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ORIGINAL ARTICLE

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Effects of laboratory versus field exercise on leukocyte subsets and cell adhesion molecule expression in children

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Abstract In adults, exercise is a powerful and natural stimulator of immune cells and adhesion molecules. Far less is known about these exercise responses during childhood and whether or not exercise in *real-life* activities of healthy children might influence immune responses. We compared laboratory exercise (10×2 min periods of heavy, constant intensity, cycle ergometer exercise with 1 min rests between exercise in nine subjects, aged 9–15 years) with field exercise (90 min soccer practice in nine different subjects, aged 9–11 years). Blood was sampled before both protocols, 5 min after the 30 min laboratory protocol, and 10–15 min after the 90 min field protocol. Both field and laboratory exercise protocols led to significant ($P < 0.05$) increases in granulocytes, monocytes, and all lymphocyte subpopulations. The mean (SEM) increases were similar for the two protocols except for the significantly greater increase in laboratory compared with field protocols for natural killer cells [142 (39)% vs 12 (16)%, $P < 0.001$] and monocytes [64 (22)% vs 32 (19)%, $P < 0.001$]. Both protocols significantly influenced adhesion molecules (such as CD54) which have not been previously studied in children. However, the adhesion molecule $CD8^+CD62L^-$ increased to a significantly ($P < 0.001$) greater extent in the laboratory [101 (25)%] versus field [34 (25)%] protocol. Finally, the density of CD62L on lymphocytes significantly decreased with laboratory exercise but showed no change in the field protocol [–20 (3)% vs –3 (3)%, $P < 0.001$]. The rapid and substantial immune response in both laboratory and field protocols suggests that exercise stimulation of the immune system occurs commonly in the real lives of children and may play a role in their overall immune status.

Keywords Exercise · Children · White blood cells · Lymphocytes · Adhesion molecules

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Introduction

It is increasingly recognized that brief episodes of physical exercise can substantially influence the type and numbers of circulating white blood cells (Nieman and Pedersen 1999; Pedersen and Hoffman-Goetz 2000). Naturally, most investigators have focused on the importance of this effect with regard to immune function and the body's ability to respond to infection. During childhood adaptive consequences of white blood cell responses to exercise may prove to be important for the overall development of the hematopoietic and immune systems as well as for the fundamental processes of growth. Few studies of exercise immune effects have been made in children compared with adults (Boas et al. 1996, 2000; Eliakim et al. 1997; Wolach et al. 1998), and, to our knowledge, no studies have been made in children under field conditions, i.e. those mimicking the kind of exercise performed by children in daily life activities.

In addition to the general phenomenon of leukocyte redistribution in response to exercise (Boas et al. 1996; Eliakim et al. 1997; Pedersen and Hoffman-Goetz 2000) recent studies in adults show that exercise also affects the expression of certain leukocyte adhesion molecules. The cell adhesion molecule L-selectin (CD62L), for example, is important for the trafficking of leukocytes in and out of the circulation, mediating the rolling and adhesion to the vessel wall (Adams and Shaw 1994; Springer 1994). Findings in adults show that exercise leads to a preferential increase of $CD62L^-$ versus $CD62L^+$ lymphocytes, as well as a decrease in the cell surface density of CD62L (Kurokawa et al. 1995; Miles et al. 1998; Mills et al. 1999). The CD54, found on the surface of lymphocytes

and endothelial cells, is responsible for firm adhesion and transendothelial migration. Few studies have examined the effects of exercise on adhesion molecules in children.

The goal of the present study was to compare acute exercise-induced alterations in certain aspects of immune function (white blood cell subpopulations and their associated adhesion molecules) in two groups of children: one performing laboratory exercise protocols and the other engaging in soccer practice such as is now frequently encountered in the lives of millions of healthy children throughout the world. We hypothesized that field studies would lead to substantially greater alterations in these immune related factors for the following reasons: first, it is our experience that children are unwilling (or unable) to exercise as vigorously and/or for as long a duration in the laboratory as they are in real life settings which tend to be more *fun* and varied compared to what is possible in a laboratory. Secondly, real life exercise, such as a soccer practice, more likely involves those forms of exercise (resistive, eccentric) that are known to cause local inflammation if not frank microfiber injury.

