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Title: Exhaled breath analysis in childhood rheumatic disorders – a longitudinal study

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Abstract

Objectives. To evaluate fraction of exhaled nitric oxide (F_ENO_{50}) and deaerated exhaled breath condensate pH (dEBCpH) as non-invasive markers of subclinical airway inflammation in pediatric patients with rheumatologic disorders.

Methods. We determined F_ENO_{50} and dEBCpH in a prospective study spanning at least 12 months, comprising 85 pediatric patients with rheumatologic disorders, including juvenile idiopathic arthritis (JIA, n=63), chronic recurrent multifocal osteomyelitis (CRMO, n=6), systemic lupus erythematosus (SLE, n=3), juvenile dermatomyositis (JDM, n=1) and other rheumatic disorders (n=12). dEBCpH was determined once in a group of children without evidence of rheumatologic or pulmonary disease (controls, n=90). Findings were correlated with results of pulmonary function tests. Atopic sensitization was assessed by RAST or skin prick test in 76 patients.

Results. Atopic sensitization was detected in 34% (26/76) of patients. Neither F_ENO_{50} nor dEBCpH correlated with disease activity, but intermediately (20-35 ppb) or highly elevated (>35 ppb) levels were observed at least once in 26 patients (31%), 19 of whom had atopic sensitization. Median dEBCpH did not differ between cases and controls (8.05 vs. 8.02; p=0.48). Median dEBCpH decreased slightly over the study period (p=0.02), whereas F_ENO_{50} values did not change significantly (p=0.89). There were several patients with significantly abnormal dEBCpH values that could not be readily explained by diagnosis, higher disease activity, medications, or atopic sensitization.

Conclusions. There were no consistent abnormalities in F_ENO_{50} or dEBCpH in this cohort of Caucasian patients with relatively stable rheumatologic disorders, but there were some patients with abnormal values of unknown significance.

Key words: exhaled breath analysis, F_ENO_{50}, dEBCpH, pulmonary function, juvenile idiopathic arthritis, chronic recurrent multifocal osteomyelitis, systemic lupus erythematosus.

Introduction

Most rheumatologic disorders of childhood can feature lung involvement in one way or another. However, clinically significant lung involvement is usually rare in the most common disease entity, juvenile idiopathic arthritis (JIA) [1], and the advent of potent disease-modifying antirheumatic drugs (DMARDs) and biologicals has reduced the burden of disease due to pulmonary involvement across the board in most childhood rheumatic disorders. On the other hand, new technologies have made it possible to noninvasively monitor relatively subtle changes in pulmonary inflammation, even in asymptomatic periods [2]. The fraction of exhaled nitric oxide (F_ENO_{50}) and deaerated breath condensate pH (dEBCpH) constitute the most widely used of these methods, both of which have been studied extensively in the context of asthma and related pulmonary diseases [3-5]. F_ENO_{50} has been found useful as a non-invasive biomarker of disease activity in several non-pulmonary diseases [6]. It has been assessed in several rheumatologic disorders in adults, where they were found to be elevated in two conditions that often feature pulmonary involvement, namely systemic lupus erythematosus (SLE), Sjögren syndrome, and systemic sclerosis [6-8], whereas dEBCpH has not received much attention in this regard. In particular, neither F_ENO_{50} nor dEBCpH have been studied in pediatric patients with rheumatologic disorders. We have therefore used these methods to screen pediatric patients with rheumatologic disorders for evidence of pulmonary inflammation and correlated findings with indices of pulmonary function and, in a subpopulation, of rheumatologic disease activity. We do not find obvious differences in F_ENO_{50} or dEBCpH between patients and controls, although significantly abnormal values were detected in a small number of patients without evidence of atopic sensitization. However, these could not be explained by diagnosis, disease activity, or medications taken.

