

Electrochemical monitoring of bronchial inflammation in pediatric athletes: A prospective study

RADU DIACONU^{1*}, FLORENTINA DUMITRESCU^{2*}, LOREDANA STOICA³,
CARMEN DIACONU⁴, MIHAELA-AMELIA DOBRESCU⁵, ADINA-DORINA GLODEANU^{6*},
MIHAELA IONESCU⁷, NIKOLAOS MAVRITSAKIS⁸ and DORU STOICA⁹

Departments of ¹Pediatrics, ²Infectious Diseases and ³Dermatology, University of Medicine and Pharmacy of Craiova, 200349, Craiova; ⁴Department of Sports Medicine, Emergency Clinical Hospital Craiova, 200642 Craiova; Departments of ⁵Medical Genetics, ⁶Internal Medicine and ⁷Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova, 200349 Craiova; ⁸Department of Physical Education and Sport, '1 Decembrie 1918' University, 510009 Alba Iulia; ⁹Physical Education and Sport Faculty, University of Craiova, 200177 Craiova, Romania

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Abstract. The assessment of inflammation by accessible, reproducible and especially non-invasive methods is one of the main goals for numerous medical specialties. One variable for assessment is the fraction of nitric oxide in exhaled air (FeNO), which correlates with the inflammatory syndrome of the airways. The objective of the present study was the biochemical evaluation of FeNO in children practicing sports in Oltenia, Romania. Between January and December 2018, children practicing sports (football, track and field, judo, fencing, handball, volleyball and basketball) were enrolled in the study. The FeNO values were compared with the asthma history and with the spirometric evaluation. A total of 23 children without a previous asthma diagnosis exhibited positive spirometry results. The prevalence of the disease was 3.6% in the cohort, and FeNO dosing showed higher values in the group at risk in children diagnosed with asthma, compared with that in children without this diagnosis. The children who performed outdoor sports (soccer, and track and field) had higher electrochemical levels of nitric oxide compared with those who performed indoor sports (mean, 29.70 vs. 20.56;

$P < 0.0005$), which led to the hypothesis that these children had an increased risk of developing bronchospasm. FeNO dosing can thus be a useful and easy-to-use tool in practice for assessing bronchial inflammation in children practicing various types of sports. The spirometric data of undiagnosed asthma patients from the present study may indicate that the disease is still underdiagnosed within Romania.

Introduction

The asthma prevalence in elite athletes is higher compared with that in the general population (1), and a number of the children practicing various types of sports are diagnosed with asthma or have asthma-like symptoms (2,3). The electrochemical detection of the fraction of exhaled nitric oxide (FeNO) may be a valuable marker of bronchial inflammation, as during airway inflammation associated with asthma, higher than normal levels of NO are released from bronchial epithelial cells. Thus, FeNO may be a tool to detect undiagnosed cases of asthma or to predict asthma exacerbation in various types of sports (4-6). Bronchial asthma is one of the life-threatening conditions in sports, so an accurate diagnosis and a good monitoring system are compulsory to avoid severe exacerbation (7).

FeNO electrochemical detection is widely used in clinical practice, as devices for detection are relatively small and portable. Most of the devices commonly used do not need maintenance or calibration (4,8,9).

The detection of exhaled nitric oxide is considered a promising tool in pneumology, but its role in the diagnosis and management of asthma cases is still under debate (10). Other medical specialties are interested in evaluating inflammation using FeNO measurements, but research is scarce, and the results are often conflicting (11,12).

Exercise-induced bronchoconstriction and the pathological entities related to it are a great concern for sports medicine, with pediatric cases being even more frequent than adult cases (6,13,14). The present study performed research in children enrolled in various types of sports in Craiova (a major

Correspondence to: Dr Mihaela Ionescu, Department of Medical Informatics and Biostatistics, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareș Street, 200349 Craiova, Romania
E-mail: mihaelaionescu.info@gmail.com

Dr Nikolaos Mavritsakis, Department of Physical Education and Sport, '1 Decembrie 1918' University, 5 Gabriel Bethlen Street, 510009 Alba Iulia, Romania
E-mail: geromed_ro@yahoo.com

*Contributed equally

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city from Dolj county, in Romania), to evaluate the degree of bronchial inflammation vs. type of sport and personal history of asthma or allergy.

Patients and methods

Study cohort. Between January and December 2018, children practicing football, track and field, and indoor sports (fencing, judo, handball, basketball and volleyball), who were admitted as outpatients for routine health checks to the Department of Pediatrics of Filantropia Municipal Hospital Craiova (Craiova, Romania) were enrolled in a prospective study. The study included children aged >6 years (mean age, 11.7 years) who were enrolled in the Department of Sports Medicine as athletes mainly practicing one of the aforementioned sports and who had the ability to perform the technical maneuvers (spirometry and FeNO measurements) required. The exclusion criteria were acute febrile illness and/or acute respiratory illness, pulmonary chronic diseases (other than asthma) and cardiovascular chronic diseases. The smokers, the subjects who performed intense physical exercise or those who ingested foods rich in dietary nitrate during the same day were also rejected.

