

Inflammatory cytokines and metabolic responses to high-intensity intermittent training: effect of the exercise intensity

AUTHORS: Fatma Rhibi^{1,2}, Hassane Zouhal², Fabio Santos Lira³, Nejmeddine Ouerghi⁴, Jacques Prioux², Sophia Besbes⁵, Jed M. Tijani⁶, Anthony C. Hackney⁷, Abderraouf Ben Abderrahman¹

¹ Laboratory of Biomonitoring of the Environment, Faculty of Science of Bizerte, University of Carthage, Tunisia

² Movement, Sport, Health and Sciences laboratory (M2S). UFR-STAPS, University of Rennes 2-ENS Cachan, Av. Charles Tillon, 35044 Rennes Cedex, France

³ Exercise and Immunometabolism Research Group, Postgraduation Program in Movement Sciences, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente, São Paulo, Brazil

⁴ Research Unit, Sportive Performance and Physical Rehabilitation, UR13JS01, High Institute of Sports and Physical Education of Kef, University of Jendouba, Kef, Tunisia

⁵ Clinical Biology Laboratory, Med Kassab Institute of Orthopedics, Tunisia

⁶ Higher Institute of Sport and Physical Education of Ksar-Said, Unit of Research, Movement Analysis and Performance Assessment, Ksar-Said, Tunisia

⁷ Department of Exercise & Sport Science, University of North Carolina, Chapel Hill, NC, United States

ABSTRACT: To examine the effects of two high-intensity intermittent training (HIIT) programs of varying intensities (100% vs. 110% of maximal aerobic velocity [MAV]) on metabolic, hormonal and inflammatory markers in young men. Thirty-seven active male volunteers were randomly assigned into: HIIT experimental groups (100% MAV [EG₁₀₀, n = 9] and 110% MAV [EG₁₁₀, n = 9]) and a control groups (CG₁₀₀, n = 9 and CG₁₁₀, n = 9). Participants performed high intensity intermittent exercise test (HIIE) at 100% or 110% MAV. Venous blood samples were obtained before, at the end of HIIE and at 15 min of recovery, and before and after 8 weeks of HIIT programs. After training, Glucose was lower ($p < 0.01$) in EG₁₀₀ ($d = 0.72$) and EG₁₁₀ ($d = 1.20$) at the end of HIIE, and at 15 min recovery only in EG₁₁₀ ($d = 0.95$). After training, Insulin and Cortisol were lower than before training in EG₁₀₀ and EG₁₁₀ at the end of HIIE ($p < 0.001$). After HIIT, IL-6 decreased ($p < 0.001$) in EG₁₀₀ ($d = 1.43$) and EG₁₁₀ ($d = 1.56$) at rest, at the end of HIIE ($d = 1.03$; $d = 1.75$, respectively) and at 15 min of recovery ($d = 0.88$; $d = 1.7$, respectively). This decrease was more robust ($p < 0.05$) in EG₁₁₀ compared to EG₁₀₀. After HIIT, TNF- α decreased ($p < 0.001$) in EG₁₀₀ ($d = 1.43$) and EG₁₁₀ ($d = 0.60$) at rest, at the end of HIIE ($0.71 < d < 0.98$) and at 15 min of recovery ($0.70 < d < 2.78$). HIIT with 110% MAV is more effective in young males on the improvements of some metabolic (Glucose), hormonal (Cortisol) and inflammatory (IL-6) markers at rest, at the end of HIIE and 15 min of recovery than training at 100% MAV.

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Corresponding author:

Hassane Zouhal
Movement, Sport, Health and Sciences laboratory (M2S)
UFR-STAPS, University of Rennes 2-ENS Cachan
Av. Charles Tillon, 35044 Rennes Cedex, France
E-mail: Hassane.zouhal@univ-rennes2.fr

ORCID:

Fatma Rhibi
0000-0003-4017-7663

Hassane Zouhal
0000-0001-6743-6464

Fabio Santos Lira
0000-0002-9645-1003

Nejmeddine Ouerghi
0000-0002-8840-1735

Jacques Prioux
0000-0002-5380-6767

Jed M. Tijani
0000-0001-8889-3816

Anthony C. Hackney
0000-0002-6607-1472

Abderraouf Ben Abderrahman
0000-0003-1351-8717

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INTRODUCTION

Low-grade systemic inflammation (characterized by small rise the pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α) and C-reactive protein (CRP)) may exhibit links with the development of insulin resistance, type 2 diabetes, metabolic syndrome and cardiovascular disease [1]. These markers are prognostic indicators of an increased risk for several chronic diseases [1]. A sedentary lifestyle leads to increased visceral adipose tissue fat accumulation, and promotes, at least in part, increased pro-inflammatory cytokine levels.

On the other hand, regular physical exercise is an important mediator of reductions in systemic inflammation (such as TNF- α and IL-6) and related metabolic parameters (such as glucose, insulin,

insulin resistance, and lipids) [2]. Numerous studies have shown the effectiveness of regular exercise training on metabolic disorders, both as a prevention and treatment, and its anti-inflammatory effects [2]. Likewise, IL-6 play an anti-inflammatory role and have been observed in increased amounts in response to exercise [3–5]. This interleukin participates in the immune system and metabolism regulations during a physical exercise. IL-6 contribute to glycogenolysis and lipolysis processes, alterations in metabolic parameters/process can be linked to the inflammatory response [6]. New evidence supports that high-intensity intermittent training (HIIT) is a very effective method in improving cardio respiratory fitness and cardiovascular health. HIIT consists of repeated, brief, and high-intensity efforts interspersed

with active or passive recovery, it has gained attention as a time-efficient strategy for improving cardio respiratory fitness with very low time commitment in a variety of populations, including trained [7] and untrained individuals [8]. Moreover, the inflammatory and metabolic response to acute high-intensity intermittent exercise (HIIE) is less known. A recent study of Lithgow and Leggate [9] observed that single bout of HIIT (5 km run intermittently; being 1-min at maximal aerobic velocity [MAV] followed by 1 min of passive recovery for 3 times per week) exercise affects only the insulin response but not the glycaemic response to a glucose load, insulin sensitivity and inflammatory markers (TNF- α , IL-6, CRP). On the other hand, study of Meckel et al. [10] showed that a single bout of HIIE (4 sets of 250-m runs on a treadmill at 80% MAV with 3 min of rest between each of the 250-m runs) increases inflammatory mediators. It has been reported that an acute bout of HIIE resulted in a significant increases in serum concentrations of several inflammatory cytokines (IL-6, TNF- α , and IL-10) and chemokines (IL-8 and MCP-1) [5, 6], however, the inflammatory response to a different HIIE intensity has not been examined, and requires further investigation.

