Journal of Asthma and Allergy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Clinical Utility Of The Exhaled Nitric Oxide (NO) Measurement With Portable Devices In The Management Of Allergic Airway Inflammation And Asthma

This article was published in the following Dove Press journal:
Journal of Asthma and Allergy

Sy Duong-Quy[1,2]

[1]Department of Respiratory Diseases, Medical and Biological Research Centre, Lam Dong Medical College, Dalat City, Lam Dong Province, Vietnam; [2]Department of Immuno-Allergology, Penn State Medical College, Hershey, PA, USA

Abstract: Nitric oxide (NO) is a potential bioactive gas produced continuously and constantly in the airways of healthy subjects. In allergic airway inflammation, the level of exhaled NO is usually increased and mediated by inducible nitric oxide synthase (iNOS) enzyme presenting in the epithelium and different inflammatory cells. The measurement of NO concentration in the airway is possible with portable devices which use an electroluminescence technique. In subjects with upper airway with allergic inflammation such as in allergic rhinitis, the measurement of nasal NO (nNO) may help to diagnose and manage the disease. In the lower airway, increased fractional exhaled NO (FENO) reflects directly the inflammatory process that occurs in the airways that are typically seen in asthma. It has been shown that there is a strong correlation between FENO levels and increased activity of airway inflammation mediated by immuno-allergic cells and mediators. Thus, FENO has higher specificity and sensitivity than other methods in diagnosing the severity of inflammation in asthmatic patients. Moreover, the correlation between increased FENO levels and a high risk of bronchial hyperresponsiveness has also been demonstrated. FENO is also a relevant biomarker to evaluate asthma status due to the change of its values occurring earlier than clinical manifestations and spirometry parameters. In addition, the measurement of FENO with portable devices helps to support the diagnosis of asthma, to follow-up the control of asthma and to personalize asthmatic patients for target treatment with biologic therapy. Therefore, measuring FENO with portable devices in the diagnosis and treatment of allergic airway inflammation, especially in asthma, is one of the most essential applications of NO biomarkers in exhaled breath.

Keywords: nitric oxide, iNOS, nNO, FENO, allergic rhinitis, asthma

Introduction

The measurement of nitric oxide (NO) in exhaled breath is a common laboratory test in many departments of functional exploration techniques in developed countries. Since the first scientific publication on the application of this technique in asthma was published in 1993,[1] after more than two decades, there have been more than 3450 scientific papers indexed in PubMed on the measurement of exhaled NO in allergic airway diseases, of which more than 3150 papers are on asthma.[2] Today, exhaled NO has been officially recognized as a biomarker of allergic inflammation related to increased eosinophils in the upper and lower respiratory tracts. Currently,

Correspondence: Sy Duong-Quy
Department of Respiratory Diseases, Medical and Biological Research Center, Lam Dong Medical College, 16 Ngo Quyen, Dalat, Vietnam
Tel +84 263918 413813
Fax +84 263 3815000
Email sduongquy.jfvp@gmail.com

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

© 2019 Duong-Quy. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

the technique of NO measurement is routinely used in clinical practice as recommended by many well-known academic societies such as the American Thoracic Society (ATS), European Respiratory Society (ERS) or French Speaking Respiratory Society, and so on.[3–6] Nowadays, the technique of exhaled NO measurement has become more common with the use of new portable and inexpensive devices (hand-held devices), which make this technique available in hospitals, clinics, health-care centers, private offices and even at patients' homes.[7,8]

The pathology of allergic inflammation in the airways is of interest in the application of exhaled NO measurement and mostly in allergic rhinitis, bronchial hyperreactivity, and asthma. This field is also the typical area where measuring exhaled NO becomes the most obviously recognized worldwide application.[9–14] In addition to allergic rhinitis and asthma, other respiratory disorders are also studied and applied for the measurement of exhaled NO, such as in allergic rhino-sinusitis, for diagnosis of a phenotype of chronic obstructive pulmonary disease (COPD) with hyper-eosinophil, and asthma–COPD overlap (ACO), etc.[15,16] Actually, the cut-off of the theoretical normal value of exhaled NO has been established in healthy children and adults with a slight variation but always below the normal range by age, height, race and habitat environment, especially for children younger than 12 years of age.[3–5]

The measurement of exhaled NO in obstructive sleep apnoea (OSA) is related to alveolar inflammation due to intermittent hypoxia-induced oxidative stress and assessed by the alveolar concentration of NO.[17] However, exhaled NO is not only used in clinical practice, but also in basic research with experimental models, where it has been considered as one of the parameters to be investigated in the pathophysiological model of airway inflammation biomarkers. Recently, the term inflammometry has been given to the measurement of exhaled NO and mentioned in some studies. This review is focused mainly on the clinical utility of exhaled NO measurement in the management of allergic airway inflammation and especially in asthma.

Biosynthesis Of Nitric Oxide In Exhaled Breath

Origin Of NO In Exhaled Breath

In the airways, NO in exhaled breath is synthesized from specialized cell types under responsible activity of the nitric oxide synthase (NOS) enzyme system including three different isoforms (neuronal NOS or nNOS/NOS-1, inducible NOS or iNOS/NOS-2, and endothelial NOS or eNOS/NOS-3). Endogenous NO production is dependent on the concentration of extracellular L-arginine, which is the substrate for both arginase, yielding L-ornithine and urea, and NOS, yielding NO and L-citrulline. NO production in airway epithelial cells is closely coupled to cellular L-arginine uptake. Therefore, in the airways, NO production depends not only on NOS isoform bioactivities but also on the bioavailability of the substrate by competing for their common substrate. After production, NO is dissolved in the cytoplasm, then diffused through the cell membrane to the extracellular environment. In the respiratory system (airways and lungs), NO acts as a signaling molecule of the intercellular information process for modulating vascular and bronchial tone, promoting bronchial and vascular dilatation, facilitating ciliary beating of epithelial cells, and playing the crucial role of neurotransmitter of the non-adrenergic and non-cholinergic systems.[18–20] NO can be detected in exhaled breath from the nose (nasal concentration of NO or nNO), through the bronchial tree (fractional concentration of exhaled NO or FE_{NO}) and to lung parenchyma (alveolar concentration of NO or C_{ANO}).[21–24] All three types of NOSs involved in NO biosynthesis are present permanently in the respiratory system for ensuring continuous NO synthesis. Thus, in healthy subjects, the concentration of NO in exhaled breath is constant and always maintained at a basic level (lower limit values). However, although the level of exhaled NO varies very slightly in children less than 12 years due to anthropometric features, exhaled NO is increased significantly in subjects with allergic airway inflammation, especially in allergic rhinitis and in asthma.[3–5]

Biosynthesis Of NO In Allergic Airway Inflammation

The level of NO in exhaled breath has a major anatomical origin from epithelium.[25–27] The main NOS enzyme involved in the biosynthesis of NO in the respiratory tract is inducible NOS (iNOS or NOS-2) for normal conditions and in inflammatory diseases. The iNOS is present in respiratory epithelial cells and different kinds of inflammatory cells. When stimulated by the mediators from an inflammatory response, iNOS produces NO at a slower rate but in large quantities (Figure 1). The hyperreactivity of iNOS causes endogenous NO concentration to be increased many times, compared to baseline levels. Thus, exhaled NO is now considered as one of the most important inflammation biomarkers in the respiratory tract. In subjects with allergic airway inflammation, there is