Methods

Sample population

The study was approved by the Institutional Review Board, University of California, Irvine (UCI). The experiment complied with the current laws of the State of California, USA. Informed consent as well as assent were obtained from the total of 18 healthy children who participated in the study (9 field study, 9 laboratory; Table 1). We did not think it feasible that sufficient numbers of children would agree to participate in both types of studies since this would involve both taking multiple blood samples and insertions of intravenous catheters. Therefore, we excluded a paired sample study design. Two separate groups were recruited and, despite our efforts, the groups did not match precisely for age, body mass, and height (see Table 1). No subjects were receiving any medications at the time of the study. The field studies were performed in December of 1999 and the laboratory studies between April and September of 2000.

Field study

The field study was designed to mimic real-life exercise, such as might be encountered in the daily activities of children. To accomplish this, we arranged a 1.5 h soccer practice modeled on typical sessions of this sport. The soccer practice was coached by one of the UCI team coaches who also had particular experience in working with children. The experiment goal was for the children to engage in approximately 40–50 min of vigorous aerobic-type exercise over the 1.5 h period. During the soccer practice, there were many water breaks and brief rest periods, first, to ensure adequate hydration and second, to reflect the intensity and tempo of this type of activity typically found in the community.

The children were instructed to have a light breakfast on the morning of the test, and after this the participants reported to the laboratory at 0900 hours. Blood samples were obtained and the children proceeded to the soccer practice on a site adjacent to the General Clinical Research Center (GCRC). After the 1.5 h practice, the children jogged back to the GCRC where further blood samples were obtained. There was a 5–15 min interval between the end of the jog back to the GCRC and the time that the blood samples were obtained. The effect of this protocol on cytokines and growth factors in these children has been published (Scheett et al. 1999).

Table 1 Subject characteristics (mean and SEM)

	Laboratory study	Field study
Number	9	9
Girls/boys	6/3	6/3
Age (years)*	12 (0.6)	10 (0.2)
Body mass (kg)*	50 (3.8)	34 (1.3)
Height (cm) *	154 (3.9)	143 (1.6)

*$P < 0.02$

Laboratory study

The exercise tests were performed at the Human Performance Core Laboratory of the UCI/University of California San Diego Satellite GCRC. Each subject underwent two separate exercise test sessions performed on different days. First, to measure cardiorespiratory responses to exercise and assess fitness, we used a ramp-type progressive exercise test on an electronically braked cycle ergometer (SensorMedics Vmax 229, Yorba Linda, Calif.). The exercise intensity increased by 10 $W \cdot min^{-1}$, and each subject exercised to the limit of his or her tolerance. Gas exchange was measured breath-by-breath (Beaver et al. 1981; Cooper et al. 1984). This approach has been used extensively in children and adolescents.

The second session consisted of a series of 10×2 min periods of constant intensity cycle ergometry with 1 min rests between each period of exercise. The exercise intensity was individualized for each subject and calculated to be equivalent to the intensity corresponding to 50% of the difference between the anaerobic or lactate threshold (determined noninvasively from the ramp test) and peak oxygen uptake. We have used this approach in previous investigations to ensure that the exercise was standardized to physiological indicators of each individual subject's exercise capability (Cooper et al. 1989). In addition, our experience with heavy intensity exercise (i.e. exercise intensities above the subject's lactate threshold) is that children often do not maintain constant exercise for more than several minutes at a time. The total duration of the second exercise protocol was 30 min (20 min of cycle ergometer exercise interspersed with 10 min of rest).