Recent studies have shown that short-term (5–8 weeks) of HIIT only or HIIT associated with strength training was enough to improve the anti-inflammatory profile in health young physically active subjects [11]. Additionally, sprint intervals including short time (few seconds) of high intensity effort have been reported to improve peripheral muscular adaptations induced by maximal workloads [12]. Pedersen and Hoffman-Goetz [13] showed that HIIE at 90–100% MAV induces immunosuppression and may explain the increased risk of infection in athletes following exercise. In endurance sports, during the cycles of increased training volume and intensity, that include consecutive training sessions with shorten recovery time, athletes may experience a temporary diminished performance concomitant with an immunodepression state [14]. However, other

authors have shown that increasing HIIE intensity from 90 to 110% $\dot{V}O_{2max}$ [15] or from 100% to 110% MAV [16] could allow a greater increase in aerobic performance.

To the best of our knowledge, no findings have been published concerning the effects of different high intensities of HIIE during training on inflammatory and metabolic indices. Therefore, the main aim of the current study was to investigate the effects of two HIIT programs of varying intensities (100% vs. 110% MAV) during 8 weeks on changes in TNF- α , IL-6, insulin, glucose in healthy young men. We hypothesized that increasing interval-training intensity by +10% MAV could lead to better aerobic performance during an interval-training session accompanied by an adaptation in inflammatory and metabolic systems.

MATERIALS AND METHODS

Participants

Thirty-seven male physical education students volunteered to participate in this study were assigned in randomized order to two control groups who resealed intermittent test with 100% MAV (CG₁₀₀, n = 9) and 110% MAV (CG₁₁₀ = 9), and two HIIT experimental groups (EG): intermittent exercise with 100% MAV (EG₁₀₀, n = 9) a HIIE with 110% MAV (EG₁₁₀, n = 9) (Table 1). Prior to participation, the participants underwent a medical examination and were fully informed about the experimental procedures and a signed consent was obtained from them. This study had been approved by the University of Rennes 2 Research Ethics Committee.

Study design

After familiarization session with all the material of the experimente, all participants performed a maximal graded test (MGT) according to the protocol of Cazorla-Léger [17] to determine their maximal oxygen uptake ($\dot{V}O_{2max}$) and maximal aerobic velocity (MAV) before and

TABLE 1. Mean (\pm SD) data measured for the age and anthropometric data

| | EG ₁₀₀ | | EG ₁₁₀ | | CG ₁₀₀ | | CG ₁₁₀ | |
|---|-------------------|-----------------|-------------------|-----------------|-------------------|-----------------|-------------------|-----------------|
| | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT |
| Age (an) | 21.3 \pm 1.1 | 21.4 \pm 1.1 | 21.9 \pm 1.3 | 22.0 \pm 1.5 | 22.0 \pm 1.2 | 22.1 \pm 1.4 | 22.0 \pm 1.2 | 22.1 \pm 1.4 |
| BM (kg) | 72.8 \pm 7.8 | 72.2 \pm 7.7 | 72.9 \pm 6.2 | 72.4 \pm 6.1 | 72.5 \pm 4.2 | 72.3 \pm 4.2 | 72.6 \pm 4.7 | 72.3 \pm 3.7 |
| Height (cm) | 178.6 \pm 5.4 | 179.0 \pm 5.3 | 180.9 \pm 6.8 | 181.0 \pm 6.7 | 180.1 \pm 6.2 | 180.2 \pm 6.2 | 179.3 \pm 5.6 | 179.5 \pm 5.7 |
| BMI (kg \cdot m⁻²) | 22.7 \pm 1.3 | 22.5 \pm 1.2 | 22.3 \pm 1.4 | 22.1 \pm 1.3 | 22.4 \pm 1.0 | 22.3 \pm 0.8 | 22.6 \pm 0.9 | 22.5 \pm 1.0 |
| BF (%) | 11.6 \pm 1.2 | 11.5 \pm 1.2 | 11.4 \pm 1.5 | 11.3 \pm 1.4 | 11.8 \pm 1.4 | 11.9 \pm 1.4 | 11.7 \pm 1.4 | 11.7 \pm 1.4 |
| FFM (kg) | 64.2 \pm 6.6 | 63.9 \pm 6.3 | 64.6 \pm 5.3 | 64.2 \pm 5.0 | 60.0 \pm 3.8 | 63.7 \pm 3.7 | 64.1 \pm 4.0 | 63.9 \pm 3.5 |
| MAV (km \cdot h⁻¹) | 15.8 \pm 1.6 | 16.7 \pm 1.5 | 16.1 \pm 2.1 | 17.6 \pm 2.2 | 16.1 \pm 1.9 | 16.1 \pm 1.8 | 15.7 \pm 1.5 | 16.0 \pm 1.3 |

Data are mean values (\pm SD), BM: body mass, BMI: body mass index, BF: Body fat, FFM: fat free mass, EG₁₀₀: trained group with 100% MAV, EG₁₁₀: trained group with 110% MAV, CG₁₀₀ and CG₁₁₀: control groups, HIIT: high intensity intermittent training, MAV: maximal aerobic velocity. *: significant differences between before HIIT and after HIIT ($p < 0.05$).

