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SHORT REVIEW

IMPORTANCE OF MEASURING FRACTIONAL EXHALED NITRIC OXIDE (FeNO) IN THE MANAGEMENT OF ASTHMA

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Abstract

Asthma is characterized by chronic airway inflammation leading to respiratory symptoms (dyspnea, wheezing, chest tightness and cough). So direct measure of the level of inflammation can be of paramount importance in the proper understanding of severity of asthma. Nitric oxide (NO) isa product of inflammation in the airways and an important regulator of immune responses that is over-produced in asthma. For this purpose, the measurement of Fractional Exhaled Nitric Oxide (FeNO) has been used since the early years of the current century as a non-invasive, easy-to-assess tool useful for diagnosing and managing asthma. In this narrative review we extended our effort to explain the usefulness of FeNO as a predictor of response to inhaled corticosteroids (ICSs), to monitor adherence and as a diagnostic tool in asthma management.

Keywords : *Asthma, FeNO, inflammation . Airway.*

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Introduction:

Asthma is a major noncommunicable disease, affecting both children and adults, and is the most common chronic disease among children, with over 350 million people affected globally,[1] resulting in significant economic and societal burdens.[2,3] Severe asthma, which is associated with increased morbidity, risk of hospitalization from exacerbations and increased risk of mortality, affects approximately 5–10% of asthma patients.[4,5]

Chronic airway inflammation triggered by exposure to allergens, respiratory tract infections, exercise, exposure to cold air, tobacco smoke or pollution, contributes to induce airflow limitation that can be assessed by lung function tests.

This airflow limitation is classically reversible after administration of inhaled bronchodilators or after prolonged (*i.e.*, after at least 4 weeks) treatment with inhaled corticosteroids (ICS). Airway hyperresponsiveness can be assessed by bronchial challenge with bronchoconstrictor drugs such as methacholine.[6] Once clinical and functional diagnosis of asthma has been established, further evaluations, including assessment of inflammation & response to standard medication could be taken into consideration by measuring Fractional Exhaled Nitric Oxide (FE_{NO})[6] Severe type 2 asthma is often associated with increased eosinophilic infiltration, raised serum immunoglobulin E (IgE) and raised fractional exhaled nitric oxide (F_{eNO}) levels.[7] There is increasing evidence that nitric oxide (NO) plays a key role in modulating type 2 inflammation and in regulating type 2 immune responses.

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Type 2 inflammation & abundance of NO:

Type 2 inflammation is a specific type of immune response pattern. It can have positive effects, like helping eliminate a parasitic infection. But it also plays a role in certain medical conditions, such as atopic dermatitis (eczema), allergic rhinosinusitis, and some types of asthma. There is increasing evidence that nitric oxide (NO) plays a key role in modulating type 2 inflammation and in regulating type 2 immune responses. [8]. In our body system NO is derived from the amino acid L-arginine in a synthesis catalyzed by three forms of the enzyme NO synthase (NOS); two constitutive NO synthases (cNOS) (generally expressed in platelets, neuronal, epithelial, and endothelial cells) are involved in physiological regulation of airway function (Figure:1). An inducible form of the enzyme (iNOS) (predominantly expressed in macrophages, neutrophils, hepatocytes, and epithelial, mesangial, endothelial, and vascular smooth muscle cells) is typically produced in response to airway inflammation and in host defense against infection.[8]

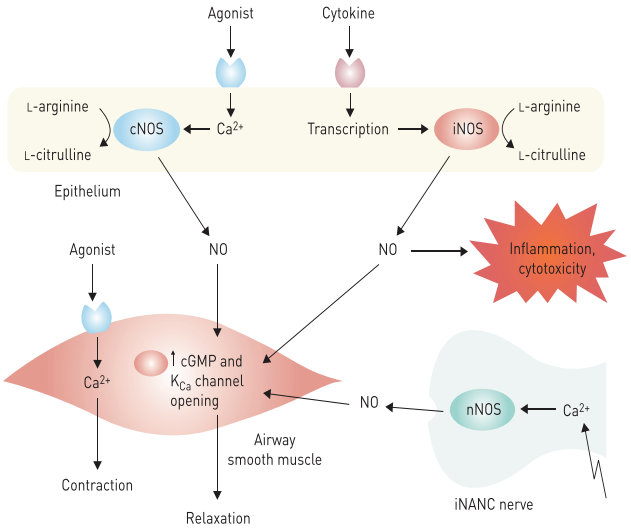

Fig.-1: *Nitric oxide metabolism in asthma pathophysiology. cGMP: cyclic guanosine monophosphate; cNOS: constitutive nitric oxide synthase; iNANC: inhibitory non-adrenergic non-cholinergic; iNOS: inducible nitric oxide synthase; nNOS: neuronal nitric oxide synthase; NO: nitric oxide. Courtesy:European Respiratory Journal 2020 55: 1901633;*