Participants, Materials and Methods

Patients were recruited between 2008 and 2011 from the Division of Rheumatology of the Department of Pediatrics, Medical Faculty “Carl Gustav Carus”, Technical University (TU) Dresden, in Dresden, Germany. Most participants were clinically stable patients who came in for follow-up appointments. The final study population (n=85) comprised patients with juvenile idiopathic arthritis (JIA, n=63, consisting of oligoarticular JIA [n=17], polyarticular JIA [n=5], enthesitis-related JIA [n=8], systemic onset JIA [n=6], psoriatic JIA [n=1], and unspecified JIA [n=26]), chronic recurrent multifocal osteomyelitis (CRMO, n=6), SLE (n=3), and miscellaneous rheumatologic disorders (n=13; consisting of 2 cases each of nonspecific periodic fever syndrome, Lyme arthritis, Wegener granulomatosis, Sjögren syndrome, and 1

case each of juvenile dermatomyositis, reactive arthritis, systemic sclerosis, and Behcet disease [n=1 of each]). Measurements were taken in 3-monthly intervals during routinely scheduled clinic visits. For dEBCpH measurements, control subjects were recruited among inpatients of the same hospital who did not have evidence of rheumatologic, atopic, or pulmonary disease and were fit enough to walk to the pulmonary function testing unit and to cooperate with the tests (n=90). Controls were matched to patients by age and sex. F_ENO_{50} was measured using a commercially available, clinically validated chemiluminescence analyzer (CLD 88 sp, Eco Medics, Duernten, Switzerland). F_ENO_{50} values were not measured among controls, since commonly accepted pediatric reference values were available [9,10]. dEBCpH was measured as described in [11]. In brief, deaeration was performed with argon, and a stable dEBCpH was achieved after 10-12 minutes at a flow rate of 350 mL/min. Disease activity of the underlying rheumatologic disease was determined in a subset of patients with the Childhood Health Assessment Questionnaire (CHAQ) [12,13]. Atopic sensitization was determined by Radio-Allergo-Sorbent-Test (RAST) or skin prick test in order to assess its contribution to any abnormalities in F_ENO_{50} and dEBCpH. Atopic sensitization was defined as a RAST class of greater than 2, a positive skin prick test response to at least 1 common airborne allergen, or both. Skin prick tests (Allergopharma, Reinbek, Germany) were performed against *Penicillium* species, *Cladosporium* species, *Aspergillus* species, *Mucor* species, *Alternaria* species, mugwort, ribwort, grasses, alder, hazelnut, birch, rye, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farina*. Sensitization was defined as a wheal at least 3 mm greater in diameter than that elicited by the negative control. Plasma total and specific IgE concentrations to common airborne allergens (same panel as skin prick test) were assessed with RAST, and total IgE and eosinophil cationic protein levels were assessed with fluorescence immunoassay (all with UniCAP 205; Phadia, Freiburg, Germany). Pulmonary function was measured by spirometry and body plethysmography using the equipment available for clinical care in the hospital (MasterScreen Body, Jaeger™, CareFusion, Hoechberg, Germany). The reference values to calculate the percent of predicted values were chosen according to Zapletal et al. [14].

Ethics approval

The study was approved by the Ethics Committee of the Medical Faculty "Carl Gustav Carus", TU Dresden. Informed consent was obtained from all parents, and assent from all participants.

Statistical analysis

Correlations between pulmonary function parameters and F_ENO_{50} and dEBCpH values were examined by Spearman's rank correlation analysis. Differences in dEBCpH between cases and controls were compared with the Mann-Whitney-U-Test, as data were not normally distributed. Changes in F_ENO_{50} and dEBCpH values over the study period were tested with the Friedman test, a nonparametric two-way analysis of variance. Statistical analyses were carried out with IBM SPSS Statistics, version 20 (IBM Corporation, Armonk, NY, USA). Figures were made with the online functions available through the R Foundation for Statistical Computing, version 3.1.3.

Results

Table 1 summarizes demographic and clinical characteristics of the patients and controls. Consistent with the predominantly Caucasian ethnicity of the patients, most of the patients had JIA, whereas SLE was rare. Atopic sensitization could be assessed in 76 patients, 26 (34%) of whom were classified as atopic. Of the 85 patients, 37 (43.5%), 36 (42.4%), 14 (16.5%) and 12 (14.1%) received nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDS (including methotrexate [MTX]), biologicals, and corticosteroid therapy, respectively (multiple choices were possible).

