

The acute effect of swimming on airway inflammation in adolescent elite swimmers

To the Editor:

Elite athletes have been found to have airway inflammation, and endurance sport, in particular, has been suggested to cause inflammation. The number of studies on airway inflammation in elite athletes is limited. Most studies have focused on the long-term effect of elite sport, and only a few studies have examined the acute effect of exercise on airway inflammation. These few studies have mainly considered adult nonelite or elite athletes who have been involved in elite sport for many years and who already seem to have had significant inflammatory changes. It remains uncertain whether exercise increases existing airway inflammation or whether exercise can induce an acute inflammatory process in individuals without airway inflammation. In this study we aimed to evaluate the acute effect of a training session in an indoor swimming pool on airway inflammation in adolescent elite swimmers.

Participants were 21 adolescent elite swimmers (9 girls). The study was approved by the local ethics committee (journal no. KF 01 261528). All participants and their parents or guardians provided informed consent.

The study consisted of 2 visits. Visit 1 was performed at our department, where we performed sputum induction (baseline findings) and other tests as part of another study (skin prick tests to 10 aeroallergens, methacholine challenge, and the eucapnic voluntary hyperpnea test).¹ At visit 2, the swimmers performed an early-morning training session of swimming at moderate intensity (approximately 45 minutes with an average heart rate of 162 beats/min) in the 8 indoor swimming pools normally used by the swimmers for training. The levels of free chlorine, combined chlorine, and pH were 0.60 to 1.04 mg/L, 0.18 to 0.35 mg/L, and 7.16 to 7.51, respectively. At visit 2, we performed sputum induction, fraction of exhaled nitric oxide (FeNO) measurement (NIOX MINO; Aerocrine, Stockholm, Sweden) at a flow of 50 mL/s, exhaled breath condensate (EBC) collection (RTube; Respiratory Research, Inc, Charlottesville, Va), and spirometry (EasyOne spirometer; Ndd Medical Technologies, Zurich, Switzerland). All tests at visit 2 were performed before the subjects entered the swimming pool area and were repeated 10 minutes after swimming, except for sputum induction, which was performed after swimming only. The pH measurements were done with a pH meter (Jenway pH meter 350; Dunmow, Essex, England) after deaeration with argon for 10 minutes. Sputum was induced and examined as described previously.¹ Sputum samples were considered adequate if they contained less than 80% squamous cells. A blinded observer counted 400 nonsquamous cells.

Paired data were compared by using the paired *t* test or the Wilcoxon matched-pairs signed-rank test as appropriate. Differences in skewed data between the preswimming and postswimming measurements were assessed by using the Mann-Whitney test. *P* values of less than .05 were considered statistically significant.

Subject characteristics are shown in Table I. The swimmers had significantly higher baseline values of FEV₁ and forced vital capacity than expected, and lung function values were unchanged after swimming (Table II). At baseline, 15 (71%) sputum samples met our criteria for being usable; 9 (43%) were usable after swimming, and only 5 sputum samples were usable at both visits. The sputum samples at baseline showed 37.3% neutrophils, 2.0%

TABLE I. Subject characteristics

Age (y)	14.5 (1.0)
Physician-diagnosed asthma	2 (10%)
Weekly exercise, recreational (h)	3.9 (1.3)
Weekly training, elite (h)	20.5 (5.6)
Duration of swimming in total (y)	9.1 (2.9)
Duration of competitive swimming (y)	2.6 (1.4)
Airway hyperresponsiveness	6 (29%)
Atopy	6 (29%)

Data are expressed as means (SDs) or numbers (percentages). Airway hyperresponsiveness was defined as a decrease in FEV₁ of at least 10% to a eucapnic voluntary hyperpnea test, at least a 20% decrease in FEV₁ at a cumulative dose of methacholine of 8 μ mol or less, or both. Atopy was defined as a wheal of at least 3 mm in diameter to at least 1 of the 10 tested aeroallergens.

lymphocytes, and 0.5% eosinophils, and in the 9 sputum samples obtained after swimming, the corresponding numbers were 36.0%, 1.5%, and 0.0% (Table III). In a paired analysis there were no changes in differential cell counts in the 5 swimmers who managed to produce usable sputum samples at both visits. The median FeNO level was 12.0 ppb before swimming and increased insignificantly to 15.5 ppb after swimming (*P* = .07, Fig 1). We found no difference in preswimming and postswimming values of EBC pH (Table II), which has been suggested as a noninvasive marker of airway inflammation.