NO is a key inflammatory mediator in the respiratory tract and is produced by a number of cell types, including epithelial cells, mast cells, macrophages, neutrophils and vascular endothelial cells. Evidence highlights several roles for NO in the regulation of pulmonary function and in pulmonary disease, as an endogenous modulator of airway function and as a proinûammatory and immunomodulatory mediator.[9]

In the context of asthma, this inflammatory response is deleterious, resulting in increased symptoms and airway obstruction.[9] Increased levels of exhaled NO in asthma, originating mainly from the lower airway, are often associated with airway eosinophilic inûammation and increased expression of corticosteroid-sensitive iNOS. Levels of exhaled NO may also be associated with exacerbations and disease severity.[9]

The measurement of exhaled NO has now been standardized for clinical use and, facilitated by the availability of mobile technology and remote monitoring, adoption in general practice has increased in recent years [10-12]. F_{eNO}testing is relatively convenient to perform, with numerous studies providing evidence of the applications of NO measurement in clinical practice.[13] Currently, F_{eNO} measurements are used to predict and document the response to ICSs[14], to monitor adherence[10] and as a diagnostic tool in ICS-naïve patients.[13]

The role of *FeNO* in asthma Management

Using FENO to Diagnose Asthma

Current National Institute for Health and Clinical Excellence (NICE) guidelines in the UK recommend the use of F_{eNO} for the initial diagnosis of patients with suspected asthma.[13] NICE standards for a positive F_{eNO} test are >40 ppb in adults and >35 ppb in children (5–16 years) (table-1).[13] However, the pre-test probability of asthma will impact on subsequent clinical decision-making with regard to the F_{eNO} measurement. A single positive test in isolation is insufficient to make a diagnosis of asthma, irrespective of the pre-test probability, and additional bronchial provocation testing can be beneficial to determine airway hyper-responsiveness.[13]

The recently published Scottish consensus statement on the role of F_{eNO} in adult asthma suggests cut-off values for F_{eNO} of >40 ppb in adult patients who are ICS naïve to support asthma diagnosis and F_{eNO} >25 ppb for adult patients taking ICSs[15]. In the Global Initiative for Asthma (GINA) report[16], ≥20 ppb F_{eNO} in conjunction with other characteristics, such as blood eosinophils ≥150 cells·μL^{-1} and/or sputum eosinophils ≥2%, could indicate patients with type 2 immune response [table-I]

Table-1

Fractional exhaled nitric oxide (F_{eNO}) cut-offs in different guidelines

Guidelines	F_{eNO} Cut-offs	Justification
Nice [28]	Adults Positive: >40 ppb Children (5-16Years) Positive: >35ppb	
Scottish consensus statement[65]	ICS-naïve patients.40ppb patients taking ICS>25 ppb	
GINA[15]	Adults ≥20 ppb	Associated with eosinophilic inflammation (in non-smokers)
ATS/ERS[40]	Adults High: >50ppb, Intermediate: 25-50ppb; Low: <25 ppb	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely
ATS/ ERS[40]	Children; High: >35 ppb; Intermediate: 20-35ppb; Low <20ppb	Eosinophilic inflammation and in symptomatic patients, responsiveness to corticosteroids likely cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely

ATS: American Thoracic Society; ERS: European Respiratory Society; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; NICE: National Institute for Health and Care Excellence.

Using F_{eNO} to Guide ICS Therapy

ICS are the mainstay of treatment for asthma. F_{eNO} seems to have a role in predicting response to corticosteroid therapy in both ICS-naïve patients and in those receiving established ICS therapy. It is a better predictor of steroid responsiveness than spirometry, bronchodilator reversibility, peak flow variability, or airway hyperresponsiveness.[16,18]

Measurement of FENO may facilitate safe step-down of ICS therapy in patients with well-controlled asthma. A recent individual patient data meta-analysis included participants in seven prospective studies (five randomized controlled trials and two observational studies) of ICS step-down, where FENO was measured before any reduction in ICS, but was not used to determine dose changes.[19]

Limitation

Although F_{eNO} levels are higher in patients with asthma characterized by type 2 inflammation, they can also be elevated in other related conditions, such as eosinophilic bronchitis, allergic rhinitis, atopy and atopic dermatitis.[20] F_{eNO} is also elevated in upper respiratory tract infections and in pulmonary infections of lung transplant patients and sometimes in patients with chronic obstructive pulmonary disease (COPD). [20, 21]