Table 1. Demographic and clinical characteristics of the study and control populations

Characteristics	Controls, n (%)	All cases, n (%)	Case subgroups, n								
	(n=90)	(n=85)	JIA (n=63)						CRMO (n=6)	SLE (n=3)	Miscella-neous (n=13)
			Oligoarticular	Polyarticular	Enthesitis-related	Systemic onset	Psoriatic	Not specified			
Sex											
Boys	33 (37%)	29 (34%)	5	2	5	2	0	7	1	1	6
Girls	57 (63%)	56 (66%)	12	3	3	4	1	19	5	2	7
Median age (range), years	13 (6-23)	13 (5-26)	12 (6-18)	12.5 (5-17)	15 (9-19)	9 (8-13)	16 (16-16)	12 (6-21)	14.5 (9-19)	15 (13-19)	13.5 (6-26)
CHAQ*											
No activity	NA	17 (20%)	5	2	1	2	NA	6	NA	NA	1
Mild activity	NA	7 (8.2%)	0	1	3	1	NA	1	NA	NA	1
Moderate activity	NA	5 (5.9%)	1	1	1	1	NA	1	NA	NA	0

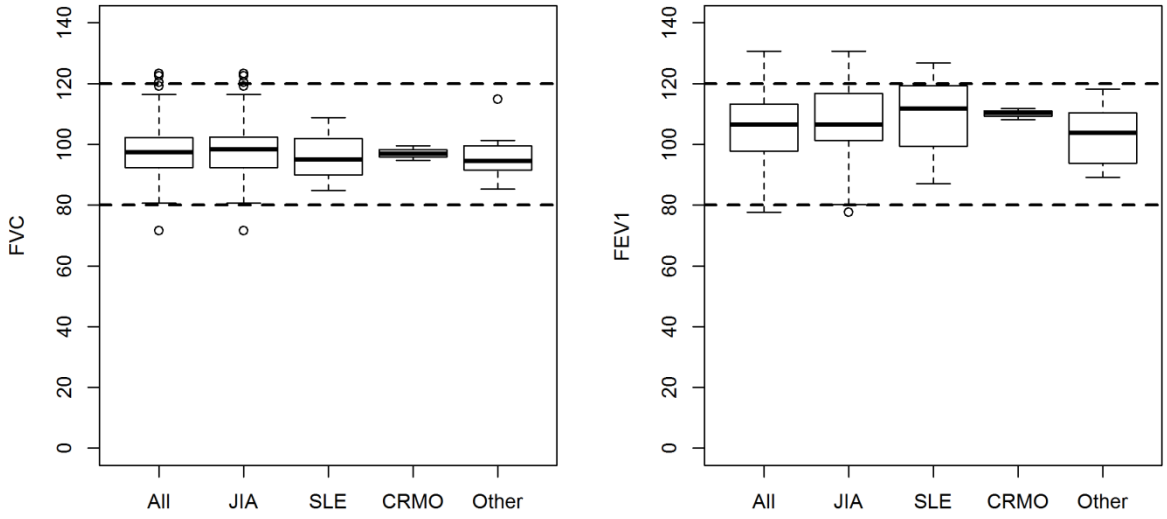
Abbreviations used: CHAQ, Childhood Health Assessment Questionnaire; CRMO, chronic recurrent multifocal osteomyelitis; JIA, juvenile idiopathic arthritis; NA, not assessed; SLE, systemic lupus erythematosus.

* Assessed at baseline

Pulmonary function tests

Fig. 1 shows the results of those successively measured PFTs that were deemed to be most relevant to the study aims, i. e. forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1). Only a few patients had abnormal FVC and FEV_1 values: two patients had values lower than 80% and seven patients had values higher than 120%. There were no significant differences in FVC and FEV_1 values across the rheumatologic diagnoses (Fig. 1).

Figure 1. Major parameters of pulmonary function tests. Forced vital capacity (left) and forced expiratory volume in 1 sec (right).



