„SCREENING" CHILDREN FOR SCREEN TIME – HOW CONCERNED SHOULD WE BE?

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Abstract

Fraction of the exhaled nitric oxide (FeNO) is used as a biomarker for eosinophilic inflammation, mostly on the respiratory tract. This tool may be used as a predictor of exercise-induced bronchospasm in children practicing various sports. The aim of our research was to study the pediatric athletes and to correlate the bronchial inflammation with the type of sport and the clinical features of the subjects. Method. We conducted a prospective study of children aged over 6, practicing outdoor and indoor sports, admitted to our pediatric department. After anamnesis and clinical examination, the patients performed FeNO measurements using the NioxVero analyzer (Aerocrine, Sweden). Results. Our study included 178 children (102 boys) practicing outdoor sports (football, track and field) and indoor sports (basketball, volleyball, handball, swimming). The FeNO levels were significantly higher in children practicing indoor vs. outdoor sports ($p = 0.0001$, t test). The prevalence of atopy was similar ($p = 0.55$, chi square) and the FeNO values in atopic children were slightly elevated but not statistically significant compared to the main sport groups. Data regarding gender, age and social status did not bring significant statistical differences. Conclusions. In our study FeNO was useful in differentiating the indoor vs the outdoor sports. The data regarding the atopic children or the demographic features were not significant.

Keywords: children, exhaled nitric oxide, athletes.

Introduction

Up to now, there is still a rather small number of systematic research to track the risk factors for broncho-obstructive pathology in children practicing various sports. In Romania there is also lacking structured data on the practice of sports in children (whether we are talking about recreational or mass sports), the small amount of data being a result of private initiatives. Bronchial asthma - the most common chronic disease in childhood - has an effort-induced component that can often be difficult to diagnose. Effort-induced bronchoconstriction may vary between 30 and 70% (1), while more recent studies (2, 3) claim that its prevalence in pediatric athletes is 15%.

Determination of bronchial inflammation is a desideratum we have approached in the last few years by the dosing of nitric oxide in exhaled air (FeNO), a reproducible marker and relatively easy to obtain, which makes it useful in the diagnosis of atopic pathology of the respiratory apparatus (4,5). Although FeNO does not yet have the importance of "classical" pulmonary function tests, the fraction of exhaled nitric oxide is an important adjunct to the diagnosis and management of atopic pathology, especially asthmatic, and may have a predictive role in the evolution and treatment of this chronic disease (6, 7, 8).

The purpose of our research was to evaluate bronchial inflammation in children practicing sports admitted to the Pediatrics Department of the Filantropia Municipal Hospital in Craiova and to try to establish a correlation between the value of FeNO, the clinical-biological status and the type of sport practiced by our subjects.

Material and methods

We conducted a prospective study of children practicing sports admitted in our clinic between January and December 2018. We included children who were able to perform pulmonary function tests (spirometry, peakflowmetry) and the determination of nitric oxide in the exhaled air using the NioxVero analyzer (Aerocrine, Sweden). The subjects admitted were over 6 years because this is the generally accepted minimum age for performing this kind of measurements (9, 10).

The analyzer used is the second generation of devices available in our clinic using a calibrated electrochemical sensor that measures the expired air composition and produces molecular results, expressed in "parts per billion" (ppB).

FeNO dosing was done after a training performed before either by the examiner using the dedicated device software or a human model, that is, another already trained child exemplifying how to use it. The results obtained after a maximum of 5 attempts, performed over a minimum of 3 minutes interval between de tests, were validated.

