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USE OF EXHALED NITRIC OXIDE AS READOUT FOR INHALED CORTICOSTEROIDS EFFICACY

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Introduction

Optimal and non-invasive monitoring of the effect of anti-inflammatory drugs in asthma is important, as asthmatic patients may require a life-long, individually tailored treatment with corticosteroids. The lack of success of the traditional parameters, lung function, airway reactivity and symptoms, in monitoring the effect of corticosteroids, especially in dose-related studies seems to be related to their relative insensitivity and slow responsiveness.

It has been suggested that it may take several weeks for inhaled corticosteroids to become effective. Recently, a variety of non-invasive approaches, such as exhaled breath analysis (exhaled gases and condensate) and induced sputum have been developed, which are changing our understanding about the speed of action of corticosteroids and their effect in asthma. However, sputum induction cannot be used for day to day monitoring, as it provokes transient neutrophilia [2; 3], and the use of exhaled condensate is still in the early stage of development.

Exhaled NO as a marker of inflammation is comparable to invasive measurements of inflammation, such as bronchial biopsies and bronchoalveolar lavage [4; 5] and induced sputum in asthma [6–8]. It is not influenced by other anti-asthma drugs, such as albuterol or salmeterol [9–11]. The inflammatory origin [5; 2–15] of elevated levels of exhaled NO in asthma [14; 16], its responsiveness to suppression by corticosteroids [17; 18] and accumulating evidence of its association with asthma severity [19–21] makes exhaled NO an effective and practical marker to monitor the effect of corticosteroid treatment in asthma. Dose-dependent reduction in exhaled NO has also been reported in mild asthmatics treated with low doses of budesonide (BUD) [22].

General Principles of Exhaled NO Measurements
Technical factors affecting exhaled NO measurements

Most of the measurements of exhaled NO have been made by a variety of commercially available chemiluminescence analysers and are based on the photochemical reaction between NO and ozone generated in the analyser. The specificity of exhaled NO measurements by chemiluminescence has been confirmed using gas chromatography-mass spectrometry [23].

There are two main approaches to measurement of exhaled NO: on-line, during a single, flow-controlled exhalation against a resistance; off-line, using similar con-

trolled exhalation during a single exhalation into reservoir. There are a few technical factors, which should be considered when exhaled NO measurements are used to monitor asthma treatment (Table 1).

Table 1
Technical factors affecting exhaled NO measurements

Increased NO	Decreased NO
Low exhalation or sampling flow rate	High exhalation or sampling flow rate
Breath holding	Spirometric manoeuvres (transiently)

The European Respiratory Society Guidelines on exhaled and nasal NO measurements were established in 1997 [24]. Recently, recommendations for standardized procedures for the on-line and off-line measurement of exhaled and nasal NO in adults and children have been published [25]. The standardization of techniques makes it possible to compare the results of clinical trials from different centres.

Conditions and habits affecting exhaled NO measurements

Conditions that may affect NO concentrations in exhaled air should be avoided, or recorded and used for the interpretation of the data (Table 2).

Table 2
Physiological, pathophysiological conditions and habits affecting exhaled NO measurements

Increased NO	Decreased NO
Allergen and/or pollen exposure	Menstruation
Air pollution	Smoking
Occupational exposure (ozone)	Acute alcohol ingestion
Arginine ingestion, nitrite/nitrate-enriched food	Mouth washing
Asthma	
Unstable/severe COPD	Non asthmatic chronic cough
Allergic rhinitis	Pulmonary hypertension
Upper respiratory tract infection	Kartagener's syndrome
Influenza vaccination	Primary cilia dyskinesia
LPS administration	Cystic fibrosis
Bronchiectasis	
Ulcerative colitis	
Tuberculosis	
Lung cancer	
Active pulmonary sarcoidosis	

Origin of Nitric Oxide in Exhaled Air

The correct use of exhaled NO as a readout for IS efficacy depends on the understanding of its origin in exhaled air. Exhaled NO has multiple origins, as NOS is

found in several cell types in the respiratory tract, e.g. epithelial and vascular endothelial cells, macrophages, eosinophils, neurons [26], and cannot be a marker of inflammatory response from a specific cell type. In fact, in most studies in normal subjects free of inflammation [27–29], cNOS rather than iNOS was found to be predominant in the airway wall.

