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Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise

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Abstract Unaccustomed, eccentrically biased exercise induces trauma to muscle and/or connective tissue. Tissue damage activates an acute inflammatory response. Inflammation requires the effective interaction of different physiological and biological systems. Much of this is coordinated by the de novo synthesis of families of protein molecules, cytokines. The purpose of the present paper was to determine changes in blood levels of various cytokines in response to exercise-induced muscle damage that was effected using high-intensity eccentric exercise. Six healthy, untrained, college-age male subjects were required to perform the eccentric phase of a bench press and a leg curl (4 sets, 12 repetitions/set) at an intensity equivalent to 100% of their previously determined one-repetition maximum. Samples of blood were drawn at the following times: before exercise and 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. These samples were analyzed for interleukins (IL): IL-lβ, IL-6, and IL-10; tumor necrosis factor-α; colony stimulating factors (CSF): granulocyte-CSF, macrophage-CSF, and GM-CSF; for cell adhesion molecules (CAM): P- and E-selectin, and intercellular cell adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1). Results were analyzed using a repeated-measures analysis of variance ($P = 0.05$). Compared to baseline values, IL-1β was reduced ($P = 0.03$) at 6, 24, and 96–144 h after exercise; IL-6 was elevated ($P = 0.01$) at 12, 24, and 72 h after exercise; IL-10 was elevated ($P = 0.009$) between 72 and 144 h after exercise; M-CSF was elevated ($P = 0.005$) at 12 and 48–144 h after exercise; and P-selectin was reduced ($P = 0.01$) between 24 and 144 h after exercise. It is concluded that when high-intensity eccentric exercise is compared to strenuous endurance exercise, post-exercise changes in cytokines do occur, but they are generally of a smaller magnitude, and occur at a later time period after the termination of exercise.

Key words Interleukins · Tumor necrosis factor · Colony stimulating factors · Cell adhesion molecules

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Introduction

Unaccustomed eccentric muscle action, involving muscle lengthening under tension, results in micro-injury to muscle and connective tissue (Macintyre et al. 1995; Smith 1991). This trauma appears to activate an acute inflammatory response, the generalized response of the body to injury regardless of the inciting stimulus (Shek and Shephard 1998), which involves the movement of fluid, plasma proteins and leukocytes into the injured tissue. The inflammatory process evolves rapidly, within minutes (Macintyre et al. 1995), and may be divided into overlapping stages according to differences in the populations of inflammatory cells (Tidball 1995). The primary purpose of acute inflammation is the repair of injured tissue (Macintyre et al. 1995; Smith 1991; Tidball 1995).

An important aspect associated with the initiation and amplification of acute inflammation is the production of a variety of protein molecules, the cytokines, that are synthesized de novo, and aid in directing inflammatory-related events (Dinarello 1997). Cytokines are

produced by a variety of cells including the vascular endothelium, tissue-resident leukocytes, and circulating leukocytes (Bagby et al. 1996; Cavaillon 1994; Dinarello 1997; Thijs and Hack 1995). Cytokines are divided into several different families, which include the interleukins (IL), tumor necrosis factors (TNFs), interferons, growth factors, colony stimulating factors (CSFs), and cell adhesion molecules (CAMs; Curfs et al. 1997). For the most part, each family of cytokines contributes to specific aspects of acute inflammation.

Cytokines may be further characterized as either pro- or anti-inflammatory, based loosely on their predominant action. At the onset of inflammation there is an up-regulation of the pro-inflammatory cytokines, IL-1β, TNF-α, and IL-6 (Cavaillon 1994; Dinarello 1997). IL-1β and TNF-α, which are most likely released by resident macrophages at the site of injury or infection (Dinarello 1997; Tidball 1995), initiate the inflammatory response and stimulate the synthesis of IL-6, typically by the local endothelium. These pro-inflammatory cytokines act locally and systemically (Cavaillon 1994; Dinarello 1997). In addition to the up-regulation and amplification of acute inflammation by pro-inflammatory molecules, there are a number of anti-inflammatory cytokines, such as the IL-1 receptor antagonist and IL-10, that play a crucial role in the containment and resolution of this process (Bagby et al. 1996; Dinarello 1997; Thijs and Hack 1995).