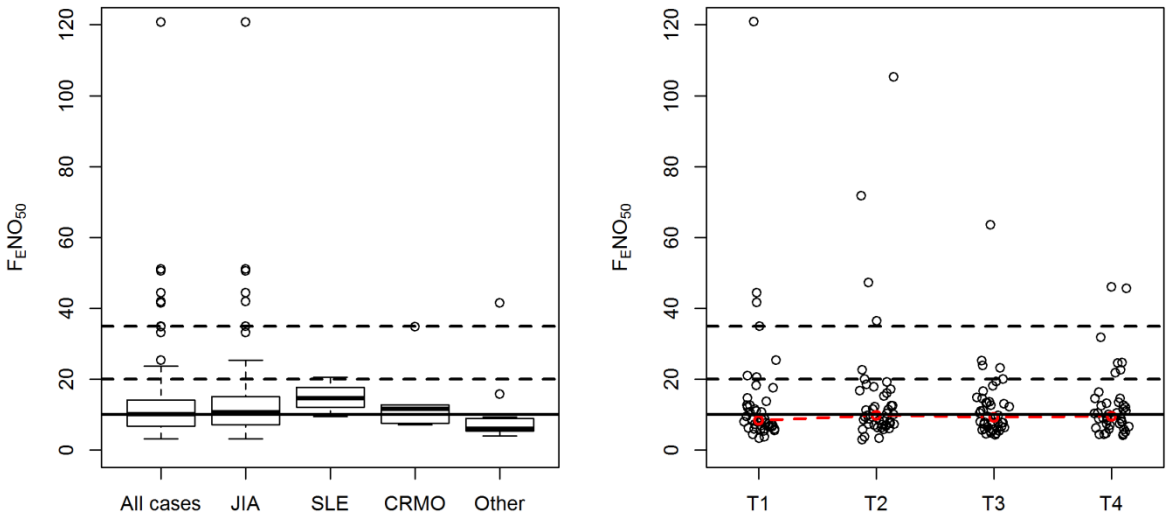
The dotted lines delineate the range of normal values.

F_ENO_{50} and dEBCpH

Fig. 2 (left panel) shows the spread of the F_ENO_{50} values across all patients and also separated according to diagnosis. The median values of F_ENO_{50} for JIA, CRMO and SLE were 10.9, 11.7 and 14.7, respectively. Fig. 2 (right panel) shows F_ENO_{50} values at the four time points of the study; the median values did not change during the study period (p=0.89, Friedman test). There were a total of 26 (31%) children with any value >20 ppb (i.e. intermediately or highly elevated levels), 19 of whom were atopic. Specifically, intermediately elevated F_ENO_{50} values (20-35 ppb) were observed in at least one visit in 14 (16%) children, 9 of whom were classified as atopic. The diagnoses of the 5 non-atopic patients in this group were JIA (n=4)

and SLE (n=1), and treatments were corticosteroids (n=2), NSAID (n=1), and sulfasalazine (n=1); one patient was without pharmacological treatment. Highly elevated F_ENO_{50} values (>35 ppb) were observed in at least one visit in 11 (13%) children, 10 of whom were classified as atopic. The one non-atopic patient in this group had stable JIA, was treated with MTX, and had no clinical evidence of lung disease.

Figure 2. Values of the fraction of exhaled nitric oxide (F_ENO_{50}) by diagnosis (left, baseline values) and at four time points of the study (right).

