УДК: 616.248-085:615.835.5:612.233.11.22

SERGEI A. KHARITONOV MD PHD

# USE OF EXHALED NITRIC OXIDE AS READOUT FOR INHALED CORTICOSTEROIDS EFFICACY

Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College School of Medicine, Royal Brompton & Harefield NHS Trust, London SW3 6LY, U.K.

## 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 1 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 spectometry [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 controlled 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 cillia diskynesia |
| LPS administration | Cystic fibrosis |
| Bronchiectasis | |
| Ulcerative colitis | |
| Tuberculosis | |
| Lung cancer | |
| Active pulmonary sacroidosis | |

## 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 nytrotyrosine 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-g and interleukin-1β 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 $FEV_1$ 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 $FEV_1$ of ≥ 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 $FEV_1$ (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 $\beta_2$-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-1β, 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.

*Table 3*

*Effect of corticosteroids on exhaled NO*

| Drug class | Effect (from a baseline) | Onset (reported) | Duration (reported) | Recovery (reported) | Reference |
|---|---|---|---|---|---|
| Corticosteroids | | | | | |
| *1600 μg/day BUD (Mi A) | ↓30%<br>↓34%<br>↓41% | | 7 days<br>14 days<br>21 days | | 18 |
| *BUD 1600 μg/day (Mil A) | ↓54% | | 28 days | | 42 |
| *BUD 100 μg/day (Mil A)<br>BUD 400 mg/day | ↓29%<br>↓50% | | 28 days<br>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<br>↑ 24 ppb | | | 4 days15 days | 81 |
| BUD 8 mg nebulized (Mod A) | ↓31% | 6 h | | | 45 |
| BMP 1 mg/day (Mil A) | ↓28%<br>↑12% | | 7 days | 7 days | 82 |
| *BUD 100 mg/day (Mil A)<br>BUD 400 mg/day | ↓15%<br>↓27%<br>↓20%<br>↓7%<br>↓26%<br>↓38%<br>↓35%<br>↓44%<br>↓3% | | 5 days<br>7 days<br>21 days<br>3 days<br>5 days<br>7 days<br>21 days | 7 days<br>5 days | Kharitonov et al.<br>(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 $FEV_1$, 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 ($NO_3$-) 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 peroxynitrite, or S-nitrosothiols. The significance of these various oxidative processes depends on local levels of $NO_2$- and $O_2$- formation. Thus, autoxidation of NO with $O_2$ 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 $NO_2$-/$NO_3$- 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 $\beta_2$-agonists

The short-acting $\beta_2$-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 $\beta_2$-agonists, salmeterol, did not reduced NO in adults or children [9–11]. This is entirely consistent with the fact that inhaled $\beta_2$-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 $D_4$ 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 $PGE_2$, 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 $H_2O_2$, hypochlorous acid and peroxynitrite [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 $E_2$ and $F_{2a}$ 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 $PC_{20}$ in asthmatics treated with seratrodast, $TXA_2$ 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 |
| β2-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)<br>*Montelukast (Mil A)<br>*Montelukast (Mil A)<br>After end of treatment | ↓15%<br>↓20%<br>↓30%<br>↑ 19% | | 2 days<br>14 days<br>28 days | 14 days | 62<br><br>63 |
| 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 $\beta_2$-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 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].

*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)<br>*L-NMMA (Mil A) | ↓44%<br>↓40% | 15-45 min | 4 h | | |
| *L-NAME* (N)<br>*Aminoguanidine (Mil A)<br>*Aminoguanidine (N)<br>*Aminoguanidine (Mil A) | ↓53%<br>↓67%<br>↓28%<br>↓53% | 15-45 min<br><br>15-45 min | 4-6 h<br><br>4-6 h | | 34 |
| *L-NAME (Mil A) | ↓55% | 30 min | 2 h | | 35 |
| L-NMMA (N) (i.v.)<br>L-NAME (N) (Neb) | ↓10%<br>↓37% | 30 min<br>10 min | | | 36 |

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-naive 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 $\beta_2$-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-

