HIGH INTENSITY INTERVAL TRAINING INDUCES A MODEST INFLAMMATORY RESPONSE IN ACTIVE, YOUNG MALES

A Thesis
by
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Abstract

HIGH INTENSITY INTERVAL TRAINING INDUCES A MODEST SYSTEMIC INFLAMMATORY RESPONSE IN ACTIVE, YOUNG MEN

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The purposes of this study were to determine the extent to which an acute session of high intensity interval training (HIIT) increases systemic inflammatory cytokines and chemokines and if two weeks of HIIT training alters the systemic inflammatory response. Eight recreationally active males performed two weeks of HIIT on a cycle ergometer (6 sessions at 8-12 intervals; 60 sec intervals, 75 sec active rest) at a power output equivalent to 100% of their pre-determined VO_2max. Serum samples were collected during the 1st and 6th training sessions at rest and immediately post-, 15, 30, and 45 minutes post-exercise. Repeated measures two-way ANOVA indicated that HIIT induced significant increases in IL-6 at each time point after exercise, compared to rest. HIIT also induced increases in IL-8 immediately after and at 30 and 45 min after exercise, compared to rest. TNFα and MCP-1 increased 42% and 29%, respectively, immediately after exercise and IL-10 increased 120%

at 45 min after exercise, compared to rest. The concentrations of IFNγ, GM-CSF, and IL-1β were unaltered with HIIT. Two weeks of training did not alter the inflammatory response to an acute bout of HIIT exercise. Maximal power achieved during a VO_2max test significantly increased 4.6%, despite no improvements in VO_2max after training. These data suggest that HIIT exercise induces a modest, yet significant inflammatory response in young recreationally active men; however, two weeks of HIIT does not alter this response.

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Foreword

Chapter 1 of this thesis is an extensive introduction and literature review. Chapter 2 of this thesis was written as a manuscript that will be submitted to *The European Journal of Applied Physiology*, an international peer-reviewed journal published by Springer and owned by Springer Science+Business Media; it has been formatted according to the style guide for that journal.

Chapter 1: Proposal

Introduction

High-intensity interval training (HIIT) is characterized by repeated sessions of relatively brief (30-60 seconds), intermittent exercise, often performed with an "all out" effort or at an intensity close to that which elicits peak oxygen uptake (i.e., ≥90% of VO_2max) and is generally performed on a cycle ergometer (Gibala et al., 2006). HIIT has proven to be a sufficient stimulus in increasing VO_2max and certain metabolic adaptations in a variety of populations. HIIT requires as little as 75 min/week of training, compared to the ACSM recommended 150 min/week, and has demonstrated itself to be superior to longer duration moderate intensity training (i.e. jogging or brisk walking) with regards to metabolic adaptations (Gaesser & Angadi, 2011).

Initial HIIT training protocols consisted of repeated Wingate tests over a period of 2 weeks (Burgomaster, Hughes, Heigenhauser, Bradwell, & Gibala, 2005; Gibala, et al., 2006). A Wingate test is an exercise test that assesses anaerobic power and consists of a 30-second "all out" sprint on a cycle ergometer pedaling against 7.5% of the subject's body weight. However, this mode of HIIT utilizes a supramaximal intensity (eg. >100% VO_2max) that may not be suitable for all subject populations. Recently, Gibala and colleagues, as an alternative to the initial HIIT training protocols, developed a low-volume HIIT protocol. Low volume HIIT consists of repeated bouts of exercise (8-12 reps) at or near maximal intensities (i.e. 90-100% VO_2max) with consistent workloads and has shown significant improvements in VO_2max, metabolic systems, and power outputs in both healthy and clinical (i.e. diabetic) cohorts (Little et al., 2011; Little, Safdar, Wilkin, Tarnopolsky, & Gibala). In addition to

metabolic changes, anaerobic and aerobic exercise bouts can result a transitory inflammatory response.

Prolonged (2-3 hours at 60-70% VO_2max) aerobic exercise induces a large systemic inflammatory response (D. C. Nieman, 1997; David C. Nieman et al., 2007; D. C. Nieman et al., 2001; D. C. Nieman et al., 2012), which may lead to an infection due to a suppression of the immune system. For example, the prevalence of upper respiratory infections in athletes is increased following a prolonged aerobic event (D. C. Nieman, Johanssen, Lee, & Arabatzis, 1990; Peters, Goetzsche, Grobbelaar, & Noakes, 1993). More recently it has been reported that even a single bout of high intensity exercise may cause an increase in plasma inflammatory cytokines (Meckel et al., 2011).

The purpose of this study is to determine if: a) an acute session of low-volume HIIT increases plasma inflammatory cytokines and b) if two weeks of low volume HIIT training alters the inflammatory response in moderately active, young men. First, I hypothesize there will be a significant increase in inflammatory cytokines after an acute bout of HIIT. Second, I hypothesize after two weeks of HIIT training the post-exercise increase in inflammatory cytokines will be significantly attenuated.

Review of Literature

Traditionally, moderate intensity aerobic exercise has been used to induce metabolic changes and improve fitness in the general population. These training protocols require long training sessions (90-120 min) before increases in skeletal muscle metabolic enzyme activity and content and improvements in max can be detected. Normally characterized as short, "all-out" efforts at or above 100% VO_2max, HIIT appears to be an effective, time-efficient alternative to traditional aerobic exercise training because of its ability to increase VO_2max and metabolic enzyme activity and content in relatively short training periods (20-30 min) compared to traditional aerobic exercise training. Recent studies have reported that a "low volume" variation of HIIT is just as effective at inducing metabolic changes as traditional supra-maximal HIIT protocols (Bayati, Farzad, Gharakhanlou, & Agha-Alinejad, 2011).

It is well known that prolonged, high-intensity aerobic exercise regimens induce substantial systemic inflammation, such that several inflammatory cytokines are elevated in the blood during and after the exercise bout. Very few studies have examined shorter, higher intensity protocols and their effect on inflammatory cytokines. Therefore, the purpose of this study is to examine the extent to which low-volume HIIT induces a systemic inflammatory cytokine response.

Training adaptions to HIIT

HIIT is generally defined as repeated bouts of relatively brief, intermittent exercise performed at intensities ≥90% VO_2max. The high intensity bouts are separated by rest periods of predetermined lengths depending on the intensity of the effort. Despite the relatively short duration of exercise (75 to 90% shorter than traditional aerobic training

(Gaesser & Angadi, 2011)), HIIT can induce similar adaptations to those of aerobic exercise training.