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Type of sport (urban/rural)	Football	Track and field	Indoor	Swimming	TOTAL
Boys	**57 (47/10)**	**14 (11/3)**	**23 (16/7)**	**8 (7/1)**	**102 (81/21)**
Girls	**6 (6/0)**	**13 (8/5)**	**41 (25/16)**	**16 (11/5)**	**76 (50/26)**
Total	**63 (53/10)**	**27 (19/8)**	**64 (41/23)**	**24 (18/6)**	**178 (131/47)**

Table 1. Athletes distribution

SPORT	Football	Track and field	Indoor	Swimming
Mean	18.58	18.77	29.57	33.29
SD	15.62	14.11	23.89	29.86
p value t test (2 tail)	Football vs. track and field		0.95	
	Football vs. indoor		**0.002**	
	Football vs. swimming		**0.003**	
	Track and field vs. indoor		**0.03**	
	Track and field vs. swimming		**0.02**	
	Indoor vs. swimming		0.65	
	All indoor vs. all outdoor		**0.0001**	

Table 2. FeNO levels vs. type of sport

SPORT	Football	Track and field	Indoor	Swimming	TOTAL
Asthma	**4**	**2**	**5**	**2**	**13**
Atopy (other)	**12**	**6**	**18**	**5**	**41**
Non-atopic, no. (%)	**47 (74)**	**19 (70)**	**41 (64)**	**17 (70)**	**124**
p value Chi square (2 tail)					
	Football vs. track and field			**0.67**	
	Football vs. indoor			**0.19**	
	Football vs. swimming			**0.72**	
	Track and field vs. indoor			**0.56**	
	Track and field vs. swimming			**0.97**	
	Indoor vs. swimming			**0.55**	
	All indoor vs. all outdoor			**0.55**	

Table 1. Distribution of atopic children vs. type of sport

Type of sport	Football	Mean	SD	t test
Football	**All athletes**	18.58	15.62	**0.02**
	Atopic	33.87	22.29	
Track and field	**All athletes**	18.77	14.11	0.24
	Atopic	26	18.6	
Indoor	**All athletes**	29.57	23.89	0.07
	Atopic	40.78	30.93	
Swimming	**All athletes**	33.29	29.86	0.11
	Atopic	56.14	41.6	

