ORIGINAL ARTICLE

THE INFLUENCE OF CONTROLLER THERAPY ON CORRELATION BETWEEN FeNO AND ASTHMA CONTROL IN CHILDREN

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Abstract

Asthma is a chronic inflammatory disorder of the respiratory tract. Asthma control is directly related to bronchial inflammation control and therefore a major component in the treatment of asthma is the anti-inflammatory controller therapy. FeNO (fractionated exhaled nitric oxide) is a non-invasive marker of atopy and bronchial inflammation and therefore might be useful as objective marker of asthma control. The aim of this study was to assess the way the controller therapy influences the correlation between FeNO value and asthma control in children. For this purpose a prospective study was initiated which included asthmatic children with FeNO measurements and asthma control status assessment, recording also if the patient was receiving or not controller therapy at the moment of the evaluation. Further, the correlation between FeNO value and asthma control status was evaluated, individually for patients who received or not controller therapy. For each of these categories the correlation was also evaluated according to atopy. The results indicate that in children FeNO is correlated with asthma control only in atopic patients receiving controller therapy.

Rezumat

Astmul bronşic este o boală inflamatorie cronică a aparatului respirator. Controlul astmului este direct legat de controlul inflamaţiei bronşice şi de aceea o componentă majoră a tratamentului astmului bronşic este terapia antiinflamatorie de tip *controller*. FeNO (*fractionated exhaled nitric oxide*) este un *marker* neinvaziv al atopiei şi al inflamaţiei bronşice şi de aceea ar putea fi util ca *marker* obiectiv al stării de control. Scopul studiului a fost evaluarea influenţei terapiei de tip *controller* asupra corelaţiei dintre valoarea FeNO şi controlul astmului la copil. În acest scop a fost iniţiat un studiu prospectiv care a inclus copii cu astm bronşic la care s-a măsurat FeNO şi s-a evaluat starea de control al astmului, notând de asemenea dacă pacientul primea sau nu tratament de tip *controller* la momentul evaluării respective. Ulterior s-a evaluat gradul de corelaţie dintre valoarea FeNO şi starea de control, separat pentru pacienţii care primeau şi pentru cei care nu primeau tratament de tip *controller*. Pentru fiecare categorie corelaţia a fost evaluată şi în funcţie de prezenţa sau nu a atopiei. Rezultatele obţinute au evidenţiat faptul că la copil, FeNO se corelează cu starea de control al astmului doar la pacienţii atopici care primesc terapie de tip *controller*.

Keywords: inflammation, asthma control, FeNO (fractionated exhaled nitric oxide), controller therapy

Introduction

Asthma is the most common chronic disease during childhood having prevalence among children of 9.3% in USA and between 5 and 27% in Europe [1-4].
The central pathogenic component of asthma is bronchial inflammation which is both genetic and environmental conditioned [2].
Bronchial inflammation is closely related to bronchial hyperresponsiveness and is underlying both the acute physiopathological changes (bronchospasm, mucosal oedema, mucus plugs), but also the chronic, irreversible changes (bronchial remodelling) [2].
The objective of asthma management is to maintain the controlled asthma status while limiting the side effects of the treatment [2].
The controlled asthma status involves lack of symptoms, minimum reliever medication intake, normal pulmonary function, control over future asthma attacks, over pulmonary function decline and over treatment side effects. In other words asthma control involves bronchial inflammation control [2].
That is the reason for the controller anti-inflammatory therapy to be a major component of asthma treatment [2].
Asthma treatment involves reliever therapy and controller therapy [5].
Reliever therapy (usually inhaled salbutamol, a bronchodilator which is a short acting beta agonist) provides a rapid relief of the symptoms and is used as needed by all patients with asthma [5].

Reliever therapy as needed is the equivalent for step 1 of asthma therapy as recommended by Global Strategy for Asthma Management and Prevention Guideline [5].

Reliever therapy is the only therapy for patients with intermittent asthma or for patients with persistent asthma which remain controlled after stepping down until completely stop the controller therapy [5].

Controller therapy is a daily taken medication and consists in anti-inflammatory therapy (inhaled corticosteroids, oral corticosteroids, leukotriene receptor antagonists, anti IgE antibody) and bronchodilator therapy (long acting beta agonist, theophylline) [5].

Controller therapy is equivalent for step 2, 3, 4 and 5 of asthma therapy as recommended by Global Strategy for Asthma Management and Prevention Guideline [5].

A higher step involves a higher dose and/or an association of more drugs. The treatment is stepped up until the controlled asthma status is achieved [5].

