

# Exercise and Recovery Responses of Lymphokines to Heavy Resistance Exercise

JILL A. BUSH,<sup>1</sup> KEIICHIRO DOHI,<sup>1</sup> ANDREA M. MASTRO,<sup>2</sup>  
JEFF S. VOLEK,<sup>3</sup> J. MICHAEL LYNCH,<sup>1</sup> N. TRAVIS TRIPLETT-McBRIDE,<sup>1</sup>  
MARGOT PUTUKIAN,<sup>1</sup> WAYNE J. SEBASTIANELLI,<sup>1</sup>  
ROBERT U. NEWTON,<sup>3</sup> KEIJO HÄKKINEN,<sup>4</sup> AND WILLIAM J. KRAEMER<sup>3</sup>

<sup>1</sup>Laboratory for Sports Medicine/Department of Kinesiology, Center for Sports Medicine, and <sup>2</sup>Department of Biochemistry and Molecular Biology, Pennsylvania State University, University Park, PA 16802; <sup>3</sup>The Human Performance Laboratory, Ball State University, Muncie, IN 47306; <sup>4</sup>Neuromuscular Research Center/Department of Biology of Physical Activity, University of Jyväskylä, Jyväskylä, Finland.

## ABSTRACT

To examine the effect of dynamic resistance exercise on the response patterns of lymphokines, 10 strength-trained men ( $21.7 \pm 0.6$  y) performed 2 resistance exercise protocols, high force (HF) and high power (HP), of equal total work (HF =  $33.0 \pm 2.5$  kJ; HP =  $33.3 \pm 2.7$  kJ) in a randomized order separated by 1 week. Resting blood samples were obtained preexercise and 0 (R-0), 15 (R-15), and 240 (R-240) minutes postexercise. Plasma lactate significantly ( $p < 0.05$ ) increased from baseline for both protocols; however, concentrations were higher in response to the HF protocol. Plasma interleukin-2 (IL-2) concentrations were significantly decreased from baseline at R-15 following the HF protocol. Plasma interferon-gamma (IFN- $\gamma$ ) concentrations decreased at R-0 following the HP protocol and returned to preexercise levels by R-15. Although the suppression of these 2 lymphokines was transient, the results indicate that the acute stress of high force and high resistance workouts induce differential IFN- $\gamma$  and IL-2 responses.

**Key Words:** resistance exercise, interferon-gamma, Interleukin-2

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## Introduction

Lymphokines (e.g., interferon-gamma [IFN- $\gamma$ ] and interleukin-2 [IL-2]) are released from various immune cells. IFN- $\gamma$  is released mainly from T-lymphocytes and natural killer (NK) cells, whereas IL-2 is secreted mainly from T-lymphocytes. One of the roles of IFN-

$\gamma$  in the immune system is to activate macrophages that are vital to tissue repair following muscle tissue damage (15–17). In addition, IL-2 is responsible for T-cell growth, which is stimulated by exercise (1, 7).

Moderate running may result in a stimulatory, up-regulating effect on the immune system, whereas excessive training may result in a decreased immune response, which creates an environment that may lead to the susceptibility of infection and illness (6). The level of intensity, duration, and mode of exercise may play an important role in modulating the immune system, in particular IFN- $\gamma$  and IL-2. The effects of exercise on the production and secretion of IFN- $\gamma$  has been shown to be variable. In highly trained runners, urinary concentrations of IFN- $\gamma$  demonstrated decreases 1 hour postexercise following a 20-km run (20). Haahr et al. (8) reported no changes in IFN- $\gamma$  levels following cycle ergometry exercise at 75%  $\dot{V}O_{2\max}$ . The effect of exercise and the role during recovery is difficult to define because of the inconsistent results reported from several studies. There are no data on the responses of IFN- $\gamma$  to acute heavy resistance exercise.