Table 2. Influence of atopy in FeNO levels

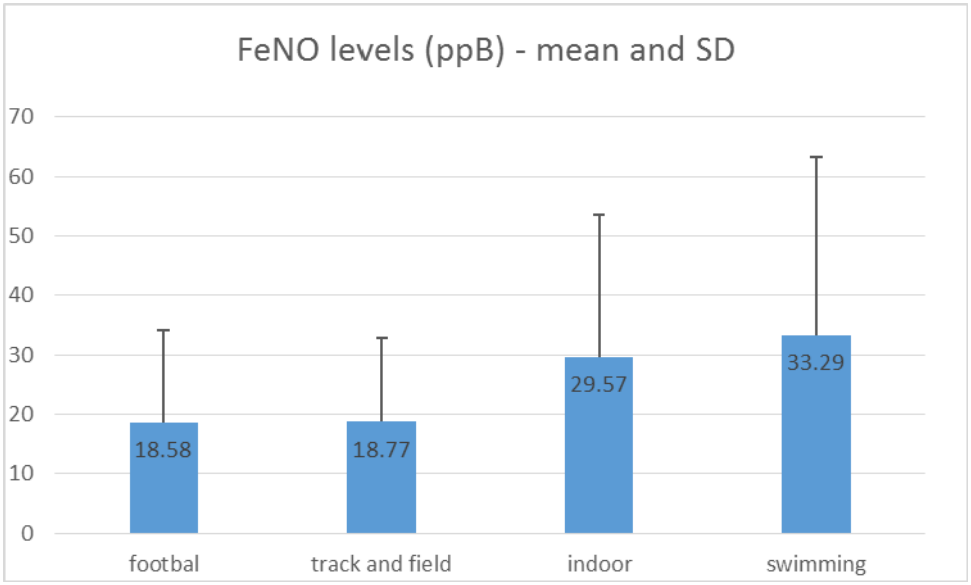

Fig. 1. Graph1. FeNO levels vs. type of sport

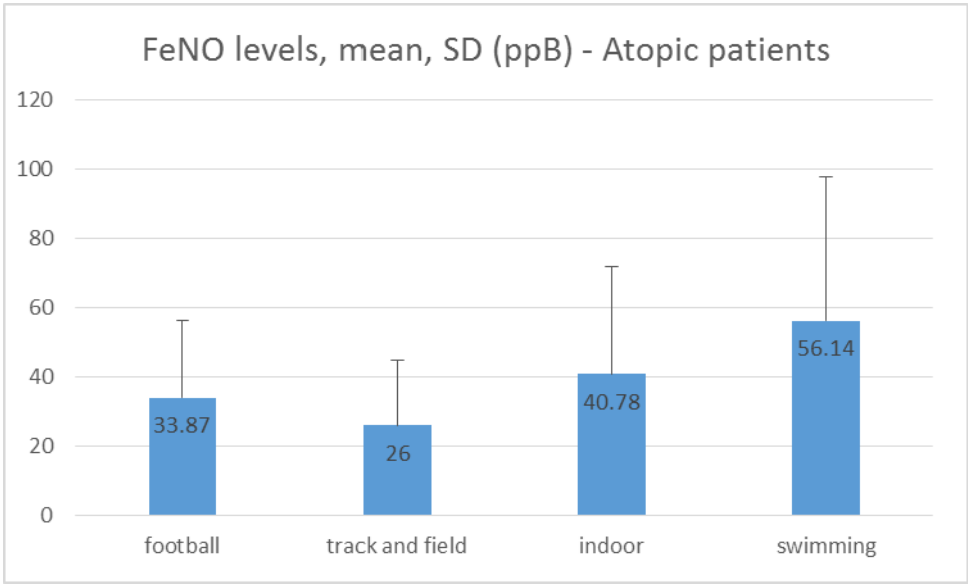

Fig. 2. Graph 2. FeNO levels in atopic patients

The determinations were performed before the functional spirometry or peak flow meters to avoid a false diminution of the values obtained - according to international guidelines (4, 5). The subjects excluded from the study were:

- ✓ children who have failed to get a correct measurement after the 5 attempts,
- ✓ those who consumed foods rich in nitrite before the determinations,
- ✓ children with extreme anxiety,
- ✓ adolescents with a well-founded suspicion of being exposed to cigarette smoke.

Statistical evaluation was performed using Excel (Microsoft Windows) and OpenEpi (Center for Disease Control, USA).

Results

178 children (102 boys) who were enrolled successively and underwent anamnesis, clinical examination, determination of nitric oxide in the exhaled air, and eventually functional ventilation samples (spirometry and/or peakflowmetry) were included in the study. Most of the children studied (131 cases) came from the urban environment, which is generally the profile of the patients admitted in our unit. The general structure of the study group is shown in Table 1

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As expected, in boys, the "king of sports" is football, chosen by 55% of those surveyed, while in girls, 53% say they practice indoor sports (basketball, volleyball, handball, etc.). Another notable gender difference is observed in swimming where several girls seem to be interested in practicing this sport, the double number of cases being statistically significant: $p = 0.05$; OR = 0.31 (95% CI: 0.12-0.79). Regarding athletics, numerical values are approximately equal and have no statistical significance ($p = 0.26$). Basically, indoor sports (gymnastics and swimming) were favored by girls, while most boys are engaged in outdoor sports.

The distribution of the mean values of nitric oxide in the expired air (mean and standard deviation) according to the type of sport practiced by the children in the study is presented in figure 1.

As we can see, the values obtained in children who performed physical activity mostly outdoors are lower compared to those who trained mostly in closed buildings. The statistical evaluation was done in this case with a t test (2 tail) between the types of athletes, and the statistical significance was considered present when the values obtained were below 0.05, as is common in medical specialties. The results are shown in Table 2.

The comparison between football and athletics, both outdoor sports show similar values of FeNO, while comparing football with gymnastics and swimming as well as athletics with indoor sports and swimming brings statistically significant results, thus athletes who have carried out their activity mainly in the interior, have obviously higher levels of nitric oxide in the exhaled air. These athletes have a predisposition to eosinophilic bronchial inflammation ($p = 0.001$, t test), which at some point might result in an exercise induced bronchospasm.