CSFs, which are released from the injured tissue and aid in the proliferation, differentiation, and activation of hematopoietic cells, include granulocyte-colony stimulating factor (G-CSF), macrophage-colony stimulating factor (M-CSF) and granulocyte-macrophage-colony stimulating factor (GM-CSF; Curfs et al. 1997).

An important aspect of acute inflammation is the selective recruitment of leukocytes to traumatized tissue, in an appropriate sequence (Tidball 1995). This involves the interaction between vascular endothelial cells and circulating leukocytes. This interaction is directed by the combined action of multiple cell adhesion molecules (CAMs). CAMs are glycoproteins that are expressed on the cell surface of leukocytes and potential target cells (Carlos and Harlan 1994; Elangbam et al. 1997). There are four main groups of adhesion molecules: the integrin family, with eight subfamilies designated βl–β8; the immunoglobulin superfamily, which includes intercellular cell adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs); selectins, including E- and P-selectin; and the cahedrins, which are major cell-to-cell adhesion molecules (Elangbam et al. 1997).

Many aspects of the cytokines and exercise-induced muscle damage have been examined. However, the majority of studies have examined this response in relation to strenuous endurance exercise (Nieman et al. 1998; Northoff et al. 1994; Ostrowski et al. 1999; Pedersen et al. 1998). The purpose of the present study was to focus on sequential changes in specific circulating cytokines, in response to a bout of unaccustomed high-intensity eccentric exercise. The cytokines assessed include: IL-lβ, IL-6, IL-10, TNF-α, G-CSF, M-CSF, GM-CSF, VCAM-1, I-CAM, E-selectin and P-selectin.

Methods

Subjects

Six active, Caucasian males who had not participated in any weight training for at least 6 months prior to the study, volunteered to participate. Their physical characteristics were as follows, mean (SEM): age 23.7 (3.3) years; height 185 (6) cm; body mass 82 (7) kg; percent body fat (as assessed from skinfold thickness at seven sites; Jackson and Pollock 1978) 10.6 (4.1)%. Subjects completed a comprehensive Health History and Activity History report and, after approval by a physician, read and signed an informed consent form that had been approved by the University Committee for Human Subjects, in accordance with guidelines established by the American College of Sports Medicine.

Exercise

Subjects performed two types of resistance exercise between 7:00 and 10:00 a.m. on the same day, using variable-resistance weight-training machines (Universal, Multi-stage and Leg Curl Machines). The particular exercises were selected because each incorporated a relatively large muscle mass, and it was believed that this would assist in maximizing the serum cytokine response.

The following procedure was followed for each bout of exercise. Initially, subjects warmed-up by performing three sets, ten repetitions per set, at 18.2, 22.7, and 27.3 kg, with 2 min of rest between each set. After a 5-min rest period, the subject's one-repetition maximum (l-RM) was assessed. Although typically the 1-RM reflects the maximum weight that can be lifted using a concentric contraction, for clarity, this was designated l-RM_{conc}, since a distinction was made in this study between the concentric and eccentric phase of the movement. Subjects then rested for 10 min before performing the high-intensity eccentric exercise.

The first exercise entailed the eccentric phase of a bench press, which targeted the pectoralis, triceps, and anterior deltoid muscle groups. To perform this exercise, subjects were required to lie supine on a bench and position themselves so that they were able to support a horizontal bar above the chest, and lower this in a controlled manner towards the chest. The second exercise entailed a leg curl, which targeted the hamstring muscle group. To perform this exercise, subjects were required to lie prone on the bench of the Leg Curl Machine, position their ankles under the support arm of the machine, and lower the weight in a controlled manner from a knee flexed to a knee extended position. They were instructed to lower the weight slowly to a count of 4 s; two assistants then returned the weight to the starting position. If subjects were unable to maintain control during the lowering phase, the resistance was reduced by 2.3 kg. On each piece of equipment, subjects performed 4 sets, 12 repetitions per set, with a 2-min rest between each set, at an intensity equal to 100% of their previously-determined 1-RM_{conc}.

Blood sampling

On the day of exercise, subjects were required to report to the laboratory at between 7:00 and 9:30 a.m.. Initially, subjects were required to sit quietly for 15 min. Venepunctures were performed before exercise, and at 1.5, 6, 12, 24, 48, 72, 96, 120 and 144 h after completion of the exercise. Standard aseptic techniques were used, and blood was drawn from an antecubital vein in either arm.