Predominantly bronchial epithelial iNOS production, has been shown to be the major source of exhaled NO in conditions in which airway inflammation is present, and this has been confirmed by direct measurements during bronchoscopy [4; 30], or in tracheotomized patients [31], as well as indirectly by a remarkable exhalation flow-dependence of exhaled NO and accumulation of NO during a breathhold [4; 32]. The inflammatory origin of NOS induction [12; 13; 15] and related increase in exhaled NO in asthma [14; 16] has been supported by high presence NO in exhaled air, and increased nitrotyrosine and iNOS in bronchial epithelium of asthmatics [5] and lung transplant recipients [33]. Exhaled NO levels were highly dependent upon the intensity and extent of expression of iNOS in bronchial epithelium and BAL neutrophilia, but not in the subepithelial area. This confirms that exhaled NO may be not only a valid non-invasive measure of airway inflammation, but also a marker of the development of airway remodelling.

The profound effect of a nebulized [34–36] vs. a comparable intravenous dose [37] of NOS inhibitors on exhaled NO strongly indicates that respiratory epithelium, but not vascular endothelial cells, is the major source of NO in exhaled air, and explains its particular sensitivity to inhaled corticosteroids.

Clinical Relevance of Exhaled NO in Asthma Use of Exhaled NO as Readout for Corticosteroids Efficacy Oral corticosteroids

The overall effect of steroids on exhaled NO depends on the prevalence and the degree of iNOS activation and, therefore, has no effect in normal subjects, and is more effective in patients with more severe disease.

Oral prednisolone (30 mg daily for 3 days) reduces the elevated exhaled NO in asthmatic patients, whereas it has no effect on exhaled NO in normal subjects [34]. Oral dexamethasone (4 mg/day for 2 days) similarly has no effect on exhaled NO or serum concentrations of interferon- γ and interleukin-1 β in normal subjects [38]. This is presumably because iNOS is the major source of increased exhaled NO in asthma, whereas the major source of exhaled NO in normal subjects is the constitutive NOS, which is not suppressed by corticosteroids.

The same dose of prednisolone (30 mg/day), however, given to mild asthmatics [34] produced a significant, but moderate (22 %) reduction in exhaled NO within 72 hours (Figure 1). Whereas a cumulative dose of methylprednisolone (180–500 mg) caused 36 % reduction within 50 h in the majority of severe patients with acute asthma [39]. A large dose (1 mg/kg/day for 5 days) of oral prednisolone normalized exhaled NO in infants and young children with wheezing exacerbations (Figure 2 A) [40],

whereas the same dose in more severe asthmatic children only shifted their exhaled NO down to the levels of mild-to-moderate asthma in spite of the improvement in lung function (Figure 3 B) [10].

Recently, it has been shown that NO levels correlated with the percentage improvement in FEV₁ from baseline to the post-steroid (30 mg prednisolone/day for 14 days) post-bronchodilator value, with an NO level of > 10 ppb at baseline having a positive predictive value of 83 % for an improvement in FEV₁ of \geq 15% [41], and therefore may be useful in predicting the response to a trial of oral steroid in asthma.

Inhaled corticosteroids

Exhaled NO has been used successfully to monitor anti-inflammatory treatment with inhaled corticosteroids in asthma [14; 18; 42–44], as it is an extremely sensitive and rapid marker of the effect of steroid treatment (Table 3). A significant reduction in exhaled NO levels has been observed 6 hours after a single high-dose (8 mg) BUD (Pulmicort Respules) in symptomatic moderate asthma [45]. Dose-dependent changes in NO have been reported during 3-week treatment with 100/400 mg BUD in mild asthma [22].

Recently, we have shown for the first time that the onset of action of inhaled BUD on exhaled NO and the time to reach the maximal reduction were dose-dependent. The higher dose of BUD rapidly reduced NO (within 3 days) and prevented night time asthma symptoms in all patients (Figure 3 A, B). This was also associated with amelioration in FEV₁ (Figure 3 C). The onset of action of 100 mg BUD was slower and its effect on NO was less, and this was related to a slower improvement in night time symptoms. The difference between the effect of 100 mg vs. 400 mg BUD on NO was apparent within 3 days and was maximal after 5 and 21 days. NO was further reduced during the 3rd wk of treatment with 400 mg BUD, in contrast to a minor NO increase in the 100 mg BUD group, which coincided with the return of asthma symptoms and increased use of β_2 -agonists.

The time scale of the effect of steroids on exhaled NO was within the scope of the time needed for inhibition of iNOS activity (24 hours) [46], or nuclear transcription-factor kB (30 minutes) after application of corticosteroids [47]. However, the main effect of corticosteroids on iNOS is probably via inhibition of inflammatory cytokines, such as TNF- α , or IL-1 β , which induced iNOS, or by inhibition of inflammatory cells such as eosinophils, which express iNOS [48].