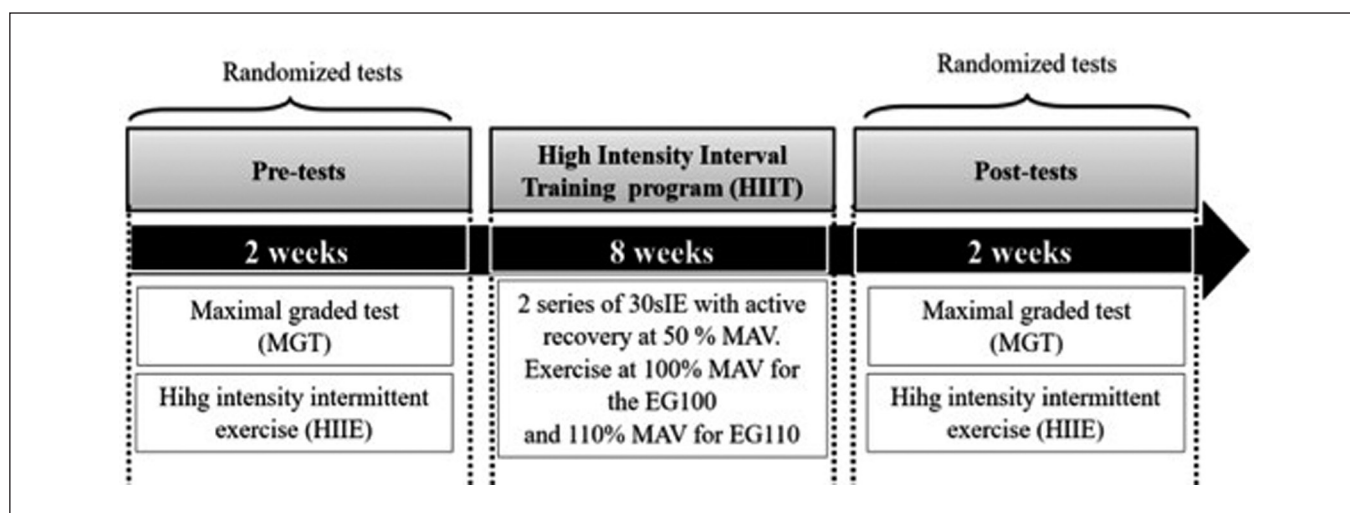


FIG. 1. Study design for both experimental groups and control groups.

TABLE 2. Training program.

| EG ₁₀₀ | | | | | | | | |
|--------------------|---------------|--------------|----------------|---------------|---------------|---------------|---------------|---------------|
| Week | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 |
| Set × (repetition) | 2× (8× 30sIE) | 2× (9×30sIE) | 2× (10× 30sIE) | 2× (11×30sIE) | 2× (10×30sIE) | 2× (12×30sIE) | 2× (12×30sIE) | 2× (11×30sIE) |
| Intensity | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% | 100% MAV/50% |
| TL | 1200 ATU | 1350 ATU | 1500 ATU | 1650 ATU | 1500 ATU | 1800 ATU | 1800 ATU | 1650 ATU |
| EG ₁₁₀ | | | | | | | | |
| Week | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 |
| Set × (repetition) | 2× (8× 30sIE) | 2× (9×30sIE) | 2× (10× 30sIE) | 2× (11×30sIE) | 2× (10×30sIE) | 2× (12×30sIE) | 2× (12×30sIE) | 2× (11×30sIE) |
| Intensity | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% | 110% MAV/50% |
| TL | 1280 ATU | 1440 ATU | 1600 ATU | 1760 ATU | 1600 ATU | 1920 ATU | 1920 ATU | 1760 ATU |

MAV: Maximal aerobic velocity; EG₁₀₀: 100% MAV training group; EG₁₁₀: 110% MAV training group; TL: Training load; ATU: Arbitrary training units. Example: [2 x (8 × 30sIE) 100/50% MAV]. It means that the subject had to run two series of eight times 30s intervals composed of 30 s running at 100% of MAV and 30 s active recovery at 50% of MAV. The subject recovers passively 5 min between each series. Each session is repeated 3 times a week.

after the HIIT. Before and after the HIIT, EG₁₀₀ and EG₁₁₀ groups carried out an intermittent exercise test consisting of repeating as long as possible 30 s intensive run at 100% MAV (EG₁₀₀) or 110% MAV (EG₁₁₀) alternating with 30 s active recovery (50% MAV) (FIG 1). The CG₁₀₀ and CG₁₁₀ only performed two MGT and HIIE (see details in following sections). They did not participate to any physical training program.

All the tests took place in the morning on a 400 m outdoor tartan track calibrated with cones, at the same time of the day, with 48 h of rest between each test.

Anthropometric measurements

Body mass was measured to the nearest 0.1 kg, with the subject in light clothing and without shoes, using an electronic scale (Kern, MFB 150K100). Height was determined to the nearest 0.5 cm with a measuring tape fixed to the wall. All measurements were performed by the same examiner in accordance with the positions and techniques established by the International Biological Program [18]. Percent body fat was determined using four skinfolds and a Harpenden caliper. The fat free mass was calculated by subtracting the fat mass from the body mass.

The high intensity interval training program (HIIT)

EG₁₀₀ and EG₁₁₀ groups participated in HIIT program three times per week for 8 weeks (24 sessions in total) (Table 2). HIIT sessions were separated by at least 48 h to allow adequate recovery. All sessions included three different periods according to the procedure described by Rhibi et al. [19]: the sessions were preceded by a standardized warm-up, which consisted of 15 min continuous jogging, followed by 5 min stretching exercises and 5 short bursts of accelerations on an outdoor track (400 m). During every training session on the track there was one subject per lane. All different distances for each athlete (running and recovery intervals) were fixed by the examiner before every session. The subjects start from a standing position, behind a cone. Then, they performed their HIIT session. For these training sessions, the subjects' pace was given by an examiner emitting sounds at regular intervals up to the end of the exercise. During the 30s recovery, subjects had to cover a distance determined according to their own MAV. At the end of the HIIT session, subjects cooled down for about 5 min, running at low intensity and performing static stretching.