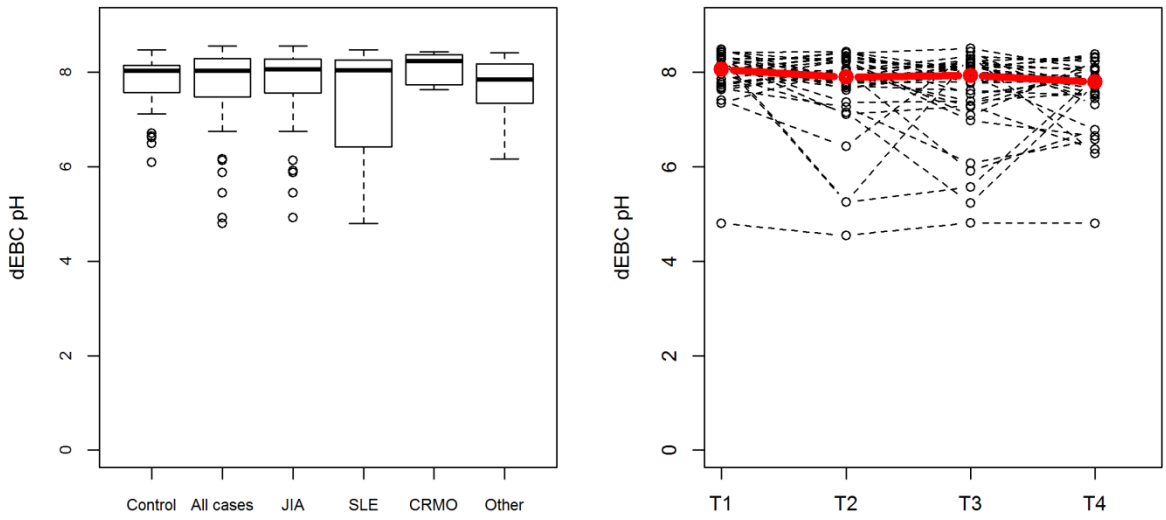


The horizontal line represents the mean F_ENO_{50} values of healthy individuals aged 13 years according to [10]. The dashed lines at 20 and 35 ppb correspond to intermediate and high risk of eosinophilic inflammation, respectively, according to [9]. The red dots on the right graph represent the median values. Changes in F_ENO_{50} values over the study period were not significant (p=0.89, Friedman test, n=43). Measurements were taken in 3-monthly intervals during routinely scheduled clinic visits.

dEBCpH values are shown in Fig. 3. Since there are no age appropriate reference values for this parameter, values were compared to a matched control group of children and adolescents without atopic, pulmonary or rheumatologic disease. The median dEBCpH values in cases and controls were 8.05 and 8.02, respectively (p=0.48, Mann-Whitney-U-test, Fig. 3, left panel). The median dEBCpH values were similar across rheumatologic diagnoses. There were several outliers, only one of whom had atopic sensitization. The most severe outlier was a boy

with anti-phospholipid antibody syndrome due to SLE, who consistently had values between pH 4 and 5, but did not have atopic sensitization. At 6 years follow-up (2015), he has not developed atopic disease or pulmonary involvement of the SLE. Longitudinal data show that dEBCpH values decreased slightly during the study period (T1: median of 8.06; T4: median of 7.79; p=0.02, Friedman test, Fig. 3, right panel).

Figure 3. Deaerated breath condensate pH (dEBCpH) values by diagnosis (left, baseline values) and changes over the study period (right).



Left panel; the difference in dEBCpH between controls and cases was not significant (p=0.48, Mann-Whitney-Test). Right panel; each dashed line represents one patient. The red line represents median values; the median dEBCpH values decreased slightly during the study period (p=0.02, Friedman test, n=31). Measurements were taken in 3-monthly intervals during routinely scheduled clinic visits

Correlations with the CHAQ score

Results of the CHAQ were available from a subgroup of patients (n=29) because they were also enrolled in a related study in which CHAQ scores were assessed. We thus looked for correlations between the CHAQ score and F_ENO_{50} or dEBCpH values. There was no significant correlation (F_ENO_{50}: Spearman's r=-0.05, p=0.80, n=26; dEBCpH: r=0.06, p=0.75, n=27).

Effects of medications

We finally addressed the question whether abnormal F_ENO_{50} or dEBCpH values could be attributed to pharmacological interventions. However, when testing for any effects due to the major classes of medications used to treat rheumatologic disorders, there were no associations between elevated F_ENO_{50} values and treatment with NSAIDs (Fisher's exact test, p=0.52), corticosteroids (p=0.21), or DMARDs including MTX (p=0.43). There was a positive association between elevated F_ENO_{50} values and treatment with biologicals (p=0.007). However, this effect disappeared after controlling for atopic sensitization as a confounding variable (p=1.0). Likewise, there was no association between abnormally low dEBCpH (here defined as pH ≤7.0, as Fig. 3 [right panel] suggests a step-off around this value) and these medication classes (NSAIDs, p=1.0; corticosteroids, p=0.76; DMARDs including MTX, p=0.27; biologicals, p=1.0).