The onset of action of steroids on exhaled NO depends not only on their dose, but also on asthma severity and, perhaps, on formulation and route of their administration. Thus, oral prednisolone given to mild asthmatics 34 produced a significant, but moderate (22 %) reduction in exhaled NO, whereas cumulative dose of methylprednisolone (180–500 mg) caused faster and more profound (36 %) reduction within 50 hours in the majority of severe patients with acute asthma [39]. The lack of changes in NO after 3 and 6 hours after the first dose 100/400 mg BUD in our study may suggest that the dose was too low and the patients had only mild asthma.

Effect of corticosteroids on exhaled NO

Drug class	Effect (from a baseline)	Onset (reported)	Duration (reported)	Recovery (reported)	Reference
Corticosteroids					
*1600 µg/day BUD (Mil A)	↓30% ↓34% ↓41%		7 days 14 days 21 days		18
*BUD 1600 µg/day (Mil A)	↓54%		28 days		42
*BUD 100 µg/day (Mil A) BUD 400 mg/day	↓29% ↓50%		28 days 28 days		22
*Pred 30 mg/day, 3 days (Mil A)	↓22%	72 h			34
Pred + IS (Sev A)	↓40%	48 h			39
Pred 1mg/kg, 5 days (Sev A)	↓46%		5 days		10
Pred 1mg/kg, 5 days (Mod A)	↓52%		5 days		40
Pred + IS, 5 days (Sev A)	↓65%		5 days		21
IS (Mil A) IS (Mod A)	↑9 ppb ↑24 ppb			4 days 15 days	81
BUD 8 mg nebulized (Mod A)	↓31%	6 h			45
BMP 1 mg/day (Mil A)	↓28% ↑12%		7 days	7 days	82
*BUD 100 mg/day (Mil A) BUD 400 mg/day	↓15% ↓27% ↓20% ↓7% ↓26% ↓38% ↓35% ↓44% ↓3%		5 days 7 days 21 days 3 days 5 days 7 days 21 days	7 days 5 days	Kharitonov et al. (ATS 2000)

An important issue that remains to be resolved is what level of exhaled NO needs to be achieved during the treatment. Exhaled NO levels in mild asthma are substantially reduced, but not normalized after a course of different doses (100 to 1600 mg) of inhaled steroids [22; 34; 44]. However, the larger dose (1mg/kg/day for 5 days) of oral prednisolone normalized exhaled NO in infants and young children with wheezing exacerbations [40], while more severe asthmatic children had exhaled NO levels reduced to the levels in mild-to-moderate asthma [10].

Affinity for the glucocorticoid receptor (GR) is, perhaps, another factor influencing the effect of steroids on NO. Fluticasone propionate (FP), for example, has a 3-fold higher GR affinity than BUD, as it is more lipophilic than BUD, and its half-life of active steroid-receptor complexes is longer (10 hours vs. 5 hours). Therefore, the rate of association of FP with the receptor is faster, and the rate of dissociation is slower than BUD [49]. The high affinity of FP might be the reason for a profound and stable NO reduction by 76 % after 2 first weeks and 77 % after 4 weeks of treatment reported with 1000 mg/day FP [44]. Indeed, NO levels were not fully recovered (83 % of the baseline) 2 weeks after stopping of treatment. High dose of BUD (1600 mg/day), however, reduced exhaled NO by only 48 % at the end of the 3rd week with further reduction to 54 % after four weeks of treatment [18; 22;

42]. The levels of NO were not fully recovered two weeks after FP was stopped, whilst NO levels in our study returned to the almost pre-treatment values within 3-5 days regardless of the dose of BUD.

Speed, magnitude and duration of changes in exhaled NO caused by steroids may be useful not only to monitor therapeutic efficacy of steroids, but also to assess their side effects, which are difficult to measure, if conventional methods are applied. Thus, despite the greater cortisol suppression caused by FP, there were no differences between the effect of FP, or BUD on FEV₁, or blood eosinophils [50].