Flow cytometry

Whole blood was preserved with EDTA and maintained at room temperature (23°C). As previously described (Mills et al. 1999), flow cytometry using CellQuest software (FACSCalibur, Becton Dickinson, San Jose, Calif.) was used to quantify leukocytes and lymphocyte subsets and CD62L and CD54 expression. A complete blood count (CBC) analysis was performed by using a Coulter STKS CBC Counter. Blood was processed within 12 h of collection and whole blood was stained with monoclonal antibodies conjugated to various fluorchromes (Becton-Dickinson and PharMingen). The lysing reagent was FACS Brand Lysing Solution (Becton-Dickinson) which resulted in a simultaneous lysis of red blood cells and partial fixation of leukocytes. Fluorescence compensation was performed using CaliBRITE beads and FACSComp software (Becton-Dickinson). Optimal amounts of antibodies were used and 8,000–15,000 events were analyzed per tube. Isotypic controls were used for each assay to determine non-specific staining. In addition to determining CD62L and CD54L expression, we determined CD62L density on mixed lymphocytes. For CD62L density, flow cytometric estimation of antibodies bound/cell (ABC) was performed using Quantibrite PE beads (Becton-Dickinson). The ABC, being the number of antibodies that bind to the specific cell or microbead population, provides a good approximation of antigen density expressed on the cell. The Quantibrite PE beads

were run at the same instrument settings as the assay and the FL2 (PE) axis was converted into the number of PE molecules bound/cell.

Statistical analysis

The data were analyzed by two-way [group (field versus laboratory) by exercise (pre-exercise versus post-exercise)] repeated measures analysis of variance. Statistical significance was taken at the $P < 0.05$ level. Data are presented as mean and SEM.

Results

Field study

As shown in Tables 2 and 3 and Fig. 1, the field exercise led to a significant increase in the number of circulating white blood cells, including granulocytes, mixed lymphocytes, $CD19^+$ B cells, $CD3^+$ T cells, $CD3^+CD8^+$ T-cytotoxic cells, and $CD3^+CD4^+$ T-helper cells. The number of $CD3^+CD8^+$ T-cytotoxic cells expressing CD62L ($CD8^+CD62L^+$), increased significantly, as did the number of $CD4^+CD62L^+$ T-helper cells and the number of T-helper cells not expressing CD62L ($CD4^+CD62L^-$). Both $CD54^+$ and $CD54^-$ mixed lymphocytes increased in circulation (Table 3, Fig. 2). No significant change was found in the number of monocytes, $CD3^-CD16^+56^+$ natural killer cells, or the density of CD62L on mixed lymphocytes in response to the soccer practice.

Laboratory study

The laboratory exercise led to a significant increase in the number of all cell types examined, including white blood cells, granulocytes, mixed lymphocytes, monocytes, $CD3^-CD16^+56^+$ natural killer cells, $CD19^+$ B cells, $CD3^+$ T-cells, $CD3^+CD8^+$ T-cytotoxic cells, and $CD3^+CD4^+$ T-helper cells (Table 2, Fig. 1). As with the soccer exercise, the number of $CD8^+CD62L^+$, $CD4^+CD62L^+$, and $CD4^+CD62L^-$ cells increased significantly. In addition, the number $CD3^+CD8^+$ T-cytotoxic cells not expressing CD62L ($CD8^+CD62L^-$) increased significantly, as did the number of $CD54^+$ and $CD54^-$ mixed lymphocytes (Table 3). In contrast to the field test, where there was no significant effect, the density of CD62L on mixed lymphocytes was decreased following the laboratory exercise (Table 3, Fig. 2).

