


Original Article

Acute inflammatory responses to high-intensity functional training programming: An observational study

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ABSTRACT

Effects of varying types of short duration workouts in high-intensity functional training (HIFT) on inflammatory biomarkers have not been adequately characterized. Objectives: The purpose of this descriptive study was to examine the acute effects of HIFT workouts on biomarkers of inflammation, over time, in two HIFT bouts. Materials and Methods: Ten apparently healthy males (28.1 ± 5 yrs) completed two HIFT sessions ("short bout:" sub-5-minute vs. "long bout:" 15-minute) in a randomized crossover design. Blood was drawn pre and post-exercise, and 1 hour, 3 hours, and 6 hours post-exercise, centrifuged, and plasma frozen for analysis. Inflammation was assessed through plasma interleukin-6 (IL-6), interleukin-10 (IL-10), and tumour necrosis factor alpha (TNF- α). Results: Repeated measures ANOVA revealed a single trial-dependent difference (IL-6, $p \leq 0.05$), and while statistically significant, this difference may not be biologically significant. The biomarkers IL-6, IL-10, and TNF- α all follow a similar pattern of peaking post-exercise and returning to baseline within 6 hours in both trials. Conclusions: Both temporal responses and concentrations were similar in the short and long bout. A practical implication is that both bouts of a HIFT elicit certain specific physiologic

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INTRODUCTION

The popularity of high-intensity based exercise programming is rapidly growing among exercise enthusiasts (Thompson, 2017), perhaps because these programs offer a time-efficient mechanism to achieve fitness benefits (Burgomaster et al., 2005; Gibala et al., 2006; Heinrich et al., 2014; Jensen et al., 2004). Exercise-induced adaptations leading to skeletal muscle growth occur against the background of a dynamic cellular and systemic physiologic environment. For example, skeletal muscle cells can be damaged by the force of their own actions, resulting in acute subclinical trauma within the tissue (Faulkner et al., 1993). This trauma elicits a well-characterized sequence of degeneration and regeneration of the muscle cells (Carlson et al., 1983; Hawke and Garry, 2001; Tidball, 1995), which intimately link with vascular networks and other cell types (Christov et al., 2007; Jensen et al., 2004). As part of this sequence, muscle cells and cells of the immune system release pro-inflammatory and anti-inflammatory cytokines, such as the interleukins, into the circulation to spatially and temporally orchestrate physiologically relevant adaptations (Christov et al., 2007). The ratio of pro-inflammatory interleukin-6 (IL-6), which responds to injury or infection, to anti-inflammatory interleukin-10 (IL-10), which acts as an antagonist to the inflammatory response (IL-6:IL-10) has been proposed as a clinically relevant index of trauma severity (Taniguchi et al., 1999). Additionally, plasma levels of tumour necrosis factor alpha (TNF- α), a pro-inflammatory cytokine that drives low-grade inflammation, increase modestly during an acute bout of exercise (Benatti and Pedersen, 2015; Petersen and Pedersen, 2005). Examining biomarkers of systemic inflammation (e.g., the IL-6:IL-10 ratio and TNF- α) provides an enhanced understanding of exercise-induced adaptive phenomena within the context of a complex, dynamic cellular environment, subject to microtrauma and inflammatory influences.

A current trend in the fitness industry is high-intensity functional training (HIFT). Though several studies have evaluated the HIFT modality, varying definitions and descriptions have been provided. In a recent review of literature, Feito et al. (Feito, et al., 2018), described HIFT as a program or training style that utilizes functional movements such as aerobics (e.g., running, rowing, swimming, etc.), calisthenics (e.g., push-ups, pull-ups, sit-ups, etc.) and weight lifting (e.g., clean, snatch, deadlift, etc.), performed at high-intensities, with a goal of improving general fitness and performance. A typical HIFT session may utilize one specific resistance exercise done repetitively for a short period of time; alternatively, a longer session may consist of a combination of resistance training, such as Olympic weightlifting and bodyweight calisthenics/gymnastics, and cardiorespiratory-focused modalities. Concerns about overuse injuries underlie the dearth of studies that focus on a “pure” comparison of HIFT bouts of differing durations (i.e., 5 minutes of one specific high-intensity exercise is associated with a small chance for a repetitive-use injury, while 15 minutes of the same specific high-intensity exercise may provide inordinate repetitive-use injury risk to the participant) (Huynh et al., 2016; Keltz, et al., 2013). Variations exist in the choice of the modalities, as well as their prescribed order, weight, and repetition scheme, all of which influence duration, with a goal of creating a high-intensity exercise bout. Thus, HIFTs provide a unique blend of modality, intensity, and duration, which impact circulating levels of biomarkers of skeletal muscle inflammation.

