

Article Title: Differences in the acute inflammatory and glucose regulatory responses between small-sided games and cycling in sedentary, middle-aged men.

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## **Abstract**

**Purpose:** This study compared the acute inflammatory and glucose regulatory response within and between rugby specific small-sided games (SSG) and stationary cycling (CYC) in sedentary, middle-aged Caucasian men.

**Method:** Nine middle-aged, sedentary men who were free from disease participated in 2 x 40 min exercise conditions (CYC and SSG) following a randomized, cross-over design. Heart rate (HR) and Rating of Perceived Exertion (RPE) were collected during each bout. Venous blood was collected at fasting, 0, 30, 60 and 240 min post-exercise for measurement of glucose, insulin, cortisol and inflammatory markers including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, IL-1 receptor agonist (ra) and C-reactive protein (CRP).

**Results:** No significant differences existed between conditions for HR and RPE ( $p > 0.05$ ). IL-6 was increased immediately post-exercise in both conditions ( $p < 0.05$ ), but greater in SSG at 240 min post-exercise compared with CYC ( $p < 0.05$ ). Glucose was lower in SSG than CYC at 30 and 240 min post-exercise ( $p < 0.05$ ). IL-1ra, insulin and cortisol showed an exercise-induced increase ( $p < 0.05$ ), with no significant differences between conditions ( $p > 0.05$ ). Results for CRP, TNF- $\alpha$  and IL-1 $\beta$  showed no significant exercise-induced changes within or between conditions ( $p > 0.05$ ).

**Conclusions:** Both SSG and CYC conditions were sufficient to stimulate an acute anti-inflammatory response as indicated by the post-exercise elevation of IL-6, IL-1ra and cortisol. The novel findings are that an acute bout of SSG bout is capable of maintaining an elevated post-exercise IL-6 response and lowered blood glucose concentration, compared with intensity- and duration-matched CYC condition.

**Key Words:** IL-6, IL-1ra, TNF- $\alpha$ , IL-1 $\beta$ , cortisol, Insulin, rugby

## Introduction

Chronic low-grade inflammation has been established as a predictor for the development of chronic diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) <sup>1</sup>. An inactive lifestyle is proposed to lead to the accumulation of adipose tissue and is accompanied by the infiltration of adipose derived pro-inflammatory proteins into the circulation <sup>2</sup>. Conversely, increased physical activity has been reported as an effective preventative approach to reduce the inflammatory risks associated with these chronic metabolic and cardiovascular diseases <sup>3,4</sup>. Notably, the reduced inflammatory state from regular exercise is proposed to occur through the heightened anti-inflammatory environment induced by the acute bout <sup>5-7</sup>.

Acute exercise has been shown to stimulate glucose disposal and inhibit the release of pro-inflammatory cytokines <sup>8</sup>. Indeed, the magnitude of the acute inflammatory and glucose regulatory response tends to be dictated by the cohort (trained and untrained), the muscle mass involved to complete the mechanical work, intensity and duration of the bout <sup>2,9,10</sup>. Typically following exercise, the active skeletal muscle increases both cellular and circulating levels of interleukin (IL)-6 <sup>11</sup>. This acute increase in IL-6 is transient and produced independently to pro-inflammatory cytokines (tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$ ) <sup>12</sup>. Moreover, IL-6 has been shown to be responsible for a successive rise in anti-inflammatory cytokine IL-1receptor agonist (ra) (agonist to IL-1 $\beta$ ), hepatic synthesis of C-reactive protein (CRP), suppression of TNF- $\alpha$  and the release of cortisol <sup>5,9,12</sup>. Additionally, IL-6 has also shown to increase basal and insulin-stimulated glucose uptake in skeletal muscle via stimulation of the AMP-kinase pathway and associated increase in glucose transporter 4 (GLUT4) translocation, while the increased release of cortisol stimulates endogenous glucose production from the liver <sup>6,13</sup>. The increased concentration of both cortisol and IL-6 collectively work to regulate blood glucose concentration during acute exercise by maintaining equilibrium between glucose disposal and production.