Currently, F_{eNO} levels are being used to monitor type 2 asthma, and the latest GINA guidelines recommend cut-offs for both blood eosinophils and F_{eNO} to help define the type 2 asthma population.[17] However, the GINA guidelines do not recommend the use of F_{eNO} to guide treatment in the general asthma population.[17]

F_{eNO} levels can also be affected (positively and negatively) by many other factors. Smoking leads to a decrease in F_{eNO} (although values are still higher in smokers with asthma than in those without).[22,24] Studies have also demonstrated an association with height and sex (the latter, however, might be attributable to differences in height). F_{eNO} may also be associated with age: children have lower levels, which increase significantly as they grow up, and elderly patients demonstrate elevated levels.[23,24]

Table-II

Factors to Be Considered When Interpreting F_{eNO} Levels in Patients With Asthma

Factors That Increase Feno	Factors That Decrease Feno
Chronic rhinosinusitis, nasal polyposis, or both *FeNo* is increased in patients with allergic rhinitis or nasal polyposis even in the absence of a concomitant asthma diagnosis[26]	Cigarette smoking•Decreases Feno by 40%-60%•Magnitude of reduction correlates with the cumulative lifetime cigarette consumption[24]
Atopy Acute exposure to allergens can increase Feno by up to 50%[26]	Inhaled steroid use*FeNo* generally is sensitive to inhaled steroids, and therefore will be low in most patients who are adherent to treatment
Rhinovirus respiratory infections Can increase Feno by 50%-150%•Rhinovirus leads to iNOS upregulation.[26]	Alcohol ingestion.[27] (Avoid before testing)
Intake of nitrate-containing food, eg, beetroot[23]Can increase Feno levels by 20%-60%Effects peak 1-2 h after intake and can last up to 15 h[25]	Certain drugs Leukotriene receptor antagonists Prostaglandins inhaled Prostaglandin E2 and iloprost downregulate iNOSexpression[28]
Air pollution (particulate matter and ozone,Possibly because of oxidative potential Effect also seen in the absence of asthma[30]	Physical exercise[29] (Avoid strenuous exercise before testing)

Summary

Currently F_{eNO} has been using to support the diagnosis of asthma, as a predictor of response to ICS therapy, to monitor adherence with treatment, to predict future risk of exacerbations, and to facilitate choice of biologic therapies. However, its measurement is subject to a wide variety of confounding factors, and it has an imperfect relationship with direct measures of airway inflammation. In diagnosing asthma, F_{eNO} should be interpreted in the broader clinical context, rather than viewed as a stand-alone diagnostic tool. F_{eNO} may aid appropriate ICS dosing and improve overall disease control in some populations with asthma, but the ambiguity of the overall evidence base in this area is reflected in divergent opinion in different international asthma management guidelines. When choosing biologic agents, some—such as dupilumab and Tezepelumab—seem to perform significantly better in patients with elevated FENO levels, whereas outcomes with the eosinophil-targeting monoclonal antibodies seem to be predicted better by blood eosinophil counts or clinical factors like comorbid nasal polyposis than by FENO measurement. The role of F_{eNO} in the asthma clinic continues to evolve, and although it remains an imperfect diagnostic tool, its use affords valuable clinic-room insights into asthma biological features, disease activity, and patient behavior.

Clinical utility of F_{eNO} in asthma

Fractional exhaled nitric oxide (F_{eNO}) is the only currently available point-of-care test of type 2 inflammation in asthma. National Education and Prevention Program (NAEPP) Expert Panel Report 4 Working Group (EPR-4) focused update to the asthma management guidelines, which made some cogent evidence-based recommendations on the utility of F_{eNO} in asthma.[31]. Considering the wide use of F_{eNO} with diagnostic accuracy for type 2 inflammation of Asthma , Physicians of Bangladesh recommending its use & many center have now F_{eNO} testing . Many Specialized hospitals in Bangladesh had already started & some are going to be start.

Conclusion

Simplification of the measurement of F_{eNO}, with advances in technology permitting its use as a biomarker in the assessment of i airway inflammatory condition , such as type 2 asthma. FENO should be interpreted in the broader clinical context, rather than viewed as a single-stand diagnostic tool. F_{eNO} may aid appropriate ICS dosing and choosing biologic agents toimprove overall disease control in some populations with asthma. At present, the use of F_{eNO} in the asthma clinic continues to evolve, and although it remains an imperfect diagnostic tool, its use affords valuable clinic-room insights into asthma biological features, disease activity, and patient behavior.

Conflict of Interest:
The authors stated that there is no conflict of interest in this study

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