Inhaled and oral corticosteroids

The mechanisms of airway inflammation in asthmatic patients who respond well to corticosteroids could be different from those patients with severe persistent asthma who remain symptomatic despite corticosteroid treatment. With exacerbations, the number of eosinophils, which are capable of expressing iNOS and producing NO [48; 51], or prevalence of neutrophilic inflammation and oxidative stress [52] may increase and this may also explain a further elevation of exhaled NO in these patients despite high dose inhaled and/or oral steroid treatment [19; 52]. Thus, over half of children with very severe asthma had raised NO levels, indicating persisting airway inflammation and oxidative stress despite maximal doses of corticosteroids [53].

The rationale to quantify endogenous NO formation as the sum of its N-oxides is that nitrite has a relatively short half-life (110 s) [54] and may be further oxidised to nitrate (NO₃⁻) by hydroxyl radical, or hypochlorous acid, or various heme proteins [55]. Therefore, it is difficult to distinguish whether the nitrite aqueous solution is derived from NO synthesis, or peroxyxynitrite, or S-nitrosothiols. The significance of these various oxidative processes depends on local levels of NO₂⁻ and O₂⁻ formation. Thus, autoxidation of NO with O₂ is of a particular importance in asthma where NO production is elevated, and increased levels of nitrotyrosine have been correlated with elevated levels of oxidants [56]. The presence of nitrotyrosine in the airways of patients who died of status asthmaticus supports the concept of widespread airway and parenchymal inflammation in asthma [57].

Corticosteroids reduce the formation of reactive oxygen species and nitrotyrosine in bronchial biopsies [5] and BAL [58] in asthma, or formation of NO₂⁻/NO₃⁻ in nasal lavage and nitrotyrosine in nasal mucosa in allergic rhinitis [59]. However, considering the importance of oxidative stress in severe persistent asthma a combination of corticosteroids with antioxidants, or/and NOS inhibitors may be considered in these patients.

Effect of Other Treatment on Exhaled NO Inhaled β₂-agonists

The short-acting β₂-agonist salbutamol (5 mg via nebulizer or 400 mg by metered-dose inhaler) has no acute effect on exhaled NO [9; 10; 60]. Similarly, 1 week of treatment with a long-acting inhaled β₂-agonists, salmeterol, did not reduced NO in adults or children [9–11]. This is entirely consistent with the fact that inhaled β₂-agonists do not have any effect on chronic inflammation in asthma and validates the use of exhaled NO to measure inflammation independently of airway calibre.

Leukotriene antagonists

A leukotriene synthase inhibitor (pranlukast) inhibits the rise in exhaled NO when the dose of inhaled corticosteroids is reduced [61]. Rapid reduction of exhaled NO has been

recently reported within 2 days of starting montelukast, leukotriene receptor antagonist, in children with asthma (Table 4). The mechanism of this moderate 15 % [62], or 30 % [63] reduction is not clear, but may reflect an inhibitory effect on inflammatory cytokines and, therefore, a reduced impact on iNOS. This data may also suggest an anti-inflammatory role for leukotriene D₄ receptor antagonism in the treatment of children with mild to moderate asthma.

iNOS inhibitors, prostaglandins and other drugs

The use of NO modulators, for example iNOS inhibitors, or prostaglandins PGE₂, are presently at the stage of clinical research. Potentially, NO modulators may be important in management of severe asthma in which a combination of airway inflammation and oxidative stress together with an inherited, or acquired resistance to steroids makes their treatment difficult.

Endogenous NO may play an important role in the persistent airway inflammation and hyperresponsiveness and treatment with aminoguanidine, a specific iNOS inhibitor, which has direct scavenging activities against H₂O₂, hypochlorous acid and peroxyxynitrite [64] may be beneficial. Both, aminoguanidine and NG-nitro-L-arginine methyl ester (L-NAME) can be safely given and have been known to cause a significant reduction in exhaled NO in asthmatic patients [34; 35] (Table 5). More long-term treatment will be required to demonstrate whether NO contributes to the persistence of asthmatic inflammation.

Prostaglandins E₂ and F_{2α} decrease exhaled NO in normal and asthmatic subjects irrespective of changes in airway calibre [65]. This effect occurs rapidly and is presumably due to an inhibitory effect of cyclooxygenase products on NOS directly rather than through altered gene transcription [66].

Despite positive changes in PC₂₀ in asthmatics treated with seratrodast, TXA₂ antagonist, there were no differences in either exhaled NO or sputum eosinophils [67]. The effect of theophylline and cromones has not yet been reported.