Previous studies examining the acute exercise-induced inflammatory responses in sedentary populations have used gym-based methods of aerobic (cycling, running) and/or resistance (machine and free weights) exercises of differing intensities and durations <sup>6,10</sup>. However, group aerobic training sessions are reported to be more enjoyable than individualised training, which can potentially affect adherence and sustainability of an exercise training program <sup>14</sup>. Recently, soccer specific small-sided games (SSG) training has been reported to incorporate high-intensity intermittent sprints into an endurance-based event, which was highlighted as capable of inducing positive training adaptations (body composition, aerobic capacity, blood pressure, strength) either comparable

to, or better than, traditional continuous training modalities such as running<sup>15, 16</sup>. To date, previous research on the acute post-exercise inflammatory response to SSG or intermittent sprint protocols has been specific to sedentary Indigenous Australians<sup>17</sup> or young athletic populations<sup>7</sup>. A further understanding of these acute inflammatory and glucose responses in a sedentary, middle-aged population may be beneficial to justify the prescription of SSG for long-term inflammatory and glucose regulatory health benefits. Accordingly, the present study aimed to quantify and compare the acute inflammatory and glucose regulatory response within and between rugby-specific SSG and CYC conditions in sedentary, middle-aged Caucasian men. It was hypothesised that when matched for intensity and duration between the conditions a similar inflammatory and glucose regulatory response will be evident.

## **Methods**

The study population comprised of 9 sedentary, middle-aged men ( $48.8 \pm 1.7$ y) who were not clinically diagnosed with any pre-existing cardiovascular or metabolic disorders. The sedentary criteria ensured those completing no more than one regular exercise session per week ( $>20$ min) within the preceding 6 months. Those excluded were those with immunological irregularities, smokers ( $<2$ yrs cessation); those suffering from recurrent or recent influenza illness (including flu shot recipients); those on cholesterol lowering, anti-inflammatory, or any other medication/condition reported to affect the inflammatory response (i.e. rheumatoid arthritis or periodontal disease). Prior to participant recruitment the study was approved by the Research in Human Ethics Committee of the University. All participants provided verbal and written consent prior to the commencement of testing procedures.

In a randomised cross-over design participants completed CYC and SSG conditions, each separated by 21d to allow adequate recovery from an unaccustomed exercise session. Testing procedures commenced between standardised times (0600-0800h), following an overnight fast (10-12h). Physical activity and diet was controlled within each participant between conditions. Participants recorded physical activities 72h prior and food/fluid ingestion 24h prior to their first condition. Participants then replicated this diet and activity profile in preparation for the remaining condition. Diaries were inspected by the research team to ensure compliance with dietary and physical activity requirements. During each condition and 240min after all testing sessions participants remained fasted and consumed water *ab libitum* ( $\sim 500$ mL).

At pre-intervention testing, stature (stadiometer: Custom CSU, Australia), body mass (HW 150 K, A&D, Japan), waist and hip girths (steel tape, EC P3 metric graduation, Australia) were obtained from all participants. Manual blood pressure was obtained with an aneroid sphygmomanometer and cuff (Welch-Allyn, Arden, USA) expressed as the mean of three measurements after being seated for 5-min. A supine whole body dual-energy x-ray absorptiometry (DXA) scan (XR800, Norland, Cooper Surgical Company, USA) was conducted with scanning resolution set at 6.5x13.0mm, and scanning speed was set at 130mm·s<sup>-1</sup>. Scans were analysed (Illuminatus DXA, ver.4.2.0, USA) for total body fat-free mass (TB-FFM) and total body fat-mass (TB-FM)<sup>18</sup>. Measurement of oxygen consumption (VO<sub>2</sub>; Parvo Medics, True2400, East Sandy, Utah, USA) during a submaximal graded exercise test (GXT) was used in preference to maximal testing to minimize associated risks in sedentary, middle-aged men<sup>19</sup>. Prior to each session, the ventilometer was calibrated using a three-litre syringe, while gas analysers were calibrated for fractional gas concentration with a gravimetric gas mixture of known concentrations (CO<sub>2</sub>, 4.1±0.1%; O<sub>2</sub>, 15.7±0.2%), in accordance with the manufacturer's instructions. The GXT was performed on an electronically braked cycle ergometer (LODE Excalibur Sport, LODE BV, Groningen, The Netherlands), which started at 25W and increased by 25W every minute. Heart rate (HR; Vantage NV, Polar, Finland) was continuously monitored, and participants exercised until attainment of 80% age-predicted (220-age) maximum heart rate (%HR<sub>max</sub>).