Cytokine analysis

Whole blood was collected in two 15-ml serum separator tubes, allowed to clot at room temperature for 30 min and then centri-

fuged at 1000 *g* for 10 min. Serum was removed and stored in 1-ml aliquots at −80 °C, until analysis. Commercial enzyme-linked immunosorbent assay (ELISA) kits (R and D Systems, Minneapolis, Minn., USA) were used to assess all cytokines. The procedures for all kits employed the quantitative "sandwich" enzyme immunoassay technique, with monoclonal antibodies specific for the cytokine, coated onto the wells of the microtiter plate. The optical density of each plate was determined using a microplate reader (BioRad, Richmond, Calif., USA) that was set at the required wavelength, and using a correction wavelength to correct for optical imperfections in the polystyrene microtiter plate. All samples were run in duplicate and percent coeffecients of variation recorded. The following cytokines were assessed IL-1β, high sensitivity (HS), IL-6, (HS), IL-10 (HS), and TNF-α (HS). CSFs included G-CSF, M-CSF, and GM-CSF. CAMs included: human soluble P-Selectin, E-Selectin (ELAM-1), ICAM-1, and VCAM-1.

Delayed-onset muscle soreness

Subjects were instructed to palpate bilaterally, muscle groups that were involved in the chest press (pectoralis major, triceps, and anterior deltoid muscle groups) and leg press (hamstring muscle group). Subjects were instructed to rate the soreness they experienced based on a subjective rating scale from 1 (no soreness) to 10 (extremely sore; Clarkson et al. 1987). These measures were assessed pre-exercise, and then every 24 h for 5 days.

Statistical analysis

Dependent variables were analyzed using a one-way repeated-measures analysis of variance. The raw data were ranked due to large individual variability. The level of statistical significance was set at $P = 0.05$. When appropriate, Fisher's least-squares difference post-hoc test was performed, comparing values to the pre-exercise baseline.

Results

For the ELISAs, the correlation coefficient for all standard curves was ≥0.99. The percent coefficient of variation between duplicate samples was less than 10%.

Cytokines

Interleukins and TNF-α

Surprisingly, IL-1β was significantly reduced ($P = 0.03$) at 6, 24, and 120 h after exercise, compared to baseline values (Fig. 1). IL-6 was significantly elevated ($P = 0.01$) over baseline values at 12, 24, and 72 h after exercise, with values approaching significance at 48 h (Fig. 2). IL-10 was significantly elevated ($P = 0.009$) over baseline values at 48, 72, 96, 120, 144 h after exercise (Fig. 3). There was no significant time effect for TNF-α ($P = 0.47$). (These data are also given in Table 1).

Colony stimulating factors

M-CSF ($P = 0.005$) was significantly elevated over baseline values at 12 h, and then from 48 to 144 h after exercise (Fig. 4). There was no time effect for G-CSF ($P = 0.2$) or GM-CSF ($P = 0.69$; Table 1).

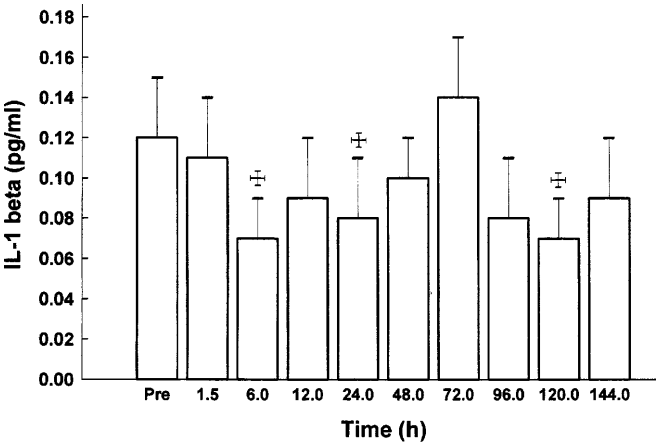

Fig. 1 Changes in serum interleukin (IL)-1β of six subjects before (*Pre*) as well as 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. Data are presented as the mean ± SEM values of the six subjects. ŦŦ$P < 0.05$ compared with the pre-exercise value

