1995). However, in asthmatics ENO has a predominant lower airway origin and is due to elevated NO levels synthesized by \(i\)NOS in alveolar epithelial and inflammatory cells (Kharitonov, 2004).

The increased NO levels in the exhaled air of asthmatic patients might be explained by an over expression of the enzyme that synthesizes NO, or \(i\)NOS (Ricciardolo et al., 2004). Cicutto et al.(2004) reported that once \(i\)NOS is induced, the
production of NO is significantly greater than with eNOS or nNOS. As a result, high NO levels appear to be more indicative of iNOS activity (Cicutto et al., 2004). Bronchial biopsy specimens reveal that iNOS is expressed in samples from individuals with asthma but not from healthy controls (Cicutto et al., 2004).

In asthma, NO synthesized by iNOS in the airways has been touted as a proinflammatory mediator causing detrimental effects, and in fact it has been suggested that elevated levels of NO in exhaled breath may reflect ongoing inflammation (Sanders, 1999). In theory, NO may have effects on a myriad of cell functions, including alterations in DNA integrity, mitochondrial respiration, apoptosis, leukocyte adherence, mast cell reactivity, and eosinophil recruitment (Sanders, 1999).

Limited studies in murine cells suggest that NO may amplify inflammation by altering the balance between helper-T (Th)1 and Th2 cell types, leading to the proliferation of Th2 lymphocytes, which putatively produce a cytokine profile that has been associated with exacerbations of asthma (Sanders, 1999). These observations, however, have not yet been extended to humans where the Th1/Th2 paradigm is less defined (Sanders, 1999).

Review of Literature on the Diagnostic Value of Exhaled NO

ENO levels have been shown to be significantly elevated in patients with asthma and other inflammatory airway disorders such as bronchiectasis, active pulmonary sarcoidosis, and rhinitis (Ricciardolo, et al., 2004). Although an elevation of exhaled NO is not specific for asthma, it may be useful in differentiating asthma from other causes of chronic cough (Chatkin, Ansarin, Silkoff, et al., 1999).
The diagnostic value of ENO measurements used to differentiate between healthy subjects with or without respiratory symptoms and patients with confirmed asthma was recently analyzed by Dupont et al. (2003). They reported a 90% specificity and a 95% positive predictive value when exhaled NO >16ppb was used as a cutoff for asthma. Dupont et al concluded that the measurement of exhaled NO might serve as a simple, quick, noninvasive test that can be used as an additional diagnostic tool for the screening of patients with a suspected diagnosis of asthma (Dupont, Rochette, Demedts, et al., 2003).

Dupont et al. further suggested the possibility of using a high and low cutoff point of ENO as a screening tool rather than a single cutoff point because of the significant overlap of exhaled NO levels between asthmatics and non-asthmatics in their study population. For example, patients with an NO level < 8ppb are not likely to have asthma, with a false-negative rate not exceeding 5%. In these patients one could argue that it would be prudent to look for other diseases other than asthma for reported symptoms. However subjects with an ENO level >18 ppb are very likely to have asthma, with a false-positive rate of <5% and because of this, it would be reasonable to perform additional diagnostic testing in order to confirm the suspected diagnosis of asthma (Dupont et al., 2003).

Dupont et al. also reported a significant correlation \( r = -0.65; p<0.0001 \) between the exhaled NO level and the degree of BHR measured as PC20 histamine. They further concluded that by using exhaled nitric oxide as a preliminary screening tool and applying this strategy, a significant number of additional diagnostic investigations could be
avoided, possibly resulting in a total reduction of health-care costs. For instance, in their study population the implementation of this strategy would have reduced the number of provocation tests by more than half (Dupont et al., 2003).

Jatakanon and coworkers reported similar findings when they examined the correlation between ENO, sputum eosinophils, and methacholine responsiveness in 35 adult subjects with mild asthma (Jatakanon, Lim, Kharitonov, et al., 1998). They found a significant correlation between exhaled NO and PC20 measured by methacholine. They concluded that NO may be useful as a marker of airway inflammation in asthma, as NO itself, or the mechanisms resulting in its increase, may contribute to the airway inflammation found in asthma (Jatakanon et al., 1998).