The evaluation of the groups of athletes on general demographic criteria did not reveal significant differences related to sex ($p = 0.76$), origin (urban vs. rural: $p = 0.09$) or age (children under 12 years vs. over 12 years: $p = 0.21$).

The next phase of our research was to evaluate the impact of atopic pathology on our lots. Although some of the children were engaged in performance sports, many of them had a history of allergic diseases and obstructive respiratory pathology (bronchiolitis, bronchitis, obstructive pneumonia, or even bronchial asthma). 5 of the cases included in the study (3 boys and 2 girls) were already diagnosed with bronchial asthma at admission and another 8 children were diagnosed along the way.

The distribution of children with atopic pathology was evaluated according to the type of sport declared (see Table 3).

23% of the subjects (54 children) were diagnosed as atopic patients during the study. The stratified analysis of indoor sports versus outdoor sports did not reveal any significant data (chi square test, 2 tail). Although our lots were not very numerous, the proportion of children with atopy is relatively similar, regardless of the type of sport involved.

We further investigated the nitric oxide values in the exhaled air in the atopic children included in the study. The results are shown in graph 2.

Individual values were calculated in sub-lots with atopy and compared with the mean and standard deviation of the corresponding total number of athletes. So we tried to see if this biomarker is increased in allergic children. The comparison was made using t test (2 tail) results are shown in Table 4.

Although at first glance the mean values and the standard deviation on the 4 sub-lots seem different when compared to those obtained in atopic patients, however the statistical interpretation is significant only in a single case (football - t test = 0.02) and the results are not highly significant. Nitric oxide values are thus higher in children with a history of allergic pathology, but this change does not allow us to assert that this parameter can be widely used in prediction of atopy in pediatric patients performing regular physical exercise.

Discussion

Respiratory atopic pathology, especially the broncho-obstructive type, is based on two physio-pathological pillars: bronchial hyper reactivity and chronic inflammation. Functional ventilatory tests were mainly focused on the first component, and these determinations have already entered the standard of management of asthmatic pathology in children and adults (6). The emergence of an inflammatory mediator that is present in a large amount in the respiratory system and which can be relatively easy measured has opened new horizons over the past 20 years in assessing the inflammatory parameter in chronic respiratory pathology. Although a number of other medical specialties appear to be interested in the evaluation

of nitric oxide in the expired air (11,12,13,14) its utility is evident primarily in pneumology, especially in terms of reducing the rate of asthma exacerbations and mostly in children because the data are still unclear in adults (6, 7).

However, the link between nitric oxide and sports is less studied, the accessible data being disparate and with different methodologies, so we were unable to identify specific recommendations in the therapeutic guidelines. Sporting activity itself is a confounding factor for the amount of nitric oxide in the expired air because although technical recommendations say that repeated effort can lead to decreased values, there are studies demonstrating higher values after physical exercise in performance athletes (15). These increases in athletes may suggest suboptimal control of asthma (16), which means that FeNO could be used as a method of preventing asthma exacerbations in performance athletes.

There are authors (17) who say that practicing a certain type of sport can lead to changes in exhaled nitric oxide probably due to specific environmental conditions. This makes even more difficult to set cut off values with utility in medical practice.

One of the main drawbacks of FeNO dosing is the multitude of factors that may affect the measurement results, which is why this biomarker does not yet have an important place in the eosinophilic inflammation guidelines. Demographic factors such as race or ethnicity (18), but also age, sex, height - especially in older children (19), inflammatory factors of the rest of the respiratory system, or produced in other organs (11,12,13) are involved. Certain eating habits such as eating rich nitrite foods, water, caffeine or alcohol can alter the recorded values (20, 21).