We found that a training session of approximately 45 minutes at moderate intensity in an indoor chlorinated pool did not influence cellular composition of sputum, FeNO, EBC pH, or lung function in adolescent elite swimmers. Our results disagree with findings in nonasthmatic amateur adult runners, in whom FeNO and differential cell counts of neutrophils and macrophages in sputum have been shown to increase after running a marathon.² Conversely, our findings are partly in line with studies on elite rowers and swimmers.^{3,4}

Whereas older elite swimmers with years of intense training have certain signs of airway inflammation, predominantly with neutrophils,⁵ the adolescent elite swimmers in the present study showed at baseline that they have not yet had major inflammatory airway changes, as evaluated based on FeNO results and cellular composition in sputum, nor did they have acute changes in response to a swimming training session of moderate intensity.¹ Interestingly, findings by Belda et al⁶ suggest that the neutrophilic inflammation observed in elite swimmers relates to the duration of training, as well as AHR, and Boulet et al⁷ found that sputum neutrophils increase in hyperresponsive swimmers after a 1-hour training session, whereas no significant difference was observed in normoresponsive swimmers. We speculate that primarily athletes with signs of airway inflammation at baseline have significant acute changes in cellular composition in response to a training session of an intensity and length as seen in our study. However, we cannot rule out that a longer or more intense training session would have caused airway changes. Furthermore, the low number of usable sputum samples both before and after swimming limits the conclusions about changes in sputum composition. One explanation why only 9 sputum samples were usable after swimming could be that much of these materials are either coughed up or swallowed during swimming.

Not only endurance sports *per se* but also factors related to endurance sport are believed to be able to induce airway inflammation. In swimming chlorinated compounds are suggested as factors that cause airway inflammation and asthma not only in

TABLE II. Lung function, FeNO, and EBC pH values

	Before swimming	After swimming	P value
FEV ₁ (L)	4.2 (3.1–5.4)	4.3 (2.7–5.7)	NS
FEV ₁ (% predicted)	115 (77–139)	115 (62–144)	NS
FVC (L)	4.8 (3.6–6.6)	4.7 (3.2–7.8)	NS
FVC (% predicted)	119 (77–139)	120 (63–143)	NS
FEV ₁ /FVC (% predicted)	101 (84–110)	101 (80–111)	NS
FeNO (ppb)	12.0 (4–31)	15.5 (5–47)	NS
EBC pH, deaerated	8.05 (5.03–8.36)	8.13 (6.82–8.51)	NS

Data are expressed as medians (ranges).

NS, Not significant; FVC, forced vital capacity.

TABLE III. Induced sputum

	Before swimming	After swimming	P value
Usable samples	15 (71%)	9 (43%)	NS
Squamous cells	21.7 (0–79.0)	14.9 (0–78.0)	NS
Eosinophils	0.5 (0–3.0)	0.0 (0–1.0)	NS
Lymphocytes	2.0 (0–8.3)	1.5 (0–5.0)	NS
Macrophages	56.5 (10.6–96.8)	49.0 (5.0–86.0)	NS
Neutrophils	37.3 (0–81.7)	36.0 (7.0–92.0)	NS
Columnar epithelial cells	4.0 (0–13.3)	2.3 (1.0–50.0)	NS

Data are expressed as medians (ranges), except “Usable samples,” which is expressed as number (percentage). The percentage of squamous cells is expressed as a percentage of the total cell count. Differential counts for other cells are expressed as a percentage of lower airway cells, excluding squamous cells.

NS, Not significant.

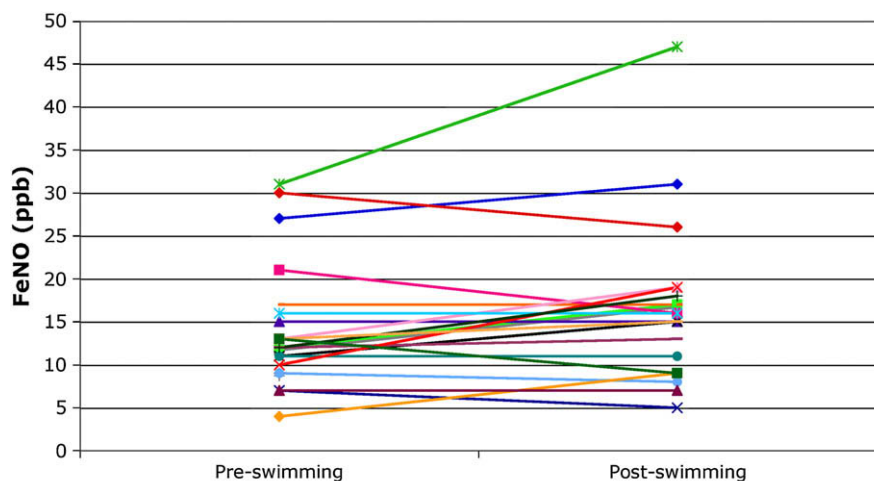


FIG 1. FeNO values before and after swimming.

elite swimmers but also in the general population frequenting swimming pools.^{8,9} It has been suggested that the increasing exposure to chlorine in swimming pools could be an important factor in the increase of asthma in developed countries, and the risk of having asthma culminates when children regularly attend chlorinated indoor pools before age 6 to 7 years.¹⁰ In contrast to this hypothesis, Carraro et al¹¹ found that children regularly attending indoor swimming pools have no signs of eosinophilic airway inflammation. Our study supports the finding by Carraro and co-workers. Even though the swimmers in our study had been involved in competitive swimming for only a few years, most had done recreational swimming since early childhood, and still they had no sign of airway inflammation.