Provocation testing is considered the “gold standard” used to definitively diagnosis asthma but, as mentioned earlier, provocation testing does have its drawbacks. It is very expensive, time consuming, requires both a skilled technician to perform the testing and an experienced physician or nurse practitioner to analyze the results. It can be very distressing to the patient and sometimes impossible to perform in young children. Therefore, the measurement of exhaled NO, which is an easily performed, safe, noninvasive procedure, may serve as a useful alternative method used to evaluate BHR and inflammation in asthmatic patients, especially in the pediatric population.

Covar et al. looked at the relationship between ENO and measures of disease severity in 118 children with mild to moderate persistent asthma. They reported that the level of ENO was significantly associated with total eosinophil count, serum IgE and ECP levels (inflammatory markers), BHR, atopy, and several other parameters of disease
severity such as hospitalization, B-agonist use, and nocturnal symptoms (Covar, Szefler, Martin, et al., 2003). No significant correlations were found between ENO and prebronchodilator and postbronchodilator FEV1, FVC% predicted, and FEV1/FVC (Covar et al., 2003).

The correlations found between ENO and various aspects of asthma severity coupled with the lack of correlation between ENO and spirometric parameters such as FEV1 suggest that different mechanisms are involved in the underlying cause of airway inflammation and airflow obstruction. Measurement of airway obstruction by itself may not be reflective of disease activity and at best is an indirect measure of airway inflammation. ENO may provide additional information to that obtained with spirometry in assessing airway inflammation in the presence of unrecognized changes in pulmonary function (i.e. mild disease) or poorly reported symptoms (Covar et al., 2003). Covar et al. concluded that because of its significant correlations with various aspects of asthma, the measurement of ENO should be considered as an adjunctive tool to current clinical practice guidelines in the evaluation of asthma in the future.

Malmberg and coworkers reported similar results when they examined 96 preschool children with a history of asthmatic symptoms and 62 age-matched healthy non-atopic controls. In the group of children with probable asthma characterized by recurrent wheeze, signs of airway inflammation (measured by ENO) were present more often than changes in lung function. In particular, bronchodilator responsiveness, considered one of the hallmarks of asthma diagnosis, was present less frequently than high levels of ENO. This is probably due to the variable nature of bronchial obstruction
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in asthma; in a cross sectional analysis such as the present study some asthmatic subjects are likely to have normal lung function (Malmberg et al., 2003). Alternatively, it may be that, in the early stages of the disease, signs of airway inflammation and symptoms precede those of abnormal lung function as Merkus and coworkers have shown in adults with asthma-like symptoms (Merkus, Mijnsbergen, Hop, et al., 2000). Malmberg et al. concluded that the measurement of ENO is superior to baseline lung function measures or indices of bronchodilator responsiveness in identifying preschool children with predominantly atopic probable asthma (Malmberg et al., 2003).

Spallarossa et al. found similar results in steroid-naïve adolescents with mild intermittent asthma. Fifty-two adolescent patients with mild intermittent asthma and 22 age-matched controls participated in the study. Results indicated that a significant proportion of the asthmatic patients had increased BHR to methacholine and elevated ENO levels despite normal pulmonary function parameters. In the asthmatic population FVC, FEV1, and FEF25-75% values were not significantly different as compared to controls. Actually, a high proportion of the mild asthmatic adolescents had normal pulmonary function parameters: FVC was >90% of the predicted value in 80% of the subjects, FEV1 was >90% of the predicted value in 92% of the subjects, and FEF25-75% was >90% of the predicted value in 76% of the subjects (Spallarossa, Battistini, Silvestri et al., 2003). By contrast, although none of the control subjects showed BHR, increased airway responsiveness to methacholine was demonstrated in the majority of the mild asthmatic adolescents studied. Hyperreactivity was severe in 36.5% of the adolescents (MCh PD20 < 400ug) and moderate in 32.7% (MCh PD20 400-1400ug). In addition,
ENO concentration levels were significantly higher in asthmatics, as compared to the control subjects (20.4+5.3ppb and 4.4+0.7ppb, respectively).

