EXHALED NITRIC OXIDE IN PEDIATRIC ASTHMA – CERTITUDES AND PERSPECTIVES

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ABSTRACT

The exhaled nitric oxide measurement is one of the methods used in bronchial inflammation assessment. Relatively new, this measurement is non-invasive and more and more accessible, thus even the pediatric patients are able to benefit. The authors are making a brief history followed by the technical details of the measurement and the practical use for the diagnosis and therapy monitoring in bronchial asthma.

Keywords: nitric oxide, asthma, child

Asthma and associated diseases have a major impact on general health, including the pediatric population (1). The pathophysiology of asthma is based on two major components: bronchial hyperactivity and bronchial inflammation, both are still „hot topics" in asthma study. The evaluation of pulmonary volumes and flows are based on „classical" methods, where the progress is achieved mainly by punctual technological advance. The study of inflammation (bronchial and/or respiratory) has become extremely attractive during the past decades.

Many molecules have been discovered lately having a place in bronchial inflammation, so the manner of study has become more complex. One of the classifications used is based on invasivity.

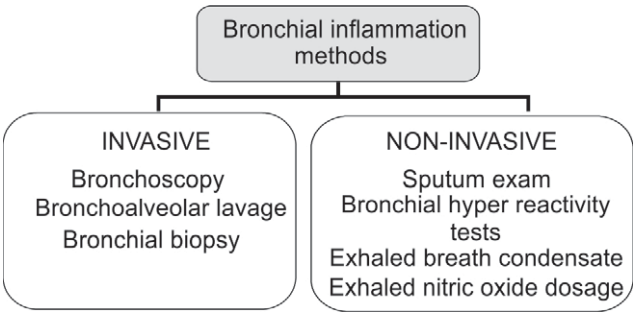

FIGURE 1. *Methods used for bronchial inflammation monitoring*

HISTORICAL DATA

The medical history of exhaled nitric oxide (FeNO) begins during the last decade of the XX century, in Karolinska Institute, Stockholm, Sweden, where professor Gustafsson identified the nitric oxide as a key marker in airway inflammation (2). Two years later, prof. K. Alving identified high nitric oxide levels in asthmatic patients, which lead to the clinical applications of the molecule. The first nitric oxide analyzer was introduced in 1999 with the diagnostic guidelines produced by American Thoracic Society (ATS).

The research continued until 2005 when a joint statement was issued by ATS and ERS (European Respiratory Society). This paper represents until today the main statement used by professionals dealing with exhaled nitric oxide in children or adults (3). In 2008 the Food and Drug Administration (FDA) approved the clinical use of the first portable device for exhaled nitric oxide.

During 2011 ATS issued a new clinical practice guideline which emphasized the clinical utility of FeNO, offering new diagnostic tools and cut-off values, as well as new approaches regarding the treatment monitoring in asthma and related diseases (4).

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Although most of the measurements are made in adult pathology, more and more children are now included in nitric oxide screening and in clinical trials with high statistical power.

TECHNICAL DATA

The FeNO measuring was initially made by chemoluminescence, which are still considered „*gold standard*", but requires expensive and voluminous devices. The portable equipment are based on electrochemical sensors (NIOX MINO, Aerocrine, Solna, Sweden is widely used), thus the measurement became more accessible, maintaining a high accuracy rate (5,6). Unlike the spirometers, the portable devices used for FeNO monitoring need no maintenance, but they have a limited life span (3 years in NIOX MINO) and this requires a new investment.

The method of measurement is based on maximal inspiration at total lung capacity, followed by continuous expiration until the patient is reaching a plateau of 50 ml/sec for 6-10 seconds. This pattern is necessary because the FeNO level depends on expiratory flow. The results are measured in ppb (parts per billion). The ATS/ERS guide (3) recommends two consecutive measurements, followed eventually by a third one (if the difference is more than 10%). There are also age limitations, the children below 5 yrs are less compliant and the data obtained have to be interpreted cautiously. Recently, some authors published data for the children aged 1 to 5 (7), but there are only few centers where the measurement can be made.

FACTORS AFFECTING THE FENO LEVELS

There are many studies regarding the circumstances affecting FeNO, thus the measurement is still on debate in asthma management.

TABLE 1. *Factors influencing FeNO measurements (8)*

Increase	*Decrease*	*Unclear*
Age	Active smoking	Passive smoking
Male	Spirometric maneuvers	Physical exercise
Height	Bronchial provocation	Chromones
Atopy	Corticoids	Methylxantines
Asthma	Leucotriene antagonists	
Nitrate (ie. from food)	Anti-IgE drugs	

Other researchers found out that age and sex seemed to have no influence in FeNO levels, at list in pediatric patients (9) and the respiratory tract infections may have a both way influence (3). The relationship with asthma and/or atopy is still controversial: some studies found a correlation between high FeNO levels and atopic status, independent of asthma (10,11), other researchers are suggesting that only the atopic asthma is associated with an increase in FeNO levels (12). Smoking is also in debate: certain authors suggest that FeNO and cigarette smoke are correlated only in atopic asthma (other kind of asthma are not influenced) (13).

THE PRACTICAL UTILITY

The medical literature offers „*normal*" values for FeNO in adults (14) and children (7,15), but we have so many confounding factors that the clinical significance in relative. This is why the last ATS guide proposes some clinical relevant cut points (4):

1. FeNO levels below 25 ppb (20 ppb in children less than 12) – the eosinophilic inflammation and the responsiveness to inhaled corticoid treatment are unlikely.
2. FeNO levels over 50 ppb (35ppb in children) eosinophilic inflammation and responsiveness to inhaled corticoid treatment are likely.
3. Levels between 25 and 50 ppbb (20-35 ppb in children) must be interpreted taking into account the clinical data.
4. A FeNO increase of more than 20% and over 25 ppb (20 ppb in children) is considered significant, but there are many individual specific features.
5. The efficacy of anti-inflammatory treatment is proved by a reduction of 20% in FeNO levels, usually after 2 to 6 weeks after initiation.

FENO AND GINA GUIDE

The GINA (Global INitiative for Asthma) guide has been recently reviewed (16), with special sections dedicated to nitric oxide. The authors are reluctant about FeNO usage for treatment monitoring due to the conflicting data gathered from literature. Also, there are no long term studies regarding the FeNO monitoring and withholding the steroid treatment. Regarding the children, the FeNO monitoring is recommended in predicting physician diagnosed asthma in children by school age. The guide also emphasizes that the method is still not widely available.

CONCLUSIONS

Although initially FeNO measurement seemed to be an excellent alternative for the investigations

needed in asthma management, today the general opinion is somehow reluctant. There are two main goals to be achieved: diagnostic correlation with the eosinophilic inflammation and the relationship with the inhaled corticosteroid treatment. Both are still controversial due to the high number of the confounding factors, the elevated inter-individual variability and lacking a precise and universal standard of measurement. Yet the medical community is still preoccupied by the matter, the number of published articles, including the pediatric ones, is steadily increasing during the last years.

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