In conclusion, we found that a swimming training session in an indoor chlorinated swimming pool did not induce airway changes in adolescent elite swimmers with no signs of prior airway inflammation. More studies are needed to determine exactly what kind and how much exercise is needed to cause airway inflammation. Furthermore, the exact effect of environmental factors, such as chlorine-containing products, on the airways requires more attention.

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Successful treatment of chronic drug-resistant urticaria with alprazolam

To the Editor:

Alprazolam has shown competitive antagonism on muscarinic and histamine H1 receptors and noncompetitive antagonism on histamine H2 receptors. The antagonistic effect of alprazolam on histamine H1 receptors has been studied in guinea pig ileum, and that on histamine H2 receptors has been studied on rat uterus.¹ Pretreatment with kadsurenone or alprazolam improved survival in hypersensitivity reactions to ovalbumin in guinea pig lung parenchymal strips and in guinea pigs *in vivo*.² This antihistaminic effect has not been tested in allergic patients, although one study found that alprazolam appeared to be safe and effective for the

treatment of anxiety and depression in adolescents with asthma.³ Exceptionally, alprazolam might induce allergic symptoms and angioedema.⁴

Chronic urticaria (CU) is a common disorder that is generally of unknown origin, although the cause might be autoimmune in some cases.⁵ In some patients severe urticaria is a distressing and disabling condition⁶ with a significant effect on the quality of life, and patients often receive various unsuccessful treatments. First-line treatment consists of the newer-generation oral antihistamines, whereas other drugs might be considered in refractory cases,⁷ although more controlled studies are necessary.

We recently studied allergic sensitization in drug abusers, who are often treated with alprazolam. Forty-two drug abusers were tested with common allergens (aeroallergens and foods) and pharmacologic drugs (nonsteroidal anti-inflammatory drugs and other suspected drugs). Histamine (10 mg/mL) was used as a positive control, and a wheal area greater than 7 mm² (an area measuring 3 × 3 mm) was considered positive. In some patients skin prick test responses with allergens were negative, but results with histamine, used as a positive control, were also totally negative. This is unusual because the histamine control should elicit a small wheal, even when the patient has taken an antihistamine. These patients denied intake of antihistamines or other antiallergic drugs, but all were taking 2 mg of alprazolam (Trankimazin; Pfizer S. A., Madrid, Spain) 3 times daily. We then decided to carry out a preliminary study to investigate whether alprazolam could be useful in severe refractory CU.

We identified 558 patients with idiopathic CU in our database of 19,736 patients followed in the allergy section during the last 20 years. All patients had undergone a protocol investigation according to recent studies^{5,6} to investigate the possible cause. Only 12 of the 558 patients had criteria of severe refractory idiopathic urticaria of more than 10 years of evolution in which treatment with all known drugs used in this disease (all first-generation antihistaminics,⁸ all newer-generation antihistamines, corticosteroids in different schemes, cyclosporine treatment,⁹ intravenous gammaglobulin,¹⁰ and omalizumab¹¹) had failed. The 12 patients were initially randomized to 2 mg of alprazolam 3 times daily or 10 mg of rupatadine (Rupafin; Uriach, Barcelona, Spain) 3 times daily, a new antihistamine platelet-activating factor (PAF) inhibitor. The drugs were introduced into identical empty capsules and administered randomly by a nurse blinded to the contents. However, only 8 patients finally consented to participate and completed the trial.

After 2 days, the urticaria disappeared in the 6 patients treated with alprazolam and persisted in the 2 patients treated with rupatadine. No secondary effects were observed. Urticaria reappeared after 36 hours after withdrawal of alprazolam and improved 8 hours after readministration.

Although both alprazolam and rupatadine are PAF receptor antagonists,^{1,2} the poor response to rupatadine suggests that the main mechanism of alprazolam in CU might be blockade of histamine H1 receptors and not PAF inhibition. The importance of this small study lies in the fact that 6 of 6 patients treated with alprazolam responded, whereas the 2 patients treated with rupatadine did not.

Because of the difficulty in identifying the causative factors involved, treatment for severe CU often focuses on measures to provide symptomatic relief. Our positive experience, although only in a small group of patients, suggests a controlled trial with