The metabolic adaptations occurring with HIIT have been extensively investigated over the past 10 years, and HIIT has been reported to increase both anaerobic and aerobic exercise capacities. Initially, Burgomaster et al. (2005) reported that only 6 sessions of HIIT (4 x 30 second "all out" efforts per session) nearly doubled exercise time to exhaustion at 80% VO_2 peak. Despite the changes in exercise capacity, VO_2max showed no improvement (Burgomaster, et al., 2005). Using the same protocol, Burgomaster et al. (2006) later demonstrated that exercise performance in a 250kJ cycling time trial improved 9.6%; and similar to the previous study, no improvement in VO_2max was observed (Burgomaster, Heigenhauser, & Gibala).

Lower intensity protocols of HIIT have been investigated showing similar results. Little et al. (2010) reported an improvement in time to complete a 50kJ and 750kJ time trial of 11% and 9%, respectively, after 2 weeks of training. The author used a low volume protocol that consisted of 8-12 intervals at a peak power (W) achieved in a VO_2max test. Changes in VO_2max were not examined (Little, et al., 2010). Though exercise capacity has previously been shown to increase, changes in the magnitude of VO_2max can vary. Rodas et al. (2000) reported a significant increase (11%) in VO_2max with 2 weeks of HIIT (4-7 reps of 15-30 sec "all out" intervals) in recreationally active individuals (Rodas, Ventura, Cadefau, Cusso, & Parra, 2000). Taken together, these findings suggest that the ability of HIIT to increase VO_2max depends on the training protocol and training status of the subject.

While there is a general consensus that more than 2 weeks of exercise training is required to induce changes in VO_2max in moderate to highly trained subjects, 2 weeks of

traditional HIIT training has been shown to improve oxidative capacity through increased in mitochondrial enzymes, such as citrate synthase (CS) and cytochrome c oxidase (COX) in skeletal muscle tissue. Burgomaster et al. (2005) reported a 38% increase in CS enzyme activity in just 6 training sessions of repeated Wingates (4 x 30 sec) in recreationally active young men and women (Burgomaster, et al., 2005). More recently, Little et al. (2011) demonstrated that a single session of repeated Wingate tests (4 x 30 sec) significantly increased CS, COX II, and COX IV protein content, while CS and COX enzyme activities were increased 14% and 19%, respectively, 24 hrs after exercise in recreationally active young men (Little, Safdar, Bishop, Tarnopolsky, & Gibala, 2011). This study demonstrates increases in protein content do not always equal increases in enzyme activity. Furthermore, oxidative capacity has been shown to increase after 2 weeks of low volume HIIT in overweight, sedentary, middle-aged adults. The authors found a significant increase (~35%) in CS and COX IV protein content (Hood, Little, Tarnopolsky, Myslik, & Gibala, 2011). The findings from Little et al. (2011) and Burgomaster et al. (2005) suggest increases in mitochondrial enzyme content and/or activity play a larger role in improving exercise capacity than does VO_2max, following 2 weeks of HIIT.

Previous research on HIIT training has demonstrated that a relatively short amount of training time (2 weeks), compared with traditional aerobic training, is required to provide an adequate stimulus to cause adaptation in many different populations. Oxidative capacity has been shown to react positively to HIIT. These adaptations, in turn, improve exercise performance, despite changes in VO_2.

Inflammatory Cytokine Response to Exercise

It is well known that prolonged, high intensity aerobic exercise and eccentric-based resistance exercise induce a robust inflammatory response, characterized by increased inflammatory cytokines in the systemic circulation. Cytokines are signaling molecules involved in the inflammatory process and can be secreted by many different cell and tissue types, such as leukocytes and skeletal muscle. It is generally believed that the aforementioned types of exercise induce damage to the muscle tissue, thus the inflammatory response functions to mediate healing of the tissue. The acute inflammatory response has been well studied with muscle damaging exercise; however, less is known about the inflammatory response to HIIT exercise. While HIIT does not cause muscle damage per se, different variations of HIIT have been reported to induce an inflammatory response. Nonetheless, further research is needed understand the mechanism by which HIIT stimulates an inflammatory response.

The inflammatory cytokine response to exercise has largely been investigated in prolonged, high-intensity aerobic exercise. Nehlen-Cannarella et al. (1997) reported that experienced marathon runners displayed a 400-700% increase in IL-6 and a 70-231% increase in IL-1 in the blood after 2.5 hours of high-intensity running (~76% of VO_2max) (Nehlsen-Cannarella et al., 1997). Nieman et al. (2001) reported plasma levels of IL-10 (~40-fold), IL-1ra (~20-fold), IL-6 (~40-fold), and IL-8 (158%) significantly increased immediately after a marathon race and remained elevated for 1.5 hours post race (D. C. Nieman, et al., 2001). Suzuki et al. (2003) reported similar results in marathon runners and also found that G-CSF (194%), M-CSF (56%), and MCP-1 (175%) increased significantly after the race (Suzuki et al., 2003). Nieman et al. (2007) examined the inflammatory

response in trained cyclists riding 3 hours per day at ~57% VO_2max for 3 consecutive days. They reported a significant increase in plasma inflammatory cytokines, IL-1, IL-6, IL-8, IL-10, TNFα, and MCP-1, after each exercise session (David C. Nieman, et al., 2007). Taken together, these studies demonstrate that prolonged, high-intensity exercise induces a large systemic inflammatory cytokine response.

Recently, Nieman et al. (2012) examined the relationship between exercise duration and intensity on the inflammatory response in male cyclists with1.75 hours of cycling at 60% watts max, followed by a 10-km time trial. The authors reported that increases in plasma levels of IL-6 and IL-8 were significantly correlated with average exercise heart rate and rating of perceived exertion. From this study it was concluded that intensity is an important factor for determining the magnitude of the acute inflammatory response to exercise (D. C. Nieman, et al., 2012). On the other hand, Reihmane et al. (2012) compared inflammatory responses in amateur half-marathoners and marathoners whose relative race intensity was not different. Increases in plasma IL-6 and TNFα were significantly higher in the marathon group, compared to the half-marathon group; therefore, the authors concluded that given the same relative exercise intensity between groups, the duration of the race was the important determinant of the magnitude of the inflammatory response (Reihmane, Jurka, Tretjakovs, & Dela, 2012). While both intensity and duration of exercise appear to be major factors in determining the magnitude of the inflammatory response, the mode of exercise also needs to be examined. Nieman et al. (1998) reported that 2.5 hours of cycling induced significantly lower post-exercise concentrations of IL-6, compared to 2.5 hours of running (D. C. Nieman et al., 1998). These previous findings suggest that intensity, duration, and mode of exercise

may potentially modulate the inflammatory cytokine response to exercise; however, the contribution of each variable is still unclear.

