Use of exhaled nitric oxide in asthma care

In this article...

- What nitric oxide is
- How exhaled nitric oxide relates to airway inflammation
- Use of exhaled nitric oxide in asthma management

Author Carol Stonham is senior nurse at Minchinhampton Surgery, Stroud, and chairs the nurse committee of the Primary Care Respiratory Society UK.


Nitric oxide in exhaled breath is a biomarker of continuing inflammatory process in the airways, and its measurement can be used to predict responsiveness to steroid treatment in patients with asthma. This article describes the range of uses of exhaled nitric oxide measurements in respiratory care, particularly in primary care settings, and reviews evidence on this non-invasive test.

The UK has the third highest prevalence of asthma in the world (To et al, 2012), causing approximately 1,200 deaths per year. This figure has not fallen with the introduction of new medications, or specialist nurses in hospital and community settings.

Hospital admissions, attendances at accident and emergency and out-of-hours departments, and unscheduled appointments continue to be a concern and reflect the underlying uncontrolled morbidity of asthma (NHS RightCare, 2013).

NHS England has set up the National Review of Asthma Deaths to identify avoidable factors and make recommendations for implementing change. This involves a systematic review of every reported death from asthma in the UK from February 2012 to January 2013 (Royal College of Physicians, 2013). Other national activities set up to improve asthma care include the convening of an asthma steering group to support the respiratory team at the Department of Health for England, which recently published a good practice guide (Primary Care Commissioning, 2012), and the National Institute for Health and Care Excellence’s recent asthma quality standard (NICE, 2013).

Using different techniques to measure response to treatment and adherence to prescribed regimens and to give feedback to patients with asthma will help them to control symptoms and improve their quality of life.

Use of nitric oxide in respiratory assessment

Chronic inflammation in asthmatic airways is multifactorial and driven by different types of inflammatory cells, including those known as T helper cells. These are believed to increase the production of nitric oxide gas by activating an enzyme in epithelial airway cells.

The production of nitric oxide is inhibited by corticosteroids (Alving and Malinovschi, 2010). The fraction of nitric oxide (FeNO) measured in exhaled breath is therefore a biomarker of the ongoing inflammatory process in the airways and can be used in clinical practice in a number of ways (Box 1). How FeNO is measured is outlined in Box 2.

Keywords: Asthma/Exhaled nitric oxide/Steroid responsiveness/Airways inflammation

This article has been double-blind peer reviewed

5 key points

1. The fraction of nitric oxide (FeNO) in exhaled breath is a biomarker of the continuing inflammation in the airways.
2. FeNO is a non-invasive test that can be done quickly and easily in patients in most age groups, although the equipment costs around £1,500.
3. Measuring FeNO predicts effectiveness of steroid treatment regardless of the diagnosis.
4. FeNO levels can be used to show patients the effects of using corticosteroids and detect poor adherence.
5. As part of a routine asthma visit, FeNO could help to identify patients at risk for future loss of asthma control.

In this article...

- What nitric oxide is
- How exhaled nitric oxide relates to airway inflammation
- Use of exhaled nitric oxide in asthma management

Author Carol Stonham is senior nurse at Minchinhampton Surgery, Stroud, and chairs the nurse committee of the Primary Care Respiratory Society UK.


Nitric oxide in exhaled breath is a biomarker of continuing inflammatory process in the airways, and its measurement can be used to predict responsiveness to steroid treatment in patients with asthma. This article describes the range of uses of exhaled nitric oxide measurements in respiratory care, particularly in primary care settings, and reviews evidence on this non-invasive test.

The UK has the third highest prevalence of asthma in the world (To et al, 2012), causing approximately 1,200 deaths per year. This figure has not fallen with the introduction of new medications, or specialist nurses in hospital and community settings.

Hospital admissions, attendances at accident and emergency and out-of-hours departments, and unscheduled appointments continue to be a concern and reflect the underlying uncontrolled morbidity of asthma (NHS RightCare, 2013).

NHS England has set up the National Review of Asthma Deaths to identify avoidable factors and make recommendations for implementing change. This involves a systematic review of every reported death from asthma in the UK from February 2012 to January 2013 (Royal College of Physicians, 2013). Other national activities set up to improve asthma care include the convening of an asthma steering group to support the respiratory team at the Department of Health for England, which recently published a good practice guide (Primary Care Commissioning, 2012), and the National Institute for Health and Care Excellence’s recent asthma quality standard (NICE, 2013).

Using different techniques to measure response to treatment and adherence to prescribed regimens and to give feedback to patients with asthma will help them to control symptoms and improve their quality of life.

Use of nitric oxide in respiratory assessment

Chronic inflammation in asthmatic airways is multifactorial and driven by different types of inflammatory cells, including those known as T helper cells. These are believed to increase the production of nitric oxide gas by activating an enzyme in epithelial airway cells.

The production of nitric oxide is inhibited by corticosteroids (Alving and Malinovschi, 2010). The fraction of nitric oxide (FeNO) measured in exhaled breath is therefore a biomarker of the ongoing inflammatory process in the airways and can be used in clinical practice in a number of ways (Box 1). How FeNO is measured is outlined in Box 2.