Maximal graded test (MGT)

The maximal graded test was performed according to Rhibi et al. [19]. The initial speed was 8 km.h⁻¹ and this was increased by 0.5 km.h⁻¹ every minute. The velocity at the last and complete stage was considered as MAV. If the subject did not succeed to complete a given stage, but stopped after the half of this stage, the velocity corresponding to the last complete stage was increased by 0.5 km.h⁻¹. The accuracy of MAV was considered to be equal to the velocity during the previous stage plus 0.5 km h⁻¹ [20].

High intensity intermittent exercise (HIIE) test

The HIIE test consisted in repeating as long as possible a 30s run at 100% MAV (EG₁₀₀) or 110% MAV (EG₁₁₀) alternating with 30s active recovery (50% MAV) according to the procedure described by Rhibi et al. [19]. These tests were carried out on the same track as the maximal graded test. Before each test we calculated, as a function of the MAV of each subject, the required distance to be covered during the 30s intensive runs at 100% MAV, 110% MAV and the 30s active recovery at 50% MAV. 30 s intermittent exercise were preceded by a standardized warm-up consisting of 10 min continuous jogging, followed by 5 min of the participant's usual stretching routine, five short bursts of accelerations on the track and 2 min rest.

Blood sampling and analysis

Three venous blood samples were drawn: upon arriving, a heparinized catheter (Insyte-W, 1.1 mm.o.d. × 30 mm, Biopol, Tunis, Tunisia) was inserted into an antecubital vein. Subjects then rested quietly, for 20 min and then the first blood sample (10 mL) were taken to determine resting (rest) biomarker concentrations, a second immediately after the intermittent exercise test (end) and the third after 15 min of recovery (15min). Samples were placed in an ice

bath and centrifuged immediately. Aliquots of the extracted plasma were stored at -80° C until analyzed.

Insulin (Ins), glucose (Glu), CRP and cortisol (Cor) concentrations were determined from plasma samples. Specifically, insulin was determined by Radiolimmunoassay (RIA) using a specific kit (cis bio international, orisindustrie sa, france). The detection limit of insulin in the described method was 2μu.ml⁻¹ and the interassay coefficient of variation was 5.5%. Plasma glucose was assayed by the glucose oxidisemethod (boehringer mannheim kit, meylan, France). The sensitivity of the assay was 0.12 mmol.l⁻¹ and the coefficient of intra-assay variation was 2.4%. Homeostasis model assessment (HOMA-IR) index was estimated by the the formula: HOMA-IR = [fasting insulin (mU/l) × fasting glucose (mmol/l) / 22.5]. Cortisol concentration was determined enzymatic method using kinetic method (UV). CRP activity was determined using an Immunoturbidimetry method using commercially available reagents and a COBAS Integra 400 system (Roche Diagnostics, Mannheim, Germany). The intra-assay coefficient of variation for the CRP kit was 1.7%. Plasma cytokine concentrations were determined by enzyme-linked immunosorbent assay (ELISA) using Human IL-6 Quantikine ELISA Kit (R&D Systems, D6050, Minneapolis, MN, USA) and Human TNF-alpha Quantikine ELISA Kit (R&D Systems, DTA00C, Minneapolis, MN, USA). The plasma levels of interleukin IL-6 (100 uL EDTA Plasma) and tumor necrosis factor-alpha (TNF-α; 200uL EDTA plasma) were analyzed according to the manufacturer's instructions. The sensitivity was 5.5 pg/mL for TNF-α and 0.7 pg/mL for IL-6 measurements. The assay Range was 15.6 – 1,000 pg/mL for TNF-α and 3.1 – 300 pg/mL for IL-6.

Statistical analysis

Data were summarized as mean and the standard deviation of the mean (± SD) and statistcail analyzed using Statistica Version 13.2 software (StatSoft, France). After testing for normal distribution (Kolmogorov–Smirnov test), differences within and between the groups were analyzed using a two-way analysis of variance (ANOVA) for repeated measurements (time × groups). After confirming significant group differences over time, a LSD-fisher post hoc test was performed. To analyze delta values, we used ANOVA for one way (4 groups). Effect size (ES) was computed using the equation $ES = (\text{mean_post} - \text{mean_pre}) / SD$. ES of 0.20-0.60, 0.61–1.19 and ≥ 1.20 were considered as small, moderate and large, respectively [21]. The% of variation (%) was measured by the application of the following formula:

$$\left(\frac{\text{final value} - \text{initial value}}{\text{initial value}} \right) \times 100.$$

Intraclass correlation coefficients (ICC) and coefficients of variation (CV) were computed to assess relative and absolute test-retest reliability. A value of p < 0.05 was accepted as the minimal level of statistical significance.

RESULTS

All subjects had a 100% adherence rate and compliance to study procedures. No significant between-groups (EG₁₀₀, EG₁₁₀, CG₁₀₀ and CG₁₁₀) baseline differences were found for any anthropometric measures neither before nor after HIIT (Table1). No significant differences were found after the HIIT program compared to before for the following measures: body mass (p = 0.21; ES = 0.09), height (p = 0.25; ES = 0.11), BMI (p = 0.16; ES = 0.04), BF (p = 0.54; ES = 0.02), fat free mass (p = 0.91; ES = 0.13). No test or training-related injuries occurred over the course of the study. Reliability measures (ICC) for assessment tests ranged from 0.84 to 0.97, while percentage values for coefficients of variation ranged from 2.2 to 4.4% (Table 3).