A few studies have examined the acute inflammatory response to HIIT. Meckel et al. (2009) reported that high-intensity running (4 x 250 meters, 80% maximal running speed) significantly increased plasma IL-6 concentrations in elite handball players, and IL-6 concentrations remained elevated for over 1 hour (Meckel et al., 2009). Subsequently, Meckel et al. (2011) examined the effects of two different running sprint interval protocols on the inflammatory response in elite handball players. Both protocols consisted of 4 sprint intervals of 100, 200, 300, or 400 meters in length, but subjects were randomized to perform either the ascending or descending protocol first. Results indicated both sprint interval protocols produced similar ~2-fold increases in IL-6 from baseline (Meckel, et al., 2011). Also, Arent et al. (2010) found a significant increase in IL-6 concentrations (100-180% increase) immediately post and 30 minutes post one Wingate and 8 intervals (10 sec at 0.1 kP/kg BW) (Arent, Senso, Golem, & McKeever, 2010). Very few studies have examined how HIIT can affect the inflammatory response over a prolonged training period. Croft et al. (2009) examined whether 6 weeks of HIIT running training (5 x 3 min) had an effect on plasma cytokine levels after an acute bout of exercise. The authors reported that 6 weeks of HIIT training significantly attenuated the post-exercise IL-6 (30-65% decrease) and IL-8 (16-48% decrease) response (Croft et al., 2009). The attenuation of the cytokine response suggests a possible training effect, such that this particular exercise stimulus is less stressful to the subject after two weeks of exercise training. Furthermore, Nieman et al. (2007) reported an attenuation of the systemic cytokine response in trained cyclists after 3

consecutive days of cycling 3 hours per day at ~57% VO_2max (2007). Although, the attenuation was significant, this is not a commonly used training method.

In addition to examining systemic cytokine concentrations following HIIT, Fisher et al. (2011) analyzed the inflammatory cell response after 4 HIIT intervals (30 sec at 90% of max anaerobic power) and reported significant increases in leukocyte, lymphocyte, and neutrophil concentrations in the blood, compared to pre-exercise levels (Fisher et al., 2011). While these studies demonstrate that HIIT training induces significant increases in IL-6 and IL-8, further studies are required to investigate the effect of different HIIT protocols, including low volume, and its effect on other inflammatory cytokines and how the inflammatory cytokines react to chronic training.

Conclusion

These studies demonstrate that different modes of exercise can induce various inflammatory responses, depending on volume, duration, and intensity of exercise. The lack of studies investigating the inflammatory response to HIIT in moderately trained individuals demonstrates the need for further investigation. To fill this gap in literature, the purposes of this study are to determine if: a) an acute session of low-volume HIIT increases plasma inflammatory cytokines, and b) if two weeks of low volume HIIT training alters the inflammatory response in moderately active, young men.

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Title

High intensity interval training induces a modest systemic inflammatory response in active, young men

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Abstract

The purposes of this study were to determine the extent to which an acute session of high intensity interval training (HIIT) increases systemic inflammatory cytokines and chemokines and if two weeks of HIIT training alters the systemic inflammatory response. Eight recreationally active males performed two weeks of HIIT on a cycle ergometer (6 sessions at 8-12 intervals; 60 sec intervals, 75 sec active rest) at a power output equivalent to 100% of their pre-determined VO_2max. Serum samples were collected during the 1st and 6th training sessions at rest and immediately post-, 15, 30, and 45 minutes post-exercise. HIIT induced significant increases in IL-6 at each time point after exercise, compared to rest. HIIT also induced increases in IL-8 immediately after and at 30 and 45 min after exercise, compared to rest. TNFα and MCP-1 increased 42% and 29%, respectively, immediately after exercise and IL-10 increased 120% at 45 min after exercise, compared to rest. The concentrations of IFNγ, GM-CSF, and IL-1β were unaltered with HIIT. Two weeks of training did not alter the inflammatory response to an acute bout of HIIT exercise. Maximal power achieved during a VO_2max test significantly increased 4.6%, despite no improvements in VO_2max after training. This data suggest that HIIT exercise induces a modest, yet significant inflammatory response in young, recreationally active men; however, two weeks of HIIT does not alter this response.

Keywords

high intensity interval training, cycle ergometer, inflammatory cytokines, exercise training

Introduction

High-intensity interval training (HIIT) is characterized by repeated sessions of relatively brief (30-60 seconds), intermittent exercise, often performed with an "all out" effort at an intensity close to that which elicits peak oxygen uptake (i.e., ≥90% of VO_2 max) and is generally performed on a cycle ergometer (Gibala et al. 2006). HIIT has proven to be a sufficient stimulus in increasing VO_2max and enzymatic metabolic adaptations in a variety of populations. HIIT requires as little as 75 min/week of training, compared to the ACSM's recommended 150 min/week of moderate intensity exercise and has demonstrated to be superior to longer duration moderate intensity training (i.e. jogging or brisk walking) with regards to metabolic adaptations (Gaesser and Angadi 2011; American College of Sports et al. 2010).

The Wingate test is an exercise test that assesses anaerobic power and consists of a 30-second "all out" sprint on a cycle ergometer pedaling against 7.5% of the subject's body weight. Initial HIIT training protocols consisted of repeated Wingate tests over a period of 2 weeks (Burgomaster et al. 2005; Gibala et al. 2006); however, this mode of HIIT utilizes supra-maximal intensities (i.e. >100% VO_2 max) that may not be suitable for all subject populations. Recently, Gibala and colleagues developed a new, lower intensity HIIT protocol as an alternative to the Wingate based HIIT training protocols. The lower intensity HIIT protocol consists of repeated bouts of exercise (8-12 reps) at or near maximal intensities (i.e. 90-100% VO_2 max) with consistent workloads. While it is unclear whether this lower intensity HIIT protocol improves VO_2max, it did significantly increase oxidative enzyme capacity and mean power output in both healthy and clinical (i.e. diabetic) cohorts (Little et al. 2010; Little et al. 2011).