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

not only iNOS that activates the epithelium to produce NO but also other inflammatory cells such as eosinophils, mast cells, B or T lymphocytes, etc.;[28,29] these inflammatory cells also contribute significantly to the increase of endogenous NO level (Figure 1). Under normal physiological conditions, the bronchial epithelium produces low levels of NO; but when the allergic inflammatory process is stimulated (e.g., in asthma), the production of exhaled NO can be increased many times.[30–32] This increased NO will be integrated into the exhaled air stream and can be measured with different flow rates for different anatomical levels of NO production. However, the activity and expression of iNOS may be inhibited by corticosteroids or leukotriene receptor antagonists.[33,34]

Method Of Exhaled Nitric Oxide Measurement

Techniques Of Exhaled NO Measurement

Currently, there are three different techniques using for exhaled NO measurement devices which use electrochemical

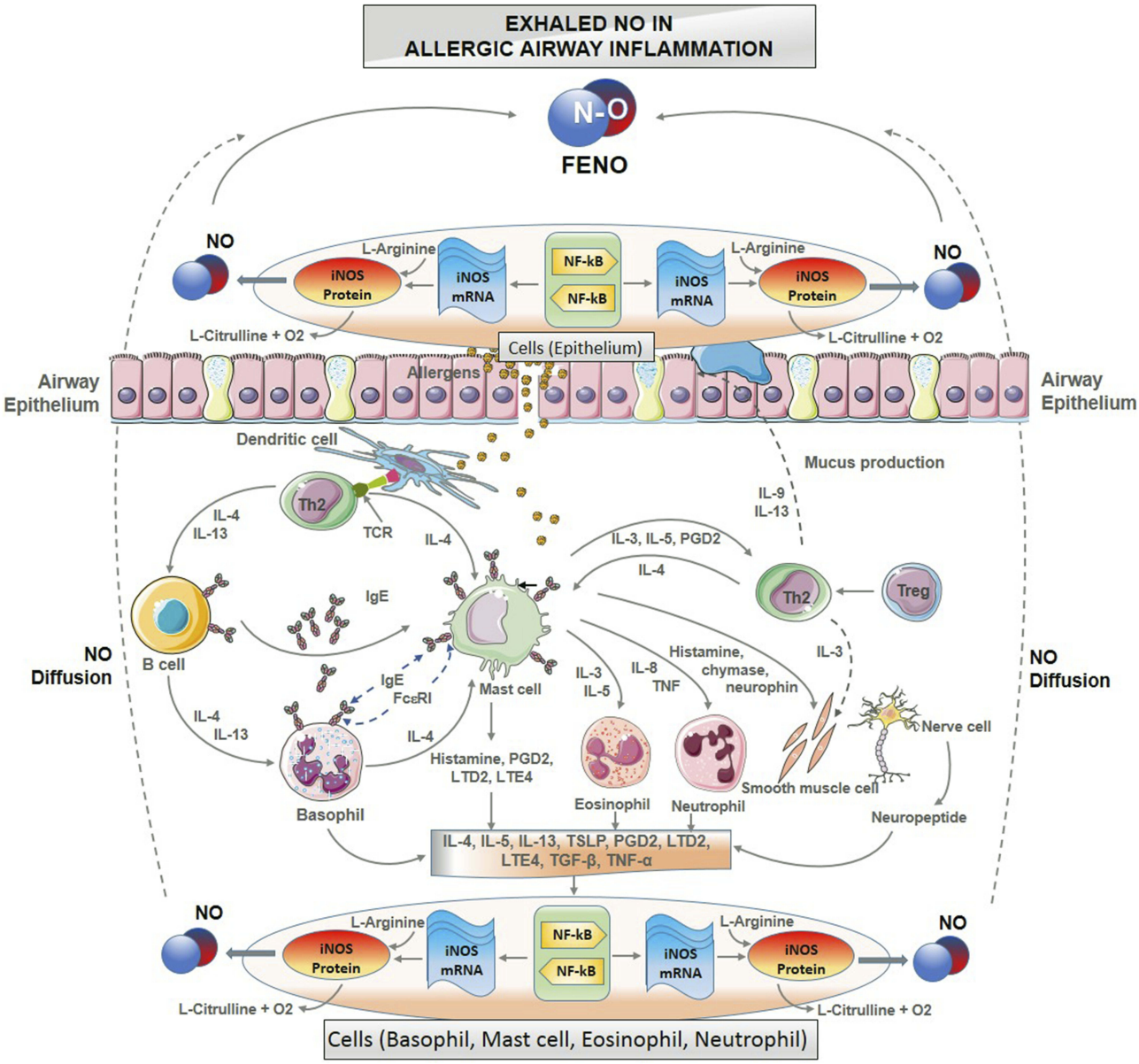

Figure 1 The mechanism of biosynthesis of NO in allergic airway inflammation. The main biosynthesis of NO in the airways is induced by iNOS presenting in respiratory epithelial cells and inflammatory cells (basophils, eosinophils, neutrophils, mast cells, B or T lymphocytes). Intracellularly produced NO will diffuse to the lumen of the airways. Hyperreactivity of iNOS caused by allergic inflammation induces high level of exhaled NO concentration in the airways.

Abbreviations: FENO, fractional concentration of nitric oxide; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NF-kB, nuclear factor-kappa B; TSLP, thymic stromal lymphopoietin; FcεRI, high-affinity IgE receptor; Treg, regulatory T cell; PGD2, prostaglandin D2; LTD, leukotriene D; LTE, leukotriene E; IL, interleukin.

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

sensors and chemiluminescence sensors or laser spectroscopy techniques. Portable devices with electrochemical sensors are commonly available in the market currently, such as Aerocrine's Niox Mino® or Niox Veri® (Aerocrine AB, Solna, Sweden). The first devices using an electrochemical sensor approved by the US Food and Drug Administration (FDA) were Bedfont's NObreath® (Rochester, UK), and Medisoft's Hypair FENO® (Sorinnes, Belgium). The devices with electrochemical technology have the advantage of cost and size, creating small and inexpensive apparatus.[8,35–38] The measurement of exhaled NO with chemiluminescence sensors is a standard technique, but the devices used this technology have relatively large sizes, complex operating conditions, and very high prices. Therefore, this technique is used only in some limited laboratories, although with a high accuracy and fast response time (NOA 280i made by Sievers or Ecomedic's of CLD 88). Recently, the new prototypes with the use of laser absorption spectroscopy techniques have been launched in some laboratories.[39–41] This novel technique has high accuracy and allows measuring simultaneously many components of exhaled gases with a lower cost than the chemiluminescence technique.