The acute inflammation response plays a key role in functionally important adaptations to chronic training (Duchesne, et al., 2017; Perandini et al., 2018; Tidball, 1995; Yang and Hu, 2018). Conversely, the chronic exposure to high levels of inflammatory cytokines may lead to untoward physiological responses such as tissue injury (Lee et al., 2017). The expression of inflammatory cytokines has been shown to be greater in exercise bouts of longer duration and less responsive to those of shorter duration (Cullen et al., 2016; Shephard, 2002). However, several studies have demonstrated increases in pro-inflammatory markers following short duration exercise (Cullen et al., 2016; Suzuki et al., 2002; Yamada et al., 2002). For instance, Cullen et al. (Cullen et al., 2016) examined 5 x 4-minute cycle intervals and found that IL-6 levels were greater

when compared to a similar trial at lower intensities, while Yamada et al., (Yamada et al., 2002) observed significant increases in IL-6 within the first 1-hour of completing a maximal exercise test. These studies suggest that the inflammatory response is rapid and is not entirely based on exercise duration. Currently there is a lack of research related to the acute inflammatory response to the HIFT modality or variations of the bouts performed within it. Therefore, the purpose of this descriptive study was to examine the acute effects of HIFT workouts on biomarkers of inflammation, over time, in two HIFT bouts. The window for acute inflammation is relatively wide, but has been shown to occur within hours of an exercise bout (Cullen et al., 2016; Wadley et al., 2016) and therefore will be the focus of this study. For operational convenience, we refer to the bouts as “short” and “long,” although time duration is not the only difference between the bouts. We speculated that long-duration and short-duration bouts of HIFT—both primarily resistance exercise protocols, albeit with different exercises—would elicit similar modest pro-inflammatory responses.

MATERIAL AND METHODS

Participants

The protocols of this study were approved by the University Institutional Review Board (16-015) for testing of human participants and are within accordance to the ethical standards of the Helsinki Declaration. Initially, fifteen healthy males volunteered for this study, while only ten completed; participant characteristics are expressed as mean \pm SD (Table 1). Prior to participation, each participant reviewed and signed the informed consent. In order to participate a minimum of three months' experience with high-intensity exercise was required. Those who reported orthopaedic problems or who were suffering from any cardiovascular, pulmonary, or metabolic diseases were excluded from the study as determined through a Physical Activity Readiness Questionnaire (PAR-Q) and the health history questionnaire. Participants with an inability to perform any of the required movements, the inability to perform 30 clean and jerks at 61.4 kg in less than 5 minutes, or any contraindication of health, were excluded from the study. Prior to the first visit, participants fasted for a minimum of four hours, abstained from alcohol and exercise for 24 hours, and avoided caffeine or any over the counter supplements for 12 hours. Additionally, participants were screened for any medications that may influence cardiovascular, metabolic, or immune activity. Prior to each exercise bout, participants were asked to eat a moderate breakfast before their arrival in order to avoid post-exercise hypoglycemia. Additionally, participants were asked to repeat this meal for consistency between trials.

Table 1. Participant Characteristics.

