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Review Article

The Air We Exhale: Deciphering the Role of Fractional Exhaled Nitric Oxide (FeNO) in Airway Diseases

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Abstract

Fractional exhaled nitric oxide (FeNO) is an important indicator of type 2 inflammation, which is frequently utilized in the assessment and treatment of asthma. It is measured in exhaled breath and provides a simple, quick, and reproducible assessment of airway inflammation status. Elevated FeNO levels are strongly associated with eosinophilic airway inflammation. It represents the synthesis of nitric oxide in the airway epithelium, which is mainly caused by inducible nitric oxide synthase under the influence of cytokines like IL-4 and IL-13. FeNO is utilized in the assessment of symptoms in patients presenting with cough, wheezing, and dyspnoea. It plays a key role in phenotyping asthma, particularly in identifying the eosinophilic asthma phenotype, which is typically T2 high and steroid responsive. FeNO measurement is also valuable in predicting medication response, as it evaluates the possible reaction to anti-inflammatory drugs, mainly inhaled corticosteroids (ICS). Furthermore, it helps in guiding treatment changes in a step-wise manner, including stepping up or stepping down the ICS dose. FeNO is useful in assessing asthma control, especially in determining whether poor control is due to airway inflammation when other contributing factors such as rhinosinusitis, anxiety, gastroesophageal reflux, obesity, and ongoing allergen exposure are present. Additionally, variations in FeNO levels may serve as a helpful supplementary tool for identifying acute complications following lung transplantation. Emerging evidence in fractional exhaled nitric oxide (FeNO) has expanded its potential role beyond asthma, demonstrating its utility in evaluating conditions such as obstructive sleep apnoea, rhinoviral infection, and radiation pneumonitis. However, values may be impacted by things like smoking, illnesses, respiratory maneuvers, airway caliber and food. Standardized testing guarantees reliability. For the best possible care, FeNO should be read in conjunction with clinical results and other studies.

Keywords: FeNO, Type 2 airway inflammation, Asthma.

Introduction

A gas that can be quantified in exhaled air is nitric oxide (NO). A systematic and quantitative technique for determining the amounts of this gas in exhaled breath is to measure the proportion of this gas during a steady-state expiration, known as the fractional exhaled NO (FeNO).[1] FeNO testing provides an objective assessment of Type 2 (T2) airway inflammation. Hence, the presence of eosinophilic inflammation can be established and is usually highly responsive to inhaled corticosteroid (ICS) therapy. Thus, FeNO has emerged as a critical, non-invasive method to accomplish this goal.[2] FeNO helps medical professionals to transition from symptom-based treatment to precision medicine in respiratory care by reflecting this underlying inflammation.

Indications for doing FeNO Testing

FeNO testing is indicated in the following situations[1,3]

- Assessment of symptoms: This is used to assess patients presenting with cough, wheezing, and dyspnoea.
- Phenotyping asthma: This is the main indication for identifying the eosinophilic asthma phenotype, which is typically T2-high and steroid-responsive.

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Table 1: Shows the physiological and pathophysiological effects of nitric oxide

Physiological (when there is optimal production of nitric oxide)	*Pathophysiological (When there is excess production of nitric oxide)*
Regulation of the airway tone	Bronchial hyperreactivity
Pulmonary blood flow regulation	Mucus hypersecretion
Ciliary beat stimulation	Inhibition of ciliary motility
Anti-inflammatory effect	Pro-inflammatory effect and cytotoxicity
Regulator of surfactant production	Vascular permeability
Regulates the permeability of alveolar capillary membrane	Vasodilation
Mediator in local immunity processes	Production of free radicals
Role in neurotransmission	Cytotoxicity
Broncho-dilatory action	

- Predicting medication response: This technique evaluates the possible reaction to anti-inflammatory drugs, mainly inhaled corticosteroids (ICS), during asthma management.
- Guiding treatment changes: FeNO testing also helps to guide changes in anti-inflammatory medication in a step-wise manner (i.e., stepping up or stepping down the ICS dose), particularly for bronchial asthma management.
- Assessing disease control: FeNO testing is also used to determine whether poor asthma control is caused by airway inflammation, especially when other factors are present (such as rhinosinusitis, anxiety, gastroesophageal reflux, obesity, and ongoing allergen exposure) etc.
- Variations in fractional exhaled nitric oxide (FeNO) levels may be a helpful supplementary tool for identifying acute complications following lung transplantation.

