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The Pro- and Anti-Inflammatory Cytokine Response to Exercise in Adolescent Swimmers

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Abstract

Objective—Whether or not individuals with allergy and asthma experience different patterns of change in the balance of both pro- and anti-inflammatory mediators with acute exercise is not known. We hypothesized that adolescent swimmers with a clinical diagnosis of respiratory allergy would have an exaggerated proinflammatory response to laboratory exercise relative to a no-allergy comparison group.

Methods—Adolescent swimmers (17 with clinical symptoms of respiratory allergy (CSRA) and 17 in comparison group) completed the American Thoracic Society (ATS) exercise challenge on cycle ergometer. Blood was collected at baseline and immediately post-exercise. All study tests were conducted at the Institute for Clinical Translational Science at the University of California, Irvine. Circulating cytokines, growth factors, and adhesion molecules were measured using ELISAs including transforming growth factor- β 1 (TGF- β 1), tumor necrosis factor- α (TNF- α), interleukin-4 (IL-4), IL-6, IL-10, P-selectin, and immunoglobulin E (IgE).

Results—There was a trend toward higher resting levels of TNF- α in the CSRA group ($P = 0.076$). Exercise induced a significant increase in P-selectin and TGF- β 1 in both groups. TNF- α increased significantly (17%) in the comparison group (pre = 0.6, post = 0.7 pg/mL), but not in the CSRA group. IL-6 increased significantly in the CSRA group (pre = 0.7, post = 0.8 pg/mL), but not in the comparison group. Circulating levels of IL-4 and IL-10 were not altered immediately post-exercise in either group.

Conclusions—A short bout of intense exercise increased inflammatory growth factors and adhesion molecules, namely TGF- β 1 and P-selectin, both of which are known to be involved in allergic airway diseases. Differences in resting IL-6 and TNF- α and exercise alterations in these cytokines may also contribute to allergic disease in adolescent elite swimmers.

Introduction

Exercise-induced allergy and asthma in child and adolescent populations remains a serious problem.^{1,2} The allergic response to exercise can vary from a relatively benign reaction such as urticaria to anaphylaxis and death. Paradoxically, exercise leads to an acute increase in

immune cells and mediators in the peripheral blood and many of these changes are also known to be involved in the allergic response.^{3,4} The factors that prevent allergic responses such as rhinitis and bronchoconstriction from occurring in everyone upon exercise despite immune activation remain unknown. Higher rates of respiratory infection, congestion, and allergy and asthma have been reported in endurance-trained athletes.⁴⁻⁶ In the case of swimmers, there is evidence that immune system adaptation to high-intensity exercise training and exposure to chlorine induces allergic disease, increases airway sensitization and reactivity.⁷⁻⁹ We hypothesized that elite-level adolescent swimmers with a clinical diagnosis of respiratory allergy would have an exaggerated proinflammatory response to laboratory exercise compared to swimmers in a non-allergic comparison group.

Exposure to stress and environmental allergens are thought to increase proinflammatory cytokines and serve as an allergy trigger.¹⁰ Exercise is one such stress that can lead to a proinflammatory state. However, since a single cytokine can both stimulate and inhibit the subsequent release of inflammatory mediators, it is important to first understand how the acute cytokine response associated with exercise may be linked to a prior diagnosis of allergy. A brief summary of the inflammatory mediators selected for the analysis can be found in Table 1. We hypothesized that the cytokine response in elite-level swimmers with a clinical diagnosis of respiratory allergy would be shifted in favor of Type I cytokines and inflammatory growth and adhesion factors (transforming growth factor- β 1 [TGF- β 1] and P-selectin) compared to matched adolescent swimmers without allergic disease. To test this theory, we analyzed circulating cytokine levels in elite-adolescent swimmers before and after a laboratory-based exercise challenge. The laboratory-based exercise setting was selected so that we could exclude the cytokine response associated with exposure to a known environmental irritant, namely, chlorine, and investigate the purely physiological response associated with brief high-intensity exercise.

