Article Title: The effect of high-intensity aerobic interval training on markers of systemic inflammation in sedentary populations.

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Abstract

Purpose: This study examined the effects of high-intensity interval training (HIIT; 30 s sprint, 4-5 min passive recovery) and prolonged intermittent sprint training (PIST; 10 s sprint, 2-3 min moderate exercise) on the systemic inflammatory markers C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α), aerobic capacity and anthropometry in a middle-aged, sedentary population.

Methods: Fifty-five sedentary adults (age 49.2 ± 6.1 y) were randomised into HIIT (n=20), PIST (n=21) or a sedentary control group (CTRL, n=14). HIIT and PIST performed 3 training sessions per week for 9 weeks on a cycle ergometer, matched for total high-intensity time, while CTRL continued normal sedentary behaviours. Pre- and post-intervention testing involved measures of anthropometry, peak oxygen consumption (VO_{2peak}), and venous blood collection for analyses of CRP and TNF-α.

Results: HIIT and PIST increased VO_{2peak} compared to CTRL (+3.66 ± 2.23 and 3.74 ± 2.62 $mL \cdot kg \cdot min^{-1}$). A group x time interaction (p=0.042) and main effect of time (p=0.026) were evident for waist girth, with only HIIT showing a significant reduction compared to CTRL (-2.1 ± 2.8cm). TNF-α and CRP showed no group x time interaction or time effect (p>0.05).

Conclusions: In sedentary individuals, 9 weeks of HIIT or PIST were effective to improve aerobic capacity; however, only HIIT significantly reduced waist girth and WHR compared to CTRL. Markers of systemic inflammation remained unchanged across all groups. Accordingly, for inflammation and $VO2_{peak}$, the distribution of sprints and the active or passive recovery periods are inconsequential provided that total duration of high-intensity efforts is similar.

KEYWORDS: cytokines, exercise, intermittent training, cycling, CRP, TNF-α.

Abbreviations

ANCOVA	Analysis of covariance
BMI	Body mass index
BP	Blood pressure
CRP	C-reactive protein
CSI	Chronic systemic inflammation
CTRL	Control group
CV	Coefficient of variation
EDTA	Ethylene diamine tetraacetic acid
GXT	Graded exercise test
HIIT	High-intensity interval training
HR	Heart rate
IL	Interleukin
PIST	Prolonged intermittent sprint training
PPO	Peak power output
RPE	Rating of perceived exertion
SSG	Small-sided games
SST	Serum separator tube
T2D	Type 2 diabetes
TNF-α	Tumor necrosis factor alpha
VO_{2peak}	Peak oxygen consumption
WHR	Waist-to-hip ratio

Introduction

Recent research highlights the link between chronic systemic inflammation (CSI) and the progression of insulin resistance, type 2 diabetes (T2D) and atherosclerosis (Berg & Scherer 2005). CSI is represented by elevated resting concentrations of pro-inflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α; Berg & Scherer 2005). Elevated basal concentrations of these markers are prognostic indicators of disease risk, and have consequently emerged as intervention targets (You et al. 2013). Specifically, exercise is suggested as an important mediator of long-term reductions in systemic inflammation, given that physical inactivity is associated with elevated CSI and disease risk (You et al. 2013). As such, exercise training may be an effective intervention to provide reductions in CSI and thus overall disease risk.

Moderate-intensity aerobic exercise training is reported to reduce basal concentrations of CRP, TNF-α and IL-6 (Kohut et al. 2006). In contrast, some studies show that this type of training has no effect on these markers, often implying an insufficient training stimulus due to the nature of the low-moderate intensity (Stewart et al. 2010). Separately, previous research indicates that high-intensity training can elicit similar, if not greater, improvements in insulin sensitivity compared with moderate-intensity modalities (Houmard et al. 2004). Given that elevated CSI has been implicated in the development of insulin resistance via inhibition of insulin receptor function (Pradhan et al. 2001), it is hypothesised that high-intensity exercise may reduce markers of CSI. Regardless, despite the increasing popularity of high-intensity training, there is limited evidence of its effect on inflammatory biomarkers.