It is well known that prolonged, aerobic exercise (2-3 hours at 60-70% VO_2max) induces a large systemic inflammatory response (Nieman 1997; Nieman et al. 2007a; Nieman et al. 2001; Nieman et al. 2012; Konrad et al. 2011b; Suzuki et al. 2003b); however, less is known about the inflammatory response to HIIT. Recently, it has been reported that a single bout of high intensity exercise increases circulating inflammatory cytokines. Interval running increases IL-6 ~2-fold in plasma immediately after running and concentrations remain elevated for 1 hr (Meckel et al. 2009), and cycling intervals have produced ~2-fold increases IL-6 immediately after exercise and concentrations remained elevated for 30 min (Arent et al. 2010). The systemic inflammatory response to lower intensity HIIT protocol has not been examined. To fill this gap in literature, the purposes of this study were to determine: a) the extent to which an acute session of lower intensity HIIT increases systemic inflammatory cytokines and b) if two weeks of lower intensity HIIT training alters the systemic inflammatory response in moderately active, young men. We hypothesized that an acute bout of HIIT would induce increases in systemic inflammatory cytokines and chemokines and two weeks of HIIT training would attenuate the systemic inflammatory response.

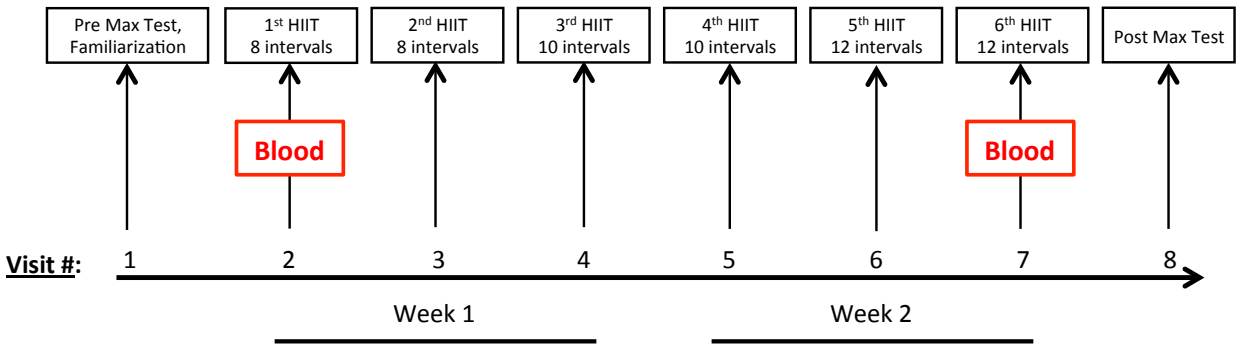
Methods

Subjects

The Appalachian State University Institutional Review Board approved all procedures in this study. A total of 19 healthy, college-aged males were recruited to participate in this study. All subjects were classified as "Low Risk" to perform exercise testing according to ACSM Risk Stratification guidelines and were non-smokers, with no history of cardiovascular, pulmonary, or neuromuscular diseases, and no lower body musculoskeletal injury in the previous 6 months. Upon completion of initial testing, subjects with a VO_2max less than 42.2 mL/kg/min were excluded from the study; this exclusion criterion was based on ACSM recommendations for individuals performing high-intensity exercise (40th percentile of normative values according to ACSM's Guidelines for Exercise Testing – 8th Edition). In the end, eight subjects completed all components of the study (age: 22 ± 2 yrs, height: 180.9 ± 7.9 cm, weight: 75.7 ± 6.6 kg, activity level: 4 ± 2 d/wk). Lastly, subjects were instructed to refrain from taking non-steroidal anti-inflammatory drugs for the duration of the study and asked to maintain normal physical activity levels for the duration of the study. All exercise testing and training took place in the Neuromuscular Laboratory at Appalachian State University and subjects signed an informed consent before participation in the study.

Experimental Design

This study consisted of 8 total visits: 1 initial testing and familiarization session, 6 HIIT exercise sessions, and 1 post-training testing session (see protocol schematic). The entire study lasted approximately 3 weeks. All testing and exercise sessions took place at approximately the same time of the day.



Visit #1 – Initial testing and familiarization session:

On the first visit, subjects completed the informed consent, exercise risk assessment, and a health history questionnaire. Height (VanBruggen et al.) and weight (kg) were recorded. Subjects then completed a maximal graded exercise test on a cycle ergometer (Lode, Groningen, The Netherlands). The maximal graded exercise testing protocol modified from a protocol used by Gibala and colleagues (Little et al. 2010) started with a warm up of 2 min at 50 watts (W). Subjects were allowed to self-select the cadence for the entire test but were instructed to remain above 60 revolutions per minute (rpm). After the warm up, the workload increased 15 W every 30 sec until volitional fatigue. During the maximal graded exercise test, metabolic parameters were measured with a metabolic cart (Parvo True2400, ParvoMedics, Sandy, UT) and workload (watts; W) was recorded. Maximal oxygen consumption was determined using the 15-second averaging analysis setting. During all exercise bouts, heart rate was monitored using a telemetric heart rate monitor (Polar, Lake Success, NY) and ratings of perceived exertion (RPE) were recorded every minute on a scale of 6-20.

After completing the maximal graded exercise test, subjects rested for 20 minutes, and then completed a HIIT familiarization session of 4 HIIT intervals on the cycle ergometer.

The HIIT familiarization protocol consisted of a 3-min warm up at 50 W, four 60-sec HIIT intervals at a workload (W) equivalent to 100% of each subject's VO_2max, and 75-sec active rest periods at 50 W between work intervals. The HIIT training protocol was modified from a previously published protocol (Little et al. 2010). Study personnel supervised all exercise testing and training sessions and provided verbal encouragement.

Visits #2-7 – HIIT training sessions:

At least 48 hours following the first visit, subjects began the two-week HIIT training program: 3 sessions per week (e.g. Monday, Wednesday, Friday) for a total of 6 HIIT training sessions. Each HIIT training session consisted of repeated 60-sec intervals of cycling on the Lode cycle ergometer at a workload equivalent to each subject's 100% VO_2max (according to the initial maximal graded exercise test). Each interval was separated by 75 sec of active recovery at a lower intensity (50 W). All subjects completed a 3-min warm-up and cool down at 50 W prior to and following each training session. During each session, RPE (6-20 scale) and HR were recorded at the end of each interval. For HIIT sessions 1 and 2, subjects performed 8 HIIT intervals; for sessions 3 and 4, subjects performed 10 HIIT intervals; and for sessions 5 and 6, subjects performed 12 HIIT intervals. At the first HIIT training session, blood samples were collected via intravenous catheter before exercise (Mitchell et al.) and immediately, 15 min, 30 min, and 45 min after completion of the HIIT exercise session for the analysis of circulating inflammatory cytokine and chemokine concentrations. Blood collection procedures were repeated at the last (sixth) HIIT training session.