Keywords: Asthma/Exhaled nitric oxide/Steroid responsiveness/Airways inflammation

This article has been double-blind peer reviewed

5 key points

1. The fraction of nitric oxide (FeNO) in exhaled breath is a biomarker of the continuing inflammation in the airways.
2. FeNO is a non-invasive test that can be done quickly and easily in patients in most age groups, although the equipment costs around £1,500.
3. Measuring FeNO predicts effectiveness of steroid treatment regardless of the diagnosis.
4. FeNO levels can be used to show patients the effects of using corticosteroids and detect poor adherence.
5. As part of a routine asthma visit, FeNO could help to identify patients at risk for future loss of asthma control.

In this article...

- What nitric oxide is
- How exhaled nitric oxide relates to airway inflammation
- Use of exhaled nitric oxide in asthma management

Author Carol Stonham is senior nurse at Minchinhampton Surgery, Stroud, and chairs the nurse committee of the Primary Care Respiratory Society UK.


Nitric oxide in exhaled breath is a biomarker of continuing inflammatory process in the airways, and its measurement can be used to predict responsiveness to steroid treatment in patients with asthma. This article describes the range of uses of exhaled nitric oxide measurements in respiratory care, particularly in primary care settings, and reviews evidence on this non-invasive test.

The UK has the third highest prevalence of asthma in the world (To et al, 2012), causing approximately 1,200 deaths per year. This figure has not fallen with the introduction of new medications, or specialist nurses in hospital and community settings.

Hospital admissions, attendances at accident and emergency and out-of-hours departments, and unscheduled appointments continue to be a concern and reflect the underlying uncontrolled morbidity of asthma (NHS RightCare, 2013).

NHS England has set up the National Review of Asthma Deaths to identify avoidable factors and make recommendations for implementing change. This involves a systematic review of every reported death from asthma in the UK from February 2012 to January 2013 (Royal College of Physicians, 2013). Other national activities set up to improve asthma care include the convening of an asthma steering group to support the respiratory team at the Department of Health for England, which recently published a good practice guide (Primary Care Commissioning, 2012), and the National Institute for Health and Care Excellence’s recent asthma quality standard (NICE, 2013).

Using different techniques to measure response to treatment and adherence to prescribed regimens and to give feedback to patients with asthma will help them to control symptoms and improve their quality of life.

Use of nitric oxide in respiratory assessment

Chronic inflammation in asthmatic airways is multifactorial and driven by different types of inflammatory cells, including those known as T helper cells. These are believed to increase the production of nitric oxide gas by activating an enzyme in epithelial airway cells.

The production of nitric oxide is inhibited by corticosteroids (Alving and Malinovschi, 2010). The fraction of nitric oxide (FeNO) measured in exhaled breath is therefore a biomarker of the ongoing inflammatory process in the airways and can be used in clinical practice in a number of ways (Box 1). How FeNO is measured is outlined in Box 2.

Keywords: Asthma/Exhaled nitric oxide/Steroid responsiveness/Airways inflammation

This article has been double-blind peer reviewed

5 key points

1. The fraction of nitric oxide (FeNO) in exhaled breath is a biomarker of the continuing inflammation in the airways.
2. FeNO is a non-invasive test that can be done quickly and easily in patients in most age groups, although the equipment costs around £1,500.
3. Measuring FeNO predicts effectiveness of steroid treatment regardless of the diagnosis.
4. FeNO levels can be used to show patients the effects of using corticosteroids and detect poor adherence.
5. As part of a routine asthma visit, FeNO could help to identify patients at risk for future loss of asthma control.
FeNO is recognised as a measurement tool of airway inflammation in guidelines by the British Thoracic Society and Scottish Intercollegiate Guidelines Network (2012) and in the Asthma Practice Guide (Primary Care Commissioning, 2012). Until recently, it has not been possible to measure airway inflammation quickly and easily in a primary care setting. NICE is reviewing FeNO testing as part of the diagnostic pathway for asthma.

**Predicting response to medication**

National and international asthma guidance emphasise the importance of continuous treatment of the underlying airway inflammation in the prevention and control of asthma (Global Initiative for Asthma, 2010).

The American Thoracic Society guideline (Dweik et al, 2011) recommends the use of FeNO in determining the likelihood of steroid responsiveness in people with chronic respiratory symptoms possibly caused by airway inflammation. The guideline suggests using cut points when interpreting individual FeNO levels. Eosinophilic inflammation and responsiveness to inhaled corticosteroids (ICS) therapy are less likely with FeNO values <25 (<20 parts per billion for children aged under 12 years), whereas high FeNO levels (50 or 35 ppb respectively) indicate significant eosinophilic airway inflammation and a high likelihood of responsiveness to ICS.

The BTS/SIGN asthma guideline states that if there is any diagnostic doubt, airway responsiveness should be measured. It also states that the place of FeNO in the diagnosis of asthma is uncertain as more evidence is needed.