Considering the proposed importance of high-intensity exercise, such interval-based training is suggested to confer superior health effects compared to moderate-intensity training, and may also appeal to time-limited individuals (Gibala et al. 2012). Specifically, high-intensity interval training (HIIT) is reported to improve endothelial function (Wisløff et al. 2007) and insulin sensitivity (Babraj et al. 2009), though research on the effects of HIIT on markers of CSI is currently lacking. Similarly, football-based small-sided games (SSG) training is classified as high-intensity exercise, given its intermittent sprint nature with interspersed moderate-intensity activity. Such training has been shown to reduce resting CRP and IL-6 (Mendham et al. 2014), and improve glycaemic control (Andersen et

al. 2014) and body composition (Andersen et al. 2010). However, the skill-specific nature of SSG training may restrict its use in non-athletic populations. Borrowing from this modality, prolonged intermittent sprint training (PIST) mimics the intensity of SSG's without the skill requirement or load-bearing nature, thus potentially broadening its appeal. Previously, research indicates that differing the patterns of high- or low-intensity exercise within a training program has little effect on physiological outcomes when total work is matched (Sylta 2016); however, it is unknown whether similar results are evident with systemic inflammatory markers. Therefore, the aim of this study was to compare the effects of two high-intensity exercise training modes (HIIT and PIST) on markers of CSI, anthropometry and aerobic capacity. It was hypothesised that, when matched for total sprint duration, HIIT and PIST would be equally effective to reduce inflammatory markers and improve physical capacity compared to inactive controls.

Methods

Participants

Fifty-five middle-aged, sedentary adults (Table 1) were recruited through newspaper advertisements within the local geographical region, and randomised to either HIIT (n=20), PIST (n=21) or a control group (CTRL, n=14; Figure 1). The variation in group sizes resulted from several participants declining their allocation to CTRL. Participants were matched based on sex, peak oxygen consumption (VO_{2peak}), and age, and randomly allocated to their respective groups by an independent consultant via de-identified numerical selections. Inclusion into the study required that participants be aged 35-60y, inactive ($\leq$ 1 session of exercise per week), non-smokers (no smoking for the 6 months preceding inclusion in the study), taking no medications, and free from diagnosed cardiovascular, autoimmune or metabolic conditions. Approval was obtained from the Institutional Human Research Ethics Committee (HREC REF NO. 2015000299) in accordance with the Declaration of Helsinki. Prior to pre-intervention testing and following an information session, participants provided written informed consent for testing and training procedures.

Overview

Participants attended testing sessions at standardised times (06:00-09:00) before and after the 9-week intervention. Each testing session comprised a resting blood pressure (BP) measurement, a venous blood sample, anthropometrical measurements, and a maximal graded exercise test (GXT). Training protocols were performed 3 days per week for 9 weeks (Table 2), while CTRL subjects were asked to continue their normal physical activity and nutrition behaviours, with ongoing reminders provided by the research team. Participants refrained from any physical activity for the 24 h prior to each testing session and arrived following an overnight fast (10-12 h). Participants documented food intake and physical activity for the 24 h preceding baseline testing. This document was copied and returned to participants before post-intervention testing to ensure that diet and exercise patterns were standardised before each testing session.

Procedures

Anthropometric measures included height, mass and waist and hip girths, and were used to calculate body mass index (BMI) and waist-to-hip ratio (WHR). After 10 min of seated rest, BP was measured in the seated position using an aneroid sphygmomanometer and stethoscope (Livingstone, Rosebery, Australia). Participants then performed a GXT using a mechanically-braked cycle ergometer (Wattbike Pro, Nottingham, United Kingdom) to determine VO_{2peak} and peak power output (PPO). Participants began the test at 25 W, and increased power output by 25 W each minute until volitional exhaustion. Heart rate (HR) was recorded at each increment to determine HR_{max} (FT7, Polar Electro, Kempele, Finland). Oxygen consumption was determined by measuring O_2 and CO_2 concentrations with a metabolic gas analyser (Medgraphics Ultima System, Saint Paul, USA). The metabolic cart was calibrated according to manufacturer's instructions and involved pneumotachometer calibration via a 3 L syringe, analysis of ambient air, and gas calibration with a gravimetric gas mixture of known concentrations (CO_2 4.1 (0.1)%; O_2 15.7 (0.2)%).