IL-2 induces proliferation of T-lymphocytes and enhances the activity of NK cells in the immune system. The plasma half-life of IL-2 is approximately 5–7 minutes (19). In trained individuals, there is a decrease in circulating IL-2 plasma concentrations postexercise (5, 12). Following a 5-K race, trained runners exhibit a 50% decrease in circulating IL-2 levels immediately postexercise, with a return to resting levels within 2 hours postexercise (5). However, in untrained men there is no change in IL-2 levels following a 60-minute cycle exercise at 75%  $\dot{V}O_{2\max}$  (8). These results may

**Table 1.** Physical characteristics of the subjects ( $n = 10$ ).

Characteristic	Mean $\pm$ SE
Age (y)	21.7 $\pm$ 0.6
Height (cm)	180.2 $\pm$ 1.2
Weight (kg)	84.3 $\pm$ 3.4
Resistance-training experience (y)	4.5 $\pm$ 0.6
Body fat (%)	14.1 $\pm$ 1.6
Fat-free mass (kg)	77.1 $\pm$ 2.1

indicate a differential effect of training level and mode of exercise on circulating IL-2 levels. Again, there are no data on the effects of resistance exercise on circulating IL-2 levels.

Manipulation of the acute program variables in a resistance exercise workout (i.e., sets, repetitions, rest periods, etc.) is known to induce differential metabolic and hormonal responses (9–11). Thus the primary purpose of this investigation was to examine the response of circulating lactate, IFN- $\gamma$ , and IL-2 concentrations to 2 different dynamic heavy-resistance exercise protocols.

## Methods

### *Approach To the Problem*

Few data exist as to the impact of an acute resistance exercise workout on IL-2 and IFN- $\gamma$ . Thus it is unclear how these lymphokines respond to resistance-exercise stress, and most studies have seen no change in decrease. Our approach was to examine the responses to 2 different workouts. More specifically, 1 workout had power output that was higher using a lighter resistance, and the other workout had a higher force output because of a heavier resistance. We then measured these lymphokines in the blood to determine if modulation involved any increases. We hypothesized that no changes (null hypothesis) would be observed in these lymphokines after heavy resistance exercise, which was based on limited exercise data (1, 7).

### *Subjects*

Ten healthy men who had prior resistance-training experience for a period of at least 2 years were recruited for this investigation. In general, the subjects were characterized as highly resistance trained individuals, training approximately 4 days per week. Training sessions involved multiple sets (i.e., 15–25 sets per workout) and moderate repetitions (i.e., 6–15 repetitions) incorporating exercises for all major muscle groups and usually involving split routines. The subjects recorded their training sessions during the course of the study. The physical characteristics of the subjects are described in Table 1.

Subjects were informed of the associated risks of the investigation prior to giving their written consent

in accordance with the University Review Board for Use of Human Subjects. Subjects were medically screened by a physician, and no endocrine, metabolic, or orthopedic disorders were detected that would affect their participation or results of this investigation (i.e., anabolic steroids, smoking, etc.). None of the subjects were under the care of a physician for either an illness or an injury during the course of the study.

### *Preliminary Testing*

The subjects were familiarized with the equipment and the exercises involved in the resistance-exercise protocols. Their 10 repetition maximum (10RM) loading (i.e., maximum load with which the subject could perform 10 repetitions) for the squat, bent-over row, bench press, and shoulder press exercises (9) was also determined during this phase of the investigation. Body composition measurements were determined via skinfolds (13).

### *Resistance Exercise Protocols*

All testing was performed on a Plyometric Power System (PPS; Norsearch Limited, Lismore, Australia), which was previously described by Wilson et al. (23). The PPS, which is similar to a Smith weight machine setup, is interfaced to a computer with an online data storage and analysis system that provides information on the kinematics and kinetics of performance. Resistance is provided by placing a specified amount of weight plates on either side of the Olympic bar. The barbell is fixed in a vertical plane along 2 vertical steel shafts on either side of the barbell. The vertical movement of the barbell provides minimal friction because of the linear bearings contained within the barbell attached the vertical steel shafts. The weight machine is connected to a rotary encoder that recorded the position and direction of the barbell within 0.0002 m. This information is transferred to a computer that calculates work (mass·gravity·distance) and mean power output (work·time<sup>-1</sup>) for all exercise repetitions.