<u>Characteristic</u>	<u>Values</u>
Weight (kg)	88.0 \pm 10.4
Height (cm)	176.1 \pm 8.0
Age (y)	28.1 \pm 5.4
Body Fat (%)	17.9 \pm 5.0
<hr/>	
Performance Markers	
GXT Max HR (b \times min ⁻¹)	186.3 \pm 11
VO ₂ Max (mL \times kg ⁻¹ \times min ⁻¹)	43.5 \pm 5.2
Short Bout Score (Seconds)	206.4 \pm 60.2
Short Bout % max HR	92.7 \pm 4
Long Bout Score (Repetitions)	274 \pm 48.6
Long Bout %max HR	91.3 \pm 3

N = 10; mean \pm SD. Demographic, physiologic, and anthropometric data were collected in initial visits to the laboratory.

Measures

For later assays of biomarkers of inflammation, blood plasma samples were collected at the following time points: pre-exercise (pre), immediately post-exercise (post), 1-hour post (1 h), 3-hours post (3 h) and 6-hours post (6 h). Participants underwent venepuncture while seated. Blood was collected using 12 mL heparinized tubes, which were inverted per manufacturer recommendations and immediately centrifuged at 2500 rpm (~1000 x g) for 15 minutes. Plasma aliquots were stored in an ultra-low freezer (-80 °C) until subsequent assays.

Prior to immunoassays, experiments were designed utilizing template maps of 96-well plates; the maps include standards, quality controls, and sample wells in duplicate. Four plates were required for the analysis of the interleukins and TNF- α (two plates for each bout duration, Intra-assay CV%: 2-13%, Inter-assay CV%: 5-19%). Frozen aliquots were thawed and cleared by centrifugation, and placed on ice. Reagents used in the assays were allowed to warm to room temperature prior to preparation. The immunoassays utilized a Millipore MagPix (Luminex, Austin Tx) for multiplex analysis of the inflammatory biomarkers, in a 96-well plate format. Manufacturer procedures for the Milliplex MAP kit were followed.

Following the assays, participant haemoglobin and haematocrit levels (previously obtained by finger stick [Alere Hemopoint h2, San Diego, CA]) were used to normalize participant samples for plasma volume shifts that occurred during and following the bouts; these corrections were based on the established protocols of Dill and Costill (Dill and Costill, 1974).

Experimental overview

Data collection occurred over three separate occasions in the Exercise Physiology Laboratory, with each visit taking place within one week of the previous, and occurring at the same time of day (between 6 and 11 AM). Initial visits consisted of a review of the procedures, signing of the informed consent, completion of a health history questionnaire, and (to further quantitatively assess fitness and body composition) a graded exercise test (GXT) and bodyfat analysis (via dual x-ray absorptiometry, DEXA). The remaining two sessions were performed in a randomized crossover design. Samples of blood were collected from each participant via antecubital venepuncture by a trained phlebotomist. After baseline samples were obtained, participants engaged in a 5-minute self-selected warm-up (such as jogging in place) followed by the exercise bout. After the completion of the bout (either Short or Long), blood was drawn immediately, and after 1, 3, and 6 hours. Haematocrit and haemoglobin were also obtained at each timepoint via finger stick, to address plasma volume shifts. Three hours following the exercise bout participants were allowed to eat, and were asked to repeat this meal for each bout.

Procedures

During the first visit, aerobic capacity (VO_2 max) was assessed through a graded exercise test (GXT) on a treadmill (Woodway USA, Waukesha, WI). The detailed GXT protocol used in this study has been previously reported (Kliszczewicz et al., 2017; Kliszczewicz, et al., 2018). Body mass was collected using an electronic physicians scale (Tanita WB 3000, Arlington Heights, IL) for height (cm) and weight (kg). Body composition analysis (percent body fat and fat free mass) was assessed using dual-energy x-ray absorptiometry scan (GE Lunar iDXA). Participant characteristics and body composition data are presented in Table 1.

The short bout chosen for this study consisted of 30 power clean & jerks at 61.4 kg using an Olympic barbell. The beginning of the movement starts with the barbell on the ground. A power clean (floor to shoulder movement) is performed, followed by a shoulder to overhead movement (i.e. jerk). Full extension at the elbow was necessary at the end of the movement for the repetition to count. These movements were repeated for

30 repetitions at a self-selected pace to complete the workout as fast as possible in five minutes or less. Participants could use any shoulder to overhead technique to complete to movement as long as full extension at the elbow was achieved during each overhead movement. Additionally, participants were allowed rest *ad libitum*.