Prior to the GXT, venous blood samples were collected using a 21-gauge needle inserted into the medial antecubital vein. Approximately 6 mL of blood was collected in both a serum separator tube (SST) and an ethylene diamine tetraacetic acid (EDTA) tube for analysis of CRP and TNF-α,

respectively. EDTA tubes were immediately centrifuged at 3500 rpm for 10 min at 4 ^{o}C, whilst SST clotted for 15-30 min before being centrifuged in the same manner. Supernatants were immediately stored at -25^{o}C. Plasma CRP concentrations were measured using a solid-phase, chemiluminescent immunometric assay (intra- and inter-assay CV 4.1% and 7.1%, respectively), and TNF-α was measured with a sandwich enzyme immunoassay technique, as per manufacturer's instructions (Luminex Corporation, Texas, USA), with intra- and inter-assay CV 2.6% and 13.0%, respectively.

All training sessions were performed in a climate controlled (20± 2^{o}C) exercise physiology laboratory on a mechanically braked cycle ergometer (Wattbike Pro, Nottingham, United Kingdom). Sessions began with a 4 min standardised warm-up at 35% individualised PPO. Participants then commenced their respective protocol with 2-6 members of their own group. The respective protocols were matched for total sprint duration, though involved different recovery durations and intensities (Table 2). Specifically, the HIIT group performed 30 s maximal sprints (20 s in week 1) interspersed with 3-5 min passive recovery periods, as has been previously reported (Burgomaster et al. 2008; Whyte et al. 2010). The PIST group performed 10 s maximal efforts, interspersed with moderate-intensity recovery (75-80% HR_{max}) of 2-3 min, reflecting the undulating intensities of football-based SSG's, which range between work:rest ratios of 1:12 and 1:16 (Gabbett & Mulvey 2008). For both conditions, total sprint volume increased progressively throughout the program and was matched between groups. During training, HR (FT7, Polar Electro, Kempele, Finland) was monitored and reported as mean and peak values. Upon finishing each session, participants provided a CR-10 rating of perceived exertion (RPE) (Borg 1998).

Statistical Analysis

Male and female data within each condition are pooled and reported as mean ± standard deviation (SD). Raw data were used to assess group x time interaction and a main effect of time using a mixed-model ANCOVA, adjusting for sex as a covariate. When significant interactions or main effects were observed, simple main effects and post hoc analyses using Tukey's pairwise comparisons were used where appropriate to locate the source of significance. A one-way ANCOVA, adjusting for sex as a

covariate, was used to determine whether the absolute changes in each variable differed between groups. Significance was accepted as $p \leq 0.05$.

Results

Adherence to training was not significantly different between training groups (HIIT 95 ± 8%, PIST 94 ± 7%; p=0.359). There was a significant effect of time for RPE (p=0.019), with increased values reported over the 9 wk intervention for both training groups, without significant differences between groups in absolute change (p=0.141; Table 2). A group x time interaction was evident for increased mean HR (p=0.001) observed in PIST compared to HIIT (137 ± 10 bpm vs 120 ± 10 bpm, p=0.001). Further, a significant group x time interaction was evident for peak HR (p=0.003), though change data revealed that both groups increased over time, without significant differences between groups (p=0.339).

All raw and change data for inflammatory markers, VO_{2peak}, PPO and anthropometrical variables are shown in Table 1. Neither TNF-α nor CRP showed a significant group x time interaction (TNF-α, p=0.623; CRP, p=0.081) or main effect for time (TNF-α, p=0.245; CRP, p=0.152). There was a significant group x time interaction for VO_{2peak} (p=0.010) with HIIT and PIST showing increased VO_{2peak} compared to CTRL (HIIT, p=0.014; PIST, p=0.020), without significant differences between training groups (p=0.989). There was no group x time interaction for PPO (p=0.231); however, there was a main effect of time (p=0.0001), which was evident for all groups (HIIT, p=0.0001; PIST, p=0.0001; CTRL, p=0.012). There was no significant group x time interaction or main effect of time for body mass, BMI, hip girth, or BP ($p>0.05$; Table 1). For waist girth there was a significant group x time interaction (p=0.042) and significant main effect for time (p=0.026). The absolute change was significant in that HIIT was significantly greater than CTRL (p=0.034). For WHR there was a significant group x time interaction (p=0.003) and significant main effect for time (p=0.009); however the absolute change was only significant in HIIT compared to CTRL (p=0.005).