Each subject completed a 10RM (higher force [HF]) and a 15-repetition (higher power due to faster movement of the lighter mass [HP]) resistance exercise protocol separated by 1 week in a balanced randomized design to prevent order effects. In order to equate work (kJ) for the 2 protocols, the load determined for the 10RM resistance was used to calculate the loads to be used in the 15-repetition protocol. Prior to the study, the volume of work was determined for the 10RM resistance-exercise protocol, and the 15RM high-power protocol was equated for total work (10). Both resistance protocols consisted of 4 sets each of the squat, bent-over row, bench press, and shoulder press exercises, with exactly 2-minute rest periods between all sets and exercises. The loads were adjusted on each set based on the performance of the previous set to maintain a 10RM or completion of 15 repetitions

on all sets. Each testing session began with a thorough warm-up consisting of 5–10 minutes of cycling on a stationary ergometer and static stretching. The average total time for each the resistance-exercise sessions was approximately 45 minutes. Each subject refrained from strenuous activity 48 hours prior to any of the testing.

As an indicator of the amount of force applied during the protocols, the mass was operationally defined as the resistance lifted in kg. Mean resistance (kg) per set for the HF and HP protocols was calculated by averaging the resistance lifted over 16 sets of resistance exercises. Total work (kJ) was operationally defined as the resistance applied over the distance the barbell traveled for 16 sets of exercises (10). The distance the barbell traveled remained constant over each repetition for each exercise. Power output (W) per repetition was calculated via software programs integrated with the PPS. Mean power output (W) per set was subsequently calculated by averaging the individual power outputs for each of the 16 sets of exercises.

### **Blood Collection**

On experimental days, blood samples were obtained using sterile techniques and a 20-gauge 1 1/4-inch Teflon cannula, 10- and 3-ml syringes, and Vacutainer set-up. The cannula was inserted into an antecubital forearm vein, secured in place, and flushed with a 0.9% saline solution to prevent clotting. Resting blood samples (15 ml) were obtained at 30 minutes preexercise (Pre), 0 (R-0), 15 (R-15), and 240 (R-240) minutes post-exercise. Blood was appropriately processed and plasma samples were stored at  $-85^{\circ}\text{C}$  until further analysis. Plasma samples were thawed only once for analysis.

Plasma lactate concentrations were measured in duplicate using a 1500 Sport L-Lactate Analyzer (Yellow Springs, Inc., Yellow Springs, OH) with intraassay and interassay variances  $\pm 5\%$ . Percent hematocrit was determined using heparinized microhematocrit capillary tubes, a Readcrit centrifuge (Sherwood Medical, St. Louis, MO), and a Spiracrit microhematocrit capillary tube reader (Sherwood). Percent changes in plasma volume were determined as previously described by Van Beaumont et al. (21). None of the hormone concentrations were corrected for plasma volume shifts because of the fact that target tissues interact with the absolute molar concentration and multiple factors (e.g., hepatic clearance) beyond just plasma volume shifts affect hormonal concentrations.

Similar to previous studies, blood samples for measurements of IFN- $\gamma$  and IL-2 (2 ml each) were collected with a vacutainer containing ethylenediamine tetraacetic acid (EDTA). Plasma IFN- $\gamma$  and IL-2 samples were analyzed using a solid phase enzyme amplified sensitivity immunoassay performed on microtiter plates coated with anti-IFN- $\gamma$  and anti-IL-2, respectively (Medgenix, INCSTAR Corporation, Stillwater,

MN) (4, 5). A conjugate of antibody to IFN- $\gamma$  or IL-2 and an antibody labeled with horseradish peroxidase (HRP) was added to each respective well containing the samples. The samples were incubated for 2 hours at room temperature on a horizontal shaker continuously set at  $700 \pm 100$  RPM. The plates underwent a series of washes (3 washes, 400 ml each, Tween 20, 20% washing solution) to remove any unbound enzyme labeled antibody. A 200-ml solution containing Chromogen tetramethylbenzidine (200 ml) and  $\text{H}_2\text{O}_2$  (7 ml in acetate/citrate buffer) was dispensed within 15 minutes of preparation into each well. The reaction was stopped with  $\text{H}_2\text{SO}_4$  (50 ml, once), and the amount of substrate turnover was determined colorimetrically by measuring the absorbances proportional to the sample concentration. The absorbances were read on a Clin-ELISA Microwell Strip Reader (model XL3000, INCSTAR Corp., Stillwater, MN) within 3 hours at 450 nm, with 630 nm as the reference filter. No interassay variances existed, since plasma samples were assayed in 1 run.