The long bout chosen for this study was a 15-minute circuit consisting of a 250-meter row on a rowing ergometer (Concept 2, Morrisville, VT), 20 kettlebell swings at 16 kg, and 15 dumbbell thrusters with two 13.6 kg dumbbells. The objective of the workout was to complete as many repetitions as possible within the 15 minutes. For scoring purposes, every 10 meters on the rowing ergometer equalled one repetition. The standard resistance for the rowing ergometer was a damper setting of six, which is a setting commonly self-reported by these athletes. Kettlebell swings began with the kettlebell at the starting position between the legs and a few inches off the ground. The kettlebell is then swung overhead until achieving an upright position with the kettlebell directly overhead with elbows in the locked position. The dumbbell thruster movement consisted of holding the dumbbells in the front rack (shoulder level) position, completing a full front squat into an overhead press with hips open and elbows locked at the end of the movement. The participant could not begin the next movement until all prescribed repetitions were completed. All movements had to be completed within the standards in order for the repetition to be counted.

Analysis

Using g-power software, *a priori* analysis based on a power of 0.8, alpha level of significance of 0.05, and an effect size of 0.5 revealed an *n* of 7 to be sufficient for this study (Faul et al., 2009). Participant plasma IL-6, IL-10, and TNF- α data were entered into the statistical software program SPSS, v.24. A 2 (trial) x 5 (time) repeated measures ANOVA with a Bonferroni adjustment was applied in order to assess differences between resting plasma biomarker concentrations and post-exercise concentrations between trials (short and long). A post-hoc paired samples t-test assessed differences between same trial-time points. The statistical significance was set to an alpha of < 0.05. Data are presented as mean \pm SD.

RESULTS

Fifteen participants initiated the study; of these, 10 completed all pre-exercise and post-exercise blood draws for short and long HIFT bouts: Two participants withdrew due to injury experienced outside the study, two participants were excluded due to vasovagal responses to the phlebotomy procedure, and one due to a scheduling conflict. Table 1 provides the characteristics performance data of the 10 participants who completed the study (Kliszczewicz et al., 2017; Kliszczewicz et al., 2018).

The response of plasma biomarkers to short and long HIFT bouts is summarized in Table 2 and Figures 1-4. A Repeated Measures ANOVA demonstrated no time-dependent differences between any marker of inflammation; IL-6 ($p = 0.843$), IL-10 ($p = 0.316$), or TNF- α ($p = 0.065$). No trial-dependent differences were observed for the markers of inflammation with the exception of IL-6 ($p = 0.045$), (TNF- α : $p = 0.988$, IL-10: $p = 0.464$). Because the range of IL-6 levels reported here falls within an expected range (Leggate et al., 2012; Pedersen et al., 2001) the statistically significant difference we note between trials may not be biologically significant. Of note, the IL-6:IL-10 remained consistent regardless of trial; a slight increase in the ratio is noted at the post-timepoint in both trials (Fig. 4).

Table 2. Inflammatory Biomarkers

IL-6	Short	Long	p	CI	Cohen's d
Pre	10.7 ± 5.5	7.0 ± 6.5	0.057	-.16, 7.5	0.61
Post	14.9 ± 10.7	8.5 ± 5.1	0.090	-1.4, 14.4	0.76
1 h	9.6 ± 6.3	6.5 ± 4.6	0.093	-.74, 6.9	0.56
3 h	11.2 ± 7.1	7.1 ± 5.4	0.046*	.11, 8.0	0.65
6 h	9.9 ± 5.6	5.6 ± 3.7	0.053	-.09, 8.6	0.90