Controller therapy is recommended for patients with persistent asthma until the controlled asthma is maintained for at least 3-6 months; afterwards it can be gradually tapered (step down) until complete stop [5].

FeNO (fractionated exhaled nitric oxide) is a non-invasive marker of atopy and bronchial inflammation and therefore might be a useful marker of asthma control [6-10].

Nitric oxide is produced by nitric oxide synthase (NOS), an enzyme with three isoforms. NOS II or iNOS (inducible isoform), which resides in epithelial and endothelial cells, macrophages, neutrophils and smooth muscle cells of the respiratory tract, is up-regulated by proinflammatory cytokines, viruses, allergens, polluting substances, etc. and is suppressed by corticosteroids [11-14].

Materials and Methods

A prospective study including 108 children diagnosed with asthma and monitored in „Victor Gomoiu" Children Clinical Hospital between April 2012 and September 2014 was conducted.

Inclusion criteria were: age between 5 and 18 years; and asthma diagnosis established using specific criteria issued out of history and clinical exam; diagnosis was confirmed by proving FEV1 (forced expiratory volume in 1 second) reversibility of at least 12% after salbutamol inhaling.

Exclusion criteria: other comorbidities.

The study was approved by the Ethics Committee of „Victor Gomoiu" Children Clinical Hospital. For all children included in the study, the written consent was obtained from the parents for using medical data, ensuring privacy and identity protection of the subjects.

After confirming the diagnosis, asthma form was established for each patient (intermittent or persistent) and an asthma control plan was handed to each of them.

The asthma control plan contained personalized prescriptions and recommendations for asthma, including reliever therapy prescription for patients with intermittent asthma and both controller and reliever therapy prescription for patients with persistent asthma.

Atopy was detected using skin allergy tests and/or total serum IgE value.

An asthma monitoring plan, written according to "Global Strategy for Asthma Management and Prevention", Global Initiative for Asthma 2012, was prescribed for each patient [5]. This plan included:

1. for intermittent asthma patients: one evaluation at one month, then 3, 6 and 12 months after the diagnosis and as needed;
2. for persistent asthma patients: one evaluation at one week, 1, 3, 6 months after the diagnosis was established and the controller therapy was initiated, after the therapy was stepped-up up or stepped-down and whenever necessary.

Each evaluation included a recall of the recent history of symptoms, counting the daytime and nocturnal symptoms, the degree of activity limitation and the need of reliever treatment (inhaled short acting bronchodilator) in the last month. At the same time FEV1 was measured using spirometry.

Using all information presented above the asthma control status was established recording for each evaluation and each patient if he was controlled, partially controlled or uncontrolled.

At each evaluation was registered if the patient was receiving controller therapy (≥ step 2) or only reliever therapy (step 1).

For uncontrolled or partly controlled patients we have prescribed specific recommendations (triggers control, controller medication step-up, etc.).

At the same time we have measured FeNO value using NIOX-MINO device with mouth piece, a chemiluminescence analyser approved for exhaled nitric oxide measurement [3, 5]. FeNO value in children is considered normal ≤ 20 ppb in children under 12 years and ≤ 25 ppb in children aged 12 years and older.

A total of 207 evaluations were recorded.

Finally we have assessed the correlation between asthma control status and FeNO value on the assumption that controlled asthma should be related to a normal FeNO value and uncontrolled or partly controlled asthma should be related to an increased FeNO value, using Kruskal-Wallis nonparametric Test. A p value < 0.05 was considered statistical significant.

Results and Discussion

Correlation between FeNO and asthma control in patients receiving only step 1 therapy

In patients receiving only step 1 therapy 77 evaluations were recorded. In this subgroup the lowest value recorded for FeNO was 5 ppb and the highest 129 ppb with a mean value of 26.35 ppb as presented in Table I.

Table I

FeNO value distribution in patients receiving only step 1 therapy

	N	Range (media Min-Max)	Min	Max	Mean	Std. Deviation	Variance
FeNO	77	124	5	129	26.35	22.084	487.704
Measurements	77						

Among patients receiving only step 1 therapy and in which FeNO value was assessed, 24 patients were controlled with a mean rank of FeNO values of 39.44 ppb, 16 were partly controlled with a mean rank of FeNO values of 31.44 ppb, and 37 were uncontrolled with a mean rank of FeNO values of 41.99 ppb, as depicted in Table II.