Method Of Exhaled NO Measurement In The Airways

Measuring instantaneous (online) exhaled NO is performed mainly by breathing directly into the device, with the result being displayed immediately on the monitor screen. For fractional concentration of exhaled NO (FENO) measurement with hand-held devices (Mino Niox®),[42] the patient sits in a comfortable position with the mouthpiece placed into his/her mouth to blow out the air from expiratory breath. The nose clip can be used if the patient is not able to blow out (expiratory breath) by mouth. During the exhalation period, some factors can affect the results of measuring FENO from the lower airways, including the contamination of high levels of NO from the upper airways, the variation of expiratory flow, and the adequate expiratory time. Fortunately, all the current devices made with the standardized features can provide accurate FENO measurement.[43]

An exhaled flow of 50 mL/s is recommended by the ATS/ERS when measuring FENO in the airways.[3–5,44] The expiratory flow of 50 mL/s is now acceptable for measuring FENO in children and adults because it reflects very well the concentration of NO in the airways. Principally, the constant expiratory flow can be achieved by integrating commonly a system that creates adequate pressure in the mouthpiece to maintain a fixed flow when patients blow out. Although one measurement is enough for FENO measurement with Mino Niox as reported previously,[45,46] it is recommended to measure two times and take the average, but it is done a third time if the difference between two measurements is over 10%.[4]

Measurement Of Exhaled NO In The Airways By Offline Method

The measurements of FENO can be realized by collecting exhaled air into a bag (Tedlar or Mylar bags) for analyzing the exhaled NO concentration. Previous studies showed that FENO measured by the offline method was almost similar to instantaneous measurement with the same exhaled air flows, and there was good agreement between two methods for FENO values.[47,48] Schiller et al. compared the conventional chemiluminescence NO analyzer with the hand-held device (Mino Niox®) and offline FENO measurement. They reported that there was a between-method agreement within a clinically acceptable range for FENO values.[49] The use of offline NO measurement may be preferred for the widespread screening of respiratory diseases in the community.[50] However, the offline measurement of FENO has some limitations, including the contamination of NO from the upper airway, the instability of exhaled NO stored in repetitive-used bags, and the lack of immediate results for a treatment decision.

Utility Of Exhaled Nitric Oxide Measurement In Allergic Airway Inflammation And Asthma

Mechanism Of Immune Response In Allergic Airway Inflammation

The immune response in allergic airway inflammation due to different allergic disorders such as allergic rhinitis, allergic bronchitis, airway hyperresponsiveness, or asthma, etc. consists of the period of sensitization and memory and the response phase. The last one is then divided into early response and late response. In the sensitive phase of allergic airway inflammation, there is the differentiation and replication of specific allergen-dependent Th2-CD4+ cells, inducing increased IL-4 and IL-13 production. These cytokines are the mediators needing to stimulate the conversion and formation of heavy immunoglobulin chains in B cells and to produce allergy-specific globulins (IgE). The

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

IgE specific to allergens will then bind to high-affinity receptors (FcεRI) on the surface of cells and eosinophils and induce the process of allergic inflammation in the airways (Figure 1). Therefore, IL-4, IL-13, and other cytokines and inflammatory mediators also induce the excessive production of NO in the inflammatory cells by increasing the transcription and synthesis of the iNOS protein (Figure 1). Hence, the measurement of exhaled NO with portable devices helps to evaluate the inflammatory reaction in the airways.

The excess production of NO in the airways, manifested by high levels of FENO, is maintained in the immediate (early) response phase (type I hypersensitivity response). In this phase, the association of IgE–FcεRI complexes on effective and sensitive cells, leading to the release of anaphylactic mediators that induce increased vascular permeability, hypersecretion, and bronchial contraction (Figure 1). If the exposure to allergens has been continued, the late response phase occurs 6–12 hr later. In this phase, allergen-specific Th2 cells are activated to produce IL-4, IL-5, IL-9, and IL-13, which play a major role in cytokine-induced exhaled NO production. In addition, the high level of exhaled NO is usually associated with mucus secretion, airway contraction, and other clinical symptoms. Other cytokines including TSLP (thymic stromal lymphopoietin), IL-25, IL-31, and IL-33, produced from epithelial cells, have also been found to have a preponderant role in Th2 inflammatory response.[51,52]

Role Of Nasal NO Measurement In Allergic Rhinitis

Origin Of Nasal NO And Technique Of Measurement

Exhaled NO is produced continuously from the epithelial layer of the nose and the paranasal sinuses under the activity of iNOS.[21,53] In patients with allergic rhinitis, iNOS over expression may be found in epithelial cells, macrophages, neutrophils, eosinophils, and other cells (Figure 1). There are different techniques used to measure the concentration of NO in the nose (nNO). Recently, the new NO analysis method based on electrochemical technology has been developed and tested for nNO in patients with allergic rhinitis, chronic rhino-sinusitis, or primary ciliary dyskinesia (Figure 2). Thus, the development of standardized methods for measuring nNO is necessary for clinical practice. Currently, the common method of nNO measuring is to introduce the sampling catheter to the nasal cavity via nostril to aspirate the internal air stream (5 mL/s) during patients' short breath-holding (10 s) for analyzing directly the nasal concentration of NO (Figure 2). Another method is to measure nNO during the circulating volume when the patient breathes normally through one nostril, while gas is removed from the other side at a rate of 5mL/s. nNO may be measured by handling devices via nasal mask with single nasal exhalation and fixed flow rates.[54–57]

Utility Of Exhaled NO Measurement In Allergic Rhinitis

Allergic rhinitis is a common upper airway disease that affects about 25% of the world's population and continues to increase worldwide.[58] In developed countries, the prevalence of allergic rhinitis is still high and this disease becomes a burden for health-care systems and public populations.[59,60] Similar to other airway inflammatory disorders such as asthma, the nasal mucosa of patients with allergic rhinitis is characterized by high iNOS expression and activity.[61,62] However, the application of nNO measuring is relatively complicated and remains controversial.[63] In the early recommendation , it was shown that nNO was increased significantly in patients with seasonal allergic rhinitis during the pollen season and nNO levels had been changed after exposure to allergens and were related to the severity of clinical symptoms.[64] Recent studies demonstrate that patients with allergic rhinitis had a higher level of nNO than healthy subjects.[10,63,65,66] The results of these studies also showed that the increased production of nNO might be triggered by airborne allergens (pollens, house dust mite, or cat or dog hairs) and could be measured by constant aspiration or with expiratory flow.

