

Acute Resistance Exercise at Varying Volume Loads Does Not Enhance Plasma Interleukin-6

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ABSTRACT

Background: Aerobic exercise has been shown to impart anti-inflammatory effects partly through increased secretion of interleukin-6 (IL-6). Still unclear, however, is whether resistance exercise (RE) also enhances IL-6 secretion. **Objective:** The present study aimed to examine the effect of RE, performed at varying volume loads (VL), on plasma IL-6. **Methods:** Ten subjects (seven males and three females: age 37.9 ± 11.4 years; height 170.81 ± 11.16 cm; weight 71.36 ± 11.26 Kg.) participated in three randomized RE protocols: high VL (HVL) (5 sets x 20 repetitions at 45% 1-repetition maximum (1-RM), medium VL (MVL) (3x12 at 75% 1-RM), and low VL (LVL) (2x4 at 90% 1-RM) each separated by 96 hours. Capillary blood for IL-6 measurements was drawn immediately pre-exercise, immediately post-exercise, and 1- and 2-hours post-exercise. **Results:** There were no significant differences in plasma IL-6 between exercise condition (LVL, MVL, HVL) or at any time point ($p=0.422$ and $p=0.870$, respectively). **Conclusion:** Plasma IL-6 levels are not acutely sensitive to RE, regardless of volume load; therefore, any reported anti-inflammatory effect of RE appears to operate outside of the exercise-induced IL-6 pathway.

Key words: Interleukin-6, Resistance Exercise, Inflammation, Exercise, Cytokine

INTRODUCTION

Regular exercise reduces the risk against all-cause of mortality primarily by protecting against cardiovascular disease, type 2 diabetes mellitus, and cancer (Chen, Apostolakis, & Lip, 2014; Reihmane & Dela, 2014). A common sign of these diseases is chronic low-grade systemic inflammation (CLGSI), a condition mediated by several pro-inflammatory cytokines. One of these cytokines, interleukin-6 (IL-6), is considered to be the major inducer of acute-phase proteins (APP) gene expression, since it, either alone or by enhancing the effects of other cytokines, induces virtually all APPs (Chen et al., 2014; Reihmane & Dela, 2014; Simpson, Hammacher, Smith, Matthews, & Ward, 1997). Furthermore, IL-6 trans-signaling leads to the upregulation of adhesion molecules on the surface of leukocytes and endothelial cells, facilitating the migration of leukocytes into the sites of inflammation (Reihmane & Dela, 2014). Additionally, IL-6 increases the production of metalloproteinases responsible for the tissue remodeling and degradation of the extracellular matrix (Reihmane & Dela, 2014). Thus, IL-6 activity represents an important frontline component of the body's armory against infection and tissue damage (Simpson et al., 1997). However, overexpression of IL-6, and consequently elevated levels of APP, have also been implicated in the pathophysiology of CLGSI (Brown, Davison, McClean, & Murphy, 2015; Gabay, 2006; Petersen & Pedersen, 2005, 2006; Reihmane & Dela, 2014; Simpson et al., 1997).

Interleukin-6 activity is not limited to pathologic states, as exercise has also been shown to increase circulating IL-6 levels (Calle & Fernandez, 2010; Petersen & Pedersen, 2005; Reihmane & Dela, 2014). During exercise, IL-6 appears to mediate an anti-inflammatory response (Starkie, Ostrowski, Jauffred, Febbraio, & Pedersen, 2003). Starkie et al. (2003) showed that IL-6, stimulated by acute aerobic exercise, was associated with reduced TNF-alpha (TNF- α) levels and overall inhibition of E-Coli endotoxin-induced inflammation. Furthermore, exercise significantly enhances the transcriptional rate and subsequent expression of the IL-6 gene in contracting muscle fibers (Petersen & Pedersen, 2006). As a result, IL-6 has been shown to be the first and most abundant cytokine present in circulation during exercise (Petersen & Pedersen, 2005), and its presence amplifies monocytic and lymphocytic secretion of anti-inflammatory cytokines such as interleukin-1 receptor antagonist, tumor necrosis factor receptor, and interleukin-10 (Brown et al., 2015; Chen et al., 2014; Nimmo, Leggate, Viana, & King, 2013; Steensberg, Fischer, Keller, Moller, & Pedersen, 2003). Szostak and Laurant (2011) demonstrated that regular aerobic exercise confers protection against the formation of atherosclerosis, through IL-6 mediated down-regulation of TNF- α . Likewise, aerobic exercise has been shown to enhance the anti-inflammatory effect of standard treatment alone in cases of early and uncomplicated post-acute myocardial infarction by further decreasing TNF- α receptor 1 (Balen et al., 2008).