Table II

FeNO value distribution in patients receiving only step 1 therapy

Control		Evaluation	Mean Rank
FeNO	**Controlled**	24	39.44
	Partial controlled	16	31.44
	Uncontrolled	37	41.99
	Total	77	

Using Kruskal-Wallis nonparametric Test to assess the correlation between the mean ranks of FeNO values and asthma control status in patients receiving only step 1 therapy, the results indicate that the correlation is not statistically significant ($p = 0.287$). This means that among patients receiving only step 1 therapy the mean rank of FeNO values in the controlled asthma subgroup is not significantly smaller than the mean rank of FeNO values in the partly controlled and uncontrolled asthma subgroups.

Correlation between FeNO and asthma control in atopic patients receiving only step 1 therapy

In atopic patients receiving only step 1 therapy 58 evaluations were recorded. In this subgroup the lowest FeNO value recorded was 5 ppb, while the highest value was 129 ppb with an average of 29.55 ppb as presented in Table III.

Table III

FeNO value distribution in atopic patients receiving only step 1 therapy

	N	Range (media Min-Max)	Min	Max	Mean	Std. Deviation	Variance
FeNO	58	124	5	129	29.55	22.100	488.427
Measurements	58						

Among atopic patients receiving only step 1 therapy who were evaluated for FeNO value, 17 patients were controlled with an average for FeNO values of 27.5 ppb, 10 were partly controlled with an average for FeNO values of 25.15 ppb, and 31 were uncontrolled, having the mean FeNO values of 32 ppb, as depicted in Table IV.

Table IV

Mean values for FeNO according to asthma control status in atopic patients receiving only step1 therapy

Control		N	Mean Rank
FeNO	**Controlled**	17	27.50
	Partial controlled	10	25.15
	Uncontrolled	31	32.00
	Total	58	

Using Kruskal-Wallis nonparametric Test to assess the correlation between the mean FeNO values and asthma control status in atopic patients receiving only step 1 therapy, the results indicate that the correlation is not statistically significant ($p = 0.611$). This means that among atopic patients receiving only step 1 therapy the mean FeNO values in the controlled asthma subgroup are significantly lower than the average of FeNO values in the partially controlled and uncontrolled asthma subgroups.

Correlation between FeNO and asthma control in patients receiving ≥ step 2 therapy

In patients receiving ≥ step 2 therapy 130 evaluations were recorded. In this subgroup the lowest FeNO value recorded was of 5 ppb, and the highest FeNO value was that of 129 ppb with an average of 27.63 ppb as presented in Table V.

Table V

FeNO value distribution in atopic patients receiving ≥ step 2 therapy

	N	Range	Min	Max	Mean	Std. Dev.	Skewness	
							Stat.	Std. Error
FeNO	130	124	5	129	27.63	25.842	2.136	0.212
Valid	130							

Patients included in this category were receiving controller therapy related to step 2, 3 or 4 (inhaled fluticasone, oral montelukast or inhaled fluticasone + salmeterol).

Among patients receiving ≥ step 2 therapy and who were evaluated for FeNO value, 70 patients were controlled with an average of FeNO values of 58.36 ppb, 32 were partial controlled with an average of FeNO values of 72.8 ppb, and 28 were uncontrolled with an average of FeNO values of 75 ppb, as depicted in Table VI.

Table VI

Mean ranks of FeNO values according to asthma control status in patients receiving ≥ step 2 therapy

Control		N	Mean Rank
FeNO	**Controlled**	70	58.36
	Partial controllled	32	72.80
	Uncontrolled	28	75.00
	Total	130	

Using Kruskal-Wallis nonparametric Test to assess the correlation between the mean values of FeNO and asthma control status in patients receiving ≥ step 2 therapy, the results indicate that the correlation is not statistically significant (p = 0.064). This means that among patients receiving ≥ step 2 therapy the mean FeNO values in the controlled asthma subgroup is not significantly lower than the mean FeNO values in the partially controlled and uncontrolled asthma subgroups.

Correlation between FeNO and asthma control in atopic patients receiving ≥ step 2 therapy

In atopic patients receiving ≥ step 2 therapy 110 evaluations were recorded. In this subgroup the lowest FeNO value was of 5 ppb, the highest FeNO value was of 129 ppb with an average of 30.25 ppb as presented in Table VII.

Table VII

FeNO value distribution in atopic patients receiving ≥ step 2 therapy

	N	Range	Min	Max	Mean	Std. Dev.	Skewness	
							Stat.	Std. Error
FeNO	110	124	5	129	30.25	27.171	1.928	0.230
Valid	110							

Among atopic patients receiving ≥ step 2 therapy and who were assessed for FeNO values, 61 patients were controlled with an average of FeNO values of 47.61 ppb, 26 were partially controlled with an average of FeNO values of 67.12 ppb and 23 were uncontrolled with an average of FeNO values of 63.3 ppb, as depicted in Table VIII.