Visit #8 – Post-training testing:

At least 48 hours following the last HIIT training session, subjects performed another maximal graded exercise test using the same protocol as stated above. During the post-training maximal graded exercise test, metabolic parameters were measured with a metabolic cart (Parvo True2400) and workload (W), HR, and RPE were recorded as stated above.

Blood collection and processing procedure:

Venous blood samples were collected at the first and last HIIT training sessions via intravenous catheter at the following time points: before exercise (Mitchell et al.), immediately after, and 15 min, 30 min, and 45 min after completion of the HIIT exercise. Approximately 10 mL of blood was collected at each time point in individual plasma and serum collection tubes (BD Vacutainer, Franklin Lakes, NJ), separated by centrifugation, aliquotted into cryovials, and stored at -80°C for analysis.

Analysis of circulating inflammatory cytokine and chemokine concentrations:

Serum samples were analyzed for inflammatory cytokines and chemokines with a bead-based multiplex assay using the MAGPIX instrument and xPONENT® analysis software (Luminex, Austin, TX). The concentration (pg/mL) of the inflammatory cytokines interleukin-1β (IL-1β), IL-6, IL-8, IL-10, tumor necrosis factor α (TNFα), and interferon-γ (IFNγ), and the inflammatory chemokines monocyte chemotactic protein-1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF) were measured using a commercially available assay kit (Millipore, Billerica, MA) according to manufacturer's specifications.

Statistical analyses:

Two-way repeated measures ANOVA (training x time point) was used to determine if differences existed in inflammatory cytokine and chemokine concentrations in serum

samples. Following a significant F-ratio, Bonferroni post-hoc analyses were used to determine differences between time points within an acute bout of HIIT and after two weeks of exercise training. Weight, VO_2max, cycling power (W), HR, and RPE data were analyzed using paired Student's t-test to determine if significant differences existed before and after 2 weeks of training. All data are reported as Mean ± SD. Statistical significance was set at $p \leq 0.05$. Statistical analyses were performed using statistical analysis software (Sigma Plot 12.0; Systat Software, Inc., San Jose, CA).

Results

It is well known that prolonged, high intensity exercise induces a significant inflammatory response, but less is known about the inflammatory response to HIIT. Therefore, the purposes of this study were to determine: a) the extent to which an acute session of HIIT increases systemic inflammatory cytokines and chemokines, and b) if two weeks of HIIT training alters the systemic inflammatory response in moderately active, young men. We hypothesized that an acute bout of HIIT will increase systemic inflammatory cytokines/chemokines, and two weeks of HIIT training will attenuate the systemic inflammatory response.

Consistent with our hypothesis, an acute bout of HIIT, i.e. 8 cycling intervals at a workload equivalent to 100% of VO_2max (~20 min of exercise), resulted in *modest*, but significant increases in serum concentrations of several pro-inflammatory cytokines (IL-6, IL-8, and TNFα), one pro-inflammatory chemokine (MCP-1), and one anti-inflammatory cytokine (IL-10) compared to resting concentrations. More specifically, IL-6 increased 104% immediately after a single bout of HIIT (0.49 ± 0.30 to 1.00 ± 0.43 pg/mL; p=0.001), and remained elevated at 15 min post (0.87 ± 0.56 pg/mL [↑78%]; p=0.003), 30 min post (1.36 ± 0.67 pg/mL [↑178%]; p<0.001), and 45 min post exercise (1.06 ± 0.57 pg/mL [↑116%]; p<0.001), compared to rest (Figure 1A). Similar increases were observed for IL-8, but to a lesser extent than for IL-6. An acute bout of HIIT significantly increased IL-8 concentrations immediately after (from 4.46 ± 2.15 to 6.88 ± 3.98 pg/mL [↑54%]; p<0.001), and at 30 min post (5.93 ± 2.11 pg/mL [↑33%]; p=0.004), and 45 min post exercise (7.44 ± 2.33 pg/mL [↑67%]; p<0.001), compared to rest (Figure 1B). IL-8 concentrations at 15 min post exercise were not significantly different than rest (p=0.140). Furthermore, MCP-1 (from 389.86 ± 171.38 to 505.57 ± 202.72 pg/mL; Figure 1C) and TNFα (from 9.95 ± 2.66 to 14.54 ± 6.08 pg/mL; Figure

1D) increased immediately after exercise (↑30%; $p<0.001$ and ↑46%; $p<0.001$, respectively), but quickly returned to resting values. As shown in Figure 1E, the anti-inflammatory cytokine, IL-10, did not increase from resting values until 45 min after the completion of exercise (from 3.32 ± 1.82 to 7.30 ± 5.11 pg/mL [↑120%]; $p=0.001$). The concentrations of IFNγ, GM-CSF, and IL-1β were not significantly altered at any time point after an acute bout of HIIT (Table 1). Of note, eight subjects completed this study, however one subject's inflammatory cytokine values were excluded from analyses because his cytokine concentrations were abnormally high (ie, >2 SD) at rest and in response to exercise, compared to all other subjects. Therefore, reported cytokine data are from an n=7.

While it appears that an acute bout of HIIT exercise induces a modest increase in several inflammatory cytokines, we found no difference in the inflammatory response to HIIT after two weeks of training (i.e. no main effect of training). In fact, the pattern of changes in inflammatory cytokine concentrations was almost identical in the first HIIT session as it was in the last (sixth) HIIT session (Figure 1 A-E).

Although two weeks of HIIT training did not increase VO_2max ($p=0.481$; Table 2), it did result in a significant increase in peak power output ($p=0.007$) and subject weight ($p=0.015$). As alternate indicators of exercise adaptation over this two-week training regimen, we examined heart rate and RPE after the 8th interval at the beginning and end of training. Heart rate and RPE after the 8th interval were significantly lower in the last (sixth) HIIT session, compared with the first HIIT session ($p=0.014$ and $p=0.028$, respectively; Table 2).