The SSG condition involved modified football (non-contact rugby league) as this is the most popular football code in this geographical region<sup>20</sup>. Participants completed 40min of six-a-side on a reduced-size pitch (width: 40m; length: 60m) to induce a mean target HR zone ~80–85%HR<sub>max</sub>. To ensure participant randomization between conditions, testing was conducted over 2 separate games (n=4 in game 1 and n=5 in game 2) with the same research assistants forming the remaining player numbers in each game. The session comprised of 4x10min bouts, interspersed by 2 min passive recovery. Speed was recorded every second using a 1Hz Global Positioning Satellite (GPS) device (SPIetite, GPSports, Australia). The GPS unit was worn in a customised harnesses between the scapulae to quantify distance and mean speed (m·min<sup>-1</sup>) of movement patterns during the session<sup>21</sup>. At the end of each 10min period, HR and Rating of Perceived Exertion (RPE; Borg's 6-20 scale) were recorded, as well as a session-RPE 30min post-exercise<sup>22</sup>.

The cycling condition was conducted on a Monark stationary cycle ergometer (Monark 828E, Varburg, Sweden) and comprised of 4x10min continuous, steady-state bouts, interspersed by 2min passive recovery. During the

session, cadence was maintained at 60-65rpm and individual resistance adjusted to maintain target HR zones (80–85%HR<sub>max</sub>). At the end of each 10min interval HR and RPE were recorded, including session-RPE 30min following exercise. It is recognized the inherent difficulties of matching external training load or metabolic cost of two different exercise modes. Despite this limitation, in an attempt to match training load between conditions the respective exercise bouts were designed to elicit similar internal training loads. The intensity and duration of the cycling condition was designed to match the approximate mean target HR zone of 80–85%HR<sub>max</sub> expected within the SSG condition<sup>15</sup>.

Venous blood was collected at rest (pre), immediately post (0min), 30, 60 and 240min post exercise. Following collection whole blood was centrifuged at 3500rpm for 15min at 4°C. Aliquots were frozen at -80°C and -20°C for EDTA and SST, respectively. Whole blood in EDTA tubes were refrigerated (4°C) for a maximum of 6h until analysis for total leukocyte count and HbA1c. Fluoride oxalate tubes were refrigerated (4°C) for a maximum of 30min until analysis of glucose and lactate. Blood was collected during baseline testing for analysis of fasting total cholesterol, high density lipoprotein, triglycerides (Enzymatic Method: Dade Behring Dimension Xpand, Siemens, Australia), total leukocyte count (Cell Counter: Cell-Dyn 3200, Abbott Laboratories, USA) and glycosylated haemoglobin (HbA1c; Liquid Chromatography: Bio-Rad Variant, Australia). During each condition, 20mL was collected at each time point for analysis of glucose, lactate (ABL825 Radiometer, Denmark), insulin, cortisol (Chemiluminescent Immunometric Assay: Immulite 2000, Diagnostic Products Corp., USA) and CRP (Particle enhanced turbidimetric immunoassay Dade Behring Dimension Xpand, Siemens, Australia). Analysis of biochemistry variables glucose, insulin, lactate, cortisol and CRP showed intra and inter-assay coefficients of variation of 4.0-7.4%. IL-6, IL-1 $\beta$ , IL-1ra and TNF- $\alpha$  were measured at each time point (ELISA Immunoassay: R & D Systems, USA), with intra and inter-assay coefficients of variation of 4.3-5.6%. Insulin resistance: homeostasis model assessment (HOMA-IR) was calculated using the formula (fasting insulin x fasting glucose)/22.5<sup>23</sup>.