In healthy subjects without allergic rhinitis, the concentration of nNO measured by aspiration is higher than that in the lower airways (350–750 vs. 5–25 ppb).[10] In fact, in the upper airways, exhaled nNO is produced not only from the sinuses by gradient diffusion, [21] but also from the NO produced by nasal mucosal membranes (epithelium)[67,68] and inflammatory cells (eosinophils) related to the upregulation of inducible NO synthase (iNOS).[63,69,70] Therefore, in patients with allergic rhinitis, nNO may be used as a biomarker of eosinophilic inflammation because of its strong correlation with clinical symptoms and airway inflammation.[10,69] Therefore, nNO may be considered a relevant biomarker for the diagnosis of allergic rhinitis and the evaluation of allergic rhinitis severity. Thus, the measure of nNO with portable (or hand-held) devices is useful for the management of

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

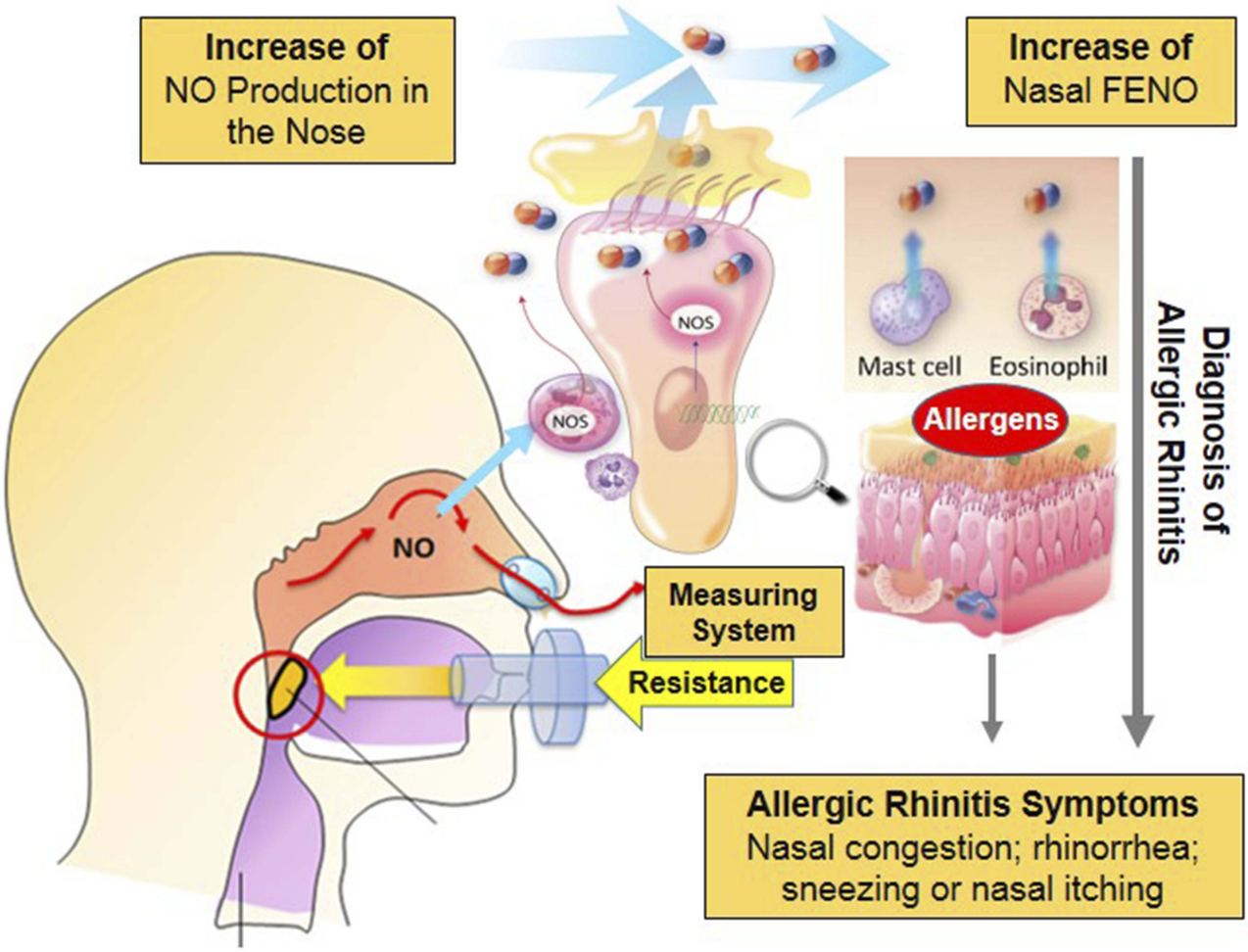

Figure 2 Origin of nasal NO and technique of nNO measurement. Exhaled NO is produced from the epithelial cells, eosinophils, mast cells, and other cells under the activity of iNOS during contact with allergens. The measurement of nNO is done by introducing the sampling catheter to the nasal cavity via the nostril to aspirate the internal air stream.
Abbreviations: nNO, nasal nitric oxide; FENO, fractional concentration of nitric oxide; iNOS, inducible nitric oxide synthase.

patients with allergic rhinitis (Figure 2).[10,63,69] However, as with the measurement of FENO in asthma, the level of nNO in healthy subjects and in patients with allergic rhinitis must be standardized and well-defined in considering its variation with confounding factors.

Role Of FENO Measurement In Asthma Management

Currently, FENO is considered a relevant biomarker of Th2 airway inflammation in asthma and is synthesized by upregulation of iNOS in epithelial cells, macrophages, neutrophils, eosinophils, and mononuclear cells (Figure 1).[71] The level of FENO is significantly increased in almost all kinds of asthma phenotypes and can be detected easily by measuring with portable devices. FENO is a non-invasive, easy-to-perform and safe technique for assessing airway inflammation in asthma. Therefore, FENO can be used as a relevant biomarker of airway inflammation in the management of adult as well as childhood asthma. Moreover, FENO may be used to predict asthma exacerbations and inhaled corticosteroid (ICS) response more consistently than spirometry, bronchodilator response, peak flow variation or the bronchial challenge test to methacholine.[5,72–74] Recently, FENO measurement has been recommended by GINA in monitoring patients with asthma.[75]

Advantages Of FENO Measurement In Asthma Diagnosis

The main advantage of FENO measurement with portable devices in the diagnosis of asthma is that it allows direct evaluation of the level of airway inflammation in association with other exploration techniques such as peak flowmeter, spirometry for measuring airway obstruction, or

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

impulse oscillation system for airway resistance measuring, etc. In asthma, chronic airway inflammation induced by eosinophils is the main characteristic of pathogenesis and also a target of treatment with ICS. The correlation between FENO and eosinophilic airway inflammation in asthma has been demonstrated previously by a large body of evidence. FENO measurement gives an additional tool in association with other functional methods used to assess only a ventilation disorder (airway obstruction), a consequence of the airway inflammation. Moreover, the sensitivity of FENO is thought to be better than the forced expiratory volume in the first second (FEV1) in prognostics of asthma exacerbation and crisis due to its early and accurate changes.[76–78]

In addition, in comparison with other laboratory techniques for assessing airway inflammation in asthma (induced-sputum count, blood eosinophil count, bronchial lavage analysis, or bronchial biopsy), FENO measurement has many advantages: this technique is non-invasive, easy to implement and perform, accurate and not expensive, and gives instantaneous results for treatment decisions. Especially, due to its easy implementation, the measurement of FENO is a useful tool in the epidemiological study and early detection of asthmatic patients in the community. The new generation of portable devices (Mino Vero®)[43] also allows this technique to be performed in clinics, in emergency departments, at patient bedsides and even in schools or residential communities.