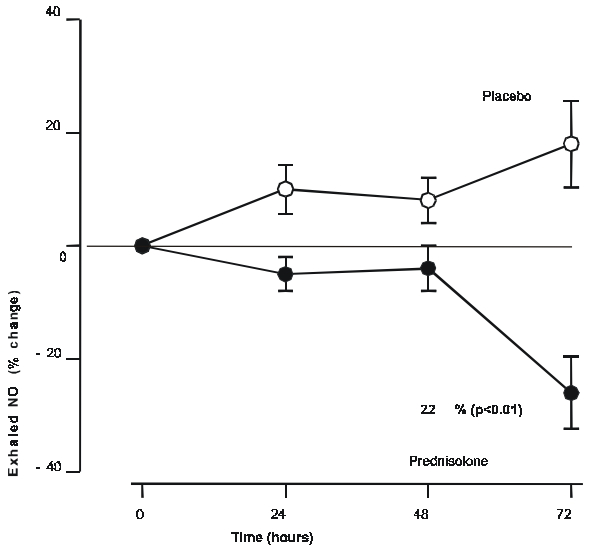


*Figure 1. The effect of inhaled prednisolone (30 mg/day) on exhaled nitric oxide (NO) in mild asthmatic patients (-□-) and normal subjects (-o-).*

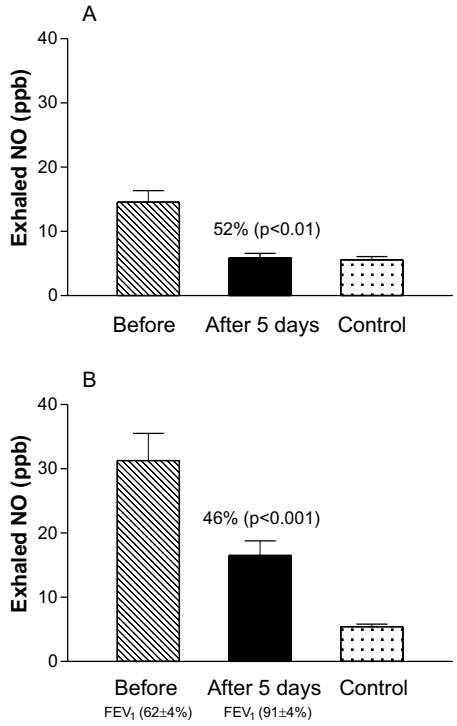


***Figure 2. The effect of oral prednisolone on exhaled NO in children with moderate-to-severe asthma.***
Panel A. Baraldi et al. AJRCCM 1999.
Panel B. Baraldi et al. J Pediatr 1997.

