# NITRIC OXIDE – MARKER OF AIRWAY INFLAMMATION IN ASTHMA AND ITS INFLUENCE ON BASIC THERAPY

**IULIA-IDA SIMINA[1], MIHAI-LEONIDA NEAMȚU[2]**

*[1]Pediatric Hospital Sibiu, Research Centre in Pediatric Respiratory Medicine, "Lucian Blaga" University of Sibiu, [2]"Lucian Blaga" University of Sibiu*

***Keywords:*** *asthma, chronic inflammation, exhaled nitric oxide, corticosteroids, immunomodulators*

***Abstract:*** *Asthma is a chronic inflammatory airway abnormality. Special emphasis is placed on monitoring allergic inflammation of the airways in asthma. A current method for this purpose is the determination of nitric oxide in exhaled air. This method has a number of advantages: it can detect eosinophilic airway inflammation, it can indicate airway response for the inhaled corticosteroid (it is a predictive factor for the response to inhaled corticosteroids - NO decreases with its administration), it can predict exacerbations (NO increases before asthma exacerbations), it allows the adjustment of the doses of inhaled corticosteroids, it detects the patients which are non-responsive to corticosteroid therapy, it is a viable and noninvasive marker of the airway inflammation, which allowed that the analysis and monitoring asthma be secure, fast and very simple. A progress is recorded in the study of two major classes of drugs, currently, used for the background therapy of asthma: inhaled corticosteroids and leukotriene inhibitors. The therapeutical results of this therapy in the inflammatory process correlate with the levels of nitric oxide in exhaled air.*

***Cuvinte cheie:*** *astm bronșic, inflamație cronică, oxid nitric exhalat, corticoterapie, imunomodulatoare*

***Rezumat:*** *Astmul bronșic este o anomalie inflamatorie cronică a căilor aeriene. Un accent deosebit se pune pe monitorizarea inflamației alergice de la nivelul căilor respiratorii în astm. O metodă de actualitate în acest sens o reprezintă dozarea oxidului nitric în aerul expirat. Această metodă prezintă o serie de avantaje: poate detecta inflamația eozinofilică a căilor aeriene, indica răspunsul căilor aeriene la corticoterapia inhalatorie (factor predictiv pentru răspunsul la corticoterapia inhalatorie - NO↓ pe măsura administrării acesteia), prezice exacerbările (NO- înaintea exacerbărilor astmatice), permite ajustarea dozelor de corticoizi inhalatori, depistează pacienții non-responsivi la terapia corticosteroidă, este un marker viabil, neinvaziv, al inflamațiilor căilor aeriene, care permite ca analiza și monitorizarea să fie sigure, rapide și simple. Un deosebit progres se înregistrează în studiul a două mari clase de medicamente utilizate la ora actuală în tratamentul de fond al astmului bronșic: corticoterapia inhalatorie și inhibitorii de leucotriene. Răsunetul acestei terapii în cadrul procesului inflamator se corelează cu nivelele oxidului nitric în aerul expirat.*

Asthma is a "chronic inflammatory airway abnormality, that involves many cells, including eosinophils and mast cells; for the susceptible person, this inflammation generates symptoms that are usually associated with large and variable airway obstruction, which is often reversible either spontaneously or with treatment, and increases airway reactivity to various allergens".(7) (Bethesda International Consensus 1992)

Asthma has been described since the time of Hippocrates, mentioned by Homer in the Iliad and known by ancient Chinese, who treated this disease with a plant containing ephedrine.

Asthma is a public health problem for both, developed countries and especially for the developing and underdeveloped countries. From 1950 until today, the number of asthmatics increased by 60%. According WHO - 300 million people worldwide suffer from asthma and it is estimated that number will increase to 100 million in 2025.

Asthma is the most common chronic disease of children. In Romania, the prevalence is 7% according to the WHO, and for children below 15 years old, there has been seen an increase in the prevalence of asthma by 41% since 1950 to the present days. The number of deaths from asthma in Romania reached about 4400 per year.

The importance and relevance of the theme are highlighted by international guidelines -GINA, ISAAC, ARIA, which developed effective strategies for prevention and control of asthma. A ICES study (Institute for Clinical Evaluative Sciences) conducted in Ontario and published in February 2010 that evaluated the risk of asthma, reveals that one in three people can expect to be diagnosed with asthma at some point during life, and asthma is likely to begin in childhood.

The methods of evaluating the pulmonary obstructive pathology are numerous. Special emphasis is placed, however, for the monitoring of allergic inflammation in the airways. A current method in this regard is the evaluation of nitric oxide (NO) in exhaled air.

This studied problem has one of the great interest among numerous medical scientific articles, as Pediatric Pulmonology 2008 – "exhaled nitric oxide for monitoring childhood asthma inflammation compared to sputum analysis, serum interleukins and pulmonary function", or "Clinical Practice Guidelines on Fractional exhaled Nitric Oxide Interpretation of (FENO) Levels" in Science Daily (September

[1]Corresponding author: Simina Iulia-Ida, Str. Bihorului, Nr. 5/18, Sibiu, Romania, E-mail: iulia.simina2011@gmail.com, Tel:+40740 316104
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1, 2011).