Patient assessment. The bronchial inflammation of the patients was assessed using the Niox Vero exhaled nitric oxide analyzer (Aerocrine AB) based on the general accepted guidelines (6), and the results were compared taking into account the personal history of asthma, the type of sport and the spirometry results. FeNO results >35 parts per billion (ppb) suggested high bronchial inflammation. The spirometry evaluation was considered abnormal (suggesting asthma) if the peak expiratory flow (PEF) and the forced expiratory volume per one second (FEV1) were <80% of the predicted values, and the FEV1/FVC ratio was <85%. The bronchodilator test was considered positive if a 12% or 200 ml increase was noted in either FEV1 or forced vital capacity (FVC), respectively.

Statistical analysis. Demographic and clinical data were initially regrouped using Microsoft Excel (Microsoft Corporation). This program was used to describe the findings in terms of percentages and group definitions. The statistical analysis was performed using SPSS version 20 (IBM Corp.). Group comparisons were performed using the non-parametric Mann-Whitney U or Kruskal-Wallis H test, followed by Dunn's procedure and Bonferroni adjustment, where appropriate, with $P < 0.05$ considered to indicate a statistically significant difference.

Results

Study group demographics. The 404 patients included in the present study originated mostly from urban areas. Overall, 59.65% (241 cases) were boys, as the main sport in the Craiova region is football and boys are prevalent in this field (Table I).

The asthma prevalence in the study group was 3.96% (16 children; Fig. 1). Asthmatic patients were diagnosed with the mild form of the disease and the physical exercise was not a trigger for asthma exacerbation.

Pulmonary function testing. After anamnesis and clinical examination, FeNO measurements followed by pulmonary function testing (spirometry: Pre- and post-bronchodilator).

In terms of spirometric evaluation, 33 children showed signs suggesting asthma (PEF and FEV1/FVC baseline levels <80% of predicted values and/or reversibility after use of a bronchodilator via Ventolin inhaler). Only 10 of these cases were previously diagnosed as asthma.

The biochemical detection of exhaled nitric oxide (FeNO) was performed before the spirometry and the results are based on molecular proportion as ppb. The patients already diagnosed with asthma had slightly elevated FeNO levels compared with the rest of the study group. The Mann-Whitney U test was performed to determine if there were any differences in FeNO values between children with asthma and children without asthma. Distribution values for these groups were not similar, as assessed by visual inspection. FeNO values for the asthma group (mean rank, 178.78) and non-asthma group (mean rank, 202.48) were not statistically significantly different ($U = 2724.5$; $z = -0.80$; $P = 0.407$; Table II).

The majority of the patients came from urban areas (mostly Craiova), as in our previous studies (15-17). There was no statistical difference with regard to living area or sex in the patient cohort. A total of 4 patients (3 already diagnosed with asthma) had very high levels of exhaled nitric oxide (>100 ppb).

The next step was to evaluate the FeNO values in various types of sports. The average and standard deviation measurements are presented in Fig. 2. The average values ranged from 21 ppb for track and field athletes to 38 ppb for fencing. It was noted that the children practicing football and track and field had slightly decreased FeNO levels, but the number of patients was too small to obtain statistical significance among groups. The outdoor (football, and track and field) and indoor (fencing, judo, handball, basketball and volleyball) sports were then compared. Children enrolled in indoor sports showed elevated levels of exhaled nitric oxide; thus, it can be concluded that they have a higher level of bronchial inflammation compared with those children who participate in outdoor sports. The Mann-Whitney U test was also performed to determine if there were any differences in FeNO values between children playing indoor sports and those playing outdoor sports. Distributions of FeNO values for these groups were similar, as assessed by visual inspection. Median FeNO level was statistically significantly higher for indoor sports (median value, 19) than for outdoor sports (median value, 12) ($U = 26811.5$; $z = 5.516$; $P < 0.0005$; Table II).

The next stage of the study compared the children at risk from asthma (the 23 cases without a diagnosis but with positive spirometry results) with the asthma group and with the children without a history or spirometry suggesting asthma.

Unexpectedly, the children at risk of asthma had even higher values of FeNO compared with the asthma group. FeNO levels had similar distributions for all groups, as assessed by visual inspection of a boxplot chart. The Kruskal-Wallis H test was performed to determine if there were differences in FeNO values between the four groups of participants (asthma group with either positive or negative spirometry, and the no asthma group with either positive or negative spirometry). Median

Table I. Demographic data.