In the last recommendations of ATS[5] and ERS,[44] they stated that FENO values in normal subjects do not exceed 20 ppb in children and 25 ppb in adults. Higher values of FENO are considered a diagnosis of asthma. However, in daily practice, the diagnostic values of FENO in asthma are limited by many confounding factors such as allergy status, cigarette smoking, previous use of corticosteroids and other upper respiratory infections, etc. Therefore, the use of FENO in the diagnosis of asthma should be used in combination with clinical and other functional exploration techniques to support diagnosis, especially in asthmatic patients who have the features of asthma – COPD overlap (ACO).[16]

Utility Of FENO Measurement In Predicting ICS Response

One of the most important benefits of FENO measurement is to help physicians to monitor objectively the effectiveness of treatment with anti-inflammatory drugs. The results of increasing published studies confirmed the reduction of FENO in asthmatic patients after treatment with anti-inflammatory drugs, especially with ICS.[79–82] The response of FENO to ICS is very quick and depends on the treatment dose. However, if the inflammatory process in the airway of asthmatic patients still exists and is not completely controlled, the concentration of FENO is still high. In that situation, the FENO level depends on the degree of bronchial hyperresponsiveness, eosinophil-induced airway inflammation and clinical symptoms of asthma. Therefore, the measurement of FENO helps to assess the severity of airway inflammation, to predict the level of ICS responsiveness, and to individualize the patients for target therapy (biotic treatment).[83,84]

In patients with diagnosed asthma, the most important issue is how to identify patients who respond well to ICS, practically in the current situation, the use of ICS has been recommended by GINA as the first-line treatment.[78] Therefore, besides the use of clinical features to identify asthmatic patients who have a phenotype responding to ICS therapy such as early asthma onset, atopy, or positive airway hyperresponsiveness, etc., the use of FENO measurement may help to determine patients who are more likely to respond to ICS.[85,86] A recent study done in a small group of asthmatic children showed that FENO level was significantly higher in patients with a positive skin-prick test for respiratory allergens and significantly correlated with blood eosinophil count and ICS doses during follow-up.[13,14] The ATS recommendations state that a FENO level less than 25 ppb (20 ppb in children) may be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely.[5]

Utility Of FENO Measurement In Following-Up ICS Response

The FENO level is significantly reduced when treated with inhaled or systemic corticosteroids; this response occurs quickly and inversely with the dose used. The increase or decrease of FENO values between two measurements are a relevant marker of loss or improvement of asthma control. The response of FE_{NO} to corticosteroids may occur after hours to weeks and depends on the initial dose. When the initial FENO concentration is high (>50 ppb in adults or >35 ppb in children), the initial dose of ICS should be higher to effectively control the airway inflammation. During the follow-up of asthmatic patients treated with ICS, the significant increase in FENO is confirmed if it is greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

next, while the reduction of at least 20% in FENO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb indicates a significant response to ICS.[5]

Utility Of FENO Measurement In Asthma Control

The use of portable devices for FENO measurements is also useful for monitoring chronic airway inflammation in patients with controlled asthma. In these patients, although clinical symptoms are absent, a high level of FENO suggests the biological evidence of persistent airway inflammation. High FENO values are similar to the existence and active status of inflammatory cells (eosinophils, mast cells, macrophages, or T lymphocytes, etc.) with compatible inflammatory mediators in the airways of asthmatic patients. Particularly, in the period of symptomatic remission, FENO measurement may help physicians to learn if there is a latent increase of inflammatory activity in the airway that leads to asthma exacerbation or airway remodeling in long-term follow-up. A high level of FENO in uncontrolled asthma may predict a difficult-to-treat asthma phenotype, leading to optimal treatment or target therapy.

In addition to its benefit in evaluating asthma control, the measurement of FENO with portable devices, e.g., the critical increase of FENO values, can help physicians in primary care to predict acute asthma exacerbations in uncontrolled or partially controlled asthmatic patients. Also, it can help predict asthma relapse needing to step-up ICS doses or combined treatment in controlled asthma. Although the use of FENO values as a sole marker to predict asthma exacerbation or asthma relapse in controlled asthma remains controversial, FENO measurement may be used in association with clinical and functional features for follow-up patients with asthma. Therefore, the change in FENO compared to the initial values may be used to personalize the appropriate and individualized FENO levels for each asthma patient because it reflects better the significant changes of airway inflammation for adapting anti-inflammatory therapy. In addition, FENO measurement with portable devices may be useful for targeting the optimal treatment in difficult-to-treat or severe asthma. Recently, the beneficial role of FENO measurement with portable devices for the titration of minimal and effective doses of ICS in asthma patients to reduce the daily dose of ICS and cost of treatment has been demonstrated.[87]

Benefit Of FENO Measurement In Other Treatments For Asthma

The measurement of FENO is also useful in asthmatic patients who are treated with leukotriene receptor antagonists (LRA). LRA may reduce FENO level in asthma patients, but the ability of this kind of drug to reduce FENO is weaker than ICS.[82,88,89] In terms of pathogenesis, patients with asthma have overexpression of cysteinyl leukotriene that has been synthesized and produced from inflammatory cells. This phenomenon contributes to the significant increase of FENO level in the airways via increased production of FENO by iNOS. Montelukast is an LRA which is capable of significantly reducing FENO from the initial values and requiring some days of treatment. The efficacy of LRA in reducing FENO also occurs before the improvement of clinical and functional features. It is therefore very useful to measure FENO with portable devices in asthma patients who are assigned to LRA treatment in a long-term therapy or combined therapy to achieve well-controlled asthma.

In patients with severe asthma who have "allergic" or T-helper 2 (Th2) features, the measurement of FENO is a useful tool for target treatment with biologic therapy. Currently, the GINA guidelines for the diagnosis and management of difficult-to-treat and severe asthma in adolescent and adult patients suggest FENO (≥20 ppb) as a relevant biomarker of the Th2-related asthma phenotype in association with other Th2 biomarkers, including blood eosinophils (≥150/μL) and sputum eosinophils (≥2%).[75] FENO may be considered as a useful biomarker for biologic treatment in patients with severe asthma. There are currently available biologics that have been approved by the US FDA for add-on maintenance therapy in asthma including anti-IgE receptor (Omalizumab), anti-interleukin (IL)-5 monoclonal antibodies (Mepolizumab and Reslizumab), an antibody that is directed toward eosinophil receptors (Benralizumab), and a human monoclonal antibody to the alpha subunit of the IL-4 receptor (Dupilumab). The efficacy of these Th-2 interventional products might be evaluated by the significant reductions in asthma symptoms and based on FENO levels.