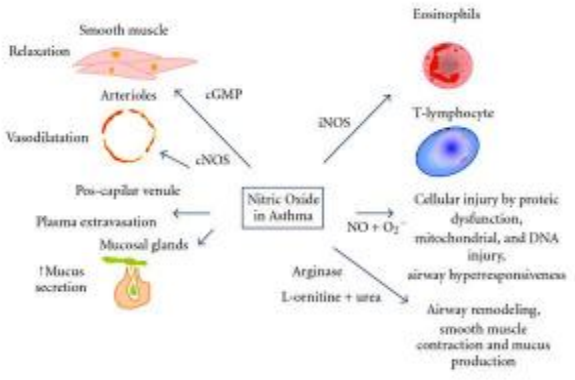
NO or endothelial relaxing factor is produced by endothelial cell under the action of NO synthase from L-arginine, molecular oxygen and NADPH. NO-synthase is activated during the inflammatory process, by proinflammatory cytokines (such as cytokines of macrophages).(10) NO that results from these reactions is a potent selective pulmonary vasodilator.(10)

To better understand the relation between high levels of NO and airway inflammation in patients with asthma (chronic inflammatory process), it is important to understand the imunopathogenesis and some notions related to asthma. The inflammatory cells involved in the pathogenesis of asthma and NO production are: mast cells, eosinophils, lymphocytes and epithelial cells of the respiratory mucosa. Th2-CD4 + lymphocytes (which induce the synthesis of specific IgE-mediated by IL-4) are the most numerous cells in pulmonary fluid in acute asthma.(16)

The inflammatory response is taking place in two phases: rapid or acute phase (minutes), in which the protagonists are cells (mast cell, lyTh2, eosinophils, neutrophils) and inflammatory mediators (histamine, bradykinin, leukotrienes, etc.) and late phase or chronic (4 -8 hours, with the persistence of 12-24 hours or more) in which the protagonists are other cells (endothelial cells, muscle cells).(2,6,14)

Eosinophil and neutrophil chemotactic factors of anaphylaxis (released by mast cells) attract the eosinophils, platelets and neutrophils at the site of the inflammatory reaction. The infiltrating cells themselves and the epithelium are additional sources of mediators and cytokines: endothelin-1, nitric oxide, PGE 2, GM-CSF, IL-8, Rantes (a chemotactic factor for memory T cells and macrophages) and eotaxin (produced by epithelial cells, the most potent chemotactic and activating factor for eosinophils).(14)

**Figure no. 1. NO - inflammatory biomarker with dual effect (benefits and side effects) in the pathology of asthma**




*Source: http: //www.hindawi.com/journals/isrn/2011/832560/fig2/*

In conclusion, the relation between high levels of NO and airway inflammation in patients with asthma is this – asthma is a chronic inflammatory process "orchestrated" by the Ly T CD4 + Th2 type which, through the release of pro-inflammatory cytokines (IL-4, IL-5, IL-13, etc.) leading to activation of macrophages and thereby the activation of NO-synthatase with subsequent release of NO.(8) Values of NO > 35 ppb means that the inflammation is eosinophilic and that is likely that will occur responsiveness to inhaled corticosteroids, NO = 20-35 ppb is interpreted according clinical context (according to symptoms), and the values of NO <20 ppb (normal value) suggests that the inflammation is not eosinophilic and that responsiveness to inhaled corticosteroids is likely not to occur.

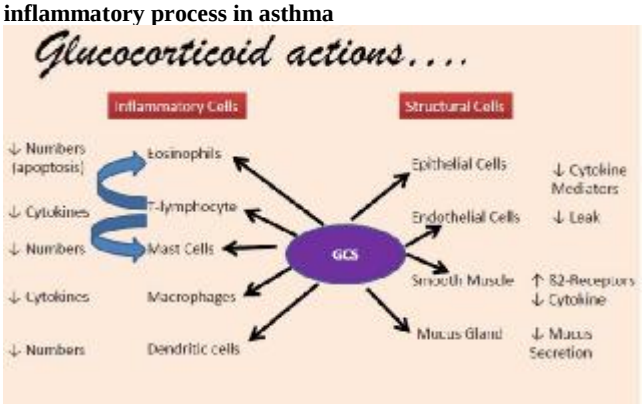
The pathogenesis of asthma is increasingly to be well understood, but also it is very dynamic. Therefore, new classes of drugs are being developed. Many studies attempt to demonstrate the effectiveness of different classes of drugs, and side effects of these therapies in children with chronic asthma.