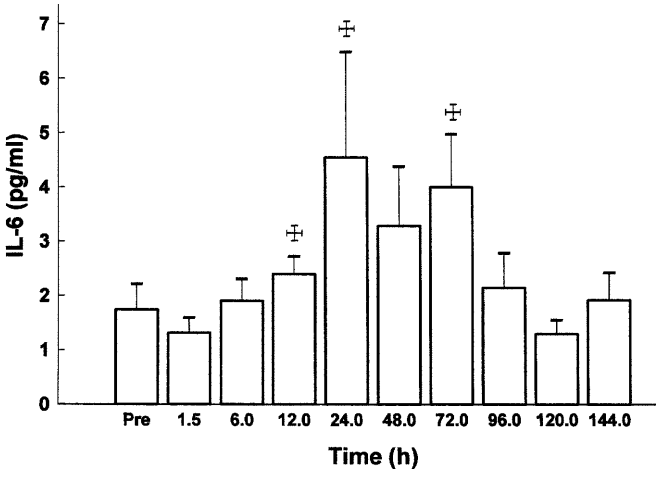

Fig. 2 Changes in serum IL-6 of six subjects before (*Pre*) as well as 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. Data are presented as the mean ± SEM values of the six subjects. ŦŦ$P < 0.05$ compared with the pre-exercise value

Cell adhesion molecules

P-selectin was significantly decreased ($P = 0.01$) compared to baseline values, between 24 and 144 h after exercise (Fig. 5). There was no significant time effect ($P > 0.5$) for either for E-selectin, ICAM-1, or VCAM-1 (Table 1).

Delayed-onset muscle soreness

In response to the bench-press exercise, the soreness assessed in the pectoralis major, triceps, and anterior deltoid muscle groups generally paralleled each other. Therefore, a statistical analysis was only run on the pectoralis muscle group, representative of the bench-press exercise, and on the hamstring muscle group,

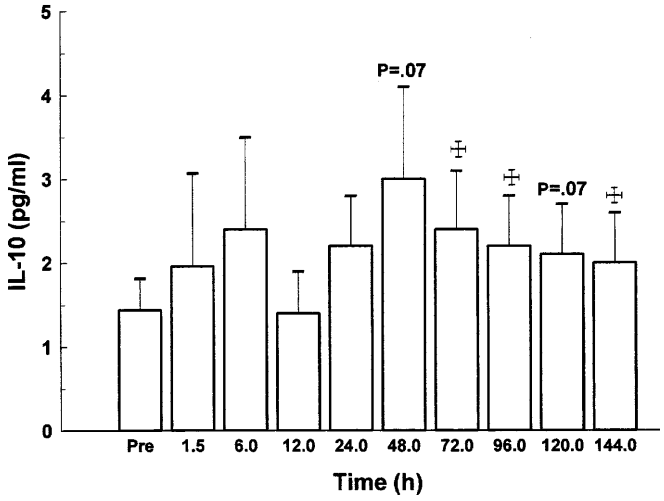

Fig. 3 Changes in serum IL-10 of six subjects before (*Pre*) as well as 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. Data are presented as the mean ± SEM values of the six subjects. ✣ $P < 0.05$ compared with the pre-exercise value

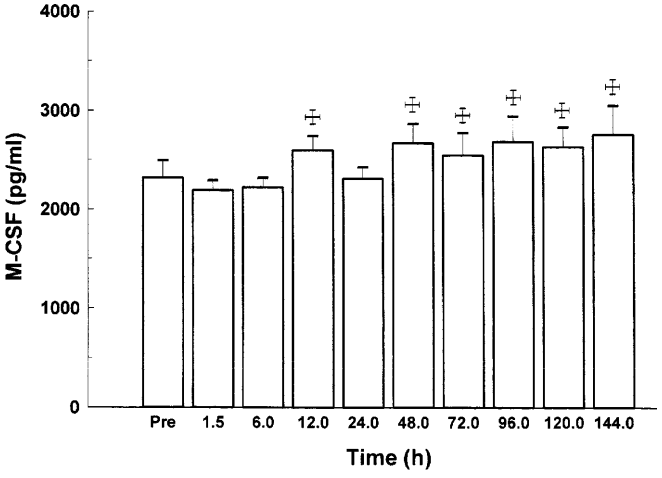

Fig. 4 Changes in serum macrophage-colony stimulating factor (*M-CSF*) of six subjects before (*Pre*) as well as 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. Data are presented as the mean ± SEM values of the six subjects. ✣ $P < 0.05$ compared with the pre-exercise value

representative of the leg-extension exercise. There was a significant time effect for delayed-onset muscle soreness (DOMS; $P < 0.001$). Peak soreness was seen at 48 h for the pectoralis and hamstring muscles. By 144 h, DOMS had almost returned to baseline levels.