IL-10	Short	Long	p	CI	Cohen's d
Pre	33.1 ± 24.5	31.3 ± 26.2	0.475	-3.9, 7.4	0.07
Post	41.6 ± 42.2	32.2 ± 19.9	0.413	-16.9, 35.8	0.28
1 h	37.3 ± 31.1	37.3 ± 25.2	0.999	-11.7, 11.7	0.00
3 h	32.2 ± 30.2	31.3 ± 26.3	0.838	-8.9, 10.6	0.03
6 h	34.4 ± 27.1	27.9 ± 20.1	0.226	-5.5, 18.3	0.27

TNF-α	Short	Long	p	CI	Cohen's d
Pre	11.5 ± 7.1	11.3 ± 9.1	0.938	-5.3, 5.7	0.02
Post	21.5 ± 24.0	16.5 ± 11.6	0.406	-8.2, 18.2	0.26
1 h	13.8 ± 13.4	12.1 ± 11.7	0.584	-5.0, 8.3	0.14
3 h	11.5 ± 10.8	14.1 ± 11.7	0.318	-4.8, 1.7	0.23
6 h	10.8 ± 13.0	10.7 ± 9.3	0.978	-6.2, 6.4	0.01

Values are presented as mean ± SD. * significantly different from Trial (p < 0.05).

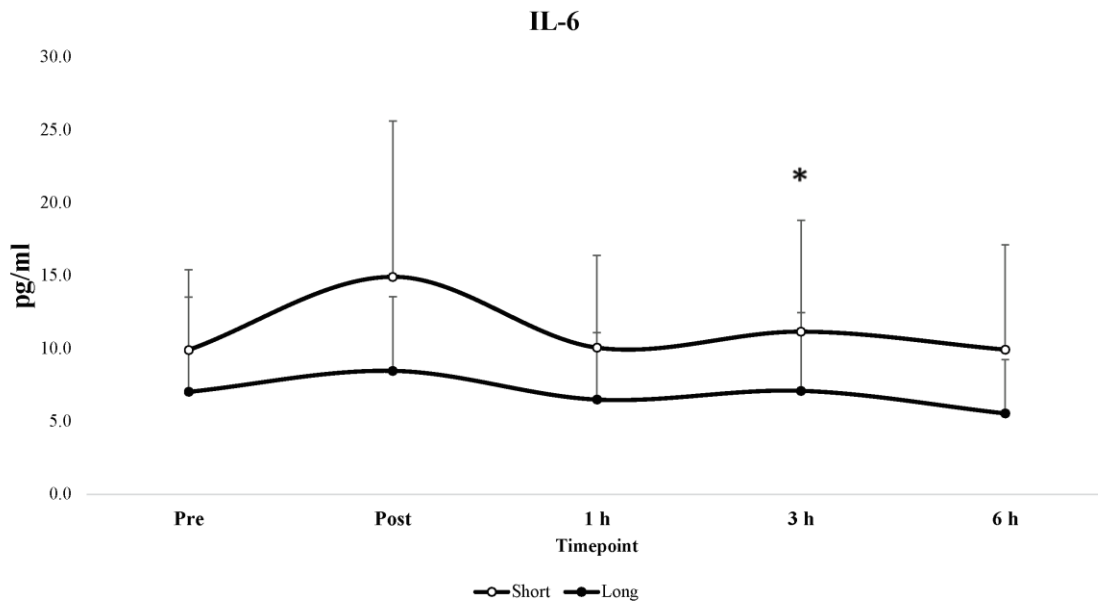


Figure 1. Plasma Biomarkers of Inflammation: IL-6. Levels before and after exercise, presented as Means and positive Standard Deviation. * denotes significantly different from Long trial.

