FeNO: Role in Respiratory Diseases

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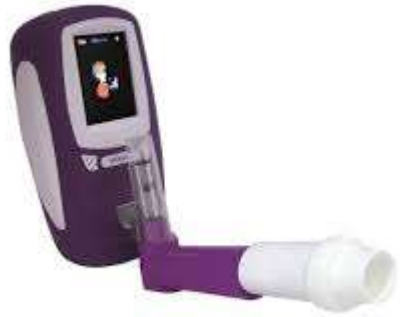


History…….

- Nitric oxide (NO) is a gaseous molecule initially considered to have a health-related role only in the context of its formation from the combustion of fossil fuels and its contribution to air pollution.

- However, this view has been greatly modified since the 1987 discovery that the free radical NO is the previously uncharacterized endothelial-derived relaxing factor.

- It is now clear that NO plays an important role in most human organ systems

- NO is produced by the human lung and is present in the exhaled breath.
- It has been implicated in the pathophysiology of lung diseases, including asthma.
- The measurement of exhaled NO has been standardized for clinical use by the American Thoracic Society (ATS) and the European Respiratory society (ERS) in 1999 and revised in 2005

- The guidelines recommend the use of the term FeNO (the fractional exhaled NO concentration) to describe the level of NO in exhaled breath

- FeNO is expressed in parts per billion which is equivalent to nanoliters per liter.

- Chemiluminescence analysis is used to detect FeNO

Role of NO in respiratory System

- Nitric oxide is a gas produced by the cells involved in the inflammation associated with allergic or eosinophilic asthma

  A FeNO test or exhaled nitric oxide test, in patients with allergic or eosinophilic asthma, is a way to determine how much lung inflammation is present and how will inhaled steroids are suppressing this inflammation.

Role of NO in respiratory System

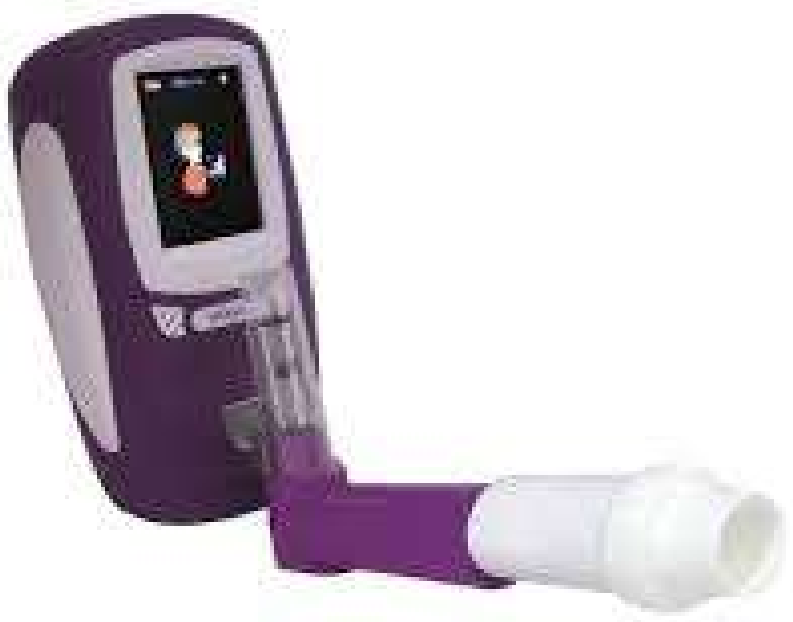
- Within the respiratory system, NO regulates vascular and bronchial tone (promoting dilation of both vessels and airways).
- Facilitates the coordinated beating of ciliated epithelial cells.
- Acts as an important neurotransmitter for non-adrenergic, non-cholinergic neurons that run in the bronchial wall.
- This molecule can be detected in exhaled gas as the fraction of exhaled NO (FeNO), which varies in health and disease

Benefits of performing FeNO tests

- Non-invasive, quick and easy to perform
- Shows patient compliance
- Shown to be superior to the majority of conventional tests of lung function, such as peak flow recording and spirometry .
- Assessment of cough, wheezing, and dyspnea
- Identifying eosinophilic asthma phenotype
- Assessing the potential response to anti-inflammatory agents, notably inhaled corticosteroids (ICS).