Limitation Of Exhaled NO Measurement In Asthma

Besides its beneficial role, the use of FENO in the management of asthma has some limitations. Recent systematic review and meta-analysis demonstrated that FENO was modestly correlated with levels of sputum and blood eosinophils.[90] In addition, the current guidelines do not strongly recommend the use of FENO values for ruling in or out a diagnosis of asthma because FENO is higher in Th-2-characterized asthma, but it is also elevated in non-asthma conditions (e.g., eosinophilic bronchitis, atopy, allergic rhinitis, eczema).[91] Moreover, FENO is not elevated in some asthma phenotypes (e.g., neutrophilic asthma).[4] Furthermore, the data from published

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

studies have revealed that FENO might be lower in smokers, during bronchoconstriction, and in the early phase of an allergic response.[4,92] Finally, until now, there have been no long-term follow-up studies confirming the safety of withholding ICS in patients with low initial FENO with regard to risk of exacerbation; therefore, in patients with diagnosed or suspected asthma, a low level of FENO cannot be recommended at present for deciding against treatment with ICS.[75]

Conclusion

The discovery of exhaled NO as a biomarker of allergic airway inflammation marks remarkable progress in this field, especially in asthma. The use of portable devices for FENO measurement makes this biomarker more useful and available in primary health-care structures. The application of FENO measurement with portable devices helps physicians to do the best practice in the management of chronic allergic airway diseases such as in allergic rhinitis or in asthma. Currently, the method of measuring exhaled NO in breathing air (FENO and nNO) is standardized by international recommendations. In asthma, the measurement of FENO has a great benefit in supporting the diagnosis, treatment, and control of asthma.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J*. 1993;6:1368–1370.
2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=exhaled+nitric+oxide++and+asthma. Accessed 12:55 PM; July 20, 2019.
3. American Thoracic Society. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children. *Am J Respir Crit Care Med*. 1999;160:2104–2117. doi:10.1164/ajrccm.160.6.ats8-99
4. American Thoracic Society/European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med*. 2005;171:912–930. doi:10.1164/rccm.200406-710ST
5. Dweik RA, Boggs PB, Erzurum SC, et al. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for clinical applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med*. 2011;184:602–615. doi:10.1164/rccm.9120-11ST
6. Dinh-Xuan AT, Annesi-Maesano I, Berger P, et al. French Speaking Respiratory Society. Contribution of exhaled nitric oxide measurement in airway inflammation assessment in asthma. A position paper from the French Speaking Respiratory Society. *Rev Mal Respir*. 2015;32:193–215. doi:10.1016/j.rmr.2014.11.004
7. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szefler SJ. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol*. 2004;114:1241–1256. doi:10.1016/j.jaci.2004.08.042
8. Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. *Respir Res*. 2006;7:67. doi:10.1186/1465-9921-7-67
9. Gratziou C, Rovina N, Makris M, Simoes DC, Papapetropoulos A, Roussos C. Breath markers of oxidative stress and airway inflammation in seasonal allergic rhinitis. *Int J Immunopathol Pharmacol*. 2008;21:949–957. doi:10.1177/039463200802100419
10. Duong-Quy S, Vu-Minh T, Hua-Huy T, et al. Study of nasal exhaled nitric oxide levels in diagnosis of allergic rhinitis in subjects with and without asthma. *J Asthma Allergy*. 2017;10:75–82. doi:10.2147/JAA.S129047
11. Deykin A, Halpern O, Massaro AF, Drazen JM, Israel E. Expired nitric oxide after bronchoprovocation and repeated spirometry in patients with asthma. *Am J Respir Crit Care Med*. 1998;157:769–775. doi:10.1164/ajrccm.157.3.9707114
12. Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J*. 2003;21:433–438. doi:10.1183/09031936.03.00066903a
13. Nguyen-Thi-Bich H, Duong-Thi-Ly H, Thom VT, et al. Study of the correlations between fractional exhaled nitric oxide in exhaled breath and atopic status, blood eosinophils, FCER2 mutation, and asthma control in Vietnamese children. *J Asthma Allergy*. 2016;9:163–170. doi:10.2147/JAA.S107773
14. Duong-Quy S, Nguyen-Thi-Bich H, Le-Thi-Minh H, Craig T. The use of exhaled nitric oxide (NO) to categorize asthma phenotype and treatment in children-Results from National Hospital of Pediatrics. *Eur Respir J*. 2018;52(suppl 62):PA1315. doi:10.1183/13993003.01675-2018
15. Wen YS, Lin CY, Yang KD, Hung CH, Chang YJ, Tsai YG. Nasal nitric oxide is a useful biomarker for acute unilateral maxillary sinusitis in pediatric allergic rhinitis: a prospective observational cohort study. *World Allergy Organ J*. 2019;12(4):100027. doi:10.1016/j.waojou.2019.100027
16. Duong-Quy S, Tran Van H, Vo Thi Kim A, Pham HQ, Craig TJ. Clinical and functional characteristics of subjects with asthma, COPD, and asthma-COPD overlap: a multicentre study in vietnam. *Can Respir J*. 2018;1(2018):1732946.
17. Duong-Quy S, Hua-Huy T, Tran-Mai-Thi HT, Le-Dong NN, Craig TJ, Dinh-Xuan AT. Study of exhaled nitric oxide in subjects with suspected obstructive sleep apnea: a pilot study in vietnam. *Pulm Med*. 2016;2016:3050918. doi:10.1155/2016/3050918
18. Belvisi MG, Ward JK, Mitchell JA, Barnes PJ. Nitric oxide as a neurotransmitter in human airways. *Arch Int Pharmacodyn Ther*. 1995;329:97.
19. Jain B, Rubinstein I, Robbins RA, Leise KL, Sisson JH. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. *Biochem Biophys Res Commun*. 1993;191:83. doi:10.1006/bbrc.1993.1187
20. Belvisi MG, Stretton CD, Yacoub M, Barnes PJ. Nitric oxide is the endogenous neurotransmitter of bronchodilator nerves in humans. *Eur J Pharmacol*. 1992;210:221. doi:10.1016/0014-2999(92)90676-U
21. Lundberg JO, Farkas-Szallasi T, Weitzberg E, et al. High nitric oxide production in human paranasal sinuses. *Nat Med*. 1995;1:370–373. doi:10.1038/nm1295-1257
22. Kobzik L, Bredt DS, Lowenstein CJ, et al. Nitric oxide synthase in human and rat lung: immunocytochemical and histochemical localization. *Am J Respir Cell Mol Biol*. 1993;9:371–377. doi:10.1165/ajrcmb/9.4.371
23. Hyde RW, Geigel EJ, Olszowka AJ, et al. Determination of production of nitric oxide by lower airways of humans–theory. *J Appl Physiol (1985)*. 1997;82:1290. doi:10.1152/jappl.1997.82.4.1290
24. Paraskakis E, Brindicci C, Fleming L, et al. Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. *Am J Respir Crit Care Med*. 2006;174:260. doi:10.1164/rccm.200510-1659PP
25. Guo FH, De Raeve HR, Rice TW, Stuehr DJ, Thunnissen FB, Erzurum SC. Continuous nitric oxide synthesis by inducible nitric oxide synthase in normal human airway epithelium in vivo. *Proc Natl Acad Sci USA*. 1995;92:7809–7813. doi:10.1073/pnas.92.17.7809