In the study by Spallarossa et al. they also reported that although asthma symptoms often seem to disappear around puberty, this “clinical remission” is not always associated with lung function normalization. Although pulmonary function tests may be within a “normal” range, subjects may continue to experience unexpected, often severe, asthma attacks. In addition, despite the fact that a history of severe asthma is one of the most important risk factors for subsequent near-fatal attacks, unexpected occurrence has been reported in adolescents without a previous diagnosis of asthma or in those whom only have mild disease (Price, 1996). Adolescents represent the highest risk group for severe life-threatening asthma attacks within the pediatric population and several hypotheses have been suggested for this phenomenon; (1) asthma is often not recognized or is undertreated in teenagers, and this may be due to a lack of disease perception by the adolescent and a reluctance to seek medical advice, and (2) and most teenagers prefer to view asthma as an episodic illness, finding it hard to accept the need to take regular medications (Fig 3) (National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, 1997).
• Past history of sudden severe exacerbations
• Prior intubation for asthma
• Two or more hospitalizations for asthma in the past year
• Three or more emergency care visits for asthma in the past year
• Hospitalization or an emergency care visit for asthma within the last month
• Use of >2 canisters per month of inhaled short acting beta2-agonist
• Difficulty perceiving airflow obstruction or its severity
• Low socioeconomic status and urban residence
• Illicit drug use

Figure 3: Risk Factors Associated with Death from Asthma (National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program, 1997).

Gruber et al. reported similar findings in a group of symptom-free adolescent patients who had reached a clinically defined remission 1 year after termination of therapy. They reported that approximately 40% of the symptom-free and medication-free patients demonstrated persistent functional abnormalities with a high prevalence of bronchial hyperreactivity and elevated NO levels (Gruber, Eber, Steinbrugger, et al., 1997). An earlier study by Martin et al. also reported that 60% of their subjects with a history of wheezing during childhood continued to have an increased BHR at age 21 years despite the lack of persistent symptoms (Martin, Landau, Phelan, et al., 1980).

From these studies reviewed ENO appears to be a better diagnostic tool for both the diagnosis and management of mild to moderate persistent asthma in children than conventional pulmonary function tests. ENO has been shown to significantly correlate (r + -0.65; p < 0.0001) with the degree of BHR as measured by PC20 methacholine and with inflammatory markers such as, total eosinophil count, and serum IgE and ECP.
ENO has also been shown to correlate with parameters of disease severity such as hospitalization, B-agonist use and nocturnal symptoms. ENO measures the two key components of asthma, BHR and inflammation. Conventional pulmonary function tests only measure airway obstruction. Given that a significant relationship between ENO, inflammation, and BHR has been confirmed in the studies reviewed, it seems logical that ENO will enable the clinician and nurse practitioner the ability to make the diagnosis of asthma more easily, confirm the diagnosis with much greater confidence, and manage the disease more appropriately than has been possible to date.

SIGNIFICANCE

Asthma remains a prevalent disease with significant morbidity and mortality. Traditional measures of asthma control do not necessarily reflect ongoing airway inflammation and may not provide clinicians with optimal information needed in the assessment and treatment of asthma. Currently, the diagnosis and treatment of asthma in the clinical setting is dependent on reported symptoms, measurements of lung function, and bronchodilator response. However, a review of current literature suggests these measures may not accurately reflect the extent of BHR or underlying inflammation in the airways.  

There is convincing evidence that both BHR and airway inflammation may be present even in mild-intermittent asthma, suggesting that an ongoing recruitment and activation of inflammatory cells may be present even in asymptomatic subjects (National Institutes of Health, 1997). The literature further suggests that the diagnostic usefulness
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of conventional pulmonary lung function tests, such as PEF and bronchodilator response, are especially limited in mild disease.

Indeed, the diagnosis and treatment of asthma based on symptoms and obstructive measures of lung function is a rather simplistic approach, and the use of a surrogate inflammatory marker, such as ENO, may be required to ensure optimum long-term asthma control in terms of exacerbations along with effects on airway remodeling. Given that a significant relationship between ENO and both sputum eosinophils and BHR has been confirmed in a number of studies previously discussed, it seems logical that the use of ENO as a surrogate test for airway inflammation and BHR may be a better means of diagnosing and managing the symptoms associated with asthma than to rely solely on physiological changes, such as airway obstruction, the measurements of which are variable over time, are often undetectable in mild cases, and correlate poorly with clinical symptoms.