Discussion

Nine weeks of HIIT and PIST training were equally effective to improve maximal oxygen consumption. Specifically, participants improved VO_{2peak}, in both training groups, with no changes observed in CTRL. Despite improved VO_{2peak}, no significant differences in TNF-α or CRP were evident within or between groups. The HIIT group demonstrated greater reductions in waist girth and WHR compared to CTRL, although there were no changes in hip girth. Consequently, the matching of high-intensity work resulted in similar VO_{2peak} adaptations, regardless of the sprint distribution (10 vs 30 s) or intensity of recovery (active vs passive). Thus, despite no changes in markers of CSI, and with the exception of waist girth, the total volume of high-intensity work performed seems a more important component for physiological adaptations in sedentary individuals.

Notably, similar adherence rates between training groups ensured a similar training exposure for the respective programs. As evidence of the success of high-intensity training in this population, adherence values were similar to those reported previously with interval-based training in middle-aged adults (Jung et al. 2015). Peak HR did not differ between training conditions, likely due to both modes being of sufficient sprint duration and intensity to invoke the same maximal cardiac response. Previous studies using HIIT have reported similar peak HR values (90-95% HR_{max}) (Helgerud et al. 2007; Jung et al. 2015). However, as expected the active nature of recovery in PIST ensured a greater mean HR than HIIT, showing values reflective of SSG training (~75-80%HR_{max}) (Andersen et al. 2010; Andersen et al. 2014). Regardless, both groups successfully engaged in similar training programs, albeit with differing sprint and recovery profiles.

Moderate-intensity aerobic training (60-85% VO_{2max}) is suggested to reduce CRP (Berg & Scherer 2005), yet no changes were evident following the higher intensities used in the present study. In explanation, a number of studies have reported reductions in CRP that coincide with reductions in body fat (Arikawa et al. 2011) and body mass (Martins et al. 2010). Specifically, exercise-induced reductions in CRP are suggested to occur only when reductions in adiposity are evident (Church et al. 2010). Given that fat mass was not quantified in the present study, and rather inferred from BMI, it is

unknown whether changes in fat occurred following training, and thus whether this response precluded changes in CRP. Moreover, the mean baseline CRP level for this cohort was not classified as high (2.31 $mg \cdot L^{-1}$) (Pearson et al. 2003), and by example, Pearson et al. (2003) reported that a basal CRP >3 $mg \cdot L^{-1}$ doubled an individual's risk of cardiovascular disease compared to a concentration <1 $mg \cdot L^{-1}$. Given the moderate CRP values evident here, it is possible that the potential for reduction was therefore minimal.

With regards to TNF-α, there were no significant within- or between-group changes, which is similar to previous studies utilising aerobic exercise of varying intensities. Mendham et al. (2014) reported no change in TNF-α after 8 weeks of either SSG's or moderate-intensity cycling, despite a reduction in fat mass in both groups. Conversely, 8 weeks of aerobic exercise combined with moderate caloric restriction elicited reductions in TNF-α and BMI in overweight adolescents (Ben Ounis et al. 2009). Further, Kohut et al. (2006) reported that both moderate-intensity aerobic and flexibility/strength exercise were effective in reducing TNF-α over 10 months, with a trend ($p=0.10$) towards reduced BMI. As with CRP, reductions in TNF-α are associated with reductions in body mass and fat, particularly given that visceral adipose tissue is a known site of TNF-α secretion (Kadoglou et al. 2007). Despite the hypothesis that high-intensity training would reduce TNF-α, it would appear that longer interventions incorporating load-bearing strategies are most effective in this regard.

Both PIST and HIIT increased VO_{2peak} following training. The PIST protocol improved VO_{2peak} by 14%, which is similar to studies utilising SSG's (Andersen et al. 2014; Krustrup et al. 2009). For example, Krustrup et al. (2009) reported a 13% increase in VO_{2max} after 12 weeks of SSG's in untrained men, while Andersen et al. (2014) observed an 11% improvement after 24 weeks of SSG training in adults with T2D. In the present study, the HIIT group also demonstrated a 14% increase in VO_{2peak}, which is similar to other HIIT protocols in healthy populations (Burgomaster et al. 2008; Whyte et al. 2010). Comparatively, Whyte et al. (2010) reported a 9.4% increase in VO_{2max} after 6 sessions of 'all-out' HIIT in sedentary men, and Burgomaster et al. (2008) observed a 7.3% improvement after 6 weeks of HIIT in sedentary adults. The greater improvement in VO_{2peak} observed