Consequently, the reduction of low-grade inflammation by IL-6 may play a role in facilitating the protective effects of regular aerobic exercise against chronic diseases.

Findings on the effect of acute resistance exercise (RE) on plasma IL-6 are less conclusive than aerobic exercise. Phillips et al. (2010) reported an increase in IL-6 after an acute bout of RE. In their study, they had two exercise protocols, one consisted of low-volume load (LVL) (13,160 kg \pm 1097 kg; 85%-1-repetition maximum (1-RM)) and another consisted of high-volume load (HVL) (17,729 kg \pm 1466 kg; 65% 1-RM). Both exercise routines showed an increase in IL-6 immediately post-exercise when compared to the control group, and the protocol with HVL produced higher levels of plasma IL-6 immediately post-exercise than the LVL. Mendham et al. (2010) also showed an increase in IL-6 immediately after their HVL (80% 1-RM, VL of 2400) full-body RE routine.

Yet, IL-6 levels do not always increase after acute RE. Fatouros et al. (2010) found no significant changes in circulating IL-6 after three cycles of 10 sets each of full-body resistance exercises performed in a circuit training fashion; each set consisted of 10 exercises \times 1 repetition at 70-75% 1-RM. Likewise, Buford et al. (2009) found no changes in plasma IL-6 after 3 sets of 10 repetitions at 80% of 1-RM of a machine squat, leg press, and leg extension exercises. Uchida et al. (2009) compared the effect of different intensities (50, 75, 90, and 110% of 1-RM) of a bench press exercise (the total volume of the exercise was matched among the exercise groups) on plasma IL-6 post-exercise and did not find any significant changes among the groups. Altogether, the lack of consistency among studies examining exercise-induced IL-6 could be attributed to the difference in post-exercise time points, methods utilized to measure the cytokines, training volume loads (Brown et al., 2015), and perhaps differences in participants circadian rhythm (Vgontzas et al., 2005).

It appears that exercise-induced IL-6 release depends on muscle glycogen availability. Low pre-exercise intramuscular glycogen increases the transcription of IL-6 mRNA in skeletal muscle and plasma IL-6 concentrations, an effect possibly mediated through the activation of AMPK and p38MAPK (Hennigar et al., 2017). Furthermore, Tsigos et al. (1997) found that infusion with recombinant human IL-6 (rhIL-6) induces a dose-dependent rise in blood glucose concentrations, indicating that IL-6 may act as a signal for hepatic glycogenolysis and gluconeogenesis (Hennigar et al., 2017). Additionally, rhIL-6 enhances lipolysis and fatty acid oxidation in adipocytes, perhaps to provide free fatty acids and energy when glycogen storage is low (Hennigar et al., 2017).

Clarifying the effects of RE on plasma IL-6 would be beneficial as RE could serve as part of a preventative treatment to improve health outcomes of populations with CLGSI; therefore, the purpose of the study was to examine the effect of RE, performed at varying volume load (VL), on plasma IL-6 levels. Since the increase in plasma IL-6 is positively related to the amount of muscle mass recruited and the intensity and duration of exercise (Brenner et al.,

1999; Nimmo et al., 2013; Reihmane & Dela, 2014), but inversely related to the muscle glycogen status (Chan, Carey, Watt, & Febbraio, 2004; Nimmo et al., 2013; Reihmane & Dela, 2014; Scott et al., 2011), it is hypothesized that the MVL RE protocol would induce the highest post-exercise levels of plasma IL-6. Based on the aforementioned evidence, the MVL was predicted to provide an optimal balance of intensity and duration to deplete glycogen, and hence, amplify the release of IL-6. Conversely, the HVL and the LVL protocols would not have the intensity or duration respectively, to stimulate the highest post-exercise levels of circulating IL-6.