Discussion

The current study investigated the systemic inflammatory response to an acute bout of high intensity interval training (HIIT), at the beginning and end of two weeks of training, on a cycle ergometer in young, recreationally active men. Herein we report significant increases in several inflammatory cytokines and chemokines, namely IL-6, IL-8, TNFα, MCP-1, and IL-10, to an acute bout of HIIT. Our findings of elevated IL-6 and IL-8 in response to HIIT are consistent with previously published studies that used various forms of HIIT, but this is the first study to demonstrate these alterations in inflammatory cytokines/chemokines with a HIIT protocol consisting of 60 sec cycling intervals (8-12 intervals per session) at a power output equivalent to 100% VO_2max, separated by 75 sec of active rest. In addition, we present novel findings of increased TNFα, MCP-1, and IL-10 in response to an acute bout of HIIT. While these inflammatory cytokine/chemokine responses are much lower than those previously observed with prolonged, high intensity exercise (e.g. a marathon), this is the first study to measure seven different inflammatory cytokines/chemokines, and one anti-inflammatory cytokine in response to HIIT using a multiplex assay. Furthermore, we demonstrate that there is no attenuation of the inflammatory cytokine/chemokine response after 2 weeks of HIIT; however, maximal cycling power does increase with 2 weeks of HIIT training, despite negligible improvements in VO_2max. We believe these novel findings provide valuable insight with regards to the inflammatory response to exercise that HIIT may be a viable alternative mode of exercise for non-athletic populations and immunocompromised individuals, such as the elderly or individuals with type II diabetes, cancer, or AIDS. Previous literature has proven that modified HIIT

protocols are a safe and effective mode of exercise for these at risk populations (Moholdt et al. 2012; Little et al. 2011; Guiraud et al. 2012).

Inflammatory responses to HIIT exercise

Several previous studies have reported substantial inflammatory responses to prolonged, high intensity, continuous exercise; however, much less is known about the inflammatory response to high intensity interval exercise. In the current study, we demonstrate significant increases in IL-6, IL-8, TNFα, MCP-1, and IL-10 in response to a single bout of HIIT in active, young men. The largest increase in IL-6 (2-2.5 fold) was observed at 30 and 45 minutes after completion of exercise. Similar studies have reported 2- to 2.5-fold increases in IL-6 immediately after interval running (Meckel et al. 2009; Meckel et al. 2011) and interval cycling (Arent et al. 2010) in trained athletes. These studies also reported the concentration of IL-6 remained elevated for 30-60 min after the completion of exercise. Compared to prolonged, high intensity exercise, in which 4- to 40-fold increases in IL-6 concentrations are observed for up to 1.5 hours after exercise (Nehlsen-Cannarella et al. 1997a; Nieman et al. 2007a; Nieman et al. 2001; Nieman et al. 2012; Suzuki et al. 2003a), the IL-6 response to HIIT appears to be much lower. Another inflammatory cytokine that is frequently measured in response to exercise is IL-8. We observed the largest increase in IL-8 (75%) at 45 minutes after the completion of HIIT exercise. This response is slightly lower than the ~100% increase in IL-8 previously reported by Croft et al. (2009) after a single Wingate, plus 8-10 sec cycling intervals at maximal effort and is still lower than the 3- to 10-fold increase in IL-8 reported in response to prolonged, high intensity exercise (Nieman et al. 2007a; Nieman et al. 2001; Nieman et al. 2012; Suzuki et al. 2003a). Furthermore, we observed significant increases in TNFα (43%), MCP-1 (29%), and IL-10 (130%) following an

acute bout of HIIT exercise. While this is the first study to report these novel findings following HIIT exercise, others have reported 20-30% increases in TNFα immediately after and 60 min after prolonged, high intensity exercise (Nieman et al. 2007a; Nieman et al. 2012; Konrad et al. 2011a). MCP-1 and IL-10 have also been examined in response to prolonged, high intensity exercise. Nieman et al. (2007a) observed ~3-fold and 4- to 20-fold increases in MCP-1 and IL-10 concentrations, respectively, following three consecutive days of 3 hr cycling bouts, while Suzuki et al. (2003a) reported approximately 3-fold increases in both MCP-1 and IL-10 following a marathon.

The inflammatory cytokine/chemokine responses to HIIT observed in this study are consistent with the normal inflammatory response to exercise. The pro-inflammatory cytokines, IL-6, IL-8, and TNFα, and the pro-inflammatory chemokine, MCP-1, appears to increase immediately or soon after the completion of exercise, whereas the anti-inflammatory cytokine, IL-10, does not increase until 45 min after the completion of exercise. Interestingly, MCP-1 and TNFα concentrations subside early in the recovery period, while IL-6 and IL-8 concentrations remain elevated for much of the time course evaluated after HIIT exercise. These finding are consistent with existing literature, given many of the aforementioned studies analyzed inflammatory cytokines in the blood immediately after and at 1 or 1.5 hours after the completion of exercise. To our knowledge, this is the only study that has analyzed inflammatory cytokine/chemokine concentrations in the blood at this many time points during the acute recovery period after exercise (immediately-post, and 15-, 30-, and 45- min post). Moreover, the inflammatory response to HIIT appears to be much more transient than that of prolonged exercise, which we posit to be due to the relative time spent exercising between HIIT (~20 min) and prolonged exercise (~2 hours).

Contrary to our hypothesis, we did not observe significant changes in GM-CSF, IL-1β, or IFNγ following an acute bout of HIIT exercise. Previous studies have reported up to 30% increases in both GM-CSF and IL-1β immediately after ~2 hours of high intensity cycling (Nieman et al. 2012) or running (Konrad et al. 2011a), as well as after a marathon race (Suzuki et al. 2003a). The available data on IFNγ vary from no change to modest (~10%) increases with exercise (Konrad et al. 2011a; Nieman et al. 2012). Given that all the aforementioned studies observed their largest increases in inflammatory cytokines immediately after exercise, our time course design was within the confines to be able to detect changes in GM-CSF, IL-1β, and IFNγ with HIIT exercise. Therefore, it is possible that our HIIT protocol may not provide enough of a stimulus to induce significant changes in GM-CSF, IL-1β, and INFγ in relatively fit males. Taken together, these findings suggest that our HIIT exercise protocol induces an inflammatory response similar to other studies using various models of high intensity interval exercise; however, the inflammatory cytokine/chemokine response to HIIT appears to be a consistently lower magnitude than that of prolonged, high intensity exercise.

The inflammatory response seems to be influenced by rest during the exercise bout. Our study and previous HIIT studies have shown that high intensity, intermittent exercise for relatively brief overall exercise time elicits a modest inflammatory cytokine response (Arent et al. 2010; Croft et al. 2009). Continuous, prolonged exercise induces a much more exaggerated inflammatory cytokine response (Nehlsen-Cannarella et al. 1997b; Nieman et al. 2012; Suzuki et al. 2003a); but recently, it was shown that prolonged swimming bouts (2hr) with high intensity interval swimming within the session induced a modest IL-6 and IL-10 response (86-147% and 64%-152%, respectively) comparable to those found in HIIT studies (Knab et al. 2013). This study

and the previous studies suggest rest can have a large effect on the inflammatory response. The inflammatory response to prolonged, continuous exercise may be reduced if rest is incorporated into sessions, but more investigation is needed.