Type of sport	Football	Track and field	Indoor sports				
			Fencing	Judo	Handball	Basketball	Volleyball
Sex, n							
Male	125	33	16	18	12	21	16
Female	10	24	14	7	42	34	32
Mean age (standard deviation), years	9.24 (1.69)	11.75 (2.04)	12.39 (2.55)	11.11 (1.95)	12.09 (1.66)	10.28 (2.19)	9.11 (1.87)
Locality, n							
Urban	102	38	21	19	39	35	29
Rural	33	19	9	6	15	20	19

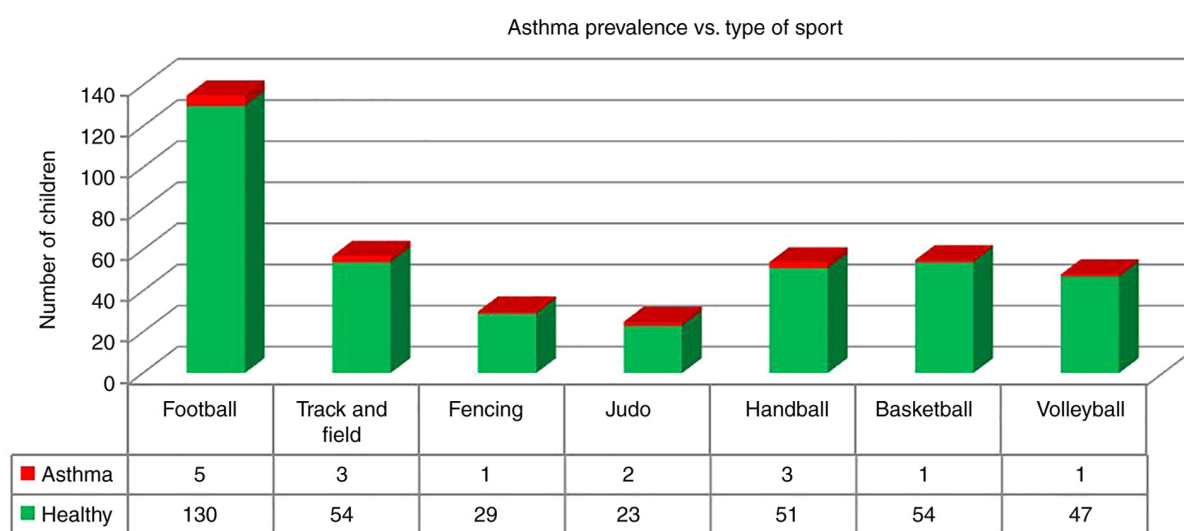


Figure 1. Asthma prevalence vs. type of sport.

FeNO levels were not statistically significantly different between groups [$\chi^2(3)$, 5.446; $P=0.142$; Table II].

Discussion

Assessing airway inflammation using FeNO is a relatively new way of monitoring, as it has only become widely available in the last two decades. Some medical specialties seem to be interested in this tool (rheumatology, dermatology, Ear, Nose and Throat, and psychiatry), but the main research is based on pneumology. The list of available pathologies is still open, as the inflammation is related to a wide range of diseases (18-22). Monitoring the inflammation in various sports may be a valuable tool in diagnosing a wide range of diseases and to predict the imminence of exacerbation (i.e. asthma attack) (23-26).

The asthma prevalence in the present study seemed low, but a number of the patients were undiagnosed, as asthma is still an underdiagnosed condition in Romania, both in children and adults. The results of the spirometry testing combined with FeNO measurements showed that a number of so called 'healthy' children had an asthmatic profile.

In the present study, children practicing 7 types of sports were enrolled and asthma cases were reported in all of them. The popularity of football, especially in the Craiova region, is so high that 33.4% of the cases were of young footballers. The FeNO measurements, stratified by type of sport, showed decreased levels in football, and track and field, followed by handball.

When the outdoor sports (football, and track and field) and indoor sports (fencing, judo, handball, basketball and volleyball) were compared, the FeNO levels were found to be significantly higher in the children practicing indoor sports, thus we hypothesize that bronchial inflammation is greater in these athletes. Although the asthma cases were not more frequent in this subgroup, the risk of having a bronchospasm may be higher, and these children may be at risk of respiratory failure during an intense effort. The precise cause of these higher levels is unknown, but it can be theorized that the environment is to blame, as a number of these children are practicing sports in old buildings, with intense humidity and molds.

Unfortunately, the data gathered until now for asthma has placed the FeNO measurement as a secondary tool in the

Table II. FeNO level distribution, according to various groupings.