MATERIALS AND METHODS

Study Design

This study used a repeated measures design, wherein participants completed all three of the exercise protocols in a randomized order; the three protocols, HVL (5 sets \times 20 repetitions at 45% 1-RM), MVL (3 \times 12 at 75% 1-RM), and (LVL) (2 \times 4 at 90% 1-RM) were separated by 96 hours. Capillary blood for IL-6 measurements was drawn immediately pre-exercise, immediately post-exercise, and 1- and 2-hours post-exercise. Before engaging in any exercise activity, participants underwent two familiarization sessions. All testing sessions took place at the Physiology of Exercise and Sport Laboratory at California State University Long Beach (CSULB). Recruitment efforts began after CSULB Institutional Review Board granted approval (approval number: 18-425). Participants provided verbal and written consent before the start of the study.

Participants

Ten healthy adults (seven males and three females: age 37.9 ± 11.4 years; height 170.81 ± 11.16 cm; weight 71.36 ± 11.26 Kg.) volunteered to participate in this study. They were excluded if they performed any type of physical activity other than walking, if they had surgery within the previous five months, major illness such as autoimmune or metabolic diseases, acute or chronic infections, or unresolved musculoskeletal or joint injury. Other exclusion criteria included irregular menstrual cycles, use of anti-inflammatory medication, smoking, drinking more than two alcoholic drinks a day, and consumption of any illegal substance. During the first familiarization session, potential participants completed the Physical Activity Readiness Questionnaire (Par-Q) and the Global Physical Activity Questionnaire (GPAQ) as part of the selections process. Once they were selected, they were instructed to continue to consume their regular diets during the entire study.

Exercise Protocols

Exercise protocol sessions were randomized for order (Excel for Mac Version 16.19 (181109)) and separated by 96 hours. Participants were instructed to consume their usual diet one hour before each exercise session. Prior to the warm-up,

participants' capillary blood was collected to measure IL-6 levels pre-exercise. The warm-up protocol consisted of five minutes of cycle ergometer (Monark, Ergomedic 828E, Vansbro, Sweden) and one set of 10 repetitions at 30% of the estimated 1-RM for each of the five exercises in the protocols. Participants rested 60 seconds between each set. Subsequently, they performed one of the three protocols assigned for that particular day. Participants' capillary blood was collected immediately after post-exercise, 1-hour post-exercise and 2 hours post-exercise to measure IL-6 levels. At the end of each exercise session, participants were asked the rate of perceived exertion (RPE) (Borg CR 10 Scale) (Riebe, Ehrman, Liguori, & Magal, 2018).

The three RE protocols (Table 1) were designed following previous established standards for program design (Haff, 2016). They consisted of HVL (5 sets x 20 repetitions at 45% 1-RM; VL=4500), MVL (3x12 at 75% 1-RM; VL=2700), and LVL (2x4 at 90% 1-RM; VL=720). During the second day of familiarization, participants learned the proper form and technique for the exercises used during the workout sessions, applying the principals described by the National Strength and Conditioning Association (NSCA) (Haff, 2016). These exercises included dumbbell squat, bench press with dumbbells, split squat with dumbbells, chest-supported back row with dumbbells, and sitting shoulder press with dumbbells (Rogue Rubber Hex Dumbbells, Rogue Fitness, Columbus, OH, USA). Once the participants demonstrated proper technique, the 1-RM was assessed for each of the exercises in the order mentioned above using the estimated 1-RM from a multiple-RM test described by NSCA (Haff, 2016). To determine their 1-RM, sequential loading was followed until they reached a load that allowed for three to six repetition maximum (achieved within three to five testing sets). The 1-RM was determined using a 1-RM conversion table (Haff, 2016).