Higher resting interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels are positively correlated with both adiposity and physical inactivity in adolescents.^{11,12} Higher resting IL-6 and TNF- α have been observed in normal-weight sedentary adolescent females compared to their active counterparts.¹² Both exercise training and favorable body composition are, therefore, associated with lower resting levels of inflammatory cytokines as well as an attenuated cytokine response to exercise.¹³

Materials and Methods

Participants

In order to control for prior fitness level, high-school elite-level swimmers were recruited from the Southern California area via circulation of fliers at invitational swim meets and contact with local swim clubs. All participants were training intensely (3 h/day, 6 days/week). All subjects completed fitness testing including: maximal exercise testing, DEXA, medical history and exam, and pulmonary function testing (PFT). The University of California at Irvine Institutional Review Board approved this study. Informed written consent and assent were obtained from all participants and their parent/guardian.

Three subjects excluded from the analysis had no prior history of allergy or asthma diagnosis; however, they self-reported persistent cough and congestion. The subjects also had either abnormally high immunoglobulin E (IgE), eosinophilia, or a clinically significant reduction in FEV₁ (forced expiratory volume in 1 second) prior to exercise. Without a prior diagnosis of asthma, we felt the subjects were most likely recovering from an upper respiratory infection or had undiagnosed allergy or asthma. Since our research protocol did not allow for us to make a formal diagnosis, they were excluded from the analysis.

Inclusion/exclusion criteria

Swimmers had to have achieved a minimum USA-Swimming Invitational time within 1 year of consent. Exclusion criteria included having had an upper respiratory infection, severe persistent asthma, or acute exacerbation within the previous 14 days, and athletes that had used parenteral corticosteroids within the month prior to study.

We separated participants based on their prior diagnosis of “Clinical Symptoms of Respiratory Allergy (CSRA).” Subjects were queried using a validated Allergy/Asthma questionnaire.¹⁴ Medical information obtained included prior clinical diagnosis of allergy triggers, frequency of symptoms, co-morbidity, and clinical treatment of respiratory disease. Seventeen swimmers met the criteria of the comparison group (no prior history of respiratory allergy), and 17 swimmers met the criteria of the CSRA Group. Three of the 37 subjects were excluded from the final analysis due to conflicting clinical and laboratory findings. Three subjects in the comparison group had mild persistent non-allergic asthma and 10 subjects in the CSRA group had mild persistent allergic asthma using current NHLBI standards.¹⁵ Note: none of the subjects in the comparison group experienced exercise-induced bronchoconstriction (>10% drop in FEV₁ and >25% drop in FEF₂₅₋₇₅).

Medical histories revealed that swimmers in the CSRA group were using over-the-counter (OTC) or prescription medications: 7 used anti-leukotrienes, 3 inhaled corticosteroids (ICCs), and 7 short-acting beta-agonists and antihistamines. All participants were instructed not to use anti-inflammatory and OTC medications for 72 h; anti-leukotrienes and ICCs for 48 h; short-acting beta-agonists for 12 h prior to visit.

Exercise protocol and pulmonary function testing

Participants reported to the Institute for Clinical Translational Science at University of California Irvine Human Performance Lab for 2 visits on separate days. All subjects completed the American Thoracic Society (ATS) exercise-induced bronchoconstriction (EIB) challenge designed to diagnose EIB in children.¹⁶

Following a brief warm up, the ATS exercise challenge consists of at least 8 min of exercise at 85% of maximal capacity.¹⁶ Note: we selected the outward limit of exercise time to ensure sufficient exercise stimulus in this group of highly trained athletes. The ATS exercise was performed in a temperature-controlled lab on an electronically braked, servo-controlled, cycle ergometer. Throughout the test, work rate was adjusted to maintain heart rate within a target range. PFTs were performed via spirometry at baseline, 5 min, and 15- to 20-min post-exercise. Subjects who experienced clinically significant drops (>10% drop in FEV₁ and or >25% drop in FEF₂₅₋₇₅) were treated with rescue medications (β-2 agonists) and

followed until post-exercise lung function returned to baseline conditions. The best, valid effort of the 3 attempts per time point was used for statistical analysis.