Nitric Oxide Production

Nitric oxide is synthesized in the respiratory tract epithelium via enzymatic conversion of L-arginine to L-citrulline. Nitric oxide (NO) is generated from L-arginine via the action of nitric oxide synthase (NOS) enzymes. The massive NO production evaluated in high FeNO is primarily mediated by the inducible NOS(iNOS) isoform.[4] Inflammatory mediators, particularly interferon gamma, cause the bronchial epithelium to produce iNOS through JAK-STAT activation (Figure 1).

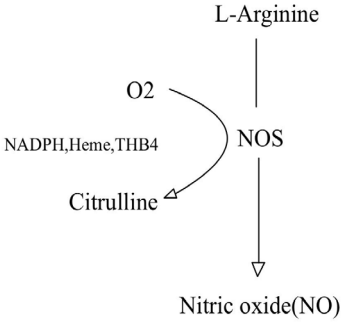

Figure 1: Represents the production of nitric oxide(NO) by nitric oxide synthases(NOS) by the enzymatic conversion of L-arginine to L-citrulline.

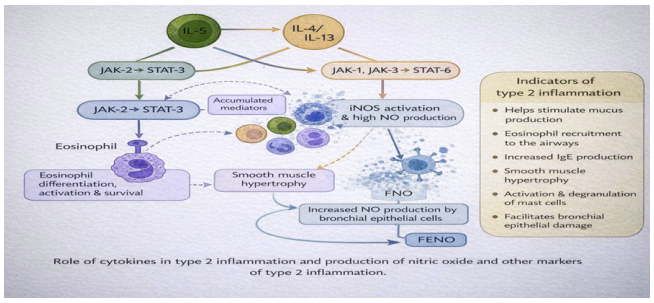

Figure 2: Role of cytokines in type 2 inflammation and production of nitric oxide and other markers of type 2 inflammation

Role of Nitric Oxide at different concentrations (NO)

In the airways, NO has two roles: at low concentrations, it is beneficial, but when it is produced in excess, it can lead to disease. Table 1 lists the functions of NO in the airway based on its concentration, ranging from physiological situations to pathological effects.[4]

Mechanism of raised FeNO levels in Type 2 Inflammation

An increase in FeNO is a characteristic feature of Type 2 (T2) airway inflammation, which is characteristic of eosinophilic asthma and allergic processes.

Despite being significant cytokines in type-2 inflammation, IL-4/IL-13 and IL-5 stimulate distinct signaling pathways. IL-5 largely stimulates the formation and survival of eosinophils by signaling through the STAT-3 pathway. On the other hand, the STAT-6 pathway is triggered by IL-4 and IL-13. Although IL-5 causes eosinophilia, it has little effect on the amount of nitric oxide (NO) in the airways.[5,6]

When interferon-γ (IFN-γ) is present, IL-4 can increase the expression of inducible nitric oxide synthase (iNOS) in airway epithelial cells. However, the signaling route mostly changes toward the JAK/STAT-6 pathway when IL-4 levels rise too high, which alters the generation of nitric oxide (NO).[4,7] Furthermore, elevated IL-13 levels, which are frequently observed in type-2 inflammation, might also stimulate the production of iNOS in the bronchial epithelium via activating the STAT-6 pathway[5,6] (Figure 2).

Method of FeNO Testing

The nitric oxide (NO) analyzer continuously samples the expirate during the procedure. The patient should be seated comfortably, with the mouthpiece properly positioned and adjusted to an appropriate height. A nose clip is not usually required. The patient is instructed to insert the mouthpiece and

Table 2: shows the Interpretation of Fractional Exhaled Nitric Oxide (FeNO) Levels According to the American Thoracic Society Clinical Practice Guideline

General outline for FENO interpretation: symptoms refer to cough and/or wheeze and/or shortness of breath