Baseline Biochemistry and Anthropometry

During the first familiarization day, capillary blood samples were taken using disposable lancets (Capiject 2.00mm x 1.5 mm blue blade REF 200103). Approximately 40 microliters of whole capillary blood was used to assess fasting plasma glucose and lipid panel (total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triacylglycerol) (Cholestech LDX Analyzer, Alere, SNAA 169339, San Diego, CA) while 4 microliters of whole capillary blood was used for Glycolated hemoglobin (HbA1c) (Afinion AS100 analyzer, Alere, AS0056528, San Diego, CA, USA). Body weight was assessed in kilograms (Kg) on a scale (DigiTOL, Mettler Toledo, 8511, Columbus, OH,

USA); height was assessed in centimeters (cm) using a wall-mounted stadiometer (SECA, Hamburg, Germany) and body composition was assessed using Dual Energy X-ray Absorptiometry (Lunar iDXA by General Electric Healthcare, Madison, WI, USA).

Interleukin-6

During the exercise protocol days, capillary blood obtained by finger pricked was drawn immediately pre-exercise, immediately post-exercise, 1-hour post-exercise and 2 hours post-exercise; the exercise-induced change in capillary and venous IL-6 has been previously correlated (Cullen, Thomas, Webb, & Hughes, 2015). Approximately 300 microliters (μL) of whole capillary blood were collected into Sarstedt CB 300 K2E Microvette tubes and immediately centrifuged at 14,000 revolutions per minute at 4°C for ten minutes. Plasma was separated ($\sim 100\mu\text{l}$) and stored at -20° C for IL-6 analysis. IL-6 was quantified using an Invitrogen Human IL-6 ELISA Assay Kit (Fischer Scientific, Cat # EN2IL6). The assay was performed according to the manufacturer's protocol and a SpectraMax M2e microplate reader (Molecular Devices, San Jose, CA, USA) was used to determine the concentration of total plasma IL-6.

Statistical Analysis

Statistical analyses were performed with IBM SPSS statistics (version 25.0 Chicago, IL, USA) with significance set *a priori* ($p \leq 0.05$). A 3x4 (exercise protocol vs time) repeated measures analysis of variance (ANOVA) was performed to determine the effect of the exercise protocol over time (pre-exercise, immediately after, 1-hour post-exercise, 2 hours post-exercise) on the plasma levels of IL-6. Total VL between the exercise protocols was compared using the Welch ANOVA and the Games – Howell post-hoc analysis was performed to analyze the differences. A one-way ANOVA was used to determine the differences in the RPE between the exercise interventions and a Tukey post-hoc analysis was used to identify where those differences occurred. Data was expressed as mean standard deviation (SD).

RESULTS

To assess the relationship between acute RE VL and plasma IL-6, ten participants performed three different RE protocols on three separate occasions. Table 2 summarizes the participants' characteristics. The VL (sets x repetitions per set x kg) of the three RE protocols was

Table 1. Prescribed volume, load, and rest period for high-volume load (HVL), medium-volume (MVL), low-volume load (LVL) resistance exercise (RE) protocols

Protocol	Intensity (I)	Sets (S)	Repetitions (R)	Volume load (I x S x R)	Rest (min)
HVL	45% of 1-RM	5	20	4500	1
MVL	75% of 1-RM	3	12	2700	2
LVL	90% of 1-RM	2	4	720	3

1-RM: one repetition maximum; min: minutes

significantly different ($p=0.001$). The VL was significantly greater in the HVL protocol ($M=4744, 25, SD=\pm 1242.08$) and in the MVL ($M=3617.68\pm 1265.32$) than it was in the LVL (1309.36 ± 458.12 ; $p<0.001$). The VL of each RE bout is presented in Table 3.

Ratings of Perceived Exertion

RPE was found to be significantly different for the three exercise protocols ($p=0.001$). The RPE was significantly greater in the HVL ($M=8.7, SD=\pm 1.49$) than it was in both the MVL ($M=7.1, SD=\pm 0.89$; $P<0.009$) and the LVL ($M=4.7, SD=\pm 0.82$; $P<0.001$). MVL was also significantly greater than the LVL ($P<0.001$). RPE scores of each RE bout are presented in Table 4.