These findings strengthen the conclusion that ENO measurement may be extremely useful in both the diagnosis and treatment of asthma, especially in pediatrics (Spallarossa et al., 2003). The measurement of exhaled NO is simple to perform, completely noninvasive, can be used in young children, and patients with severe airflow obstruction where more invasive techniques are not possible.

During the past decade a plethora of studies have unraveled the multiple roles of NO in airway physiology and pathophysiology. The measurement of ENO in clinical research trials has provided a tremendous amount of useful insight into the understanding of the pathogenesis, pathophysiology, and treatment of asthma. The advent of ENO
measurement to evaluate airway inflammation in asthma represents a significant advance in respiratory medicine and one that may potentially become a major advance in the clinical management of asthma in the future.

The measurement of exhaled NO may someday be used a simple diagnostic means for which the clinician can predict the severity of BHR and the degree of airway inflammation, allowing a more accurate diagnosis and more appropriate treatment of the disease than possible to date. It may well be that evaluating asthma control with surrogate inflammatory markers such as ENO along with conventional parameters, will lead to better long-term outcomes. This in turn may ultimately reduce the overall burden of asthma within our society.

Updates to current national guidelines have highlighted the potential diagnostic role of exhaled nitric oxide measurements in asthmatic patients. It is anticipated that with the development of smaller, less expensive devices the measurement of ENO will be easily incorporated into routine pediatric pulmonary care and possibly into the NAEEP guidelines. It is important that nurse practitioners stay abreast of these rapidly evolving areas because of their contribution to the understanding of the underlying mechanisms of the disease and perhaps in the near future, assisting with the diagnosis and treatment of childhood asthma.

THEORETICAL FRAMEWORK

The theoretical framework for this paper is based on the pathophysiology of asthma (Figure 4). Asthma is an inflammatory disease characterized by eosinophilic airway inflammation and bronchial hyperresponsiveness leading to variable airway
obstruction. Establishing the relationship between pathologic changes and the clinical features of asthma has been difficult. Fortunately, knowledge gained from fiberoptic bronchoscopy and bronchial biopsies have provided new insight into the mechanisms involved in the pathophysiology of the disease.

Data from fiberoptic bronchoscopy with lavage suggest that there is an increase in the number of ciliated cells, eosinophils, macrophages, and monocytes in the lavage fluid obtained from asthmatics as compared to controls (Cicutto et al., 2004). Histological examination of airway biopsies demonstrates an infiltration of a variety of inflammatory cells, primarily eosinophils. Macrophages and lymphocytes may also be present in the airways, particularly in proximity to the basement membrane. In cases of severe asthma, denuded epithelium may permit exposure of underlying nerve endings making them susceptible to a variety of environmental factors leading to airway narrowing (Cicutto et al., 2004). The clinical application of these methods or techniques has helped to define, not only the cell populations present in the airways of asthmatics, but also the presence of inflammatory mediators and cytokines (Cicutto et al., 2004).

Asthma has traditionally been divided into two basic types, extrinsic and intrinsic. Extrinsic asthma is initiated by a Type I hypersensitivity reaction induced by exposure to an extrinsic antigen. In contrast, intrinsic asthma is initiated by diverse, nonimmune mechanisms, including ingestion of aspirin, pulmonary infections, especially viral; inhaled irritants, stress, and exercise (Cotran, Kumar, Collins, et al., 1999). As with other classification schemes, patients often ignore categories and manifest overlapping characteristics (Cotran et al., 1999).
The mechanisms involved in the pathophysiology of asthma begin with a susceptible individual, or someone with asthma. The Asthma Predictive Index (API) describes specific characteristics that make a person susceptible to the development of asthma (Martinez, Wright, Trussing, et al., 1995). These characteristics include; a history of at least 4 wheezing episodes in the past year, along with either one major criteria or two minor criteria. The major criteria include, a parent with asthma, a diagnosis of atopic dermatitis, or an aeroallergen sensitivity. The minor criteria include, food sensitivity, peripheral eosinophil count of >4%, or a history of wheezing apart from colds or viral infections.