- Establish a baseline F_ENO during a period of clinical stability for subsequent monitoring of chronic persistent asthma
- To guide changes in anti-inflammatory medications in a step-wise manner
- 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 (eg, rhinosinusitis, anxiety, gastroesophageal reflux, obesity, continued allergen exposure)

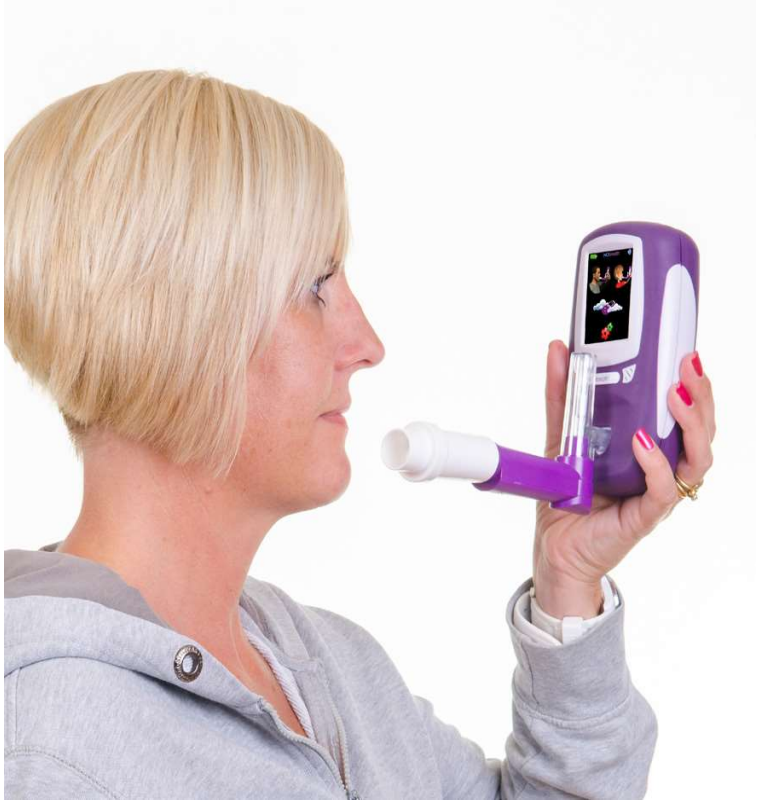
Procedure to detect FeNO



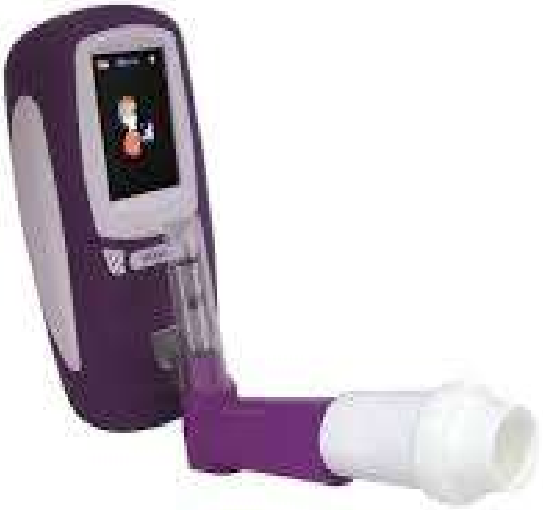
Procedure to detect FeNO

- Non-invasive, quick and easy to perform
- Procedure depending on the patient's condition
- Online: In patient who are able to cooperate, exhale directly into the analyzer.
- Offline: In patient who are unable to cooperate, exhale into the reservoir.

Single breath online measurement is the technique of choice, who are able to cooperate



Measuring FeNO with NObreath® it's as easy as 1, 2, 3



1

Inhale

2

Exhale

3

Readings instantly available

Test interpretation

Aid in diagnosis using the NObreath® FeNO monitor

FeNO (ppb) Levels	LOW <25ppb (<20ppb in children)	INTERMEDIATE 25-50ppb (20-35ppb in children)	HIGH >50ppb (>35ppb in children) or rise in FENO of >40% from previously stable levels
Symptomatic (chronic cough and/or wheeze and/or shortness of breath during past 6 wk)	**Allergic airway inflammation unlikely Unlikely to benefit from ICS	Be cautious Evaluate clinical context Monitor change in FeNO over time	Allergic airway inflammation present Likely to benefit from ICS
Possible Diagnosis	• Non-allergic asthma • Rhinosinusitis • Reactive airways dysfunction syndrome • Bronchiectasis • Cystic fibrosis, primary ciliary dyskinesia • Extended post-viral bronchial hyperresponsiveness syndrome • Vocal cord dysfunction • Non-pulmonary/airway causes: • Anxiety-hyperventilation • Gastroesophageal reflux disease • Cardiac disease/pulmonary hypertension/pulmonary embolism	Evaluate clinical context	• Allergic asthma • Atopic asthma • Allergic bronchitis • COPD with mixed inflammatory phenotype