Table 2. Baseline participant characteristics

Descriptive	Mean \pm SD
Age (yrs)	37.9 \pm 11.38
Height (cm)	170.81 \pm 11.16
Weight (Kg)	71.36 \pm 11.26
BMI (kg/m ²)	24.47 \pm 3.38
Body Fat (%)	29.3 \pm 7.24
Fasting Glucose (mg/dL)	92.3 \pm 5.25
Total Cholesterol (mg/dL)	166.2 \pm 1.07
HDL-c (mg/dL)	48.6 \pm 12.81
LDL-c (mg/dL)	98.8 \pm 34.97
Triacylglycerol (mg/dL)	138.9 \pm 69.95
HbA1c (%)	5.29 \pm 0.32

SD: standard deviation Yrs: years; cm: centimeter; Kg: kilograms; BMI: body mass index; m: meters; mg: milligrams; dL: deciliter; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; HbA1c: glycated hemoglobin

Table 3. Volume load (Kg x repetitions x sets) for high-volume load (HVL), medium-volume load (MVL), and low-volume load (LVL) resistance exercise protocols

Intervention	Mean \pm SD
HVL (kg)	4744.25 \pm 1242.08*
MVL (kg)	3617.68 \pm 1265.32*
LVL (kg)	1309.36 \pm 458.12

Kg: kilograms; SD: standard deviation; *significantly different ($p<0.05$) from LVL

Table 4. Ratings of perceived exertion (RPE) for high-volume load (HVL), medium-volume (MVL), low-volume load (LVL) resistance exercise (RE) protocols using Borg CR 10 Scale [22]

Intervention	Mean \pm SD
HVL	8.7 \pm 1.49*†
MVL	7.1 \pm 0.89*
LVL	4.7 \pm 0.82

*Significantly different ($p<0.05$) from LVL and; †significantly different from MVL ($p<0.05$)

Plasma IL-6 Concentrations

Throughout all three testing sessions, capillary blood was collected pre-exercise, immediately after exercise, 1-hour post-exercise, and 2 hours post-exercise to measure plasma IL-6. A two-way repeated measures ANOVA determined that there were no main effects for RE protocols (HVL, MVL, LVL; $p=0.422$) or for time ($p=0.870$). Additionally, there was no statistically significant interaction between RE protocols and time ($p=0.205$). The plasma levels of IL-6 for each RE bout at different time points is presented in Figure 1.

DISCUSSION

The purpose of this study was to compare plasma IL-6 concentrations following acute bouts of RE exercise at different intensities and volumes to assess the relationship between VL (LVL, MVL, and HVL) RE and plasma IL-6 concentrations. While we hypothesized that the MVL RE protocol would elicit the highest post-exercise plasma IL-6 concentrations, our primary findings show that neither LVL, HVL, nor MVL RE elicited a change in plasma IL-6 levels. Thus, workload, as represented by VL, did not impact plasma IL-6.

The present study chose to use three distinct RE volume loads to characterize the relationship between RE VL and plasma IL-6. The HVL protocol's total VL (kg x sets x repetitions; 4744.25kg \pm 1242.08kg) was 24% and 72% greater than the VL of the MVL (3617.68kg \pm 1265.32kg) and the LVL (1309.36kg \pm 458.12kg) protocols respectively. Furthermore, RPE of the HVL and MVL protocols was greater than LVL, which correlates with Phillips et al. (2010), who found that RPE was greater in their HVL protocol compared to their LVL protocol.

Similar to the present study, others have found that RE does not reliably alter IL-6 levels. Brenner et al. (1999) and Bufford et al. (2009) found no changes in plasma IL-6 after a short bout of RE with a VL (relative load (% 1-RM) x sets x repetitions) of 2100 (60-70% 1-RM) and 2400 (80% 1-RM) respectively. Similarly, studies comparing the effect of different intensities with same VL on plasma IL-6 found no IL-6 changes. For example, Uchida et al. (2009)