As depicted in Figure 4, the inflammatory cascade begins with an environmental trigger in a “susceptible” individual, or a person with asthma. Environmental triggers include aeroallergens, viral, and bacteria infections. Common aeroallergens include, mold, grass, weed, tree, pollen, dust mites, and coach roaches. These environmental triggers facilitate the release of chemotactic molecules from bronchial mast cells, macrophages, and T lymphocytes. These chemotactic molecules encourage eosinophil migration along with the accumulation of other cells that participate in the inflammatory process and secrete inflammation-enhancing cytokines (Cotran et al., 1999). These cytokines include, histamine, leukotriene, prostaglandin, and nitric oxide. All of these cytokines act directly on airway epithelial and indirectly on neural mechanisms which increase airway smooth muscle tone, vascular permeability, mucous secretion, and produce structural changes in the airway.
The left side of the framework indicates that these cytokines produced during the inflammatory cascade increase the smooth muscle tone of the airways leading to bronchial hyperresponsiveness. This underlying bronchial hyperresponsiveness of the airways is then triggered by a precipitant. Precipitants that augment airway hyperresponsiveness in asthmatic patients can include, cold air, exercise, cigarette smoke, pet dander, chemical irritants, bacterial and/or viral infections. These precipitants cause bronchconstriction of the airways leading to airway obstruction. This bronchconstriction can be often be quite sudden and severe, depending on the degree of underlying inflammation and bronchial hyperresponsiveness present in the airways.

The right side of the framework indicates that these cytokines also cause an increase in the microvascular permeability of the airways (swelling of the airways), an increase in the production of mucous, and a decrease in mucociliary function; all of which lead to airway obstruction and the symptoms associated with asthma. These symptoms include, coughing, wheezing, chest tightness, and breathlessness.

It is clearly evident from this diagram that the primary mechanism involved in the pathophysiology of asthma is inflammation. The factors contributing to airway inflammation in asthma are multiple and involve a variety of different inflammatory cells. Asthma is not caused by either a single cell or single mediator, but rather from complex interactions among a number of inflammatory cells and mediators secreted into the airways.
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Increased vascular permeability
Increased mucous production

Figure 4: Mechanisms Involved in the Pathophysiology of Asthma
“Best practice” for confirming the diagnosis of asthma is currently based on assessing abnormal airway physiology, or the degree of airway obstruction. Clinical diagnosis is based on symptom scores reported by the patient, peak expiratory flow rates (PEF), and bronchodilator response. The most definitive test to diagnosis asthma is provocation challenge with methacholine, and as stated earlier, this is typically reserved for research studies and specialized pulmonary clinics. To date, the only diagnostic tests used in clinical practice measure the degree of airway obstruction not the degree or severity of airway inflammation and/or BHR (Fig. 5). The only means of directly assessing airway inflammation is bronchoalveolar lavage or bronchial biopsy both of which are invasive and have the potential for adverse events. Therefore, neither one of these procedures are used routinely in pediatric practice.

Because of the limitations in diagnostic testing, the nurse practitioner can only speculate the degree or severity of inflammation that might be present in the airways from the patient’s demonstrated degree of airway obstruction and BHR. Despite the fact that traditional measures of lung function have been shown to be poorly sensitive in the diagnosis of asthma, these traditional pulmonary function tests are still the best objective means of diagnosing and treating asthma available today.
Figure 5: The Use of Traditional Pulmonary Function Tests in the Diagnosis and Treatment of Asthma
The introduction of exhaled nitric oxide has sparked great interest in the pulmonary community. Exhaled nitric oxide is derived from airway epithelial cells, macrophages, and Th1 cells. NO is produced early in the inflammatory cascade associated with asthma. NO amplifies and perpetuates the cell-mediated inflammatory response by promoting the production of chemotactic factors or chemokines. This suggests the possibility that NO acts as part of a positive-feedback loop in which inflammatory cells produce NO and thereby promote their further recruitment through the action of chemokines (Fabio, 2003).

Since NO is produced early in the inflammatory process it makes sense that by monitoring the level of ENO in asthmatic patients, the clinician can potentially treat the underlying inflammation in asthma earlier in the course of the disease and more appropriately thus, alleviating the symptoms of asthma and possibly preventing the sequelae of airway remodeling (Fig. 6). The measurement of exhaled nitric oxide in clinical practice may allow clinicians to objectively and quantitatively measure airway inflammation in asthmatic patients thus facilitating better diagnosis, treatment, and management of pediatric asthma.
Figure 6: The Use of ENO in the Diagnosis and Treatment of Asthma
CHAPTER II