Table 4

Effect of non-steroidal drugs on exhaled NO

Drug class	Effect (from a baseline)	Onset (reported)	Duration (reported)	Recovery (reported)	Reference
Non-steroidal anti-inflammatory drugs	↓				
*Ibuprofen 2.4 g, (N after i.v. endotoxin)					83
β ₂ -agonists					
*Terbutaline (Mil A)	No effect				18
*Salbutamol, *salmeterol (Mil A)	No effect				11; 84; 85
Interleukin inhibitors					
IL-4receptor (Mo A) (Neb)	↓ 8 ppb	4 days	15 days		81
Leukotriene antagonists					
*Montelukast (Mil A)	↓ 15%		2 days		62
*Montelukast (Mil A)	↓ 20%		14 days		
*Montelukast (Mil A)	↓ 30%		28 days	14 days	63
After end of treatment	↑ 19%				
Pranlukast (Mil A)	↓		4 wk		61

Exhaled NO and Other Means of Asthma Monitoring Symptoms, lung function and airway hyperreactivity

There is accumulating evidence about the strong relationship between exhaled NO, clinical signs and symptoms of asthma, especially during acute episodes, or asthma exacerbations. However, longitudinal studies are needed to confirm that exhaled NO may be used not only for a short-term management, but as a guide for long-term management and treatment of asthma of differing severity.

The traditional means of monitoring asthma are not sensitive enough to demonstrate dose-dependent effect of inhaled steroids, especially in mild asthma. The fundamental limitation of lung function and PC_{20} measurement, which reflect airway obstruction and airway hyperresponsiveness, in monitoring of asthma, is that they are not directly related to airway inflammation. In addition, FEV_1 has a little room for improvement in mild asthma and PC_{20} is affected by corticosteroids and cannot be routinely performed in severe asthmatics. Both parameters are slow to change and lack a discriminating power to distinguish the effect of different doses of steroids.

For example, only moderate positive changes in FEV_1 and PC_{20} were seen in mild asthma after 4 weeks of treatment with high (1600 mg) dose of BUD, but these changes were not significantly different from the placebo group [42]. Indirect inhaled spasmogens, such as AMP, might be more specific and demonstrate dose-dependent changes in PC_{20} when compared with placebo after moderate (400 mg/day), or high (1600 mg/day), but not low (100 mg/day) doses of inhaled steroids, as has been shown for the novel corticosteroid ciclesonide [68]. However, a significant reduction in exhaled NO, which was better than the placebo and which coincided with improvement in asthma symptoms and lung function, was seen after this and much lower doses of BUD 100 mg and 400 mg [22]. The latter changes were also dose-dependently different.

The advantage of exhaled NO measurements is that the changes in NO during steroid treatment are dose-dependent and precede the improvement in symptoms, FEV_1 [17] and sputum eosinophils 6 in asthma. Recently, we have demonstrated that 400 mg BUD rapidly reduced NO within 3 days and abolished night time asthma symptoms in all patients (unpublished observation). This was also associated with amelioration in FEV_1 . The onset of action of 100 mg BUD was slower and its effect on NO was less marked and this was reflected in a slower improvement in night time symptoms.

Rapid recovery of exhaled NO levels on stopping steroid treatment precedes the reduction in lung function, with FEV_1 , or PC_{20} returning to the pre-treatment level over 1 week [69]. Exhaled NO measurements may therefore serve as a fast responding indicator to assess patients compliance with therapy and to titrate their steroid treatment. For example, increasing levels of exhaled NO, asthma symptoms and use of β_2 -agonists during the third week of treatment with low dose of BUD might be an indication of the loss of asthma control and the need to increase the

Table 5
Effect of NOS inhibitors on exhaled NO

Drug class	Effect (from a baseline)	Onset (reported)	Duration (reported)	Recovery (reported)	Reference
NOS inhibitors					
*L-NMMA (N) *L-NMMA (Mil A)	↓44% ↓40%	15-45 min	4 h		
L-NAME (N) *Aminoguanidine (Mil A) *Aminoguanidine (N) *Aminoguanidine (Mil A)	↓53% ↓67% ↓28% ↓53%	15-45 min 15-45 min	4-6 h 4-6 h		34
*L-NAME (Mil A)	↓55%	30 min	2 h		35
L-NMMA (N) (i.v.) L-NAME (N) (Neb)	↓10% ↓37%	30 min 10 min			36

dose of steroids. On the other hand our data further supports the fact that most patients with mild-to-moderate asthma may require low doses of steroids taken once daily to achieve or to maintain adequate control [70].

