

and shock. The provocative dose of aspirin was insufficient to block urinary COX metabolites—PGE₂-M and 11-dehydro-TXB₂. In fact, levels of both these metabolites rose rather than declined. This indicates that a patient with unusually high overproduction of cys-LTs was extremely susceptible to pharmacological inhibition of COXs, at the doses that did not depress any systemic metabolites of these enzymes. Reactions to both drugs were accompanied by an increase in PGD₂, the marker of mast cell activation.⁷ Thus, this cell seemed critical for triggering of an acute episode, progressing to a life-threatening shock when cys-LTs were involved by aspirin.

Our patient produced extreme amounts of cys-LTs, and the severity of the respiratory reactions during aspirin challenge was reported⁸ to be associated with the degree of baseline LTE₄ urinary excretion. We suspect that massive cys-LTs overproduction was related to severe chronic rhinosinusitis⁹ and inheritance of 1 genetic variant of LTC₄ synthase. The remarkable efficacy of the leukotrienes biosynthesis inhibitor, zileutone,¹⁰ which caused a regression of sinusitis concurrently with a return of urinary LTE₄ to the normal range, suggests that the patient's upper airway inflammation was mediated mainly by cys-LTs. Thus, in a patient with severe sinusitis and asthma, pharmacologic inhibition of leukotriene biosynthesis might be a worthy therapeutic option.

Lucyna Mastalerz, MD, PhD
Marek Sanak, MD, PhD
Agnieszka Gawlewicz, MD
Anna Gielicz, MSc
Jacek Faber, MSc
Andrew Szczeklik, MD, PhD

From the Department of Medicine, Jagiellonian University School of Medicine, Krakow, Poland.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

- Dahlen B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. *N Engl J Med* 2001;344:142.
- Viola M, Quarantino D, Gaeta F, Caringi M, Valluzzi R, Caruso C, et al. Celecoxib tolerability in patients with hypersensitivity (mainly cutaneous reactions) to nonsteroidal anti-inflammatory drugs. *Int Arch Allergy Immunol* 2005;137:145-50.
- Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Perez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;87:201-4.
- Grimm V, Rakoski J, Ring J. Urticaria and angioedema induced by COX-2 inhibitors. *J Allergy Clin Immunol* 2002;109:370.
- Baldassarre S, Schandene L, Choufani G, Michils A. Asthma attacks induced by low doses of celecoxib, aspirin, and acetaminophen. *J Allergy Clin Immunol* 2006;117:215-7.
- Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A* 1999;96:7563-8.
- Dahlen SE, Kumlin M. Monitoring mast cell activation by prostaglandin D₂ in vivo. *Thorax* 2004;59:453-5.
- Daffern PJ, Muilenburg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E₄ excretion during aspirin challenges with severity of respiratory responses. *J Allergy Clin Immunol* 1999;104:559-64.
- Higashi N, Taniguchi M, Mita H, Kawagishi Y, Ishii T, Higashi A, et al. Clinical features of asthmatic patients with increased urinary leukotriene E₄ excretion (hyperleukotrienuria): Involvement of chronic hyperplastic rhinosinusitis with nasal polyposis. *J Allergy Clin Immunol* 2004;113:277-83.
- Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187-94.

Available online August 25, 2006.
doi:10.1016/j.jaci.2006.06.028

Swimming pool attendance and exhaled nitric oxide in children

To the Editor:

In Western countries many children regularly attend indoor swimming pools, and swimming is recommended as the most appropriate sport for asthmatic children.¹ In the last few years, however, a certain interest has focused on the potentially harmful effects of chronic lung exposure to low concentrations of the chlorine derivatives that are used to disinfect the water in swimming pools.^{2,3} Free chlorine reacts with substances containing nitrogen (eg, sweat and urine) to form byproducts that can be detrimental to the respiratory system.² The most important of these byproducts seems to be nitrogen trichloride, a trichloramine that is almost insoluble in water and consequently highly concentrated in the air above the surface of the water. Bernard et al² recently showed that, in children who regularly attend swimming pools, serum surfactant proteins, biomarkers of lung epithelial damage, are increased, and their concentrations correlate with serum IgE levels. Moreover, these authors found a significant association between asthma prevalence and swimming pool attendance, suggesting that repeated exposure to chlorine derivatives can predispose to asthma development.^{2,4}

Exhaled nitric oxide (NO) levels are significantly increased in asthmatic patients, and they are considered an accurate biomarker of eosinophilic airway inflammation.^{5,6} The maneuver required to measure exhaled NO is quick and can easily be performed by children starting from the age of 4 years.⁷

Moving from the above-reported findings, we hypothesized that if chlorine exposure is associated with asthma development, then increased concentrations of exhaled NO, as a marker of eosinophilic airway inflammation, should be detectable in children regularly attending swimming pools.