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

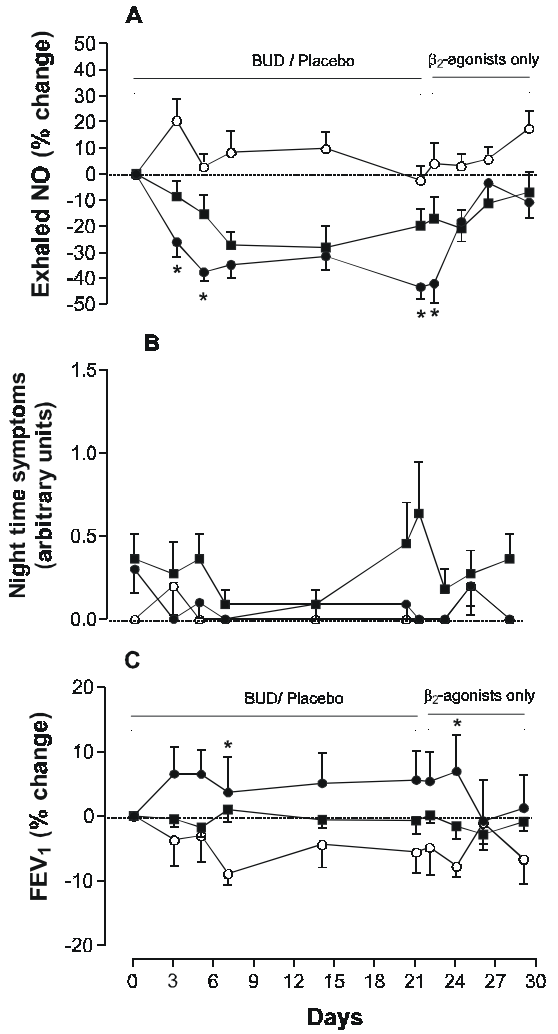


*Figure 3*

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 $FEV_1$ 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
$FEV_1$: forced exhaled volume in 1s
IL-5: interleukin-5
IL-8: interleukin-8
LPS: lipopolysaccharide
LT: leukotrienes
MPO: neutrophil myeloperoxidase
NO: nitric oxide
$PC_{20}$: provocative concentration of methacholine (histamine, or other spasmogen) causing a 20 % drop in $FEV_1$
PEF: peak expiratory flow
$SaO_2$: 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 their levels of $PC_{20}$ to methacholine [77]. Apart from small changes in $PC_{20}$ (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 sensitive 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 nanve 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.

REFERENCE LIST


1. *Hargreave F.E., Leigh R.* Induced Sputum, Eosinophilic Bronchitis, and Chronic Obstructive Pulmonary Disease. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 53–57.
2. *Nightingale J.A., Rogers D.F., Barnes P.J.* Effect of repeated sputum induction on cell counts in normal volunteers. // Thorax. — 1998. — № 53(2). — P. 87–90.
3. *Changes* in sputum composition between two inductions performed on consecutive days. / Holz O., Richter K., Jorres R.A. et al. // Thorax. — 1998. — № 53. — 83–86.
4. *The elevated* level of exhaled nitric oxide in asthmatic patients is mainly derived from the lower respiratory tract. / Kharitonov S.A., Chung F.K., Evans D.J. et al. // Am. J. Respir. Crit Care Med. — 1996. — № 153. — P. 1773–1780.
5. *Increased* formation of the potent oxidant peroxynitrite in the airways of asthmatic patients is associated with induction of nitric oxide synthase: effect of inhaled glucocorticoid / Saleh D., Ernst P., Lim S. et al. // FASEB J. — 1998. — № 12. — P. 929–937.
6. *Correlation* between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma / Jatakanon A., Lim S., Kharitonov S.A. et al. // Thorax. — 1998. — № 53. — P. 91–95.
7. *Detection* of inducible NO-synthase (iNOS) in sputum cells of healthy and asthmatic subjects / Holz O., Weng B., Mucke M. et al. // Am. J. Respir. Crit. Care. Med. — 1998. — № 157(3). — P. A612.
8. *Methods* for sputum induction and analysis of induced sputum: a method for assessing airway inflammation in asthma / Kips J.C., Fahy J.V., Hargreave F.E., Ind P.W. // Eur. Respir. J. Suppl. — 1998. — № 26. — P. 9S–12S.
9. *Yates D.H., Kharitonov S.A., Barnes P.J.* Effect of short- and long-acting inhaled $beta_2$-agonists on exhaled nitric oxide in asthmatic patients // Eur. Respir. J. — 1997 — № 10. — P. 1483 – 1488.
10. *Corticosteroids* decrease exhaled nitric oxide in children with acute asthma / Baraldi E., Azzolin N.M., Zanconato S. et al. // J. Pediatr. — 1997. — № 131. — P. 381–385.
11. *Effect* of salmeterol treatment on nitric oxide level in exhaled air and dose-response to terbutaline in children with mild asthma / Fuglsang G., Vikre J.J., Agertoft L., Pedersen S. // Pediatr. Pulmonol. — 1998. — № 25. — P. 314–321.
12. *Induction* of nitric oxide synthase in asthma / Hamid Q., Springall D.R., Riveros-Moreno V. et al. // Lancet. — 1993. — № 342. — P. 1510–1513.
13. *Barnes P.J., Liew F.Y.* Nitric oxide and asthmatic inflammation // Immunology Today. — 1995. — № 16. — P. 128–130.
14. *Increased* nitric oxide in exhaled air of asthmatic patients / Kharitonov S.A., Yates D.H., Robbins R.A. et al. // Lancet. — 1994. — № 343. — P. 133–135.
15. *Marshall H.E., Stamler J.S.* Exhaled Nitric Oxide (NO), NO Synthase Activity, and Regulation of Nuclear Factor (NF)-kappaβ // Am. J. Respir. Cell. Mol. Biol. — 1999. — № 21. — P. 296–297.
16. *Alving K., Weitzberg E., Lundberg J.M.* Increased amount of nitric oxide in exhaled air of asthmatics // Eur. Respir. J. — 1993. — № 6. — P. 1368–1370.
17. *Changes* in the dose of inhaled steroid affect exhaled nitric oxide

