

II. Executive Summary

2.1. General Background

NO is an important endogenous regulatory molecule that is widely distributed throughout the body. It acts as a messenger in many different biological processes, i.e. regulation of peripheral blood flow, platelet function, immune reactions and neurotransmission. [Bhagat K and Vallance P 1996] In biological tissues, NO is highly reactive, making direct determination of NO very difficult. In the gas phase, however, NO is fairly stable at low concentrations and diffuses readily to nearby cells. Thus, when NO is formed in tissues and organs where it can diffuse into a lumen, it can be detected in gas samples collected from such organs.

The detection of NO in exhaled air was first reported in 1991, [Gustafsson LE *et al.* 1991] and, soon after, it was discovered that NO in exhaled air was elevated in patients with asthma. [Alving K *et al.* 1993] Since then, many studies have confirmed the clinical usefulness of NO measurements in exhaled air. Exhaled NO is only increased during bronchospasm when there is coexisting inflammation. Therefore, exhaled NO has a valuable role in differentiating between the inflammatory and bronchospastic components of clinical asthma, and can be used for guiding the therapeutic use of steroids and other anti-inflammatory agents. [Ashutosh K 2000]

2.2. Clinical Summary

Evidence shows there are links between exhaled NO, eosinophilic inflammation, and asthma: [Taylor DR 2006]

- Exhaled NO levels correlate well with eosinophilic airway inflammation.
- Eosinophilic airway inflammation is associated with a positive response to steroid treatment.
- Raised exhaled NO levels predict steroid responsiveness in patients with non-specific respiratory symptoms.
- The use of ICS treatment in asthma results in a decrease in exhaled NO, and there is a dose-dependent relationship between ICS and exhaled NO.

The following clinical summaries correspond to Chapter IV: Exhaled NO in Clinical Situations (Sections 4.1. – 4.14.).

4.1. Diagnosis of Asthma

Exhaled NO measurement has been shown to be superior to the majority of conventional tests recommended in international clinical guidelines for the diagnosis of asthma in symptomatic patients. Correct asthma diagnosis can be ascertained in around 80% of patients, using a cut-off of around 25 ppb in adults and 20 ppb in children (depending on age).

4.2. Alternatives to Airway Hyperresponsiveness Test

Exhaled NO is a simple, time-efficient and resource-efficient screening tool for airway hyperresponsiveness and exercise-induced bronchoconstriction. Patients will not demonstrate bronchial hyperresponsiveness using a pre-exercise cut-off of < 12 ppb. In this respect, exhaled NO may replace bronchial provocation tests and outperforms FEV₁ as a predictor for airway hyperresponsiveness.

4.3. Prediction of Steroid Response

A high level of exhaled NO (> 47 ppb in adults) serves as a positive indicator that the patient will respond to inhaled corticosteroids. Exhaled NO assessment is important when considering the potential usefulness of inhaled anti-inflammatory therapy.

4.4. Response to Anti-inflammatory Treatment

An impressive number of studies show that anti-inflammatory treatment reduces levels of exhaled NO in asthma. The response to corticosteroids is both rapid (within 1 week, potentially as early as 48 hours) and dose-dependent. The higher the exhaled NO value the higher the dose needed to normalize it. Anti-leukotrienes also reduce exhaled NO levels in asthma, albeit to a lesser extent. Exhaled NO measurement is easily performed and provides objective assessment of the effect of anti-inflammatory therapy.

4.4.1. Corticosteroid Treatment

Inhaled corticosteroids have a marked effect on exhaled NO in keeping with their anti-inflammatory properties. The response to corticosteroids is both rapid (within 1 week, potentially as early as 48 hours) and dose-dependent. The higher the exhaled NO value, the higher the ICS dose needed to normalize it. Exhaled NO measurement is easily performed and provides objective assessment of the effect of anti-inflammatory therapy.

4.4.2. Combination Treatment

Long-acting β_2 -agonists (LABA) may mask ongoing underlying inflammation, which can be detected by exhaled NO. When combination treatment is used, exhaled NO measurements still reflect the ICS responsiveness.

4.4.3. Anti-leukotriene Treatment

Anti-leukotrienes also reduce exhaled NO levels in asthma, albeit to a lesser extent than inhaled corticosteroids.

4.4.4. Other Anti-inflammatory Treatment

Effective anti-inflammatory treatment reduces clinical and spirometric indicators of asthma severity, and is thereby in line with reduction of exhaled NO.

4.4.5. IgE Treatment

Omalizumab is a monoclonal antibody to IgE that is used in the treatment of moderate-to-severe atopic asthma. IgE treatment may inhibit airway inflammation measured as a decrease in exhaled NO levels during steroid reduction; however, more clinical studies are required.