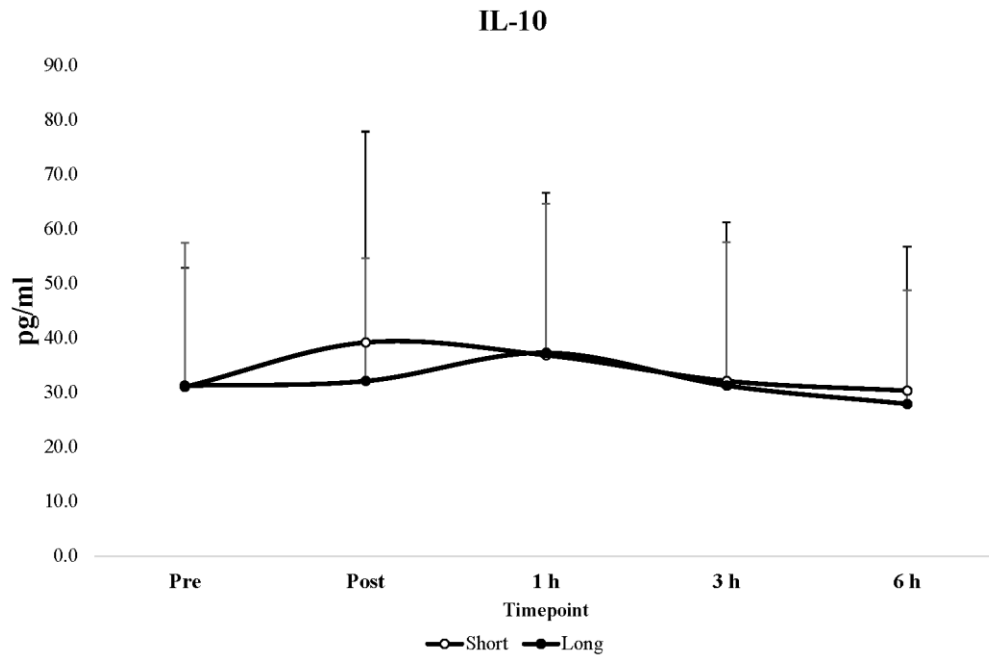


Figure 2. Plasma Biomarkers of Inflammation: IL-10. Levels before and after exercise, presented as Means and positive Standard Deviation.

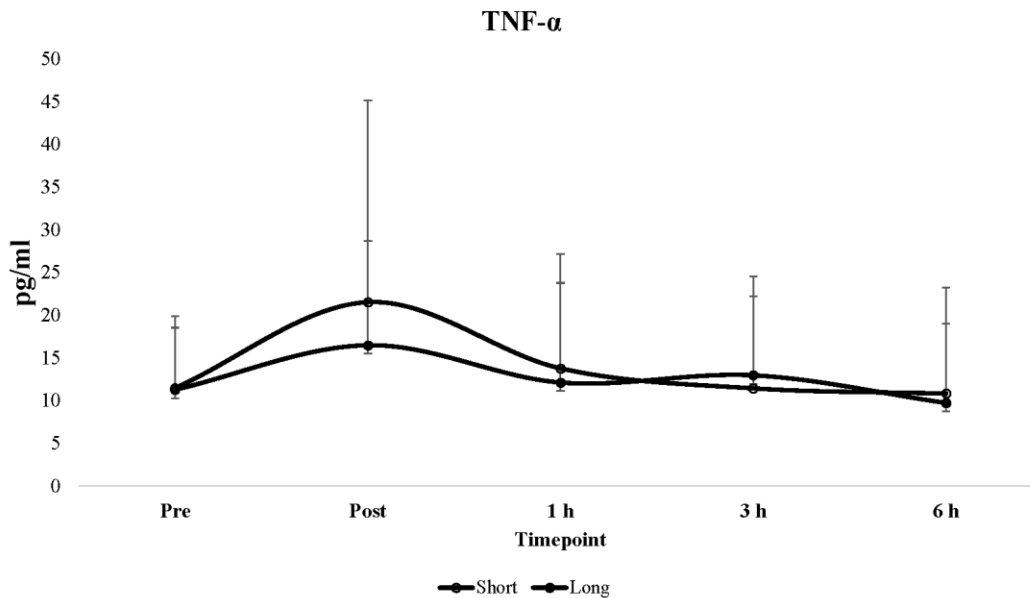


Figure 3. Plasma Biomarkers of Inflammation: TNF-α. Levels before and after exercise, presented as Means and positive Standard Deviation.