### *Statistical analysis*

All data are reported as mean  $\pm$ SEM. Within and between condition and time-point differences were assessed using two-way repeated measures ANOVA (condition x time). When significant interactions were observed, Tukey's pairwise comparisons were employed to assess the source of significance, which was set at  $p < 0.05$ . All statistical analyses were performed using PASW<sup>TM</sup> for MS-Windows v17.0 (Statistical Package for the Social

Sciences, Chicago, IL, USA). Standard effect sizes (ES; Cohen's *d*) analyses were used in interpreting the magnitude of difference between conditions at each time-point. An ES was classified as trivial (<2.0), small (0.20-0.49), moderate (0.50-0.89) or large (>0.90).

## Results

All participant characteristics (anthropometry, body composition,  $\text{VO}_2$  and fasting blood chemistry) are presented in Table 1. Glucose, insulin and CRP concentration were collected prior to each exercise condition, thus, baseline values presented in Table 1 are the mean between the two respective pre-exercise time-points.

Total distance covered during the SSG was  $3173 \pm 104\text{m}$ , at a speed of  $79 \pm 3\text{mmin}^{-1}$ , with  $146 \pm 91\text{m}$  of high-speed running above  $14\text{kmh}^{-1}$ . Mean resistance for the CYC condition was  $1.9 \pm 0.2\text{kp}$ . No significant differences were evident between conditions for  $\%HR_{\text{max}}$  (SSG  $86 \pm 2\% HR_{\text{max}}$ ; CYC  $84 \pm 1\% HR_{\text{max}}$ ;  $p=0.22$ ;  $d=0.04$ ) and session-RPE (SSG,  $13 \pm 1\text{AU}$ ; CYC,  $14 \pm 1\text{AU}$ ;  $p=0.40$ ;  $d=0.01$ ). Blood lactate peaked immediately post-exercise at  $2.3 \pm 0.4$  and  $2.1 \pm 0.5\text{mmolL}^{-1}$  for CYC and SSG, respectively ( $p>0.05$ ;  $d=0.15$ ).

The acute IL-6, IL-1ra, TNF- $\alpha$  and IL-1 $\beta$  response of SSG and CYC conditions are shown in Figure 1. The acute IL-6 response shows a significant increase immediately post-exercise within both conditions ( $p<0.05$ ). Significant differences were evident between conditions at 240min post-exercise ( $p=0.04$ ;  $d=0.53$ ) with SSG remaining elevated above pre ( $p=0.005$ ), though not in CYC ( $p=0.154$ ). IL-1ra was significantly increased immediately post-exercise ( $p<0.05$ ) and remained elevated above pre values at 240min in both SSG and CYC ( $p<0.05$ ), without significant differences between conditions ( $p>0.05$ ;  $d=0.00-0.55$ ). Results for CRP, TNF- $\alpha$  and IL-1 $\beta$  showed no significant changes within or between conditions ( $p>0.05$ ). Moderate ES were evident between conditions at 120min for TNF- $\alpha$  ( $d=0.57$ ), and IL-1 $\beta$  ( $d=0.72$ ).

The acute cortisol, glucose, insulin and HOMA-IR responses of SSG and CYC conditions are presented in Figure 2. Cortisol was significantly increased in both conditions immediate post-exercise ( $p<0.05$ ), though decreased at 60min ( $p<0.05$ ) and remained below pre-values at 240min post-exercise ( $p<0.05$ ), without differences between conditions ( $p>0.05$ ;  $d=0.06-0.48$ ). In both conditions glucose increased immediately post-exercise ( $p<0.05$ ) followed by a significant decline at 30min ( $p<0.05$ ). Glucose concentrations for SSG were significantly lower than CYC at 30min ( $p=0.02$ ;  $d=0.82$ ) and 240min post-exercise ( $p=0.03$ ;  $d=0.98$ ). Insulin