Blood sampling

An indwelling catheter was inserted into the antecubital vein. A baseline sample was taken 30 min after placement of catheter to ensure physiological parameters of stress (eg heart rate/blood pressure) were at baseline levels. A second blood sample was obtained immediately after exercise. The plasma was separated and stored at -80°C and thawed once for analysis. Whole blood was used to quantify primary WBC subpopulations using standard methods from the Clinical Hematology Laboratory at our institution. Blood lactate levels were measured in the fielding using a YSI Glucose and Lactate Analyzer.

Cytokine measurement

Blood samples were collected from athletes pre- and post-exercise. Plasma was separated in an EDTA anticoagulant. IL-4, IL-6, IL-10, TNF- α , TGF- β 1, P-selectin were measured using R&D Technologies kits. The sensitivity of the tests were: IL-4 (0.03 pg/mL), IL-6 (0.016 pg/mL), IL-10 (0.5 pg/mL), TNF- α (0.038 pg/mL), TGF- β 1 (4.6 pg/mL), and P-selectin (0.5 ng/mL). IgE was measured using Alpco Elisa kit with a sensitivity of 5.0 IU/mL. Pre- and post-exercise samples were analyzed on the same assay plate to decrease interkit assay variability.

Statistical analysis

Data are expressed as mean $\pm$ standard error of the mean (SEM). Statistical analysis was performed using the Version 15 SPSS statistical software. Results of analysis are for concentrations of cytokine relative to volume of plasma. Most cytokine concentrations were not normally distributed. Therefore, we utilized more conservative nonparametric techniques to analyze all data. Pre- to post-exercise comparison was made using Wilcoxon nonparametric paired t -test and group differences using Mann–Whitney nonparametric t -test. In the analysis of size- or gender-dependent variables (FEV_1 , $\text{VO}_{2\text{max}}$), linear regression was used to control for the contribution of gender, group, and height.

Results

Participants and baseline evaluation

Descriptives are provided in Table 2. The CSRA group had higher total IgE and eosinophil levels than the comparison group. Gilbert et al. showed that circulating IgE and eosinophil counts were highly correlated with aeroallergen sensitization in children.¹⁷

Swimmers in the comparison and CSRA groups did not differ for any of the anthropometric or fitness measures. The average FEV_1/FVC ratio (ratio of forced expiratory volume at 1 s to forced vital capacity) is shown in Table 2. The CSRA group had a statistically significantly, but not clinically relevant lower FEV_1/FVC ratio. All of the subjects were within the normal range (FEV_1/FVC ratio >0.70) at both baseline and post-exercise (see Table 3). The CSRA group had higher baseline TNF- α 0.8 ± 0.1 pg/mL than comparison

group 0.6 ± 0.1 pg/mL and the differences came very close to reaching significance, $P = 0.076$.

Exercise effect

A summary of the exercise response is reported in Table 3. There was a significant increase in the average blood lactate levels. Peak lactate did not differ by group, nor did exercise-induced leukocytosis (EIL). After controlling for gender, height, and age, the differences in pulmonary function between the CSRA and comparison groups were not statistically significant. However, we point out that the FEV_1/FVC ratio, a non-size-dependent measure of pulmonary function, was statistically lower at baseline and post-exercise in the CSRA group. A prior diagnosis of non-allergic asthma had no influence on the exercise response, asthmatics and nonasthmatic subjects did not differ.