Another major purpose of this study was to determine if two weeks of HIIT would attenuate the inflammatory response to an acute bout of HIIT exercise. Contrary to our hypothesis, we observed no significant difference in the pattern of responses in any of the cytokines/chemokines analyzed, between HIIT session #1 and HIIT session #6. Previously, Croft et al. (2009) reported that 6 weeks of high intensity interval running (5-3 min intervals at 90% VO_2max) significantly attenuated the IL-6 response to an acute interval bout by ~40%. While this study increased the interval intensity by 5% every 2 weeks of training, the exercise intensity was reduced back to starting levels for their final interval exercise bout and blood draws for determination of IL-6 concentrations. On the other hand, our study increased exercise volume by 50% (from 8 to 12 intervals) over the 2-week training period. Therefore, inflammatory cytokine/chemokine concentrations at HIIT session #6 were determined when subjects were performing 50% more exercise, compared to HIIT session #1. We believe this directly contributed to why we did not observe attenuation in the inflammatory response after 2 weeks of HIIT, thus revealing a potential limitation in our experimental design. It has been demonstrated that prolonged, high intensity cycling on 3 consecutive days significantly attenuates the inflammatory response to exercise, a response the authors attributed to an adaptation in immune system function (Nieman et al. 2007b; Nieman et al. 2007a). Though we did not observe any significant differences in the inflammatory responses between HIIT sessions #1 and #6, the 50% increase in exercise volume did not increase the inflammatory response. This

could be interpreted as an adaptation in immune function to 2 weeks of HIIT, but further investigation is needed to determine the validity of this hypothesis.

Alterations in physiological variables with HIIT

Previous research investigating whether HIIT improves VO_2max is inconclusive. Our study found no significant improvements in VO_2max after 2 weeks of HIIT exercise. This is consistent with the majority of previous HIIT studies of this duration. Although previous studies using both supra-maximal intensity (i.e. Wingate intervals) and maximal or near-maximal intensity intervals (90-100% VO_2max) have reported no increases in VO_2max after just 6 sessions of training (Burgomaster et al. 2006; Burgomaster et al. 2005), other studies have demonstrated significant increases in oxidative enzyme capacity with HIIT (Burgomaster et al. 2006; Burgomaster et al. 2005; Little et al. 2011; Little et al. 2010). Studies demonstrating increased VO_2max following 2 weeks of HIIT often utilize higher training volumes than our current study (Rodas et al. 2000; Talanian et al. 2007). The HIIT protocol used by Rodas et al. (2000) consisted of 14 training sessions within a two week training period, while Talanian et al. (2007) used 7 training sessions of over 40 min of high intensity exercise. Also, this study utilized subjects with relatively low initial VO_2max values. It has been shown that HIIT can consistently increase VO_2max ~9% when training lasts from 4-6 weeks (Bayati et al. 2011; Croft et al. 2009). Our study included moderately fit, young males (initial VO_2max = 49.2 ±2.6 mL/kg/min) and only consisted of 6 sessions of 8 to 12 minutes of high intensity exercise. One possible explanation for these discrepancies may be the initial relative fitness levels of the subjects used in these studies. It appears that studies using more active/fit subject populations (with higher initial VO_2max values) for two week training periods, may not experience improvements in VO_2max. It would be interesting if future investigations

would perform HIIT studies in subjects with different fitness levels to determine the threshold for observing improvements in VO_2max with HIIT exercise.

Although we did not demonstrate improvements in VO_2max after two weeks of training, we did observe significant increases in peak power (+4.6%) achieved during the VO_2max test, as well as significant decreases in heart rate and RPE after the eighth interval between session #1 and session #6 (-3.2% and -15%, respectively). The changes in these physiological parameters following HIIT exercise training suggest that, despite the lack of change in VO_2max, exercise tolerance or exercise capacity increased in response to 2 weeks of HIIT. Another possible limitation of our study was the low sample size (n=8).

In summary, the results of this study suggest that HIIT induces a modest, yet significant inflammatory response; however, the response to HIIT is much lower than previously reported for prolonged, high intensity exercise. Furthermore, we demonstrate that 2 weeks of HIIT did not alter the inflammatory response to an acute bout of HIIT, likely due to a 50% increase in exercise volume between the first and last HIIT sessions. Additionally, we demonstrate that while 2 weeks of our HIIT protocol may not be sufficient to improve VO_2max in a moderately active population, it is sufficient to increase maximal cycling power. Taken together, these our findings add to the growing body of literature that HIIT may be a beneficial and time-efficient exercise activity for a variety of populations. Future research utilizing HIIT protocols should investigate its efficacy in individuals with different exercise capacities, including clinical populations.

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Tables

Table 1. Inflammatory cytokines not significantly altered by HIIT

	Rest		Immediately post		15 min post		30 min post		45 min post		p-value		
	HIIT #1	HIIT #6	HIIT #1	HIIT #6	HIIT #1	HIIT #6	HIIT #1	HIIT #6	HIIT #1	HIIT #6	Interaction	Time point	Training
GM-CSF (pg/mL)	1.01 ±1.20	1.05 ±1.12	1.76 ±2.47	1.10 ±1.91	0.98 ±1.13	0.38 ±0.37	0.61 ±0.38	0.68 ±0.61	0.31 ±0.15	0.77 ±0.91	0.382	0.172	0.484
IFNγ (pg/mL)	1.49 ±1.52	1.63 ±2.11	3.51 ±5.85	3.87 ±7.86	2.74 ±5.22	0.84 ±0.35	1.18 ±0.92	1.42 ±1.74	1.00 ±0.86	1.76 ±2.76	0.518	0.286	0.266
IL-1β (pg/mL)	0.57 ±0.40	0.46 ±0.32	0.65 ±0.48	0.56 ±0.43	0.78 ±1.10	0.43 ±0.27	0.43 ±0.33	0.43 ±0.33	0.38 ±0.21	0.41 ±0.22	0.425	0.205	0.195

Values are Mean ±SD (n=7). GM-CSF: granulocyte macrophage colony-stimulating factor; IFNγ: interferon-γ; IL-1β: interleukin-1β; HIIT #1: HIIT session #1; HIIT #6: HIIT session #6.