Discussion

The purpose of the present study was to observe changes in circulating levels of several different families of cytokines, after a bout of high-intensity eccentric exercise. IL-6 was significantly elevated at 12, 24, and 48 h after exercise, while TNF-α showed no significant changes over time. There was a significant increase in the anti-inflammatory cytokine IL-10 between 48 and 144 h post-exercise. Significant elevations were seen in M-CSF at 24–144 h after exercise. Surprisingly, IL-1β was significantly reduced at 6, 24, and 120 h after exercise, while P-selectin was reduced between 24 and 144 h after exercise.

For the most part, changes in cytokine levels have been examined in subjects after strenuous endurance exercise, with varying results (Northoff et al. 1994; Ostrowski et al. 1999; Pedersen et al. 1998; Suzuki et al. 2000). The only study that is somewhat comparable to the present study, is that of Nosaka and Clarkson

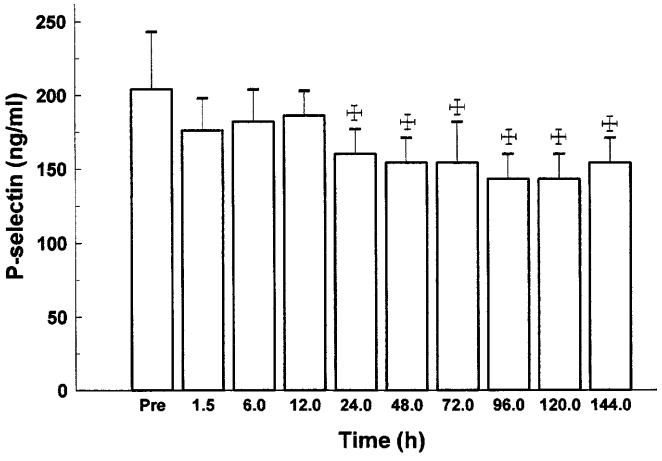

Fig. 5 Changes in the serum cell adhesion molecule, P-selectin, of six subjects before (*Pre*) as well as 1.5, 6, 12, 24, 48, 72, 96, 120, and 144 h after exercise. Data are presented as the mean ± SEM values of the six subjects. ✣ $P < 0.05$ compared with the pre-exercise value

Table 1 Non-significant serum cytokine values [means (SEM)] obtained before (*Pre*-) and 1.5, 6, 12, 24, 48, 72, 96, 120 and 140 h after exercise. Values are given in pg/ml, unless stated otherwise. (*TNF-α* Tissue necrosis factor α, *G-CSF* granulocyte-colony stimulating factor, *GM-CSF* granulocyte-macrophage-colony stimulating factor, *ICAM* intercellular cell adhesion molecule, *VCAM* vascular cell adhesion molecule)

Cytokine	Pre-	1.5 h	6 h	12 h	24 h	48 h	72 h	96 h	120 h	144 h
TNF-α	2.2 (0.4)	1.8 (3)	2.6 (0.6)	2 (0.3)	2.5 (0.9)	1.8 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.8 (0.3)
G-CSF	12.5 (5)	9.6 (3.1)	9.8 (2.6)	10.9 (2.6)	11 (3)	9 (2.4)	7.5 (1.7)	8.7 (1.9)	9.3 (2.4)	8 (2.5)
GM-CSF	28.9 (8.4)	29.2 (8.4)	29.5 (7.3)	31.5 (6.2)	37.2 (5.4)	29.1 (6.8)	20.2 (5.2)	24.6 (8.4)	26.7 (7.5)	37.6 (5.4)
E-Selectin (ng/ml)	66 (8)	76 (6)	68 (14)	78 (8)	76 (6)	80 (9)	83 (10)	70 (3)	65 (8)	71 (8)
ICAM (ng/ml)	266 (30)	312 (44)	364 (28)	356 (12)	326 (22)	310 (20)	330 (24)	302 (60)	298 (48)	266 (32)
VCAM (ng/ml)	1005 (110)	1470 (285)	1180 (150)	1580 (140)	1370 (165)	1045 (145)	1160 (205)	1355 (200)	1270 (230)	1273 (195)