Although rarer in pediatrics, exposure to cigarette smoke has a paradoxical and controversial effect, but it seems that most authors tend to accept the decrease of the concentration of nitric oxide in the exhaled air (22, 23). The presence of asthma did not influence the effect of smoking on fraction of nitric oxide (24).

Anti-inflammatory (corticoid or leukotriene inhibitor) therapy, used in most chronic respiratory diseases, also has a controversial relationship with FeNO values. The most likely association could be with inhaled corticosteroids and therefore nitric oxide was proposed as a method of monitoring this kind of therapy (6).

Conclusions

Our lot was set up in collaboration with the Sports Department of the Craiova Emergency Clinical Hospital, because only this way we managed to gather a fairly consistent number of children practicing sports. The lack of structured data does not allow us to say that our group is representative for the situation of pediatric sports in our city or at regional or national level. That is why our research continues and with the help of our pediatric colleagues from 2 other national centers, we are trying to complete a multicenter study with higher statistical significance. The most important data obtained so far could be systematized as follows:

- most of the included children were from urban areas because this was the profile of the patients common to the two medical institutions involved in the study. As expected, boys have had a greater attraction for football and so male sex has been involved mainly in outdoor sports, while girls have preferred indoor sports;

- FeNO values were significantly higher in children who practiced indoor sports than those who practiced outdoor exercise;

- the presence of allergic manifestations in children practicing sports cannot be ignored, with almost a quarter of our subjects being atopic; however, the FeNO value was not significantly higher in these subgroups than the total values for the corresponding groups of athletes;

- demographic data related to gender, age and social status did not bring significant statistical differences.

The final conclusion of our research is that the dosage of nitric oxide in the exhaled air appears to be modified especially in athletes practicing indoor sports without being able to tell whether this is the consequence of the sport itself or the environmental conditions in which it occurs. In literature, we have found quite a few papers to cover this type of patient, and the reported results are also insignificant in terms of both the predictability of asthmatic manifestations (24) and the differences between different types of sports (25, 26).

However, the performance athlete is an organism that is pushed to the limit of its physiological capabilities, and therefore any method that may prevent the occurrence of an acute severe manifestation such as an effort-induced bronchospasm is welcome. This is probably the best argument to continue evaluating inflammatory biomarkers in sports pathophysiology, especially in children.

References

1. Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capao-Filipe M, Passali D, Randolph C, Storms W. American Academy of Allergy, Asthma & Immunology work group report: exercise-induced asthma. J Allergy Clin Immunol 2007;119:1349–1358.
2. de Aguiar KB, Anzolin M, Zhang L. Global prevalence of exercise-induced bronchoconstriction in childhood: A meta-analysis. Pediatr Pulmonol. 2018 Apr; 53(4):412-425.
3. John D. Brannan and John M. Weiler, Asthma in Athletes, Allergy and Asthma, 10.1007/978-3-319-58726-4_18-1, (1-37), (2018).
4. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005 Am. J. Respir. Crit. Care Med. 171 (8): 912.
5. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical

practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011; 184: 602-15.
6. https://ginasthma.org/gina-reports/ - accessed in December 2018.
7. Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. Cochrane Database of Systematic Reviews 2016, Issue 11.
8. Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. Cochrane Database of Systematic Reviews 2016, Issue 9.
9. Rickard Kathleen, Jain Neal, MacDonald-Berko M. (2018). Measurement of FeNO with a portable, electrochemical analyzer using a 6-second exhalation time in 7-10-year-old children with asthma: comparison to a 10-second exhalation. The Journal of asthma: official journal of the Association for the Care of Asthma. 1-6. 10.1080/02770903.2018.1541350.
10. Crater Glenn, Rickard Kathy, Jain Neal. (2017). Successful Fractional Exhaled Nitric Oxide Measurements with NIOX VERO using 6- and 10-s Exhalation Modes in Children with Asthma Aged 4–10 Years: A Randomized Study. Pulmonary Therapy. 10.1007/s41030-017-0028-4.
11. Faekah Gohar, Christoph Kessel, Miha Lavric, Dirk Holzinger, and Dirk Foell Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks? Arthritis Res Ther. 2016; 18: 163.
12. Sara Torretta, Lorenzo Drago, Paola Marchisio, Maurizio Cappadona, Vittorio Rinaldi, Erica Nazzari, Lorenzo Pignataro Recurrences in chronic tonsillitis substained by tonsillar biofilm-producing bacteria in children. Relationship with the grade of tonsillar hyperplasy. Int J Pediatr Otorhinolaryngol. 2013 Feb; 77(2): 200–204.
13. Faekah Gohar, Christoph Kessel, Miha Lavric, Dirk Holzinger, and Dirk Foell Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks? Arthritis Res Ther. 2016; 18: 163.
14. Vannacci A, Ravaldi C, Giannini L, Rotella CM, Masini E, Faravelli C, Ricca V. Increased nitric oxide production in eating disorders. Neurosci Lett. 2006; 399: 230–233 Can Respir J. 2018 Mar 18;2018:4646852. doi: 10.1155/2018/4646852. eCollection 2018.
15. Thornadtsson A, Drca N, Ricciardolo F, Högman M. Increased levels of alveolar and airway exhaled nitric oxide in runners. Ups J Med Sci. 2017 Jun; 122(2):85-91. Respir Med. 2016 Sep: 118:15-21.
16. Selge C, Thomas S, Nowak D, Radon K, Wolfarth B. Asthma prevalence in German Olympic athletes: A comparison of winter and summer sport disciplines. Respir Med. 2016 Sep; 118: 15-21.
17. Levai IK, Hull JH, Loosemore M, Greenwell J, Whyte G, Dickinson JW. Environmental influence on the prevalence and pattern of airway dysfunction in elite athletes. Respirology. 2016 Nov; 21(8):1391-1396.
18. Wang D, Wang Y, Liang H, David JE, Bray CL. Race and ethnicity have significant influence on fractional exhaled nitric oxide. Ann Allergy Asthma Immunol. 2018 Mar; 120(3):272-277.
19. Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC. Childhood Asthma Management Program Research Group. Decreased response to inhaled steroids in overweight and obese asthmatic children. J Allergy Clin Immunol. 2011;127:741–749.
20. Jartti T, Wendelin-Saarenhovi M, Heinonen I, et al. Childhood asthma management guided by repeated FeNO measurements: a meta-analysis. Paediatr Respir Rev. 2012; 13(3):178–183.
21. Linn WS, Rappaport EB, Eckel SP, et al. Multiple-flow exhaled nitric oxide, allergy, and asthma in a population of older children. Pediatr Pulmonol. 2013; 48(9):885–896.
22. Xu X, Hu H, Kearney GD, Kan H, Carrillo G, Chen X. A population-based study of smoking, serum cotinine and exhaled nitric oxide among asthmatics and a healthy population in the USA. Inhal Toxicol. 2016 Dec; 28(14):724-730.
23. Jacinto T, Malinovschi A, Janson C, Fonseca J, Alving K. Differential effect of cigarette smoke exposure on exhaled nitric oxide and blood eosinophils in healthy and asthmatic individuals. J Breath Res. 2017 Aug 21; 11(3): 036006.
24. Voutilainen M1, Malmberg LP, Vasankari T, Haahtela T. Exhaled nitric oxide indicates poorly athlete's asthma. Clin Respir J. 2013 Oct; 7(4):347-53.
25. Martin N, Lindley MR, Hargadon B, Monteiro WR, Pavord ID. Airway dysfunction and inflammation in pool- and non-pool-based elite athletes. Med Sci Sports Exerc. 2012 Aug, 44(8):1433-9.
26. Pedersen L1, Lund TK, Barnes PJ, Kharitonov SA, Backer V. Airway responsiveness and inflammation in adolescent elite swimmers. J Allergy Clin Immunol. 2008 Aug, 122(2):322-7.

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