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REVIEW ARTICLE

Measurement of Fractional Exhaled Nitric Oxide (FENO), A Complementary Tool

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Abstract:

Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FENO) is a quantitative, noninvasive, simple,

and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. Common reasons for measuring FENO are to assessing the etiology of respiratory symptoms, to help identify the eosinophilic asthma phenotype, to assess response or failure to respond to anti-inflammatory agents, notably inhaled corticosteroids (ICS). ATS recommend that FENO 50 parts per billion (35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence). ATS also recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously with reference to the clinical context. It may be used to asses airway inflammation in asthma patient. In asymptomatic individuals, including patients with well-controlled asthma, low FENO suggests that ICS dose could be reduced or even that ICS treatment may be withdrawn altogether. FENO also predict response to omalizumab. Other conditions FENO may be useful are COPD, Pulmonary hypertension and cystic fibrosis. Conclusion and future directions :Advances in technology and standardization have made FENO measurements simple, permitting their use as a biomarker in the assessment of inflammatory airways diseases. Countries like Bangladesh where parasite infestation as well as eosinophilia is high which may interfere with FENO. Research is needed in this aspect.

Key words: FENO, eosinophilic asthma, ATS, ICS

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Introduction:

Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FENO) is a quantitative, noninvasive, simple,

and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. NO is present in the exhaled breath of all humans.[1] It plays key roles in all aspects of lung biology and has been implicated in the pathophysiology of lung diseases, including asthma.[2] The functions of NO in the lung/airways reflect its key roles as a vasodilator, bronchodilator, neurotransmitter, and inflammatory mediator. Patients with eosinophilic asthma have high levels of NO in their exhaled breath and high levels of inducible nitric oxide synthase (NOS2) enzyme expression in the epithelial cells of their airways, suggesting a role for NO in asthma pathogenesis.[3] The use of chemiluminescence analyzers allowed for the

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detection of NO in exhaled breath in the early 1990s.[2] Patients with asthma were found to have high FENO in their exhaled breath[4-7] that decreased in response to treatment with corticosteroids.[8] Advantages for FENO include the noninvasive nature of the test, ease of repeat measurements, and the relatively easy use in patients with severe airflow obstruction where other techniques are difficult to perform.[9] By providing information about airway inflammation,[10,11] FENO adds a new dimension to the traditional clinical tools (history, physical exam, and lung function tests).

Why should a FENO test be obtained?

Common reasons for measuring FENO.

- To assessing the etiology of respiratory symptoms.
- To help identify the eosinophilic asthma phenotype'
- To assess response or failure to respond to anti-inflammatory agents, notably inhaled corticosteroids (ICS)
- To establish a baseline FENO during clinical stability for subsequent monitoring of chronic persistent asthma
- To guide changes in doses of anti-inflammatory medications: step-down dosing, step-up dosing, or discontinuation of anti-inflammatory medications.
- To assist in the evaluation of adherence to anti-inflammatory medications
- To assess whether airway inflammation is contributing to poor asthma control particularly in the presence of other contributors (e.g., rhinosinusitis, anxiety, gastro-esophageal reflux, obesity, or continued allergen exposure).

Can FENO be used to diagnose asthma?

Asthma is a clinical diagnosis and there is no single diagnostic test for the disease. Pathology of asthma is often but not always due to eosinophilic airway inflammation. The two are not synonymous. This is extremely important in the interpretation of FENO measurements. In cases of asthma not due to airway eosinophilia, FENO may be low. Similarly, the value of exhaled FENO as a predictor of steroid responsiveness is high even in the absence of induced sputum eosinophils.[12]

FENO is associated with eosinophilic airway inflammation.

There are several inflammatory phenotypes in asthma most commonly described as eosinophilic, neutrophilic, mixed, and paucigranulocytic.[13] Determination of the subtype may help a physician decide which therapies to select or stop.[14]

FENO predicts likelihood of corticosteroid responsiveness.

Treatment response in asthma is heterogeneous.[15-17] Not all patients respond to corticosteroids and an important reason to use FENO is to help decide who might benefit from steroid treatment, and who should try other medications (e.g., leukotriene modifiers). FENO may also be used to determine patients in whom steroid therapy may be safely withdrawn. FENO has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or AHR to methacholine.[18-20]

FENO can support a diagnosis of asthma. The diagnosis of asthma is well defined, and the background pathology is often but not always due to eosinophilic airway inflammation. Early studies in populations comprising mainly patients with eosinophilic asthma explored the performance characteristics of FENO as a diagnostic test. The predictive values for FENO (usually at cut points of 25 ppb) were shown to be sufficiently robust for it to be used in this context.[10, 21, 22] Further, the predictive values for FENO are higher than for conventional measurements such as peak flows and spirometry,[10] and similar to those associated with bronchial challenge tests.[22]

FENO may predict AHR.

Irrespective of the specific underlying inflammatory signal which FENO represents, measurements appear to reflect the dynamic interrelationships between the response to allergen or other triggers and evolving eosinophilic airway inflammation/AHR.[2,23]

Normal values versus relevant cut points for FENO.