Table VIII

Mean values of FeNO according to asthma control status in atopic patients receiving ≥ step 2 therapy

Control		N	Mean Rank
FeNO	**Controlled**	61	47.61
	Partial controlled	26	67.12
	Uncontrolled	23	63.30
	Total	110	

Using Kruskal-Wallis nonparametric Test to assess the correlation between the mean values of FeNO and asthma control status in atopic patients receiving ≥ step 2 therapy, the results indicate that the correlation is statistically significant (p = 0.014). This means that among atopic patients receiving ≥ step 2, therapy, the mean FeNO values in the controlled asthma subgroup are significantly lower than the mean FeNO values in the partially controlled and uncontrolled asthma subgroups.

Conclusions

Controller therapy has a significant influence on the correlation between FeNO and asthma control status only in atopic patients.

In atopic patients receiving controller therapy, FeNO is correlated with asthma control status, unlike the atopic patients who are not receiving controller therapy.

References

1. Asthma, World Health Organization, Fact sheet N°307, Updated November 2013. http://www.who.int/mediacentre/factsheets/fs307/en/.
2. Current Asthma Prevalence Percents by Age, Sex and Race/Ethnicity, United States, 2012, National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention. http://www.cdc.gov/asthma/asthmadata.htm.
3. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma, 2014.

4. Prevalence of Asthma and Allergies in Children, European Environment and Health Information System, fact sheet no.3.1, May 2007, http://www.euro.who.int/__data/assets/pdf_file/0012/96996/3.1.pdf.
5. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma, 2012.
6. Dinakar C., Exhaled Nitric Oxide in Pediatric Asthma. *Current Allergy and Asthma Reports*, 2009; 9: 30-37. Current Medicine Group LLC ISSN 1529-7322.
7. Dweik R.A., Boggs P.B., Erzurum S.C., Irvin C.G., Leigh M.W., Lundberg J.O., Olin A.C., Plummer A.L., Taylor D.R., on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications, An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. *Am. J. Respir. Crit. Care. Med.*, 2011; 184: 602-615. DOI: 10.1164/rccm.912011ST.
8. Ferrante G., Malizia V., Antona R., Corsello G., La Grutta S., The value of FeNO measurement in childhood asthma: uncertainties and perspectives. *Multidisciplinary Respiratory Medicine*, 2013; 8(1): 50. http://www.mrmjournal.com/content/8/1/50; published online 2013 Jul 31. doi: 10.1186/2049-6958-8-50.
9. Jang W.N., Park I.S., Choi C.H., Bauer S., Harmin S., Seo S.C., Choi I.S., Choung J.T., Yoo Y., Relationships Between Exhaled Nitric Oxide and Atopy Profiles in Children With Asthma Allergy. *Asthma Immunol. Res.*, 2013; 5(3): 155-161. http://dx.doi.org/10.4168/aair.2013.5.3.155, pISSN 2092-7355, eISSN 2092-7363.
10. Nistor C., Ciuche A., Pantile D., Davidescu M., Ranetti A.E., The importance of drug therapy in lung multifocal hydatidosis. Farmacia, 2013; 61(4): 764-771.
11. Jartti T., Wendelin-Saarenhovi M., Heinonen I., Hartiala J., Vanto T., Childhood asthma management guided by repeated FeNO measurements: a metaanalysis. *Paediatric Respiratory Reviews*, 2012; 13: 178-183. 1526-0542 – see front matter, 2011, Elsevier Ltd. doi:10.1016/j.prrv.2011.11.002.
12. Price D., Ryan D., Burden A., Von Ziegenweidt J., Gould S., Freeman D., Gruffydd-Jones K., Copland A., Godley C., Chisholm A., Thomas M., Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. *Clinical and Translational Allergy*, 2013; 3: 37. http://www.ctajournal.com/content/3/1/37.
13. Ratnawati R., Thomas P.S., Exhaled nitric oxide in paediatric asthma, Faculty of Medicine, UNSW and Department of Respiratory Medicine, Prince of Wales Hospital, Randwick, Australia. *Chronic Respiratory Disease*, 2005; 2: 163-174. www.CRDjournal.com.
14. Ricciardolo F.L.M., Sterk P.J., Gaston B. Folkerts G., Nitric Oxide in Health and Disease of the Respiratory System. *Physiol. Rev.*, 2004; 84: 731–765. 10.1152/physrev.00034.2003. 0031-9333/04, American Physiological Society Physiol Rev, Vol 84, July 2004.