concentrations showed a significant decline below pre-values at 240min post-exercise in SSG ( $p=0.02$ ) and CYC ( $p=0.01$ ), with no significant difference between conditions ( $p=0.61$ ). Moderate ES were evident between conditions for insulin at 0 ( $d=0.54$ ) and 120min ( $d=0.59$ ). HOMA-IR increased immediately post-exercise in SSG ( $p=0.028$ ). Differences between conditions were evident in the change from pre to 0min ( $p=0.04$ ;  $d=0.61$ ) and 0min to 30min post-exercise ( $p=0.01$ ) with a moderate trend between conditions at 0min ( $d=0.61$ ).

## Discussion

The sedentary, middle-aged men recruited for the present study can be classified as obese ( $n=8$ ) or overweight ( $n=1$ ), with elevated CRP ( $>2.0\text{mgL}^{-1}$   $n=6$ ) and high cholesterol hazard ratio ( $\geq 4:1$   $n=6$ )<sup>1, 24</sup>. These characteristics place the participants at 'high risk' of developing metabolic and cardiovascular diseases<sup>24</sup>. The novel findings of the present study were that an acute bout of SSG is capable of inducing and maintaining a similar elevated post-exercise in IL-6, IL-1ra and cortisol as observed in CYC, although SSG lowered blood glucose concentration to a greater extent. Regardless, both SSG and CYC conditions lowered blood glucose concentration and provided a post-exercise anti-inflammatory milieu several hours after the exercise bout.

During muscle contraction IL-6 is released into the circulation from the active myocytes, which initiates an anti-inflammatory environment by stimulating the release of IL-1ra and cortisol into the circulation<sup>2, 9, 11</sup>. The present findings showed that despite both conditions showing a similar response in IL-6 immediately post-exercise, IL-6 remained elevated in the SSG compared to CYC at 240min. One other study has reported on the acute IL-6 response to SSG in untrained sedentary Indigenous Australian men and showed no differences between SSG and CYC<sup>17</sup>. Given the current study attempted to match intensity and duration between conditions, the recruitment of greater muscle mass (i.e. both upper and lower body are involved) in the SSGs may explain sustained elevation in plasma IL-6. However, it should be recognised that these IL-6 responses could also be explained by the potential differences in energy cost (despite similar HR and RPE response) and the load-bearing (i.e. SSG on ground/direct impact) versus weight-supported nature of stationary cycling<sup>25</sup>. Consistent with previous research, IL-1ra peaked at 60min post-exercise and remained elevated for up to 240min in both conditions<sup>5, 17</sup>. These results suggest the release of IL-6 and subsequent release of IL-1ra represents as an exercise-induced anti-inflammatory environment within both SSG and CYC conditions<sup>9, 26</sup>. Differences between conditions for IL-6 occurred at 240min post-exercise; hence, the effect on IL-1ra is unknown because it is likely that any differences may occur after the 240min time-point. Regardless, both SSG



and CYC exercise modes stimulated positive acute anti-inflammatory response. Given the only difference between conditions in IL-6 occurred at an isolated time-point, future studies may be directed towards determining potential differences in inflammatory responses and ensuing adaptations between SSG and CYC conditions for the prevention and treatment of T2DM and CVD <sup>4</sup>.