Population-based studies have demonstrated that regular use of low-dose ICS is associated with a decreased risk of death from asthma (Suissa et al, 2000). However, there are still concerns about adverse effects related to long-term steroid use especially at high doses, and it is important to balance these potential effects against the benefit of the treatment before prescribing these drugs.

In recent years, interest in defining the different genetic subgroups of asthma has increased; one of the aims of this is to make personalised treatment possible. One patient subgroup identified is those with high FeNO levels and elevated levels of sputum eosinophils. Patients with these characteristics respond particularly well to ICS treatment, whereas response is lower in those with low FeNO and low sputum eosinophil levels (Wenzel, 2012).

Several clinical studies have shown FeNO to be a useful marker of steroid responsiveness. One study demonstrated that FeNO was the most reliable test in predicting steroid response, when compared with conventional tests such as peak flow measurements, spirometry, bronchodilator response and airway hyper-responsiveness provocation testing. The authors concluded that assessing airway inflammation is of more practical value than diagnostic labelling when considering the potential benefits of inhaled anti-inflammatory therapy, especially ICS (Smith et al, 2005). A high FeNO value has also been shown to be predictive of steroid responsiveness even in the absence of induced sputum eosinophils (Cowan et al, 2010).

As a marker of steroid-responsive inflammation in the airways, FeNO predicts clinical improvement by steroid treatment regardless of the diagnosis; for example, patients with chronic cough and high FeNO values have been shown to benefit from ICS treatment (Hahn, 2007). FeNO can also predict a preferential clinical response to an inhaled ICS compared with a leukotriene receptor antagonist (LTRA) (Knuffman et al, 2009).

**Measuring the effect of anti-inflammatory therapy**

In patients with an accurate diagnosis, FeNO can be used to measure the effect of ICS treatment. Since FeNO is a sensitive measurement of steroid responsiveness, scores should fall in response to the anti-inflammatory action of the medication.

**Poor ICS treatment adherence**

FeNO can be used to monitor whether patients take their prescribed medicine correctly, as high levels have been shown to correlate with low treatment adherence. In a paediatric study of 527 children on ICS, increased FeNO values were associated with a lower chance of good adherence (Koster et al, 2011). A study undertaken in Belfast showed patients who were non-adherent at the start of the study had a greater reduction in FeNO after ICS treatment under observation than adherent patients. It was concluded that FeNO could identify non-adherent patients (McNicholl et al, 2012).
Evidence for and against FeNO

The use of FeNO in monitoring airways inflammation in patients with diagnosed asthma is recommended by the American Thoracic Society. A decrease of >20% in FeNO values from one visit to the next is considered a significant response to anti-inflammatory therapy (Dweik, 2011).

Powell et al (2011) used FeNO to guide therapy and achieve inflammation control in women with asthma during pregnancy. This study showed a substantial reduction in asthma exacerbation rate in the FeNO managed group compared with the control group. Better perinatal outcomes (such as higher birthweight and fewer neonatal hospitalisations) were also observed in the FeNO group. In summary, the FeNO-guided algorithm resulted in a lower rate of exacerbations, a reduction in mean daily ICS dose as well as an improved quality of life (Powell et al, 2011).

In a UK primary care study, FeNO values measured in patients with asthma were used to decide whether ICS therapy should be adjusted or not (Hewitt et al, 2009). This strategy resulted in an overall increase in the number of well-controlled patients (from 40% to 70%), as well as a reduction in the number of exacerbations (Zeiger et al, 2011a). Negative studies on the use of FeNO for adjusting asthma treatment have been published. A Cochrane meta-analysis of six randomised controlled studies aimed to evaluate the efficacy of FeNO based treatment compared with treatment based on clinical symptoms (Petsky, 2009). It concluded that using exhaled nitric oxide to tailor ICS dosage cannot currently be routinely recommended for clinical practice. However, these studies have mainly evaluated small numbers of patients, the majority of whom had mild-to-moderate asthma, and used varying outcome measures.

Data from the paediatric studies included in the Cochrane analysis paper were re-analysed by Mahr et al (2013), who found different outcomes. Their re-analysis showed that the rate of exacerbations was significantly lower in FeNO-guided children compared with controls.

Conclusion

FeNO is a non-invasive test that can be undertaken in primary care settings quickly and easily in patients in most age groups (Box 2), although it does require the purchase of equipment costing approximately £1,500.

Measuring exhaled nitric oxide provides an accurate predictor of steroid responsiveness in respiratory symptoms and can therefore guide decisions about treatment. It can also be used as an educational tool to demonstrate the anti-inflammatory effect of ICS to patients, and to detect and open dialogue in poor adherence. FeNO can also be used to safely guide step down in medication.

References


Primary Care Commissioning (2012) Designing and Commissioning Services for Adults with Asthma: a Good Practice Guide. Tinyurl.com/ asthmaaguide


Zeiger RS et al (2011a) Association of exhaled nitric oxide to asthma burden in asthmatics on inhaled corticosteroids. Journal of Allergy and Clinical Immunology; 128: 2, 412-414.