(1996). They had 14 male subjects perform 24 maximal eccentric actions involving the biceps brachii, but found no changes in any serum cytokine levels. The differences between their results and the present study could be due to a number of factors, such as the amount of muscle mass involved in performing the exercise, the timing of the blood sampling, and the sensitivity of the assay kits used (Thijs and Hack 1995).

IL-1β, TNF-α and IL-6 are the early-response, pro-inflammatory cytokines that are most likely synthesized by resident macrophages and local post-capillary vascular endothelium, with de novo synthesis occurring rapidly after the onset of injury or infection (Cavaillon 1994). There have been conflicting reports regarding changes in serum IL-1β after a bout of strenuous endurance exercise. Northoff and Berg (1991) found that running a marathon resulted in no detectable changes in IL-1β, whereas Evans et al. (1986) reported that 45 min of downhill running resulted in a two-fold elevation. Sprenger et al. (1992) reported undetectable levels of IL-1β in plasma in 22 subjects after a 22-km race, but found significant elevations in urinary IL-1β between 3 and 24 h after the same race. Using muscle biopsy samples from human subjects, Cannon et al. (1989) reported an increased intensity of staining for IL-1β at 45 min after a 45-min bout of downhill running; this was still evident 5 days after termination of the exercise. There have been no reports of significant decreases in IL-1β, as was seen in the present study. However, measurement of circulating levels of IL-1β may not be an accurate means for assessing the up-regulation of IL-1β, since assessment is complicated by a variety of factors, such as rapid clearance from the circulation (Sprenger et al. 1992). Furthermore, depending upon the activation signal, IL-1β may accumulate in the cell or be released, suggesting a dissociation between intracellular IL-1 production and release (Cavaillon 1994). It is possible that the decreases seen in the present study were due to rapid clearance (Northoff and Berg 1991; Sprenger et al. 1992) or an undetectable accumulation at the site of injury (Cannon et al. 1989; Cavaillon 1994). It should also be noted that the aforementioned studies entailed strenuous endurance exercise.

With regard to TNF-α, a number of researchers have reported significant increases, albeit modest, in response to strenuous, aerobically biased exercise (Northoff et al. 1994; Ostrowski et al. 1999; Sprenger et al. 1992), while others have reported no change (Suzuki et al. 2000). In the present study there were no significant elevations in TNF-α after the bout of eccentric exercise, which is in agreement with the results of Nosaka and Clarkson (1996). A number of factors could account for differing results in this and other studies, including timing of the blood sampling, the type of exercise performed, and methodological issues (MacKinnon 1999). As is the case with IL-1β (Thijs and Hack 1995), a number of factors may influence the detection of circulating TNF-α. A variety of cells are able to effectively trap TNF-α, the result being that plasma TNF-α levels may not reflect synthesis by cells; this would explain why there is no correlation between plasma TNF-α and monocyte-associated TNF-α in septic patients (Thijs and Hack 1995). Furthermore, TNF-α may be bound to soluble TNF-α receptors that are shed into the circulation; many assays do not detect this bound form. Measuring only the biologically active fraction will show consistently lower levels compared to immunoassays that can measure both the active and bound forms of TNF-α (Thijs and Hack 1995).

IL-6 appears to be the cytokine most consistently elevated in response to trauma (Biffl et al. 1996) and to strenuous exercise (Nieman et al. 1998; Northoff et al. 1994; Ostrowski et al. 1999; Pedersen et al. 1998; Suzuki et al. 2000). Although it is produced early in inflammation, shortly after IL-1 and TNF-α, and displays several pro-inflammatory properties, it can not be regarded as a typically pro-inflammatory cytokine, since it possesses some anti-inflammatory properties (Curfs et al. 1997). Pedersen and Hoffman-Goetz (1999) suggest that IL-6 values peak at the end of a strenuous bout of exercise, or within a few hours, and then decrease rapidly to baseline levels. In the present study, IL-6 was elevated at 12 h, 24 h, and 72 h after exercise, and when compared to previous reports, these increases were modest. The dissimilar exercise protocols may explain, at least in part, the differing responses. However, the overall implication of the difference in magnitude and the time of increase, is not clear.