TABLE 3. Intraclass correlation coefficients (ICCs) for relative reliability and coefficients of variation for absolute reliability of the applied physical fitness tests and blood parameters measurements.

| Measures | ICC | 95% CI | % CV |
|----------|------|-------------|------|
| MAV | 0.92 | 0.91 – 0.99 | 4.4 |
| GLUCOSE | 0.95 | 0.84 – 0.98 | 4.0 |
| INSULIN | 0.89 | 0.76 – 0.88 | 3.0 |
| CORTISOL | 0.84 | 0.83 – 0.96 | 2.7 |
| IL-6 | 0.97 | 0.74 – 0.97 | 2.7 |
| TNF-α | 0.89 | 0.61 – 0.97 | 2.2 |
| CRP | 0.94 | 0.76 – 0.98 | 4.1 |

ICC – intraclass correlation coefficient; CI – confidence interval; CV – coefficient of variation. MAV: maximal aerobic velocity; IL-6: interleukin 6; TNF-α: tumor necrosis factor alpha; CRP: C-reactive protein.

TABLE 4. Plasma glucose (Glu), insulin (Ins), Cortisol (Cor) concentrations and HOMA-IR values measured during HIIE before (pre-test) and after (post-test) HIIT in all groups (EG₁₀₀, EG₁₁₀, CG₁₀₀ and CG₁₁₀).

| Variables | EG ₁₀₀ | | EG ₁₁₀ | | CG ₁₀₀ | | CG ₁₁₀ | | p (Cohen´s d) | | | |
|---------------|-------------------|----------------------------|--|---------------------------|---|----------------------------|---------------------------|---------------------------|---------------------------|------------------|--------------------------|------------------|
| | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT | Main effect group | Main effect time | Interaction group x time | |
| Glu | Rest | 4.8 ± 0.3 | 4.6 ± 0.3 | 4.7 ± 0.5 | 4.6 ± 0.5 | 4.7 ± 0.5 | 4.7 ± 0.4 | 4.8 ± 0.5 | 4.7 ± 0.4 | | | |
| | End | 6.4 ± 1.3 _b | 5.6 ± 1.0 ^a _b | 8.2 ± 1.0 _b | 6.9 ± 1.1 ^a _b _c | 6.2 ± 0.7 _b | 6.2 ± 0.7 _b | 8.1 ± 0.8 _b | 8.1 ± 0.8 _b | p = 0.021 (0.48) | p < 0.001 (0.72) | p < 0.001 (0.33) |
| | 15 min | 5.8 ± 1.0 _b | 5.3 ± 0.8 _b | 7.5 ± 1.6 _b | 6.3 ± 1.0 ^a _b | 5.9 ± 1.2 _b | 5.5 ± 0.8 _b | 7.2 ± 0.9 _b | 7.1 ± 0.7 _b | | | |
| Ins | Rest | 12.8 ± 2.1 | 12.2 ± 1.5 | 12.3 ± 2.5 | 11.4 ± 1.9 | 12.8 ± 0.7 | 12.6 ± 0.6 | 12.6 ± 1.5 | 12.6 ± 1.4 | | | |
| | End | 16.9 ± 1.7 _b | 15.5 ± 1.7 ^a _b | 18.7 ± 4.4 _b | 14.7 ± 2.7 ^a _b _c | 16.6 ± 1.4 _b | 16.4 ± 0.8 _b | 18.7 ± 2.6 _b | 18.4 ± 1.8 _b | p = 0.017 (0.18) | p < 0.001 (0.77) | p = 0.007 (0.16) |
| | 15 min | 18.3 ± 2.9 _b | 17.2 ± 1.8 _b | 19.4 ± 3.3 _b | 18.3 ± 1.9 _b | 18.2 ± 1.8 _b | 18.3 ± 2.6 _b | 19.5 ± 1.6 _b | 19.4 ± 1.7 _b | | | |
| HOMA-IR index | 2.7 ± 0.4 | 2.51 ± 0.3 | 2.58 ± 0.5 | 2.3 ± 0.3 | 2.7 ± 0.3 | 2.6 ± 0.2 | 2.7 ± 0.6 | 2.7 ± 0.5 | p = 0.427 (0.12) | p = 0.132 (0.54) | p = 0.69 (0.18) | |
| Cor | Rest | 275.3 ± 74.6 | 293.6 ± 68.7 | 270.3 ± 70.5 | 292.7 ± 60.8 | 271.2 ± 81.5 | 270.2 ± 73.0 | 275.7 ± 68.6 | 292.7 ± 55.8 | | | |
| | End | 386.0 ± 95.9 _b | 465.7 ± 60.0 ^a _b | 412.4 ± 78.5 _b | 543.4 ± 99.5 ^a _b _c | 390.3 ± 84.9 _b | 397.9 ± 70.0 _b | 423.7 ± 74.3 _b | 450.2 ± 90.8 _b | p = 0.342 (0.09) | p < 0.001 (0.62) | p = 0.030 (0.14) |
| | 15 min | 370.4 ± 126.9 _b | 393.7 ± 135.3 _b | 395.8 ± 69.7 _b | 458.0 ± 87.8 ^a _b | 366.6 ± 102.2 _b | 360.1 ± 68.4 _b | 396.6 ± 84.7 _b | 372.7 ± 86.1 _b | | | |

Data are mean values (± SD), glucose (Glu), and insulin (Ins) and cortisol (Cor) concentrations measured at rest (rest), at the end of HIIE (end) and after 15 min of recovery (15min); EG₁₀₀: trained group with 100% MAV, EG₁₁₀: trained group with 110% MAV, CG₁₀₀ and CG₁₁₀: control groups without HIIT, HIIT: high intensity interval training. a: significant difference between before and after HIIT. b: significant difference compared to rest values. c: significant difference between EG₁₀₀ and EG₁₁₀.