levels in asthmatic patients / Kharitonov S.A., Yates D.H., Chung K.F., Barnes P.J. // Eur. Respir. J. — 1996. — № 9. — P. 196–201.
18. *Kharitonov S.A., Yates D.H., Barnes P.J.* Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients // Am. J. Respir. Crit. Care. Med. — 1996. — № 153. — P. 454–457.
19. *Exhaled* NO is elevated in difficult asthma and correlates with symptoms and disease severity despite treatment with oral and inhaled corticosteroids / Stirling R.G., Kharitonov S.A., Campbell D. et al. // Thorax. — № 53. — P. 1030–1034.
20. *Comparison* of exhaled nitric oxide, serum eosinophilic cationic protein, and soluble interleukin-2 receptor in exacerbations of pediatric asthma / Lanz M.J., Leung D.Y., McCormick D.R. et al. // Pediatr. Pulmonol. — 1997. — № 24. — P. 305–311.
21. *Lanz M.J., Leung D.Y., White C.W.* Comparison of exhaled nitric oxide to spirometry during emergency treatment of asthma exacerbations with glucocorticosteroids in children // Ann. Allergy. Asthma. Immunol. — 1999. — № 82. — P. 161–164.
22. *Effect* of differing doses of inhaled budesonide on markers of airway inflammation in patients with mild asthma / Jatakanon A., Kharitonov S.A., Lim S., Barnes P.J. // Thorax. — 1999. — № 54(2). — P. 108–114.
23. *Nitric* oxide is present in exhaled breath in humans: direct GC- MS confirmation / Leone A.M., Gustafsson L.E., Francis P.L. et al. // Biochem. Biophys. Res. Commun. — 1994. — № 201. — P. 883–887.
24. *Kharitonov S.A., Alving K., Barnes P.J.* Exhaled and nasal nitric oxide measurements: recommendations // Eur. Respir. J. — 1997. — № 10. — P. 1683–1693.
25. *Anonymous* Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide in Adults and Children // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 2104–2117.
26. *Palmer R.M., Ferrige A.G., Moncada S.* Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor // Nature. — 1987. — № 327. — P. 524–526.
27. *Immunohistochemical* localization of nitric oxide synthase and the oxidant peroxynitrite in lung transplant recipients with obliterative bronchiolitis / McDermott C.D., Gavita S.M., Shennib H., Giaid A. // Transplantation. — 1997. — № 64. — P. 270–274.
28. *Expression* of inducible nitric oxide synthase and formation of peroxynitrite in posttransplant obliterative bronchiolitis / Mason N.A., Springall D.R., Pomerance A. et al. // J. Heart. Lung Transplant. — 1998. —№ 17 . — P. 710–714.
29. *Giaid A., Saleh D.* Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension // N. Engl. J. Med. — 1995. — № 333. — P. 214–221.
30. *Elevated* nitric oxide concentrations in isolated lower airway gas of asthmatic subjects / Massaro A.F., Mehta S., Lilly C. et al. // Am. J. Respir. Crit. Care Med. — 1996. — № 153. — P. 1510–1514.
31. *Primarily* nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome / Lundberg J.O., Weitzberg E., Nordvall S.L. et al. // Eur. Respir. J. — 1994. — № 7. — P. 1501–1504.
32. *Marked* flow-dependence of exhaled nitric oxide using a new technique to exclude nasal nitric oxide / Silkoff P.E., McClean P.A., Slutsky A.S. et al. // Am. J. Respir. Crit. Care Med. — 1997. — № 155. — 260–267.