The relationship between exhaled NO and FEV_1 depends on the severity of asthma. There is no strong link between exhaled NO, FEV_1 and symptoms in mild steroid-naïve asthma measured under stable conditions [14; 16]. However, higher concentrations of exhaled NO were linked to recent symptoms of bronchial obstruction [71], and NO was 2.6 times higher in children with recent symptoms compared with symptom-free subjects [71]. Exhaled NO correlated with symptom frequency and with rescue β_2 -agonists use, and is significantly higher in those patients with difficult/severe asthma who have the highest symptom score where changes in lung function may have limited sensitivity [19].

Induced sputum

The combination of exhaled NO measurements and sputum induction is the most beneficial approach in the use of these non-invasive assessments of airway inflammation in asthma. Recently, it has been shown that a combination of sputum eosinophilia and increased NO levels resulted in a positive predictive value of 72 % and a negative predictive value of 79 % in predicting the response to a trial of oral steroid in asthma [41]. Elevated levels of exhaled NO have been validated against invasive measurements of inflammation such as bronchial biopsies or BAL [4; 5; 30] and induced sputum [6], and a significant correlation has been found between exhaled NO and iNOS positive granulocytes in sputum eosinophils [7; 8].

One of the most attractive features of exhaled NO measurements is that they can be repeated at short intervals without affecting endogenous NO production, or causing discomfort to the patients. This is invaluable to study an acute effect and onset of action of a variety of drugs, that influence NO production in patients of different severity and age.

Sputum induction, however, can cause an excessive bronchoconstriction despite pre-treatment with salbutamol [8] and significant fall in SaO_2 [72] during the inhalation of hypertonic saline solution, as well as neutrophilia detect-

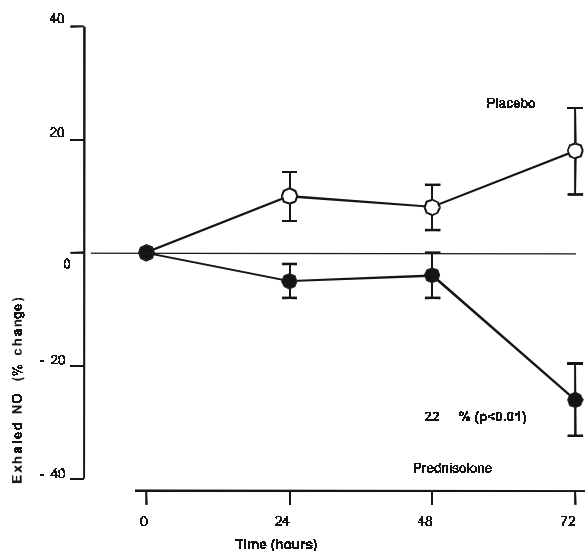


Figure 1. The effect of inhaled prednisolone (30 mg/day) on exhaled nitric oxide (NO) in mild asthmatic patients (-□-) and normal subjects (-o-).

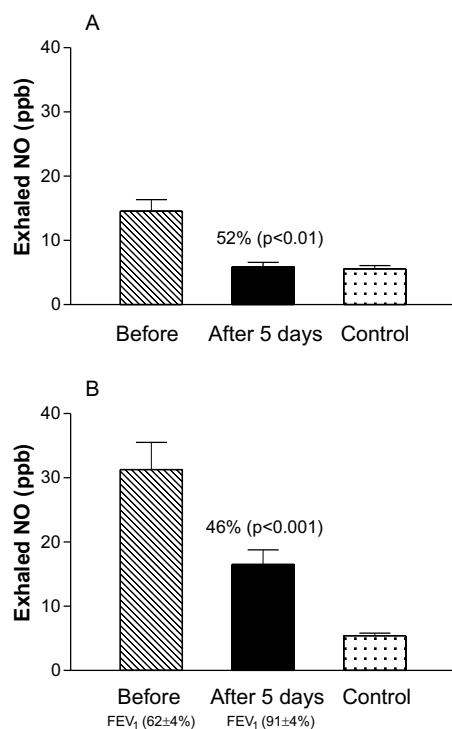


Figure 2. The effect of oral prednisolone on exhaled NO in children with moderate-to-severe asthma.

Panel A. Baraldi et al. AJRCCM 1999.
 Panel B. Baraldi et al. J Pediatr 1997.

able for at least [24] hours 2 thereafter, and other changes in their cellular and biochemical composition, both in healthy subjects and mild asthmatic patients [3; 73].