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

26. Donnelly LE, Barnes PJ. Expression and regulation of inducible nitric oxide synthase from human primary airway epithelial cells. *Am J Respir Cell Mol Biol*. 2002;26:144–151. doi:10.1165/ajrcmb.26.1.4477
27. Lane C, Knight D, Burgess S, et al. Epithelial inducible nitric oxide synthase activity is the major determinant of nitric oxide concentration in exhaled breath. *Thorax*. 2004;59:757–760. doi:10.1136/thx.2003.014894
28. Silvestri M, Spallarossa D, Frangova Yourukova V, et al. Orally exhaled nitric oxide levels are related to the degree of blood eosinophilia in atopic children with mild-intermittent asthma. *Eur Respir J*. 1999;13:321–326. doi:10.1034/j.1399-3003.1999.13b17.x
29. Ihre E, Gyllfors P, Gustafsson LE, et al. Early rise in exhaled nitric oxide and mast cell activation in repeated lowdose allergen challenge. *Eur Respir J*. 2006;27:1152–1159. doi:10.1183/09031936.06.00142905
30. Dweik RA, Comhair SA, Gaston B, et al. NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. *Proc Natl Acad Sci USA*. 2001;98:2622–2627. doi:10.1073/pnas.051629498
31. Erpenbeck VJ, Jorres RA, Discher M, et al. Local nitric oxide levels reflect the degree of allergic airway inflammation after segmental allergen challenge in asthmatics. *Nitric Oxide*. 2005;13:125–133. doi:10.1016/j.niox.2005.05.008
32. Guo FH, Comhair SA, Zheng S, et al. Molecular mechanisms of increased nitric oxide (NO) in asthma: evidence for transcriptional and post-translational regulation of NO synthesis. *J Immunol*. 2000;164:5970–5980. doi:10.4049/jimmunol.164.11.5970
33. Hämäläinen M, Lilja R, Kankaanranta H, Moilanen E. Inhibition of iNOS expression and NO production by anti-inflammatory steroids. Reversal by histone deacetylase inhibitors. *Pulm Pharmacol Ther*. 2008;21(2):331–339. doi:10.1016/j.pupt.2007.08.003
34. Sade K, Schwartz I, Schwartz D, et al. Effect of montelukast pretreatment on inducible nitric oxide synthase mRNA expression in the lungs of antigen-challenged allergic mice. *Clin Exp Allergy*. 2003;33(12):1741–1746. doi:10.1111/j.1365-2222.2003.01798.x
35. Baraldi E, Scollo M, Zaramella C, Zanconato S, Zacchello F. A simple flow-driven method for online measurement of exhaledNOstarting at the age of 4 to 5 years. *Am J Respir Crit Care Med*. 2000;162:1828–1832. doi:10.1164/ajrccm.162.5.2002014
36. Bates CA, Silkoff PE. Exhaled nitric oxide in asthma: from bench to bedside. *J Allergy Clin Immunol*. 2003;111:256–262. doi:10.1067/mai.2003.103
37. Spahn JD, Malka J, Szefler SJ. Current application of exhaled nitric oxide in clinical practice. *J Allergy Clin Immunol*. 2016;138:1296–1298. doi:10.1016/j.jaci.2016.09.002
38. Menzies D, Nair A, Lipworth BJ. Portable exhaled nitric oxide measurement: comparison with the "gold standard" technique. *Chest*. 2007;131:410–414. doi:10.1378/chest.06-1335
39. Wojtas J. Application of cavity enhanced absorption spectroscopy to the detection of nitric oxide, carbonyl sulphide, and ethane—breath biomarkers of serious diseases. *Sensors (Basel)*. 2015;15(6):14356–14369. doi:10.3390/s150614356
40. Maniscalco M, Vitale C, Vatrella A, Molino A, Bianco A, Mazzarella G. Fractional exhaled nitric oxide-measuring devices: technology update. *Med Devices (Auckl)*. 2016;9:151–160.
41. Henderson B, Khodabakhsh A, Metsälä M, et al. Laser spectroscopy for breath analysis: towards clinical implementation. *Appl Phys B*. 2018;124(8):161. doi:10.1007/s00340-018-7030-x
42. Available from: http://pdf.medicalexpo.com/pdf/aerocrine/niox-mino-brochure/85229-103071.html. Accessed May 15th, 2019.
43. Available from: https://www.niox.com/en/niox-vero/about-niox-vero/. Accessed May 15th, 2019.
44. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society technical standard: exhaled biomarkers in lung disease. *Eur Respir J*. 2017;49(4). doi:10.1183/13993003.00965-2016.
45. Khalili B, Boggs PB, Bs L. Reliability of a new hand-held device for the measurement of exhaled nitric oxide. *Allergy*. 2007;62:1171–1174. doi:10.1111/j.1398-9995.2007.01456.x
46. McGill C, Malik G, Turner SW. Validation of a hand-held exhaled nitric oxide analyzer for use in children. *Pediatr Pulmonol*. 2006;41:1053–1057. doi:10.1002/(ISSN)1099-0496
47. Kissoon N, Duckworth LJ, Blake KV, et al. Exhaled nitric oxide concentrations: online versus offline values in healthy children. *Pediatr Pulmonol*. 2002;33:283–292. doi:10.1002/(ISSN)1099-0496
48. Kissoon N, Duckworth LJ, Blake KV, Murphy SP, Taylor CL, Silkoff PE. Fe(NO): relationship to exhalation rates and online versus bag collection in healthy adolescents. *Am J Respir Crit Care Med*. 2000;162:539–545. doi:10.1164/ajrccm.162.2.9909124
49. Schiller B, Hammer J, Barben J, Trachsel D. Comparability of a hand-held nitric oxide analyser with online and offline chemiluminescence-based nitric oxide measurement. *Pediatr Allergy Immunol*. 2009;20(7):679–685. doi:10.1111/j.1399-3038.2009.00853.x
50. Menou A, Babeanu D, Paruit HN, Ordureau A, Guillard S, Chambellan A. Normal values of offline exhaled and nasal nitric oxide in healthy children and teens using chemiluminescence. *J Breath Res*. 2017;11(3):036008. doi:10.1088/1752-7163/aa76ef
51. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*. 2008;7:827–840. doi:10.1038/nrd2660
52. Wang YH, Angkasekwinai P, Lu N, et al. IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. *J Exp Med*. 2007;204:1837–1847. doi:10.1084/jem.20070406
53. Lundberg JO, Weitzberg E. Nasal nitric oxide in man. *Thorax*. 1999;54:947–952. doi:10.1136/thx.54.5.439
54. Maniscalco M, de Laurentiis G, Weitzberg E, Lundberg JO, Sofia M. Validation study of nasal nitric oxide measurements using a hand-held electrochemical analyser. *Eur J Clin Invest*. 2008;38:197–200. doi:10.1111/eci.2008.38.issue-3
55. Qian W, Djupesland PG, Chatkin JM, et al. Aspiration flow optimized for nasal nitric oxide measurement. *Rhinology*. 1999;37:61–65.
56. Ragab SM, Lund VJ, Saleh HA, Scadding G. Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy. *Allergy*. 2006;61:717–724. doi:10.1111/all.2006.61.issue-6
57. Palm JP, Graf P, Lundberg JO, Alving K. Characterization of exhaled nitric oxide: introducing a new reproducible method for nasal nitric oxide measurements. *Eur Respir J*. 2000;16:236–241. doi:10.1034/j.1399-3003.2000.16b09.x
58. Santos CB, Pratt EL, Hanks C, McCann J, Craig TJ. Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol*. 2006;97(5):579–587. doi:10.1016/S1081-1206(10)60969-6
59. Bhattacharyya N. Incremental healthcare utilization and expenditures for allergic rhinitis in the United States. *Laryngoscope*. 2011;121:1830–1833. doi:10.1002/lary.22034
60. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy*. 2007;62(Suppl 85):17–25. doi:10.1111/j.1398-9995.2007.01549.x
61. Kawamoto H, Takeno S, Yajin K. Increased expression of inducible nitric oxide synthase in nasal epithelial cells in patients with allergic rhinitis. *Laryngoscope*. 1999;109:2015–2020. doi:10.1097/00005537-199912000-00023
62. Kawamoto H, Takumida M, Takeno S, et al. Localization of nitric oxide synthase in human nasal mucosa with nasal allergy. *Acta Otolaryngol Suppl*. 1998;539:65–70. doi:10.1080/00016489850182161
63. Nesic VS, Djordjevic VZ, Tomic-Spiric V, Dudvarski ZR, Soldatovic IA, Arsovic NA. Measuring nasal nitric oxide in allergic rhinitis patients. *J Laryngol Otol*. 2016;130(11):1064–1071. doi:10.1017/S0022215116009087

Journal of Asthma and Allergy downloaded from https://www.dovepress.com/ by 84.220.142.25 on 21-Nov-2019
For personal use only.