	FENO < 25 ppb (<20 ppb in children)	FENO 25-50 ppb (20-35 ppb in children)	FENO > 50 ppb (> 35 ppb in children)
DIAGNOSIS			
Symptoms present during past 6 wk	- Eosinophilic airway inflammation unlikely - Alternative diagnoses - Unlikely to benefit from ICS	- Be cautious - Evaluate clinical context - Monitor change in FENO over time	- Eosinophilic airway inflammation present - Likely to benefit from ICS
Monitoring (in Patients with Diagnosed Asthma)			
Symptoms present	- Possible alternative diagnoses - Unlikely to benefit from increase in ICS	- Persistent allergen exposure - Inadequate ICS dose - Poor adherence - Steroid resistance	- Persistent allergen exposure - Poor adherence or inhaler technique - Inadequate ICS dose - Risk for exacerbation - Steroid resistance
Symptoms absent	- Adequate ICS dose - Good adherence ICS taper	- Adequate ICS dosing - Good adherence - Monitor change in FENO	- ICS withdrawal or dose reduction ma result in relapse - Poor adherence or inhaler technique

inhale steadily over two to three seconds through the mouth up to total lung capacity (TLC), or near TLC, followed by an immediate and controlled exhalation for 10 seconds, as any breath-holding may lead to accumulation of nitric oxide and affect the results.

During exhalation, the instrument provides visual and audio cues to help the patient maintain the correct exhalation pressure and technique. For accuracy and reproducibility, the FeNO measurement using the NiOX VERO in adult 10-second mode requires maintaining a constant exhalation flow rate of 0.05 L/sec for the full duration. In cases where children are unable to sustain a 10-second exhalation, a shorter 6-second test may be used as an alternative.

Patient Factors Influencing Exhaled NO Value are listed below

The FeNO levels may be influenced by following factors[1,8,9]

- Age: While there is no correlation between age and exhaled NO levels in adults, it has been noted that exhaled NO levels rise with age in children.
- Respiratory maneuvers: Exhaled NO analysis should be done prior to spirometry because spirometric maneuvers have been demonstrated to momentarily lower exhaled NO levels.
- Airway caliber: Exhaled NO levels can change following bronchodilators and when there is bronchial obstruction.
- Food, medication, and beverages: Prior to exhaled NO analysis, patients should abstain from eating and drinking.
- Nitrates and nitrate-containing meals, such as spinach and lettuce, have been shown to raise exhaled NO; drinking water and consuming coffee may cause temporarily changed exhaled NO levels.
- Drinking alcohol lowers blood pressure in both healthy individuals and asthmatic patients.
- Following therapy with oral or inhaled corticosteroids and inhaled NO synthase inhibitors, exhaled NO levels decrease.
- Smoking: Cigarette smokers have been shown to have a persistently lower level of exhaled NO. In the hour prior to measurements, subjects should abstain from smoking.
- Infection: Asthma patients who have upper and lower respiratory tract viral infections may exhale more NO. A decrease in exhaled NO is also linked to HIV infection.
- Hypoxia: Also known to reduce exhaled NO levels.

Interpretation of FeNO

Reference ranges for adults are as follows:[1]

- <25 ppb: Low (unlikely eosinophilic inflammation)
- 25–50 ppb: Intermediate (possible inflammation)
- >50 ppb: High (likely eosinophilic inflammation)

Reference ranges for children are as below:[1]

- <20 ppb: Low
- 20–35 ppb: Intermediate
- >35 ppb: High

Table 2 demonstrates the practical approach in interpreting FeNO levels for diagnosis and monitoring of asthma

Raised Fractional Exhaled Nitric Oxide levels

The following conditions are associated with increased FeNO levels[3,10-14]

- Asthma
- Allergic rhinitis
- COPD with asthma overlap
- In COPD exacerbation, FeNO levels are higher compared to stable COPD patients.
- Bronchiectasis
- Primary lung cancer
- Lung transplant (acute rejection)
- Rhinoviral infection
- Obstructive sleep apnea
- Early radiation-induced pneumonitis

Diseases associated with Low FeNO levels

The following conditions are associated with low FeNO levels[4]

- Non-atopic asthma
- Primary ciliary dyskinesia
- Bronchopulmonary dysplasia
- Cystic fibrosis
- Extensive emphysema
- Asthma associated with obesity, smoking and non-atopic variant

Low FeNO values in PCD are hypothesized to be due to high NO metabolism along with decreased production of NO by airway epithelial cells and abnormalities in the paranasal sinuses leading to obstruction or reduced production at that site.

Conclusion

FeNO has emerged as a pivotal tool in respiratory medicine. It provides a window into type-2 airway inflammation and allows clinicians to make informed decisions regarding diagnosis, treatment, and prognosis in asthma. The integration of FeNO into clinical practice embodies the movement towards personalized medicine. However, it must always be interpreted in the context of clinical symptoms, spirometry, and other biomarkers. Ongoing research continues to expand

the utility of FeNO in various respiratory and systemic diseases.

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