We have shown that after inhaled steroid dose reduction, exhaled NO and sputum eosinophil numbers are increased in parallel with loss of airway function [74]. Exhaled NO has a low threshold towards the effect of steroids and therefore, even a low dose of locally applied steroids are capable of a significant reduction in exhaled

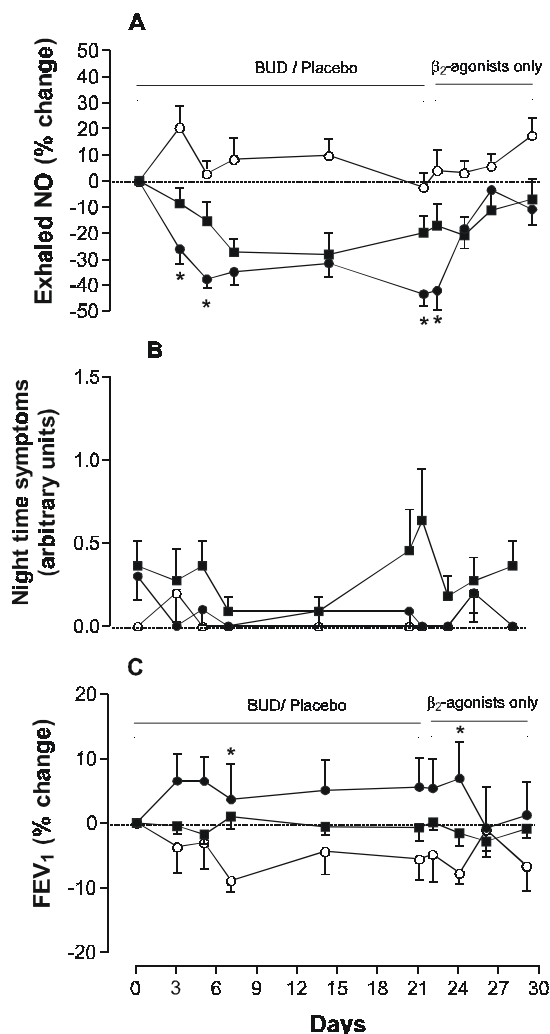


Figure 3

Panel A. The effect of inhaled budesonide (BUD) on exhaled nitric oxide (NO) in mild asthmatic patients. Mean values ± SEM in patients treated with 400 mg BUD (-□-) or 100 mg BUD (sGs) or placebo (-o-). Level of significance of difference between 400 mg BUD and 100 mg BUD: * = p<0.05.

Panel B. The effect of inhaled 400 mg, or 100 mg BUD, or placebo on night-time asthma symptoms in patients with mild asthma.

Panel C. The effect of inhaled 400 mg, or 100 mg BUD, or placebo on FEV₁ in patients with mild asthma. Level of significance of difference from placebo: * = p < 0.05.

Abbreviations:

- AHR: airway hyperresponsiveness
- AMP: adenosine-5'-monophosphate
- ECP: eosinophil cationic protein
- eNO: exhaled nitric oxide
- FEV₁: forced exhaled volume in 1s
- IL-5: interleukin-5
- IL-8: interleukin-8
- LPS: lipopolysaccharide
- LT: leukotrienes
- MPO: neutrophil myeloperoxidase
- NO: nitric oxide
- PC₂₀: provocative concentration of methacholine (histamine, or other spasmogen) causing a 20 % drop in FEV₁
- PEF: peak expiratory flow
- SaO₂: arterial oxygen saturation
- URTI: upper respiratory tract infection

NO. The use of sputum Eos as readout for steroid treatment efficacy might be limited. It has been shown that only high (1600 mg/day), or medium (400 mg/day) [42; 68], but not low (100 mg/day) doses [22; 68] of inhaled steroids were able to significantly reduce the number of Eos in sputum. No dose-dependent changes were observed in sputum Eos after either low, or moderate [22], or high [68] dose of inhaled steroids. Sputum Eos may not reflect the full extent of asthma severity, or the effect of inhaled steroids, as the cellular and biochemical composition of the larger airways (higher presence of Eos, neutrophils and ECP) is different from the peripheral airways (higher presence of macrophages, surfactant protein) and depends on the duration of sputum induction [75].

However, the combined use of exhaled NO measurements and sputum induction is of particular importance in severe persistent, or steroid-resistant asthma, which is associated with elevated levels of exhaled NO [19; 52], despite high dose steroid treatment, neutrophilia [52] and oxidative stress. It has been shown that elevated ECP levels, but not Eos numbers in induced sputum of corticosteroid-dependent asthmatics with recent exacerbations may be a more accurate assessment of airway inflammation in these patients [76]. The correct identification of these patients by their profile of inflammatory cells and mediators in sputum is crucial, as they may require a different treatment.