### **Statistical Analyses**

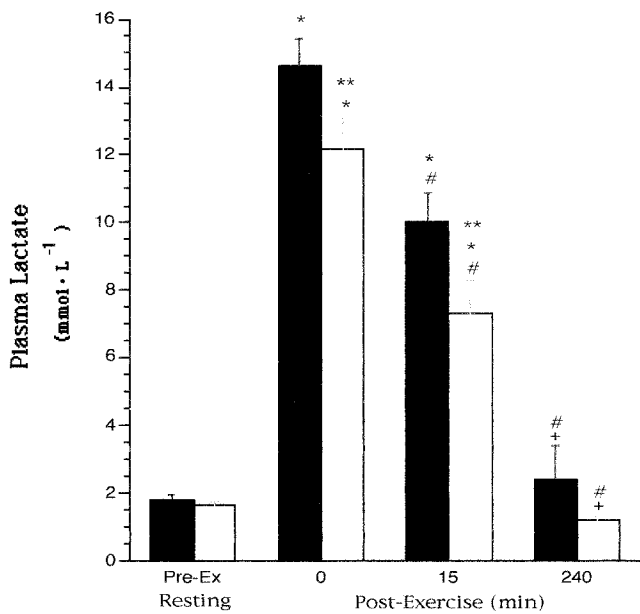
The data were statistically evaluated by using a 2-way analysis of variance technique with repeated measures (18). Test-retest reliability for the exercise data showed no differences over time and demonstrated intraclass coefficients of  $R \geq 0.95$  over the experimental time frame. Simple and stepwise multiple regression analyses were used to determine selected relationships between and among variables. Statistical significance in this investigation was chosen as  $p \leq 0.05$ .

## **Results**

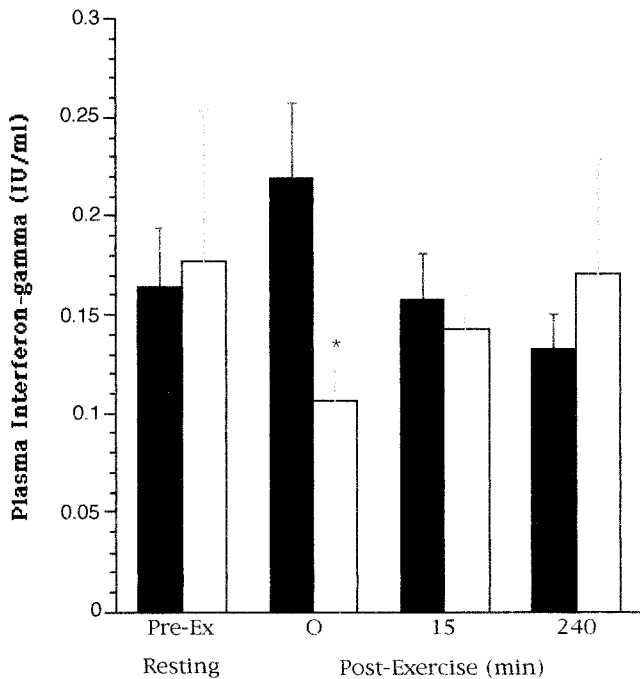
Performance of the HP resistance protocol resulted in significantly higher mean ( $\pm SE$ ) power outputs ( $325.2 \pm 25.3$  W) per set compared with the HF ( $254.1 \pm 33.9$  W) protocol. The mean resistance (kg) per set lifted was significantly higher during the HF ( $68.83 \pm 3.86$  kg) protocol than during the HP ( $46.69 \pm 2.87$  kg) protocol. The total work (kJ) performed was not significantly different between the 2 resistance protocols (HF =  $33.0 \pm 2.5$  kJ; HP =  $33.3 \pm 2.7$  kJ).