TABLE 5. IL-6, TNF- α and CRP concentrations measured during HIIE before (pre-test) and after (post-test) HIIT in EG₁₀₀, EG₁₁₀, CG₁₀₀ and CG₁₁₀.

| Variables | EG ₁₀₀ | | EG ₁₁₀ | | CG ₁₀₀ | | CG ₁₁₀ | | p (Cohen's d) | | | |
|---------------|-------------------|---------------------------|--|---------------------------|--|---------------------------|---------------------------|----------------------------|---------------------------|---------------------|--------------------------|---------------------|
| | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT | Before HIIT | After HIIT | Main effect group | Main effect Time | Interaction group x time | |
| IL-6 | rest | 2.1 ± 0.6 | 1.5 ± 0.3 ^a | 2.0 ± 0.5 | 1.4 ± 0.3 ^a | 1.9 ± 0.6 | 1.8 ± 0.4 | 1.9 ± 0.4 | 1.9 ± 0.5 | p = 0.139 (0.14) | p < 0.001 (0.81) | p = 0.030 (0.26) |
| | end | 4.7 ± 1.2 _b | 3.5 ± 1.1 ^a _b | 4.7 ± 1.1 _b | 2.8 ± 1.0 ^a _b | 4.5 ± 1.6 _b | 4.4 ± 1.0 _b | 4.6 ± 1.1 _b | 4.5 ± 1.1 _b | | | |
| | 15 min | 4.3 ± 1.1 _b | 3.2 ± 1.3 ^a _b | 4.3 ± 1.0 _b | 2.7 ± 0.9 ^a _b | 4.3 ± 1.1 _b | 4.3 ± 0.8 _b | 4.5 ± 0.9 _b | 4.5 ± 0.9 _b | | | |
| TNF- α | rest | 3.2 ± 1.2 | 2.7 ± 1.1 ^a | 2.9 ± 1.3 | 2.2 ± 1.2 ^a | 2.9 ± 1.2 | 2.9 ± 1.2 | 3.0 ± 1.1 | 2.9 ± 1.1 | p = 0.886 (0.17) | p < 0.001 (0.84) | p = 0.007 (0.16) |
| | end | 6.8 ± 1.7 _b | 5.2 ± 1.6 ^a _b | 6.7 ± 1.9 _b | 5.3 ± 1.9 ^a _b | 6.4 ± 1.5 _b | 6.3 ± 1.1 _b | 6.2 ± 1.3 _b | 6.0 ± 1.0 _b | | | |
| | 15 min | 6.4 ± 1.6 _b | 5.1 ± 1.6 ^a _b | 6.2 ± 1.9 | 4.9 ± 2.0 ^a _b | 6.1 ± 1.4 _b | 6.1 ± 1.2 _b | 6.17 ± 1.3 _b | 5.8 ± 1.2 _b | | | |
| CRP | rest | 4.0 ± 0.8 | 3.5 ± 0.5 ^a | 3.5 ± 1.1 | 3.2 ± 0.8 ^a | 3.8 ± 0.7 | 3.7 ± 0.7 | 3.3 ± 0.5 | 3.3 ± 0.8 | p = 0.168 (0.09) | p < 0.001 (0.41) | p = 0.063 (0.02) |
| | end | 4.6 ± 0.7 _b | 4.5 ± 0.5 _b | 4.5 ± 0.8 | 4.4 ± 0.8 _b | 4.4 ± 0.5 _b | 4.6 ± 0.5 _b | 4.2 ± 0.7 _b | 4.4 ± 0.7 _b | | | |
| | 15 min | 4.8 ± 0.4 _b | 4.6 ± 0.5 _b | 4.5 ± 0.8 | 4.4 ± 0.8 _b | 4.7 ± 0.5 _b | 4.3 ± 0.9 _b | 4.3 ± 0.5 _b | 4.2 ± 0.7 _b | | | |

Data are mean values (\pm SD), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α) concentration measured at rest (rest), at the end of the HIIE (end) and after 15 min of recovery (15min); EG₁₀₀: trained group with 100% MAV, EG₁₁₀: trained group with 110% MAV, CG₁₀₀ and CG₁₁₀: control groups without HIIT, HIIT: high intensity intermittent training. a: significant difference between before and after HIIT. b: significant difference compared to rest values. c: significant difference between EG₁₀₀ and EG₁₁₀.

Main effect of time

The physical fitness test and all biological parameters displayed significant main effects of time (before HIIT vs. after HIIT). ES magnitudes ranged from small-to-large for all tests. Significant main effect of time was recorded for MAV ($p < 0.001$, $d = 0.71$) (Table 1). Main effects of time across training were observed for Glu ($p < 0.001$, $d = 0.72$), Ins ($p < 0.001$, $d = 0.77$), HOMA-IR ($p = 0.132$, $d = 0.54$). Similarly, main effects of time were also observed for Cor ($p < 0.001$, $d = 0.62$), IL-6 ($p < 0.001$; $d = 0.81$), TNF- α ($p < 0.001$, $d = 0.84$) and CRP ($p < 0.001$, $d = 0.41$) (Tables 4 and 5).

Main interaction effects

Tables 4 and 5 present group x time interactions for all assessed variables. Results revealed significant interactions for MAV ($p < 0.001$; $d = 0.61$), Glu ($p < 0.001$; $d = 0.33$), Ins ($p = 0.007$; $d = 0.16$), Cor ($p = 0.030$; $d = 0.14$). Moreover, significant interactions were found for IL-6 ($p = 0.030$; $d = 0.26$) and TNF- α ($p = 0.007$; $d = 0.16$). However, presents no significant interactions for CRP ($p = 0.063$; $d = 0.02$) were detected (Table 5).

Relative to the HIIE response, before and after HIIT, our results showed significant increase ($0.001 < p < 0.035$; $0.31 < d < 1.55$)

in concentration measures at the end of the HIIE and after 15 min of recovery compared to rest values for Glu, Ins, Cor, IL-6 and TNF- α in all groups.