Future directions

There has been an interesting attempt to direct treatment with steroids in patients with moderate asthma according to their levels of PC₂₀ to methacholine [77]. Apart from small changes in PC₂₀ (1.1 double dilution), the major limitation of this and others single-parameter-based-guidelines is its relatively weak link with airway inflammation. The advantage of exhaled NO is that it has a much stronger association to airway inflammation, asthmatic/atopic inflammation in particular, and is much more sen-

sitive to anti-inflammatory treatment so that the control of the disease can be improved without the risk of over-treatment.

Measurements of lipid mediators, such as cysteinyl-leukotrienes and other eicosanoids, in induced sputum [78] and exhaled condensate are promising approaches. However, the methodological issues, such as considerable within-subject variability of most sputum eicosanoid concentrations [78] needs to be addressed. Exhaled condensate, is less contaminated with saliva and proteins and is easy to collect in a controlled fashion, and perhaps therefore has the advantage. Recently, we have determined significantly different levels of LT E₄, C₄, D₄, LTB₄ in exhaled condensate of asthmatic patients of different severity before and after treatment with corticosteroids.

Therefore, a combination of exhaled NO measurements with determination of other inflammatory markers and mediators in exhaled breath condensate, such 8-isoprostane [79; 80], leukotrienes and prostaglandins, is a promising non-invasive approach towards asthma and COPD management.

Objective, non-invasive and effort independent monitoring of respiratory symptoms in adults and children with asthma is vital for optimizing their anti-inflammatory treatment. Recently, we have used a quantitative method for tracking breath sounds overnight and during the day in mild-to-severe asthma patients. The overnight wheeze scores were over 20-times higher in moderate asthmatics on inhaled steroids when compared with mild steroid naive asthmatics (unpublished observation).

A combination of the cornerstone asthma sign such a wheeze, which is also related to airway obstruction, with a variety of inflammatory markers in exhaled breath and exhaled condensate may be clinically useful in detection and management of cytokine-mediated inflammatory lung disorders.

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УРОВЕНЬ СОДЕРЖАНИЯ ОКСИДА АЗОТА В ВЫДЫХАЕМОМ ВОЗДУХЕ КАК МАРКЕР ЭФФЕКТИВНОСТИ ТЕРАПИИ БРОНХИАЛЬНОЙ АСТМЫ С ПРИМЕНЕНИЕМ ИНГАЛЯЦИОННЫХ СТЕРОИДОВ

С. ХАРИТОНОВ

Резюме

В статье представлены данные про применение исследования содержания оксида азота (NO) в выдыхаемом воздухе в качестве критерия эффективности противовоспалительного лечения больных бронхиальной астмой, общие принципы измерения уровня NO в выдыхаемом воздухе, технические факторы, условия и состояния, влияющие на измерение содержания NO в выдыхаемом воздухе; что является источником NO. Показана клиническая значимость содержания NO при бронхиальной астме, представлены данные об использовании выдыхаемого NO как критерия эффективности кортикостероидной терапии при применении оральных, ингаляционных стероидов, влиянии других классов веществ (ингаляционных β₂-агонистов, антагонистов лейкотриенов, ингибиторов iNOS, простагландинов и других препаратов), их влияние на содержание NO; применение его и других методик (индуцированной мокроты, комбинирования исследования индуцированной мокроты с изучением содержания NO в выдыхаемом воздухе, их преимущества и недостатки) для мониторинга протекания астмы. Обозначены перспективные направления в этой отрасли.

USE OF EXHALED NITRIC OXIDE AS READOUT FOR INHALED CORTICOSTEROIDS EFFICACY

SERGEI A. KHARITONOV

Summary

General principles of exhaled NO measurements, technical factors affecting exhaled NO measurements, conditions and habits affecting exhaled NO measurements, origin of Nitric Oxide in exhaled air are represented in the article. It was pointed on clinical relevance of exhaled NO in asthma, use of exhaled NO as readout for corticosteroids efficacy (during the treatment with oral and inhaled corticosteroids, effect of other treatment on exhaled NO – inhaled β₂-agonists, leukotriene antagonists, iNOS inhibitors, prostaglandins and other drugs), their influence on the exhaled NO, use of the exhaled NO measurements and other methodics of Asthma Monitoring (induced sputum, it's combination with exhaled NO measurements, their advantages and lack, future directions also given in this paper.