In a clinical study, Shaw and colleagues reported that the optimum cut point for a clinically significant FENO (corresponding to a sputum eosinophil count of > 2%) was 26 ppb . Similarly,

studies designed to determine the optimum cut point to diagnose asthma using FENO have usually pointed to a diagnostic cut point ranging from 20 to 25 ppb.[10,24–26]. However, in patients with stable, well-controlled asthma, FENO values range from 22 to 44 ppb.[27] Clearly, there is considerable overlap between mean FENO levels in healthy and populations with stable asthma.

Confounding factors that may affect FENO.

FENO values can be affected by several factors, including measurement technique, exhalation flow rate, nasal NO contamination, the NO analyzer used,[28] age, height, smoking, and antiinflammatory medications.

ATS recommend that FENO 50ppb (35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence). ATS also recommend that FENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously with reference to the clinical context (strong recommendation, low quality of evidence).

Low FENO (<25 ppb [20 ppb in children): implies noneosinophilic or non-aiway inlammation

Low FENO can help diagnosis of GERD, smoking related or anxiety related cough, brochiectasis.

Monitoring airway inflammation in asthma

Serial measurements obtained when patients' asthma is both stable and unstable allows each patient to act as his/her own control when assessing subsequent measurements and as a result "personal best" can be used.[29-34] The same cut points used in detecting airway inflammation apply when monitoring patients with asthma. In asymptomatic individuals, including patients with well-controlled asthma, low FENO suggests that ICS dose could be reduced or even that ICS treatment may be withdrawn altogether. In a study of children with stable asthma, withdrawal of ICS did not result in symptom relapse when FENO remained consistently low (optimum cut point 22 ppb) when measured 2 to 4 weeks after treatment withdrawal .

Minimally important differences, and prognostic significance of FENO .

In one study, FENO levels were 50% higher during acute asthma compared with when stability was restored.[35] Data obtained from steroid withdrawal studies show that the mean increase in FENO associated with the advent of loss of control ranges from 16 ppb to 25 ppb,[36] the latter representing a 60% increase from baseline. However, the range of the increase in FENO between stability and loss of control is high (up to 141 ppb) . Michils and colleagues have reported that the transition from good control to poorly controlled asthma is likely to be associated with a rise in FENO of 40% or greater.[37] An acute rise (over 12–24 h) in FENO may occur after infection or exposure to an allergen to which the patient is sensitized. The magnitude of the rise may be as high as 150 ppb. FENO also predict response to omalizumab.

How should a FENO measurement be interpreted and reported?

1. ATS/ERS guidelines should be followed for the measurement of FENO. . Breath should be taken upto TLC over 2-3 second through mouth piece and nasal NO contamination should be avoided. Exhalation should be performed at a flow rate of 50 ml/second.
2. Reason for the test should be determined and the type of subject being tested: does the patient have asthma-like symptoms or an already established diagnosis of asthma?
3. Interpretation of FENO measurement: clinically relevant cut points.
4. Minimum reporting requirements for FENO. When reporting FENO results, a minimum information set should be included.

This should include but not be limited to: date, time of the day, age, sex, ethnicity, height, smoking status, reason for the test, and prior diagnosis (if known), and whether or not the patient was using inhaled or oral corticosteroids at the time of testing.

The format of the reporting should include the device used to make the measurement, the number of measurements made, and the flow rate (currently approved FDA devices use 50 ml/s flow rate).

Other situations in which FENO may be useful COPD.

The exact role of exhaled nitric oxide

measurements in patients with established COPD remains to be defined. In a significant

number of patients, an overlap comprising features of both asthma and COPD is found . The airway inflammatory cell infiltrate may be mixed, including eosinophilic inflammation. Studies show that, at least in the short term, the response to corticosteroids is likely to be greater in patients with COPD who also have sputum eosinophilia.[38,39] or elevated FENO.[40] This raises the possibility that FENO measurements might be used in predicting steroid responsiveness in COPD.

Pulmonary hypertension. NO is one of the important pathophysiological mediators of pulmonary hypertension. Interestingly, patients with pulmonary hypertension have low levels of FENO.[41-42] Although this is a far more complex issue than the simple lack of a vasodilator,[43] giving NO therapeutically seems to work well.[44] Therapies that target the NO pathway have revolutionized the treatment of this disease, including the widely used phosphodiesterase type 5 (PDE5) inhibitors, which prevent the breakdown of the NO effector molecule 39,59-cyclic guanosine monophosphase (cGMP), thus prolonging NO effects on tissues (122).

Cystic fibrosis and nasal NO measurements.

Continuous and high production of NO takes place in the human nose and paranasal sinuses , and this NO is readily measurable by noninvasive techniques . It has been shown that the nasal NO levels are altered in several respiratory disorders—including primary ciliary dyskinesia (PCD) , cystic fibrosis (CF) , and allergic rhinitis,[45,46] and this has led to the proposal that nasal NO may be clinically useful in diagnosis and monitoring of these diseases.

Conclusions and Future Directions

Advances in technology and standardization have made FENO measurements simple, permitting their use as a biomarker in the

assessment of inflammatory airways diseases. Countries like Bangladesh where parasite infestation as well as eosinophilia is high which may interfere with FENO. Research is needed in this aspect.

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