IMPLICATIONS FOR PRACTICE

The advent of exhaled NO measurements to evaluate airway inflammation in asthma represents a significant advance in respiratory medicine, but its application in day-to-day clinical practice as a diagnostic tool has not yet been defined. As stated earlier, asthma is an inflammatory disease characterized by airway inflammation, variable airway obstruction, and BHR. Given that a significant relationship between ENO, inflammation, and BHR has been confirmed in a number of studies previously discussed, it seems much more logical to use ENO as a surrogate test for airway inflammation than to solely rely on physiological changes such as airway obstruction, the measurement of which is variable over time, are often undetectable in mild cases, and correlates poorly with clinical symptoms. With evidence mounting that ENO is a reliable, reproducible measure of airway inflammation, focus on its usefulness in the diagnosis and treatment of asthma in the pediatric setting is underway.

Most children who develop asthma do so by 5 years of age. Many children begin by having recurrent episodes of wheeze and/or cough with viral infections during the first years of life (Martinez et al., 1995). Early diagnosis and treatment are crucial in the development of the disease. Therefore, there has been much interest in the diagnostic value of ENO in asthmatic children.

Dupont (2003) and coworkers examined the utility of ENO as a diagnostic tool for the diagnosis of asthma in preschool children. They reported a 90% specificity and a 95% positive predictive valued when an ENO level of > 16ppb was used as a cutoff value.
for the diagnosis of asthma. They concluded that the measurement of ENO appears to be a better means of assessing airway inflammation than traditional pulmonary function tests, which only measure the degree of airway obstruction. Therefore, the measurement of ENO may offer the clinician a simple, reliable, noninvasive means for which to predict the severity of BHR and the degree of airway inflammation, allowing a more accurate diagnosis of asthma than possible to date.

ENO may also prove to be a valuable tool in the management of long-term anti-inflammatory controller medications for asthmatics patients. This is important because asymptomatic asthmatic patients with remission of symptoms for up to 1 year have been shown to have continued eosinophilic inflammation and increased hyperresponsiveness despite normal spirometry (Henriksen, Lingaas-Holmen, Sue-Chu, et al., 2000). Kharitonov et al. reported that changes in NO during steroid treatment were dose-dependent and preceded the improvements in symptoms, FEV1, and sputum eosinophils in asthmatic children (Kharitonov, 2000).

The measurement of ENO has been used in research trials to quantify airway inflammation and the effect of various treatments. In a study by Jones et al. ENO levels were reported to be elevated in steroid-naïve asthmatic children and these levels decreased with appropriate anti-inflammatory treatment (Jones, et al., 2001). It is believed that the use of corticosteroids inhibits the expression of iNOS, the enzyme responsible for the production of NO related to inflammation (Fabio et al., 2004). Therefore, it is thought that corticosteroids reduce ENO in individuals with asthma by inhibiting iNOS expression and activity.
There has also been considerable debate regarding the usefulness of ENO measurement as a predictive means of asthma control during corticosteroid withdrawal. Jones et al. demonstrated that ENO had a positive predictive value of 80%-90% for loss of asthma control when withdrawing inhaled corticosteroids from asthmatics and that it was as useful a marker as induced sputum in assessing airway inflammation (Jones et al., 2001). From their findings, Jones et al. concluded that elevated levels of ENO in mild to moderate persistent asthmatics could predict poor asthma control despite stable symptoms, spirometry, and medication use (Jones et al., 2001).

If the clinician could reliably predict asthma exacerbations with simple noninvasive measures in the clinic, a number of exacerbations may be prevented with intensification of therapy, thus reducing the morbidity, mortality, and associated costs of asthma. So it seems reasonable to conclude that because ENO is a sensitive marker of airway inflammation, it may be used as a reliable diagnostic tool in pediatrics to monitor the efficacy of anti-inflammatory medications used in the treatment of asthma.

LIMITATIONS AND FUTURE PERSPECTIVES IN PRACTICE

Although the measurement of ENO is a novel, noninvasive means of assessing eosinophilic inflammation that may prove to be beneficial in the clinical assessment and treatment of asthma in children, there still remains some important limitations that exclude its use in routine pediatric practice to date.