There were no significant differences between preexercise concentrations of lactate, IFN- $\gamma$ , and IL-2 between the HF and HP protocols. No differences were seen between the mean percent change in plasma volume for HF ( $-13.2 \pm 1.8\%$ ) and HP ( $-7.7 \pm 1.4\%$ ). At R-0 and R-15, lactate concentrations for both protocols were significantly elevated compared with preexercise concentrations during both protocols (Figure 1). The HF protocol resulted in significantly higher concentrations at R-0 and R-15 than did the HP protocol.

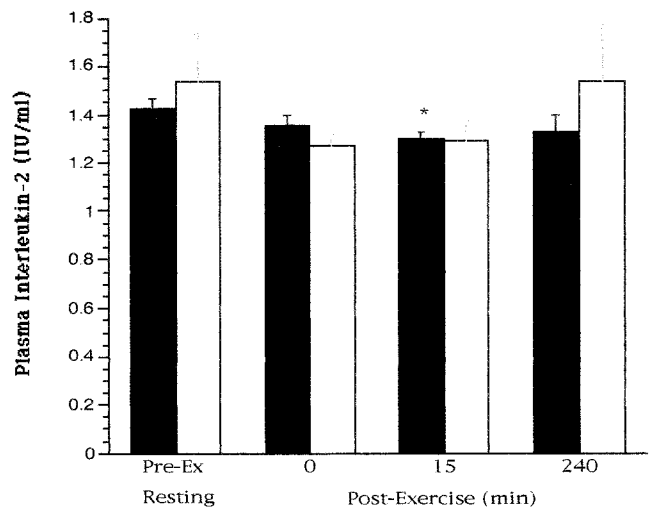
The only significant decrease from preexercise plasma IFN- $\gamma$  concentration was observed at R-0 following the HP protocol (Figure 2). Plasma IFN- $\gamma$  con-



**Figure 1.** The effect of resistance exercise on plasma lactate levels. \*\* =  $p \leq 0.05$  between the high-force and high-power protocols. \* =  $p \leq 0.05$  from corresponding preexercise concentrations. # =  $p \leq 0.05$  from corresponding R-0 concentrations. + =  $p \leq 0.05$  from corresponding R-15 concentrations. Solid bars = high force; open bars = high power.



**Figure 2.** Plasma interferon-gamma concentrations in response to high-power and high-force resistance exercise protocols. \* =  $p \leq 0.05$  from corresponding preexercise levels. Solid bars = high force; open bars = high power.



**Figure 3.** Plasma interleukin-2 concentrations in response to high-power and high-force resistance exercise protocols. \* =  $p \leq 0.05$  from corresponding preexercise levels. Solid bars = high force; open bars = high power.

centrations returned to preexercise levels by R-15. Significantly decreased plasma IL-2 concentrations (from preexercise levels) were observed at R-15 following the high force protocol only (Figure 3) and returned to preexercise levels by R-240.

## Discussion

Few investigations have examined the response patterns of IFN- $\gamma$  and IL-2 to exercise, and no study has examined dynamic heavy resistance-exercise stress. Since 1 of the roles of IFN- $\gamma$  in the immune system is to activate macrophages that are vital to tissue repair following muscle tissue damage, it might be theorized that heavy resistance exercise would increase concentrations of IFN- $\gamma$  in the blood (15–17). Yet no exercise data would strongly argue for this response. With such a need for tissue repair and the role of IL-2 in T-cell growth, it was further theorized that IL-2 would also be increased by heavy resistance-exercise stress (1, 7). This investigation found that both of these lymphokines either decreased or saw no changes to resistance-exercise stress, in part supporting our null hypotheses following various heavy resistance-exercise protocols. Although these data initially contradict what might be theorized in most stress-response situations to resistance exercise, the lack, change, or significant decreases could be because of greater cell trafficking of immune-hormone complexes out of the plasma and into the buffy coat (i.e., white blood layer) or into the intercellular spaces. Further study will be needed to address this very dynamic “trafficking” movement of immune-hormone complexes out of the plasma biocompartment in order to determine the impact of this mechanism or mechanisms (14). In a prior animal study using resistance exercise, it was observed that a dynamic