Cytokine response

Exercise induced a significant increase in P-selectin and TGF- β 1 in both the CSRA and comparison groups ($P < 0.001$) with no significant differences in anti-inflammatory cytokines (see Fig. 1 and Table 4). TNF- α increased significantly ($\sim 17\%$) in the comparison group (pre = 0.6 pg/mL, post = 0.7 pg/mL), but failed to reach significance in the CSRA group ($P < 0.05$) (Fig. 2). IL-6 increased significantly in the CSRA group (pre = 0.7 pg/mL, post = 0.8 pg/mL), but circulating levels but did not change in the comparison group ($P < 0.05$). Circulating levels of IL-4 and IL-10 were not altered by exercise in either group. The group comparison did not reveal differences between the CSRA and comparison group. We recognize the necessity of investigating differences in the cytokine response attributed to exercise training. Studies in non-athlete populations have been published previously by our group^{17–19} and training studies are underway.

Discussion

Thirty-four trained adolescent swimmers completed the study. We observed similar levels of EIL in the CSRA and comparison groups ($\sim 50\%$ increase in total leukocytes). This finding is consistent with two previous studies by our group, where we observed similar levels of EIL in adolescents with asthma and allergy compared to healthy controls.^{3,18}

Recent studies of changes in gene expression associated with acute exercise show that the degree of up-regulation in some genes cannot be explained solely by the migration of a different population of immune cells into the peripheral circulation; that is, cells expressing different patterns. Several genes in the “cytokine receptor functional group” have been shown to change with exercise.^{19,20} Dramatic changes in leukocyte gene expression and alterations in extracellular cytokine concentrations that we observed in this study (namely increases in TGF β 1, P-selectin, IL-6, and TNF- α) suggest that leukocytes are reactive to the stress of exercise and that these alterations may contribute to exercise-induced allergy and asthma.^{21,22}

In this study, we demonstrated that brief high-intensity exercise induced a robust increase in P-selectin and TGF- β 1. P-Selectin promotes leukocyte recruitment to tissue and is known to play a critical role in the attraction/adhesion of inflammatory cells to endothelial tissue in

eosinophilic asthma.²³ TGF- β 1 also increased dramatically in both groups. This cytokine regulates downstream immune activity by promoting apoptosis and cell differentiation; TGF- β 1, though classified as a Type I cytokine, has been linked to immunoregulatory pathways. It promotes the conversion of T lymphocytes to T-regulatory cells (Tregs) and may be implicated in the control of allergy since higher levels of Tregs have been found in allergy.^{20,24} These studies suggest that higher levels indicate a failed attempt to blunt the inflammatory response, though the exact reason for the breakdown in this mechanism is not understood. Additionally, the extent to which other cytokines act as signaling agents is not known. Circulating levels of TGF- β 1 have been shown to increase 2.7-fold following 2 h of strenuous exercise in young adult males.²⁵ In a previous study, we showed that Tregs increased following swim exercise in highly trained adolescent swimmers.²⁰ Unfortunately, TGF- β 1 levels were not measured in parallel, therefore we were unable to determine whether changes in cytokine levels were predictive of allergic responsiveness.

Of note were the differences observed for IL-6 and TNF- α . Both of these cytokines are involved in the early activation phase of the immune response.¹³ Lower resting levels and reduced IL-6 mRNA production has been previously reported in endurance-trained athletes.²⁶ The significance of this finding is yet to be determined. Comparison of potential differences in the pro- and anti-inflammatory cytokine response in non-athletes versus athletes is therefore of interest in future studies.

Gokhale compared circulating levels of TNF- α and IL-6 following ~1 h of intense endurance exercise in both athletes and non-athletes.¹³ The cytokine response varied by group with the majority of both athletes and non-athletes showing increases in IL-6 and decreases in TNF- α .¹³ The influence of resting cytokine levels on the exercise response was not reported. There is a paucity of data focusing on acute changes in circulating anti-inflammatory mediators following intense exercise; and more importantly, how the balance of certain mediators relates to the risk of allergy in athletes.