in the current study may be explained by the longer training duration and low baseline fitness. However, Sloth et al. (2013) noted that previous studies showed no relationship between program duration and the magnitude of change in VO_{2max}, hypothesising that large improvements occur in the early stages of HIIT, and the rate of adaptation diminishes thereafter. Nonetheless, these findings reiterate that high-intensity intermittent exercise is effective in improving aerobic capacity in sedentary populations. Notably, there was no difference between HIIT and PIST for changes in VO_{2max}, suggesting that the distribution of sprints and the active or passive recovery periods are inconsequential provided that total duration and intensity of sprints are similar. Such outcomes may have practical implications for exercise prescription in sedentary populations, promoting training variety to aid long-term exercise adherence.

Finally, with regards to anthropometry, HIIT showed a greater reduction in waist girth and WHR compared to CTRL. These outcomes concur with findings by Whyte et al. (2010), who reported reductions in waist and hip girths after only 2 weeks of HIIT (30 s sprints, 4-6 repetitions) in obese men. Although the present study involved participants who were not classified as obese, and whose baseline hip girths (105.92 ± 9.04 cm) were lower than those of the participants in the aforementioned study (110.9 ± 2.2 cm), similar effectiveness was evident. With regards to PIST, Mendham et al. (2014) reported no change in waist or hip girths following 8 weeks of SSG's in middle-aged, sedentary men; however, participants did demonstrate improvements in body composition. These outcomes may result from the load-bearing, eccentric element of SSG's, indicating that field-based SSG's confer an effect that PIST does not. As surmised above, HIIT was a more effective modality to reduce waist circumference; however, there were no differences in body mass or BMI, indicating that a longer, load-bearing training program may provide more significant changes in anthropometrical parameters.

Despite the above findings, some limitations are acknowledged within the present study. Firstly, it was not possible to match energy cost between training groups. Although the total time spent at high intensity was equal between HIIT and PIST, differences in recovery intensities mean that the energy

cost difference is a theoretical limitation. Additionally, in the small increase in PPO, without concomitant increase in VO_{2peak}, in CTRL suggests a familiarisation effect occurred with this test, which may have confounded these results. Also, equipment issues, including analysis kits, resulted in the loss of 2 additional cytokines (IL-6 and IL-1β), which would have offered further insight into changes following exercise training. Particularly, IL-6 would be a prudent inclusion given its antecedent relationship with CRP (Berg & Scherer 2005), and IL-1β would be beneficial alongside IL-1 receptor antagonist (IL-1ra) as the primary function of the latter is to inhibit IL-1 binding, and thus concurrent analysis would provide greater insight into training adaptations (Ridker et al. 2011). Furthermore, the menstrual cycle was not reported in the present study, which is also noted as a limitation. However, the associated fluctuations in CRP are small in magnitude, ranging from 0.18 to 0.38 $mg \cdot L^{-1}$ (Blum et al. 2005; Jilma et al. 1997). Comparatively, training-induced reductions in CRP have been shown to be much greater, with changes as large as 1.41 $mg \cdot L^{-1}$ (Arikawa et al. 2011) and 1.99 $mg \cdot L^{-1}$ (Martins et al. 2010) observed in sedentary individuals. In addition, it is suggested that there is no cyclical pattern of change for TNF-α throughout the menstrual cycle (Jilma et al. 1997) and further, current research examining pre-post-menopausal differences in TNF-α is equivocal.

Conclusions

Interval-based training may be effective to improve cardio-metabolic risk factors, namely aerobic capacity and WHR, though no changes in CRP or TNF-α were evident. Further, the lack of difference in inflammatory outcomes following HIIT and PIST suggests that sprint distribution and recovery intensity were not of primary consequence when high-intensity volume is matched. Therefore, provided that total sprinting time does not change, sprint duration and recovery intensity can be manipulated without impacting upon these outcomes. To support such an assertion, future research should consider the effects of HIIT and PIST on a wider array of cytokines, alongside comparisons to continuous exercise modes.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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