Discussion

We have analyzed F_ENO_{50} and dEBCpH in a heterogeneous population of patients with rheumatologic disorders of childhood and found, overall, few abnormal values, most of which could be explained by a co-existing atopic sensitization. This suggests that subclinical airway inflammation due to pulmonary involvement in pediatric rheumatologic disorders is rare in populations such as ours, which are usually clinically stable due to effective treatments. Indeed, recent studies of pulmonary function in pediatric patients with rheumatologic disorders have shown mostly normal function and age-appropriate development (e.g., ref. [15]). F_ENO_{50} has been assessed in adult patients with rheumatologic disorders. For instance, a study of adult SLE patients showed that F_ENO_{50} values were about twice as high as in controls and correlated with disease activity [8], and a study of patients with Sjögren syndrome revealed F_ENO_{50} values about 50% higher in patients than in controls [7]. dEBCpH has proven useful in the detection of subclinical airway inflammation in children at risk of asthma during asymptomatic intervals [11], suggesting that it is a sensitive method to detect clinically inapparent pulmonary inflammation. However, we detected abnormal values only in a small number of patients, and their clinical significance is uncertain.

What may be the reasons for the small number of clearly abnormal values that could not be explained by atopic sensitization? dEBCpH values were persistently lowest in a boy with anti-phospholipid antibody syndrome due to SLE. At the time of the measurements he had stable disease, was not atopic, and did not develop pulmonary involvement during 5 years follow-up. At the time of the measurements he was on treatment with mycophenylate mofetil and

ramipril, both of which are known to cause pulmonary side effect. Thus, his persistent, remarkably low dEBCpH values may have been due to pharmacological interventions, although there are no data to support this hypothesis. Likewise, unexplained elevated F_ENO_{50} levels were detected in 5 non-atopic patients with intermediated elevation (20-35 ppb), and in one non-atopic patient with severe elevation (>35 ppb). It is currently not possible to explain the observed abnormalities in this small subset of patients (n=6; i.e. 7%), but this phenomenon certainly deserves to be addressed in future studies.

Limitations of the presented study

This study is limited by the fact that the patients were clinically stable and that no newly-diagnosed, treatment-naïve patients were included. It is conceivable that in newly manifesting disease, in particular SLE, abnormal values (reflecting disease-associated lung inflammation, albeit subclinical) might have been detected. Likewise, due to the composition of the patient population at our center, we could not include patients with sarcoidosis and only 1 patient with systemic sclerosis, both constituting disorders that typically feature lung involvement. However, it is known that at least F_ENO_{50} is not elevated in adult patients with sarcoidosis [16] or interstitial lung disease associated with connective tissue diseases [17]. Furthermore, analysis for concentrations of nitric oxide metabolites, e.g. nitrites and nitrates, would have been of great interest but was not available during the study period. This should be included in future studies. Moreover, comparing F_ENO_{50} and dEBpH with established screening tools for interstitial lung involvement such as diffusion lung capacity and echocardiography (to assess pulmonary artery pressure) would be important. Lastly, CHAQ scores were available for only a subpopulation of participants. However, the correlations between the CHAQ score and F_ENO_{50} or dEBCpH were so clearly not significant that it is highly unlikely that availability of CHAQ scores for a larger proportion of participants would reveal any significant associations.

Conclusions

In summary, in this clinically stable Caucasian population, F_ENO_{50} and dEBCpH values were mostly normal, and most abnormal values could be explained by concomitant atopic sensitization. However, the small number of patients with abnormal values not explained by atopic sensitization suggests that F_ENO_{50} and/or dEBCpH may have some value as biomarkers of abnormal pulmonary or systemic processes in selected cases. Further research will be necessary to identify such narrowly defined subpopulations or clinical scenarios in which

F_ENO_{50} and/or dEBCpH testing may be of clinical value in pediatric patients with rheumatologic disorders.