Recently, there has been considerable emphasis on the role of anti-inflammatory cytokines that function to contain the amplification of the pro-inflammatory cytokines (Dinarello 1997). IL-10 is a primary anti-inflammatory cytokine that acts by inhibiting pro-inflammatory cytokine production by activated monocytes and macrophages. Previous studies have shown significant increases of a large magnitude immediately after strenuous exercise (Northoff and Berg 1991; Ostrowski et al. 1999; Suzuki et al. 2000). However, in the present study, IL-10 was significantly elevated at 72, 96, and 144 h post-exercise, with values approaching significance at 48 and 120 h ($P = 0.07$). It is not clear why elevations were seen at different times. However, in the present study this time period would fit well with the period of resolution of an acute inflammatory response (Macintyre et al. 1995), and may, in part, be responsible for the reduction in pro-inflammatory IL-1β, which was significantly reduced between 96 and 144 h post-exercise.

CSFs represent another class of cytokines that is generally associated with hematopoeitic function. The major CSFs are GM-CSF, G-CSF and M-CSF (Curfs et al. 1997). Suzuki et al. (2000) reported a significant elevation in G-CSF immediately after a marathon, with no change in GM-CSF; they do not appear to have measured M-CSF. The only significant elevation seen in the present study was a significant elevation in M-CSF at 12 h, and between 48 and 144 h after exercise (Fig. 4). M-CSF induces mononuclear phagocyte colony formation, and activates the host defenses against viral, bacterial, parasitic and fungal infections (Curfs et al. 1997).

Although hypothetical, it is possible that the primary role of elevated levels of M-CSF at 12 h after exercise is related to mononuclear phagocytic colony formation, since this fits well with the time-frame for inflammatory recruitment of monocyte/macrophage leukocytes (Tidball 1995). The later elevations may be more closely related to an activation of immune defenses against anticipated antigens (Curfs et al. 1997), although unwarranted in this instance.

CAMs are intimately involved in the well-documented sequence of events regarding recruitment of leukocytes from the post-capillary venule to the site of tissue injury (Elangbam et al. 1997). The first step in recruitment involves the establishment of contact between leukocyte and endothelium, and is mediated by members of the selectin family, including P-selectin, and E-selectin. In the present study, the only change in circulating levels of the measured adhesion molecules was seen for P-selectin, which was significantly reduced between 24 and 144 h after exercise. P-selectin is pre-formed and is stored within the Weibel-Palade bodies of endothelial cells and the α granules of platelets. Within minutes of stimulation by specific cytokines such IL-1 or TNF-α, endothelial cells transport the preformed P-selectin to the surface, and may bind to a glycoprotein on leukocyte surfaces. The expression of P-selectin on endothelial cells leads to the rolling phenomenon of leukocytes along the vessel wall, thus promoting the initial localization of leukocytes and platelets at the site of inflammation. Although hypothetical, a possible explanation for the decrease in P-selectin between 24 and 144 h after exercise may be related to the process of desensitization (Colditz and Movat 1984), which may act to protect the damaged tissue from repeated invasion by phagocytic cells. This would in part be consistent with the "repeated bout effect" (Clarkson et al. 1987), whereby damage to muscle tissue is reduced after an individual has performed an initial bout of eccentrically biased exercise (Smith et al. 1998).

In summary, there were significant elevations in plasma IL-6, IL-10, and M-CSF. For the most part, these elevations were modest compared to cytokine levels seen after strenuous endurance exercise (Nieman et al. 1998; Northoff et al. 1994; Ostrowski et al. 1999; Pedersen et al. 1997, 1998; Sprenger et al. 1992; Suzuki et al. 2000). There was a significant decrease in IL-1β and in P-selectin. No changes were seen in TNF-α, G-CSF, GM-CSF, E-selectin, ICAM-1 and VCAM-1. It is recommended that the differing responses to the mode of exercise be investigated further, using a larger sample size and more frequent blood sampling, especially during the initial 12 h after the completion of exercise.

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