FeNO levels, ppb	Average	Standard deviation	P-value
Diagnosis			0.407 ^a
Asthma group			
Female	29.80	40.99	
Male	27.90	37.17	
No asthma diagnosis			
Female	27.86	25.83	
Male	23.42	22.34	
Location of sport			<0.0005 ^{a,b}
Indoors			
Female	29.29	26.03	
Male	30.29	24.86	
Outdoors			
Female	23.56	26.71	
Male	19.79	21.22	
Diagnosis			0.142 ^c
Asthma diagnosis, positive spirometry	29.10	39.23	
Asthma diagnosis, negative spirometry	27.5	35.56	
No asthma diagnosis, positive spirometry	38.13	33.71	
No asthma diagnosis, negative spirometry	24.41	22.96	

^aMann-Whitney U test. ^bP<0.05. ^cKruskal-Wallis H test. FeNO, fraction of nitric oxide in exhaled air; ppb, parts per billion.

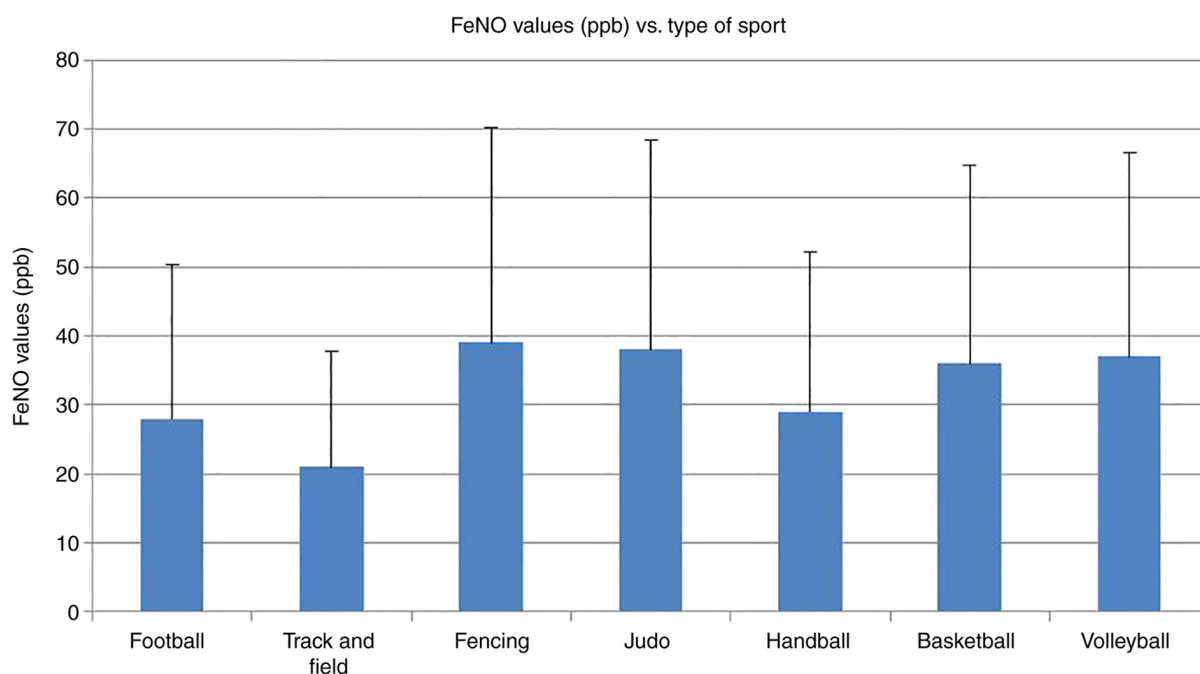


Figure 2. Fraction of nitric oxide in exhaled air values (parts per billion) vs. type of sport.

diagnosis and management of asthma, as the research recorded has had conflicting results (10,27,28). However, the technique is widely available, easy to perform and non-invasive, so the interest in clinical settings remains high.

In conclusion, using a portable electrochemical analyzer to evaluate children at risk of an asthma attack, especially

athletes, may be an opportunity to prevent exacerbation of the condition, which may be life threatening. Encouraging children to practice sports is one of the cornerstones of pediatric education, but the advantages and the dangers of this activity must be balanced. The electrochemical evaluation of bronchial inflammation is an accessible tool that can help medical staff

to identify children at risk of developing a bronchospasm during intense physical activity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RD, FD and ADG conceptualized the study, prepared the initial draft and shared first authorship. CD, DS and MAD acquired the raw data, and also performed the literature data collection. RD and DS confirm the authenticity of all the raw data. LS, NM and MI analyzed and interpreted the patient data. NM and DS also provided essential critical revisions. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Informed consent was obtained from parents or legal guardians for all children. Prior approval for the study was obtained from the Ethics Committee of the University of Medicine and Pharmacy of Craiova (Craiova, Romania). The Filantropia Municipal Hospital, the Infectious Disease Hospital and the Clinical Emergency County Hospital are all part of the Clinical Departments of the University of Medicine and Pharmacy of Craiova.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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