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Authors' contributions

NH recruited the patients, performed the F_ENO_{50} and dEBCpH measurements, and collected the pulmonary data. MKA performed data analysis, made the figures and edited the manuscript. JH acquired the CHAQ scores. CV oversaw the pulmonary aspects of the study and edited the manuscript. FP conceived and oversaw the study, wrote the first draft of the manuscript, had access to all data and takes responsibility for their integrity.

References

(1) Richardson AE, Warrier K, Vyas H. Respiratory complications of the rheumatological diseases in childhood. Arch Dis Child 2016 Jan 14.

(2) Munoz X, Bustamante V, Lopez-Campos JL, Cruz MJ, Barreiro E. Usefulness of Noninvasive Methods for the Study of Bronchial Inflammation in the Control of Patients with Asthma. Int Arch Allergy Immunol 2015 Feb 27;166(1):1-12.

(3) Nicolaou NC, Lowe LA, Murray CS, Woodcock A, Simpson A, Custovic A. Exhaled breath condensate pH and childhood asthma: unselected birth cohort study. Am J Respir Crit Care Med 2006 Aug 1;174(3):254-9.

(4) Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005 May 26;352(21):2163-73.

(5) Stewart L, Katial RK. Exhaled nitric oxide. Immunol Allergy Clin North Am 2012 Aug;32(3):347-62.

(6) Bucca C, Cicolin A, Guida G, Heffler E, Brussino L, Rolla G. Exhaled nitric oxide (FENO) in non-pulmonary diseases. J Breath Res 2012 Jun;6(2):027104.

(7) Ludviksdottir D, Janson C, Hogman M, Gudbjornsson B, Bjornsson E, Valtysdottir S, Hedenstrom H, Venge P, Boman G. Increased nitric oxide in expired air in patients with Sjogren's syndrome. BHR study group. Bronchial hyperresponsiveness. Eur Respir J 1999 Apr;13(4):739-43.

(8) Rolla G, Brussino L, Bertero MT, Colagrande P, Converso M, Bucca C, Polizzi S, Caligaris-Cappio F. Increased nitric oxide in exhaled air of patients with systemic lupus erythematosus. J Rheumatol 1997 Jun;24(6):1066-71.

(9) Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011 Sep 1;184(5):602-15.

(10) Jacinto T, Malinovschi A, Janson C, Fonseca J, Alving K. Evolution of exhaled nitric oxide levels throughout development and aging of healthy humans. J Breath Res 2015 Sep;9(3):036005.

(11) von Jagwitz M., Pessler F, Akmatov M, Li J, Range U, Vogelberg C. Reduced breath condensate pH in asymptomatic children with prior wheezing as a risk factor for asthma. J Allergy Clin Immunol 2011 Jul;128(1):50-5.

(12) Hofer M, Ruperto N, Saurenmann R, Sauvain MJ, Huppertz HI, Landgraf JM, Prieur AM. The Swiss German and Swiss French versions of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol 2001 Jul;19(4 Suppl 23):S151-S157.

(13) Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, Tortorelli A, Landgraf JM, Singh G, Martini A. Cross-cultural adaptation and psychometric

evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001 Jul;19(4 Suppl 23):S1-S9.

(14) Zapletal A, Paul T, Samanek M. [Normal values of static pulmonary volumes and ventilation in children and adolescents]. Cesk Pediatr 1976 Oct;31(10):532-9.

(15) Schmeling H, Stephan V, Burdach S, Horneff G. Pulmonary function in children with juvenile idiopathic arthritis and effects of methotrexate therapy. Z Rheumatol 2002 Apr;61(2):168-72.

(16) Choi J, Hoffman LA, Sethi JM, Zullo TG, Gibson KF. Multiple flow rates measurement of exhaled nitric oxide in patients with sarcoidosis: a pilot feasibility study. Sarcoidosis Vasc Diffuse Lung Dis 2009 Jul;26(2):98-109.

(17) Guilleminault L, Saint-Hilaire A, Favelle O, Caille A, Boissinot E, Henriet AC, Diot P, Marchand-Adam S. Can exhaled nitric oxide differentiate causes of pulmonary fibrosis? Respir Med 2013 Nov;107(11):1789-96.