Concerning HIIT effect, post-hoc tests revealed significant before-to-after HIIT increase for MAV ($p < 0.001$, $d = 0.58$, +5.4%) and for Cor_{end} ($p < 0.001$, $d = 1.04$, +17.1%) for EG₁₀₀. Moreover, For EG₁₀₀ our post hoc analyses presented significant before-to-after HIIT decrease for Glu_{end} ($p = 0.009$, $d = 0.72$, -14.7%), Ins_{end} ($p < 0.001$, $d = 0.85$, -9.5%), IL-6_{rest} ($p < 0.001$, $d = 1.43$, -34.4%), IL-6_{end} ($p < 0.001$, $d = 1.03$, -33.7%) and IL-6_{15min} ($p < 0.001$, $d = 0.88$, -32.8%), as well as for the TNF- α _{rest} ($p = 0.002$, $d = 0.45$, -19.0%), TNF- α _{end} ($p < 0.001$, $d = 0.98$, -30.9%), TNF- α _{15min} ($p < 0.001$, $d = 2.78$, 19.65%) and for the CRP_{rest} ($p = 0.02$, $d = 0.77$, -14.28%) (Tables 4 and 5).

For EG₁₁₀, post-hoc tests also revealed significant before-to-after HIIT increase for MAV ($p < 0.001$, $d = 0.70$, 8.5%) and for Cor_{end} ($p < 0.001$, $d = 1.45$, +24.1%), Cor_{15min} ($p = 0.040$, $d = 0.79$, +13.6%). Moreover, for EG₁₁₀ our post hoc analyses presented significant before-to-after HIIT decrease for Glu_{end} ($p < 0.001$, $d = 1.20$, -18.8%), Glu_{15min} ($p = 0.002$, $d = 0.95$, -19.9%), Ins_{end} ($p < 0.001$, $d = 1.12$, -27.2%), IL-6_{rest} ($p < 0.001$, $d = 1.56$, -40.8%), IL-6_{end} ($p < 0.001$, $d = 1.75$, -22.8%) and

IL-6_{15min} ($p < 0.001$, $d = 1.7$, -14.2%), as well as for the TNF- α _{rest} ($p < 0.001$, $d = 0.60$, -30.5%), TNF- α _{end} ($p < 0.001$, $d = 0.71$, -25.1%), TNF- α _{15min} ($p < 0.001$, $d = 0.70$, -27.4%) (Tables 4 and 5).

Our results showed significantly greater values in EG₁₁₀ compared to EG₁₀₀ for MAV ($p = 0.017$, $d = 0.49$, 5.11%) and Cor_{end} ($p = 0.04$, $d = 0.97$, +0.14%). Results showed that Glu_{end} was significantly lower ($p = 0.012$; $d = 0.26$) in EG₁₁₀ (-15%) compared to EG₁₀₀ (-12%). Results showed also that responses of Ins_{end} and IL-6_{end} were significantly lower ($p = 0.008$; $p = 0.030$, respectively) in EG₁₁₀ (-21%; -39%, respectively) compared to EG₁₀₀ (-8%; -25%, respectively). However, no significant difference in TNF_{end} values was observed between EG₁₀₀ and EG₁₁₀ after HIIT program.

DISCUSSION

The primary finding of our study is that 8 weeks of HIIT induced a significant increase in MAV in both EG₁₀₀ and EG₁₁₀. Furthermore, the increased MAV performance was associated with reduced Glu, Ins, Cor, TNF- α and IL-6 at the end of and HIIE test, in response to the HIIT program. These decreases were greater after the HIIT program using 110% MAV, except for TNF- α , and the 100% MAV program.

Our results showed an increase in TNF- α and IL-6 concentrations at the end of HIIE and at 15 min of recovery compared to rest values in all groups before and after HIIT. These results are in accordance with previous studies [4, 22]. In fact, the exercise induced a general response to the stress involving the activation of immune system [10]. Cabral-Santos et al. [4] demonstrated that HIIE of a 5 km run induced an increase of TNF- α , IL-6 and IL-10 levels. Similarly, Dorneles et al. [23] demonstrated that 85–90% MAP intensity separated by 75s at 50% MAP might cause a progressive increase of IL-6 levels immediately and 30 min after the end of exercise. Wadley et al. [24] demonstrated that IL-6 increased significantly after 30 min of recovery following a HIIE. Finally, Nieman et al. [25] showed that an extended and intense exercise at 70% MAV until exhaustion increased muscular protein concentration and IL-6 plasma levels.

No studies have verified if a lower duration level of intermittent exercise could produce the same inflammatory response. However, Cabral-Santos et al. [26] showed that both HIIE protocols (~6 or 11 bouts, 1:1 at 100% at sVO_{2peak}) using the same intensity were effective to increase IL-6 after acute exercise. These authors observed that only IL-10 response was related to exercise duration. In the literature, contradictory findings do exist, but do not describe any changes of plasma TNF- α induced by physical activity [27]. In this context, Laskowski et al. [28] revealed a decrease of IL-4 and an increase of IL-10 after exercise, but no variation was observed in IL-6 and TNF- α level. Wedley et al. [24] suggested that the cytokine level (e.g., TNF- α) increase in response to exercise depends on its intensity of the activity. This hypothesis has also been suggested by

other researchers [5, 6] who demonstrated that higher anti-inflammatory responses after a HIIE related to the activities intensity. However, our results demonstrated no significant difference between the two intensities of HIIE (granted though, our intensity difference, were relatively small). Thus, one might speculate that IE duration (more extended IE) might also be an important variable in addition to exercise intensity. In fact, skeletal muscle is a major source of some cytokines and the response depend on exercise duration and intensity [29]. The increase of IL-6 at the end of HIIE could be explained by glucose variation in response to the HIIE. In fact, muscle glycogen concentrations were negatively correlated with muscular protein levels of IL-6 modifications [25]. These results are in accordance with our findings in which glucose decreased at the end of IE in EG₁₀₀ and EG₁₁₀ to the same extent among the two groups.