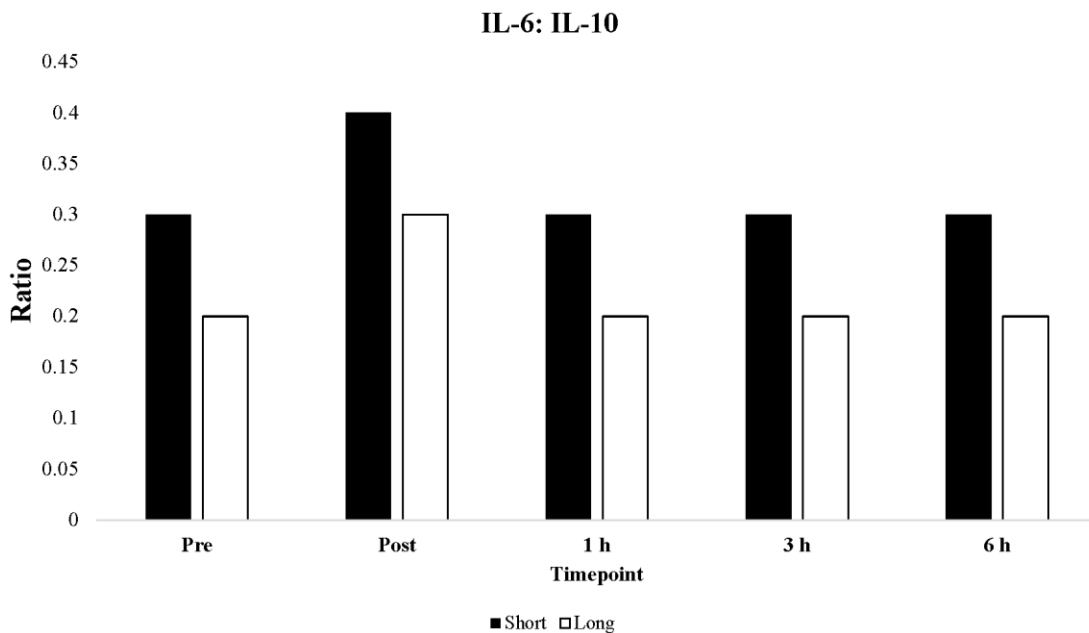


Figure 4. IL-6 to IL-10 Ratio (IL-6: IL-10).

DISCUSSION

As HIFTs become more mainstream, athletes and trainers will have questions about their physiologic effects. The purpose of this study was to examine the effects of two representative examples of HIFT bouts on circulating levels of pro- and anti-inflammatory markers. Primary findings of this study suggest that acute responses to short and long bouts of HIFTs are equivalent, in terms of inflammatory biomarkers. Prior to the study, we speculated that a sub-5-min bout of resistance exercise, consisting exclusively of repetitions of the clean and jerk movement, would elicit similar inflammatory responses as a 15-min bout of mixed resistance exercises. Our data appear to support this speculation.

Cytokines are small proteins that regulate cell movement. One category of cytokines is the family of interleukins, which are cytokines that regulate movement of immune cells. Interleukins can be categorized as pro-inflammatory or anti-inflammatory, and play key roles in inflammation. During the acute phase response to injury, infection, and/or inflammation, the most responsive pro-inflammatory cytokine is IL-6. As an endogenous counterbalance, levels of the anti-inflammatory cytokine IL-10 will increase in kind, antagonizing inflammatory responses. Following each of the bouts, increases in both IL-6 and IL-10 were observed; however, these increases were only significantly different for IL-6, 3 h post exercise, with the short bout eliciting a greater response.