Monitoring (in patients with diagnosed asthma) using the NObreath® FeNO monitor

FeNO (ppb) Levels	LOW <25ppb (<20ppb in children)	INTERMEDIATE 25-50ppb (20-35ppb in children)	HIGH >50ppb (>35ppb in children) or rise in FENO of >40% from previously stable levels
Symptomatic (chronic cough and/or wheeze and/or shortness of breath during past 6 wk)	Possible alternative diagnosis (see below) 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
Possible Diagnosis	• **Non-allergic asthma (probably steroid unresponsive) • Vocal cord dysfunction • Anxiety-hyperventilation • Bronchiectasis • Cardiac disease • Rhinosinusitis • Gastroesophageal reflux disease	Evaluate clinical context	• Allergic asthma • Atopic asthma • Allergic bronchitis • COPD with mixed inflammatory phenotype
Asymptomatic	Implies adequate dosing and good adherence to anti-inflammatory therapy ICS dose may possibly be reduced (repeat FeNO 4 week later to confirm this judgment; if it remains low then relapse is unlikely).	Adequate ICS dosing Good adherence Monitor change in FENO	ICS withdrawal or dose reduction may result in relapse Poor adherence or inhaler technique

Use in other respiratory diseases

Diseases & factors that affect FeNO		
INCREASED	**DECREASED**	**VARIABLE**
Asthma	Cystic fibrosis	COPD
Exposure to pulmonary allergens	Primary ciliary dyskinesia	Bronchiectasis
Pollution	Pulmonary hypertension	Fibrosing alveolitis
Apnea	Pneumonia	Sarcoidosis
Bronchodilators (transient)	Gastroesophageal reflux	Systemic sclerosis
Viral respiratory infection	Laryngeal tracheomalacia	
Pulmonary tuberculosis	Sputum induction	
Allergic rhinoconjunctivitis. Nasal polyposis	Bronchoconstriction	

Use in other respiratory diseases

Chronic obstructive pulmonary disease:

- FENO levels are minimally elevated in stable COPD, but may increase with more severe disease and during exacerbations.
- Current smokers have approximately 70 percent lower levels of FENO.
- In patients with COPD, FENO levels may be useful in establishing the presence of reversible airflow obstruction and determining glucocorticoid responsiveness.

Bronchiectasis and cystic fibrosis —

Children with cystic fibrosis (CF) have lower FENO levels than appropriately matched controls. This may be due to elevated arginase activity; arginase competes for L-arginine, the substrate of nitric oxide synthesis.

Pulmonary hypertension: patients with PAH have low FENO values

Cough variant asthma —

- FENO has moderate diagnostic accuracy in predicting a diagnosis of cough variant asthma (CVA) in patients with chronic cough.
- optimal cut-off range for FENO was 30 to 40 ppb

Nonasthmatic eosinophilic bronchitis —

FENO are increased in a range similar to patients with asthma. Thus, FENO is more useful to confirm NAEB, than to exclude it

Upper respiratory infections —

- without underlying pulmonary disease, viral upper respiratory infections resulted in increased FENO .
- These levels were dramatically reduced when rechecked three weeks later.

Interstitial lung disease and sarcoidosis :

Variable results have been reported

Primary ciliary dysfunction —

Nasal NO is very low or absent in patients with primary ciliary dysfunction (PCD).

Other conditions —

other conditions associated with low FENO levels include hypothermia, and bronchopulmonary dysplasia, as well as the use of alcohol, tobacco, caffeine, and other drugs

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
- Age, height, smoking, and
- Anti-inflammatory medications

Conclusion…

- Use of FeNO as a biomarker that adds a new dimension to the traditional clinical tools in the assessment and management of airways diseases.
- Inclusion of FENO as an endpoint in clinical trials would be very helpful in understanding the role of FENO in monitoring response to therapy
- FeNO is not a definitive indication of asthma and should be used in conjunction with spirometry, patient history& symptoms

- According to ATS guideline, more work is still needed to better define the use of FeNO in different clinical settings.

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Thank you….