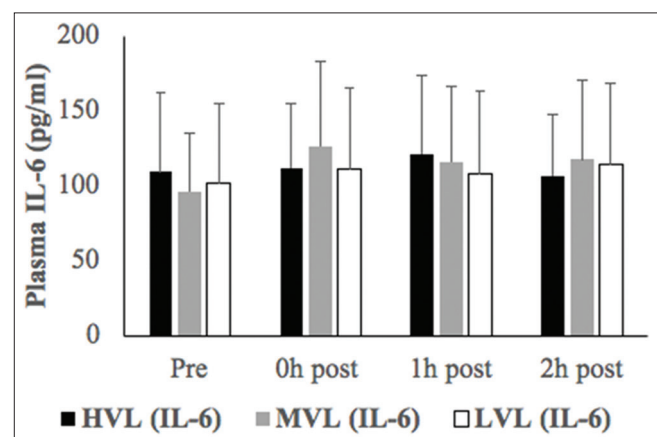


Figure 1. Plasma IL-6 concentrations (Mean \pm SD) for high-volume load (HVL), medium-volume load (MVL), and low-volume load (LVL) resistance exercise protocols at pre-exercise, immediately post-exercise, one-hour post-exercise, and two hours post-exercise

compared 50, 75, 90, and 110% 1-RM intensities that had a VL of approximately 4000, and Cornish et al. (2018) compared 60, 72, 80% 1-RM intensities that had a VL of 8600. Neither of these studies found a difference in plasma IL-6 post-exercise regardless of the intensity or VL.

Still, previous research has shown that RE can amplify IL-6 (Mendham et al., 2011; Phillips et al., 2010). Phillips et al. (2010) reported an increase in plasma IL-6 following two bouts of what the authors considered to be high (17,729 kg \pm 1466 kg; 65% 1-RM) and low (13,160 kg \pm 1097 kg; 85%-1RM) VL RE. Both protocols showed an increase in plasma IL-6 post-exercise when compared with the control group, and the high VL protocol displayed a greater increase in plasma IL-6 than the lower VL protocol. Notably, the VL of both protocols in Phillips et al. (2010) was greater than any of the aforementioned studies (Brenner et al., 1999; Buford et al., 2009; Cullen et al., 2015; Mendham et al., 2011; Uchida et al., 2009) and was also greater than any of the VL used in the current study (4744.25 kg \pm 1242.08kg; 3617.68kg \pm 1265.32kg; 1309.36kg \pm 458.12kg). Mendham et al. (2010) also showed an increase in plasma IL-6 in their HVL (80% 1RM, VL of 2400) when compared to the LVL (65% 1-RM, VL of 1800). Furthermore, both Phillips and Mendham utilized eight-full body exercises compared to others using six or fewer (Brenner et al., 1999; Buford et al., 2009; Cullen et al., 2015; Uchida et al., 2009). The same could be said about the current study, which incorporated a protocol consisting of five full-body exercises. Thus, both VL and the amount of muscle mass activated may play a strong role in dictating a potential IL-6 response.

This study intended to examine whether RE, performed at varying volume loads, could provoke an exercise-induced IL-6 response. As aerobic exercise-induced IL-6 acts anti-inflammatory (Starkie et al., 2003), we sought to understand the parameters of RE that could potentially be used in the future as a preventive treatment to improve health outcomes in populations with CLGSI. However, in the present study, RE did not cause an increase in plasma IL-6 at the VL applied, suggesting that either the VL here was not enough to elicit an IL-6 response, or if RE does in fact confer an anti-inflammatory effect, it may not be through the canonical exercise-induced IL-6 pathway. Either way, answering these questions is critical in order to best understand how to apply RE as a clinically valuable tool.

Primary limitations were the relatively low sample size as well as the prescribed exercise parameters. Perhaps plasma IL-6 responsiveness would be encouraged by increasing sample size along with reducing intra-set rest periods and increasing the number of exercise sets.

CONCLUSION

The results of the current study show that acute bouts of RE at different VL did not increase post-exercise plasma levels of IL-6. It is possible that since the levels of plasma IL-6 post-exercise seem to be inversely related to the glycogen content in the muscle (Chan et al., 2004; Nimmo et al., 2013), the VL adopted in this study did not cause a sufficient

depletion in muscle glycogen to elevate IL-6. Future studies should further examine the effect of different VL on muscle glycogen and its influence on plasma IL-6. Understanding the specific parameters of RE capable of stimulating an IL-6 response is critical, as the implementation of such parameters could be effective in helping treat or prevent low-grade inflammation associated with chronic diseases. Finally, the present study examined VL, but did not attempt to determine which of the two factors of VL (volume or intensity) is more important in affecting IL-6; future research in the area is needed.

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