The interplay of these cytokines correlates with tissue injuries (Taniguchi et al., 1999), and may be a valuable indicator of the systemic inflammatory environment following various types of trauma to soft tissues—perhaps including the microtrauma induced by intense exercise. However, it must be noted that increased levels of IL-6 may appear in the blood following exercise that does not elicit muscle damage (Petersen and Pedersen, 2005); this observation led to the conceptualization of certain interleukins as myokines, which are cytokines produced and released by contracting skeletal muscle fibres that exert influence across tissue and organ

systems. Furthermore, IL-6 of muscular origin may be considered anti-inflammatory, while IL-6 emanating from monocytes and macrophages (as in the acute phase response to injury) is popularly viewed as pro-inflammatory (Benatti and Pedersen, 2015). It is important to note that the participants of this study were familiar with this type of exercise modality and perhaps require a greater stress in order to experience dynamic shifts in interleukins following an acute exercise bout. Future studies will attempt to describe the origin of IL-6 following high-intensity exercise, in trained and untrained athletes.

Circulating levels of the pro-inflammatory cytokine, tumour necrosis factor alpha (TNF- α), provide insight into the systemic inflammatory environment following bouts of exercise (Monchanin et al., 2007; Reihmane et al., 2013). Interventions that lower TNF- α levels may confer health benefits, particularly in those with rheumatic disease, and it is therefore a commonly examined cytokine; however, research studies describing TNF- α kinetics (including release from adipose tissue) following high-intensity exercise are limited (Leggate et al., 2012). Of note, our data focus on plasma markers reflecting inflammation, a potentially important variable to consider when prescribing exercise in health and disease (Benatti and Pedersen, 2015; Hartman and Frishman, 2014). Across timepoints, we note minimal influence of either bout on the IL-6: IL-10 ratio (Figure 4), and no statistically significant differences between trials on TNF- α (Figure 3). With regards to TNF- α , the muted effect of the two exercise trials we describe here is consistent with the literature, which shows that even prolonged strenuous exercise (marathon) results in only small increases in TNF- α in the plasma (Pedersen et al., 2001). Thus, we suggest that while TNF- α may be an important cytokine to monitor in athletes with inflammatory rheumatic diseases (Charles et al., 1999), in healthy athletes it may not be as informative as IL-6, particularly if the origin of IL-6 is examined.

Results must be interpreted in the context of certain limitations. Given the experimental design, we knew *a priori* that it would not be possible to attribute differences or similarities between bouts to the duration of the exercise bout. However, this study is just the first investigation of a larger and longer examination of these responses, intended only to describe inflammatory responses to two real-world high-intensity exercise protocols, at specific timepoints. Another limitation was that participants were allowed to eat at the 3 h timepoint; this may have influenced blood markers. However, blood draws were taken prior to the meal, so any effects of the meal would only influence the 6 h timepoint. Furthermore, we felt the meal would be important to participants, both in terms of recruitment/retention and avoiding hypoglycemia following the intense protocols. Another limitation—exercise-induced plasma volume shift—exists, and was addressed. Because changes to plasma volume can occur during acute exercise, even in the absence of observable perspiration, we calculated changes in plasma volume concentration using methods previously described (Dill and Costill, 1974). A future study may compare bouts of high-intensity *endurance* exercise with each other, and versus bouts of high-intensity *resistance* exercise; in this case normalization of plasma volumes will again be important. Additionally, we did not evaluate subjects' diet over the course of the study. Future studies would be strengthened with the inclusion of a Sports Dietician. Finally, additional markers of skeletal muscle damage and inflammation should be evaluated in conjunction with inflammatory mediators such as IL-1, IL-8, CRP, creatine kinase, and myoglobin, in order to better interpret physiological importance.

CONCLUSION

This study examined plasma biomarkers of inflammation following high-intensity exercise bouts of ~5 or 15 minutes duration. Similar responses were observed regardless of duration; thus we conclude that 5 minutes of HIFT exercise may be just as effective as 15 minutes with regards to the inflammatory response. However, because the exercise protocols in the short and long bouts were different, we cannot attribute the inflammatory similarities between bouts to time alone. Nonetheless, a bout of a HIFT, whether 5 min or 15

min, is a popular and time-efficient means of reaping the fitness benefits of exercise (Heinrich et al., 2015; Klisczewicz et al., 2013). This is consistent with previous findings (Burgomaster et al., 2005) and may have important ramifications for health/fitness professionals who design HIFTs, and for the athletes who enjoy these programs.

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