4.4.6. Immunotherapy Treatment

Immunotherapy produces significant immunomodulatory changes, demonstrated by the rise in exhaled NO.

4.5. Dose Optimization of Steroid Treatment

A number of studies indicate that monitoring inflammation and titrating the dose of anti-inflammatory medication accordingly has real clinical benefits. As the measurement of exhaled NO is simpler and less time-consuming than measurement of sputum eosinophils, it is better suited for routine clinical practice and allows more frequent assessment of inflammation in the airways.

4.6. Monitoring Asthma Control

Although exhaled NO levels are reduced by inhaled corticosteroids they are not totally suppressed and continue to correlate with clinical markers of disease control, such as symptom frequency and with the need for rescue medicine. NO levels are higher in patients who require an increased dose of inhaled corticosteroids.

4.7. Monitoring Compliance with Anti-inflammatory Treatment

Exhaled NO measurement is an easily performed, non-invasive tool to monitor adherence to steroid treatment.

4.8. Exhaled NO and Steroid Resistance

Persistently elevated levels of exhaled NO in symptomatic patients on corticosteroid treatment are most likely caused by poor compliance or poor inhaler technique. Possible other reasons include insufficient corticosteroid dosage and continuous high allergen exposure. In rare cases it may indicate true steroid resistance.

4.9. Prediction of Loss of Asthma Control

High levels of exhaled NO and sputum eosinophils are markers of loss of asthma control. There is a high positive predictive value (a rise in exhaled NO is very likely to be followed by loss of control), but the negative predictive value is low; i.e. a low exhaled NO value does not exclude the possibility of exacerbation.

4.10. Emergency Care

Further research is required to determine the value of exhaled NO measurement in emergency care.

4.11. Safe Withdrawal of Inhaled Corticosteroids

Elevated exhaled NO predicts a relapse of symptoms after withdrawal from inhaled corticosteroids. An exhaled NO level of > 49 ppb at 2–4 weeks after steroid withdrawal was highly indicative of asthma relapse.

4.12. Other Clinical Indications

4.12.1. Chronic Cough

An increased level of exhaled NO may assist in the differential diagnosis of chronic cough. Patients with asthma and chronic cough, and patients with a high cough frequency have higher exhaled NO levels than controls.

4.12.2. Rhinitis

Elevated exhaled NO in patients with allergic rhinitis suggests the presence of inflammation in the lungs even in the absence of asthma symptoms. Since allergic rhinitis is a major risk factor for asthma, regular assessment of lower airway inflammation is recommended for patients with rhinitis.

4.12.3. COPD

Exhaled NO may be increased in unstable COPD. It is likely that the pathogenesis of COPD is variable. It may be associated with eosinophilic inflammation and increased exhaled NO levels. This form of COPD responds to anti-inflammatory treatment.

4.13. Quality of Life

Elevated exhaled NO levels correlate inversely with quality of life in patients with asthma (i.e. a decreased exhaled NO value is associated with better quality of life). However, in patients without asthma symptoms, there is no correlation between exhaled NO and quality of life.

4.14. Health Economics

Measurement of exhaled NO has the potential to ensure better clinical outcomes and improve the cost-effectiveness of asthma diagnosis and treatment.

2.3. Practical Conclusions

This document concludes that in asthma:

- exhaled NO is a sensitive measure of airway inflammation that reacts rapidly in response to treatment or exacerbation of disease
- clinical applications of exhaled NO measurement include monitoring compliance and response to treatment, disease activity, and the notification of loss of control
- NO measurements are superior to lung function tests
- exhaled NO can be used for immediate and non-invasive identification of ICS responsiveness
- by using exhaled NO as a guide to treatment, the dose of inhaled corticosteroids can be reduced without compromising asthma control
- exhaled NO is an effective predictor of asthma relapse
- measurement of exhaled NO is non-invasive, easy, and convenient for patients
- simple and sensitive methods have been developed to determine exhaled NO.

References

- Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. *Eur Respir J* 1993; **6**: 1368-70.
- Ashutosh K. Nitric oxide and asthma: a review. *Curr Opin Pulm Med* 2000; **6**: 21-5.
- Bhagat K, Vallance P. Nitric oxide 9 years on. *J R Soc Med* 1996; **89**: 667-73.
- Gustafsson LE, Leone AM, Persson MG, *et al*. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem Biophys Res Commun* 1991; **181**: 852-7.
- Taylor DR. Nitric oxide as a clinical guide for asthma management. *J Allergy Clin Immunol* 2006; **117**: 259-62.