The increased concentrations of IL-6 and IL-1ra create an anti-inflammatory environment which has been shown to inhibit the release of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$  <sup>12, 27</sup>. The present study showed no post-exercise change in plasma concentrations of pro-inflammatory (TNF- $\alpha$  and IL-1 $\beta$ ) cytokines. These results are consistent with different models of moderate-intensity aerobic conditions (running, intermittent running, SSG and CYC) within sedentary populations <sup>17, 28</sup>. The non-significant changes reported in the current and previous studies may be due to the sedentary characteristics of the participants restricting the intensity and duration of exercise that can be prescribed; as it is likely that more strenuous and longer duration exercise prescribed in active and athlete populations may be required to induce immunological strain and an elevated post-exercise IL-1 $\beta$  and TNF- $\alpha$  <sup>5</sup>. These strenuous and long duration training methods are generally not prescribed within sedentary middle-aged cohorts, hence the lack of literature describing changes in pro-inflammatory markers in response to acute exercise. Prolonged and intermittent exercise can also lead to the release of CRP within 24–48h following exercise - with the magnitude of increase dependant on the hepatic synthesis of IL-6 and/or muscle damage <sup>7, 29</sup>. The present study showed no exercise-induced response to SSG or CYC in plasma CRP. A limitation is that CRP was only measured up to 240min post-exercise and may explain the negligible response observed within CYC and SSG conditions. Previous research has shown an increase in CRP 24h post-exercise in accordance with an increase in muscle damage from high-intensity resistance exercise compared with intensity and duration-matched cycling <sup>10</sup>. As such, future research should assess the association between CRP and markers of muscle damage within the 24–48h period post SSG, when compared with CYC.

Cortisol is known to have potent anti-inflammatory effects, which can also be augmented by the increase in IL-6 and subsequent down regulation of pro-inflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) by immune cells <sup>2, 5, 9</sup>. The cortisol response to both aerobic and resistance exercise is dependent on intensity and duration, more so than the exercise mode <sup>10, 30</sup>. Accordingly, the current study showed a similar cortisol response between SSG and CYC conditions matched for duration and intensity. Specifically, cortisol functions as an energy sensor to augment hepatic glucose release and provide sufficient fuel for metabolic demands <sup>9</sup>. In the present study a moderate

effect for increased insulin following SSG compared with CYC was evident, which may have contributed to a greater reduction in blood glucose concentration following SSG. As such, two potential reasons for the difference in post-exercise glucose concentration may relate to the respective differences and effects between conditions in the immediate post-exercise HOMA-IR and insulin responses. Taken collectively, the fluctuations in HOMA-IR between 0 and 30min post-exercise and the associated increase in circulating insulin, alongside an amplified IL-6 response simultaneously are likely to have caused an increase in peripheral glucose metabolism and thus a lower plasma glucose concentration in SSG compared an intensity- and duration-matched CYC condition.

### **Conclusion**

Similar to an intensity and duration-matched CYC condition, an acute bout of SSG is capable of inducing and maintaining an anti-inflammatory milieu several hours after the exercise bout. Furthermore, both conditions stimulated lowered blood glucose concentration, although SSG lowered blood glucose concentration to a greater extent when compared with CYC. Given the lack of inflammatory based research within SSG training for sedentary populations, it is suggested future studies examine the chronic adaptations of SSG training and its role for long-term health benefits.

### **Practical Implications**

- Rugby specific small-sided games (SSG) is a novel mode of intermittent exercise that stimulates a systemic anti-inflammatory milieu for several hours after the exercise bout.
- An acute bout of SSG or CYC lowers blood glucose concentration, which has important implications for daily glucose regulation in sedentary, men at risk of developing metabolic abnormalities.
- Group-based exercise through SSG can be utilised as a method for acute exercise prescription, within sedentary men

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### Conflict of Interest

None

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## Figure Captions

### Figure 1.

Mean  $\pm$  SEM response of IL-6, IL-1 $\alpha$ , TNF- $\alpha$ , IL-1 $\beta$  and CRP within and between the respective conditions. Significant difference from baseline within the cycling condition <sup>a</sup> P<0.05; Significant differences from baseline within the small-sided games condition <sup>b</sup> P<0.05; Significant difference between groups <sup>c</sup> P<0.05.

**Figure 2.**

Mean  $\pm$  SEM response of glucose, insulin, cortisol and HOMA-IR within and between the respective conditions.

Significant differences from baseline within the cycling condition <sup>a</sup> P<0.05; Significant differences from

baseline within the small-sided games condition <sup>b</sup> P<0.05; Significant difference between groups <sup>c</sup> P<0.05.