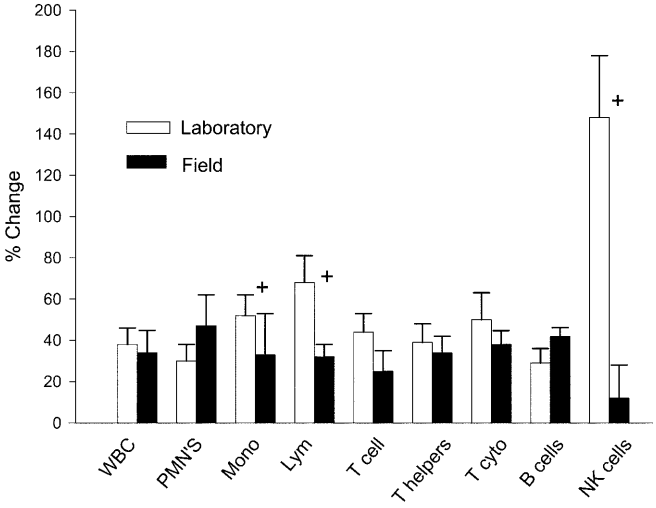

Fig. 1 Effect of laboratory and field exercise protocols on white blood cells (*WBC*), total lymphocytes (*lym*), T-lymphocytes (*T cells*), T-helper cells (*T helpers*), T-cytotoxic cells (*T cyto*), B-lymphocytes (*B cells*), natural killer cells (*NK cells*), monocytes (*Mono*), and polymorphonuclear leukocytes (*PMN*) in healthy children. Data are presented as percentage changes. There were substantial and significant increases in all cell types shown. Statistically significant greater increases in NK cells, mono and lym were found in the laboratory as compared with the field protocol. $^+P < 0.005$

Differences between the field and laboratory exercise

Statistically significant differences (significant group by exercise interactions) were found between the field and

Table 2 Mean (SEM) numbers of circulating leukocytes and lymphocyte subsets before (*Pre*) and after (*Post*) the two kinds of exercise in the two groups of children

($cells \cdot \mu l^{-1}$)	Laboratory study		Field study	
	Pre	Post	Pre	Post
White blood cells[a,b]	7,247 (595)	10,255 (979)	6,667 (922)	8,544 (913)
Granulocytes[a,b]	4,210 (642)	5,577 (804)	3,307 (700)	4,533 (745)
Lymphocytes[a,b,c]	2,556 (218)	3,917 (287)	2.154 (129)	2,832 (163)
Monocytes[a,c]	480 (36)	820 (85)	532 (83)	633 (76)
$CD3^-$ $CD16^+56^+$ NK cells[a,c]	316 (39)	740 (87)	367 (41)	402 (74)
$CD19^+$ B cells[a,b]	443 (70)	593 (75)	339 (47)	419 (57)
$CD3^+$ T cells[a,b]	1,745 (132)	2,500 (185)	1,426 (110)	1,891 (163)
$CD8^+$ T-cytotoxic cells[a,b]	619 (66)	975 (115)	505 (43)	703 (72)
$CD4^+$ T-helper cells[a,b]	976 (91)	1,254 (89)	792 (73)	1,110 (93)

[a]Increase with laboratory exercise, $P < 0.01$
[b]Increase with field exercise, $P < 0.05$
[c]Change greater with laboratory exercise, $P < 0.05$

Table 3 Mean (SEM) lymphocyte adhesion molecule expression before (*Pre*) and after (*Post*) the two kinds of exercise in the two groups of children

(cells·μl^{-1})	Laboratory study		Field study	
	Pre	Post	Pre	Post
$CD8^+CD62L^{+a,c}$	440 (39)	629 (77)	387 (32)	546 (35)
$CD8^+CD62L^{-a,c,d}$	179 (34)	345 (55)	118 (24)	157 (42)
$CD4^+CD62L^{+a,c}$	874 (86)	1111 (85)	724 (63)	1016 (86)
$CD4^+CD62L^{-a,c}$	102 (10)	143 (15)	67 (17)	94 (12)
$CD54^+$ lymphocytes[a,c]	926 (88)	1,572 (147)	1,254 (91)	1,566 (141)
$CD54^-$ lymphocytes[a,c]	1,630 (167)	2,344 (196)	900 (58)	1,266 (73)
CD62L density lymphocytes[b,d]	7,085 (784)	5,640 (606)	7,194 (580)	6,993 (567)

[a]Increase with laboratory exercise, $P < 0.05$
[b]Decrease with laboratory exercise, $P < 0.01$
[c]Increase with field exercise, $P < 0.05$
[d]Change greater with laboratory exercise, $P < 0.05$