To test this hypothesis, children attending a primary and a secondary school in Padova were asked to perform fractional exhaled NO (FE_{NO}) measurement. FE_{NO} was measured with the NIOX system (Aerocrine, Stockholm, Sweden)⁸ by using a single-breath online technique, with a target expiratory flow of 50 mL/s, according to the American Thoracic Society/European Respiratory Society recommendations.⁷ Two hundred forty-one subjects were enrolled in the study. After obtaining written consent from

TABLE I. Demographic characteristics and clinical history of the studied population

	Total sample (n = 241)		Non-SP children (n = 141)		SP children (n = 100)		P value
	n	%	n	%	n	%	
Demographic data							
Age (y), median (IQR)	9 (7-10)		9 (8-10)		7 (7-10)		.001*
Female sex	121	50.2	72	51.1	49	49.0	.752†
Anamnestic data							
Atopic diseases in the family	85	35.3	49	34.7	36	36.0	.842†
Upper airway infection in last week	76	31.5	44	31.2	32	32.0	.896†
Asthmatic symptoms	43	17.8	26	18.4	17	17.0	.774†
Allergic rhinitis	43	17.8	25	17.7	18	18.0	.957†
Atopic eczema	40	16.6	28	19.9	12	12.0	.106†
Passive smoke exposure	24	10.0	16	11.3	8	8.0	.393†

SP, Swimming pool.

*Student *t* test.

† χ^2 test.

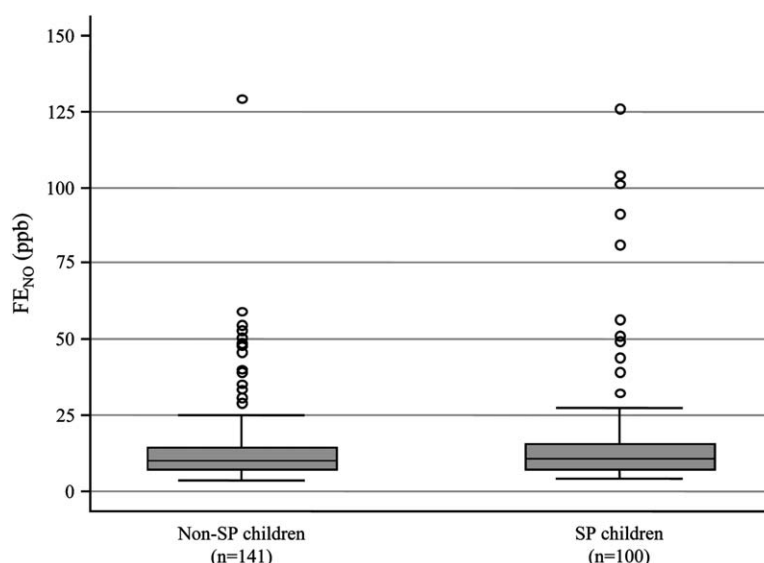


FIG 1. Distribution of FE_{NO} by swimming pool attendance. Box plots represent medians and IQRs. The error bars extend to the upper and the lower adjacent value, which is defined as the largest data point less than or equal to 75th percentile + $1.5 \times$ IQR and the smallest data point greater than or equal to 25th percentile + $1.5 \times$ IQR, respectively. Circles represent outliers.

their parents, children were given a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire,⁹ with additional questions on swimming pool attendance (they were asked whether they were regularly attending a swimming pool, since when, and for how many hours a week). We classified as swimming pool attendees (SP children vs non-SP children) those children who, at the time of recruitment for the study, had been attending an indoor swimming pool for at least 6 months and for at least 1 hour a week. The study was reviewed and approved by the ethics committee of our hospital.

One hundred children were regularly attending a swimming pool, and 141 were not. The children's demographic characteristics and clinical history, considering the group as a whole and the 2 subgroups, are given in

Table I. The distribution of FE_{NO} levels is presented in Fig 1. The median values of FE_{NO} and interquartile ranges (IQRs) were similar in the 2 subgroups: 9.9 ppb (IQR, 7.1-14.6) in non-SP children and 10.5 ppb (IQR, 7.2-15.4) in SP children ($P = .4$, median test). The number of outliers was also similar: 15 in the non-SP group and 11 in SP group. FE_{NO} levels higher than 75 ppb were found in 6 subjects (1 non-SP child and 5 SP children), all with self-reported (International Study of Asthma and Allergies in Childhood questionnaire) personal or family histories of atopic diseases. Multiple linear regression was performed to control confounding in the relationship between FE_{NO} and swimming pool attendance. Because of the marked skewness of FE_{NO} values, robust methods¹⁰ were used (STATA 8; Stata Corp, College Station, Tex). FE_{NO} levels

were not different in children attending and not attending swimming pools (mean difference, 0.43 ppb; 95% CI, -0.79 to 1.65), whereas they were higher both in children with upper airway infections in the last week (mean difference, 2.20 ppb; 95% CI, 0.85 to 3.55) and in those who had a history of asthmatic symptoms (mean difference, 2.51 ppb; 95% CI, 0.75 to 4.27).