Resting TNF- α levels, however, were of interest because of the trend to be significantly lower in non-allergic athletes (mean = 0.7 ± 0.1 pg/mL). The CSRA group had higher baseline TNF- α 0.8 ± 0.1 pg/mL than comparison group 0.6 ± 0.1 pg/mL and the differences came very close to reaching significance, $P = 0.076$. The nonsignificant increase in TNF- α may have been due to higher resting levels of TNF- α more so than the response to exercise.

Circulating levels of IL-4 and IL-10 did not change significantly immediately post-exercise for either group. Since anti-inflammatory cytokine concentrations have been shown to respond to changes in inflammatory mediators under inflammatory conditions, it is likely that these cytokines may rise later after exercise during recovery. Therefore, one limitation of this study is measurement of cytokine levels at only one post-exercise time point.

Conclusion

We observed that swimmers with allergy tend to have higher baseline levels of TNF- α and showed greater increases in IL-6 compared to their healthy counterparts. These findings, in addition to the robust increase in TGF- β 1 and P-selectin, all have the potential to contribute

to inflammation and allergy. The variation in cytokine response may explain why some athletes respond adversely to intense exercise training, while others do not. It appeared that with short bouts of intense exercise, inflammatory mediators, at least acutely, may drive immune modulation. Further evaluation of pro- and anti-inflammatory balance during recover is warranted since differences during recovery may explain the propensity toward allergy.

We demonstrated that circulating levels of P-selectin were significantly higher after exercise in both groups. TGF- β 1 also showed significant increases in both groups and is known to play a role in immune suppression. Together, these findings suggest further investigation of the mechanisms by which these mediators are altered by exercise. Moreover, this knowledge may help to improve our understanding of how exercise can reduce the risk of diseases such as cardiovascular disease and cancer as well as exacerbate inflammatory diseases such as asthma and allergy.

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FIG. 1.

Effect of exercise on transforming growth factor (TGF)- β 1 in elite-level adolescent swimmers with clinical symptoms of allergy (CSRA; $n = 17$) and a no-allergy comparison group ($n = 14$, 3 subjects out of range of assay). TGF- β 1 increased significantly in both groups (pre-exercise = white bar; post-exercise = black bar). *Indicates significance at $P < 0.05$.

FIG. 2.

Effect of exercise on tumor necrosis factor (TNF)-α and interleukin (IL)-6 in elite-level adolescent swimmers with clinical symptoms of allergy (CSRA; $n = 17$) and a noallergy comparison group ($n = 17$). TNF-α increased significantly following exercise in the comparison group, IL-6 increased significantly following exercise group ($P < 0.05$). There was a trend toward higher baseline TNF-α level in the CSRA group (pre-exercise = white bar, post-exercise = black bar). *Indicates significance at $P < 0.05$.

Table 1
Regulatory Family and Functions of Select Cytokines

Cytokine/inflammatory mediator	Cytokine family	Functions
P-Selectin	Cell adhesion molecule	Responsible for initial recruitment of leukocytes to site of injury
TNF- α	Tumor necrosis factor family, type I, proinflammatory cytokine	Induces apoptosis and inflammation, inhibits tumorigenesis
TGF- β 1	Transforming growth factor family, type I, proinflammatory cytokine	Regulates immune function, promotes cell growth, proliferation; converts T-helper cells to T-regulatory cells
IL-6	Interleukin family, pro- and anti-inflammatory cytokine	Important mediator of the acute phase inflammatory response
IL-4	Interleukin family, type II, anti-inflammatory cytokine	Regulates immune function, induces naive T cells to become T-helper effector (type II) cells. Induces B-cell switching to IgE
IL-10	Interleukin family, type II, anti-inflammatory cytokine	Down-regulates proinflammatory cytokines and enhances B-cell release of IgE

Abbreviations: IgE, immunoglobulin E; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

Table 2
Descriptive Statistics for All Subjects

	<i>Comparison (n = 17)</i>	<i>CSRA (n = 17)</i>	<i>P values</i>
Gender (#, % male)	5, 30	10, 59	
Age (years)	15.4	15.3	0.91
Height (cm)	171.4	175.8	0.12
Body mass (kg)	61.8	67.4	0.21
VO _{2max} /l _{bm} (mL/min/kg)	60.1	59.0	0.66
Eosinophils (#/μL)	106	235	0.01
IgE (IU)	10	105	0.008
Asthmatic (#, % of total)	3, 18	10, 59	
FEV ₁ /FVC ratio	0.85	0.79	0.003

Abbreviations: CSRA, clinical symptoms of respiratory allergy; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.