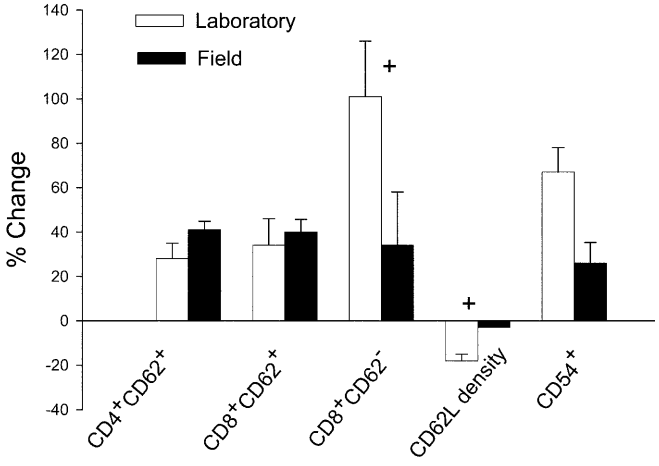

Fig. 2 Effect of laboratory and field exercise protocols on adhesion molecules in healthy children. There were highly significant and consistant increases in $CD4^+CD62L^+$ and $CD8^+CD62L^+$ molecules following both protocols, and no between-group differences were found. There were increases in CD8 + CD62L$^-$ in both groups, but the increase in laboratory exercise was significantly greater.The density of CD62L molecules significantly decreased following laboratory exercise, but no significant change was found with the field exercise. $^+P < 0.01$

laboratory exercise tests for several immune cells and cell adhesion markers. The laboratory exercise elicited a greater increase in lymphocytes, monocytes, and $CD3^+CD16^+56^+$ natural killer cells, as well as $CD8^+CD62L^-$ T-cells (Fig. 2). In addition, the density of CD62L on lymphocytes in the laboratory exercise showed a statistically significant decrease compared to the field study.

Discussion

To our knowledge, this represents the first study to compare the effect of a complex pattern of field exercise versus laboratory cycle ergometry on immune responses in children. In addition, a novel focus of this research was on the effect of exercise on adhesion molecules, which has not been studied in children to date. In contrast to our hypothesis, a shorter duration, single activity type of exercise (i.e. cycle ergometry) performed in the laboratory led to at least as marked an immune response in children as did a field activity comparable to the soccer practices performed routinely by millions of children throughout the world. Despite the similarities, there were notable differences between laboratory and field studies with respect to natural killer cells, monocytes, and both of the adhesion molecules that we studied (CD54 and CD62L).

In adults, a number of investigators have demonstrated that maintained exercise leads to an abrupt increase in leukocytes (first 10–20 min) followed by a more gradual increase as the exercise continues (Gabriel and Kinderman 2001). In our study, leukocytosis in response to exercise occurred in the children as well. However, the magnitude of the increase was virtually the same in laboratory and field exercises despite the fact that the duration of laboratory exercise was shorter than in the field protocols (Table 2, Fig. 1).

There are a number of mechanisms that can explain this: first, it is possible that despite the shorter duration, the intensity of the individual 2 min periods of laboratory exercise exceeded the intensity of the repeated bursts of exercise that characterized the field exercise. Unlike spontaneous soccer-practice exercise in which the subject has control over the intensity of work performed, the duration of individual exercise, and the between exercise rest periods (i.e. each child could choose to run faster or slower, jump higher or lower, and take longer rests, in response to the coach's instruction), the laboratory protocol required each child to perform heavy exercise at a constant intensity for fixed durations. Unfortunately, while the exercise intensity is easily measured with cycle ergometer exercise, assessing exercise intensity during brief, spontaneous physical activity is quite difficult.