Table 2. Anthropometric and physiological variables before and after two weeks of HIIT exercise training

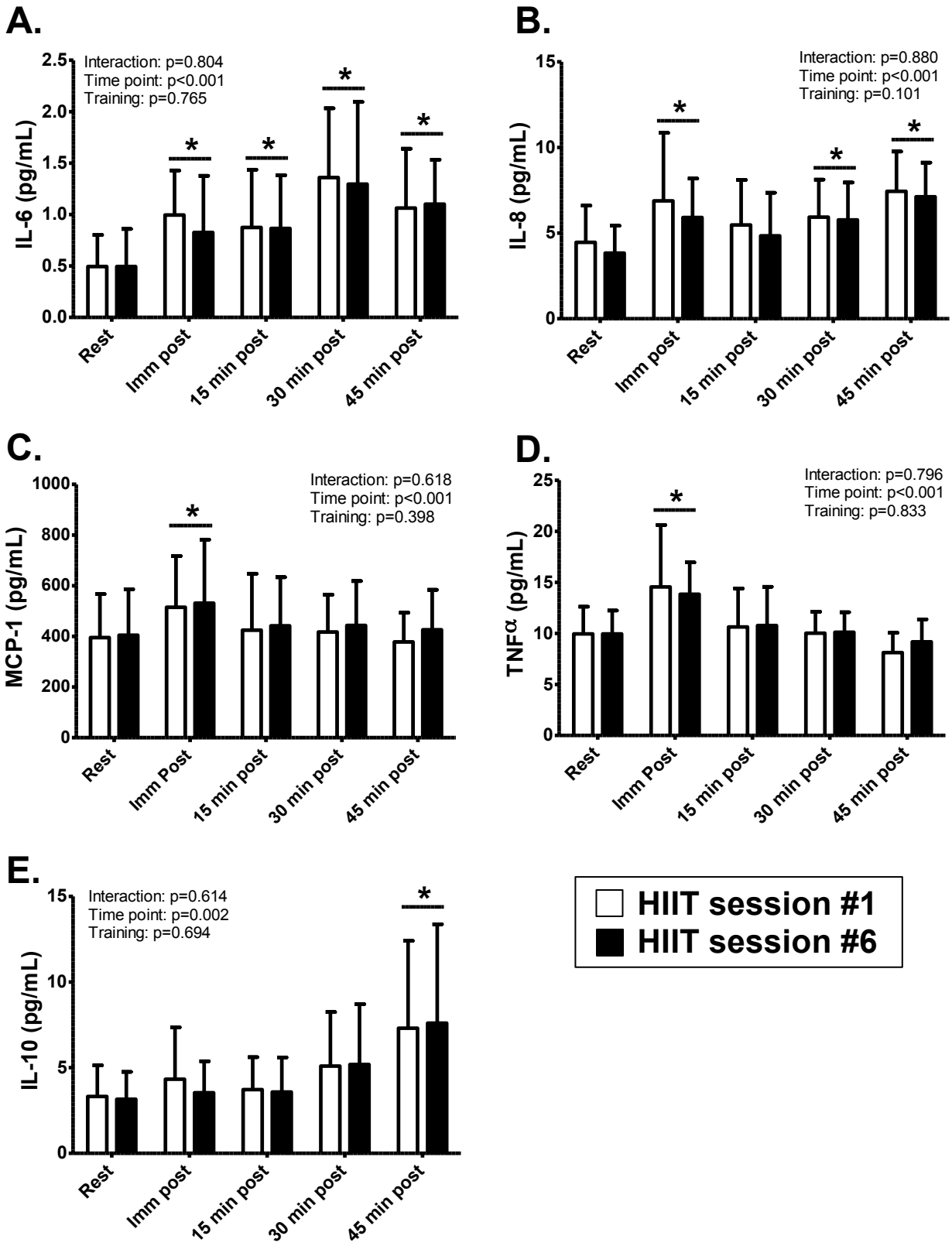
	PRE	POST	% Change	p-value
Weight (kg)	75.7 ±6.6	76.4 ±6.2*	0.9%	0.015
VO2max (mL/kg/min)	49.2 ±2.6	49.6 ±2.0	0.8%	0.481
Peak Power (Watts)	324 ±40	339 ±39*	4.6%	0.007
Watts at 100% VO2max	314 ±45	326 ±35	3.8%	0.190

Values are Mean ±SD (n=8). PRE: before two weeks of HIIT exercise training; POST: after two weeks of HIIT exercise training; * - indicates significantly different from HIIT #1

FIGURE LEGEND

Figure 1. Serum inflammatory cytokines in response to an acute bout of high intensity interval training (HIIT). Inflammatory cytokine concentrations were measured before (Mitchell et al.) and immediately, 15 min, 30 min, and 45 min after completion of an acute bout of HIIT exercise (at a workload equivalent to 100% of VO_2max) on a cycle ergometer during the first and sixth (last) HIIT exercise sessions. HIIT exercise increased IL-6 (**A**) above rest at all time points after exercise (main effect of time point). IL-8 (**B**) increased immediately after, and at 30 and 45 min after exercise (main effect of time point). MCP-1 (**C**) and TNFα (**D**) both increased immediately after exercise (main effects of time point), but returned to resting levels by 15 min after exercise. IL-10 (**E**) levels remained low until increasing 45 min after exercise (main effect of time point). There were no main effects of training on the increases observed in inflammatory cytokines from HIIT session #1 to HIIT session #6. Open bars: 1st HIIT session; Filled bars: 6th HIIT session. Data are reported as Mean ± SD; n=7. * - indicates significantly different from Rest.

Figure 1.


A.
Interaction: p=0.804
Time point: p<0.001
Training: p=0.765
IL-6 (pg/mL)
2.5
2.0
1.5
1.0
0.5
0.0
Rest
Imm post
15 min post
30 min post
45 min post
B.
Interaction: p=0.880
Time point: p<0.001
Training: p=0.101
IL-8 (pg/mL)
15
10
5
0
C.
Interaction: p=0.618
Time point: p<0.001
Training: p=0.398
MCP-1 (pg/mL)
1000
800
600
400
200
0
Imm Post
D.
Interaction: p=0.796
Time point: p<0.001
Training: p=0.833
TNFα (pg/mL)
25
20
15
10
5
0
E.
Interaction: p=0.614
Time point: p=0.002
Training: p=0.694
IL-10 (pg/mL)
HIIT session #1
HIIT session #6

Vita

Casey John was born in Ames, Iowa, in July 1987. After completing work at Ballard High School, Casey entered Iowa State University in Ames, Iowa. He received his Bachelor of Science in Kinesiology and Health in May 2010. After spending 8 months interning abroad, he was accepted into the Master of Science program at Appalachian State University in Boone, North Carolina, for Exercise Science. Upon arrival, he received a Graduate Assistantship in the Exercise Science Biochemistry Laboratory. He received a Master of Science degree in Exercise Science in May 2013.