Table 3
Exercise-Induced Alterations by Group and Total

	Comparison (n = 17)	CSRA (n = 17)	All (n = 34)	P values
Lactate peak (mmol)	4.3 ± 0.5	3.9 ± 0.3	4.1 ± 0.3	0.48
Total WBC increase (#/μL)	2,588 ± 363	3,088 ± 301	2,838 ± 236	0.30
Granulocyte increase (#/μL)	1,116 ± 216	1,447 ± 216	1,281 ± 153	0.29
Lymphocyte increase (#/μL)	1,268 ± 194	1,298 ± 167	1,283 ± 126	0.91
Monocyte increase (#/μL)	196 ± 44	344 ± 62	270 ± 40	0.06
FVC (% drop)	1.7 ± 0.1	0.8 ± 0.6	1.2 ± 0.5	0.41
FEV ₁ (% drop)	0.1 ± 0.1	3.0 ± 1.1	1.5 ± 0.8	0.05
FEF ₂₅₋₇₅ (% drop)	1.7 ± 1.7	6.8 ± 2.2	4.3 ± 1.4	0.08
PEF (% drop)	3.7 ± 2.3	10.6 ± 5.2	7.1 ± 2.9	0.23
ATS work rate (watts)	175 ± 13	181 ± 11	178 ± 8	0.71
ATS max heart rate (bpm)	175 ± 1	173 ± 2	174 ± 1	0.87
Peak FEV ₁ /FVC ratio	0.87	0.77	0.82	<0.001

Abbreviations: ATS, American Thoracic Society; CSRA, clinical symptoms of respiratory allergy; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow rate; WBC, white blood cell count.

Table 4
Mean Plasma Cytokine Concentrations by Group and Pre- and Post-Exercise

	Comparison group (n = 17)		CSRA group (n = 17)		Total (n = 34)	
	Pre	Post	Pre	Post	Pre	Post
P-Selectin (ng/mL)	1.5 ± 0.1	1.9 ± 0.3 *	1.5 ± 0.1	1.7 ± 0.2 **	1.5 ± 0.1	1.8 ± 0.2 **
TNF-α (pg/mL)	0.6 ± 0.1	0.7 ± 0.1 *	0.8 ± 0.1	0.9 ± 0.1	0.7 ± 0.1	0.8 ± 0.2 *
TGF-β1 (pg/mL)	3,359 ± 1,028	4,669 ± 1,580 *	1,922 ± 298	7,997 ± 5,246 *	2,571 ± 500	6,494 ± 2,937 **
IL-4 (pg/mL)	0.1 ± 0.02	0.1 ± 0.02	0.1 ± 0.01	0.1 ± 0.02	0.1 ± 0.01	0.1 ± 0.02
IL-6 (pg/mL)	1.2 ± 0.5	1.2 ± 0.3	0.7 ± 0.1	0.8 ± 0.2 *	0.9 ± 0.2	1.0 ± 0.2
IL-10 (pg/mL)	0.3 ± 0.04	0.4 ± 0.03	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1

Values represent mean ± standard error of the mean.

Difference between comparison and CSRA group was not significant; comparison using Mann-Whitney nonparametric *t*-test.

* Indicates post-exercise level significantly different than pre-exercise concentration, *P* < 0.05.

** Indicates post-exercise level significantly different than pre-exercise concentration, *P* < 0.001, comparisons using Wilcoxon nonparametric paired *t*-test.

Abbreviations: IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.