Another mechanism that might have distinguished the two protocols was the level of psychological stress, a factor that is known to produce immune responses that are, in some respects, similar to exercise (Mills and

Dimsdale 1996; Song et al. 1999). While the field exercise was perceived as being fun and was a familiar activity to virtually all of the participants, the laboratory experience was new. Although we did not quantify the subject's feelings about the protocol, it was our impression that the laboratory study was not a particularly pleasant exercise experience for most of the subjects. In contrast to the field protocols in which the children eagerly resumed vigorous exercise after the rests, it tended to become increasingly difficult to cajole subjects to resume cycle ergometry as the in-laboratory protocol continued. Thus, the possibility remains that the increased psychological stress associated with laboratory exercise protocol stimulated a white cell response over and above that due to exercise alone.

Despite the generally similar responses between the two exercise protocols, intriguing differences were observed. The increases in natural killer cell numbers and monocytes were substantially higher with laboratory exercise (Table 2, Fig. 1). This finding might be explained by factors noted above such as unmeasured differences in the intensity of individual exercise bouts [N.B. natural killer cells are known to be dependent upon exercise intensity (Pedersen and Ullum 1994)] or the increased psychological stress associated with the laboratory protocols. Alternatively, it is possible that with a longer duration of exercise, natural killer cell numbers might begin gradually to reduce even as exercise continues, and so the differences in the two protocols would reflect the fact that the end of exercise occurred after 30 min in the laboratory protocol and after about 90 min in the field exercise.

This study demonstrates that in children, like in adults, exercise, both field and laboratory, influences adhesion molecules (Rehman et al. 1997; Miles et al. 1998). The CD62L on circulating lymphocytes was decreased, and there was a preferential increase in $CD62L^-$ versus $CD62L^+$ T-cell subsets. The relative increase in circulating $CD62L^-$ lymphocytes is believed to result from a preferential release into the circulation of $CD62L^-$ cells rather than an actual down-regulation of L-selectin in response to exercise (Kurokawa et al. 1995; Mills et al. 2000). Since L-selectin is typically shed from T-lymphocytes as the cell changes from a naïve to a post-antigen presented memory T-cell (Bevilacqua 1993; Mills et al. 2000), these findings suggest that exercise in children leads to recruitment into the peripheral circulation of memory T cells.

Lymphocytes expressing CD54 [known also as intercellular adhesion molecule-1 (ICAM-1)] also increased in response to exercise in both protocols, a response similar to what has been observed previously in adults (Rehman et al. 1997). The CD54 is an inducible cell adhesion glycoprotein expressed on the surface of a wide variety of cell types. The CD54 is constitutively expressed on the cell surface and is up-regulated in response to a variety of inflammatory mediators, including proinflammatory cytokines, hormones, cellular stresses, and virus infection. Interestingly, CD54 is now known to be elevated in children with asthma (Cengizlier et al. 2000; Marguet et al. 2000). Whether the exercise associated increase in CD54 that we observed in healthy children under field and laboratory conditions plays a role in the common occurrence of childhood exercise-induced asthma remains an intriguing, as yet unexamined possibility.

We recognize several deficiencies in the design and execution of this study. First, we were unable to match the two protocol groups by age. The participants in the laboratory protocol were older (Table 1), and the possibility remains that differences in the response between the two groups may be related to the degree of maturation. Very little is known about the effect of growth and development during childhood on the immune response to exercise. However, the clear response that we observed in children of different ages suggests that exercise may serve as a minimally invasive and safe means of assessing how the immune response changes with growth in healthy children and in those with chronic diseases [e.g. as Boas and coworkers (Boas et al. 2000) recently showed in their studies of children suffering from cystic fibrosis].

In summary, this study provided preliminary data on the effects of laboratory and field exercise on changes in immune cell subsets and cellular adhesion markers in children. Both challenges led to a significant redistribution of circulating leukocytes. Differences between the two protocols did occur and might have been related to factors such as maturity, sampling intervals, exercise intensity, and the influence of psychological stress. We also demonstrated the effect of exercise on adhesion molecules such as CD54. The rapid and substantial immune response in both laboratory and field (real-life) protocols suggests that exercise stimulation of the immune system occurs commonly in the lives of children and may play a role in their immune status. Whether or not these exercise responses play a role in pathological states in susceptible individuals (such as exercise-induced asthma) is as yet unknown.

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