33. *In Stable* Lung Transplant Recipients, Exhaled Nitric Oxide Levels Positively Correlate with Airway Neutrophilia and Bronchial Epithelial iNOS / Gabbay E., Haydn W.E., Orsida B. et al. // Am. J. Respir. Crit. Care. Med. — 1999. — № 160. — P. 2093–2099.
34. *Effect* of a nitric oxide synthase inhibitor and a glucocorticosteroid on exhaled nitric oxide / Yates D.H., Kharitonov S.A., Robbins R.A. et al. // Am. J. Respir. Crit. Care Med. — 1995. — № 152. — P. 892–896.
35. *Endogenous* nitric oxide is decreased in asthmatic patients by an inhibitor of inducible nitric oxide synthase / Yates D.H., Kharitonov S.A., Thomas P.S., Barnes P.J. // Am. J. Respir. Crit. Care Med. — 1996. — № 154. — P. 247–250.
36. *Effect* of nitric oxide synthesis inhibition with nebulized L-NAME on ventilation-perfusion distributions in bronchial asthma / Gomez F.P., Barbera J.A., Roca J. et al. // Eur. Respir. J. — 1998. — № 12. — P. 865–871.
37. *Exhaled* nitric oxide does not provide a marker of vascular endothelial function in healthy humans / Sartori C., Lepori M., Busch T. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160 — P. 879–882.
38. *Lack* of inhibitory effect of dexamethasone on exhalation of nitric oxide by healthy humans / Sato K., Sumino H., Sakamaki T. et al. // Intern. Med. — 1996. — № 35. — P. 356–361.
39. *Expired* nitric oxide levels during treatment of acute asthma / Massaro A.F., Gaston B., Kita D. et al. // Am. J. Respir. Crit. Care Med. — 1995. — № 152. — P. 800–803.
40. *Exhaled* nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children / Baraldi E., Dario C., Ongaro R. et al. // Am. J. Respir. Crit. Care. Med. — 1999. — № 159. — P. 1284–1288.
41. *Non-invasive* markers of airway inflammation as predictors of oral steroid responsiveness in asthma / Little S.A., Chalmers G.W., MacLeod K.J. et al. // Thorax. — 2000. — № 55. — P. 232–234.
42. *Effect* of inhaled budesonide on lung function and airway inflammation / Lim S., Jatakanon A., John M. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 159. — P. 22–30.
43. *An inhaled* steroid improves markers of airway inflammation in patients with mild asthma / Jatakanon A., Lim A., Chung K.F., Barnes P.J. // Eur. Respir. J. — 1998. — № 12. — P. 1084–1088.
44. *Effect* of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma / Van R.E., Straathof K.C., Veselic-Charvat M.A. et al. // Thorax. — 1999. — № 54. — P. 403–408.
45. *Kharitonov S.A., Barnes P.J., O'Connor B.J.* Reduction in exhaled nitric oxide after a single dose of nebulised budesonide in patients with asthma // Am. J. Respir. Crit. Care Med. — 1996. — № 153. — P. A799.
46. *Dexamethasone* increases survival and attenuates induction of inducible nitric oxide synthase in experimental skin flaps / Gribbe O., Lundeberg T., Samuelson U.E., Wiklund N.P. // Plast. Surg. — 1999. — № 42. — P. 180 – 184.