Additionally, our results revealed a significant decrease of TNF- α and IL-6 at rest, at the end of HIIE and at 15 min recovery in EG₁₀₀ and EG₁₁₀ after HIIT in comparison with concentrations measured in baseline. Our results showed an important decrease in EG₁₁₀ compared to EG₁₀₀ only in IL-6_{end} after HIIT. These results agree with the results of Croft et al. [30] who demonstrated that 6 weeks of HIIT (at 90% MAV) significantly reduced responses to IL-6 by 40%. These authors increased the HIIE intensity by 5% every 2 weeks of training, the intensity of exercise was reduced at last exercise to ensure good conditions for blood sampling. Similarly, in our training program, we increased our HIIT training volume progressively by increasing the number of repetitions, but did reduce the volume during its last week. Similarly, Laskowski et al. [28] demonstrated a significant modification in blood cytokine level (TNF- α) after three days of judo training sessions (i.e., randori fight). Zweetsoot et al. [5] observed no significant modifications of cytokine levels two weeks after HIIT precisely between the first and the sixth session of it. According to these authors, the 50% increase in exercise volume they implemented did not increase the inflammatory responses. Additionally, other studies demonstrate that athlete who took a high-intensity aerobic training program presented normally elevated muscular glycogen storage which would reduce the needs in IL-6 as an energetic sensor [31], which can explain the decrease of IL-6 after HIIT in the two groups. Lira et al. [6] observed that higher levels of TNF- α and an immune-endocrine profile can exert a potential effect on the lipolysis process. Rosa et al. [32] also reported that an exhaustive exercise induced pro-inflammatory response in adipose tissue which leads to higher levels of IL-6 and TNF- α in it, which might contribute to lipolysis and to a release of fatty acids. In fact, cytokines exert many functions and play a crucial role in energy metabolism. As an example, IL-6 and TNF- α , which play an important role in anti-inflammatory response and exert effects on glucose and lipids metabolism, stimulating increases in lipolysis which is a process of glycogenolysis to provide energy supply to skeletal muscles [6]. In the current study, positive changes in inflammatory and metabolic indices were observed in EG₁₀₀ and EG₁₁₀ after HIIT without reduction of body mass can mainly be explained by the absence of CRP

concentrations variation after HIIT in both groups. In fact, previous studies observed significant correlations between plasma inflammatory markers concentrations and % body fat and fasting plasma glucose [33]. However, Blüher *et al.* [34] showed that body fat content was only a significant predictor of CRP plasma concentration variations.

Our results demonstrated an increase of Glu_{end} , Ins_{end} , $\text{Glu}_{15\text{min}}$ and $\text{Ins}_{15\text{min}}$ when compared to measured values at rest in the two groups before and after 8 weeks of HIIT. However, our results also showed that Ins concentration varied depending on IE intensity. Ins was lower in EG_{110} compared to EG_{100} after HIIT program. In this context, Galbo [35] demonstrated that Ins variations depends directly on exercise intensity and duration. This investigator observed that Ins decreases at intensities lower than 70% and increases beyond it. This decrease was found to reach 50% of initial value after two hours of moderate intensity exercise (40–50% MAV). However, Ben Abderrahman *et al.* [36] demonstrated an increase of Glu and Ins when stopping IE and after 10 min of recovery following a maximal graded exercise. These results are in accordance with our finding which also showed increases in Glu and Ins in response to IE at 100% and 110% MAV. Importantly, IL-6 does have beneficial effects on metabolism [37], since, this response exerts effects on the translocation GLUT4 in the muscle which increases glycogen synthesis, insulin sensitivity in muscular central and peripheral organs [38]. Moreover, since IL-6 and TNF- α contribute to glycogenolysis and lipolysis processes, alterations in metabolic parameters/process can be linked to the inflammatory response. Our results mentioned above (Glu and Ins variations) might be due to many physiological adaptations, as the insulin sensitivity and glucose transit during high intensity training [39]. Thus one could speculate that a probable mechanism associated to HIIT which promoted Glu uptake. Hence, the decrease of Glu might be explained by the decrease of its transport under insulin action and the rise of the insulin sensitivity [37].

The current results demonstrated an increase of Cor_{end} and $\text{Cor}_{15\text{min}}$ in comparison with Cor_{rest} in the four groups before and after HIIT. These results are in accordance with literature, as a number of authors have demonstrated an increase of Cor from 60% MAV intensity and this increase became more important when power is increased [40]. In contrast, during low intensity exercise, Cor level increase is so low that its nyctohemeral variations may be undetectable [41]. However, a decrease of Cor during exercise with intensity lower than 60% MAV had been observed [42].

On the other hand, our results demonstrated a significant increase of Cor_{end} in EG_{100} and EG_{110} after HIIT, this increase was significantly greater in EG_{110} than EG_{100} . In fact, it was demonstrated that an intensive training (maximal effort exercise of 30s) increased Cor_{rest} and Cor_{end} concentrations [43]. These results might be explained by the subjects training level; in fact, cortisol response to physical exercise is more important in subjects with high level training practice [44].

The present study has few limits. The first is the small sample size in each of our 4 groups (experimental and control groups). In addition, our study focuses only on healthy, active and young men. Hence, our results can not be generalized to women or to unhealthy, sedentary or old people.

CONCLUSIONS

In conclusion, this study provides evidence to suggest that varying intensities (100% vs. 110% MAV) HIIE may be an effective intervention strategy for promoting metabolic and inflammatory adaptations after 8 weeks of HIIT program. Both protocols lead to improvements in the anti-inflammatory status (decreases IL-6 and TNF- α levels in rest), although the EG_{110} exhibited a greater impact on MAV. Nonetheless, future studies are required to provide a more comprehensive understanding of the effects of 110% MAV HIIT on inflammatory and metabolic function, particularly during intermittent exercise.

Practical applications

The present study can potentially help the sports trainers and coaches to prescribe more efficient training programs. As a best practice, we recommend the HIIT program based on IE at 110% MAV to assure greater aerobic performances without increasing inflammatory (IL-6, TNF- α and CRP) concentrations.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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