64. Kharitonov S, Alving K, Barnes PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J*. 1997;10:1683–1693. doi:10.1183/09031936.97.10071683
65. Liu D, Huang Z, Huang Y, Yi X, Chen X. Measurement of nasal and fractional exhaled nitric oxide in children with upper airway inflammatory disease: preliminary results. *Int J Pediatr Otorhinolaryngol*. 2015;79(12):2308–2311. doi:10.1016/j.ijporl.2015.10.033
66. Takeno S, Okabayashi Y, Kohno T, Yumii K, Hirakawa K. The role of nasal fractional exhaled nitric oxide as an objective parameter independent of nasal airflow resistance in the diagnosis of allergic rhinitis. *Auris Nasus Larynx*. 2016;44(4):S0385-8146(16)30369–8.
67. Scadding G, Scadding GK. Update on the use of nitric oxide as a noninvasive measure of airways inflammation. *Rhinology*. 2009;47(2):115–120.
68. Cho WS, Kim TH, Kim KH, et al. Increased expression of arginase I and II in allergic nasal mucosa. *Laryngoscope*. 2011;121(2):236–240. doi:10.1002/lary.21288
69. Bautista AP, Eisenlohr CP, Lanz MJ. Nasal nitric oxide and nasal eosinophils decrease with levocetirizine in subjects with perennial allergic rhinitis. *Am J Rhinol Allergy*. 2011;25(6):383–387. doi:10.2500/ajra.2011.25.3668
70. Irander K, Palm JP, Borres MP, Ghafouri B. Clara cell protein in nasal lavage fluid and nasal nitric oxide - biomarkers with anti-inflammatory properties in allergic rhinitis. *Clin Mol Allergy*. 2012;6(10):4. doi:10.1186/1476-7961-10-4
71. Prado CM, Martins MA, Tibério IF. Nitric oxide in asthma physiopathology. *ISRN Allergy*. 2011;2011:832560.
72. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax*. 1998;53:91–95 91. doi:10.1136/thx.53.2.91
73. Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. *Thorax*. 2005;60(5):383–388. doi:10.1136/thx.2004.031104
74. Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest*. 2003;123:751–756. doi:10.1378/chest.123.3_suppl.424s
75. Global strategy for asthma management and prevention (GINA); 2019. Available from: www.ginasthma.org. Accessed June 16th, 2019.
76. Silvestri M, Sabatini F, Sale R, et al. Correlations between exhaled nitric oxide levels, blood eosinophilia, and airway obstruction reversibility in childhood asthma are detectable only in atopic individuals. *Pediatr Pulmonol*. 2003;35(5):358–363. doi:10.1002/ppul.10264
77. Sippel JM, Holden WE, Tilles SA, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. *J Allergy Clin Immunol*. 2000;106(4):645–650. doi:10.1067/mai.2000.109618
78. Smith AD, Cowan JO, Filsell S, et al. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med*. 2004;169(4):473–478. doi:10.1164/rccm.200310-1376OC
79. Syk J, Malinovschi A, Johansson G, et al. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. *J Allergy Clin Immunol Pract*. 2013;1(6):639–648. doi:10.1016/j.jaip.2013.07.013
80. Beck-Ripp J, Griese M, Arenz S, Köring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. *Eur Respir J*. 2002;19(6):1015–1019. doi:10.1183/09031936.02.01582001
81. Smith AD, Cowan JO, Brassett KP, Herbison P, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med*. 2005;352(21):2163–2173. doi:10.1056/NEJMoa043596
82. Bisgaard H, Loland L, Oj JA. NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast. *Am J Respir Crit Care Med*. 1999;160:1227–1231. doi:10.1164/ajrccm.160.4.9903004
83. Medrek SK, Parulekar AD, Hanania NA. Predictive biomarkers for asthma therapy. *Curr Allergy Asthma Rep*. 2017;17(10):69. doi:10.1007/s11882-017-0739-5
84. Diamant Z, Vijverberg S, Alving K, et al. Towards clinically applicable biomarkers for asthma - An EAACI position paper. *Allergy*. 2019. doi:10.1111/all
85. Knuffman JE, Sorkness CA, Lemanske RF, et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. *J Allergy Clin Immunol*. 2009;123:411–416. doi:10.1016/j.jaci.2008.11.016
86. Gibson PG. Using fractional exhaled nitric oxide to guide asthma therapy: design and methodological issues for AStHma TReatment ALgorithm studies. *Clin Exp Allergy*. 2009;39(4):478–490. doi:10.1111/j.1365-2222.2009.03226.x
87. Duong-Quy S, Doan-Thi-Quynh N, Tran-Thanh D, et al. The cost and benefits of exhaled nitric oxide (NO) measurement in asthma-The results from three years follow-up study. *Eur Respir J*. 2018;52(suppl 62):PA5499. doi:10.1183/13993003.01675-2018
88. Straub DA, Minocchieri S, Moeller A, Hamacher J, Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. *Chest*. 2005;127:509–514. doi:10.1378/chest.127.2.509
89. Whelan GJ, Blake K, Kissoon N, et al. Effect of montelukast on time-course of exhaled nitric oxide in asthma: influence of LTC4 synthase A(−444)C polymorphism. *Pediatr Pulmonol*. 2003;36:413–420. doi:10.1002/ppul.10385
90. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3:290–300. doi:10.1016/S2213-2600(15)00050-8
91. Fahy JV. Type 2 inflammation in asthma–present in most, absent in many. *Nat Rev Immunol*. 2015;15:57–65. doi:10.1038/nri3786
92. Haccuria A, Michils A, Michiels S, Van Muylem A. Exhaled nitric oxide: a biomarker integrating both lung function and airway inflammation changes. *J Allergy Clin Immunol*. 2014;134:554–559. doi:10.1016/j.jaci.2013.12.1070

Journal of Asthma and Allergy

Dovepress

Publish your work in this journal

The Journal of Asthma and Allergy is an international, peer-reviewed open-access journal publishing original research, reports, editorials and commentaries on the following topics: Asthma; Pulmonary physiology; Asthma related clinical health; Clinical immunology and the immunological basis of disease; Pharmacological interventions and new therapies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/journal-of-asthma-and-allergy-journal