47. *Functional* assay of NF-kappaB translocation into nuclei by laser scanning cytometry: inhibitory effect by dexamethasone or theophylline / Tomita K., Chikumi H., Tokuyasu H. et al. // Naunyn Schmiedebergs Arch. Pharmacol. — 1999. — № 359. — P. 249–255.
48. *Eosinophils* transcribe and translate messenger RNA for inducible nitric oxide synthase / del Pozo V., de-Arruda C.E., de A.B. et al. // J. Immunol. — 1997. — № 158. — P. 859–864.
49. *Johnson M.* Development of fluticasone propionate and comparison with other inhaled corticosteroids // J. Allergy Clin. Immunol. — 1998. — № 101. — P. S434–S439.
50. *Systemic* Effects of Inhaled Fluticasone Propionate and Budesonide in Adult Patients with Asthma / Derom E., Van S.J., Verhaeghe W. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 157–161.
51. *Jeffery P.K.* Structural and inflammatory changes in COPD: a comparison with asthma. // Thorax. — 1998. — № 53(2). — P. 129–136.
52. *Neutrophilic* Inflammation in Severe Persistent Asthma / Jatakanon A., Uasuf C.G., Maziak W. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 1532–1539.
53. *Wilson N.M., James A.J., Bush A.* Exhaled nitric oxide in children with very severe asthma: response to two weeks of oral corticosteroids // ERJ. — 1998. — № 12. — P. 142S.
54. *Kelm M.* Nitric oxide metabolism and breakdown // Biochim.Biophys. Acta. — 1999. — № 1411. — P. 273–289.
55. *Reactive* Nitrogen Species and Tyrosine Nitration in the Respiratory Tract. Epiphenomena or a pathobiologic mechanism of disease // Van Der V.A., Eiserich J.P., Shigenaga M.K., Cross C.E. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 1–9.
56. *Ischiropoulos H.* Biological tyrosine nitration: a pathophysiological function of nitric oxide and reactive oxygen species // Arch. Biochem. Biophys. — 1998. — № 356. — P. 1–11.
57. *Nitrotyrosine* formation in the airways and lung parenchyma of patients with asthma / Kaminsky D.A., Mitchell J., Carroll N., James A. // J. Allergy Clin. Immunol. — 1999. — № 104. — P. 747–754.
58. *Changes* in bronchoalveolar lavage inflammatory cells in asthmatic patients treated with high dose inhaled beclomethasone dipropionate / Duddridge M., Ward C., Hendrick D.J., Walters E.H. // Eur. Respir. J. — 1993. — № 6. — P. 489–497.
59. *Increased* nitric oxide in nasal lavage fluid and nitrotyrosine formation in nasal mucosa—indices for severe perennial nasal allergy / Sato M, Fukuyama N, Sakai M, Nakazawa H. // Clin. Exp. Allergy. — 1998. — № 28. — P. 597–605.
60. *Exhaled* nitric oxide during acute changes of airways calibre in asthma / Garnier P., Fajac I., Dessanges J.F. et al. // Eur. Respir. J. — 1996. — № 9. — P. 1134–1138.
61. *Decreased* exhaled nitric oxide in mild persistent asthma patients treated with a leukotriene receptor antagonist, pranlukast / Kobayashi H., Takahashi Y., Mitsufuji H. et al. // Jpn. J. Physiol. — 1999. — № 49. — P. 541–544.
62. *Bisgaard H., Loland L., Oj J.A.* NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 1227–1231.
63. *Exhaled* nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: A preliminary study / Bratton D.L., Lanz M.J., Miyazawa N. et al. // Pediatr. Pulmonol. — 1999. — № 28. — 402–407.