trafficking of immune cells does take place, in part supporting the results of this investigation and the hypothesis that there is dynamic trafficking of immune cells in response to resistance exercise stress (14). Although subtle differences were observed in the pattern of responses (i.e., some individual time-point differences) in the blood variables, both protocols produced very similar results. Despite distinct differences in force and power production for the heavy resistance-exercise protocols used in this investigation, when total work is equated, the physiological response of these lymphokines are apparently similar, indicating that greater differences in resistance-exercise stress (e.g., larger differences in total work) may be needed to elicit larger differential patterns of responses.

The dramatic increases in lactate (approximately 15 mmol·L<sup>-1</sup> immediately postexercise) demonstrated that the exercise protocols presented a significant anaerobic stress to the body. Plasma lactate was higher in response to the high force protocol when compared with the high power protocol, despite total work being equal. Thus different loading patterns influence lactate production. However, higher lactate production may be partially attributed to the greater sympathetic demands of the high force protocol (11). Similar changes in the magnitude of the blood lactate were observed in both protocols despite a significantly higher response in the HF exercise protocol. However, the lack of any significant relationships with the responses of blood lactate and lymphokines makes the role of anaerobic metabolism in lymphokines production unclear.

The response patterns of lymphokines in the circulation have not been previously examined with dynamic heavy resistance exercise. Although a decrease in plasma concentrations of IL-2 to the high force exercise protocol in our study is consistent with previously reported decreases in response to high-intensity endurance exercise (5, 12), the magnitude of the decrease in IL-2 (i.e., 4 vs. 40–50%) was less with heavy resistance exercise. This might be partially because of the differences in the various modes of exercise (e.g., high ground-reaction forces with running), intermittent exposure time of muscle to high forces, and/or differences in intensity levels between the different modes of exercise. However, the high force protocol seemed to have a greater impact on the sympathetic and immune system as increased levels of lactate and decreased levels of IL-2 were detected in the circulation 15 minutes postexercise.

There are conflicting results (i.e., both no changes and increases observed) in the literature concerning even the pattern of responses of IFN- $\gamma$  to endurance exercise (8, 20, 22). In contrast, we observed decreases in the high-power workout and no changes in the high-force workout. Clearly, the pattern of transient responses at 15 minutes of recovery is sensitive to the

specific characteristics of the resistance exercise protocol as plasma IFN- $\gamma$  levels returned to preexercise levels. The physiological mechanisms that mediate such acute differential responses to subtle changes in the external demands of the resistance exercise remains unknown.

In summary, IFN- $\gamma$  and IL-2 differentially respond with exercise and into recovery in response to heavy resistance exercise. Although IFN-g decreased immediately postexercise and IL-2 levels were reduced 15 minutes into recovery, the suppression of these parameters of the immune system were transient and seemed to have been affected by the specific characteristics of the 2 heavy resistance-exercise protocols.

## Practical Applications

This study provides a basic biological basis for understanding the acute exercise responses of a heavy resistance-training workout. Subtle changes in the force output or power output in an overall workout do not appear to impact the responses of these 2 lymphokines. Interestingly, HF workout with the same total work produces greater concentrations of lactate in the blood, demonstrating a greater glycolytic demand during high-force efforts, even with only subtle differences in the force output. Recovery and repair of tissue is a dynamic process after a resistance-training workout. It involves the interaction of hormones, lymphokines, and immune cells. A greater understanding of the stresses associated with the workout and the natural recovery process will help in our understanding of the biological basis of resistance exercise.

*Note:* Jill A. Bush, PhD is now at the Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX; N. Travis Triplett-McBride, PhD is with the Department of Exercise and Sport Science, University of Wisconsin-LaCrosse, LaCrosse, WI; and J. Michael Lynch, MD is at Quincy University, Quincy, IL.

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