Therefore the present study showed that FE_{NO} level, an exhaled biomarker of eosinophilic airway inflammation, is similar in children who regularly attend a swimming pool and in those who do not.

The potentially harmful effect of chlorinated substances on the respiratory health of swimmers and persons working at swimming pools has only lately become a matter of interest.³ Helenius et al¹¹ demonstrated increased bronchial responsiveness and mild eosinophilic and lymphocytic airway inflammation in highly trained competitive swimmers. These elite swimmers used to train for up to 30 hours a week, actively inhaling large amounts of air right above the water surface, where nitrogen trichloride concentrations are reportedly in the range of 0.14 to 0.8 mg/m³.² Conversely, the children enrolled in our study were recreational swimmers attending the pool for an average 1.7 hours a week, which is probably typical of the time spent at the pool by children attending swimming lessons. Our findings suggest that this level of exposure to chlorine derivatives does not induce eosinophilic inflammation in children, as reflected by exhaled NO levels. In keeping with this result, we found no difference in asthma symptoms between SP and non-SP children.

Although our data lead us to believe that an asthma-like inflammation in the airways of SP children is unlikely, few data are available in human subjects on the pathobiology of chlorine-induced lung damage, and we cannot rule out an underlying inflammatory response driven by cells other than eosinophils and unrelated to FE_{NO} levels.

In the present study we also evaluated several other variables potentially related to exhaled NO, and we found a significant correlation between FE_{NO} levels and a personal history of asthma and of recent upper airway infection, confirming previous results.¹²

In conclusion, we found that children regularly attending indoor swimming pools for 1 to 2 hours a week do not have increased FE_{NO} levels, suggesting that intermittent exposure to chlorine derivatives does not induce eosinophilic airway inflammation. Further studies might be useful to evaluate whether such exposure can induce any other inflammatory responses in the airways of recreational swimmers.

Silvia Carraro, MD^a
Maria Francesca Pasquale, MD^a
Monica Da Frè, MSc^b
Franca Rusconi, MD^c
Gea Bonetto, MD^a
Stefania Zanonato, MD, PhD^a
Eugenio Baraldi, MD^a

From ^athe Department of Pediatrics, Allergy and Respiratory Medicine Unit, Padova, Italy; ^bthe Unit of Epidemiology, Regional Health Agency of

Tuscany, Firenze, Italy; and ^cthe Department of Epidemiology, AOU Meyer, Firenze, Italy.

Disclosure of potential conflict of interest: E. Baraldi has served on the Scientific Advisory Board of Aerocrine. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Fitch KD, Morton AR, Blanksby BA. Effects of swimming training on children with asthma. *Arch Dis Child* 1976;51:190-4.
2. Bernard A, Carbonnelle S, Michel O, Higuier S, de Burbure C, Buchet J-P, et al. Lung hyperpermeability and asthma prevalence in schoolchildren: unexpected associations with the attendance at indoor chlorinated swimming pools. *Occup Environ Med* 2003;60:385-94.
3. Nemery B, Hoet PHM, Nowak D. Indoor swimming pools, water chlorination and respiratory health. *Eur Respir J* 2002;19:790-3.
4. Bernard A, Carbonnelle S, Nickmilder M, de Burbure C. Non-invasive biomarkers of pulmonary damage and inflammation: application to children exposed to ozone and chloramines. *Toxicol Appl Pharmacol* 2005;206:185-90.
5. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adult with asthma. *Clin Exp Allergy* 2005;35:1175-9.
6. Strunk RC, Szeffer SJ, Philips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;112:883-92.
7. Baraldi E, de Jongste JC. ERS/ATS statement. Measurement of exhaled nitric oxide in children, 2001. *Eur Respir J* 2002;20:223-37.
8. Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szeffer SJ. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol* 2004;114:1241-56.
9. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
10. Goodall C. M-estimators of location: an outline of the theory. In: Hoaglin DC, Mosteller F, Tukey JW, editors. *Understanding robust and exploratory data analysis*. New York: John Wiley & Sons; 1983. p. 339-431.
11. Helenius I, Ryttilä P, Sarna S, Lumme A, Helenius M, Remes V, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002;109:962-8.
12. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;58:1048-52.

Available online August 29, 2006.
doi:10.1016/j.jaci.2006.07.016

Correlation of *FCER1B* gene haplotypes with histamine release from basophils in atopic asthma

To the Editor:

The pathophysiologic features of atopic disorders, including atopic asthma, consist of enhanced IgE production, increased mediator release from inflammatory cells, and hypersensitivity of target organs.¹ The interaction between allergen-specific IgE and its high-affinity receptor, FcεRI, which is present on the surface of human mast cells and basophils, is the key to the onset and propagation of allergic diseases.²