64. *Yildiz G., Demiryurek A.T., Sahin-Erdemil I., Kanzik I.* Comparison of antioxidant activities of aminoguanidine, methylguanidine and guanidine by luminol-enhanced chemiluminescence // Br. J. Pharmacol. — 1998. — № 124(5). — P. 905–910.
65. *Prostaglandins* $E_2$ and $F_2$ reduce exhaled nitric oxide in normal and asthmatic subjects irrespective of airway calibre changes / Kharitonov S.A., Sapienza M.A., Barnes P.J., Chung K.F. // Am. J. Respir. Crit. Care Med. — 1998. — № 158. — P. 1374–1378.
66. *Prostaglandins* mediate bradykinin-induced reduction of exhaled nitric oxide in asthma / Kharitonov S.A., Sapienza M.M., Chung K.F., Barnes P.J. // Eur. Respir. J. — 1999. — № 14. — P. 1023–1027.
67. *Effects* of thromboxane $A_2$ antagonist on airway hyperresponsiveness, exhaled nitric oxide, and induced sputum eosinophils in asthmatics / Aizawa H., Inoue H., Nakano H. et al. // Prostaglandins Leukot. Essent. Fatty Acids. — 1998. — № 59. — P. 185–190.
68. *A dose-dependent* effect of the novel inhaled corticosteroid ciclesonide on airway responsiveness to adenosine-5'-monopho-sphate in asthmatic patients / Taylor D.A., Jensen M.W., Kanabar V. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 237–243.
69. *Time course* of change in bronchial reactivity with an inhaled corticosteroid in asthma / Vathenen A.S., Knox A.J., Wisniewski A., Tattersfield A.E. // American Review of Respiratory Disease. — 1991. — № 143. — P. 1317–1321.
70. *Administration* of budesonide once daily by means of turbuhaler to subjects with stable asthma / McFadden E.R., Casale T.B., Edwards T.B. et al. // J. Allergy. Clin. Immunol. — 1999. — № 104. — P. 46–52.
71. *Childhood* asthma: exhaled nitric oxide in relation to clinical symptoms / Artlich A., Busch T., Lewandowski K. et al. // Eur. Respir. J. — 1999. — № 13. — P. 1396–1401.
72. *Effect* of sputum induction on spirometric measurements and arterial oxygen saturation in asthmatic patients, smokers, and healthy subjects / Castagnaro A., Chetta A., Foresi A. et al. // Chest. — 1999. — № 116. — P. 941–945.
73. *Changes* in sputum composition during sputum induction in healthy and asthmatic subjects / Holz O., Jorres R.A., Koschyk S. et al. // Clin. Exp. Allergy. — 1998. — № 28. — № 284–292.
74. *Jatakanon A., Lim S., Barnes P.J.* Changes in sputum eosinophils predict loss of asthma control // Am. J. Respir. Crit. Care Med. — 2000. — № 161. — P. 64–72.
75. *Fractional* analysis of sequential induced sputum samples during sputum induction: evidence that different lung compartments are sampled at different time points / Gershman N.H., Liu H., Wong H.H. et al. // J. Allergy Clin. Immunol. — 1999. — № 104. — P. 322–328.
76. *Eosinophilic* inflammation assessed by induced sputum in corticosteroid-dependent asthma / Tarodo P., Romagnoli M., Carlsson L. et al. // Respir. Med. — 1999. — № 93. — P. 183–189.
77. *Clinical* control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group / Sont J.K., Willems L.N., Bel E.H. et al. // Am. J. Respir. Crit. Care Med. — 1999 — № 159. — P. 1043–1051.
78. *Induced* Sputum Eicosanoid Concentrations in Asthma / Pavord I.D., Ward R., Woltmann G. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. — P. 1905–1909.
79. *Increased* 8-Isoprostane, a Marker of Oxidative Stress, in Exhaled Condensate of Asthma Patients / Montuschi P., Corradi M., Ciabattoni G. et al. // Am. J. Respir. Crit. Care Med. —1999. — № 160. — P. 216–220.
80. *Breath* condensate analysis of 8-isoprostane: a new approach for assessment of oxidative stress in patients with chronic obstructive pulmonary disease / Montuschi P., Corradi M., Ciabattoni G. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 159. — P. A798.
81. *Interleukin*-4 Receptor in Moderate Atopic Asthma. A phase i/ii randomized, placebo-controlled trial / Borish L.C., Nelson H.S., Lanz M.J. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 160. P. 1816–1823.
82. *Exhaled* nitric oxide and bronchial reactivity during and after inhaled beclomethasone in mild asthma / Silkoff P.E., McClean P.A., Slutsky A.S. et al. // J. Asthma. — 1998. — № 35. — P. 473–479.
83. Down-regulation of nitric oxide production by ibuprofen in human volunteers / Vandivier R.W., Eidsath A., Banks S.M. et al. // J. Pharmacol. Exp. Ther. — 1999. — № 289. — P. 1398 – 1403.
84. Y*ates D.H., Kharitonov S.A., Barnes P.J.* Effect of short- and long-acting inhaled $beta_2$-agonists on exhaled nitric oxide in asthmatic patients // Eur. Respir. J. — 1997. — № 10. — P. 1483–1488.
85. *Exhaled* nitric oxide after $beta_2$-agonist inhalation and spirometry in asthma / Silkoff P.E., Wakita S., Chatkin J. et al. // Am. J. Respir. Crit. Care Med. — 1999. — № 159. — P. 940–944.

## 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 $\beta_2$-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 $b_2$-agonists, leukotriene antagonists, iNOS inhibitors, prostaglandins and other drugs), their influence on the exhaled NO, use of the exhaled NO measurments and other methodics of Asthma Monitoring (induced sputum, it's combination with exhaled NO measurments, their advantages and lack, future directions also gived in this paper.