Most importantly is the cost of the equipment used to measure exhaled nitric oxide. Currently NIOX is the only FDA approved system available for online ENO measurement in the United States. The unit is manufactured by Aerocrine in Sweden and
Exhaled Nitric Oxide runs approximately $40,000, which is significantly higher than current diagnostic tools used in routine practice. A peak flow meter typically costs $15 and portable spirometry machines are approximately $1000.

There have also been problems with billing (CPT codes) and reimbursement from insurance companies. Aeorcrine is currently working on standardizing CPTs to facilitate payment by health insurance companies here in the United States.

Another important drawback to the implementation of ENO in pediatric practice is the large number of confounding factors that can influence the measurement of ENO. There are quite a few physiological and pathophysiological conditions and habits can affect the level of ENO in an individual. These conditions must be taken into consideration when testing an individual. The patient must refrain from eating; drinking, smoking, and exercising 1 hour prior to testing in order to get accurate results. Foods containing nitrate, such as lettuce, will increase the ENO level in an individual, whereas smoking and exercise will decrease the ENO level in this person. The performance of spirometry can also reduce ENO; therefore, measurement of ENO should precede spirometry. Finally, upper and lower respiratory tract infections can increase levels of ENO; therefore, measurements should be deferred until recovery from the illness or the presence of a respiratory infection noted in the patient’s chart.

Although the measurement of ENO has proven to be very useful in the research setting NO analyzers are very expensive and are mainly used in academic research and specialized pulmonary laboratories. The value of this diagnostic test will depend on technological advances resulting in the development of smaller, less expensive analyzers
that will facilitate the widespread clinical use of exhaled NO. Manufactures, such as Aerocrine, have already begun to develop smaller, less expensive units that will be marketed towards clinical use in the near future.

CURRENT POLICY

Healthy People 2010 is a national initiative to improve the health of all Americans through a coordinated and comprehensive emphasis on prevention. The cornerstone of this effort is set of national health promotion and disease prevention objectives for the year 2010. The report, Healthy People 2010: National Disease Prevention and Health Promotion Objectives, is a product of an unprecedented cooperative effort among government, voluntary and professional organizations, business, and individuals, and is coordinated by the U.S. Public Health Service (PHS). Organized under the broad categories of health promotion, health protection, and preventive services, the national objectives provide individuals, decision makers, organizations, and communities with a 10-year agenda to improve the Nation’s health through individual, collective, and environmental change (Centers for Disease Control, 1999).

Healthy People 2010 targets asthma as one of the respiratory diseases that is a significant public health burden to the United States. They report that asthma is responsible for about 500,000 hospitalizations, 5,000 deaths, and 134 million days of restricted activity a year despite the fact that most of the problems caused by asthma could be averted if persons with asthma and their health care providers managed the disease according to established guidelines (Centers for Disease Control, 1999). Healthy People 2010’s goal is to promote respiratory health through better prevention, detection,
treatment, and educational efforts. They believe that these prevention efforts are essential to interrupt the progression from disease to functional limitation and disability and to improve the quality of life for persons with asthma (Centers for Disease Control, 1999).

Healthy People 2010 acknowledges the fact that scientific research and the establishment of national guidelines has led to greater asthma control than was available in the early 1980s. These national guidelines have prompted improvements in the treatment and management of asthma by the use of objective monitoring techniques by both the patient and the health care professional (Centers for Disease Control, 1999). This encourages patients to become active participants in the management of their own disease (Centers for Disease Control, 1999).

For researchers in the field of pulmonary medicine, the goals set by Healthy People 2010 have facilitated the availability of government funding for clinical research trials that will advance our knowledge and understanding of asthma and ultimately lead to better diagnosis, treatment, and possibly the prevention of childhood asthma.

SUMMARY

During the past 20 years we have witnessed an unforeseen revolution in airway physiology. The discovery of the role of NO in the homeostasis of various cellular functions and in the dynamic behavior of the airways has lead to a new, rapidly evolving area of physiological science, which has direct bearing on our understanding of asthma. Although we have made tremendous progress in understanding the pathophysiology of asthma through the use of exhaled breath constituents, we still have a great deal to learn. The complexity of NO synthesis and wide functional profile of its various bioactive
forms have not been resolved in full detail yet. Ongoing research in this area will undoubtedly provide novel targets for suitable interventions in the prevention and treatment of asthma.
Exhaled Nitric Oxide

References