A great progress is being made in the study of two major classes of drugs used in present as basic therapy in asthma: inhaled corticosteroids and leukotriene inhibitors, medication which is recommended from the initial stages of the disease. There are studies demonstrating a decrease in the frequency of symptoms and nocturnal attacks in both cases (inhaled corticosteroids and leukotriene inhibitors). However, there are conflicting data regarding the action of montelukast on FEV1 or data supporting the effectiveness of inhaled corticosteroid (most of the literature). (NPC study "Montelukast Sodium Oral vs. Inhaled Fluticasone Propionate in Mild Persistent Asthma", 2008).

Inhaled corticosteroid (fluticasone, budesonide, ciclesonide, mometasone etc.) are background therapy in mild and medium stages of asthma.(17) Advantages of inhaled corticosteroid are – inhallatory doses are about 10-20% of the systemic doses, are better tolerated, have bronhoselectivity, effectively pronounced adverse effects are low compared to other methods of administrating the treatment (oral, injection.- reserved for severe cases) .

The mechanisms of inhaled corticosteroids are: they interfere with the metabolism of arachidonic acid and prostaglandin and leukotrienes synthesis and reduce the extravasation of plasma from the capillaries, inhibit the production and secretion of cytokines, prevent the migration and activation of inflammatory cells, increase responsiveness to β2-receptors in the smooth muscle fibres of the airways.

**Figure no. 2. Effects of glucocorticoid therapy on the inflammatory process in asthma**




*Source: http://www.intechopen.com/source/html/41142/media/image1_w.jpg*

The effect of corticosteroids on the pathophysiological process in asthma: decrease bronchial obstruction by reducing edema and bronchial hypersecretion, reduce airway responsiveness, improve the tolerance of the body during the effort, prevent or delay chronic inflammatory organization at the level of the bronchial tissues (= source of cytokines that activate NOS of the macrophages that increase the production of NO), prevent or delay tissue remodelling (14,15), improving prognosis and quality of life.

As with systemic therapy, treatment with inhaled corticosteroid, is not without side effects, but they are much lighter and do not affect only just a little the quality of life of patients with asthma.

The effectiveness of inhaled corticosteroid as background or basic therapy in asthma was evaluated in numerous studies. Resuming the background modulation therapy of asthma, by the correlations with the values of nitric

oxide in exhaled air, clinical studies have demonstrated the following aspects:

- Increased NO by 20% compared with a previous determination in patients with initial NO> 35 ppb means the absence of the response to corticosteroids and the persistence of the inflammatory process;(10)
- NO levels declined by 20% compared with a previous determination in patients with initial NO> 35 ppb means a good answer to the inhaled corticosteroids and the decrease of inflammation.(10)

The identification of the main types of interleukins involved in the pathogenesis of asthma paved the way for modern therapies. Immunomodulatory (leukotriene inhibitors) drugs are a new class of drugs that in asthma are primarily addressed to the immune inflammation by antagonizing proinflammatory mediators.

Leukotriene inhibitors (montelukast) are inhibitors of 5-lipoxygenase pathway. This enzyme determines the generation of arachidonic acid products (cistenil-leukotrienes), products that play a major role in the pathophysiology of asthma. Leukotrienes (LTB4, LTC4, LTD4) increase the expressiveness of the eosinophil adhesion proteins, activate the release of mediators from granules of eosinophils, neutrophils and enhance the effects of neutrophils and eosinophils. The result is increased levels of interleukins in the pulmonary tissue. A major role is given to IL-13.

IL-13 is a glycoprotein secreted by activated LyT predominantly by LyTh2CD4 +, LyTCD8+ and LyT-NK. Moreover, this cytokine is produced also bz non-T cell populations: eosinophils, basophils, mast cells. IL-13 is a potent stimulator of metalloproteinases and cathepsin proteases in the lung, resulting emphysematous changes and metaplasia. On the nitric oxide synthethase, IL-13 plays a role of a stimulator resulting increased values of NO.

Regardless of the therapeutic approach, regular monitoring is essential for the patients with asthma, to assess the development of this chronic disease. It is necessary to evaluate the condition of small airways or the degree of bronchiolar obstruction and pathological changes that occur after a period of the disease (bronchial remodelling).

In this regard, numerous studies are pursuing the development of protocols for the determination of the ideal parameters (easily determined by non-invasive methods) which can help physicians and patients to modulate asthma therapy. This is the purpose of this article, to demonstrate the following assumptions:

- exhaled nitric oxide indicates the eosinophilic inflammation of the airway,
- exhaled nitric oxide indicates the response of the airway to inhaled corticosteroids,
- exhaled nitric oxide can help to adjusts the corticotherapy doses,
- exhaled nitric oxide can detect the patients which are non-responsive to corticosteroid therapy,
- exhaled nitric oxide is a viable and non-invasive marker of airway inflammation,
- exhaled nitric oxide allows that the analysis and the monitoring of disease progression and also the monitoring of the treatment to be secure, fast, and simple.

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